بسم الله :

IV infusion dosing

PK theory lec. 7 & 8

* في أدوية بدل التأثير تاعها
يكون لفترة طويلة
وبالتالي لازم يضل
بالدم لطول فترة

IV bolus يعطى خلال time zero. [دخل الدوا كله مع بعض]

Introduction

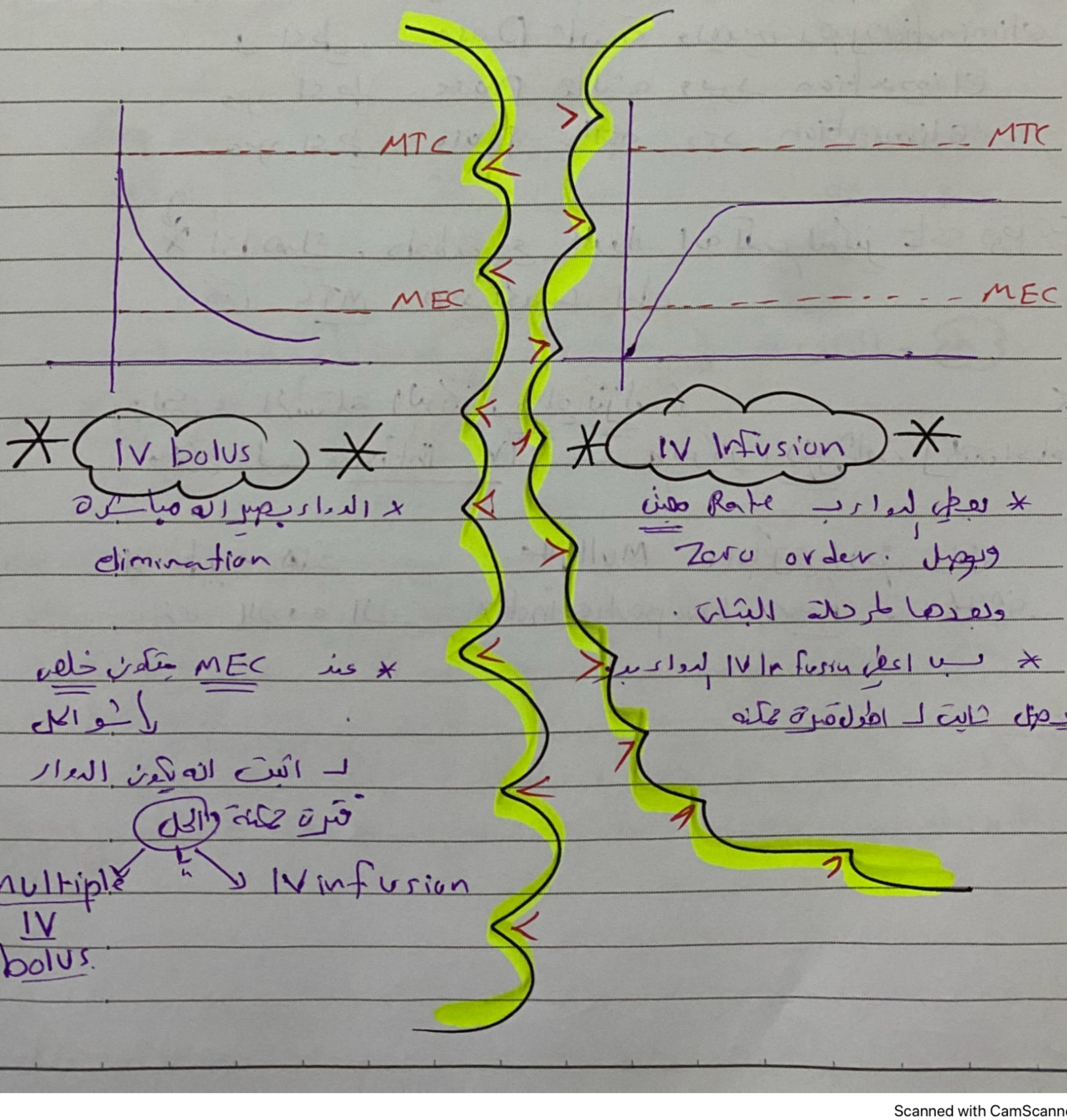
- While a single intravenous bolus dose of a drug may produce the desired therapeutic concentration and, therefore, the desired pharmacological effect immediately, this mode of administration is unsuitable when it is necessary to maintain plasma or tissue concentrations at a concentration that will prolong the duration of its action.
- One way of achieving this target is utilizing intravenous infusions. It is common practice in the hospital setting to infuse a drug at a constant rate (constant rate input or zero-order input), which permits precise and readily controlled drug administration to fit individual needs.
- IV infusion can maintain an effective constant plasma drug concentration by eliminating wide fluctuations between the peak (maximum) and trough (minimum) plasma drug concentration.

Lecture 7+8

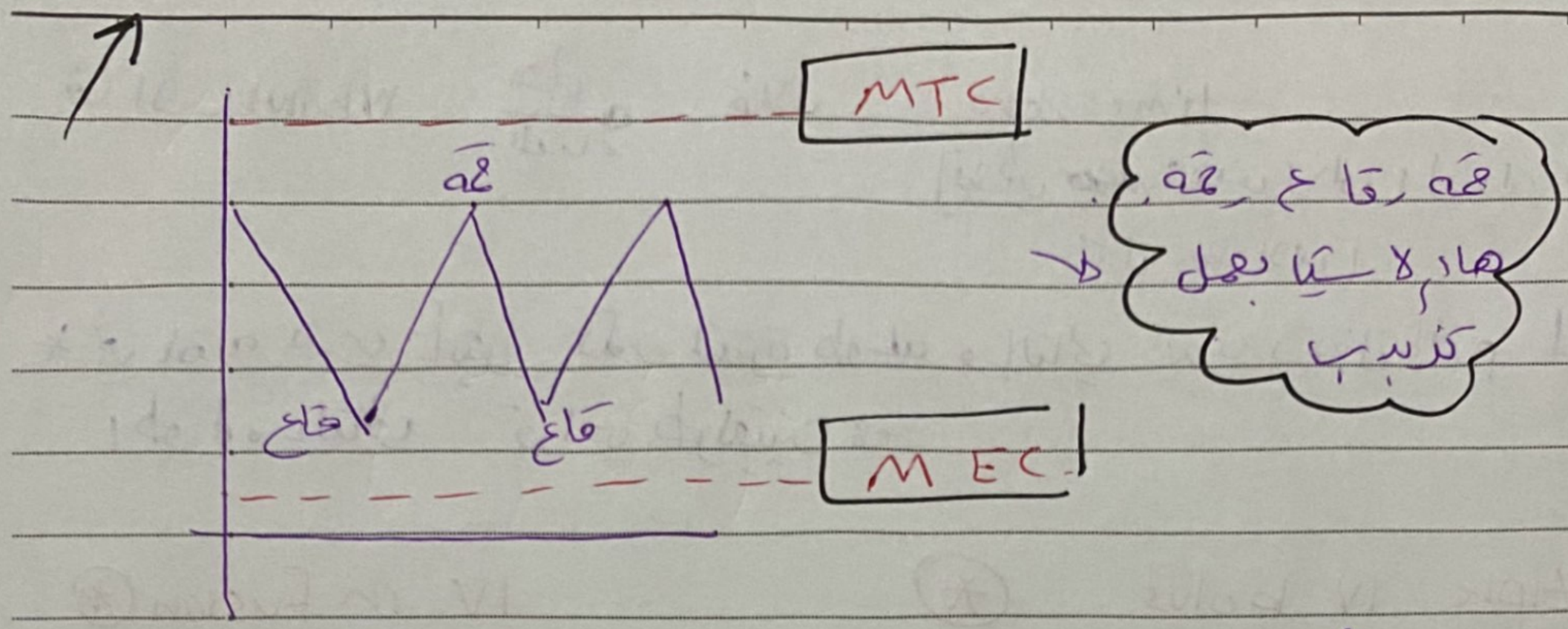
في الـ IV bolus يعطى الدواء خلال time zero
[يعطى بعض الدواء يدخل كله مع بعض]

* في ادويه بدي تأثير تكون لفترة طويله وبالتالي بدي يدخل بالدم لفترة طويله بالتالي فرامي طريقتين :-

multiple IV bolus (*) IV in fusion (*)



Multiple IV bolus هادا سمة



* أول مرة اعطيت الـ Dose قبل ما توصل MEC
بدا اعطي Dose ثانية وبعدين بصير elimination
وبدا اعطي Dose ثالثة وبدا elimination
وبدا اعطي Dose رابعة وبدا elimination

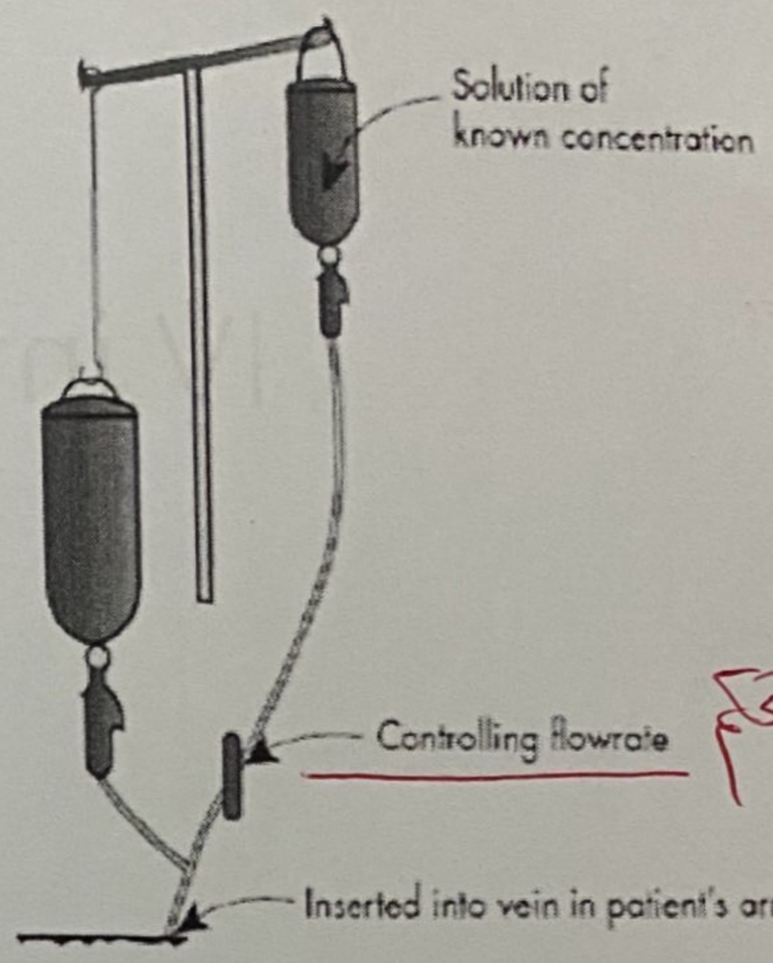
* أنا هيك حافظة ع الدواء انه لكون لتركيز تاعه فوق MEC
كتير MTC وهاد الي بدي اياه

Peak ← ولكن ٤- المشكلة التركيز بطلع بنزل)
ولكن بالـ IV infusion التركيز بضل ثابت (كتير احلى ع

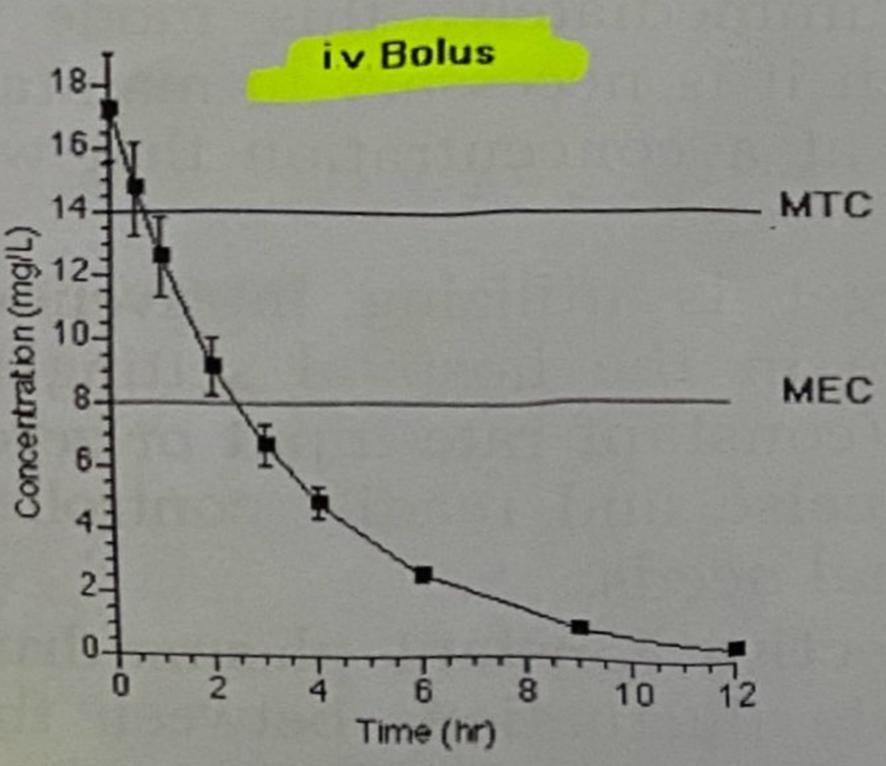
* طيب هاد Multiple. ما بأثر ع مريض. ولكن
زي الادوية الـ narr therapeutic index كتير كارثة.

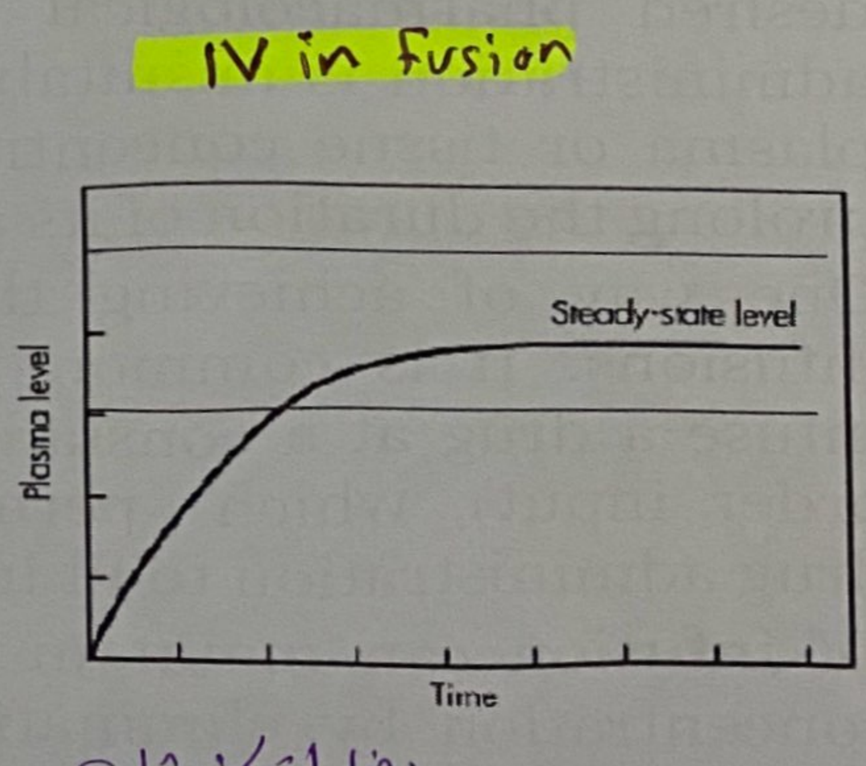
Introduction

- The infusion rate of a drug is controlled by:
  1. flow rate (e.g., mL h^{-1})
  2. concentration (g mL^{-1}, %w/v, etc.) of the drug in solution.
- *Flow rate* is controlled by adjusting the height of an infusion bottle or by regulating the aperture size of the tube that connects the bottle to the needle. When greater precision and control of drug administration is desired, an infusion pump is used.



One compartment IV bolus vs IV infusion





One compartment IV infusion

- Gradual increase in plasma concentration from zero to maximum allows precise control of drug levels. This is especially important for drugs with narrow therapeutic windows
- i.v. infusion maintains an effective constant plasma drug concentration by eliminating wide fluctuations between the peak (maximum) and trough (minimum) plasma drug concentration
- Infused drugs may be given with i.v. fluids including electrolytes and nutrients
- Duration of drug therapy may be maintained or terminated as needed using i.v. infusion

Cont,

- At zero time: no drug present in the body
- Drug is infused in a zero-order rate
- Amount of drug in the plasma increases gradually (in constant rate/zero-order), then elimination process starts at a first-order rate.
- At any given time: the amount of the drug in the body will be subject to two opposing forces (kinetics); the input function and the various first order elimination processes (output)

i.v. infusion (compared to i.v. bolus routes):

- Initially, the plasma concentration is very low thus the elimination rate is low and as a result infusion rate will be significantly higher than the elimination rate → drug accumulates in the body
- With time the quantity of drug in body increases, which leads to an increase in the elimination rate. But since the input function (K_o) is constant, the rate of drug build-up in the body decrease
- When rate of infusion = rate of drug elimination → constant amount of drug in the body. This is called *steady-state* level or *plateau* where rate of change in drug level = zero ($dC_p/dt = 0$)

Cont,

- dX/dt = rate of infusion − rate of elimination

$$\boxed{\frac{dX}{dt} = K0 - kX}$$

$$\frac{dX}{dt} = k_0 - kX$$

- K_o: infusion rate constant
- K: elimination rate constant
- X: amount of drug in the body

Cont,

$$\frac{dX}{dt} = k_0 - kX$$

$$\frac{dC}{dt} = k_0 - k(C \ * V_D)$$

$$dC = k_0 - k(C \ * V_D) * dt$$

$$C = \frac{k_0}{V_D * k} (1 - e^{-kt})$$

ع الدفتر، (الخط المستقيم الثابت)

Steady state condition

- Prior to the attainment of a true steady-state condition, the rate of infusion is always greater than the rate of elimination (i.e., Ko> KX) and only at true steady state does Ko= KX.
- As time elapses and reaches infinity, the value of e^{-kt} becomes very small and approaches zero, so the equation is reduced to: $$C_{ss} = \frac{k_0}{V_D * k}$$
- C_{ss} is called steady state plasma concentration

$$C_{ss} = \frac{k_0}{Cl}$$

- So, steady state depends on infusion rate and total body clearance $$k_0 = C_{ss} * (k * VD)$$

Cont,

- If we substitute amount for concentration:

$$k_0 = C_{ss} * (k * VD)$$

$$\boxed{k_0 = X_{ss} * k}$$

- We, again, reached the assumption that at steady state rate of infusion = rate of elimination
- Xss = amount of drug in the body at steady-state

* لما أوصل الـ Steady state بكون هنا Rate in = Rate out

قبل ما أوصل الـ Steady state بكون هنا Rate in أعلى وهاد الاشي صح

لانه بدي k_0 دائماً يكون أعلى من Kx عشان الدواء يضل يزيد

الـ Conc و [لانه عارفين قصدي كيف؟ يعني أنا بدي يوصل لـ Conc الي انا بدي اياه فـ ع الأكيد انا بدي اياه يضلها يزيد.]

Cont,

أنا عرفت انه الدواء بطلوع شكل First order وأنا بعرف الي بتحكم فيه Kx

اشتقاق قانون

هون انتبهوا: قيمة X K ثابتة

$$k_0 = C_{ss} * (k * VD) \qquad k_0 = X_{ss} * k$$

لانه X هون مش زي الـ IV bolus! قاعدة وتتناقص لانه انا قاعد بدخل الدواء ع الجسم، وكل ما يزيد ↑k X↑ وبالتالي بتزيد فيه الـ Rate out وبعدها Rate in وهاد الي بصلح.

To determine

- the amount of the drug at steady state, you need to know (K_0) the infusion rate ① and elimination rate constant ② K
- Css, you need to know clearance and infusion rate

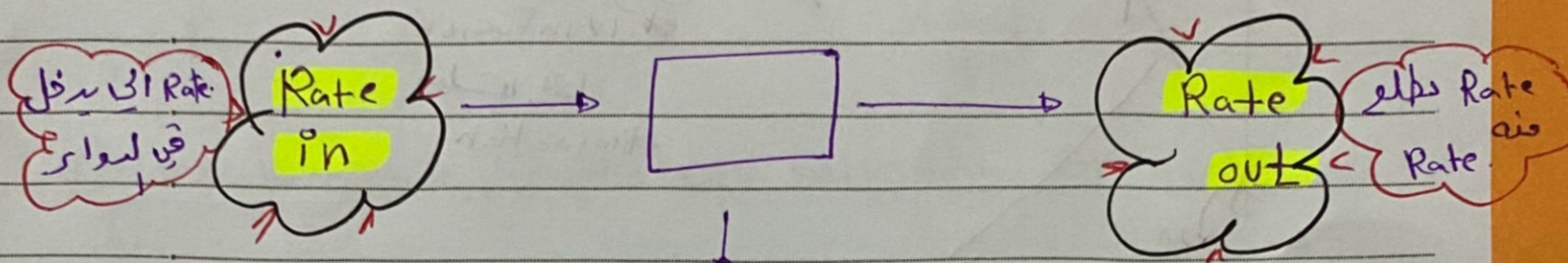
لو هكالي احدد الـ amount steady state المطلوب مني → K_0, K

- It could be concluded that:
- all drugs that have the same clearance and are infused at the same rate, have the same C_{ss}
- the amount of the dug in the body at plateau is the same for drugs that are infused at the same rate and have the same half life (the same k)

انه الدواء بضل يتراكم وتزيد فيه X (K_0 − Kx)

* في الـ (IV bolus) ← دخلت الدواء كله مع بعضه
وبطلع بـ First order وما وصل constant.

* في الـ (IV infusion) ← ما دخلت الدواء كامل (دخلته بـ Rate)



تبع الـ Zero order

$$\frac{dx}{dt} = k_0$$

(IV infusion)

$$\frac{dx}{dt} = k_0 - kx$$

تبع الـ First order

$$\frac{dx}{dt} = kx$$

* وبالتالي عند 2 Forces بتتحكم بالدواء :-

(1) Rate in

(2) Rate out

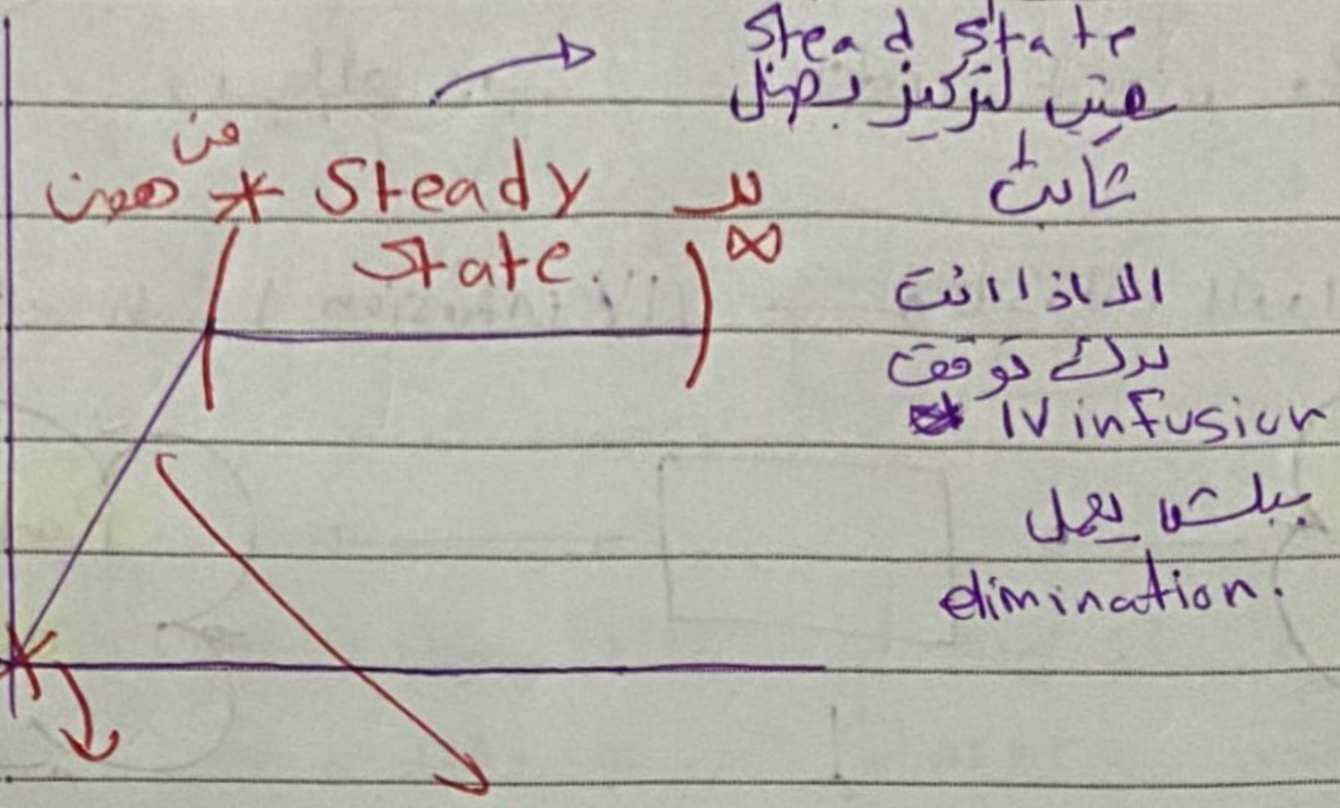
(First order: rate out) الي بتحكم في

* الاشي الي بتحكم في IV bolus ← elimination
* الاشيا الي بتحكم في IV infusion ← ∴ Rate (in) , Rate (out)

* في (oral) كل الدواء بطلع ع شكل First order

∴ (x) in rate سواء (oral أو bolus أو infusion) ← بطلع ع شكل First order

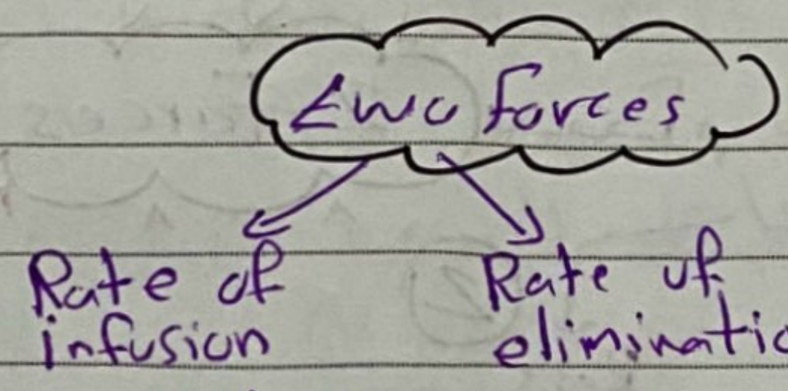
Steady State Condition :-



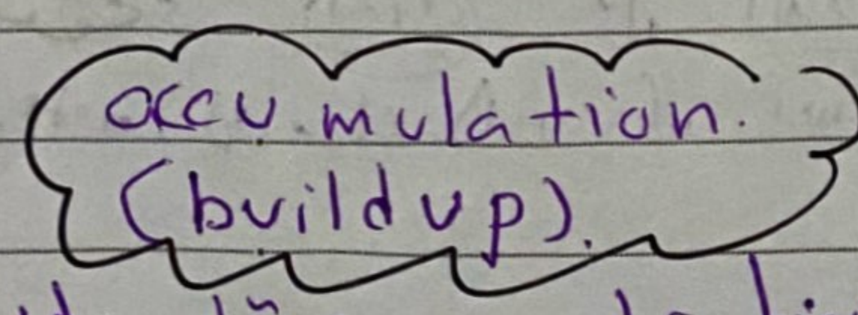
هاي الحالة بتكون
Steady state
هيي لتركيز بضل
ثابت
الا اذا انت
بدك توقف
* IV infusion
بيلش يعمل
elimination.

$t = 0$ هاي بتخلي هاد الرسم
$C = 0$

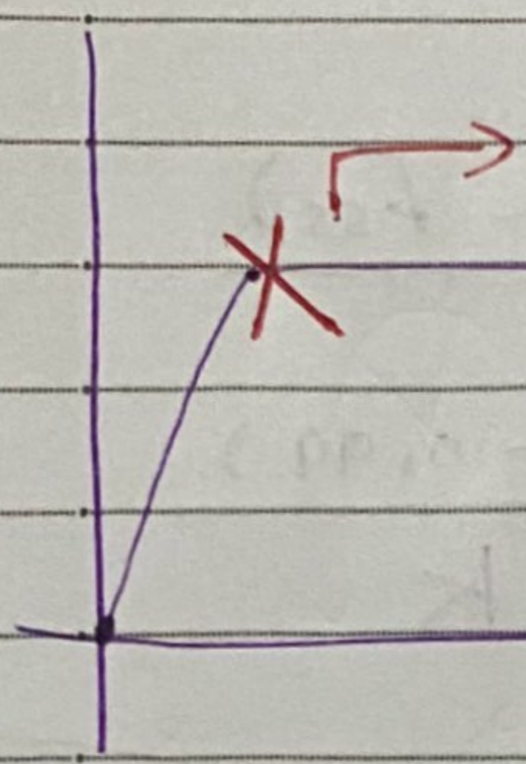
(بيلش يعمل شغل)
هون عرف انه الي
بيتحكم بالدواء
$$\frac{dx}{dt} = K_0 - AX$$



* بمرحلة لزيادة بيدخل للدواء بمرحلة الـ Zero order
وبالتالي الـ Plasma conc قاعد بطلع ، بالتالي
الـ amount قاعدة بتزيد
بين K_0 عاعطيت مريلة (KX)
(Rate of infusion) أكبر من (Rate of elimination)
بهيك بيصير



وهاد بيعني انه رح يصير
وهاد بفسرلي ليه الـ concentration قاعد بطلع.
(داخل خلايا) لا تتزيد وانتقل K_0 وقت
الأشيا الوحيدة اللي بصير
* أنه كل مالها بحجم (X) بتزيد لانه
الـ amount of drug داخل الـ blood بتزيد دال conc بتزيد وهاد طبعي
(لانه الدواء قاعد بتراكم جوى داخل الجسم) K_0 بتزيد



* سارفين هاي الدفعه بكون عندي
داخل اكبر تحميه من الدواء وهل عندي
قيمه x بس اصغر شوي من k وقاري Ko

$$[\ Kx = Ko\ ]$$

$$\frac{dx}{dt} =$$

بيكون Zero ماقي اي تفير ع الدواء اللي دخل كم وقتها بكون عندي

↳ Ko rate of infution = rate elimination

وبهذل ثابت لـ (∞)

أوتيه لـ هون

$$C = \frac{Ko}{CL}\ (1 - e^{-KE})$$

قبل الـ Steady State

$$Css = \frac{Ko}{CL}$$

بعد الـ Steady State

اذا فهمتوا علي ادعولي
واذا ما فهمتوا برضو
عادي ادعولي

☺

$K_0 = ?$ $C_{ss} = 5$

$X_{ss} = ?$ $CL = 44$

$K = 0.21$

xample

The desired steady state for ciprofloxacin is 5 mg/L, clearance of the drug is 44 L/hr, elimination rate constant = 0.21 hr^{-1}. Determine the required infusion rate and amount of drug at steady state?

$$k_0 = X_{ss} * k$$

$$C_{ss} = \frac{k_0}{Cl}$$

- K_0 = 5 mg/L * 44 L/hr → K_0 = 220 mg/hr
- Xss = (220 mg/hr)/0.21 hr^{-1} → Xss = 46.2 mg
- Or Cl = k*VD → VD = 0.21*44 = 9.24.
- Css * VD = Xss → Xss = 5 * 9.24 = 46.2mg

$C_{ss} = \frac{K_0}{CL}$

$5 = \frac{K_0}{44}$

$K_0 = 220$

$K_0 = X_{ss} \times K$

$220 = X_{ss} \times 0.21$

$= 46.2$

هاد حكي كنا حكينا قبل

Fraction riming $= (\frac{1}{2})^n$ → $t/t_{1/2}$

Fractio eliminted = 1 − F

Fraction achieved of steady state concentration (F_{ss})

كم النسبة الي قدرت احصلها من Steady State

$$C = \frac{K_0}{KVd}(1 - e^{-Kt})$$

since $C_{ss} = K_0 / KVd$ previous equation can be represented as:

Fraction reming = zero بال حال طلع كامل منجسم.

* هون ما في elimination فيه عنا build up فبطلب مني كم النسبة الي انت حصلتها من steady state.

$$C = C_{ss}(1 - e^{-Kt})$$

$$\Rightarrow F_{ss} = \frac{C}{C_{ss}} = 1 - e^{-Kt}$$

$$\Rightarrow F_{ss} = 1 - e^{-t \cdot \frac{\ln(2)}{t_{1/2}}} = 1 - \left(\frac{1}{2}\right)^{\frac{t}{t_{0.5}}}$$

ال steady state حصل عليها لتكون 100% فقط عند ∞

$$F_{ss} = 1 - \left(\frac{1}{2}\right)^{\frac{t}{t_{0.5}}} \quad \text{or} \quad F_{ss} = 1 - e^{-Kt}$$

لو وصلت 95% واعلى مقبول ولكن هيك لا انا وصلت steady state. زي لما كنا نحكي بال IV bolus بس يطلع 99% هاد مقبول

Example

- A drug with an elimination half life of 10 hrs. Assuming that it follows a one compartment pharmacokinetics, fill the following table:

Time	F_{ss}
10	1
30	3
50	5
70	7
90	9

$f_{ss} \rightarrow 1-\left(\frac{1}{2}\right)^n$.

Time	Number of elapsed half-lives	F_{ss}
10	1	0.5
30	3	0.875
50	5	0.969
70	7	0.992
90	9	0.998

Time required to reach C_{ss}

$$C = \frac{k_0}{V_D * k}\ (1-e^{-kt})$$

- After very long time of infusion (~ infinity), Css is theoretically reached
- However, the time to reach 90%, 95%, and 99% of the steady-state drug concentration, C_{ss}, can be calculated by applying in above equation
- At ~ 5 half-lives: 95% of the C_{ss} is reached
- At ~ 7 half –lives: 99% of the C_{ss} is reached

* حالة الي بزيد فيها Ko حتى نزيد half live اذا بدي اوصل للـ effected المطلوب. (لبعد سلامين يجعلها مش هون)

...me required to reach C_{ss}

$$C = \frac{k_0}{V_D * k}(1 - e^{-kt}) \qquad \frac{C}{C_{ss}} = (1 - e^{-kt})$$

$$C = C_{ss}(1 - e^{-kt})$$

$$1 - F_{ss} = e^{-kt}$$

$$F_{ss} = (1 - e^{-kt})$$

$$t = -\frac{\ln(1 - F_{ss})}{k}$$

$$-kt = \ln(1 - F_{ss})$$

$$t = \frac{-t_{1/2}\ln(1 - F_{ss})}{0.693}$$

هاد لحال تون يحكيلي الوقت الي بحتاجو لـ اوصل الـ Steady State.

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

فش غير هاد المجهول

We can conclude that half-life of a drug is the **only** factor that determines the time to reach any fraction from steady state

* الـ Ko ما بيتحكم بالوقت الي رح أوصل فيه لـ Steady State الاشيا الوحيد الي بتحكم لوصولك لـ Steady State هو فقط t1/2

يعني مثال :- لو حكالي كنت نعطي دواء ما معين لـ 5mg/hr ، وحكالي بالسؤال انا مستعجل اوصل لـ steadystate بسرع وقت ف انا مجبور اوصل 5mg/h لـ ⟵ 10 mg/h هلا رح اوصل لـ steady state ؟ ✗ ، والسبب زي ما حكينا فوق اوكيه !!

Example

Ceftizoxime has a volume of distribution of 20 L and effective steady state level ≥ 24 μg/ml. If you know that time required to reach 99% of steady state is 15 hours. Determine infusion rate needed to maintain this concentration?

المعطيات :-
Vd = 20 L
Css = ≥ 24 mg/ml
Fss 99% of steady state
↳ 15 hours
(t)

$$C_{ss} = \frac{k_0}{V_D * k} \qquad t = -\frac{\ln(1 - F_{ss})}{k}$$

ع الدفتر

- k =- ln(1-Fss)/t → k = -ln (0.01)/15 → k = 0.3 hr-1
- K0 = Css * VD * k → k0 = 24 μg/ml * 20000 ml * 0.31 hr-1 → k0 = 144000 μg/hr=149 mg/hr

$$C_{ss} = \frac{K_0}{VD \times K}$$

مجهول السؤال

$$C_{ss} = \frac{K_0}{V_D \times K}$$

$$t = \frac{\ln(1 - f_{ss})}{k}$$

$$24 = \frac{k_0}{20 \times K}$$

$$15 = \frac{\ln(1 - 0.99)}{k}$$

$$2000\ mcg/mg$$

$$24 = \frac{k}{20 \times 0.307}$$

$$k = 1 \cdot \frac{0.01}{15} = 0.307\ hr^{-1}$$

$$k = 142\ mg/hr.$$

Example

آخر half lives لأوصل 95%

- What is the minimum number of half lives needed to achieve at least 95% of steady state?

- At least (5) half lives (not 4) are needed to get to 95% of steady state

طيب ... متى ازيد Ko ؟

① الحالة الي بزيد فيها Ko لحتى يزيد عدد الـ half live هي لما بدي أوصل لـ effected المطلوب.

② اذا المشتقا، انا نعطي للدواء، انه الدواء قاعد يعمل (accumulation) عالي وطلع التركيز لـ minimum toxic وبهاي الحالة بنزل (Ko)

Changing infusion rate (k_0)

- Why we may change rate of infusion?
  - (1) Inadequate pharmacologic response
  - (2) or toxicities
- After changing the infusion rate the time required to reach the new steady state will depend on half-life

Determination of k from Css

1. From data during infusion using clearance. This is the preferred method to determine k

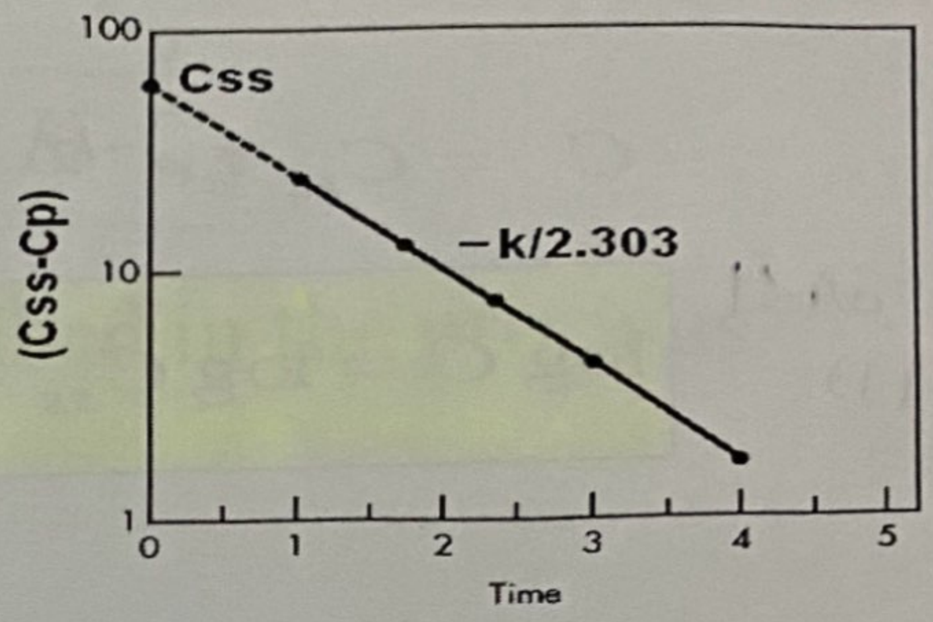
$$C_{ss} = \frac{k_0}{Cl}$$

$$C = \frac{k_0}{V_D * k} \quad (1 - e^{-kt})$$

$$C_{ss} = \frac{k_0}{V_D * k}$$

$$C = C_{ss}(1 - e^{-kt})$$

$$\log(C_{ss} - C) = \log C_{ss} - \frac{kt}{2.303}$$



k is determined during infusion from the slope of log(Css-Cp) vs time

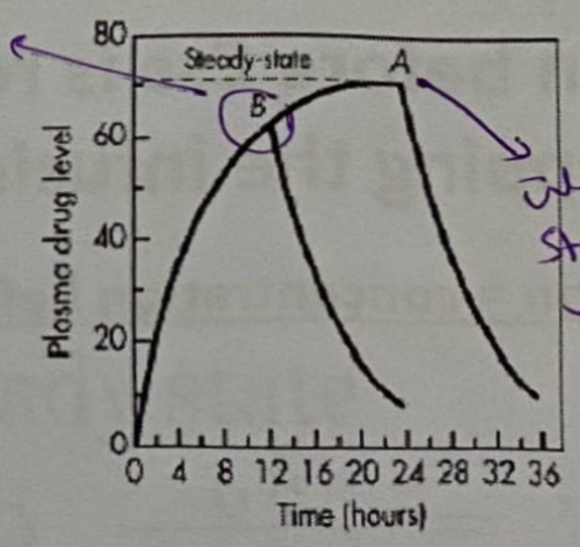
Determination of k from Css post infusion

Post-infusion

- Once the infusion is stopped (point A or B), the amount of drug in the body falls by first order kinetic elimination. C at any time post infusion can be obtained from the following equation

$$C = Clast * e^{-kt}$$

Clast: Conc الى هو اخر



- Two cases:
  - Cessation of infusion after Css is reached (A point on the plot)
  - Cessation of infusion before Css is reached (B point on the plot)

Post-infusion after Css is reached C_{last}= Css

- Concentration = steady state concentration * first order decline

$$\frac{dX_B}{dt} = -kX$$

$$C = \frac{k_0}{V_D * k} \quad e^{-kt}$$

$$X_B = X_B^0 e^{-kt}$$

$$C = C_{ss} * e^{-kt}$$

الحالة (1)

$$\log C = \log C_{ss} - \frac{kt}{2.303}$$

t: time elapsed after the stop of infusion

Determination of k from Css post infusion

Post-infusion before Css is reached C_{last}= C (at any time prior stopping the infusion

- Concentration = concentration before reaching steady state * first order decline

$$C = \frac{k_0}{V_D * k} \quad (1 - e^{-kT}) * e^{-kt}$$

الحالة (2)

$$\log C = \log \frac{k_0}{V_D * k}(1 - e^{-kT}) - \frac{kt}{2.303}$$

(infusion, elimination)

اذا وقفت قبل ما يوصل Steady State.

Where T = infusion time and

t = time during the declining phase (postinfusion)

olume of distribution calculation using post nfusion data

- If you reached steady state conc ($C^* = C_{SS}$):

$$C_{ss} = \frac{K_0}{K \cdot Vd} \Rightarrow Vd = \frac{K_0}{K \cdot C_{ss}}$$

- where k is estimated as described in the previous slide

Volume of distribution calculation using post infusion data

- If you did not reached steady state ($C^* = C_{SS}(1\text{-}e^{-kT})$):

$$C^* = \frac{k_0}{k \cdot Vd}(1 - e^{-kT}) \Rightarrow Vd = \frac{k_0}{k \cdot C^*}(1 - e^{-kT})$$