Al-Azhar University-Gaza

Pharmaceutical Chemistry and Pharmacognosy Department

CNS DDRUGS

CNS DEPRESSANTS

MedChem-III

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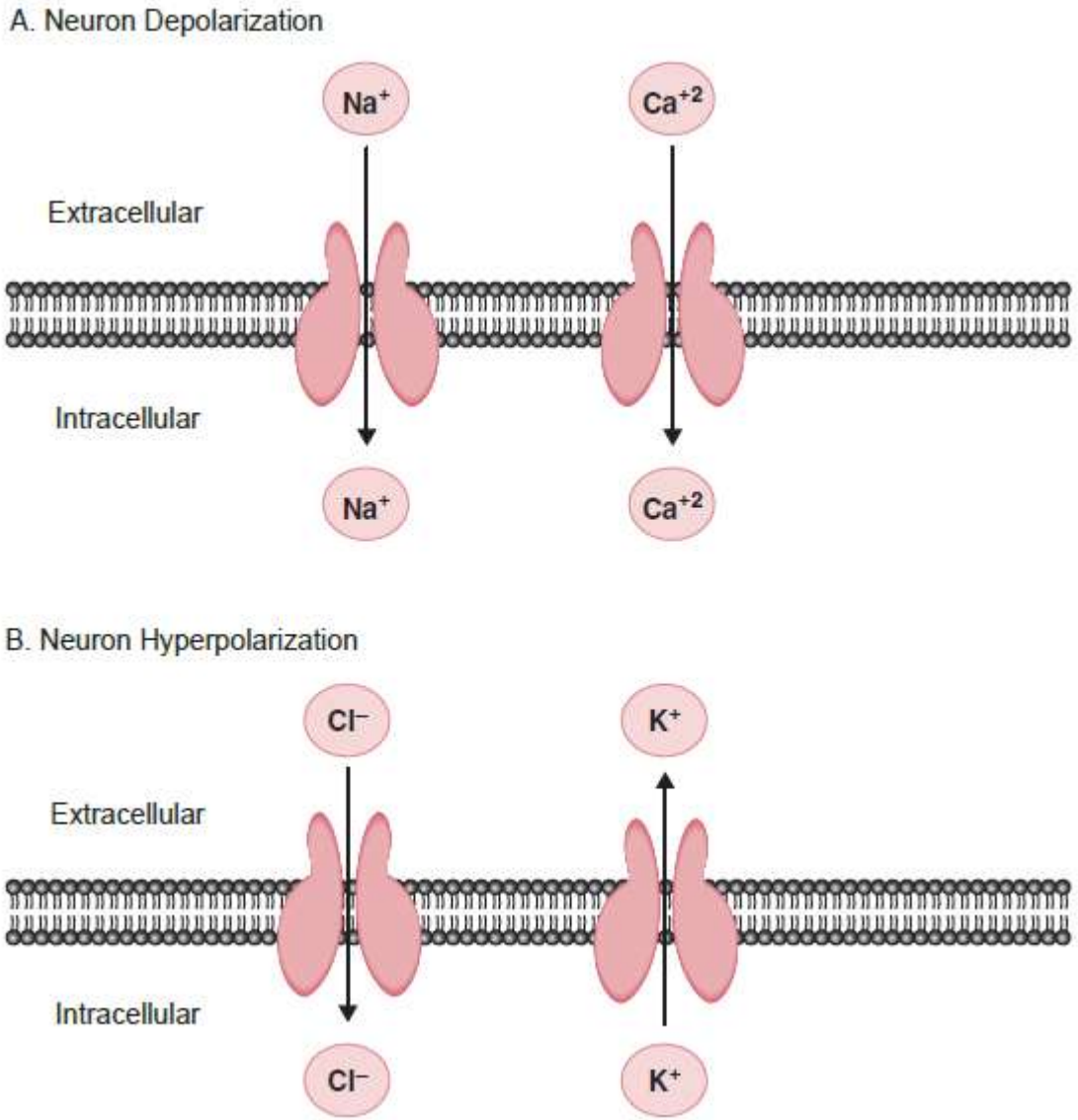
CNS Depressants:

CNS depressants are substances that can slow or depress normal brain function. Because of this property, some CNS depressants are useful in the treatment of anxiety and sleep disorders. In higher doses, some CNS depressants can be used as general anesthetics



Electrophysiology of excitatory and inhibitory neurotransmitters. The tendency of an ion to move across the membrane depends on the difference in its electrochemical gradient on either side of the membrane.

Classes of CNS depressants

General anesthetics

Sedative-hypnotics

Anxiolytics

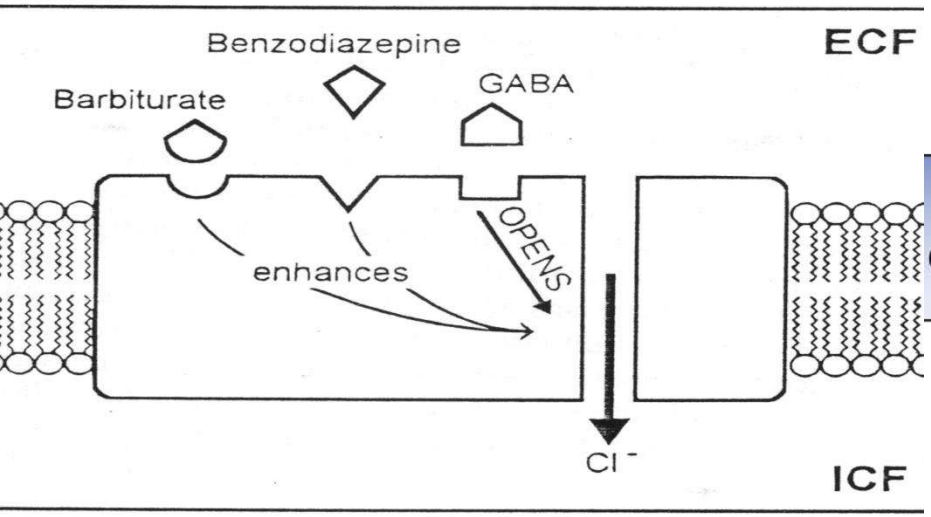
Anticonvulsants

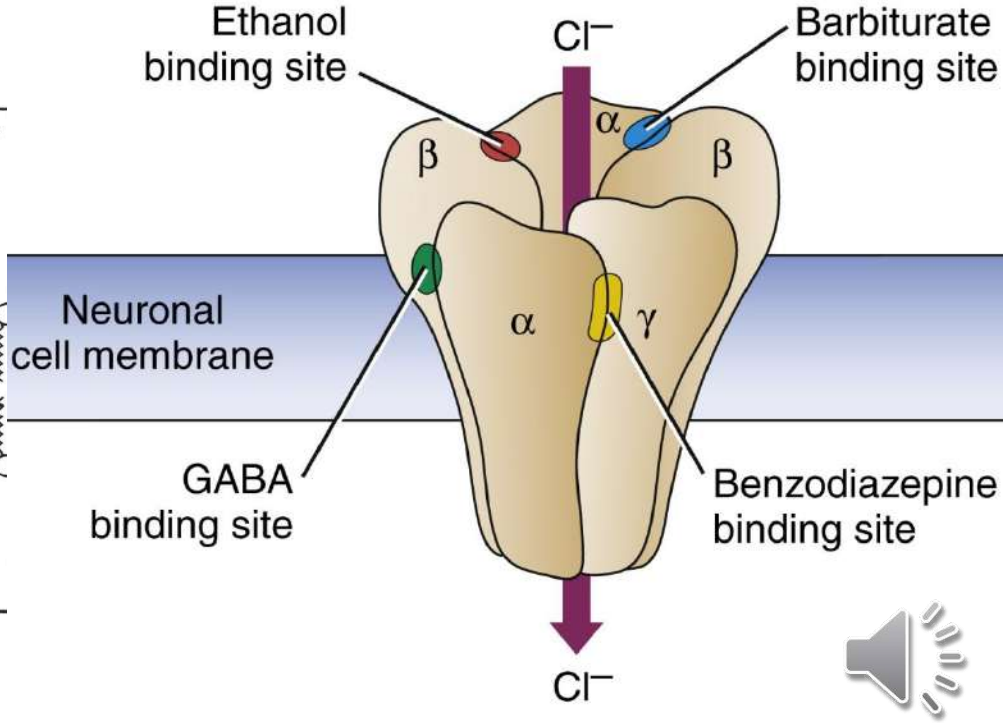
Antipsychotics

There is a considerable overlap among these groups, the first four groups have much in common

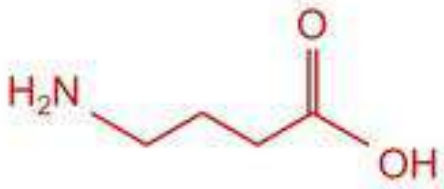
Mechanisms of action:

- The first four groups bind to the allosteric site of $GABA_A$ receptor , which potentiate the effect of GABA in opening the chloride channels that give the relaxant effect





GABA – gamma-aminobutyric acid



- Most inhibitory neurones in the brain use GABA or glycine – as many as a third of the synapses in the brain use GABA[1]
- The predominant precursor for GABA is glutamate[1]
- GABA is removed from the synapse by specific transporters, and the retrieved GABA is metabolised[1]

- GABA is found throughout the brain, rather than being localised to specific areas or pathways[1]
- There are three types of GABA receptor, which although varied can typically be separated as follows:[1]
  - **$GABA_A$** – ionotropic chloride channel
  - **$GABA_B$** – metabotropic G-protein coupled receptor
  - **$GABA_C$** – ionotropic chloride channel
- Glycine, the other major inhibitory neurotransmitter, has a more localised distribution, and can be found in the spinal cord[1]

Other mechanisms of action

- A number of anesthetics appear to inhibit glutamic acid binding to its receptors. Since glutamic acid has an exciting effect on the CNS system so inhibition of its binding to its receptor will produce general CNS depression.
- Agonism at A1 receptors (Adenosine receptors)
- Inhibition of neuronal flux of Ca^{2+} and Na^{+}

Mechanism of action of antipsychotics

- By, blocking D_2, D_3 and/or D_4 receptors
- They may be selective presynaptic DA receptor agonists
- By depleting neuronal DA. (Ex. Rawolfia alkaloids, which are seldom used nowadays as antipsychotics
- Or they may have more than one mechanism, giving a net effect of which is to reduce the release of DA into the synapse .

General Anaesthetics - Introduction

General anaesthesia: loss of sensation with reversible loss of conciousness & Depression of defense and muscle reflexes.

Anesthetics are depressant drugs that produce a partial or total loss of the sensation.

Stages of anaesthesia produced by general anaesthetics

Stage 1	Stage 2	Stage 3	Stage 4
Analgesia	**Delirium**	**Surgical Anesthesia**	**Respiratory Paralysis**
Analgesia Euphoria	Excitement Delirium	Unconsciousness Regular respiratioon	No eye movement Respiratory & Cardiac arrest

General anaesthesia involves administration of different drugs:

1. **Premedication**
2. **Inducing agent(s)**
3. **Maintenance agent(s)**

General Anaesthetics - Introduction

Premedication

- Prevention of bradycardia, bronchial secretion, muscle spasm
  - Benzodiazepines (Diazepam)
  - Narcotic analgesics
  - Anticholinergic drugs (Scopolamine)
  - Skeletal muscle relaxants (CNS)

Inducing agent

- Normally an intravenous anaesthetic
  - Barbituate (thiopentone, methohexitone)
  - Non-barbituate (propofol, ketamine)

Maintaining anaesthesia

- Normally an inhaled gas
  - halogenated hydrocarbons and ethers
  - nitrous oxide (and….)

Anti-emetic agents may be required post-anaesthesia

Mechanisms of anesthesia

1-Blocking the NMDA and glutamate controlled channels.

Glutamate or NMDA (N-methyl-D-aspartate) receptors in the CNS are activated by the excitatory AA neurotransmitter glutamic acid.

Antagonists:
Ketamine blocks NMDA receptors, causes CNS depression (anesthesia)

2- Activation of the inhibitory GABA receptor controlled channel.

Binding of GABA (inhibitory transmitter) to their receptors will open the Cl^- channel, leading to the influx of Cl^- and hyper- polarization of the neuron.

Halothane and isoflurane inhibit the synaptic destruction of GABA, thereby increasing the GABA-ergic neurotransmission.

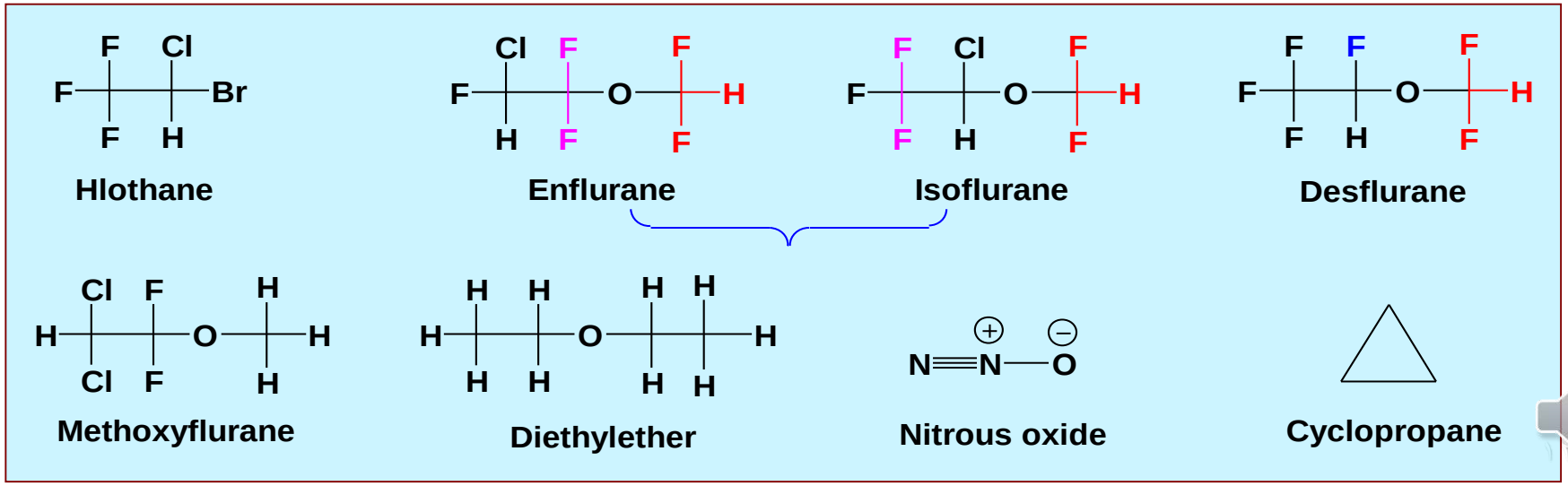
Benzodiazepines and barbiturates: Inhance GABA opening Cl channels

Depending on route of administration, general anesthetics are classified

1- Inhalation **(pulmonary)** Anesthetics: - Gases or vapors of volatile liquids that inhaled in a mixture with air or O_2.

2- Intravenous Anesthetics: Agents are psychologically well tolerated. They are quite useful as induction agents for inhalation anesthesia.

3- Combination Anesthesia: Combinations of medications is preferred to broaden the therapeutic range. Moreover, minimal doses of several substances are administered for particular goals of anesthesia.



General anesthetics:

Intravenous anesthetics

Ultra short acting barbiturates

Methohexital sodium

Thiamylal sodium

Thiopental sodium

Benzodiazepines

Etomidate

Alphaxolone

Propofol

Ketamine hydrochloride

Inhalation anesthetics:

Halothane

Enflurane

Isoflurane

Methoxyflurane

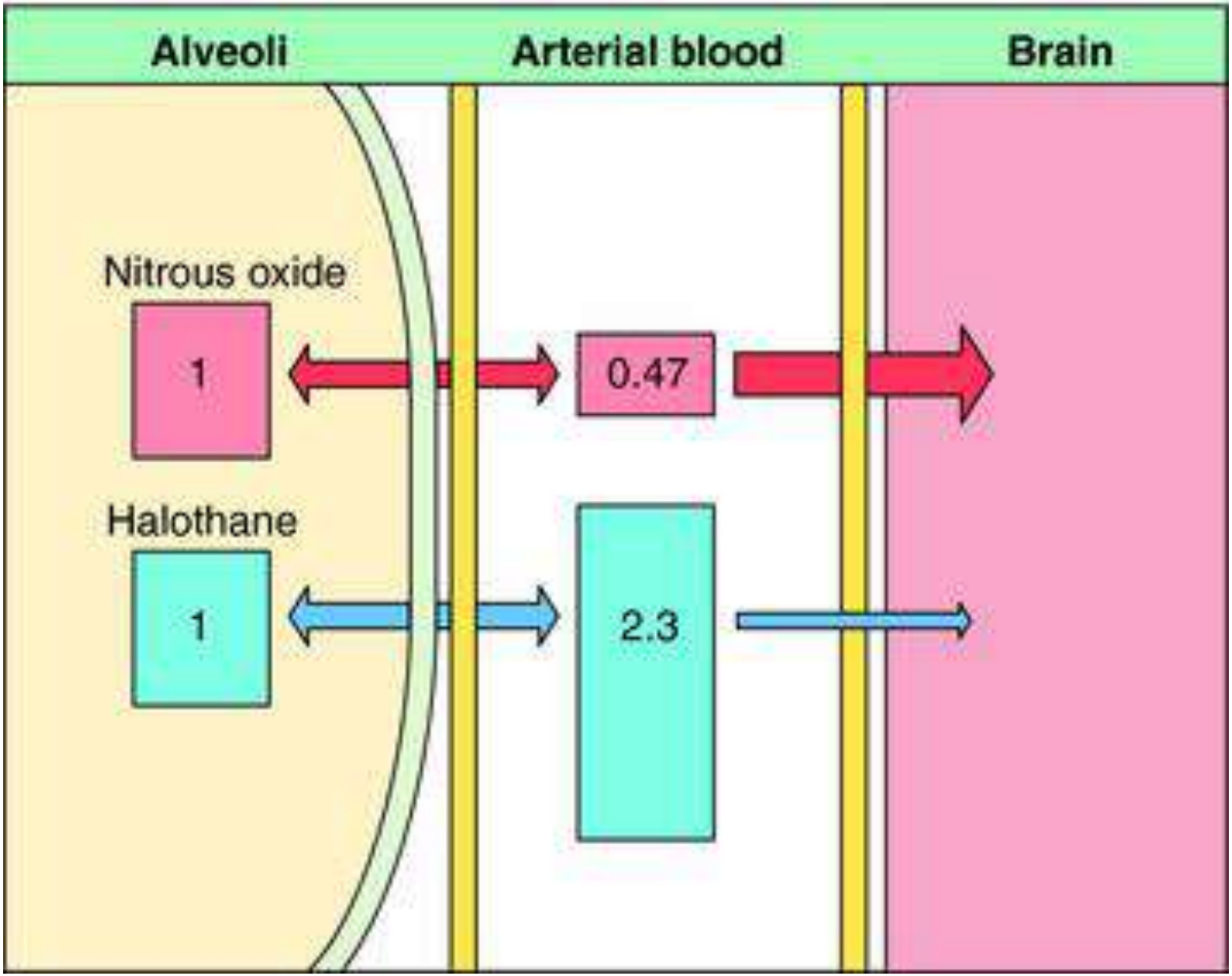
Sevoflurane

Disflurane

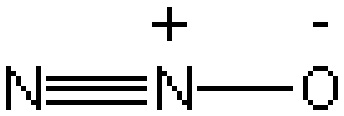
Nitrous oxide

Ideal properties

TABLE 16.1 Characteristics of the Ideal General Anesthetic Agent
Rapid and pleasant induction of surgical anesthesia
Rapid and pleasant withdrawal from surgical anesthesia
Adequate relaxation of skeletal muscles
Potent enough to permit adequate oxygen supply in mixture
Wide margin of safety
Nontoxic
Absence of adverse effects
Nonflammable/nonexplosive
Chemically compatible with anesthetic devices
Nonreactive
Inexpensive


Alveoli
Arterial blood
Brain
Nitrous oxide
1
0.47
Halothane
1
2.3

Inhaled anesthetics

1. **Nitrous oxide:** N_2O, laughing gas 

- A colorless gas, exerts low anesthetic effect.
- It is mixed with oxygen and ether or halothane, as deep anesthesia cannot be achieved with it alone.
- Has good analgesia & minimal toxicity, it has poor m. relaxant effect.

Dosage:

For induction, 70% nitrous oxide with 30% oxygen for 2 to 3 minutes.

For maintenance, 30 to 70% nitrous oxide with oxygen.

2. Non-halogenated Hydrocarbons:

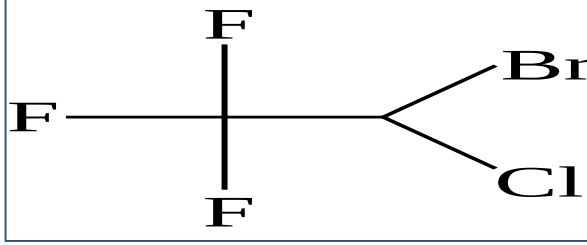
1. They have a tendency to produce cardiovascular toxicity.
2. The longer chain of the hydrocarbon, the higher the potency.

Cyclopropane is

- colorless, *explosive* and *flammable, may cause laryngospasms.*
- the only hydrocarbon still in use.
- mixed with oxygen (15 – 30% Cyclopropane) for medical purposes.
- In contrast to nitrous oxide, its concentration of 20% can produce anesthesia.

3. Halogenated hydrocarbons Halothane

2-Bromo-2-chloro-1,1,1-trifluoroethane



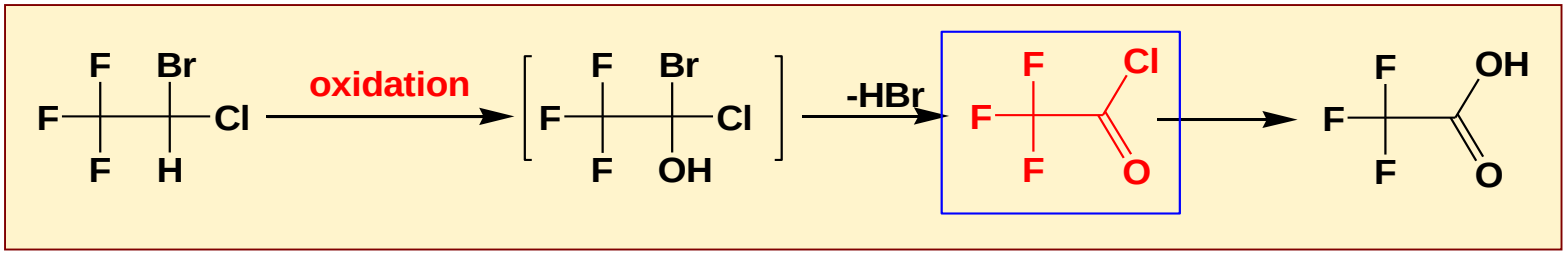
- A volatile halogenated hydrocarbon

- Has been the standard inhalation anesthetic agent

- Nonflammable. Has high potency

- Has low blood/gas partition coefficient so induction and recovery from anesthesia are relatively rapid

- Respiratory depression notable so mechanical ventilation and oxygen supply is needed
- Usually combined with nitrous oxide and opioids to produce analgesia

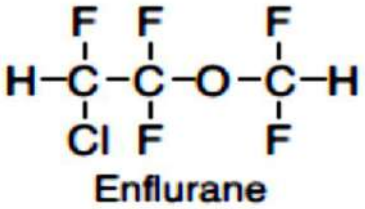


4- Halogenated ethers.

Polyfluorinated ethers have analgesic and muscle-relaxing properties but are more difficult to control. In addition, some are inflammable.

-Enflurane

2,Chloro-1,1,2-trifluoroethyl difluoromethyl ether



Enflurane

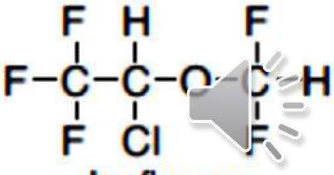
✓volatile liquid

✓blood/gas partition coefficient is about three fourth that of halothane consequently induction is relatively easy although an ultra short acting barbiturate is usually used for this purpose.

✓Low frequency of adverse effects

✓Respiration is depressed so mechanical ventilation and oxygen supply is needed.

✓It is replaced now with isoflurane, sevoflurane, and desflurane.

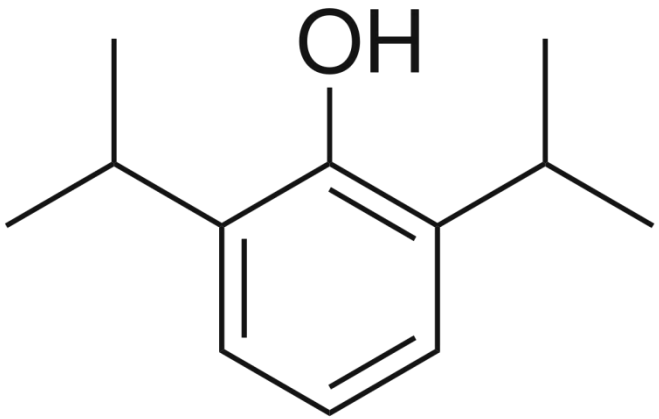


Isoflurane

Intravenous Anesthetics

- Intravenous anesthetics are non-explosive solids. They produce rapid loss of consciousness but insufficient anesthesia. So, they are seldom used alone.

Propofol: (Diprivan)

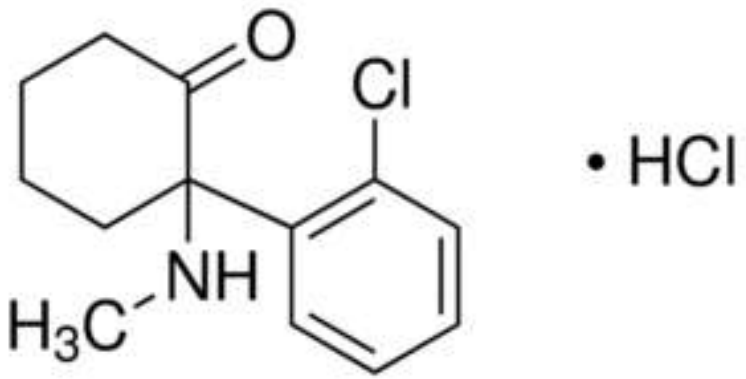


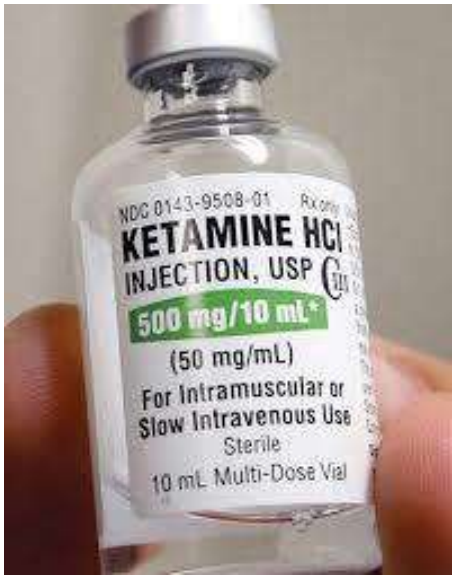
- Phenols cause tissue destruction and general toxicity due to the presence of the hydroxyl group

- Presence of 2,6 isopropyl groups in this compound favorably influence the biological properties of the OH group

- Has a high lipid/water partition coefficient so posses a rapid onset of action and low duration

Ketamine hydrochloride:





- 2-(2-Chlorophenyl)-2-methylaminocyclohexanone

✓**Blockage of glutamic acid NMDA receptor explains many of its actions**

✓**Low incidence of hallucinations is reported**

✓**Produce a sense of dissociation from events being experienced, followed by anesthesia, analgesia and sometimes amnesia**