

تفريغ كايبتك

محاضرة: PK Phandamental parameters: Lec4

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لجان الدفعات



PK fundamental parameters

PK theory lec.4

Area under the curve (AUC)

Area Under the Conc. Time Curve (AUC) calculation

- Two methods:
 - Model dependent: can be used only for one compartment IV bolus
 - Model independent: Can be used for any drug with any route of administration

How to calculate AUC?

- The **trapezoidal rule** is a numerical method frequently used in pharmacokinetics to calculate the area under the plasma drug concentration-versus-time curve, called the *area under the curve* (AUC).

$$AUC = AUC_A + AUC_B + AUC_C + AUC_D$$

مساحة شبه منحرف
 (الإرتفاع × مجموع القاعدتين ÷ 2)

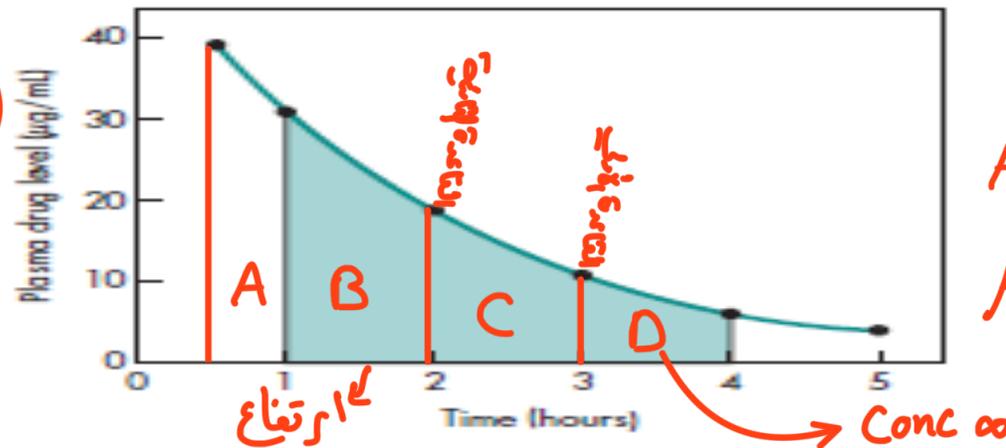


FIGURE 2-2 Graph of the elimination of drug from the plasma after a single IV injection.

$$AUC_B = \frac{1}{2} (C_{t=1} + C_{t=2}) * (t_2 - t_1)$$

$$AUC_A = \frac{1}{2} (C_0 + C_{t=1}) * t_1$$

$$AUC_D = \frac{C_{last}}{K} * t = 3$$

$$AUC_D = \frac{1}{2} (C_{t=3} + C_{\infty}) * (t_{\infty} - t_3)$$

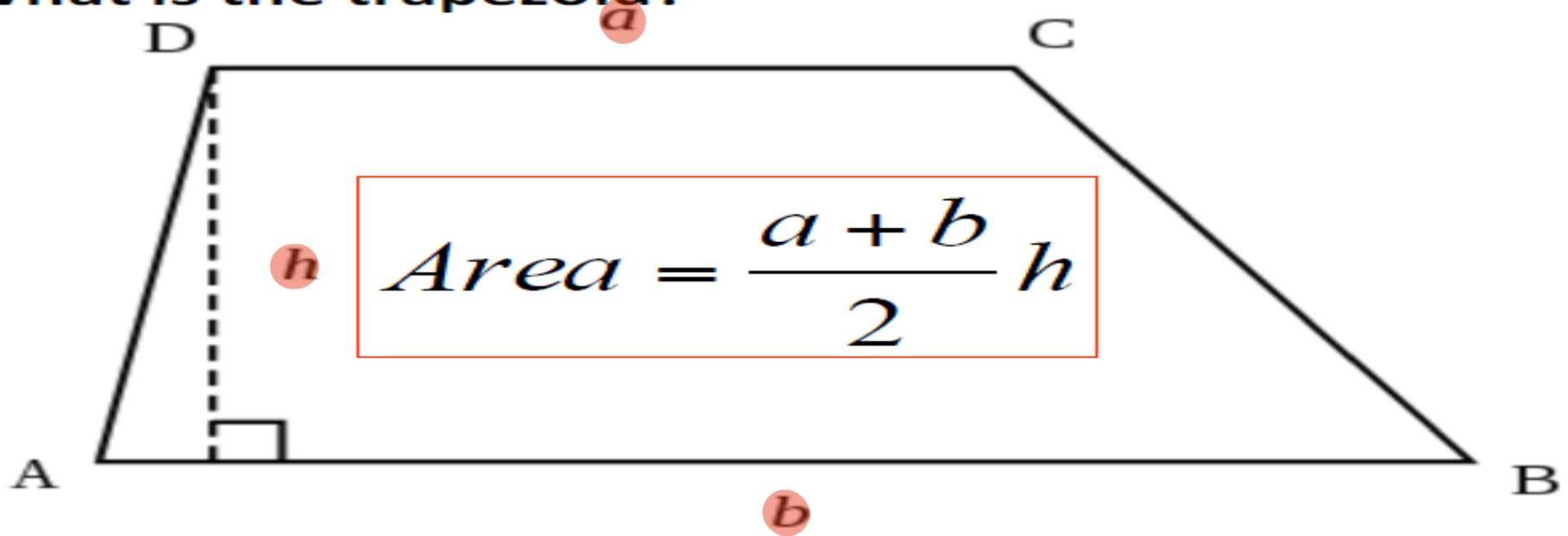
$$= \frac{1}{2} (C_{t=3} + 0)$$

Fig. 2-2 shows a curve depicting the elimination of a drug from the plasma after a single intravenous injection. The drug plasma levels and the corresponding time intervals plotted in Fig. 2-2 are as follows:

Cont,

For sure you know!

- What is the trapezoid?

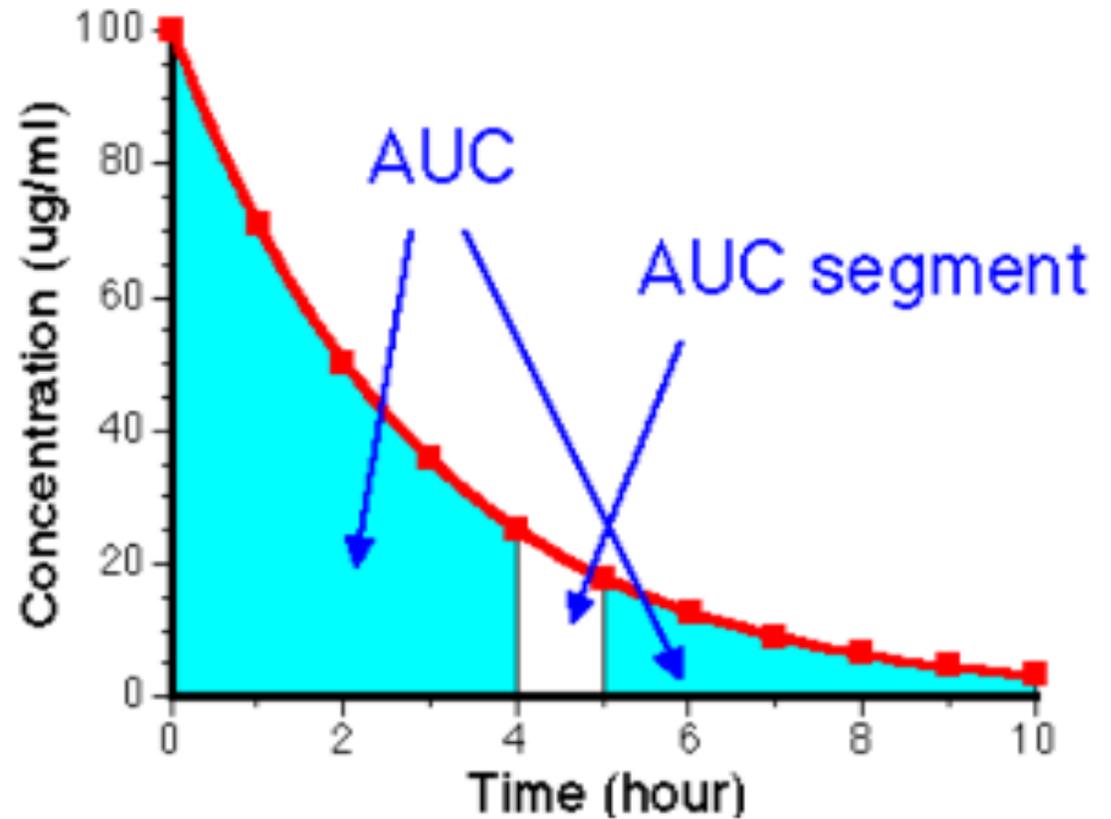


- The area of the trapezoid is equal to what?

Cont,

Area under the plasma concentration versus time curve

- In the absence of the knowledge of the intercept of the plasma concentration versus time plot and the rate constant(s), **the trapezoidal method** permits determination of the area under the plasma concentration time curve (AUC). The method, however, requires knowledge of plasma concentrations at various times.



Cont,

Area under the plasma concentration versus time curve

- To use the linear trapezoidal method:
 - 1) Divide the area into different trapezoids based on the observed data (the previous figure can be divided to ten trapezoids).
 - 2) Calculate the area for each trapezoid the area of a trapezoid can be calculated as follows:

$$\text{area} = \frac{C_2 + C_1}{2} \cdot (t_2 - t_1)$$



Model-independent Approach

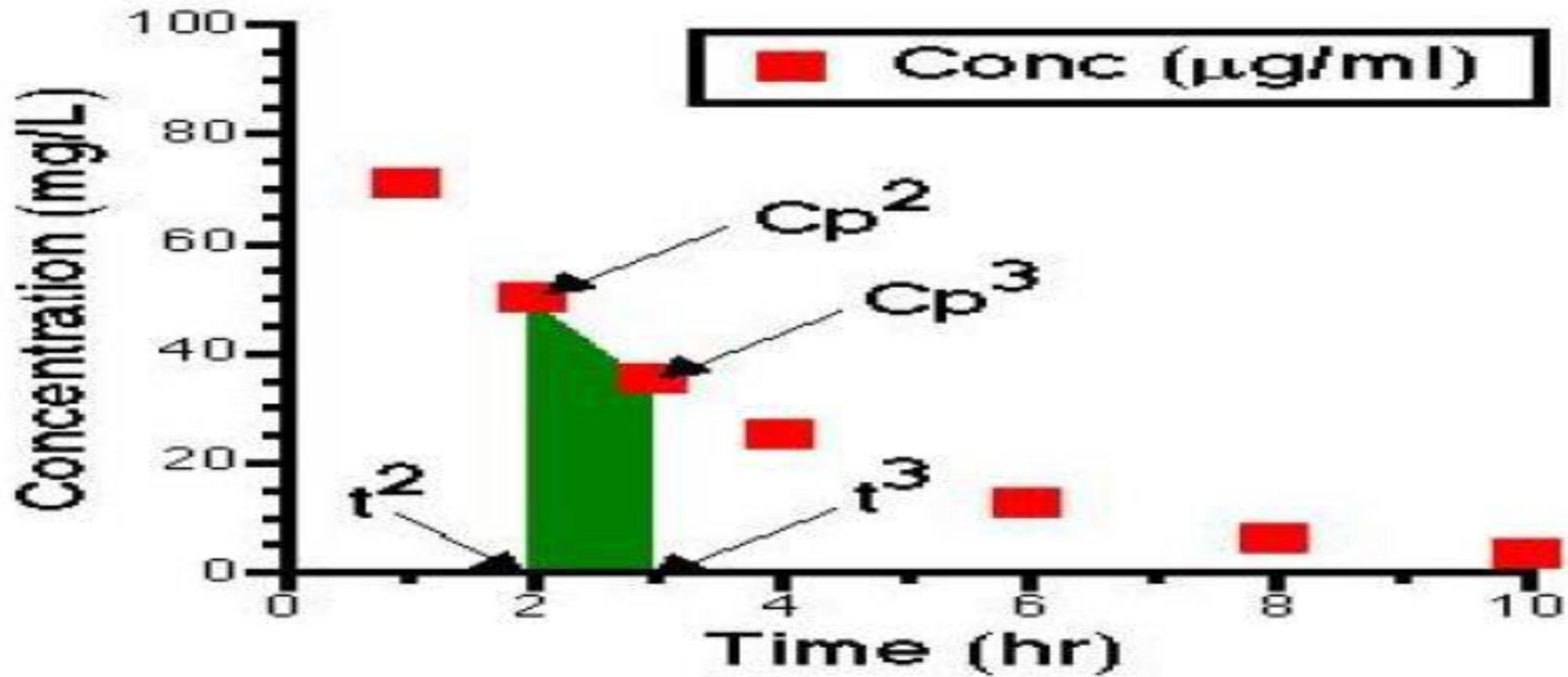
Trapezoidal Rule

- The area between time intervals is the area of a trapezoid and can be calculated with the following formula:

$$[\text{AUC}]_{t_{n-1}}^{t_n} = \frac{C_{n-1} + C_n}{2} (t_n - t_{n-1})$$

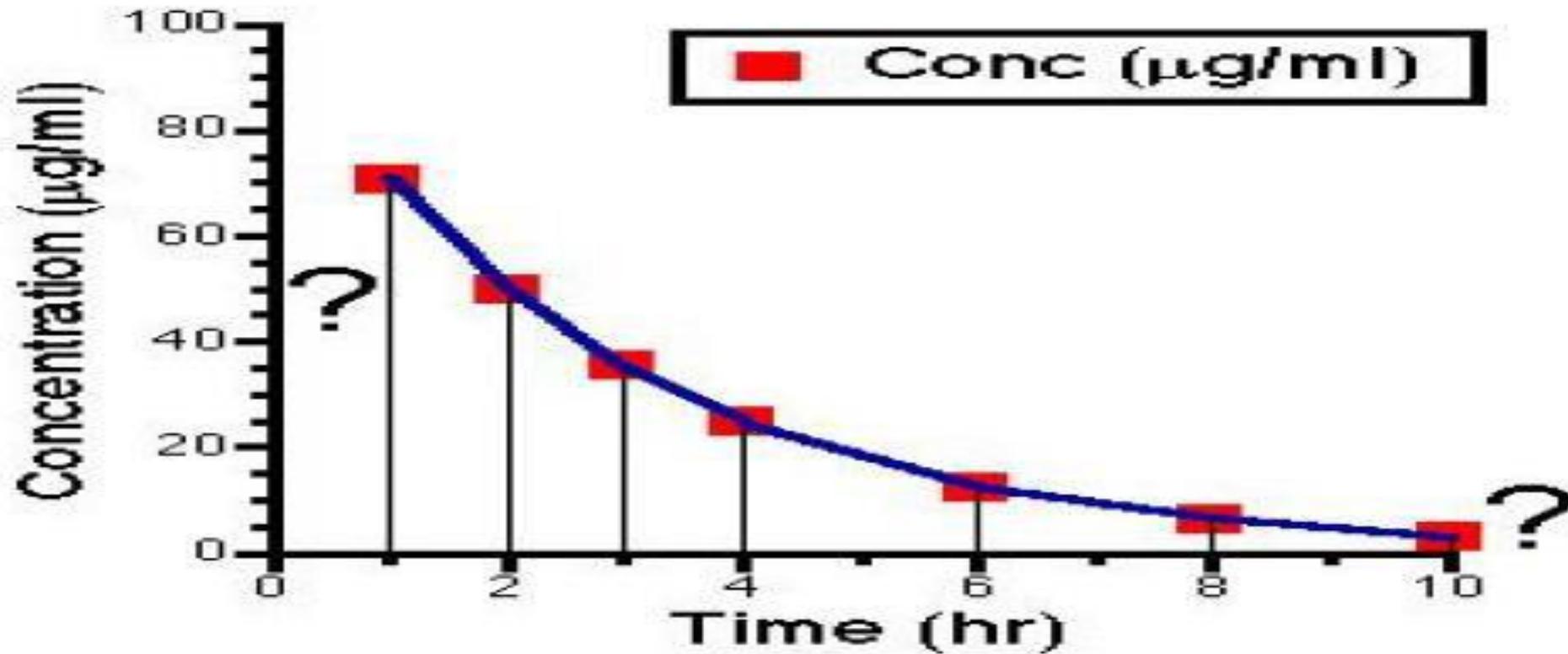
Cont,

Area between t_2 and t_3



Cont,

Total Area



Cont,

- The first segment:
- We need to determine $C_p^0 \rightarrow$ HOW?

$$AUC_{0-1} = \left\{ \frac{C_{p_0} + C_{p_1}}{2} \cdot (t_1) \right\}$$

- The last segment:

$$AUC^{t_{last}-\infty} = \int_{t=t_{last}}^{t=\infty} C_p \cdot dt = \frac{C_{plast}}{k}$$

- Then:

$$AUC^{0-\infty} = \quad | \quad ?? \quad |$$

AUC unit: Conc. * time

Ex: $mg \cdot ml^{-1} \cdot h = mg \cdot h/ml$

example

- To obtain the AUC from 1 to 4 hours, each portion of this area must be summed. The AUC between 1 and 2 hours is calculated by proper substitution

$$[AUC]_{t_1}^{t_2} = \frac{30.3 + 18.4}{2} (2 - 1) = 24.35 \mu\text{g} \cdot \text{h/mL}$$

Time (hours)	Plasma Drug Level ($\mu\text{g/mL}$)
0.5	38.9
1.0	30.3
2.0	18.4
3.0	11.1
4.0	6.77
5.0	4.10

Cont,

$$\frac{(11.4 + 18.4)}{2} * (3 - 2)$$

- Similarly, the AUC between 2 and 3 hours is calculated as **14.75 mg·h/mL**, and the AUC between 3 and 4 hours is calculated as **8.94 mg·h/mL**. The total AUC between 1 and 4 hours is obtained by adding the three smaller AUC values together. :

$$\begin{aligned} [AUC]_{t_1}^{t_4} &= [AUC]_{t_1}^{t_2} + [AUC]_{t_2}^{t_3} + [AUC]_{t_3}^{t_4} \\ &= 24.35 + 14.75 + 8.94 \\ &= 48.04 \mu g \cdot h/mL \end{aligned}$$

Time (hours)	Plasma Drug Level ($\mu g/mL$)
0.5	38.9
1.0	30.3
2.0	18.4
3.0	11.1
4.0	6.77
5.0	4.10

example

كمية (amount) إذا $V_d = 10 L$ ؟؟
 $Conc = \frac{A_0}{V} = 125 = \frac{A_0}{10}$
 $A_0 = 1250 \text{ mg}$

كم الوقت الذي يحتاجه كرات أجسام
 $t_{1/2} = \frac{0.693}{K} = \frac{0.693}{0.35} = 2$
 $\Rightarrow 7 t_{1/2} = 7 \times 2 = 14$
 حفظ
 مسان أجسام من الدواء بنسبة 99% بين 7-14

$AUC = \frac{C_{last}}{K}$
 $11.1 = \frac{3.875}{K} \Rightarrow 0.35$

Area under the plasma concentration versus time curve-Example

Assume the following data were obtained following intravenous administration of a drug ($K=0.35$). Calculate the AUC

Time (hr)	Conc (mg/L)	AUC of trapezoids
0	125	
1	88.75	106.88
2	62.5	75.63
3	43.75	53.13
4	31.25	37.50
6	15	46.25
8	7.75	22.75
10	3.875	11.63
Inf	0	11.1
	sum	364.82

$V_d = \frac{\text{amount}}{\text{conc}}$
 $x = \frac{1250}{125} = 10$

Elimination rate

Elimination rate constant (K)

إذا بيطلع قيمة K
عنك مرتين -8

$$\textcircled{1} K = -\text{slope} \times 2.303$$

$$\log C = \frac{-K}{2.303} t + \log C_0$$

or

$$\ln \Rightarrow K = -\text{slope}$$

$$\textcircled{2} t_{1/2} = \frac{0.693}{K}$$

- Elimination rate constant represents the fraction of drug removed per unit of time
- K has a unit of reciprocal of time (e.g. minute⁻¹, hour⁻¹, and day⁻¹)
- With first-order elimination, the rate of elimination is directly proportional to the serum drug concentration

K is an overall elimination constant

- $K = K_{\text{renal}} + K_{\text{metabolism}} + K_{\text{...}}$
- All are responsible of decline of plasma concentration

Elimination rate constant estimation

1. Plot $\log(C)$ vs. time

$$\text{Ex: } \ln C = -\underbrace{0.1}_K t + 1$$

$$t_{1/2} = ??$$

$$\text{A) } 6.93 \text{ hr}^{-1} \quad t_{1/2} = \frac{0.693}{0.1} = 6.93 \text{ hr}$$

B) 6.93 hr

2. Plot the best-fit line

C) 30.09 hr

D) 30.09 hr^{-1}

E) non of the above.

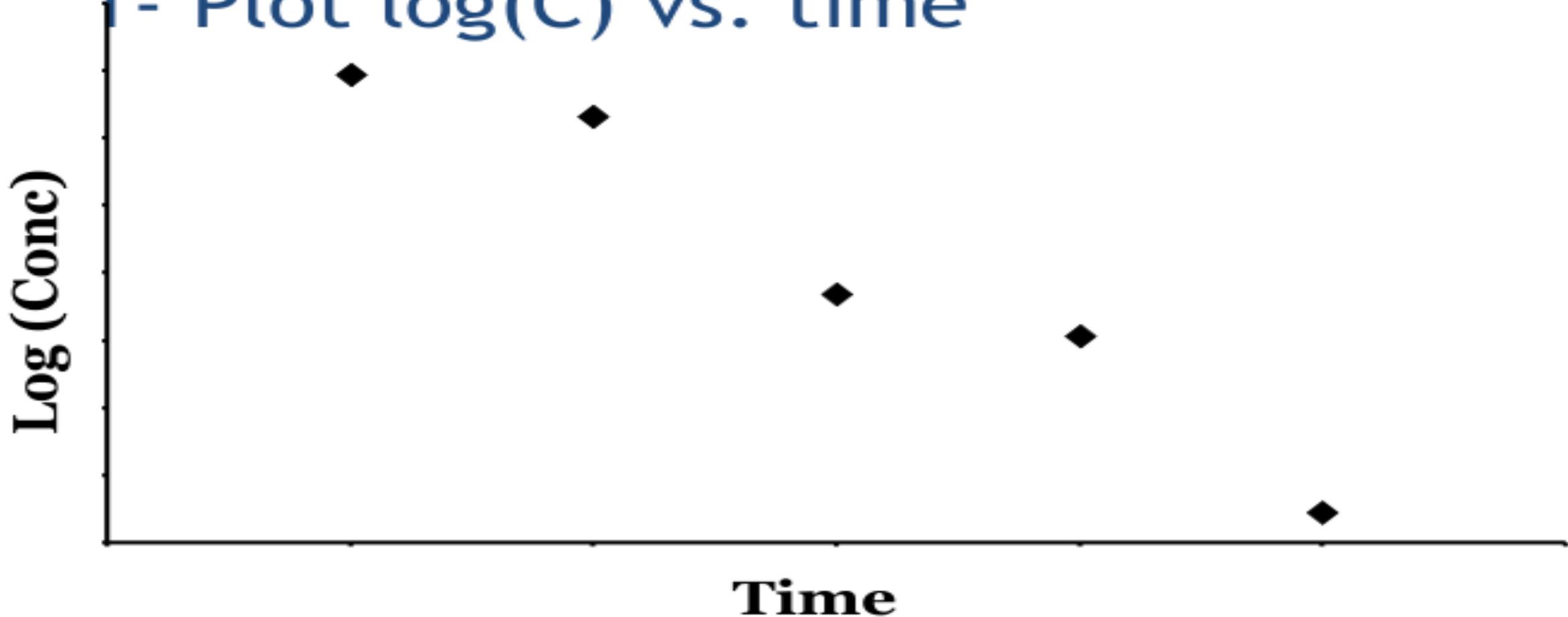
3. Calculate the slope using two points on the best-fit line

4. Estimate K:

$$K = -\text{Slope} \cdot 2.303$$

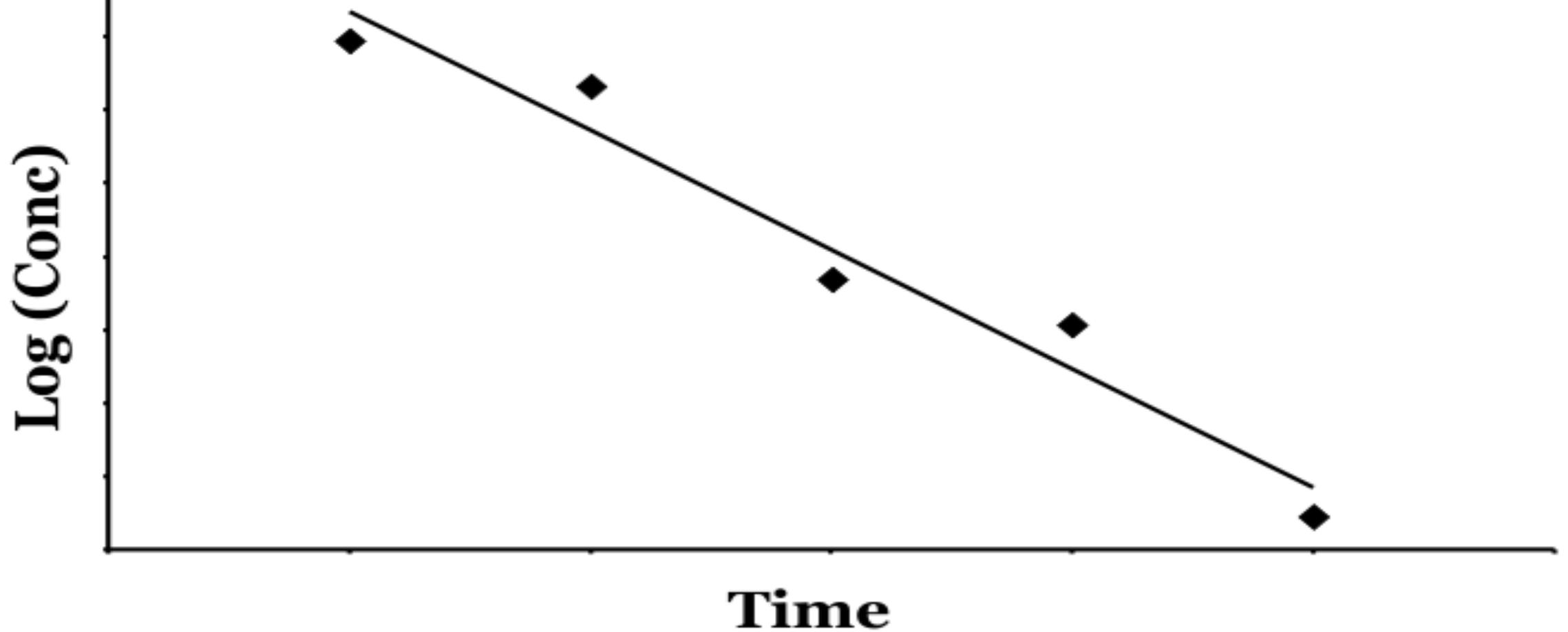
Cont,

1- Plot $\log(C)$ vs. time



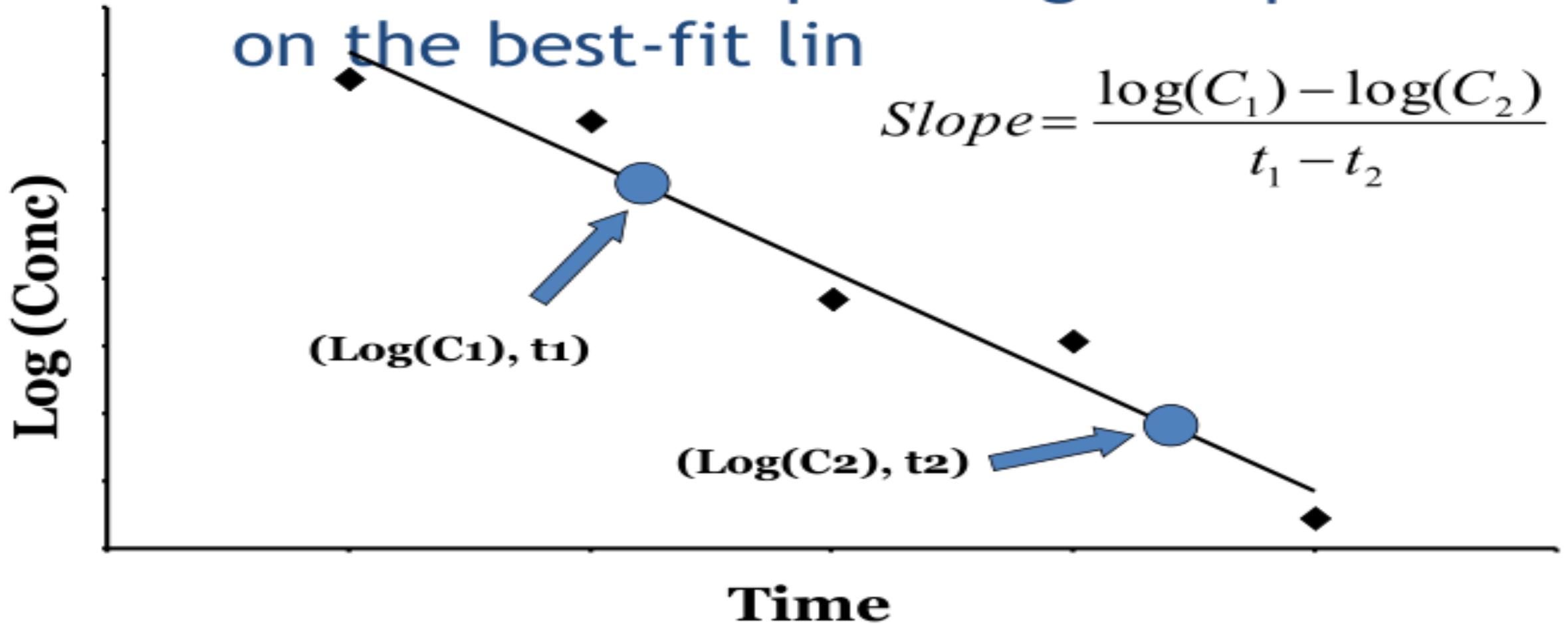
Cont,

2- Plot the best-fit line

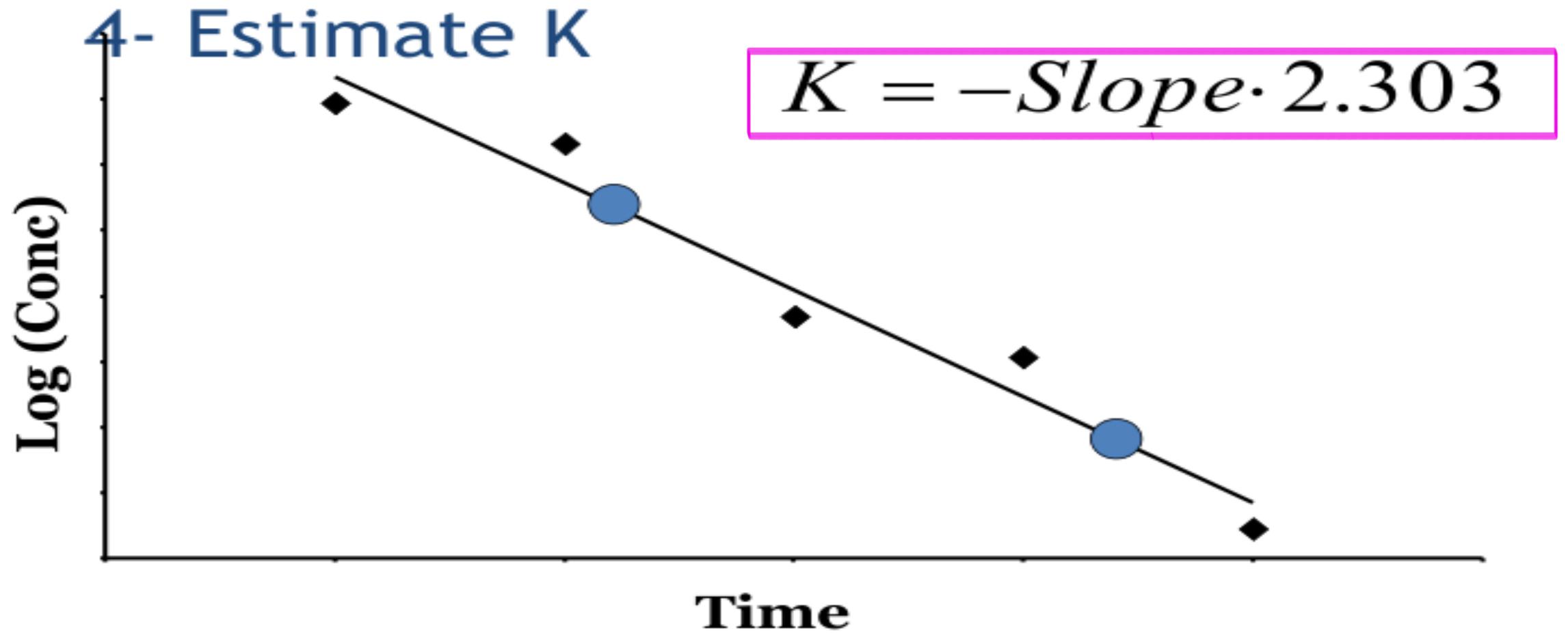


Cont,

3- Calculate the slope using two points on the best-fit line

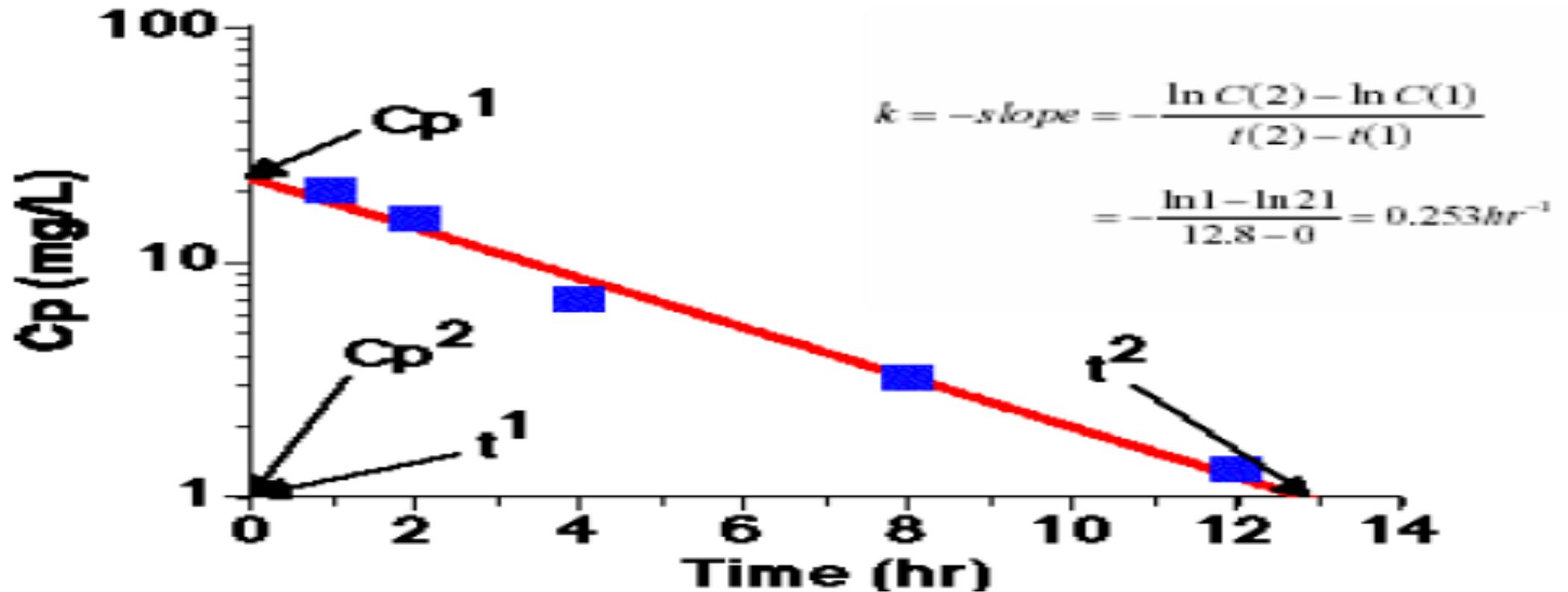


Cont,



example

Cp versus Time Data					
Time (hr)	1	2	4	8	12
Cp (mg/L)	20	15	6.8	3.2	1.3



Elimination half life

$$\rightarrow t_{1/2} = \frac{0.693}{K}$$

- **Elimination half-life ($t_{1/2}$)**
- Definition: Elimination half-life is the time it takes the drug concentration in the blood to decline to one half of its initial value.
- It is a **secondary parameter**: The elimination half-life is dependent on the ratio of clearance CL and VD.
- Unit : time (min, h, day)

Elimination half life ($t_{1/2}$) estimation

- Two methods:

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

- From the value of K:

- Directly from Conc vs. time plot

- Select a concentration on the best fit line (C_1)
 - Look for the time that is needed to get to 50% of C_1
→ **half-life**

Calculation of $t_{1/2}$

$$\frac{C_0}{2} = C_0 * e^{-k(t_2-t_1)} \quad \rightarrow \quad \frac{C_0}{2} / (C_0) = e^{-k(t_{1/2})}$$

$$\frac{C_0}{2C_0} = e^{-k(t_{1/2})} \quad \rightarrow \quad \frac{1}{2} = e^{-kt_{1/2}}$$

\rightarrow

$$\ln 0.5 = -kt_{1/2} \quad \rightarrow \quad -0.693 = -kt_{1/2}$$

القانون
الوقت

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

Cont,

Elimination half life ($t_{1/2}$)

- In **1** half-life **50.0 %** of the drug **remains** in the body and **50%** of the drug is **eliminated**
- In **2** half-lives **25.0 %** of the drug **remains** in the body, **75.0 %** of the drug is **eliminated**
- In **3** half-lives **12.5 %** **remains** in the body and **87.5 %** of the drug is **eliminated**
- In **4** half-lives **6.25 %** of the drug **remains** in the body, **93.75 %** is **lost**
- In **5** half-lives **3.125 %** of the drug remains in the body, **96.875 %** of the drug is **eliminated**
- In **6** half-lives **1.563 %** of the drug **remains** in the body, **98.438 %** is **lost**
- In **7** half-lives **0.781 %** of the drug remains in the body , **99.219 %** is lost

→ جس وقت دوا کا
بطلان ہو جائے
مناظرہ

• Thus over 95 % is lost or eliminated after 5 half-lives. Typically, with pharmacokinetic processes, this is considered the completion of the process [Although in theory it takes an infinite time]. Others may wish to **wait 7 half-lives** where over 99% of the process is complete.

clearance

Clearance

$$\begin{aligned} &\rightarrow Cl = k * Vd \\ &\rightarrow Cl = \frac{D_0}{AUC} \\ &\rightarrow Cl = \frac{\text{rate of elimination}}{\text{conc at specific time}} \end{aligned}$$

- Clearance is a measure of the removal of drug from the body
- Plasma drug concentrations are affected by the rate at which drug is administered, the volume in which it distributes, and its clearance
- The most general definition of clearance is that it is “a proportionality constant describing the relationship between a substance’s rate of elimination (amount per unit time) at a given time and its corresponding concentration in an appropriate fluid at that time.”

$$CL = \frac{\text{Rate of elimination}}{C_{\text{in plasma}}}$$

$C_{\text{in plasma}}$



Cont,

Clearance (Cl)

- Drugs can be cleared from the body by different pathways, or organs, including hepatic biotransformation and renal and biliary excretion. Total body clearance of a drug is the sum of all the clearances by various mechanisms.

ماہرہ یجیہ علیہ سوال
کسی

$$CL = CL_{\text{RENAL}} + CL_{\text{HEPATIC}} + CL_{\text{pulmonary}} \dots \text{other}$$

renal + nonrenal

* **Clearance** is the most important pharmacokinetic parameter

Calculation of clearance

Calculation of Clearance (1)

- Rate of drug change/elimination in the body =

$$\frac{dX_t}{dt} = -kX_t$$

- Amount of drug in the body =

$$X_t = V_D C_t$$

- Substituting X_t in above equation

$$\frac{dX_t}{dt} = -kV_D C_t$$

Unit: Volume/Time [L/h] or adjusted for body weight [l/h/kg]

- Dividing equation on both sides by C_p yields

$$\frac{dD / dt}{C} = \frac{-kV_D C}{C}$$

$$\frac{dD / dt}{C} = -kV_D = -Cl$$

Cont,

$$\frac{dA}{dt} = -k \cdot A \quad \rightarrow c \cdot V$$
$$\frac{1}{C} \times \frac{dA}{dt} = \frac{-k \times \cancel{C} \times V}{\cancel{C}} \Rightarrow \left(\frac{dA}{dt} \right) \frac{1}{C} = -k \times Vd = cl = k * Vd \dots \textcircled{2}$$

• Thus, elimination of drug with respect to drug concentration = Clearance

$$Cl = k V_D$$

$$k = \frac{Cl}{V_D}$$

• k is dependent on clearance & V_D

Rewriting concentration equation in one compartment i.v. bolus using V_D and Cl

$$C_p = \frac{X^0}{V_D} e^{-(Cl/V_D)t}$$

Remember that:

$$k = Cl/V_D$$

Concentration = dose/volume

Cont,

Clearance (Cl) estimation

- For ALL LINEAR pharmacokinetics (including one compartment), clearance is calculated using:

$$Cl = \frac{\text{dose}}{AUC} \quad AUC = \frac{D_0}{K \times V_d} \Rightarrow AUC = \frac{D_0}{Cl} \Rightarrow Cl = \frac{D_0}{AUC} \quad \text{--- (3)}$$

where AUC is the area under the concentration curve (it will be discussed later)

Clearance

Clearance of a drug is can also be defined by the ratio of the rate of elimination by all routes to the concentration of drug in plasma.

$$Cl = \frac{\text{Rate of elimination}}{C_{\text{in plasma}}} \quad \frac{[mg/h]}{[mg/L]}$$

Unit: Volume/Time [L/h] or adjusted for body weight [l/h/kg]

Units are in L/hr or L/hr/kg

هذا القانون مش مطلوب للإمتحان

$$Cl = Q * E_{\text{ratio}} \quad Cl = Q = \left(\frac{C_A - C_V}{C_A} \right) \quad \text{--- (4)}$$

Time to get certain concentration

Time to get to certain conc.

- Time to get to certain concentration (C^*) is given by:

$$C^* = C_0 \cdot e^{-K \cdot t} \quad \longrightarrow \quad e^{K \cdot t} = \frac{C_0}{C^*}$$

$$\longrightarrow \quad K \cdot t = \ln\left(\frac{C_0}{C^*}\right)$$

$$\longrightarrow \quad t = \frac{\ln\left(\frac{C_0}{C^*}\right)}{K}$$

لو ايجاني السؤال بالعكس وجماني كم ال time
اللي اهتمته حتى اول حد ال Conc .
بستعمل حد القانون ←

كلمة عن ال Conc المطلوب اول ال ال بيظهر اياه في المثال

Fraction of Dose Remaining (F)

- After absorption phase (if any) is complete, fraction of the drug gets to be eliminated and this is manifested by k .
- If $k = 0.1 \text{ hr}^{-1}$, it means that 10% of the drug is eliminated by the end of 1 hour. If $k = 0.3 \text{ min}^{-1}$, this means that 30% of the drug is eliminated by the end of 1 minute
- The remaining drug (un-eliminated) is called fraction of dose remaining (F)

Cont,

تعريف النصفية التي ضللت من الدواء بالجسم .

Fraction of Dose Remaining (F)

➤ **F** varies with time and can be easily determined knowing the time passed and **t_{1/2}**

If

$$X_t = X^0 e^{-kt}$$

$$\frac{X_t}{X^0} = e^{-kt}$$

$n = t / t_{1/2}$
number of t half

and

$$F = \frac{X_t}{D^0}$$

and

$$n = t / t_{1/2}$$

$$t = n * t_{1/2}$$

مثلا بحسب سؤال في مثلا كم عدد الـ $t_{1/2}$ التي انا اجتازها عشانا أخلص من الدواء بكل على حاد الأول .

then

$$F = e^{-kt}$$

$$F = e^{-\left[\frac{0.693}{t_{1/2}} * n(t_{1/2})\right]}$$

مثلا إذا ابر مكالي الـ $t_{1/2}$ تساعدي 6 ساعات كم قيمة n بعد 12 ساعة .

$$F = e^{-0.693n}$$

$$F = \left(\frac{1}{2}\right)^n$$

$$n = \frac{12}{6} = 2$$

n is the number of Half-lives elapsed after a bolus dose

لو مكالي مثلا بدعي كمية الدواء التي ضللت عندي بالجسم

$$F = \left(\frac{1}{2}\right)^2 = 0.25\% \quad n=2 \quad \text{كانت}$$

Remaining عن 25% ضل و 75% طلع من الجسم .

Cont,

- By knowing $t_{1/2}$ we can determine the fraction of remaining dose in the body at any time point after bolus i.v. injection

- Example, how many half-lives is required to eliminate 90% of a drug?

➤ This means that 10% is remaining

(F)

$$\text{➤ } 0.1 = (1/2)^n \rightarrow \log_{0.5} 0.1 = n$$

$$\text{➤ } n = \log_{10} 0.1 / \log_{10} 0.5$$

$$\text{➤ } n = -1 / -0.3 = 3.333 \text{ half-lives}$$

$$F = \left(\frac{1}{2} \right)^n$$

$$0.1 = \left(\frac{1}{2} \right)^n \Rightarrow \log 0.1 = n \log \frac{1}{2}$$

$$n = \frac{\log 0.1}{\log 1/2} = \frac{-1}{-0.3} = 3.33$$

معناها بعد ما يبقى القيمة بنسبة 90% من الدواء .

example

$$t_{1/2} = \frac{0.693}{K} = \frac{0.693}{0.2} = 3.48 \text{ hr}$$

ساعة الـ conc

2 ينزل عن 4 إلى 2 ف بالفرع الثاني من السؤال عشان أتأكد إني بجد مع
بأنه طلب الـ conc عند 4 h ف لازم يطالع أمثل عن 2 .

Case 1

→ amount (A₀)

A 40-mg dose of a drug was administered as an intravenous bolus injection. The drug has the following pharmacokinetic parameters: $k = 0.2 \text{ h}^{-1}$ and $Vd = 10\text{L}$

→ plasma & interstitial في الدواء

elimination rate constant

first order

1. Calculate the initial concentration (C_0) = $\frac{\text{amount}}{V} = \frac{40}{10} = 4 \text{ mg/L}$
2. Calculate the plasma concentration 4h following administration $\ln C = \ln C_0 - K \Rightarrow \ln C = \ln 4 - 0.2 = 1.38 - 0.2 = 0.58$
3. Calculate the time required for the concentration to drop to 1 mg $\Rightarrow \ln C = 0.58$
 $C = 1.79 \text{ mg/L}$
كأنه أقل من 2 معناها حل مع .
4. If the initial C_p is unsatisfactory, Calculate the dose required to provide an initial plasma concentration of 6 mg/L

Cont,

Example 1

4) If the initial C_p of 4 is unsatisfactory, Calculate a dose to provide an initial plasma concentration of 6 mg/L

$$C_0 = \frac{\text{dose}}{Vd} \quad \longrightarrow \quad \text{dose} = C_0 \cdot Vd$$
$$\text{dose} = 6 \frac{\text{mg}}{\text{L}} \cdot 10 \text{ L} = \underline{60 \text{ mg}}$$

Or we can say that a dose of 40 mg resulted in a concentration of 4 mg/L, how much does is required to achieve 6 mg/L

$$X_0 = \frac{6 * 40}{4} = 60 \text{ mg}$$