تلخيص

حركية 2

(نصفي)

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مكتبة الطالب . الأزهر

Lec ① [Chapter one] Mohammad Sha...
Pharmac. le...

Pharmaco Kinetics.

- Ph. Kinetics لا فتحسن يؤكد فاتحصـ Absorption لعملية بـ
- أي Drug بيصير له absorption فـ عاملة أنه كفاية local effect.
أما الدواء ما ... absorption فاعلم انه هنا ليه local effect.

- لازم تعرف انه عملية LADME في عمليات متتابعة متسلسلة حال توافر بسرعة لكل منها.

Semi-solids
Solids } → عندهم Liberation , liquids : absorption ... و I.V عم طول DME.

(*) PharmacoKinetics / the study of factors that govern the time course of drug conc in the body.
يعني عندي علاقات بين الـ conc والـ time ، هذا العلم بيدرس التغير في تراكيز الأدوية مع مرور الوقت في الجسم.

PharmacoKinetics / [تعريف آخر] /
- the study of the rates of the transfer processes associated with the ADME of a drug in the intact subject.
دراسة معدلات تنقل الدواء من مرحلة لأخرى ضمن الـ ADME ، وهذا يؤكد أنهم عمليات متسلسلة.
[the study of (adme) باختصار هي]

[العودة للمخطط منه في مارية ①]

4-operati

الهدف الـ Absorption لجزيئات الدواء الذائبة هو الحركة لعملية Distribution في الجسم ، ويحدث تقسيم لقسمين ليتم equillibrium بينهم / هو:
6 absorption
6 excretion
6 metabolizim

Free drug Particles ⇄ (ازالة / eqn) complex (Protein + drug)

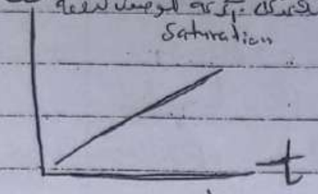
(*) الـ Free هم اللي رح يرتبطوا بالـ receptors فيصيروا يعطوا تأثير علاجي.
فكل ما قل تركيزهم بيتم تعويضهم عبر إطلاق جزيئات من الـ complex.

Pharmaco Kinetics

Linear (1st order Kinetics)

- Dose independent

Ct — لا تتحرك بكرة الوصل لتقية Saturation



Linear (1st order)

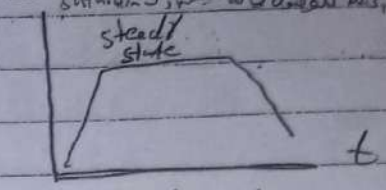
- Open linear Kinetic — الدواء الي دخل لازم يتم طرده لاخره (اخراجه)
- Close linear Kinetic — العلاج يتم أخذه لا يتم اخراجه وانما يستقر في الجسم

Drugs / مثل — Nutrients / مثل

non-Linear (michalis menten Kinetics)

- Dose dependent

Ct — تقدر تحرك بكرة للوصول لل saturation



mixed order

- Low conc → 1st order
- high conc → steady state (zero order)

non-Linear Pharmacokinetics must be / - Detected - Prevented Cancelled?

← لأنه بعد الوصول للـ saturation لن نستفيد أي شئ من زيادة الـ dose لذلك الأفضل منعها

[Open model]

One Compartment model

- All type of tissues interact with drug Particles in the same rate

Case ① → Intra Vascular

Case ② → Extra Vascular

Two Compartment model (Central / Peripheral) ← نوعين من الأنسجة

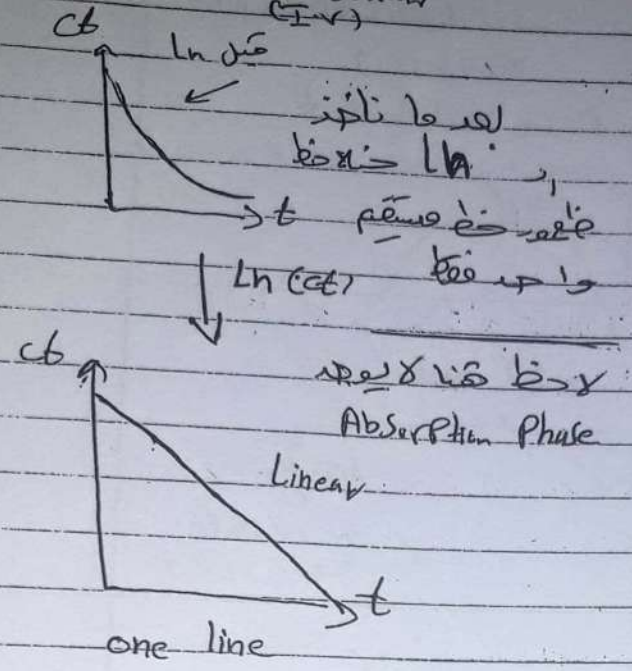
- Not all type of tissues interact w drug in the same rate

Case ① → Intra Vascular

Case ② → Extra Vascular

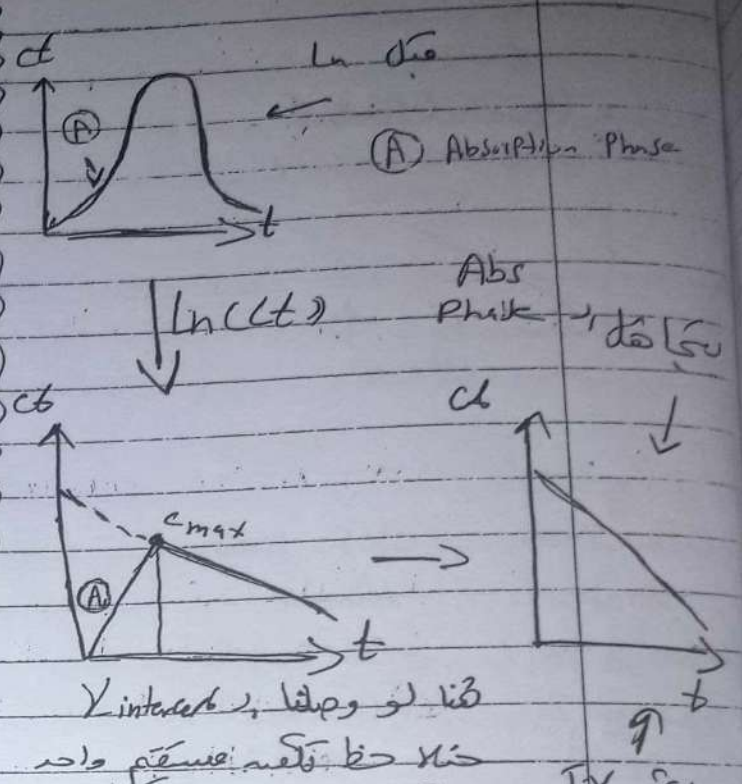
One Compartment model

Intravascular (I.V)



Absorption Phase
Linear

Extravascular



A Absorption Phase

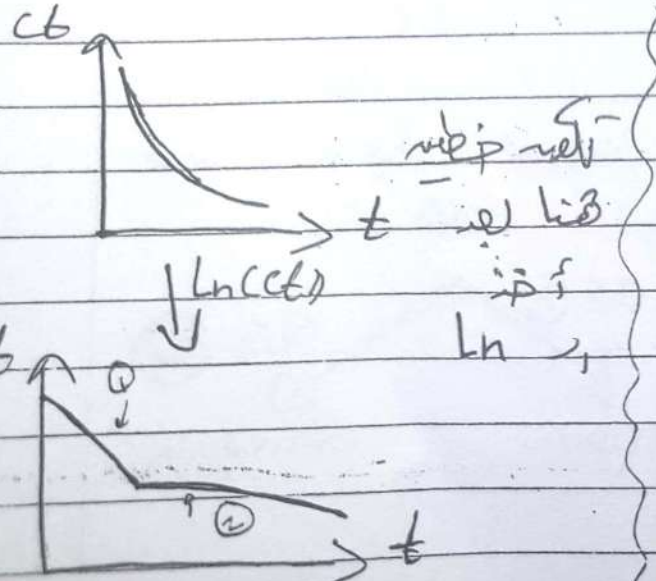
Y intercept

Absorption Phase

I.V

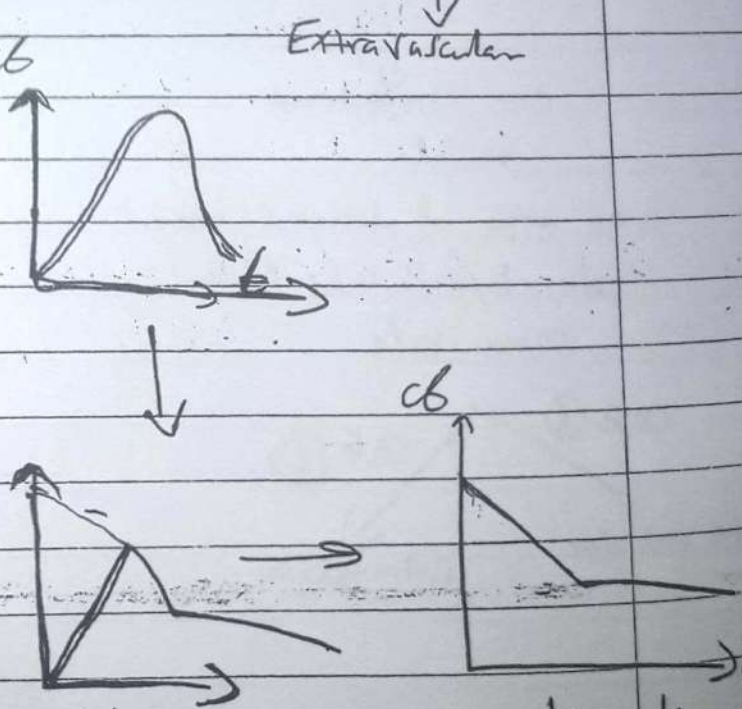
Two Compartment model

Intravascular (I.V)



Two lines

Extravascular



Y-intercept

Abs-Phase

two lines

I.V

Lec (2)

Compartment and Ph. Kinetics models

(*) Compartment / An entity which can be described by a definite Volume and a conc of drug in that vol.

Conc → $Ct = \frac{D}{V}$ ← Dose / ← Volume

Another definition / A group of tissues with similar blood flow and drug affinities.

tissues ← one compartment ← ... / ...

(1) The same blood flow
(2) The same Partition coefficient.
(3) The same Permeability

Results in / the same drug affinity.

Pharmacokinetics models / mathematical model devised to simulate the rate Processes of drug Absorption, distribution and elimination.

Results in / equations to describe drug conc in the body as a function of time.

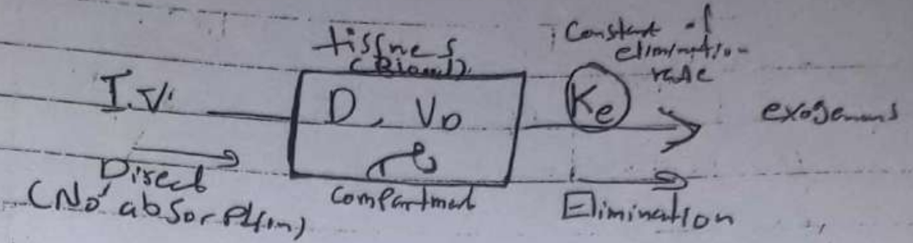
... ADME ...

Pharmacokinetics models

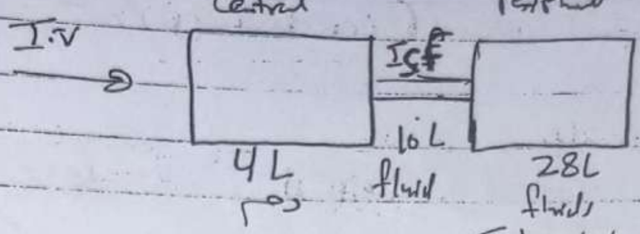
Intravascular — Extra Vascular.

[I.V administration]

Case I: One Compartment open model :-



only one constant / ثابت واحد

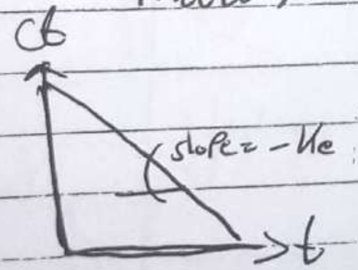


الاجمالي 42 L

(Vd)

≤ 4L	14 > X > 4	> 14
One Compartment		
حيضل في منطقة Central	طالما لم يوصل Peripheral	حيوصل Peripheral
ويتعامل فيه فقط	يبقى لم يوصل Two Compartment	وعليه حيكون عندي Two Compartment
One Constant (Ke) فقط		(حيشتغل overlap)

→ only one line
$\ln C_t = \ln C_0 - K_e t$
(Very simple model)



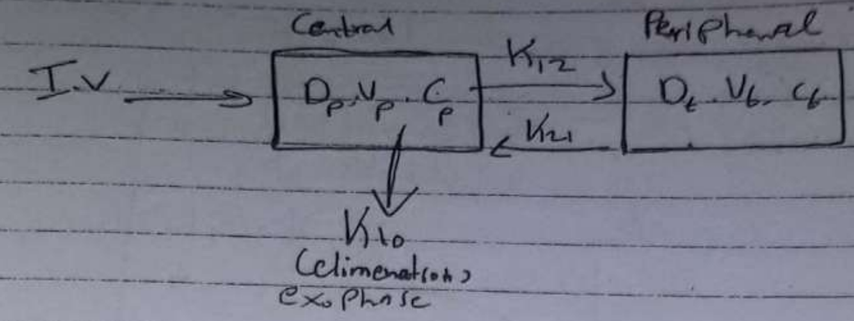
كلما كان الـ Vd عالي وبيوصل الـ tissues أكثر وتدخل two compartmental models
فتتحكم به عوامل:
1. liposolubility
2. duration
3. Ke

* يعني أنا شغال على تركيز وحجم، ويعنيه إذا الدواء دخل دم تعامله وطرده حتى الـ Central يبقى عندي / one compartment. أما إذا دخل وسم جزء انتقل على الـ Peripheral ورجع تاني ثم طرده يبقى حنشتغل two compart.

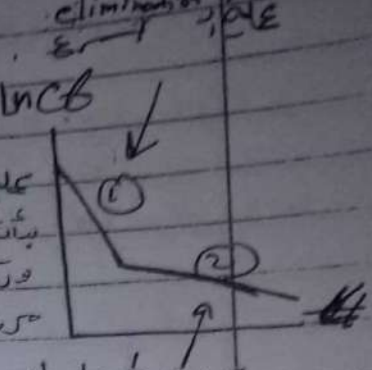
D = Dose (Amount)

Hint: In two compartment model (Sus) → elimination begin (fast) and become slower by the time

Case ②: Two compartment open model



عملية الطرد بتاعة سريعة وتباطئت مع مرور الوقت



K_{10} / عملية الطرد لجزء من الدواء (Constant ①)

K_{12} / عملية الـ transffer (نقل) جزء من الدواء للطرفي (Constant ②)

K_{21} / عملية العودة من الطرفي إلى [illegible] من الدم (Constant ③)

يعني اللي بيتحكم في العملية ككل /

③ Constants

الاستنتاج هنا /

The Process of elimination in the case of one Compartment is faster than in Case of two.

→ Posology وهذا يجعل [illegible]

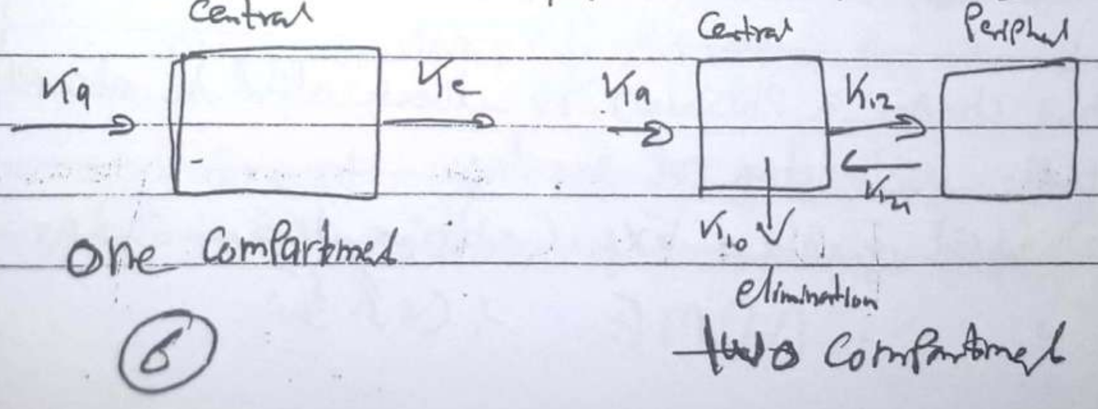
Posology // the study of drug doses that can be administrated.

Extravascular administration

(عكس ما يحدث بـ I.V [illegible])

فيه عندي New Constant

K_a / Absorption rate constant



One Compartment

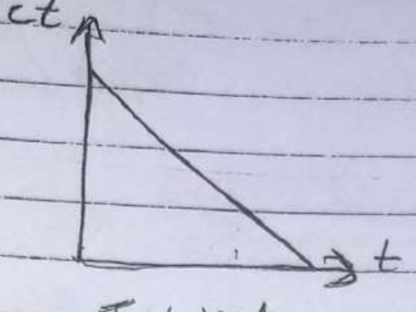
two Compartment

Lec ③

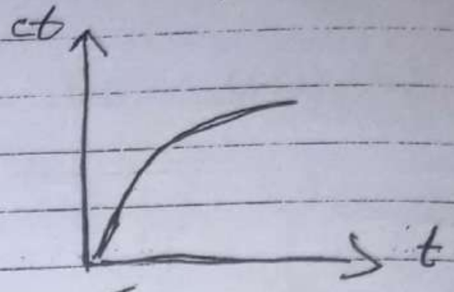
(Uses of Pharmacokinetic models)

✓ ① Predict Plasma, tissue and urine drug levels with any dosage regimen.

توقع التحديد كمية الأدوية د, بجسم (Conc ، متواجدة في ، الدم ، في الخلايا أو التي طالعة برة ومتواجدة في البول .



I.V route
[In Plasma]



In urine
دليل على أنه يتم عملية elimination
صح مرور بالجسم .

✓ ② Calculate the dosage regimen for each patient individually (why ??)

يتم تحديد لكل مريض جرعة مناسبة له بشكل منفصل عن غيره (ليش ؟)

• Due to the response of each body to any drug not the same.

← إستجابة الأجسام مش نفسها للأدوية تختلف حسب عدة عوامل متعلقة بجسم كل فرد .

✓ ③ Estimate the possible accumulation of drug/or metabolites.

إفهام فيها لو كله هناك تراكم للعلاج (slow elimination

← في الجسم أو لا ؟ دخلنا موضوع لتحديد عدد جرعات وكمية كل منها

حتى لا تراكم في الجسم لل elimination ، فيحدث toxic .

✓ ④ Correlate drug conc with Pharmacological or toxic activity.

← بيانه / ربط تركيز الأدوية بالتأثير العلاجي أو السام حيث

↑ Drug conc. on receptor , ↑ Activity . / أ

✓ ⑤ Describe how changes in Physiology or disease affect the absorption, distribution or elimination of the drug.

وصف كيف التغيرات في الجسم أو الأمراض تؤثر (...) ، رياضية

ADME تؤثر على .

⑦

⑥ Give a good Picture Concerning Protein binding.

drug free « Active » ⇌ (eqm) drug — Proteins (complex) « In active »

ازالته

كل ما تم استهلاك جزء ← يتم التعويض بسرعة

⑦ Evaluate differences on the rate or extent of bioavailability between formulations.

[illegible] تختلف الفعالية وتوفر الدواء عند الـ receptor حسب اختلاف التركيبة النهائية للأشكال المختلفة

⑧ Explain drug interactions :-

(*) هناك interactions تؤثر على عملية الـ Absorption و distribution والـ Elimination

الـ Ph. Kinetic ستعطيك بالـ curves والحسابات وكل شيء
كل ما أعطاك // interactions على تركيز الدواء في الوقت نفسه [illegible]

مثال (*) //

Ⓐ Enzyme induction of liver (↑), (↑) elimination so amount of each dose (↑), or Num of doses (↑)

[التأثير على الـ Elimination]

Ⓑ Some substances (↑) absorption for some drugs and other substances (↓) absorption for other drugs.

(*) ex/ Ca^{+2} lead to ↓ absorption of tetracycline by form unabsorbable complex.

:: One compartment model :-
A) I.V administration 1- direct injection of drug into vein

(*) Advantages :-
1. Drug injected into blood as active form.
2. Useful in emergency states due to fast and immediate effect.
3. Useful in an unconscious patients.
4. Desired blood conc can be obtain.

(*) Disadvantages /
1. withdrawal of drug after injection is impossible.
2. High risk of toxicity.
3. drugs that ppt in blood can't be administrated.
4. Unwanted reactions if occure are immediately.
5. Special person only inject it.
6. Slow administration rate ex. Pentothal (General anesthetic)
rate يقلل LD50 بعض — أبعد — لعلاقة
لتقع injection بكثير طويل.

(*) ما هو الـ LD50 ?
Dose of drug that kill a 50 % from group of laboratory animals.
← علاقة عكسية بين LD50 و rate of injection (↑rate, ↓LD50)
(*) كل ما كان الـ Rate أعلى في الـ injection كل ما كانت
الـ Dose التي تقتل أقل LD50.
بتقلل more fatal قاتل

Manners of administration
(*) I.V bolus
(**) I.V infusion

✓ or X
(9) (X) when a drug is injected in faster rate, this mean the LD_{50} will be low and the drug is Safe.
Fatal الجواب

∴ One compartment model :-

A) I.V administration | — direct injection of drug into vein.

(*) Advantages :-

1. Drug injected into blood as active form.
2. Useful in emergency states due to fast and immediate effect.
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4. Desired blood conc can be obtain.

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1. withdrawal of drug after injection is impossible.
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3. drugs that ppt in blood can't be administrated.
4. Unwanted reactions if occurs are immediately.
5. Special person only inject it.
6. Slow administration rate ex. Pentothal (General anesthetic)
   علشان أبعد عن الـ LD50 بقلل الـ rate
   تبقى الـ injection تاخد وقت طويل.

(*) ما هو الـ LD_{50} ؟

Dose of drug that kill a 50 % from group of laboratory animals.

← علاقة عكسية بين الـ LD_{50} و الـ rate of injection ($\uparrow$rate, $\downarrow LD_{50}$)

(*) كل ما كان الـ Rate أعلى في الـ injection كل ما كانت الـ Dose اللي هتوصل الـ LD_{50} أقل.

مو يعني more Fatal قاتل

Manners of administration

(*) I.V bolus

(**) I.V infusion

— or ✗

(✗) when a drug is injected in faster rate, this mean the LD_{50} will be low and the drug is safe.

9

Fatal المميت

$X_t = V_d * C_t$ | $C_t = \frac{X_t}{V_d}$ | $V_d = \frac{X_t}{C_t}$

(عكس الاختبار)

(*) I.V bolus :-

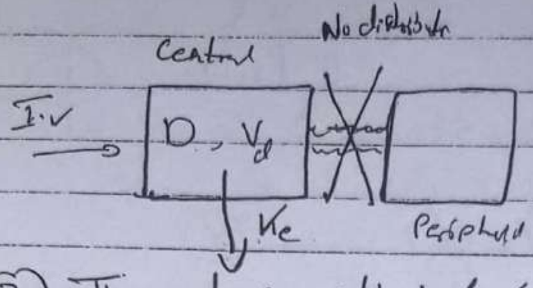
→ Assumptions /

① Single compartment model $\bar{w}$ Volume Vd.

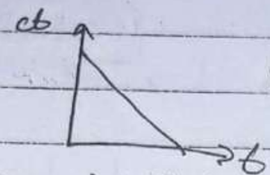
$V_d = X_t / C_t$

② No distribution Phase /

المقصود هنا انه (Uniformity distribution) ما في انتقال بين ال Central و Peripheral.



③ The drug eliminated by 1st order kinetic.



Proportional elimination

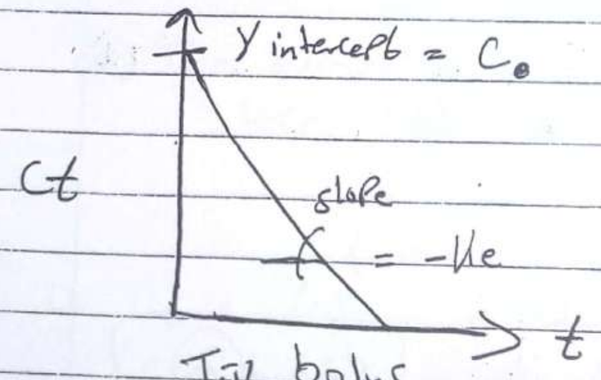
محصور بوقت زمني الطرد.

④ Any changes in plasma level of drug reflect proportional changes in tissue drug level.

يعني / لو كانت عالية بالدم رح تكون عالية فيما ← يعكس زيادة

زيادة بواسطة الانسجة.

⑤ Biological fluids (Blood, Urine, Saliva) are used to determine drug conc



$$\ln C_t = \ln C_0 - K_e t$$

انتهاء المحاضرة

مع تمنياتي

بالتوفيق

(10)

صفحة ١٣

(*) اشتقاق القانون / ((I.V bolus))

conc of drug can be eliminated

rate of elimination

$$\frac{dC_t}{dt} = -K_e \cdot C_t \quad \text{—— (1)}$$

$$\frac{dC_t}{C_t} = -K_e \cdot dt \quad \text{—— (2) } \left(\int_0^t\right)$$

$$\int_0^t \frac{dC_t}{C_t} = -K_e \int_0^t dt \quad \text{—— (3) } (\ln)$$

$$\ln C_t - \ln C_0 = -K_e (t - t_0) \quad \text{—— (4)}$$

$$\boxed{\ln C_t = \ln C_0 - K_e \cdot t} \quad \text{—— Result}$$

$$Y = b \mp a \cdot X$$

b: Y-intercept, a: slope

لو بينا كمية / Amount

$\to$ Anti ln $\Rightarrow C_t = C_0 \cdot e^{-K_e \cdot t}$

while $C_t = \frac{X_t}{V_d}$ & replacement

$$C_0 = \frac{X_t}{V_0}$$

$$\frac{X_t}{V_d} = \frac{X_0}{V_d} \cdot e^{-K_e \cdot t} \quad \text{—— } (\times V_d)$$

$$X_t = X_0 \cdot e^{-K_e \cdot t} \quad \text{—— } (\ln)$$

$$\boxed{\ln X_t = \ln X_0 - K_e \cdot t} \Rightarrow \text{Result 2}$$

The elimination half life ($t_{1/2}$) "biological half life" :-

Definition (تعريف) :-

the time at which the amount of unchanged drug becomes half of the initial one.

الوقت الذي عنده يكون تركيز الدواء في الجسم قد نقص إلى النصف.

- Determination of the elimination half life :-

تحديد عمر النصف / الطرق (*)

$$\ln C_t = \ln C_0 - K_e \cdot t$$

$$C_t = \frac{C_0}{2} \quad \text{(*)} \quad ; \quad t_{1/2}$$

$$\ln \frac{C_0}{2} = \ln C_0 - K_e \cdot t_{1/2}$$

$$\ln \frac{C_0}{2} - \ln C_0 = -K_e \cdot t_{1/2}$$

$$\ln \left[\frac{C_0}{2} \times \frac{1}{C_0} \right] = -K_e \cdot t_{1/2}$$

$$\ln 1/2 = -K_e \cdot t_{1/2} \qquad \ln 1/2 = -0,693$$

$$+0,693 = +K_e \cdot t_{1/2}$$

$$\therefore \boxed{t_{1/2} = \frac{0,693}{K_e}} \quad \text{(*)}$$

(*) The elimination rate constant /

$$K_e = \frac{\ln C_0 - \ln C_t}{t} \Longrightarrow (?)$$

$$\ln C_t = \ln C_0 - K_e \cdot t$$

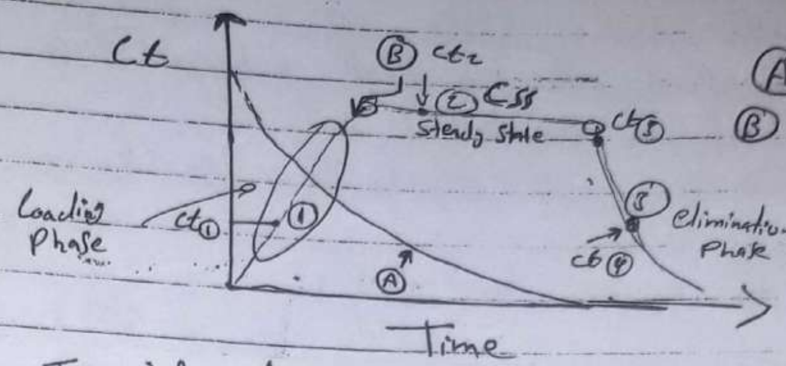
$$\ln C_t - \ln C_0 = -K_e \cdot t \quad (\div t)$$

$$\frac{\ln C_t - \ln C_0}{t} = -K_e \quad (\times -1)$$

$$K_e = \frac{\ln C_0 - \ln C_t}{t} \quad \text{(*)}$$

(مهم جداً)

(*) سؤال الفرق بين I.V infusion و I.V bolus من جهة نظر الـ Pharmaco Kinetics ؟



I.V infusion / used in order to obtain (give) a constant rate of drug dose effect. [نحافظ على تركيز ثابت لفترة معينة] [Steady State] للحصول على Css

I.V bolus / In emergency states [للتخلص من الحالة الطارئة]

[IV. infusion]

$$dx/dt = K_0 - K_e \cdot x_t$$

(K_0: معدل الدخول، K_e: معدل الخروج)

$K_0 > K_e$ / لتركيز ثابت

$$\int_0^t \frac{dx}{K_0 - K_e \cdot x_t} = \int_0^t dt \Rightarrow dt = t - t_0 \Rightarrow t$$

$$\int_0^t \frac{dx}{b \pm ax} = \frac{1}{a} \ln(ax + b) + P$$

$$-1/K_e \cdot \ln(K_0 - K_e \cdot x_t) + P$$ ← عوض

when $t = 0$

$$-1/K_e \cdot \ln(K_0) + P \Rightarrow P = \frac{1}{K_e} \ln(K_0)$$

$$t = -1/K_e \cdot \ln(K_0 - K_e \cdot x_t) + \frac{1}{K_e} \ln(K_0) \quad [* K_e]$$

$$K_e \cdot t = \ln(K_0 - K_e \cdot x_t) + \ln(K_0) \quad [* -1]$$

$$-K_e \cdot t = \ln(K_0 - K_e \cdot x_t) - \ln(K_0)$$

$$-K_e \cdot t = \ln \frac{K_0 - K_e \cdot x_t}{K_0} \Rightarrow e^{-K_e \cdot t} = \frac{K_0 - K_e \cdot x_t}{K_0}$$

$$e^{-K_e \cdot t} = 1 - \frac{K_e \cdot x_t}{K_0} \Rightarrow \frac{K_e \cdot x_t}{K_0} = 1 - e^{-K_e \cdot t} \quad \text{—} \quad V_d = x/C_t$$

$$\frac{K_e \cdot Ct_1 \cdot V_d}{K_0} = 1 - e^{-K_e \cdot t} \Rightarrow Ct_1 = \frac{K_0}{K_e \cdot V_d}(1 - e^{-K_e \cdot t_1})$$

(*) Ct_1

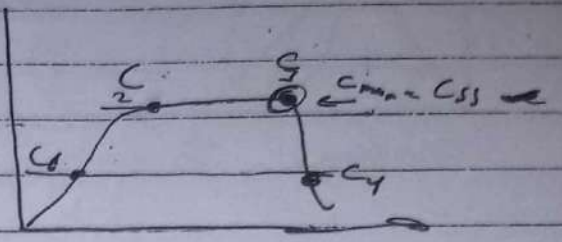
$K_e = K_o$ ⟵ (C_{ss}) Steady state ، في

$$C_{ss} = \frac{1}{V_d}\left(1 - e^{-K_e \cdot t_{ss}}\right)$$

$K_o = K_e$ في حالة التوازن

$$C_{t_3} = C_{ss} \cdot e^{-K_e \cdot t_3}$$

C_{ss} ← C_{max}



$$C_{t_3} = \frac{1}{V_d}\left(1 - e^{-K_e \cdot t_{ss}}\right) \cdot e^{-K_e \cdot t_3}$$

$K_e > K_o$

$$C_{t_4} = C_{t_1} \cdot e^{-K_e \cdot t_4}$$

$K_e >> K_o$ (failure in System)

$$C_{t_4} = \frac{K_o}{K_e \cdot V_d}\left(1 - e^{-K_e \cdot t_1}\right) \cdot e^{-K_e \cdot t_4}$$

elimination half life

6.10.2019

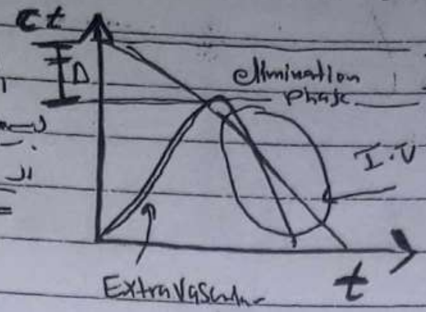
[Chapter two]

Lec (5)

One Compartment open model (Extravascular)

* Extravascular → Absorption phase is present.

F بعوضها I.V و يسمى ال extravascular ال



I gap

* بلاحظ ال elimination phase مشترك (common) بين ال I.V و ال extravascular.

In I.V / Bioavailability (100 %)

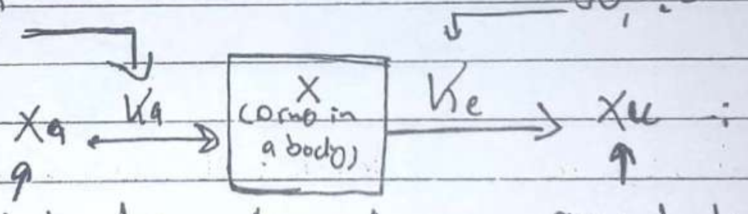
Extravascular route / Bioavailability **never** reach 100 %

F : Bioavailability ← [Amount reach blood circulation]

* Choose / While F = 100 % , so X_a is equal to :-
a) Zero b) 0.5 **c) 1** ✓ d) 2

← لما تكون ال Bioavailability = 100 % يعني ال dep amount (X)

$X_a = 1$ / ثابت عملية Absorption ال

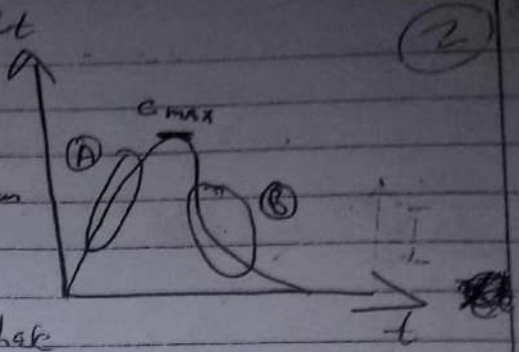


لانه يتعامل بنفس الطريقة وكأنه مع الدم بالضبط ⇒ [one group of tissue]

الستدعا / علشان أقدر أحدد ال conc of drug in the body dx/dt لازم

أحدد الكمية اللي طلعت Absorption وأطرح منها الكمية اللي طلعت elimination.

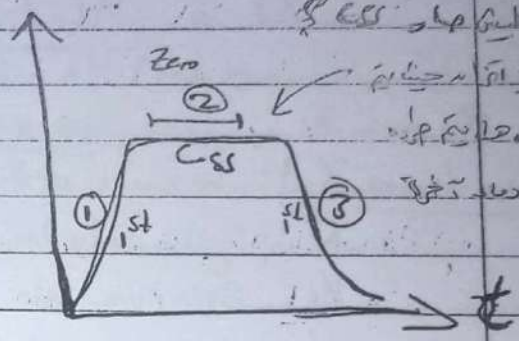
[$X_a - X_u$ = drug amount in the body]



$\frac{dx}{dt}$ = Abs Phase − Elimination Phase

$K_a \cdot x_a$ − $K_e \cdot x_e$

Conc in body



① First order release of drug

② Zero order absorption ، steady state ،

③ First order elimination ،

* Assumptions :-

① Drug exhibits the characteristics of one compartment model.

② Absorption and elimination of a drug follow 1st order and passive diffusion is operative at all time.

③ Drug is eliminated in Unchanged form.

→ Due to No metabolism → one compartment model.

④ Drug is monitored in the blood.

(3)

① Drug remaining to be absorbed, or drug remaining at the site of administration :-

Absorption

$$\frac{dx}{dt} = -K_a \cdot X_t \qquad \left(\int_0^t \right)$$

$$\int_0^t \frac{dx}{dt} = -K_a \int_0^t dt$$

$$\ln X_{at} = \ln X_{a0} - K_a \cdot t \Rightarrow \text{Anti Ln} \Rightarrow \boxed{X_{at} = X_{a0} \cdot e^{-K_a \cdot t}}$$

بعطينا في النهاية / سلسلة اشتقاقات

[Buteman equation]

$$\frac{dx}{dt} = K_a \cdot X_a - K_e \cdot X_e$$

$$X_{a(t)} = X_0 \cdot e^{-K_a \cdot t}$$

$$\frac{dx}{dt} = K_a \cdot X_0 \cdot e^{-K_a t} - K_e X$$

$$\int dx = K_a \cdot X_0 \cdot e^{-K_a t} \int dt - K_e$$

$$X_t = \frac{K_a \cdot F \cdot X_0}{K_a - K} \left[e^{-Kt} - e^{-K_a t} \right]$$

(VUI) — يعني ①

[administered dose = X_0] : the amount of drug in the body at time zero.

F : Fraction of drug absorbed or bioavailability.

K_a : Absorption rate constant.

K : elimination rate constant.

Buteman eq.

$$\frac{K_a \cdot F \cdot X_0}{(K_a - K) V_d} (e^{-Kt} - \ldots)$$

Y-intercept

② Monitoring drug in the blood :-

$$\frac{dx}{dt} = K_a X_a - K_e X_e$$

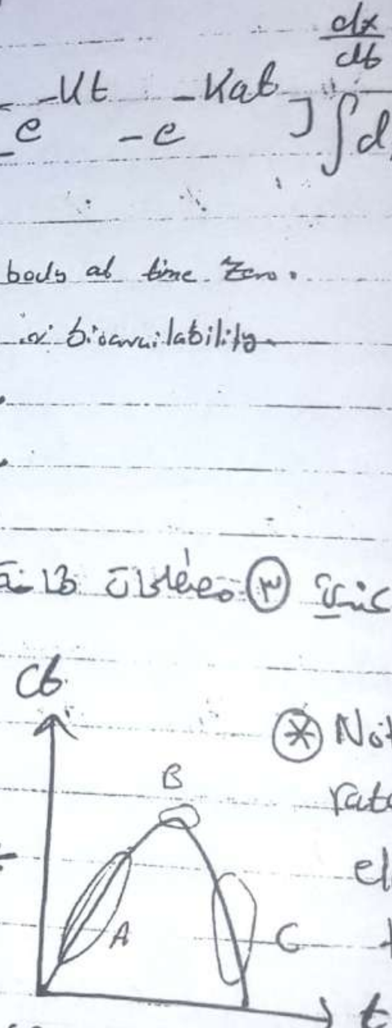
عندي ③ مراحل هامة /

A: Prior to peak time :-
[absorption rate > elimination rate]

بيقل $K_a X_a - K_e X_e$ ...

B: at peak time exactly :-
[absorption rate = elimination rate]

C: Post peak time :-
[absorption rate < elimination rate]



((BiExponential Profile))

(*) Note// with time, the rate of absorption and elimination change but the constants (K_a, K) not change.

④ ملاحظة /
Absorption rate constant is greater than elimination rate constant.

Lec ⑥

[Calculations]

Problems

Q1 : A drug has an elimination $t_{1/2}$ = 6 hrs and follows 1st order kinetics. if a single 200 mg is given by I.V bolus - 68 kg male Patient.

what Percent of the dose is lost in 24 hrs ?

[Solution ...]

: أولاً / Ke إيجاد $t_{1/2}$ علاقة

$$t_{1/2} = \frac{0.693}{Ke} \Rightarrow 6 = \frac{0.693}{Ke} \Rightarrow Ke = \frac{0.693}{6}$$

$$\therefore Ke = 0.1155 \ 1/hr$$

$$\underline{Ln\,Xt} = \underline{Ln\,X_0} - Ke \cdot t$$

$$= Ln\,200\,mg - (0.1155 * 24)$$

$$Ln\,Xt = 2.52 \rightarrow \text{Shift } (Ln \rightarrow)$$

$$Xt = 12.42\ mg$$

$$X\,\% = \frac{Xt}{X_0} * 100\,\% \Rightarrow \frac{12.42}{200} * 100\,\%$$

$$= \boxed{6.214\ \%} \leftarrow \text{remaining \%}$$

ثانياً / إيجاد كم فقد

$$\%\,100 - 6.214$$

$$= 93.8\ \%$$

$$\therefore \boxed{93.8\ \% \text{ from the drug eliminated}}$$

Q2: If the amount of drug in the body declines from 100 %. of the dose to 25% [IV bolus] in 8 hrs.
→ What is the elimination $t_{1/2}$ for the drug.
[Hint: Assuming first order Kinetic]

[Solution ...]

$X_0 = 100\ \%$ $\quad X_t = 25\ \%$ $\quad t = 8$ hrs

$K_e = ?$

1g = drug إرشادي

$\ln X_t - \ln X_0 = -K_e \cdot t$

$\ln 1 - \ln 4 = -K_e \cdot 8 \Rightarrow 1.38 = 8K_e$

$t_{1/2} = \frac{0.693}{K_e} \Rightarrow \frac{0.693}{0.1735} = 4$

100 % → 50 % → 25 %

$t_{1/2}$ هي

$t_{1/2}$ هي

$\frac{2\,t_{1/2}}{2} = \frac{8}{2}$

$t_{1/2} = 4$ hrs

Q3: A drug has $t_{1/2} = 8$ hrs follows 1st order Kinetic, if a single 600 mg dose is given to an adult female = 62 Kg by I.V bolus, (A) what percent of this drug eliminated (Lost) in 24 hrs ?

[Solution ...]

$t_{1/2} = 0.693/K_e \Rightarrow K_e = 0.693/8 \Rightarrow K_e = 0.0866\ 1/h$

$\ln X_t = \ln X_0 - K_e \cdot t$

$? = \ln 600\text{mg} - 0.0866 \cdot 24$

$= 6.4 - 2.0784 = 4.32 = \ln X_t$

$X_t = 75.31$ mg — remaining

$X_{lost} = 600 - 75.31$

$= 524.7$ mg

$\% = \frac{524.7}{600} \times 100$

$= 87.5\ \%$

(B) Assuming that Vd = 400 ml/kg, what is the exact Plasma Conc at 24 hrs ?

$$Ct = \frac{Xt}{Vd} \qquad \frac{75,31}{Vd} = Cb$$

400 ml → 1 kg
X ml → 62 kg ⇒ $Vd = 24800$ ml

$$Cb = \frac{75,31}{24800} = 3,036 \times 10^{-3} \text{ mg/ml}$$

10.10.2019

Lec (7) Feathering method or Curve stripping
or method of residuals

(الهدف من هذه الطريقة) //

Separation of the monoexponential constituents of a biexponential plot in order to //

① Determination of $t_{1/2}$ rate of elimination and absorption.

② Determination of Ka and Kc.

الوضع الطبيعي عندنا //

$$dx/dt = Ka.x_a - Ke.xt$$

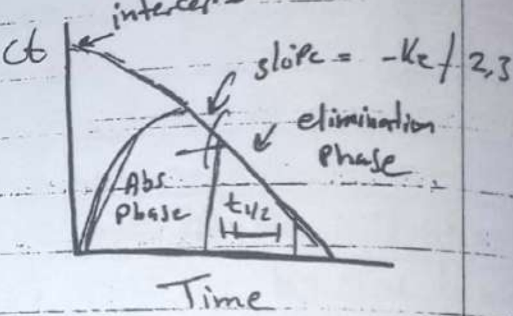
← يتم إهمالها عمليا ← ↑

باعتبار أنه عملية ال Absorption انتهت

وعليه نعتبرها Zero

وبالتالي فإن e^{-Kat} من المعادلة بتسقط ، وتبقى المعادلة هيك //

$$(Cp)t = \frac{KaFX_0}{V(Ka-K)}[e^{-Ket}]$$



by using Y intercept $\frac{KaFX_0}{V(Ka-Ke)}$

بنجيب ال Ke من ال slope

ثم بنقارنه بال

$$\frac{.693}{Ke} = t_{1/2}$$

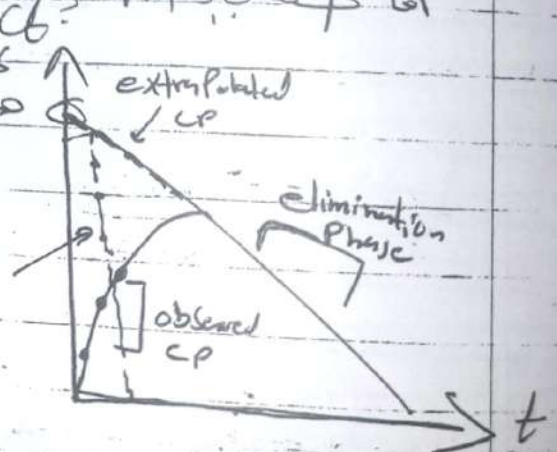
أما لحساب ال Ka ؟

بنجيب ال ln للفرق بين كل نقطتين

وحدة بالتيمب من ال (Cp extrapolated)

و ال Cp observed

ثم نرسم خط من النقاط الناتجة عندنا



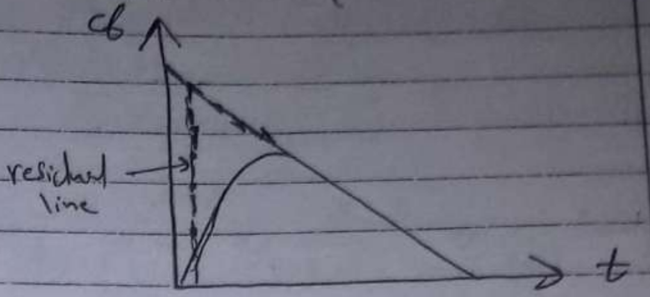
← إذا تقاطع ال residual line مع ال Y intercept

في القانون ال point بنحصل على intercept عامل ثابت

$$\frac{KaFX_0}{V(Ka-Ke)}[e^{-Ket} - e^{-Kat}]$$

5

بعض ما رسمنا الـ residual line ده لازم عند نقطة
تلاقي الـ Extrapolated Point مع الـ intercept



في الحالة دي يكون عندي شكلين
Absorption و elimination
→ Intercept مختلف

عندي الـ Intercept ده في هو ال
ال elimination هو (A) والتاني
Absorption هو (B) فالقانون يصبح كالتالي

$$dx/dt = (A).e^{-Ke\,t} - (B).e^{-Ka.t}$$

(A) → Intercept ال elimination

(B) → Intercept ال Absorption

التنقيط خاصة

→ The apparent volume of distribution (V) //
" Amount reach circulation " F بسبب عدم معرفة قيمة
ما بنقدر نحسب الـ V حسب القانون //

$$\text{Intercept} = \frac{Ka\,F\,X_0}{V\,(Ka - K_e)}$$

ولأنه الـ F مجهول فبناخد الـ V جانب واحد معاها
فيصير // ratio

$$\frac{V}{F} = \frac{Ka\,X_0}{Ka - Ke} * \frac{1}{\text{intercept}}$$

ونطلع قيمة الـ $\frac{V}{F}$

Lec (8)

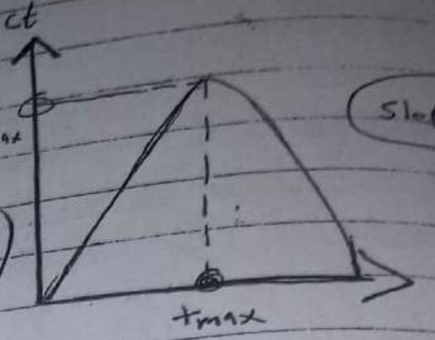
Calculation of t_{max}

// Peak time //

t_{max} // the time at which the drug reach the body in maximum Concentration أي الوقت اللي الدواء بيوصل فيه لأعلى Conc بالجسم

mathematically // يعني

$$\frac{dc_{max}}{dt} = 0 \Rightarrow A \cdot \frac{K_a}{K_a - K_e}\left(e^{-K_e \cdot t_{max}} - e^{-K_a \cdot t_{max}}\right) c_{max}$$



Slope = K_e

$C_t = 0$

$$\Rightarrow A \cdot \frac{K_a}{K_a \cdot K_e}\left(-K_e \cdot e^{-K_e \cdot t_{max}} - (-K_a \cdot e^{-K_a \cdot t_{max}})\right)$$

$$-K_e \cdot e^{-K_e \cdot t_{max}} + K_a \cdot e^{-K_a \cdot t_{max}} = 0$$

$$\frac{K_a}{K_e} = \frac{e^{-K_e \cdot t_{max}}}{e^{-K_a \cdot t_{max}}}$$ ([illegible] نعوض ln)

$$\ln \frac{K_a}{K_e} = -K_e \cdot t_{max} + K_a \cdot t_{max}$$

$$= t_{max}(K_a - K_e)$$

$$t_{max} = \frac{\ln K_a/K_e}{K_a - K_e} = \ln \frac{K_a}{K_e} \times \frac{1}{K_a - K_e}$$

Note // Any factor affect elimination or absorption will affect the t_{max} (Peak time)

← زيادة سرعة الامتصاص يعني أن Ka عالية وهذا قلل الوقت اللازم للوصول لـ t_{max} أقل

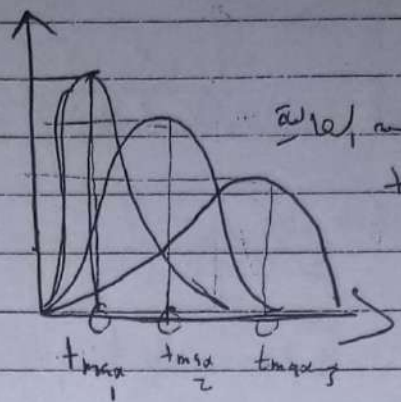
↑ Absorption, ↑ Ka, ↓ t_{max}

(*) Factors affecting Ka //

(1) LipoSolubility : (1st and 2nd Fick's Law)

(↑) LipoSolubility , (↑) absorption , (↑) Ka

(↓) tmax



(2) PH of the media and PKa of the Subs. (Handerso Hasselbalch)

(↑) ionized Parts lead to (↓) absorption

so (↓) Ka and tmax (↑)

(3) GI - motility

(↑) motility , (↑) spreading , (↑) absorption

tmax (↓)

(4) Gastric emptying rate (G.E.R) ?

↓ Basic drug and drug absorbed in intestine

↑ GER , ↑ absorption

↓ Acidic drug and drug absorbed in Stomach

↑ G.E.R , ↓ absorption

(5) Food

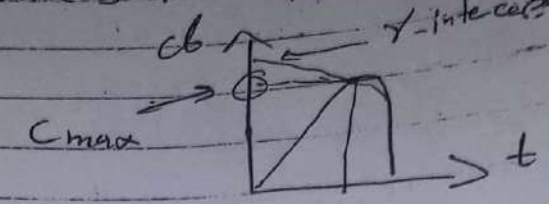
regarging to food-drug interaction:

(6) Pathophysiology //

↓ blood flow lead to ↓ absorption

(*) Maximum Plasma Concentration $(C_p)_{max}$ - L

(Curve) Plot بالرسم // الطريقة الأولى



الطريقة الثانية // بالمعادلة الآتية

$$(C_p)_t = \frac{K_a F X_0}{V(K_a - K_e)} [e^{-K_e t} - e^{-K_a t}]$$

[t بدل بـ tmax]

$$(C_p)_{max} = \frac{K_a F X_0}{V(K_a - K_e)} [e^{-K_e t_{max}} - e^{-K_a t_{max}}]$$

$$Y\text{-intercept} = I$$

$$\therefore (C_p)_{max} = I [e^{-K_e t_{max}} - e^{-K_a t_{max}}]$$

(*) Factors affecting $(C_p)_{max}$ //

(1) Dose : ↑dose : ↑ Cmax // Saturation

(2) F : ↑F , ↑Cmax

(3) Ke : ↑Ke , ↓Cmax

(4) Ka : ↑Ka , ↑Cmax

(5) Vd : ↑Vd , ↓Cmax

[Other methods to calculate Ct] (9)

① Area Under the Curve method (AUC) //

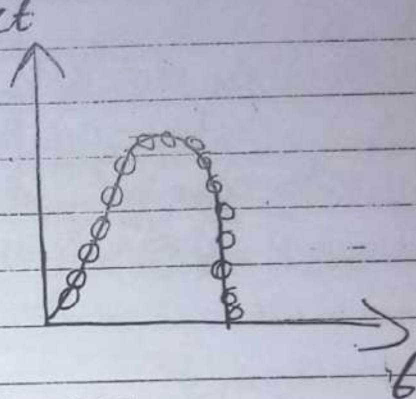
$$\int_0^t Ct = \frac{F_a \cdot X_o \cdot K_a}{V(K_a - K_e)} \int_0^t [e^{-K_e t} - e^{-K_a t}]$$

$$= [AUC]_0^{\infty}$$

(*) كل ما كان الدواء lipsoluble أكثر، كل ما كان Absorbed أحسن، كل ما قلّت الـ tmax وزادت الـ Cmax.

② Simpson method //

Ct	t
2	1
3	2.3
1	6.7



$$[AUC]_0^t = \frac{h}{3}[\Sigma E + 2P + 4I]$$

h / time of take sample

E / Extremes = the highest result + the lowest result (not zero)

P / Summation of pairs (مجموع الأعداد الزوجية)

I / Summation of impairs (مجموع الأعداد الفردية)

Mohammad Shoaib Al Farra

Oct. 2019

chapter (3)

(Lec 9) Two Compartment open model
[A single I.V bolus]

(*) Assumptions //
(1) Distribution, disposition and elimination of the drug are فرضيات follow → 1st order Pharmacokinetic.

✓ or X

(X) In single I.V bolus : the Pharmacokinetics via two compartmental open model are follow both first order and Zero order.
→ first order // غلط

(2) the drug is being monitored in blood.
بنفحص أعداد test للتركيز Drugs وممنوع سميات tissue ومع
أخذ عينات من الدم.

(3) The organ responsible for removal of the drug is in the central compartment.
بحدد نوع الـ compartment هو أخذ عينات مباشرة بعد
ما ضخت الدم بالعادة من خلال هذا بستطيع احدد
هذا النوع //

(one) compartment model → (two) compartment model

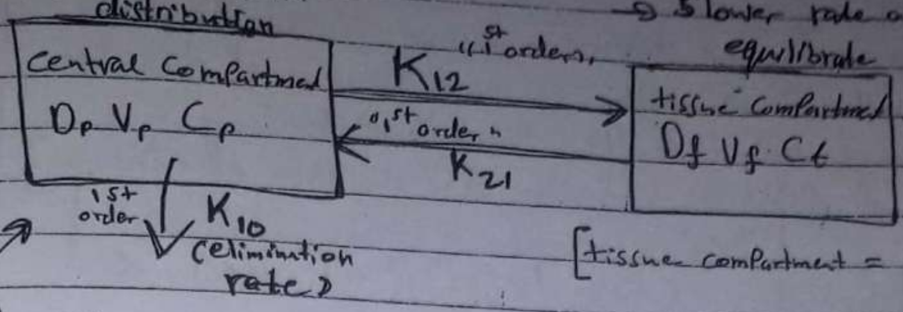
// (two comp) إحنا اليوم شغلنا كله عن الـ

لا أقول two compartment
two differed types من tissue
رح تتعامل مع الـ drug بطريقة مختلفة.

لا أحكي عن two comp بعني رح نفهم عنها هنا
قال I.V حيث مع جسم عندي هو Distribution عدوانية
يحصل جسم المحروب (α) Alpha

Def Amount of drug in Central — Def Amount of drug in tissue

(1) → rapid and uniform distribution — → slower rate of equilibrate (2)



[tissue compartment = Peripheral compartment]

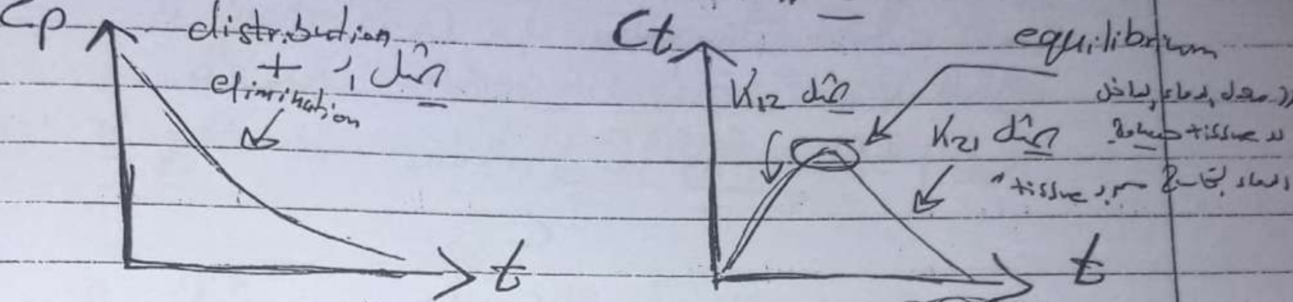
عند (0 = t)

$C_p = 100\%$ and C_t = Zero

عند distribution curve مع مرور لوقت سيصير الـ Central

الـ tissue تركيز الـ Cp قادمة بتتناقص وبـ Ct تتزايد

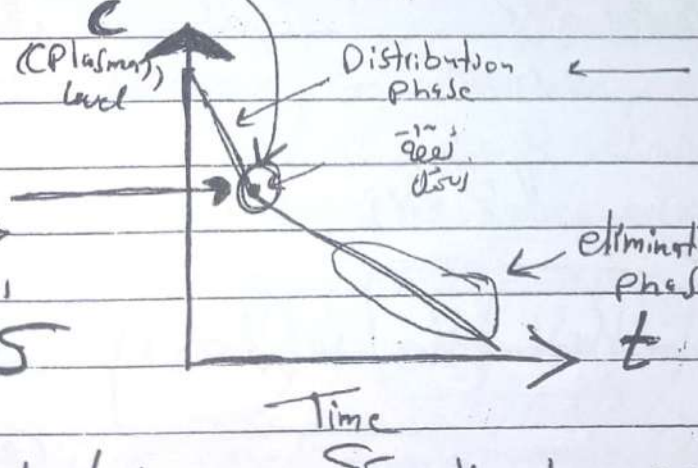
كالتالي //



(*) K_{21} / elimination — الـ tissue — وأيضاً slow

مدمجة كالتالي

(*) هاي النقطة هي نهاية Distribution



بعد هذه النقطة الكثير مع تختص في مرحلة الـ elimination 1st order

(*) الجزء الأول ... رمزه α

(*) الجزء الثاني ... رمزه β

(*) ملاحظة: عملية elimination بتكون من الـ Central compartment فقط

ملاحظة: الـ curve هنا Not single exponential → وانما هي biexponential لأن عملية 1st order

Distribution — Elimination

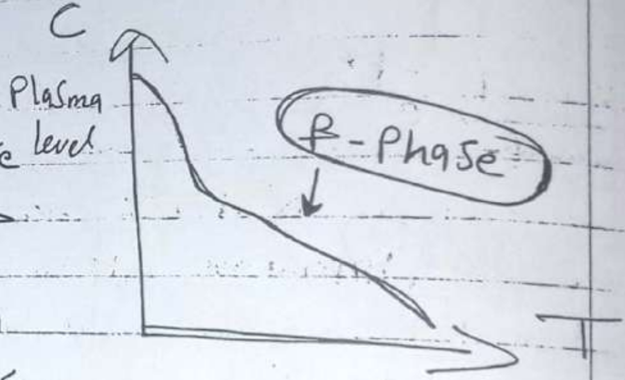
* مع السابق نستنتج الآتي //

→ Drug elimination and distribution occure concurrently during the distribution phase, there is a net transfer of drug from the central compartment to the tissue compartment.

[the rate of distribution is faster than the rate of elimination]

← المقصود أن أيضًا خلال عملية الـ distribution بنشيل من الـ central للـ tissue يوجد أيضًا عملية elimination
وهذا ما يفسر وجود ثابت التحويل K_{10} مع وجود ثابت K_{12}
ولكن في الـ Distribution أكبر وأسرع من الـ Elimination

* نلاحظ // في الـ Curves، كل ما كان الفرق بين عمليتي الـ Distribution والـ Elimination أكبر، كل ما كان ظهور الـ two compartment أوضح وقابل للقياس.
((more conspicuous))



* β-Phase = elimination phase
خلال هذه الـ Phase بنتعامل مع الـ drug
↳ decline (eliminated) parallel
بشكل متوازي بين الاثنين فيبقى
كأنه one compart ← β

* يمكن بالمعادلات التفاضلية التعبير عن K_{12}
فبدل الاثنين طالعين من الـ Central

$$\frac{dx}{dt}_{(Central)} = -K_{10} - K_{12} + K_{21}$$

← داخل الـ Central

(β-Phase المسؤول عن) (α-Phase المسؤول عن)

$$\frac{dx}{dt}_{(Peripheral)} = K_{12} - K_{21}$$

K_{12}: داخل الـ tissue
K_{21}: طالع من الـ tissue

> اللي بيحكوا عليه في الـ Distribution هم ثابتين //
- K_{12} - K_{21}
أما الـ K_{10} فمالوش علاقة .

[فالمعادلة مطلوبة في امتحان الشابتر كل المسائل]

(*) بعد سلسلة من الاشتقاقات وصلنا للمعادلة الآتية //
بواسطة العالم الفرنسي → Laplace

$$C_p = \frac{D_p^0}{V_p}\left(\frac{K_{21}-\alpha}{\beta-\alpha}e^{-\alpha t} + \frac{K_{21}-\beta}{\alpha-\beta}e^{-\beta t}\right) \leftarrow \text{احفظ}$$

لكن بنلاحظ منها الآتي :

$$\frac{K_{21}-\alpha}{\beta-\alpha}e^{-\alpha t} = \text{Intercept of distribution Process}$$

$$\frac{K_{21}-\beta}{\alpha-\beta}e^{-\beta t} = \text{Intercept of elimination Process}$$

ولاحظ في كل الـ Intercepts عندي الـ α و β يعني أنه في هنا نوع من الـ Kinetic اللي تداخل بين الـ α و β (Hyperdization)
لكن لو لاحظ في الـ Intercept الخاص بالـ distribution فإن عدد مرات ظهور α أكثر من عدد مرات ظهور β وهذا طبيعي لأنه α هي التي تعبر عن الـ distribution مع القليل في الـ Intercept المعبر عن الـ elimination تجد ظهور β أكثر من α في الثانية لأنه β هي المعبرة عن الـ elimination Phase.

> حيث نعتبر الـ K_{12} و K_{21} عبارة عن Microconstant
أو transfer constant .

لأنهم بيعبروا عن انتقال الدواء من الدم لـ tissue
ومن الـ tissue للدم .

$$\boxed{\alpha\beta = K_{21}\cdot K_{10}} \leftarrow \text{مهم} \ \text{Ttop}$$

(5)

في هذه المعادلة //

$$C_p = \frac{D_p^0}{V_p} \left(\frac{k_{21}-\alpha}{\beta-\alpha} e^{-\alpha t} + \frac{k_{21}-\beta}{\alpha-\beta} e^{-\beta t} \right)$$

ممكن نعتبرها (A)   ممكن نعتبرها (B)

$$C_p = (A) e^{-\alpha t} + (B) e^{-\beta t}$$

Y-Intercepts

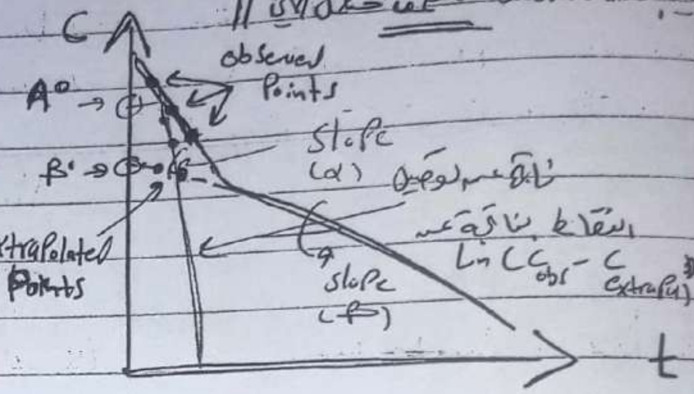
كيف ممكن الحصول على قيم α و β ؟؟
ممكن ذلك من رسم المنحنى التالي //

→ feathering or method of residuals ←

distribution انتقالها الأولى //

$\ln(C_{obs} - C_{extrapol}) = \square$

كل نقطة من رسم ثم بنوصل لنعمل Line



← من الـ slope بنجيب قيمة α أو β ومن ثم بنحسب
ومن ثم بنقدر نجيب الـ $t_{1/2}$ لكل منهما

Distribution

$$t_{1/2} = \frac{0.693}{\alpha}$$

elimination

$$t_{1/2} = \frac{0.693}{\beta}$$

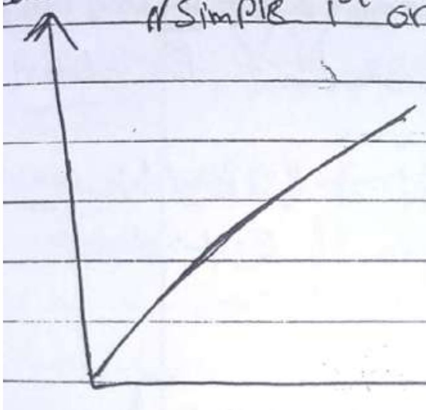
← لو الخط الذي ينتج من القسم الثاني للخط الأساسي ملاصق لـ Y-intercept
نصبح عامل مشترك ونصبح المعادلة هيك //

$$C_p = A(e^{-\alpha t} + e^{-\beta t})$$

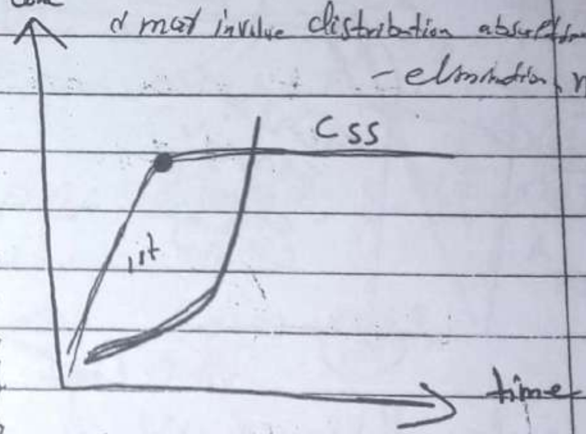
Chapter 4

Lec (10) — [Non Linear PharmacoKinetics] — (1)

Linear PharmacoKinetics	non Linear PharmacoKinetics
(1) $t_{1/2}$ – K, Vd – clearance are constants c̄ changes in doses. قد ما غيرنا في كمية الجرعات ، فإن هذه القيم لا تتغير .	(1) $t_{1/2}$ – K, Vd – clearance are not constants c̄ changes of doses لما نغير في dose ، رح تتغير قيمهم بصورة ملحوظة .
(2) Direct Proportion b/w time and Plasma Conc of drug. علاقة طردية بين التركيز والوقت .	(2) Non linear Proportion b/w time and Plasma Conc. مش علاقة طردية خطية
(3) Dose independent related to First order pharmacoKinetics. لا تعتمد على الجرعة وتتبع الحركية الخطية	(3) Dose dependent related to mixed order PharmacoKinetics → First order [early] / steady state [later] — elimination
(4) Only one type of Kinetics (Simple 1st order)	(4) more than one type of Kinetics (may involve distribution, absorption, elimination)



↑dose lead to ↑AUC means ↑conc of drug



(*) بيتضمن أكثر من نوع Kinetic بمعنى ممكن يكون في أي Phase (elimination, distribution, absorption)

أمثلة على non linear Ph. Kinetics //

(1) Phenytoin + C_2H_5OH (2) Absorption of amoxicillin (↑dose ↓ extent of abs)
(3) Plasma Protein binding of disopyramide (Saturation at therapeutic Conc → ↑ Vd c̄ ↑dose)
(4) Renal excretion of antibacterial agent dicloxacillin.
(Saturable active Secretion in kidneys → ↓ renal Clearance → ↑ dose)

[Capacity limited metabolism]
"Michaeles-Menten kinetic or mixed order kinetic"

Free particles of drug

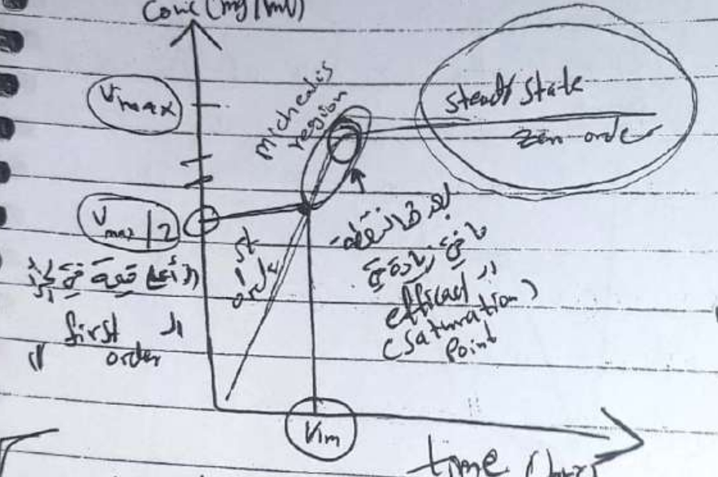
$[D] + [E] \underset{K_2}{\overset{K_1}{\rightleftharpoons}} [DE] \xrightarrow{K_{cat}} [M] + [E]$

([E] = Enzyme free; [DE] = Intermediate complex; [M] = metabolite; [E] = Free enzyme, which goes back to the start)

K_1 and K_2 // forward and backward rate constants.

K_{cat} // the rate constant of metabolite formation.

طول ما ال DE complex بيجي عملية توجيه نحو اعطاء M يعني انا
حيكون ماشي ع 1st order → عند ما يصير ال Saturation لل E ،
عند نقطة ما حتصير عن ال steady state ، بعد هاي النقطة مهما اعطينا
جرعات ما رح نحصل على اي فعالية زيادة اذا اعطيك جرعة عالية
لازم تكون حدها الاقصى هو لعند بداية ال steady state .



✓ 1st order region // (At low drug dose)
D-M → M + E

✓ Zero order region // (when dose increase)
Saturation of E → No increase in metabolism.

[mixed order // يعني بنبدأ ب 1st order وانتهينا ب Zero order]

Michaelis equation (rate of metabolism) //

$$\frac{dm}{dt} = \frac{V_m \cdot S}{K_m + S}$$

V_m // max. velocity of metabolism

K_m // michaelis constant → determine the affinity of drug binding to protein

S // Conc of drug substrate

← ما أهمية الـ Km ؟

measure the affinity b/w the drug and Protein (enzyme)
and the bond strength

يعني قوة الرابطة بين البروتين وجزيئات الدواء .

[↑ Km mean ↓ bond strength]

Higher Km → Low affinity

1st order السلوك الخطي //

Lower Km → High affinity

mixed order السلوك الخطي //

$$\frac{V}{V_{max}} = \frac{V_{max} \cdot S}{K_m + S} \times \frac{1}{V_{max}} \Rightarrow \boxed{V/V_{max} = \frac{S}{K_m + S}}$$

شكل آخر للقانون ليثبت الـ Km

عندما S = Km ، فإن الـ $V/V_{max} = \frac{1}{2}$

وهو ما يعني أن $K_m = \frac{V_{max}}{2}$ وهي أقصى معدل للـ metabolism

← مع زيادة الـ S على حساب الـ Km ، فإن الـ Km يتم تجاهلها تماما

→ No change in system ←

القانون يصبح //

$$\boxed{\frac{dm}{dt} = V_{max}}$$

← لو زادت الـ Km على حساب الـ S ، فإن القانون يصبح //

$$\boxed{\frac{dm}{dt} = \frac{V_m}{K_m} \cdot A}$$

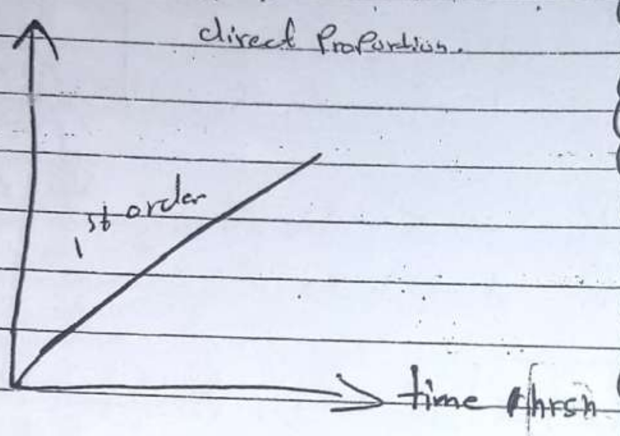
CamScanner ← الممسوحة ضوئيا بـ

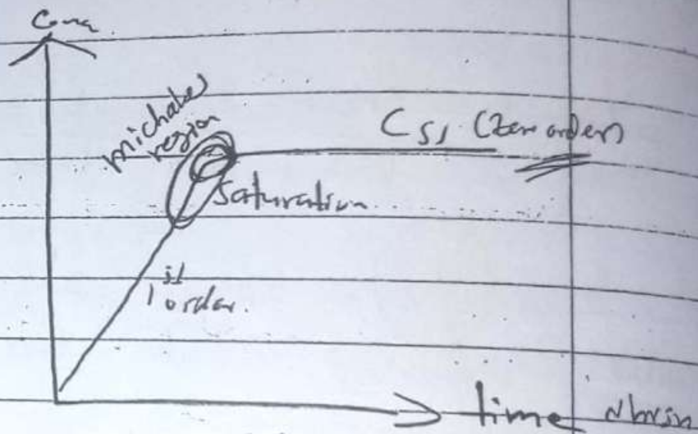
تابع الأمر

$$\frac{dm}{dt} = \frac{V_{max} \cdot S}{K_m + S}$$ Michales equation //

يعني فيه Low affinity → $K_m >> S$	$K_m << S$ ← يعني فيه High affinity
$dM/dt = \frac{V_{max}}{K_m} \cdot S$	$dm/dt = V_{max}$
→ 1st order Ph. Kinetics.	→ mixed order Ph. Kinetic.
→ Linear relation.	→ Non linear relation.
→ dose independent.	→ dose dependent.
⊛ ما في Saturation رح يضل ماشي نوصل لل Steady state	⊛ زيادة بـ dose رح نوصل أصعب لل steady state

Conc ↑↑dose, ↑ rate ↳ direct Proportion.





⊛ ملاحظة :-

⊛ معظم الأدوية therapeutic conc لا بعلى أو ما بتوصل لل Km لذلك بتسلك 1st order

معظم الأدوية إلا في مثل Phenytoin

ال therapeutic conc بعلى أكثر من Km

فرح تسلك mixed order

انتهت المحاضرة

By// Mohammad Shoaib AL Farra

Oct. 2019

(*) Factors affecting the distribution from the Plasma to interstitum space ?

(1) lipoSolubility : (Capillary Permeability) // « HydroPhobi
↑ lipoSolubility → ↑ Permeability → ↑ Absorption → ↑ distri

(2) Blood flow :
↑ blood flow → ↑ Vd → ↑ distribution

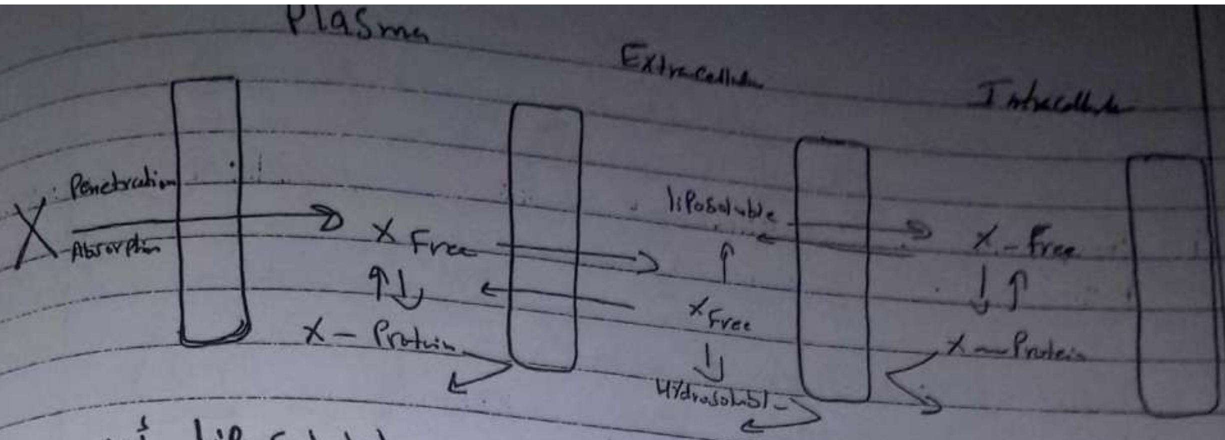
(3) Binding of drug Protein :
↑ binding of Protein means (High affinity) = highly
so → Want higher dose to ↑ distribution.
[to get more free Particles]

((Zieg))

(1) IF Vd = 4L // this means the following :-
1) Low (short) $t_{1/2}$ 4) rapid excretion ((High Ke))
2) HydroSoluble 5) only in Plasma
3) MonoCompartmental model 6) Short duration

(2) IF Vd = 9L // this means the following :-
1) Longer $t_{1/2}$ 4) reach interstitium space
2) more lipoSoluble 5) Longer duration
3) MonoCompartmental model

(3) IF Vd = 50L // this means the following :-
1) too long $t_{1/2}$ 4) reach tissues
2) strong lipoSoluble 5) too Long duration
3) two Compartmental models 6) Highly binding to Protein
[Tissue → Plasma ... Protein binding ... Reversible] (*)
Plasma
Reversible ←



← كل ما كان الـ X له خواص liposoluble أعلى
كل ما راح يقودنا لشغلتين //

↑ Penetration , Absorption

↑ Affinity to Proteins

كل ما زودنا الـ X رح راح يزيد الـ X Free ويزيد الـ absorption
و الـ Penetration ويقصر الوقت حتى يزيد ارتباطه بالبروتينات
و الـ X Free راح توصل للـ Intracellular .

← عند حدوث تكيس X - Protein في كل من الـ Plasma
و الـ tissue ، أما الـ interstitium لا .

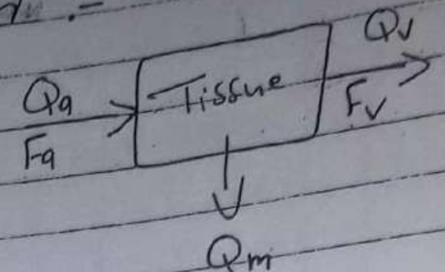
← الـ Hydrosoluble راح ترجع وتضل في الدم أكثر لأنها أقل منه
لعدم قدرتها على الـ Penetration .

✱ معلومة // ↑ Vd يعني ↑ $t_{1/2}$ يعني ↑ duration

← ما يميز البشر عن بعضهم البعض هو النفس الطويل
والقدرة على الاستمرار في التقدم ←

(*) Drug distribution influenced by // ② tissue vol ③ Partition coefficient
① Drug conc (accumulated) in tissue

Kety's theory :-



Qa / Amount of drug in blood artery.
Qv / Amount of drug in blood vein.
Qm / Amount of drug metabolized.
Fa / Artery blood flow.
Fv / Vein blood flow.
← حتى يستفيد الجسم من ال drug لازم يكون ال Q_v و Q_a لا يساوي صفر.

① Amount of accumulated drug in tissue XT

$$\frac{dXT}{dt} = Q_a - (Q_m + Q_v)$$

Zero = Q_m اذا

$$\frac{dXT}{dt} = Q_a - Q_v \Longleftarrow Q_a > Q_v$$

[illegible]

$Q_a - Q_v = 0 = \frac{dXT}{dt}$ ⟹ ما في تراكم drug

$Q_a = F_a \cdot C_a$, $Q_v = F_v \cdot C_v$, $F_a = F_v = F$

$$\frac{dXT}{dt} = F(C_a - C_v)$$ — First Kety's theory

(*) Factors affecting accumulation rate of drug in tissue?
① F (طردية) ② Ca (طردية) ③ Cv (عكسية)

[illegible] Vd [illegible] saturation [illegible] tissue [illegible] Conc [illegible]

Vd → (↑) blood flow and (↑) drug conc in artery lead to (↑) drug Conc in tissue.

[(↑↑) distribution [illegible]]

② Tissue Volume VT :-

$$\frac{d\,(XT)}{dt} = F\,(Ca - Cv)$$

$$\frac{d\,(CT \cdot VT)}{dt} = F\,(Ca - Cv)$$

$XT = CT \cdot VT$

XT / amount in tissue

CT / Conc in tissue

VT / the vol of tissue in which drug is distributed

$$\boxed{\frac{dCT}{dt} = \frac{F}{VT}\,(Ca - Cv)}$$

└ second Kety's theory

① (↑) VT lead to (↓) CT, (↑) Vd ← [illegible]

② (↑) F lead to (↑) CT [illegible] tissue [illegible]

③ (↑) Ca lead to (↑) CT [illegible] distribution

④ (↑) Cv lead to (↓) CT [illegible] $\frac{dCT}{dt}$ [illegible] Vd [illegible]

← [illegible] Volume [illegible] Conc [illegible]

③ Partition Coefficient (Tissue / Blood)

λ : Partition coefficient.

$$\frac{dCT}{dt} = \frac{F}{VT}\,(Ca - Cv) \qquad Cv = \frac{CT}{\lambda}$$

$$\frac{dCT}{dt} = \frac{F}{VT}\left(Ca - \frac{CT}{\lambda}\right) = \frac{Fm}{VT \cdot \lambda}\,(Ca\lambda - CT)$$

- m / diffusion coefficient
- $\frac{dCT}{dt}$: accumulation rate in tissue.

→ ↑ Partion (λ) → ↑ distribution → ↑ accumulation in tissue + ↓ accumulation in blood

$$\frac{dCT}{dt} = \frac{Fm(Ca - CT)}{VT \cdot \lambda}$$

m = 0
(Diffusion = 0)
- hydrosoluble drug
- distribution = 0
- No reach to tissue

↓

$$\frac{dCT}{dt} = Zero$$

[one Compartmental model]

m = 1
→ diffusion and distribution available
→ lipoSoluble drug
→ reach tissue

↓ عكسية ↓ طردية طردية

$$\frac{dCT}{dt} = \frac{F}{VT \cdot \lambda}(Ca - CT)$$

عكسية

[two Compartmental model]

Q1// Explain two equations first and Second Ketty's theory?

← تكلم عن المعادلات
← كل رمز لازم يعود
← العلاقات بينهم بالظروف (طردية / عكسية)

انتهت المحاضرة

lec (12)

How the dCT changes w the time?

$$\frac{dCT}{dt} = \frac{F}{VT \cdot \lambda}(Ca \cdot \lambda - CT)$$

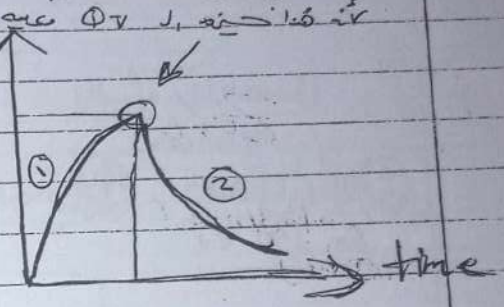
$$\frac{dCT}{(Ca \cdot \lambda - CT)} = \frac{F}{VT \cdot \lambda} \cdot dt$$

assum that :
$\frac{F}{VT \cdot \lambda} = K$

$$\int_0^t \frac{dCT}{(Ca \cdot \lambda - CT)} = K \int_0^t dt$$

then integration //

$$\therefore \quad CT = Ca \cdot \lambda (1 - e^{-K \cdot t})$$



- Ca = Constant
- CT = 0 , t = 0

desaturation ② elimination 1st order

// Integration

$$CT_t = CT_{t_0} \cdot e^{-Ke \cdot t}$$

Ke: elimination Constant rate from tissue to blood.

Conc of drug in tissue at time t = CTmax = Conc of drug at initial time

Conclusion: 1st order

CT ↓ desaturation
CT ↑ CTmax

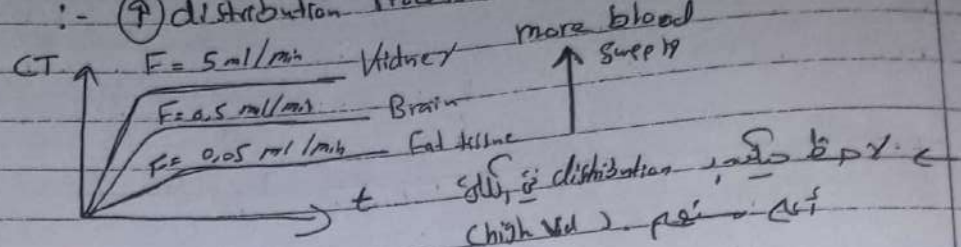
[Summery]

(*) Factors affecting the drug's distribution //

(1) Blood Perfusion of organs :-

(↑) blood supply ((↑) blood flow) ⇒ (↑) drug reach to organ

:- (↑) distribution Process.



(2) Diffusability of drug in tissue (m) :-

m : Diffusion coefficient ((↑) m , (↑) vd)

// تزيد

Permeability of the membrane

(↑) liposolubility , (↑) Permeability.

so , (↑) Vd

Properties of the drug :-

1- Partition (tissue / blood)

(↑) Partition , (↑) vd

Pka and PH

(↑) ionization , (↓) Permeability through membrane so (↓) vd

Molecular weight

((↑) MW (↓) Vd)

(3) Individual factors //

a) Age // Infants (high Permeability membrane) ⇒ higher (faster) Vd.)

- adult's (Selective Permeable membrane) ⇒ (↓) Vd)

b) Pathological factors (inflammation //

W inflammation , Vd increase (↑)

c) Physiological factors : Pregnancy //

increase Vd (↑)

(4) Capacity for binding $\bar{c}$ Plasma and for tissue Proteins //

$$\alpha T = \frac{CTL}{CTT} \qquad \alpha P = \frac{CPL}{CPT}$$

- αT: Free fraction of drug in tissue
- CTL: Free conc of drug in tissue
- CTT: total conc of drug in tissue

- αP: Free fraction of drug in Plasma
- CPL: Free conc of drug in Plasma
- CPT: Total drug conc in Plasma.

(*) Free fraction → distributed from Plasma to tissue according to liposolubility.

Assume there is equilibrium b/w Plasma and tissue Volume then:

$$CPL = CTL$$

يبقى //

$$\lambda = \frac{\alpha P}{\alpha T} = \frac{CPL}{CPT} \cdot \frac{CTT}{CTL} = \frac{CTT}{CPT}$$

$$\boxed{\lambda = \frac{\alpha P}{\alpha T} = \frac{CTT}{CPT}}$$

(5) other factors //

$10 - (2 + 0) = 8$

A) Qm :-

$$\frac{dXT}{dt} = Qa - (Qm + Qv)$$

بزيادة

[↑ Qm, ↑ Vd]

. Qv بيقل لأنه عكسية

لو زاد ؟ يبقى بيقل Qv
وعليه قادر Qv [illegible]
عكسية & Vd يبقى
↑ Vd

B) Passage to other tissues //

(↑ Vd) بزيادة

C) Active transport //

(↑ Vd) بزيادة

[انتهت [illegible]]

[Factors affecting drug distribution] // تابع

(4) Capacity for binding with Plasma and for tissue Proteins //

$\alpha T = \frac{CTL}{CTT}$

- αT: Free fraction of drug in tissue
- CTL: Free conc of drug in tissue
- CTT: total conc of drug in tissue

$\alpha P = \frac{CPL}{CPT}$

- αP: Free fraction of drug in Plasma
- CPL: Free conc of drug in Plasma
- CPT: Total drug conc in Plasma.

(*) Free fraction → distributed from Plasma to tissue according to liposolubility.

Assume there is equilibrium b/w Plasma and tissue Volume then:

$CPL = CTL$

يبقى //

$$\lambda = \frac{\alpha P}{\alpha T} = \frac{CPL}{CPT} \cdot \frac{CTT}{CPL} = \frac{CTT}{CPT}$$

$$\boxed{\lambda = \frac{\alpha P}{\alpha T} = \frac{CTT}{CPT}}$$

(5) other factors //

$$\frac{dXT}{dt} = Q_a - (Q_m + Q_v)$$

A) Q_m :- طردية

[↑ Q_m, ↑ Vd]

. Q_v ; علاقة عكسية

لو زاد ↑ يبقى ↓Q_v

ويبقى قادر ; Q_v علاقة

عكسية & Vd يبقى

↑Vd

B) Passage to other tissues //

طردية (↑Vd)

C) Active transport //

طردية (↑Vd)

[انتهت المحاضرة]

[CLR قوانين حساب]

→ Equations :-

① By using dx_u/dt and VE //

$VE = VF + (VS - VR)$

- clr // renal clearance
- VF // value filtred
- VS // value secreted
- VR // value reabsorbed

$dx_u/dt = VE$

where $Clr = \frac{dx_u/dt}{Cp} = \frac{VE}{Cp} = \frac{VF}{Cp} + \frac{VS - VR}{Cp}$

$dx_u/dt = \frac{X_{u2} - X_{u1}}{t_{i2} - t_{i1}}$ ⟹ $t_i = \frac{t_1 + t_2}{2}$ (intervals)

Conclusion ⟹ $Clr = \frac{\Delta X_u / \Delta t_i}{Cp}$ — (1)

When $Cp = Cp_0 \cdot e^{-K_e \cdot t_i}$

② By using GFR value //

$Clr = \frac{VE}{Cp} = \frac{VF}{Cp} + \frac{VS - VR}{Cp}$ (VF = GFR . α . Cp)

So $Clr = \frac{GFR . \alpha . Cp}{Cp} + \frac{VF - VR}{Cp}$ (C ÷ GFR.α)

(2) — $\frac{Clr}{GFR . \alpha} = W$ ← to determine which mechanism involved in process (filtration, secretion or reabsorption)

W

- > 1 : (Filtration + Secretion) (VS > VR)
- = 1 : only filtration (VS = VR = 0)
- < 1 : Reabsorption + filtration (VR > VS)

Hint // GFR : Glomerular filtration rate

α : free drug particles

③ $\frac{VE}{CP} = Clr$ // By using $[AUC]_0^\infty$

$Clr = \frac{VE}{CP} = \frac{dX_4/dt}{CP} \Rightarrow Clr \cdot CP = \frac{dX_4}{dt}$

$Clr \cdot CP \cdot dt = dX_4$ // By integration $\int_0^\infty$ >

$Clr \int_0^\infty CP \cdot dt = \int_0^\infty dX_4$ while $\int_0^\infty CP \cdot dt = [AUC]_0^\infty$

while $\int_0^\infty dX_4 = X_4^\infty$

So $Clr = [AUC]_0^\infty = X_4^\infty$

$\therefore Clr = \frac{X_4^\infty}{[AUC]_0^\infty}$ ——— ③

Mohammad Shoaib Al Farra
January 2020

④ first Vetter's theory :=

$\frac{dXT}{dt} = Q_a - (Q_m + Q_v)$ when $Q_m = 0$ Q_a: amount of drug in artery.

so $dX/dt = Q_a - Q_v$, if $Q_a - Q_v = 0$ Q_v: amount of drug in vein

so // $Q_a = F_a \cdot C_a$, $Q_v = F_v \cdot C_v$ F_a: blood flow in artery

assume $F_a = F_v = F$ ——— ④ F_v: blood flow in vein

$dx/dt = F(C_a - C_v)$ ——— 1st Vetter's theory F: total blood flow

C_a: conc of drug in artery.

C_v: conc of drug in vein

dx/dt: accumulation rate in tissue.

) Second Vetter's theory :=

$\frac{dXT}{dt} = F(C_a - C_v)$ while $XT = VT \cdot CT$

$\frac{d(CT \cdot VT)}{dt} = F(C_a - C_v)$

$\therefore \frac{dCT}{dt} = \frac{F}{VT}(C_a - C_v)$

CT: conc of drug in tissue

VT: vol of distribution in tissue

XT: amount of drug in tissue

Calculation of dCT/dt using Partition coefficient //

$$\frac{dX_T}{dt} = Q_a - (Q_m + Q_v) \quad \text{while } Q_m = 0$$

$$= Q_a - Q_v \quad \text{while } Q_a - Q_v = 0$$

$$\therefore F_a \cdot C_a - F_v \cdot C_v \quad \text{while } F_v = F_a = F$$

$$\frac{dX_T}{dt} = F(C_a - C_v) \quad \text{—— (1)}$$

$$X_T = C_T \cdot V_T$$

$$\frac{d(C_T \cdot V_T)}{dt} = F(C_a - C_v)$$

$$\frac{dC_T}{dt} = \frac{F}{V_T}(C_a - C_v) \quad \text{—— (2)} \qquad \text{while } C_V = \frac{C_T}{\lambda}$$

$$\frac{dC_T}{dt} = \frac{F}{V_T}\left(C_a - \frac{C_T}{\lambda}\right)$$

$$\frac{dC_T}{dt} = \frac{F_m}{V_T \cdot \lambda}(C_a \cdot \lambda - C_T) \quad \text{—— (3)}$$

m = 0 ⇒ one compartment — no distribution — hydrosoluble.

m ≠ 0 ⇒ two compartment — available distribution — liposoluble.

m: diffusion coefficient   λ: Partition coefficient

How CT changes with time (By equations) //

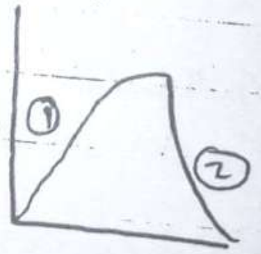
$$\frac{dC_T}{dt} = \frac{F_m}{V_T \cdot \lambda}(C_a\lambda - C_T) \qquad \text{assume } \frac{F_m}{V_T \cdot \lambda} = K$$

$$\int_0^t \frac{dC_T}{C_a\lambda - C_T} = \int_0^t K \, dt \quad \text{—— by integration}$$

then ⇒ subs cross $\int_0^t$

$$C_T = C_a \cdot \lambda (1 - e^{-K \cdot t})$$

$$C_{T_t} = C_{t_0} \cdot e^{-K_e \cdot t}$$



at Point (1) // C_T = Zero → saturation phase, C_a = constant

at Point (2) // $C_T = C_{max}$ → desaturation phase, C_a = Zero

⊕ Calculation of apparent volume of distribution //

$X = X_P + \Sigma X_T$, $X_T = C_T \cdot V_T$

$X = X_P + \Sigma (C_T \cdot V_T)$, $C_T = \lambda \cdot V_T$

$X = X_P + C_P \Sigma (V_T \cdot \lambda)$

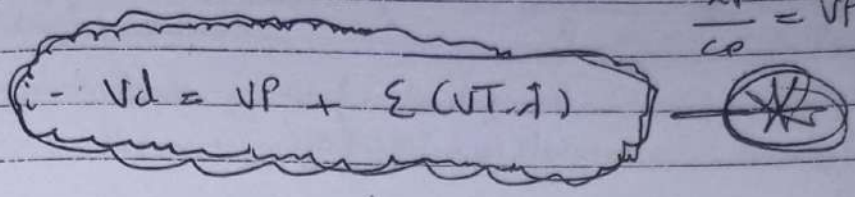
$X = V_d \cdot C_P$

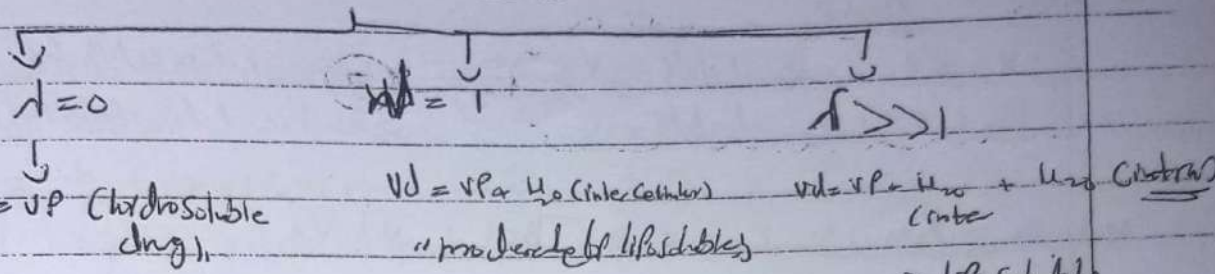
$V_d \cdot C_P = X_P + C_P \cdot \Sigma (V_T \cdot \lambda)$ $\div C_P$

$V_d = \frac{X_P}{C_P} + \Sigma (V_T \cdot \lambda)$

$\frac{X_P}{C_P} = V_P$

$\therefore V_d = V_P + \Sigma (V_T \cdot \lambda)$





$V_d = V_P$ (hydrosoluble drug).

$V_d = V_P + H_2O$ (intercellular) "moderately liposoluble"

$V_d = V_P + H_2O$ (inter) $+ H_{2g}$ (intra) ⇒ liposoluble

⊕ Determination the Union of several Points //

$[PF] + [MF] \xrightleftharpoons{K_a} [MP]$, $K_a = \frac{[MP]}{[PF][MF]}$

$[MP] = [PF][MF] \cdot K_a$

$r = \frac{MP}{PT}$

$= MP + PF$

$\therefore r = \frac{MP}{MP + PF} = \frac{K_a[PF][MF]}{PF + K_a[PF][MF]}$

$\frac{K_a[MF]}{1 + K_a[MF]}$ ⟵ for one Union

$Union = \frac{K_a[MF]}{1 + K_a[MF]} \cdot N$

MF: free drug conc

MP: Protein drug complex

PT: Total Protein

PF: free Proteins

N: Number of binding sites

r: ratio of binding

⊛ Laws //

- $X_t = \frac{X_0 . F . K_a}{Vd(K_a - K_e)} (e^{-K_e t} - e^{-K_a . t})$ —— bateman equation
  " for one compartment - extravascular

- $t_{max} = \frac{Ln(K_a/K_e)}{K_a - K_e}$ " for one compartment - extravascular

- $\frac{D_p^\circ}{V_P} \left(\frac{K_{21} - \alpha}{\beta - \alpha} . e^{-\alpha . t} + \frac{K_{21} - \beta}{\alpha - \beta} . e^{-\beta . t} \right)$ → to show hyperbolic elimination / distribution

- $\frac{dm}{dt} = \frac{V_m . S}{V_m + S}$ → michaelis menten equation
  - $K_m > S \Rightarrow dm/dt = \frac{V_m}{K_m} . S$ ⇒ linear / dose independent / ...
  - $K_m < S \Rightarrow dm/dt = V_m$ ⇒ non linear / dose dependent / ...

- $Vd = \frac{X_0}{K_e [AUC]}$ and $TBCl = Vd . K_e$

- $r = \frac{K_a . [MF]}{1 + K_a [MF]}$ → determination of union.

- $Clr = \frac{\Delta X_u / \Delta t_i}{C_{P_i}}$ ⇒ $\Delta t_i = (t_1 + t_2)/2$
  $\Delta X_u = X_{u2}^\infty - X_{u1}^\infty$

- $Clr = \frac{X_u^\infty}{[AUC]_0^\infty}$, $\frac{Clr}{GFR_\alpha} = (Z)$ " determine the pre... mechanism

- $f_u = X_u^\infty / X_0 = K_u / K_e = Clr / TBCl$

- $K_u = \frac{X_u^\infty}{X_0} . K_e$, $X_u^\infty = \frac{K_u}{K_e} . X_0$

- $\frac{dX_T}{dt} = K_u . X_0 . e^{-K_e . t}$, $\frac{dX_T}{dt} = \frac{K_u . X_0}{K_e} (1 - e^{-K_e . t})$

- $\frac{1}{r} = \frac{1}{N} + \frac{1}{K_a N} * \frac{1}{[MF]}$ —— lineweaver equation

- $\frac{r}{[MF]} = K_a . N - r . K_a$ —— Scachard representation

(*) objectives of bioavailability studies //
① Development of new formulations.
② Determine drug safety and efficacy.
③ quality control of drug Products.
④ show the influence of Physicochemical Properties of drug and storage condition upon drug absorption
⑤ Determine the influence of Processing Conditions, Packaging, excipients, formulations on the drug absorption.
⑥ Determine drug duration and Correlate the drug amount in Pharmacological effect and toxicity.

(*) Factors affecting drug distribution //
① blood Perfusion ↓ Tissue.
② diffusibility //
A) lipophilicity ↓ ↓ rate
B) Partition // ↓ rate
C) M.W // ↓ rate
③ Ionization //
ionized, ↓ absorption ⇒ ↓ distribution
④ Individual factors
- Age (Neonates > elderly)
- Pathophysiology (inflammation) ↓ rate
- Pregnancy ⇒ ↓ rate
⑤ Protein binding capacity //
// dose dependent
⑥ Qm // ↓ rate
⑦ Active transport // ↓ rate

(*) Significance of Vd //
① reflects the distribution of drug in body fluid and tissues. ② ↑Vd results in ↓ CP
③ determine amount of drug outside sampling compartment
④ TBCL = Vd . Ke.
⑤ $X_o = Vd \cdot CP$
⑥ for each drug Vd is constant.

(*) factors affecting the determination of Protein binding // ① drug Polarities and Concentration
② Capacity and nature of Protein
③ Affinity between drug & Protein
④ Drug interactions (Competetion and alteration of affinity.
⑤ Pathophysiology //
- Uremic Patient / live Cirrhosis.
// ↓ Protein binding

(*) Determination of bioavailability // (طريقة)
① Method of Simpson
$$(AUC)_0^{\infty} = \frac{h}{3}(\Sigma E + 2P + 4I)$$
② Method of integration // Batmanis equation
$$(AUC)_0^{\infty} = \frac{X_o F}{Ke.Vd}$$
) Trapezoidal method
$$(C_{n+1} - C_n)(t_n + t_{n-1}) + \frac{Clast}{Ke}$$

Assessing of bioavailability // (تقييم)
Plasma Conc/time curve.
Urine data
Pharmacological effects.

tors affecting bioavailability //
) Properties & Surface area, Solubility, ionization
ktion, lipophilicity ... etc ② formulation
// excipients, lubricant, viscosity, disintegrant >
ol (↑ bulk, ↑ viscosity, ↓ dissolution
d at same rate, ↑ rate for same extent ↑ extent
different rate ... by //
ER B) ↑ bi Secretion C) Complexation
) interaction

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① Method of Simpson
$(AUC)_0^{\infty} = \frac{h}{3}(\Sigma E + 2P + 4I)$
② Method of integration // Batmanis equations
$(AUC)_0^{\infty} = \frac{X_0 F}{Ke.Vd}$
③ Trapezoidal method
$(C_{n-1} - C_n)(t_n + t_{n-1}) + \frac{C_{last}}{Ke}$

(*) Assessing of bioavailability // (بقسم)
① by Plasma conc/time curve.
② by urine data
③ Pharmacological effects.

(*) Factors affecting bioavailability //
① Drug Properties // Surface area, Solubility, ionization, Partition, lipophilicity - etc> ② formulation factors // excipients, binders, viscosity, disintegrant >
③ food (↑ bulk, ↑ viscosity, ↓ dissolution // ↑ extent at same rate, ↑ rate for same extent, ↑ extent w different rate >> by //
A) ↑ GER B) ↑ bile Secretion C) complexation
④ Drug interaction

(*) Factors affecting drug distribution //
① blood Perfusion ∝ ↑ rate.
② diffusibility //
A) lipophilicity ∝ ↑ rate
B) Partition // ↑ rate
C) M.w // ↓ rate
③ Ionization //
ionized, ↓ absorption ∝ ↓ distribution
④ Individual factors
- Age (Neonates > elderly)
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⑤ Protein binding capacity //
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④ Drug interaction (Competition and alteration of affinity.
⑤ Pathophysiology //
- Uremic Patient / live Cirrhosis.
// ↓ Protein binding>

(*) Factors modify Protein binding //

(1) Physiological factors and habits :-

A) New born (low Proteins)

B) Elderly (low albumin, high glycoProtein)

c) Pregnancy (low albumin, high α1-glycoprotein)

d) Tobacco, ↓ Albumin conc.

(2) Pathological factors //

A) Acute Process ⇒ ↓ Albumin, ↑ globulin.

B) tumors malignancy ⇒ ↓ Albumin synthesis

c) MI, rheumatic fever, Peritonitis, ↓ Albumin.

d) Surgeries and burns // ↓ extravascular Proteins

e) Hepatic/renal disorders // ↓ Albumin

f) Schizophrenia and Psychosis // ↑ Albumin

(3) alteration in Protein structure leads to influence the affinity.

(4) Interactions with endogenous Substances or drugs such as sulfonamide and billirubin.

(*) Factors affecting filtration rate //

(1) S.A مساحة (6) Pores size حجم المسام

(2) Viscosity لزوجة (7) temp حرارة

(3) Solid Particles in fluids (8) Pressure gradient فرق الضغط

(4) molecular weight وزن

(5) membrane thickness سمك

(*) Factors affecting tubular reabsorption //

(1) LipoPhilicity. ذوبان

(2) flow rate معدل

(3) ionization (PH of urine, Pka of drug)

" non ionized reabsorbed better

$X_0 = 100$ mg

- $K_e = 0,17$
- $K_a = -1,5$
- $V_d = \frac{X_0 \times F}{\text{Y-intercept}} = \frac{45}{\text{Y-intercept}}$

$$t_{max} = \frac{\ln(K_a/K_e)}{K_a - K_e} = \frac{\ln(1,5/0,17)}{1,5 - 0,17}$$

$t_{max} = 1,63$ hr

$$C_{max} = 45\,(e^{-0,17 \times 1,63} - e^{-1,5 \times 1,63}) = 30,2 \text{ mg/mL}$$

$K_e = 0,17$

$\frac{0,693}{0,17} = t_{1/2}$

$25 = \frac{0,33 \times X_0}{9 \times (0,16)}$

$36 = 0,0817\, X_0$

$X_0 = 438,5$ mg

(A) $\frac{\ln(K_a/K)}{K_a - K} = \frac{\ln(\frac{1}{0,2})}{0,8} = 2,011$

(A) $C_{max} = \frac{K_a \cdot X \cdot F}{V_d(K_a - K)} (e^{-K \cdot t_{max}} - e^{-K_a \cdot t_{max}})$

$\frac{1 \cdot 500 \times 1}{10,000(ml) \times 0,8} (e^{-0,2 \times 2,011} - e^{-1 \cdot 2,011})$

$= 0625 \times$

C_{max} (A) $= 0,0334$ mg/L

$C_{max(A)} = \frac{0,6 \times 1 \times 500}{1000 \times (0,6 - 0,4)} (e^{-0,4 \times 2,02} - e^{-0,6 \times 2,02})$

$C_{max} = 0,1074 \times 0,1481$

$C_{max} = 0,0158$ mg/mL

$= 15,8$ mg/L

$14 = \frac{0,72 \times 1 \times X_0}{13 \times (0,72 - 0,15)} (e^{-0,15 \cdot 6} - e^{-0,72 \cdot 6})$

$103,74 = 0,72 X_0 \times 3932$

$103,74 = 0,283\, X_0$

366 mg

$\ln CP = \ln CP_0 - K_e t$

$\ln 10,59 = \ln CP_0 - 0,055 \times 1$

$\ln CP_0 = 2,478$

$CP_0 = 12648$ mL/L

$CP^\circ = \frac{X_0}{Vd} \Rightarrow Vd = \frac{500}{12648}$

$Vd = 40,03$ L

$K_m = \frac{X_4^\infty}{X_0} \Rightarrow K_e = \frac{100}{500} \cdot 0,055 = 0,011$ hr

$Clr = K_m \cdot Vd$

$= 0,011 \cdot 40,032$

$0,44$ L/hr

$\frac{Clr}{GFR_\alpha} = \frac{0,44 \times \frac{1000}{60}}{130 * \frac{24}{100}} = \frac{0,73}{31,2} = 0,023$

reabsorption

$\% \text{ of Process} = \frac{Clr}{TBcl} = \frac{15}{19,2} * 100 = 78,1$

Extra req $= 100 - 78,125$

$= 21,875$

$\frac{Clr}{GFR_\alpha} = \frac{15 * \frac{1000}{60}}{130 * 0,3} = 8,55 > 1$

$TBCl = K_e \cdot Vd \Rightarrow K_e = ?$

$Clr = K_m \cdot Vd \quad K_m = ?$

$K_m = K_e - K_4$

$X_0 = 30\ mg$

$$K_e = \frac{\ln(y_2) - \ln(y_1)}{t_2 - t_1} = \frac{\ln(5,7) - \ln(7,8)}{2,5} = 0,0934\ hr^{-1}$$

$$t_{1/2} = \frac{0,693}{K_e} = \frac{0,693}{0,0934} \Rightarrow \boxed{7,45\ hrs}$$

$7,2\ \frac{mg}{L}$ $\quad t = 2,5$

$\ln C_{Pb} = \ln C_{P_0} - K_e t$

$\ln(7,2) = \ln C_{P_0} - 0,0934 \cdot 2,5$

$1,974 = \ln C_{P_0} - 2,335$

$4,309 = \ln C_{P_0}$ (anti ln) $\Rightarrow$ ~~7,486 mg/L~~

$C_P^\circ = \frac{X^\circ}{Vd}$ ~~$Vd = 1$~~

$\ln C_P = 2,192$ $\quad C_P^\circ =$

$9,056\ mg/L$

$Vd = \frac{30}{9,056}$ $\quad \boxed{Vd = 3,138\ L}$

$\frac{Cl_r}{GFR \cdot \alpha}$

* Volum of fluid containing drug which cleared from drug Pe unit time.

ml/min
L/hr

$Clr = K_u \cdot Vd$

$Clr = f_u \cdot CLT$

$f_u = \frac{X_u^{\infty}}{X_0} = \frac{K_u}{K_e} = \frac{Clr}{CLT}$

$dx/dt = VE \Rightarrow \frac{dx/dt}{CP} = VE = \frac{K_u \cdot Vd \cdot CP}{CP}$

$Clr = K_u \cdot Vd$

$Clr = \frac{dx_u/dt}{C.P}$ ∴ $dx_u/dt = VE = Vd \cdot K_u \cdot CP$

$Clr = \frac{K_u \cdot Vd \cdot CP}{CP} \Rightarrow \boxed{Clr = K_u \cdot Vd}$

$\frac{dx_u}{dt} = K_u \cdot X_0 \cdot e^{-K_e t}$

$dx_u = K_u \cdot X_0 \cdot e^{-K_e t} \cdot dt$, integration, $\int_0^{\infty}$

$\int_0^{\infty} x_u = K_u \cdot X_0 \int_0^{\infty} e^{-K_e t} \cdot dt$

$[x_u]_0^t = K_u \cdot X_0 \cdot \left[\frac{e^{-K_e \cdot t}}{-K_e}\right]_0^t$ $\quad e^0 = 1$

$= K_u \cdot X_0 \left[\frac{e^{-K_e t}}{-K_e} - \frac{1}{-K_e}\right]$

$\frac{K_u \cdot X_0}{K_e} = [1 - e^{-K_e t}]$

when $t \to \infty$

$e^{\infty} = 0$

Pharmaceutical alternative //
dosage مختلف , AI نفس ; نفس

The rate and extent of drug absorption and becomes available in blood ...

1) Development of new form ... (m) ...
2) Dete... of ... (O) Bioequivalence //
3) Determ... of ... bioavailability , نفس
... المادة الفعالة بنفس ...

$$\frac{[C_{oral}]_0^{\infty}}{[I.v]_0^{\infty}} \times \frac{dose\ (I.v)}{dose\ (oral)}$$ Amount , $\frac{[extravascular]_0^{\infty}}{[I.v]_0^{\infty}}$, مقارنة

system , دخول
rel

Pharmaceutical equivalent
Drugs (group)
dosage نفس AI نفس
1, 2, 3 therapeutic activity , نفس
Standard
reference , Brand
① Tetracycline + Antacid (↓ absorption)
② Adsorbent ... + ... (↓ absorption)

$$\frac{K_a}{K_e} \times \frac{1}{K_a - K_e} = t_{max}$$

Mineral oil + liposoluble vit → ↓ Abs
Metoclopramide + Paracetamol → ↑ Abs.

data from Plasma conc curve

Therapeutic alternative

$$A \frac{K_a}{K_a - K_e}\left(e^{-K_e \cdot t_{max}} - e^{-K_a \cdot t_{max}}\right) = C_{max}$$

Therapeutic equivalent //
dosage ... نفس

$$\frac{F \cdot X_0}{Vd \cdot K_e}$$

the same extents with different rates
the same rate with different extent
the extent increased

[7 / Jan. 2020]

write by equations only , the assessment from Plasma data

21 / Jan / 2

$$K_u \cdot X_0 \cdot e^{-K_e t} = \frac{dX_u}{dt}$$ Rate of excretion via urine

(15)

$$[AUC]_0^{\infty} = \frac{h}{3}(E + 2P + 4I)$$

⊛ two or more drugs with identical AI and the same dosage form different in the characters (taste, shape, color, packaging or expire date)

$$\frac{C_{n-1} + C_n}{2}$$ + C Last / Ke

(1) $X_0 = 500\ mg$, $Vd = 21L\ (21000mL)$
$t_{1/2} = 6\ hrs$, $X_u^{\infty} = 400\ mg$.

① f_u ?
② K_e, Cl_r, $TBCl$ and Cl_m ?

① $f_u = \frac{X_u^{\infty}}{X_0} = \frac{400}{500} = 0,8$

معناها ٪80 صار elimination لهذه drug
بعد 48 ساعة

② - $K_e = \frac{0,693}{t_{1/2}} = \frac{0,693}{6} = 0,1155\ hr^{-1}$

- $Cl_r = Vd \cdot K_u$

كيف أحسب K_u ؟

$K_u = f_u * K_e$
$= 0,8 * 0,1155$
$\therefore K_u = 0,0924\ hr^{-1}$

$\therefore Cl_r = K_u \cdot Vd = 0,0924 * 21$
$= 1,9404\ L/hr$

$TBCl = K_e \cdot Vd = 0,1155 * 21$
$= 2,4255\ L/hr$

$Cl_m = TBCl - Cl_r$
$= 2,425 - 1,9404$
$= 0,4846\ L/hr$

[2] t = 5 hrs , (I.V bolus) one compartment , X_0 = 300 mg

CP = 3 ug/ml (3 mg/L)
Vd = 12 L (12000 mL)
Clr = 3 L/hr.

Calculate the maximum amount of drug excreted by urine (X_u^∞) ?

$$X_u^\infty = \frac{K_u}{K_e} X_0 \quad K_u ? \quad K_e ?$$

$$C_0 = \frac{X_0}{Vd} = \frac{300 (mg)}{12 (L)} = 25 \text{ mg/L}$$

I.V bolus One Compart ل Ke نحسب من العلاقة التي نعرفها

$$\ln(CP) = \ln C_0 - K_e \cdot t$$
$$\ln 3 = \ln 25 - K_e \cdot 5$$
$$1 = 3.218 - K_e \cdot 5 \Rightarrow K_e = 0.424 \text{ hr}^{-1}$$

$$Clr = K_u \cdot Vd$$
$$3 \frac{(mg)}{L} = 12 L \cdot K_u \Rightarrow K_u = \frac{3}{12} = 0.25 \text{ hr}^{-1}$$

$$X_u^\infty = \frac{K_u}{K_e} \cdot X_0$$

$$= \frac{0.25}{0.424} * 300$$

$$\therefore X_u^\infty = 176.8 \text{ mg}$$

// ملاحظة

$$X_u^\infty = f_u \cdot X_0$$
$$f_u = \frac{X_u}{X_0} = \frac{K_u}{K_e}$$

Mohammad Shoaib Al Fama

$CLT = Cl_r + Cl_m + Cl_{extra}$

$Vd \cdot K_e = K_u \cdot Vd + K_m \cdot Vd + K_{extra} \cdot Vd$

$K_e = 0.693 / t_{1/2}$

$f_u = X_u^{\infty} / X_0$, $f_m = X_m^{\infty} / X_0$, $f_{extra} = X_{extra}^{\infty} / X_0$

$K_u = f_u \cdot K_e$, $K_m = f_m \cdot K_e$, $K_{extra} = f_{extra} \cdot K_e$

(*) هدول بيجوا فكرة سؤال حسابي مهم جداً
لازم تكونوا حافظينهم .

$f_u + f_m + f_{extra} = 1$

(*) آلية الكلية Possible mechanisms of renal excretion :-

① بنحسب ال cl drug

② بنطبق العلاقة الآتية /

renal clearance عبر ← $\frac{Cl\ drug}{130}$ ⇒ ع.ت

- $= 1$ → only filtration
- < 1 → Filtration and reabsorption
- > 1 → Filtration + Secretion

(*) طريقة ثانية لتحديد mechanism الإخراج /

$\frac{Cl_r}{GFR \cdot \alpha}$ = ع.ت

- $1 =$ → Filtration only
- > 1 → Filtration + Secretion
- < 1 → Filtration + reabsorption

α : free particles of drug

$\frac{X_u^{\infty}}{[AUC]_0^{\infty}} = Cl_r$

حساب K_4 ؟

$$\frac{\Delta X_4}{\Delta t} = K_4 \cdot X_0 \cdot e^{-K_e \cdot t_i}$$

من قانون //

كيف نحسب الـ K_e ؟

من قانون /

$$\frac{\ln\left[\frac{\Delta X_4}{\Delta t}\right]_2 - \ln\left[\frac{\Delta X_4}{\Delta t}\right]_1}{t_{i2} - t_{i1}}$$

كيف نحسب الـ t_i ؟

$$\frac{t_1 + t_2}{2}$$

t_1: الحد الأول للـ interval

t_2: الحد الثاني للـ interval

حساب الـ X_4^{∞} //

$$X_4^{\infty} = \frac{K_4}{K_e} \cdot X_0$$

while $\frac{K_4}{K_e} = f_4$ so $X_4^{\infty} = f_4 \cdot X_0$

ويمكن نعتبر الـ K_4 مجهول ونستخدم القانون لإيجاده //

$$\frac{X_4^{\infty} \cdot K_e}{X_0} = K_4$$

$$X_4^{\infty} = \frac{K_4}{K_e}$$

حيث أنه

$$f_4 = \frac{X_4^{\infty}}{X_0}$$

so $K_4 = f_4 \cdot K_e$

70 Kg

0,5	40,2
1,5	37,5
3,1	34,9
4,5	30,5

$$\frac{\ln\left(\frac{\Delta x_1}{\Delta t}\right)_2 - \ln\left(\frac{\Delta x_1}{\Delta t}\right)_2}{t_{i2} - t_{i1}} = \frac{\ln(37,5) - \ln(40,2)}{1,5 - 0,5\ (1)}$$

$$\frac{3,62 - 3,693}{1} = \boxed{0,673\ hr^{-1}}$$

3 mL/min

$$\frac{3 * 10^{-3}}{30} =$$