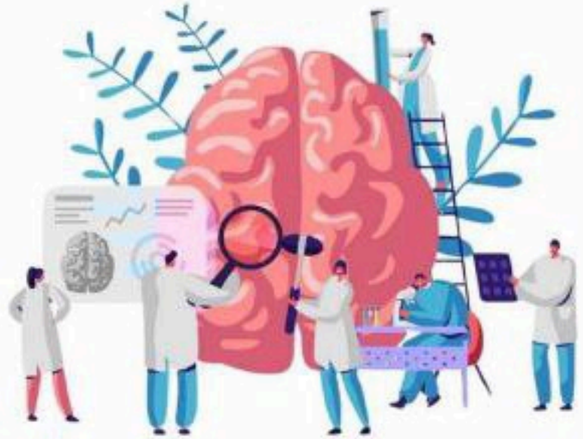


تفريغ لحاينتك

محاضرة: *IV Infusion Dosing lec7&8*

الصيدلاني\ة: *Alaa Otoum*

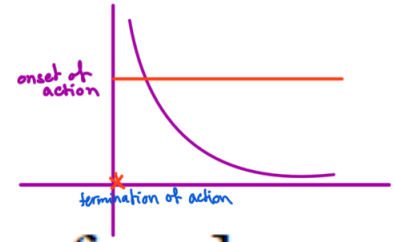
لجان الدُّفعات

Soul Academy

IV infusion dosing

PK theory lec. 7 & 8

Introduction



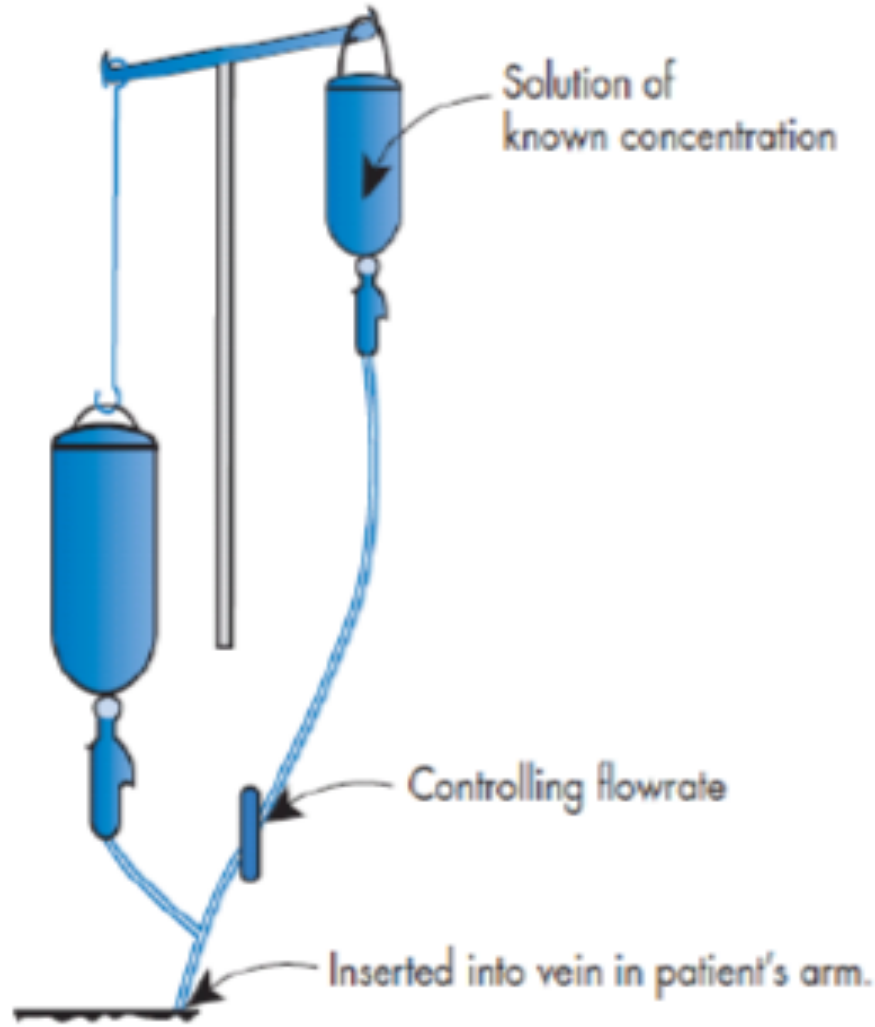
- While a single intravenous bolus dose of a drug may produce the desired therapeutic concentration and, therefore, the desired pharmacological effect immediately, this mode of administration is unsuitable when it is necessary to maintain plasma or tissue concentrations at a concentration that will prolong 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.

Introduction

- The infusion rate of a drug is controlled by:
- flow rate (e.g., mL h^{-1}) معدل التدفق
- concentration (g mL^{-1},%w/v, etc.) of the drug in solution.
- *Flow rate* is controlled by adjusting the height of an infusion bottle ① (gravity) or by regulating the aperture size ② 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.

حجم الفتحة

more precise لأدوية معينة فيكون very specific أحيانا لازم تكون

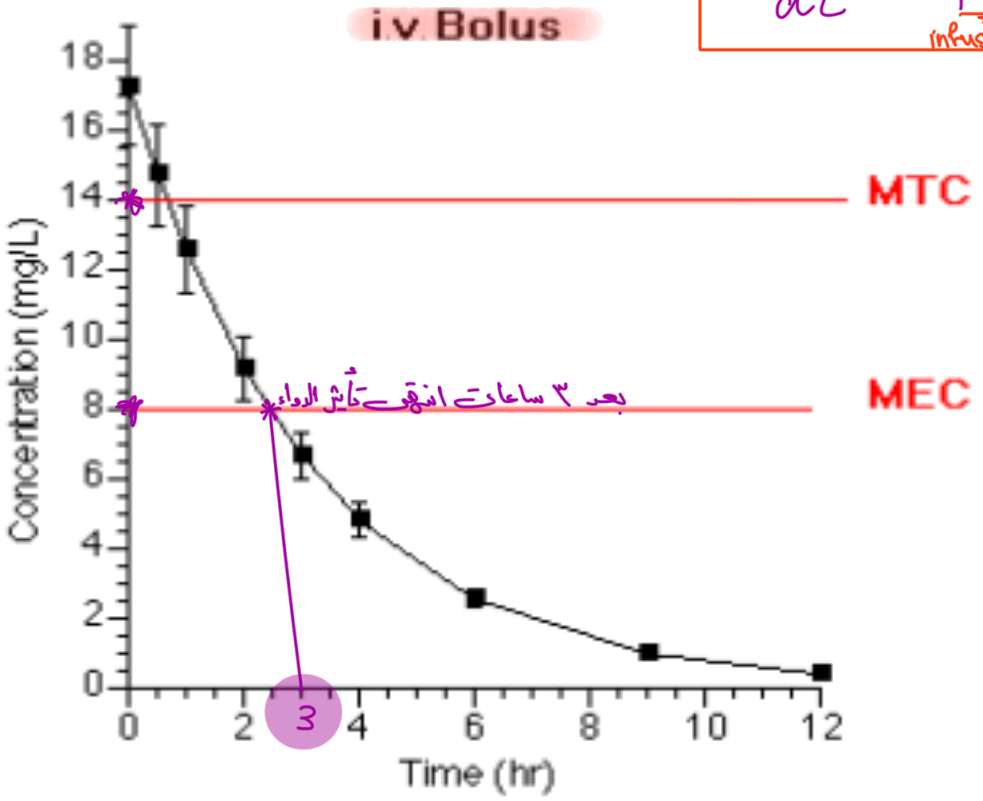


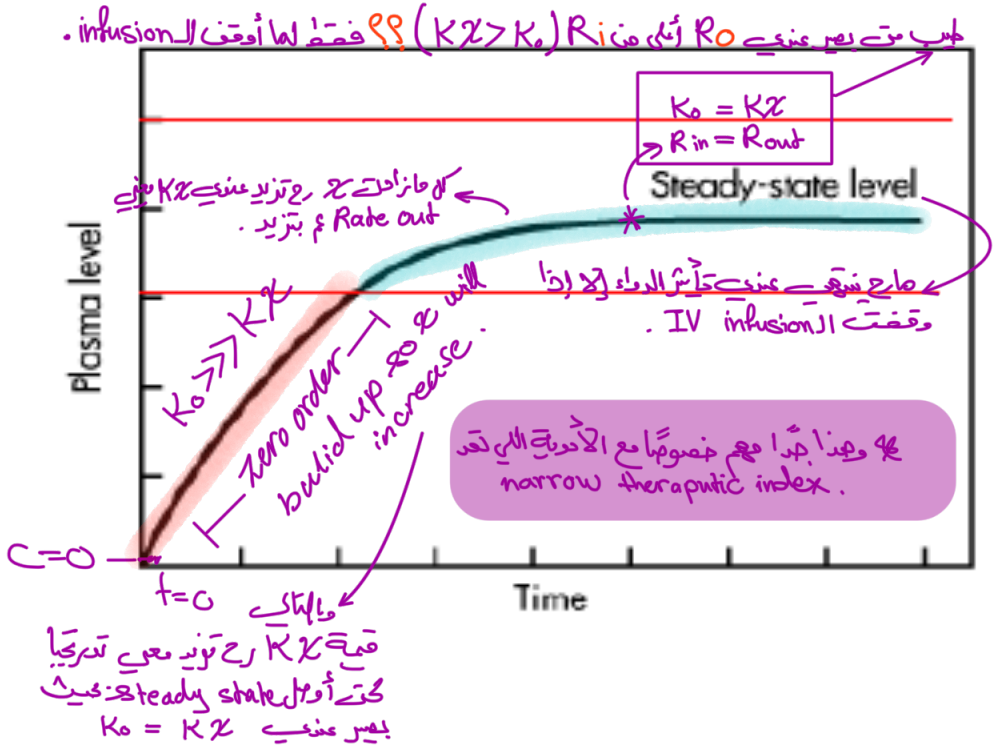
One compartment IV bolus vs IV infusion

$$\frac{dx}{dt} = R_{in} - R_{out} = K_0 - Kx$$

R_{in}: zero order — infusion rate

R_{out}: first order — elimination rate

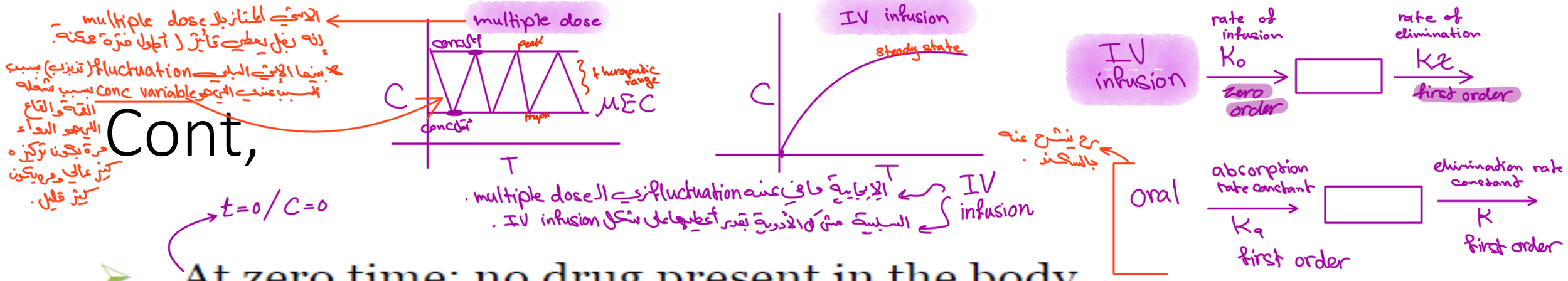




One compartment IV infusion

- 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

  (Kx — $K_o \gg Kx$)

- 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

  (input → infusion rate)

  * مشروح هذا الكلام على الرسمة اليمين بسلايد 4

- 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 ($dC_p/dt = 0$)

  ($K_o = Kx$ & $K_{in} = K_{out}$ and this occure after (5-7)T half)

Cont,

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

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

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

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

Cont,

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

Conc * volume

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

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

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

$V_D * k$ → Cl

$(1 - e^{-kt})$ ليش مكينا $(1-e^{-kt})$ لأنه أناموت بيكي accumulation نفس ما مكينا في شابتر urine.

Steady state condition

قبل الوصول

- 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:

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

- C_{ss} is called steady state plasma concentration

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

- So, steady state depends on infusion rate and total body clearance

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

Cont,

- If we substitute amount for concentration:

conc * volume
Css * Vd

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

Zero order first order

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

$X_{ss} = C_{ss} * VD$

* زي ما شفنا هي فقط في حالة الـ steady state.
* أذا يعني القانون أثبت أنه فعليا عند الـ steady state
$K_o = K X$

- 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

Cont,

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

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

- To determine
  - the amount of the drug at steady state, you need to know the infusion rate (k_o) and elimination rate constant (k) ③ *T half*
  - Css, you need to know clearance ① and infusion rate ②
- 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)

Example

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?

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

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

- ① K_0 = 5 mg/L * 44 L/hr → K_0 = 220 mg/hr
- ② Xss = (220 mg/hr)/0.21 hr^{-1} → Xss = [illegible] mg
- Or Cl = k*VD → VD = 0.21*44 = [illegible]
- Css * VD = Xss → Xss = 5 * [illegible] = [illegible] mg

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

الجزء الي تم تحقيقه من تركيز الsteady state

قبل وصول الsteady state ←

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

عند وصول الsteady state ←

since $C_{ss} = Ko / K'Vd$ previous equation can be represented as:

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

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

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

$$F_{ss} = 1 - \left(\frac{1}{2}\right)^{n}, \quad n = \frac{t}{t_{0.5}}$$

or

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

Example

هنا أنا فقط بحصل على F_{ss} بنسبة (95-99%) عند $t=\infty$ ولكن زي ما بتعرف أنه الكابنيك نعمة نظريات في بعض الحالة فرضنا أنه مجرد ما وصلنا 5 t_{half} يعني $n=5$ رح تكون النسبة 95% وبالتالي بعتبر حالي steady state وصلت

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	
30	
50	
70	
90	

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

$\frac{t}{t_{half}}$

تطبيق على القانون

$F=(1-\frac{1}{2})^{\frac{10}{10}}=0.5$

$(1-(\frac{1}{2})^{\frac{30}{10}})$

Time required to reach C_{ss}

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

طب لفترض أنا بدي أوصل الـ steady state بدون ما استنى بعد ما IV bolus وبعدها بعطيه IV infusion. كم بقدر أوصلها؟ بيأخذ (5-7) t half

- 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

So we need (5-7) t half to reach steady state.

Time required to reach C_{ss}

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

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

$$F_{ss} = (1 - e^{-kt}) \qquad t = -\frac{\ln(1 - F_{ss})}{k}$$

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

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

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

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?

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

- 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 = 148800 µg/hr≅149 mg/hr

Example

- 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

Changing infusion rate (k_0)

- Why we may change rate of infusion?
  - Inadequate pharmacologic response ⟶ حيث ما أنزل MEC وأصير في حالة subtherapeutic
  - or toxicities ⟶ above MTC عشان ما أصير ما دخل في toxicity
- 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

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

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

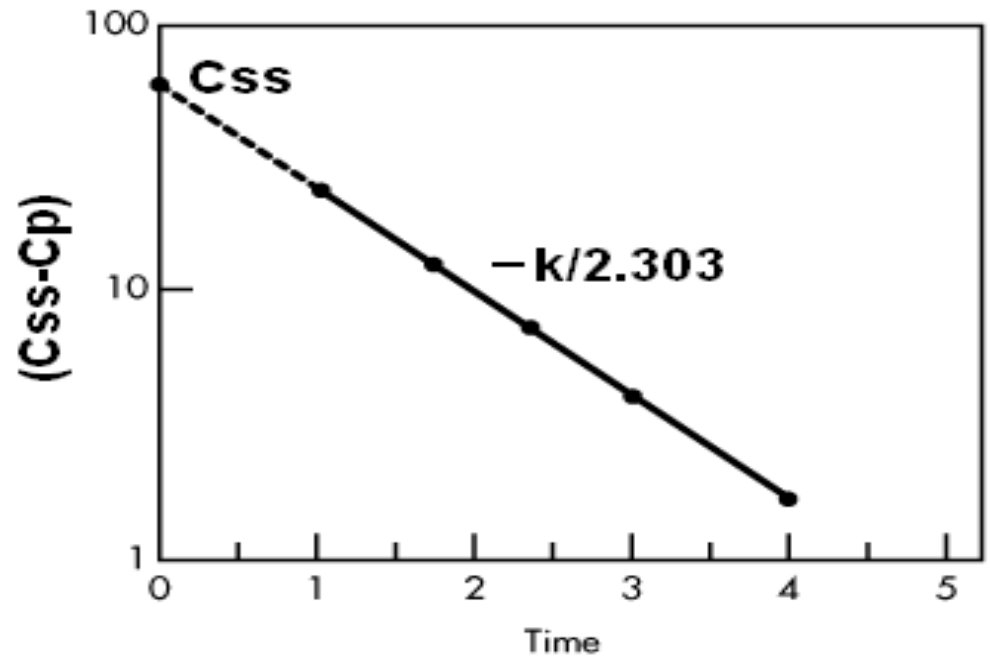
$$C_{ss} = \frac{k_0}{V_D * k}$$

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

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

intercept

slop



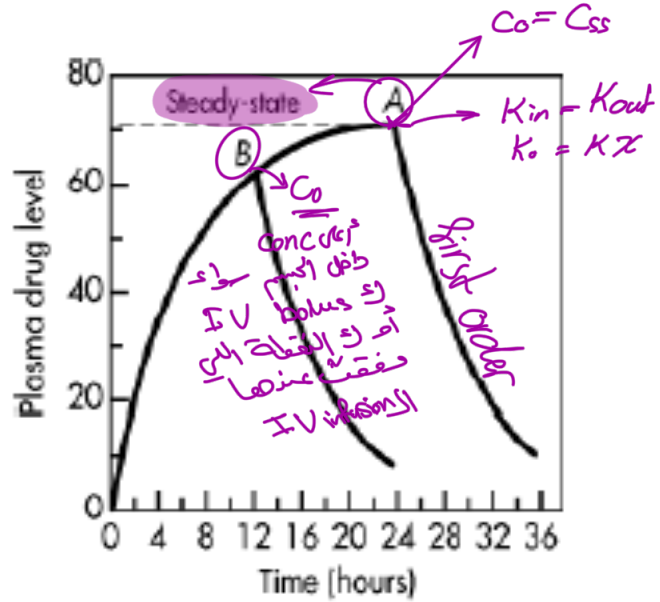
k is determined during infusion from the slope of log(Css-Cp) vs time

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

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



- 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

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

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

curve A

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

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

intercept

slope

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

t: time elapsed after the stop of infusion

Determination of k from Css post infusion

curve B مالي بمثل من الرسمة الي قبل

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

befor reach steady state

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

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

infusion time

* الوقت بعدما وقفت الـ infusion وبلش decline عندي
* post infusion بسميه

Where T = infusion time and

t = time during the declining phase (postinfusion)

Volume of distribution calculation using post infusion data

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

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

- where k is estimated as described in the previous slide

Volume of distribution calculation using post infusion data

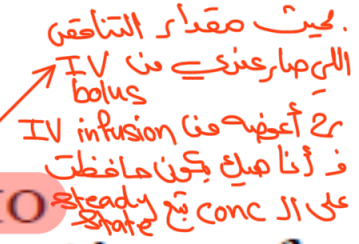
- If you did not reached steady state ($C^* = C_{SS}(1-e^{-kT})$):

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

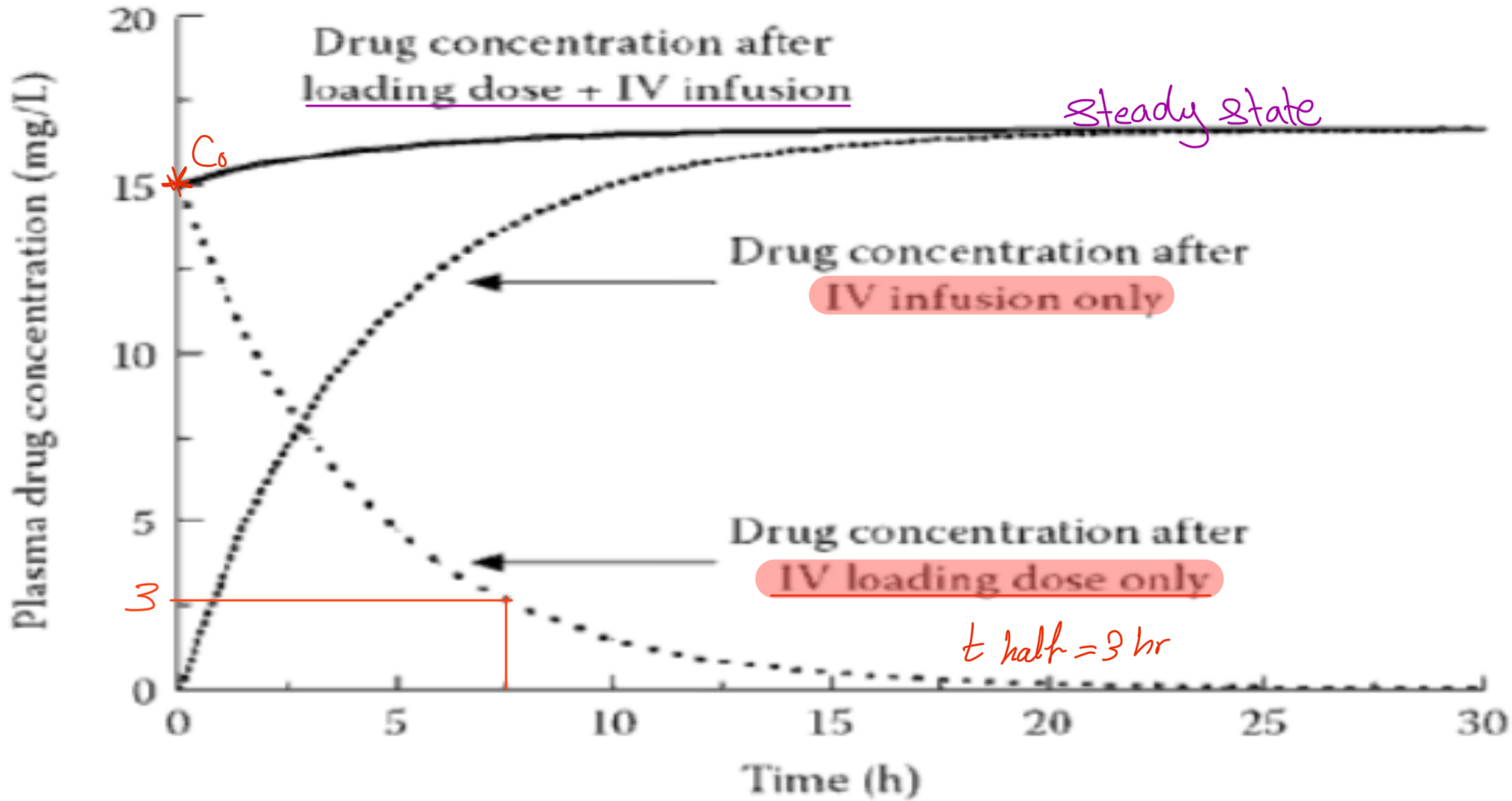
IV infusion + Loading IV bolus

Chapter 8

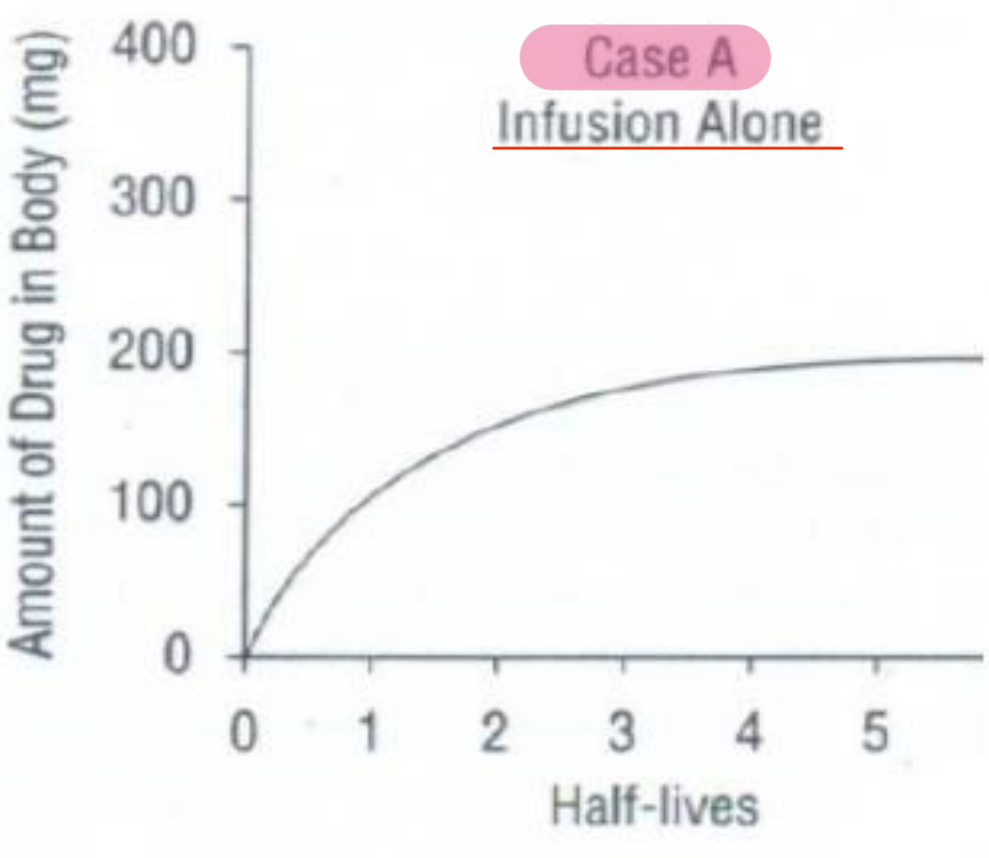
- During constant rate IV administration, the drug accumulates until steady state is achieved after five to seven half-lives
- This can constitute a problem when immediate drug effect is required and immediate achievement of therapeutic drug concentrations is necessary such as in emergency situations
- In this ease, administration of a loading dose will be necessary. The loading dose is an IV bolus dose administered at the time of starting the IV infusion to achieve faster approach to steady state. So administration of an IV loading dose and starting the constant rate IV infusion simultaneously can rapidly produce therapeutic drug concentration. The loading dose is chosen to produce Plasma concentration similar or close to the desired plasma concentration that will be achieved by the IV infusion at steady state

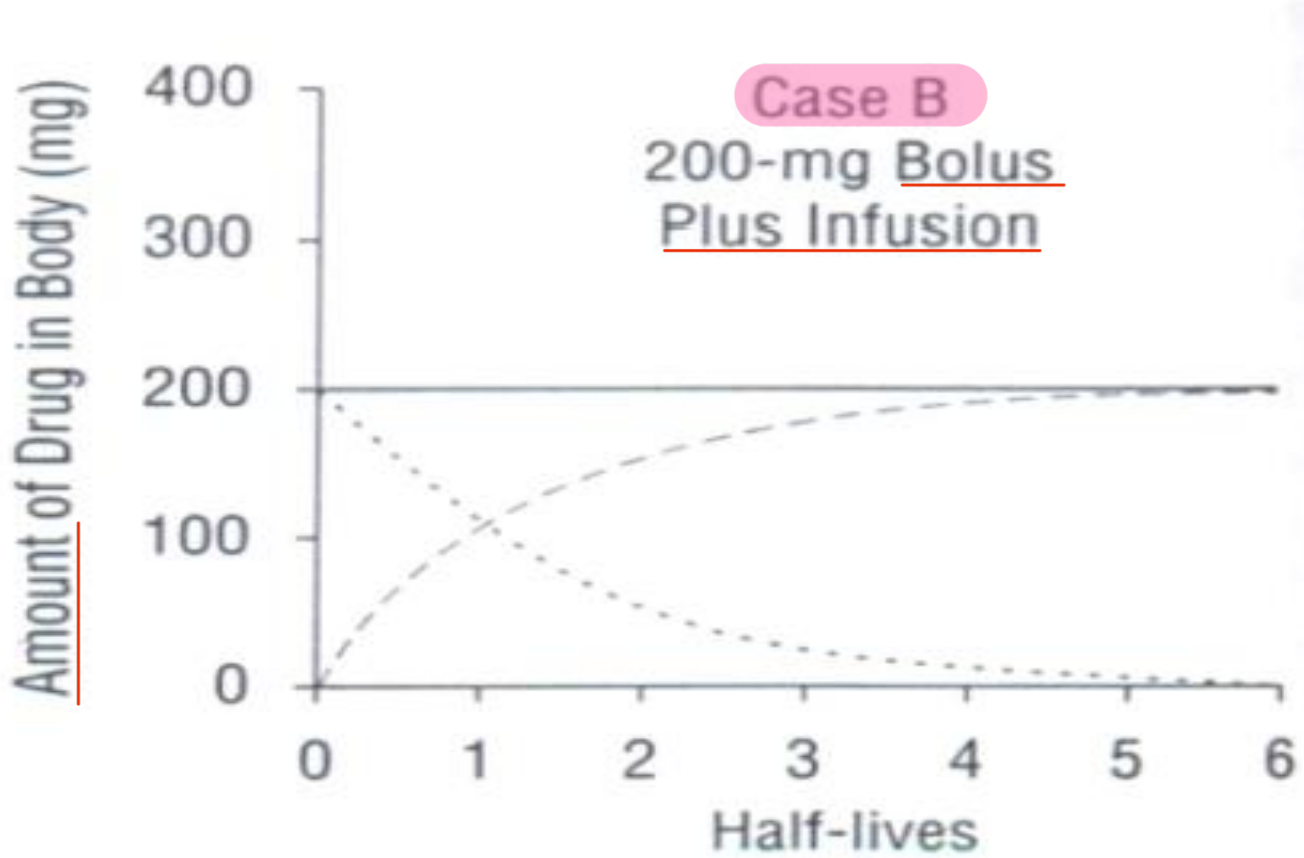


IV infusion + Loading IV bolus



IV infusion + Loading IV bolus





Case A: Drug is infused alone and amount rises reaching the plateau after 5-7 half lives

Case B: When the bolus dose and infusion rate are exactly matched, so a bolus dose (200mg) immediately attains the plateau and infusion rate maintains it after

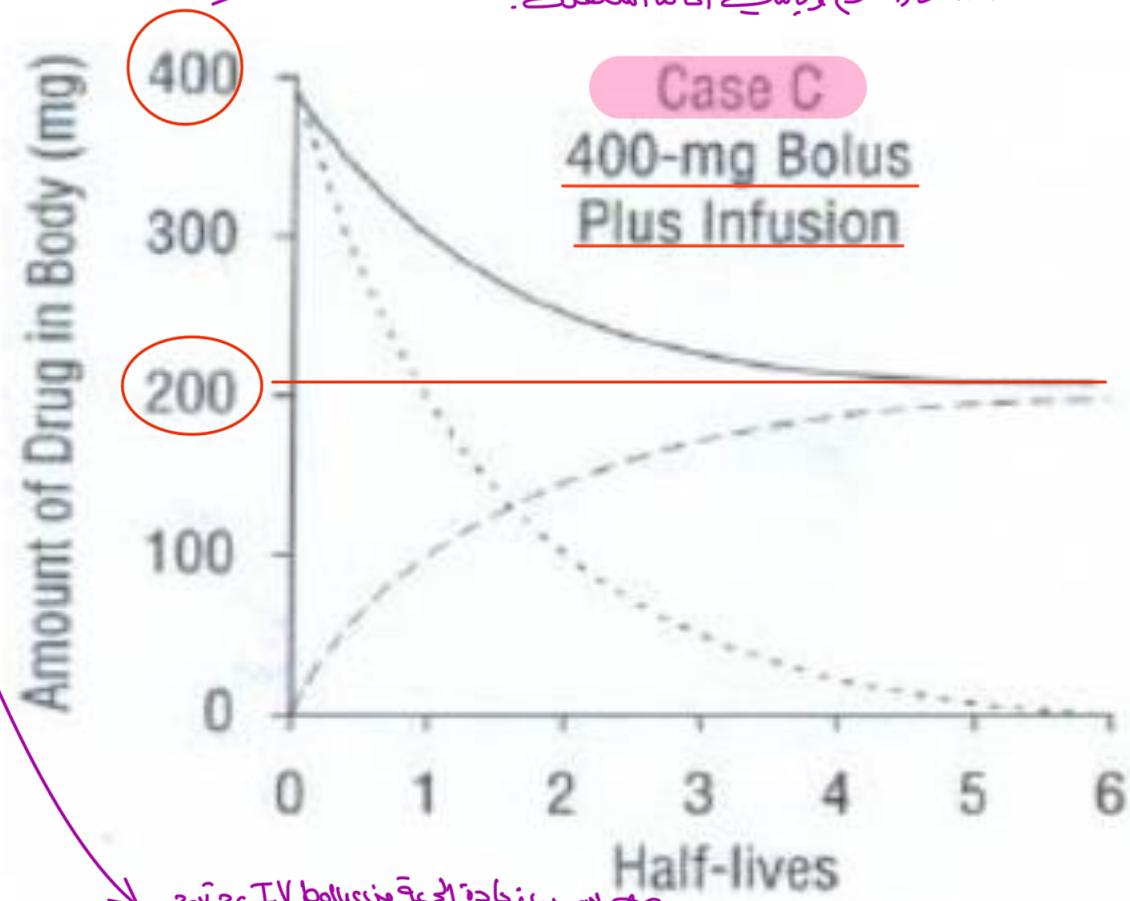
IV infusion + Loading IV bolus

* شغلة تانية في حال هذا الدواء كان narrow therapeutic index و أنا بداعلت صين في امثال احمل بـ toxicity

* أنا ما بقدر أعطي dose عالي عشان أوصل الـ steady state بطريقة أسرع لأنه بربط هون كما فاعفت الـ dose اجتت الـ t-half (5-7) وبالتالي أنا ما استفدت.

Case C: a bolus dose of 400 mg is given, this is excessive; because the rate of loss is initially greater than the input, amount in the body falls. Excess amount continues to fall until the same plateau as in Case B is reached.

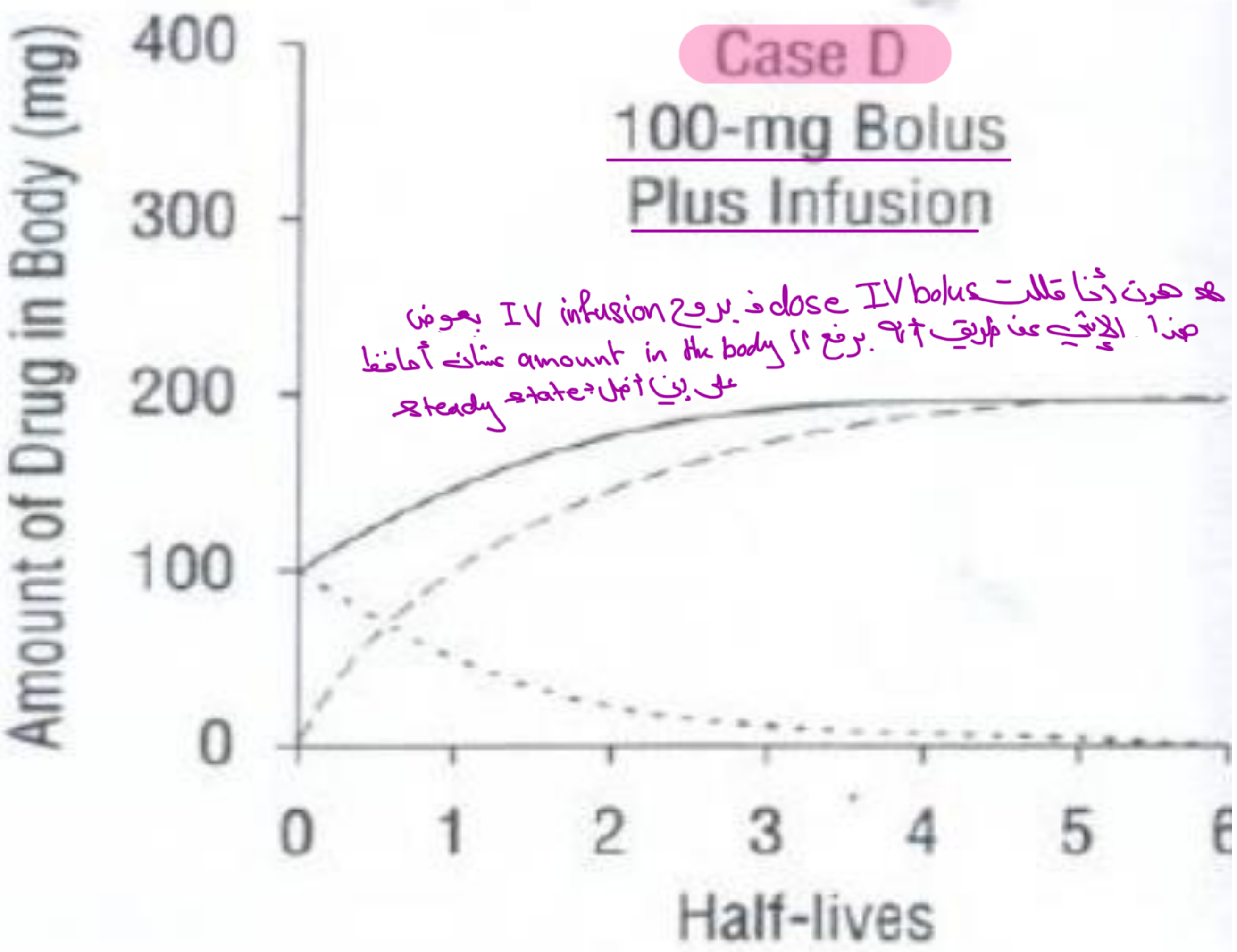
It should be noticed that the time to reach the plateau depends solely on the half-life of the drug, approximately 5-7 half-lives, little of the bolus dose remains and the plateau is reached



* بسبب زيادة الجرعة من IV bolus رح تروح منتب بتع IV infusion تقلل الجسم عشان تقدر تحافظ عـ steady state فعشان هيك أنا ما بستفيد من زيادة جرعة الـ IV bolus بوقف أوصل الـ steady state بطريقة أسرع.

IV infusion + Loading IV bolus

Case D: the bolus dose of 100 mg is below the plateau amount. Because the rate of infusion now exceeds the rate of drug elimination, the amount in the body continuously rises until the same plateau is reached



هون زدنا قللت IV bolus dose ف بروح IV infusion بعوض هذا الإشي عن طريق انه برفع ال amount in the body عشان أحافظ على إني أضل steady state

برضه احتجت (5-7) t half فبالتالي لازم من البداية أكون حاسب بشكل صحيح ال dose.

IV infusion + Loading IV bolus

- To achieve a target steady state conc (C_{ss}) the following equations can be used:
  - For the infusion rate:

$$K_0 = Cl \cdot C_{ss}$$

  - For the loading dose:

IV bolus

$$LD = Vd \cdot C_{ss}$$

$$LD = \frac{k_0}{k}$$

IV infusion + Loading IV bolus

- The conc. resulting from both the bolus and the infusion can be described as:

$$C_{total} = C_{bolus} + C_{infusion}$$

مثلاً:- في case(A) أنا فقط رح احسب Cinfusion
بس مثلاً في case(B) رح يتحكم كمان فقط IV bolus ليش لأنه الـ IV infusion الي احسبها رح تكون صفر لأنه t=0 فـ الي أطبق على القانون رح تكون $\frac{K_0}{KVd}(1-e^0)$ ← (1-1) ← zero

$$C_{(total)} = \frac{X^0}{V_D} e^{-kt} + \frac{k_0}{kV_D}(1 - e^{-kt})$$

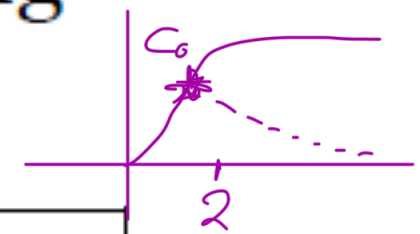
amount / volume

k_0 ← $\frac{K_0}{Cl}$

Example 1

Following a two-hour infusion of 100 mg/hr plasma was collected and analysed for drug concentration. Calculate kel and V.

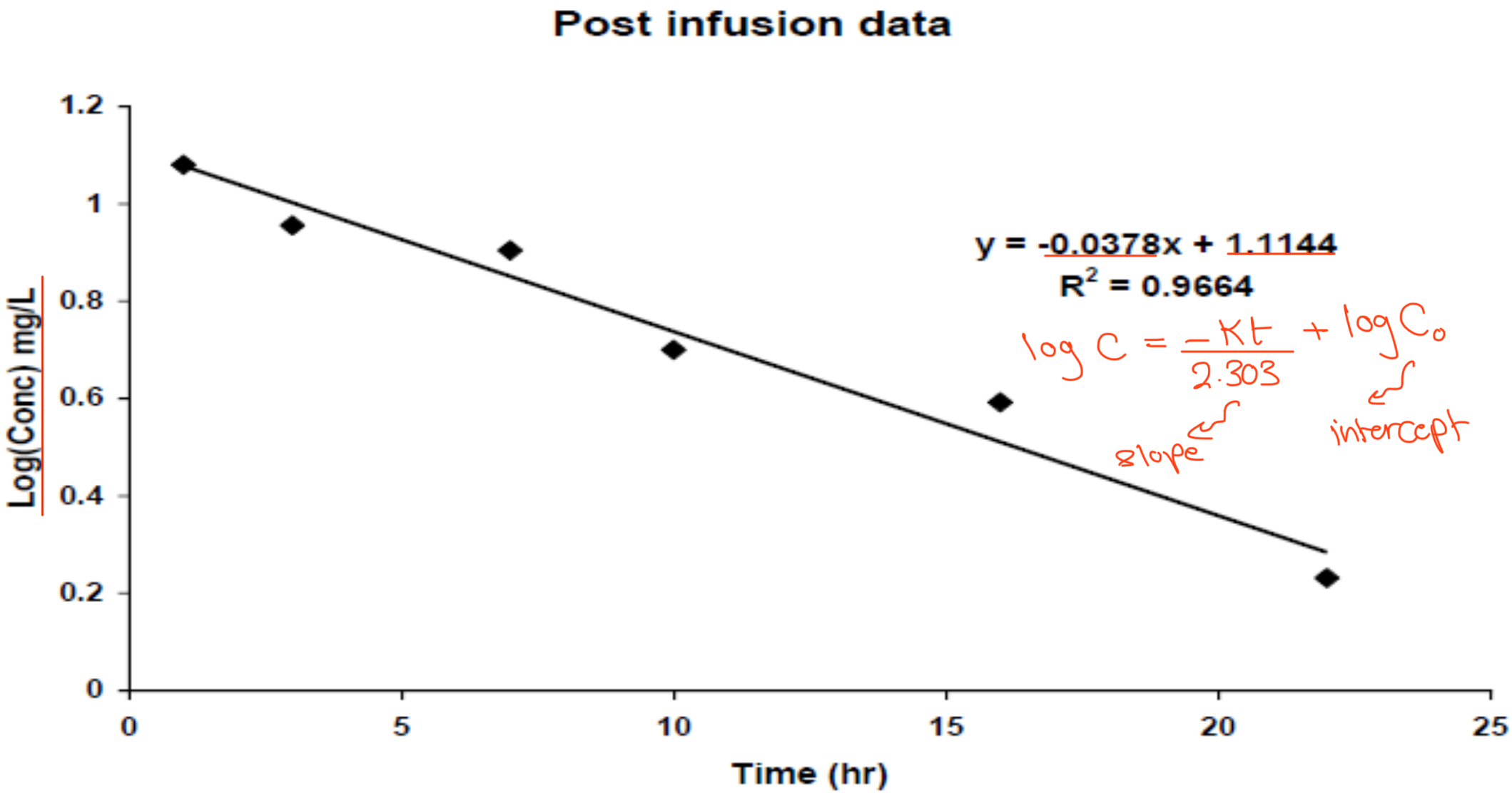
zero order



يعني بعد ما وقفت الinfusion

Time relative to infusion cessation (hr)	1	3	7	10	16	22
Cp (mg/L)	12	9	8	5	3.9	1.7

IV bolus



Time is the time after stopping the infusion

Example 1

* إذا بدي احسب الـ t half :

$t_{half} = \frac{0.693}{0.087} = 7.96 \simeq 8 * 5 = 40\,hr$

كم بدي ٤٥ ساعة عشان اعدي (٥-٧) t_{half} وهو حكالي بعد ٤٠ ساعتين معناها أنا أكيدها وصلت Steady State !!

* معناها أنا ماشي واصل الـ steady state

- From the slope, K is estimated to be:

$$k = -2.303 \cdot Slope = -2.303 * -0.0378 = 0.087\ 1/hr$$

← هو آخر conc أنا وصلته قبل ما يبلش decline.

- From the intercept, C* is estimated to be:

$$\log(C^*) = intercept = 1.1144$$

$$C^* = 10^{1.1144} = 13\ mg/L$$

* معناها أنا راح أوصل الـ steady state بعد ٥٥ ساعة.

← الـ conc قبل ما أوقف الـ infusion.

Example 1

- Since we did not get to steady state:

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

$$Vd = \frac{100}{(0.087)\cdot(13)}(1 - e^{-0.087*2}) = 14.1L$$

معطى في السؤال

حتى لي بعد ساعتين وقفت الـ infusion.

intercept كـ C_0^* حسبناها من

Example 2

- **Estimate the volume of distribution (22 L), elimination rate constant (0.28 hr-1), half-life (2.5 hr), and clearance (6.2 L/hr) from the data in the following table obtained on infusing a drug at the rate of 50 mg/hr for 16 hours.**

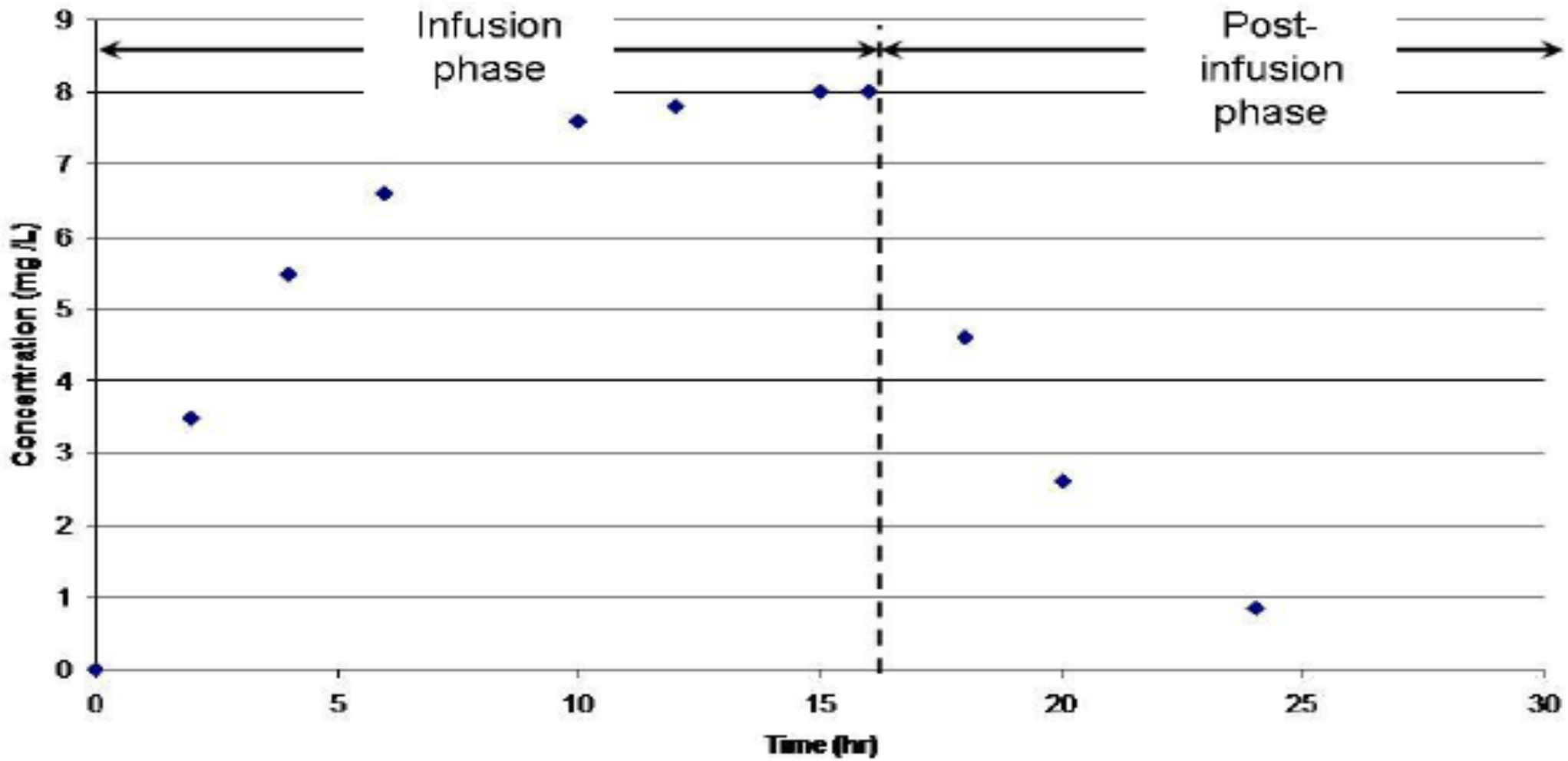
IV infusion

decline

Time (hr)	0	2	4	6	10	12	15	16	18	20	24
Conc (mg/L)	0	3.48	5.47	6.6	7.6	7.8	8	8	4.6	2.62	0.85

Conc at steady state = 8

Example 2


Infusion phase
Post-infusion phase
Concentration (mg/L)
Time (hr)
0
1
2
3
4
5
6
7
8
9
0
5
10
15
20
25
30

Example 2

1. Calculating clearance:

It appears from the data that the infusion has reached steady state:

$(CP(t=15) = CP(t=16) = C_{SS})$

$$C_{ss} = \frac{K_0}{Cl} \Rightarrow Cl = \frac{K_0}{C_{ss}} = \frac{50\,\text{mg/hr}}{8\,\text{mg/L}} = \underline{6.25\,\text{L/hr}}$$

أو بعد ما اعرف Vd
بطلعها من قانون
$Cl = k * Vd$

Example 2

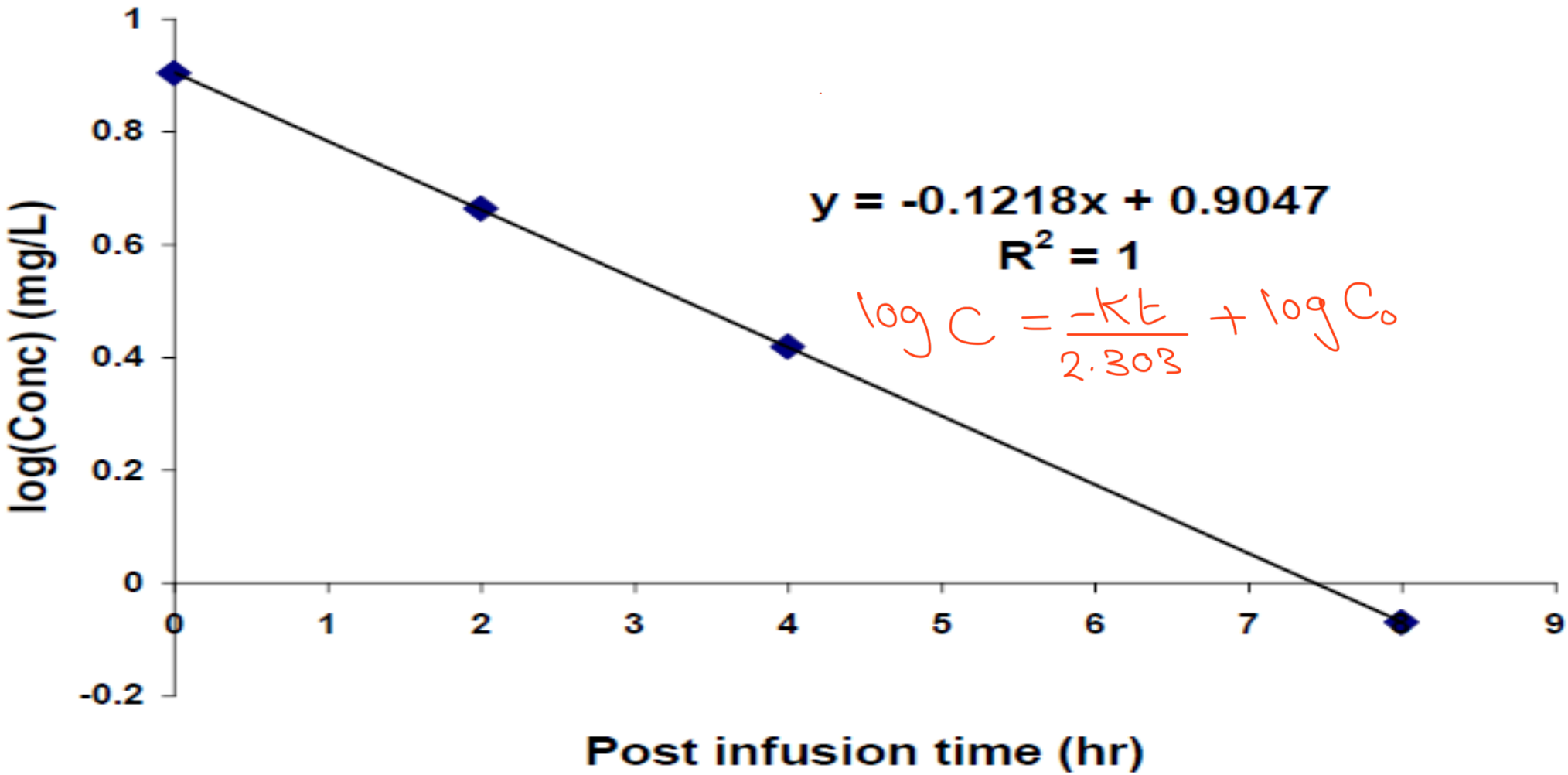
2. Calculating elimination rate constant and half life:

From the post infusion data, K and t1/2 can be estimated. The concentration in the post infusion phase is described according to:

$$C_P = C_{SS} \cdot e^{-K \cdot t_1} \Rightarrow \log(C_P) = \log(C_{SS}) - \frac{K}{2.303} t_1$$

where t1 is the time after stopping the infusion. Plotting log(Cp) vs. t1 results in the following:

Example 2


1
0.8
0.6
0.4
0.2
0
-0.2
log(Conc) (mg/L)
0
1
2
3
4
5
6
7
9
Post infusion time (hr)
y = -0.1218x + 0.9047
R² = 1
log C = -kt / 2.303 + log C₀

Example 2

K=-slope*2.303=0.28 hr-1

Half life = 0.693/K=0.693/0.28= 2.475 hr

2.475 * 5 thalf = 12.37 hr معناها آنا وصلت steady state الدواء بتكيل بعد 16 hr .

3. Calculating volume of distribution:

$$V_D = \frac{Cl}{K} = \frac{6.25\ \text{L/hr}}{0.28\ \text{hr}^{-1}} = 22.3\ \text{L}$$

Calculate K from pre-infusion cessation data

Example 3

- **A drug that displays one compartment characteristics was administered as an IV bolus of 250 mg followed immediately by a constant infusion of 10 mg/hr for the duration of a study. Estimate the values of the volume of distribution (25 L), elimination rate constant (0.1hr-1), half-life (7), and clearance (2.5 L/hr) from the data in the following table**

Example 3

الفترة

Time(hr)	0	5	20	45	50
Conc(mg/L)	10	7.6	4.8	4.0	4.0

المفروض لازم عند $t=0$ تكون عندي C تساوي 4 بس هون هو فات الأول حاسب ال bolus غلط.

رح تكون هيك

$C_{total} = C_{infusion} + C_{bolus}$

الأسهل احسبي عند $t=0$

steady state

$C_{ss} = 4$

Example 3

- The equation that describes drug concentration is:

$$C_P = \text{Drug from IV bolus} + \text{Drug from IV infusion}$$

$$= \frac{X_0}{V_D} e^{-K \cdot t} + \frac{K_0}{K \cdot V_D}\left(1 - e^{-K \cdot t}\right)$$

a- Calculating volume of distribution: $\frac{\text{amount}}{\text{conc}} = \frac{250}{10}$

At time zero,

$$C_P(t=0) = \frac{X_0}{V_D} \Rightarrow V_D = \frac{X_0}{C_P(t=0)} = \frac{250\,\text{mg}}{10\,\text{mg/L}} = 25\,\text{L}$$

$10\,\text{mg/L} \rightarrow C_0$

Example 3

b- Calculating elimination rate constant and half life:

Since the last two concentrations (at time 45 and 50 hrs) are equal, it is assumed that a steady state situation has been achieved.

$$C_{SS} = \frac{K_0}{K \cdot V_D} \Rightarrow K = \frac{K_0}{C_{SS} \cdot V_D} = \frac{10\,\text{mg/hr}}{4\,\text{mg/L} \cdot 25\,\text{L}} = 0.1\,\text{hr}^{-1}$$

من الجدول اللي عند t=0 Con هاخدها .

Half life = 0.693/K=0.693/0.1= 6.93 hr ≈ 7

7 * 5 t half = 35 hr

7 * 7 t half = 49 hr

معناها أنا بين (35-49) بكون وصلت لـ steady state .

Example 3

c- Calculating clearance:

$$Cl = K \cdot V_D = 0.1 \cdot 25 = 2.5\ \text{L/hr}$$

Example 4

- For prolonged surgical procedures, succinylcholine is given by IV infusion for sustained muscle relaxation. A typical initial dose is 20 mg followed by continuous infusion of 4 mg/min. the infusion must be individualized because of variation in the kinetics of metabolism of suucinylcholine. Estimate the elimination half-lives of succinylcholine in patients requiring 0.4 mg/min and 4 mg/min, respectively, to maintain 20 mg in the body. (35 and 3.5 min)

X_{ss} ← $LD = Vd * C_{ss}$ ← $LD = X_{ss}$

X_{ss} ← amount of steady state.

loading dose

Example 4

① $LD = \frac{K_0}{K}$

$20 = \frac{4}{K} \Rightarrow K = 0.2\ min^{-1}$

$t_{half} = \frac{0.693}{0.2} = 3.46\ min$

② $LD = \frac{K_0}{K}$

$20 = \frac{0.4}{K} \Rightarrow K = 0.02\ min^{-1}$

$t_{half} = \frac{0.693}{0.02} = 34.6\ min$

For the patient requiring 0.4 mg/min:

$$A_{ss} = \frac{K_o}{K} = K_0 \cdot \frac{t_{1/2}}{0.693} \Rightarrow t_{1/2} = \frac{A_{SS} \cdot 0.693}{K_0}$$

$$t_{1/2} = \frac{A_{SS} \cdot 0.693}{K_0} = \frac{(20)(0.693)}{0.4} = 34.65\,\text{min}$$

For the patient requiring 4 mg/min:

$$t_{1/2} = \frac{A_{SS} \cdot 0.693}{K_0} = \frac{(20)(0.693)}{4} = 3.465\,\text{min}$$

Example 5

A drug is administered as a short term infusion. The average pharmacokinetic parameters for this drug are:

K = 0.40 hr-1

Vd = 28 L

This drug follows a one-compartment body model.

Example 5

1) A 300 mg dose of this drug is given as a short-term infusion over 30 minutes. What is the infusion rate? What will be the plasma concentration at the end of the infusion?
2) How long will it take for the plasma concentration to fall to 5.0 mg/L?
3) If another infusion is started 5.5 hours after the first infusion was stopped, what will the plasma concentration be just before the second infusion?

Example 5

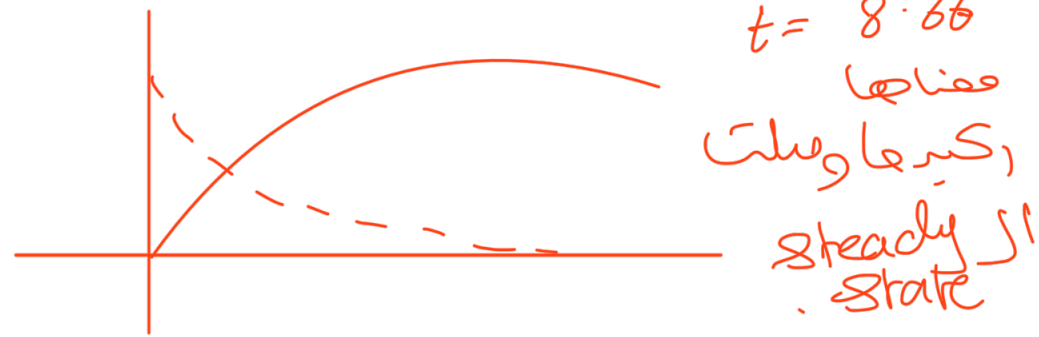
amount/time or mass/time

1) The infusion rate (Ko) = Dose/duration = 300 mg/0.5 hr = 600 mg/hr.

مولت ل hr 0.5 كام وحده K عاشان hr

Plasma concentration at the end of the infusion:

Infusion phase:

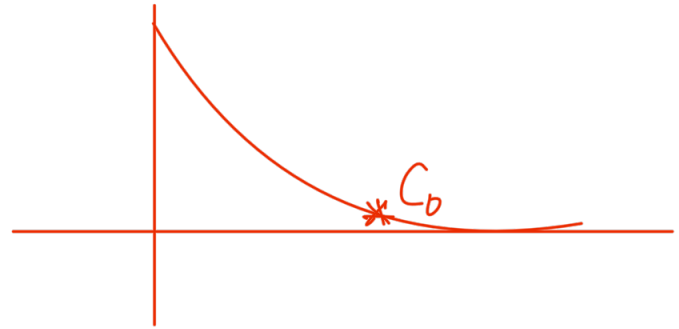


t = 8.66 هفناها ركيزها وبلت ال steady state.

$$C_P = \frac{K_0}{K \cdot V_D}\left(1 - e^{-K \cdot t}\right)$$

$$C_P(t = 0.5\,\text{hr}) = \frac{600\,\text{mg/hr}}{(0.4\,\text{hr}^{-1})(28\,\text{L})}\left(1 - e^{-(0.4)(0.5)}\right) = 9.71\,\text{mg/L}$$

Example 5



2) Post infusion phase:

$$C_P = C_P(\text{at the end of infusion}) \cdot e^{-k \cdot t_2}$$

$$\Rightarrow \ln(C_P) = \ln(C_P(\text{at the end of infusion})) - K \cdot t_2$$

$$\Rightarrow t_2 = \frac{\ln(C_P(\text{at the end of infusion})) - \ln(C_P)}{K} = \frac{\ln(9.71) - \ln(5)}{0.4} = \underline{1.66\,\text{hr}}$$

The concentration will fall to 5.0 mg/L 1.66 hr after the infusion was stopped.

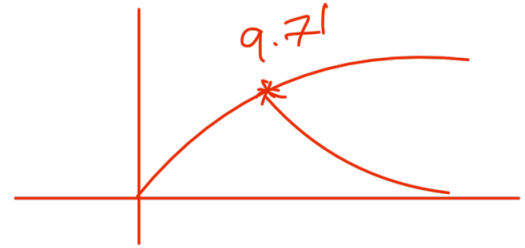
$C = C_0 * e^{-Kt}$

$t = \ln\left(\frac{C}{C*}\right)/K$

أو طريقة ثانية

$t = \ln\left(\frac{9.7}{5}\right)/0.4 = 1.66$ hr

Example 5



3) Post infusion phase (conc 5.5 hrs after stopping the infusion):

$$C_P = C_P(\text{at the end of infusion}) \cdot e^{-k \cdot t_2}$$

$$C_p(t = 5.5\,\text{hr}) = (9.71)e^{(-0.4)(5.5)} = 1.08\,\text{mg/L}$$

$C = C_0 * e^{-Kt}$

$C = 9.71 * e^{-(0.4*5.5)} = 1.08$