

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

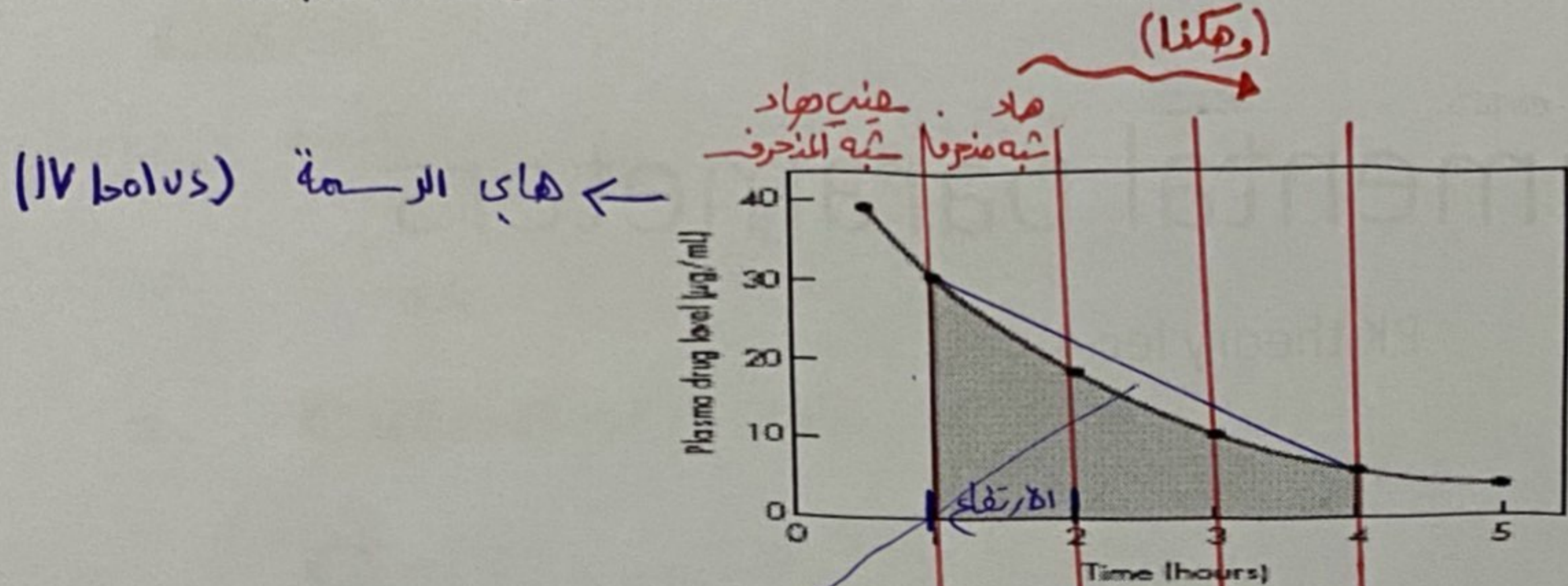
AUC $\xrightarrow{\text{عن طريق}}$ $AUC = \frac{C_0}{k}$
 $\xrightarrow{\text{trapezoidal rule}}$

* بالامتدحان ما راح يكون في سوال انه شبه منحرف واقعد اقسّم ارك تكون الـ [AUC] بتكون جاهزة.

How to calculate AUC?

(مساحة شبه المنحرف)

- 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)**.



شو هيا مساحة شبه المنحرف
 بيدي اقسّم هيا الرسة
 ل مجموعة Parts

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

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:

* لو هيا ايسب الـ $[AUC]_1^4$

راح فوخرها ع $[AUC]$ من $[AUC]_1^2 + [AUC]_2^3 + [AUC]_3^4$

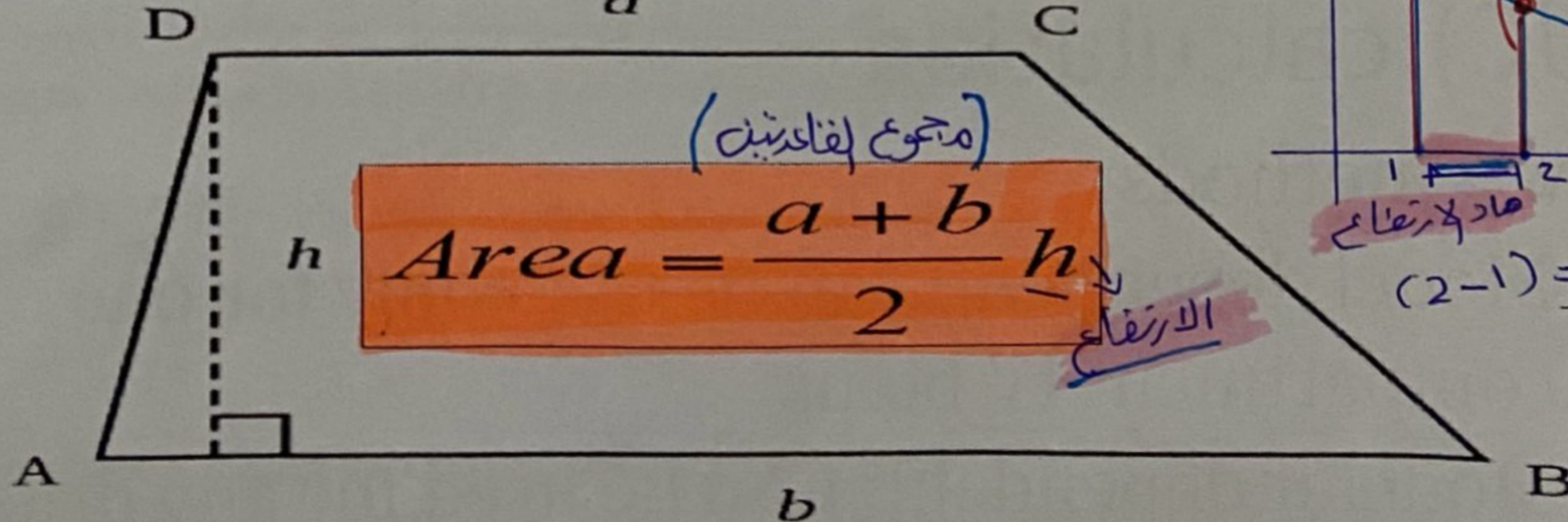
طب راح تسأل حالك ليه ما فوخرها من $[AUC]_1^4$ مباشرة بدون ما تقسم

لانه حاكم في مافه
 زيادة
 وهياي ثمانية ما راح
 اقدر اكتبها

Cont,

For sure you know!

- What is the trapezoid?

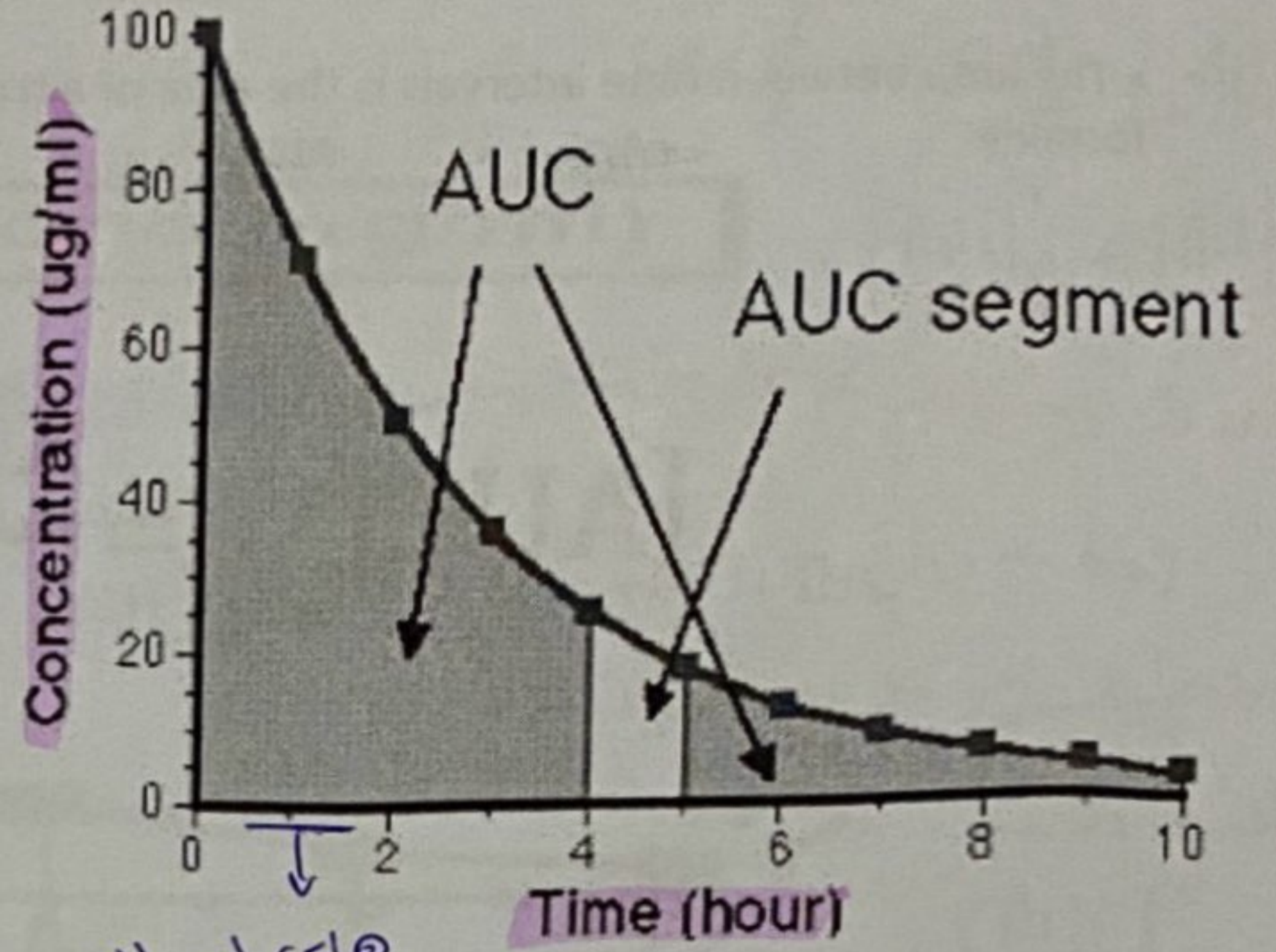


- The area of the trapezoid is equal to what?

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.



ہائی لحسابہ
ہیلا ارتفاع

* کہیپ ہون لکھیلنا انو مچبور اوخندو کہ اقسام

بردا عید ال [AUC] بالامتحان جابزة تمام؟

ہین ہاد لبقسیم والسبہ منخوف مشا رح محتاجوا

خلص ہو یون معطلین انو ال $(AUC)_2^3$ فلا کنا

دش ولا لام

Cont,

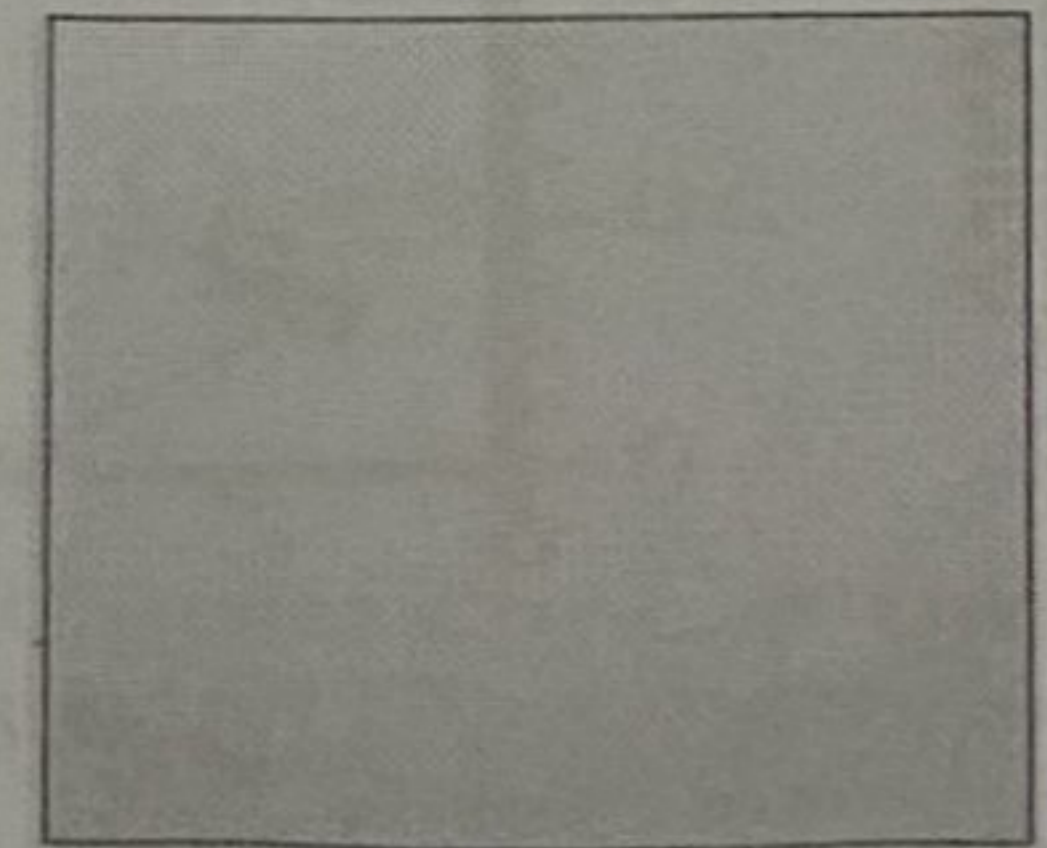
Area under the plasma concentration versus time curve

- 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:

المجموع إقاعہین
concentration ال

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

الارتفاع = فرق لوقت



Model-independent Approach
Trapezoidal Rule

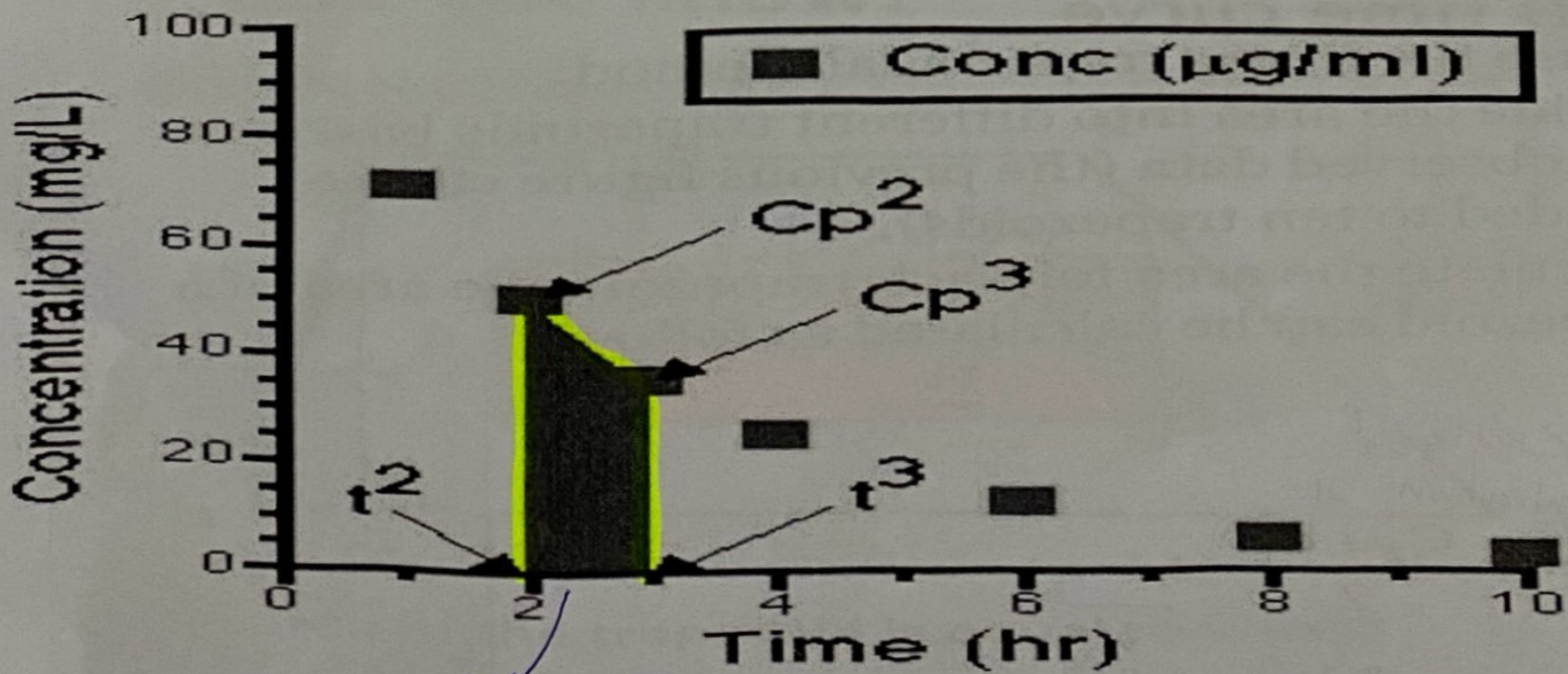
- The area between time intervals is the area of a trapezoid and can be calculated with the following formula:

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

هنا يمكننا ان نستخدم قاعدة
trapezoidal
[AUC] نأخذ كل
كالها

Cont,

Area between t2 and t3

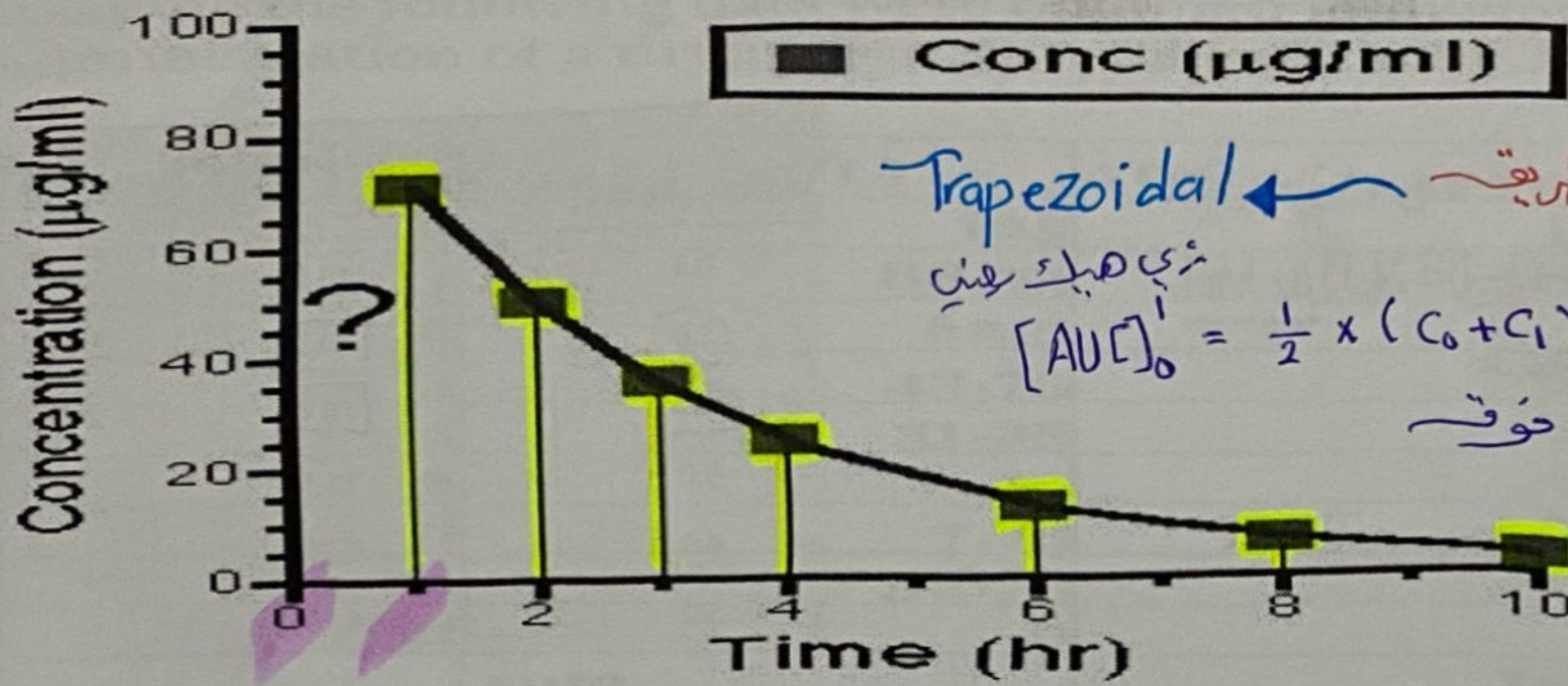


هي مساحة شبه المثلث

$$[AUC]_2^3 = \frac{1}{2} \times (C_2 + C_3) \times (3 - 2)$$

Cont,

$$\text{Total Area} = [AUC]_0^1 + [AUC]_1^2 + [AUC]_2^3 + [AUC]_3^4 + [AUC]_4^5 + [AUC]_5^6 + [AUC]_6^7 + [AUC]_7^8 + [AUC]_8^9 + [AUC]_9^{10}$$



* كل هادول بوجودهم عن طريقه
Trapezoidal

$$[AUC]_0^1 = \frac{1}{2} \times (C_0 + C_1) \times (t_1 - t_0)$$

بنطبق على كل ابي فوق

$$[AUC]_{10}^{\infty}$$

ما عدا الـ
بنطبق على هاد القانون
للتناظر وحدة
الـ (Last) الى صنف اوجدها من لـ
بنطبق على هاد القانون

$$[AUC]_{10}^{\infty} = \frac{C_{Last}}{K}$$

Cont, ليه عالوا نشوف كيف بدنا نوجد الـ [AUC]

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

$$AUC_{0-1} = \left\{ \frac{C_{p0} + C_{p1}}{2} \cdot (t_1) \right\}^{(1-0)=1}$$

- The last segment:

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

- Then: $AUC^{0-\infty} =$???

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

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

الارتفاع (فرق الوقت)

Time (hours)	Plasma Drug Level ($\mu\text{g}/\text{mL}$)
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,

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

$$[AUC]_{1-4}^h = [AUC]_{1-2}^h + [AUC]_{2-3}^h + [AUC]_{3-4}^h$$

$$= 24.35 + 14.75 + 8.94$$

$$= 48.04 \mu\text{g}\cdot\text{h}/\text{mL}$$

$\frac{30.3 + 18.4}{2} \times (2-1) = 24.35$
 $\frac{18.4 + 11.1}{2} \times (3-2) = 14.75$
 $\frac{11.1 + 6.77}{2} \times (4-3) = 8.94$

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

[AUC] جاهزة ت

example] → (زي هيك بلون)
السؤال الامتحان
(مش زي سبغ الحروف)

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

→ [AUC]₀¹
→ [AUC]₁²
→ [AUC]₂³
→ [AUC]₃⁴
(1-2)

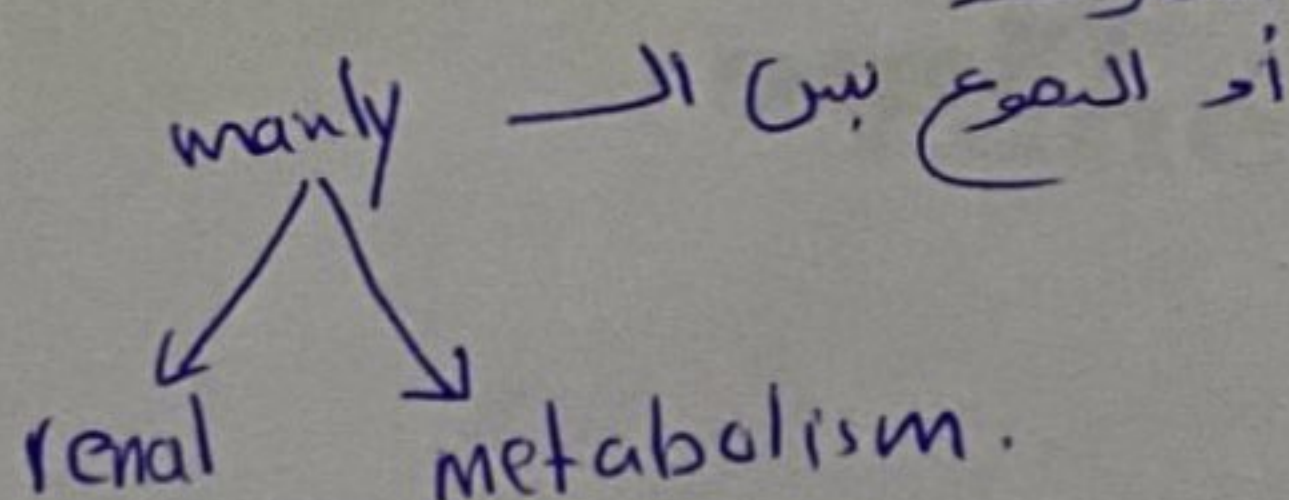
Elimination rate

Elimination rate constant (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

- $K = K_{\text{renal}} + K_{\text{metabolism}} + K_{\text{...}}$ ————— يمكن ديه بغير عفن
الـ elimination لـ drug
- All are responsible of decline of plasma concentration ————— عن طريق التعرف



Elimination rate constant estimation

1. Plot $\log(C)$ vs. time
2. Plot the best-fit line
3. Calculate the slope using two points on the best-fit line
4. Estimate K:

لانه لا
قاع بنزل
elimination

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

elimination rate constant estimation :-

سلاپ

In log

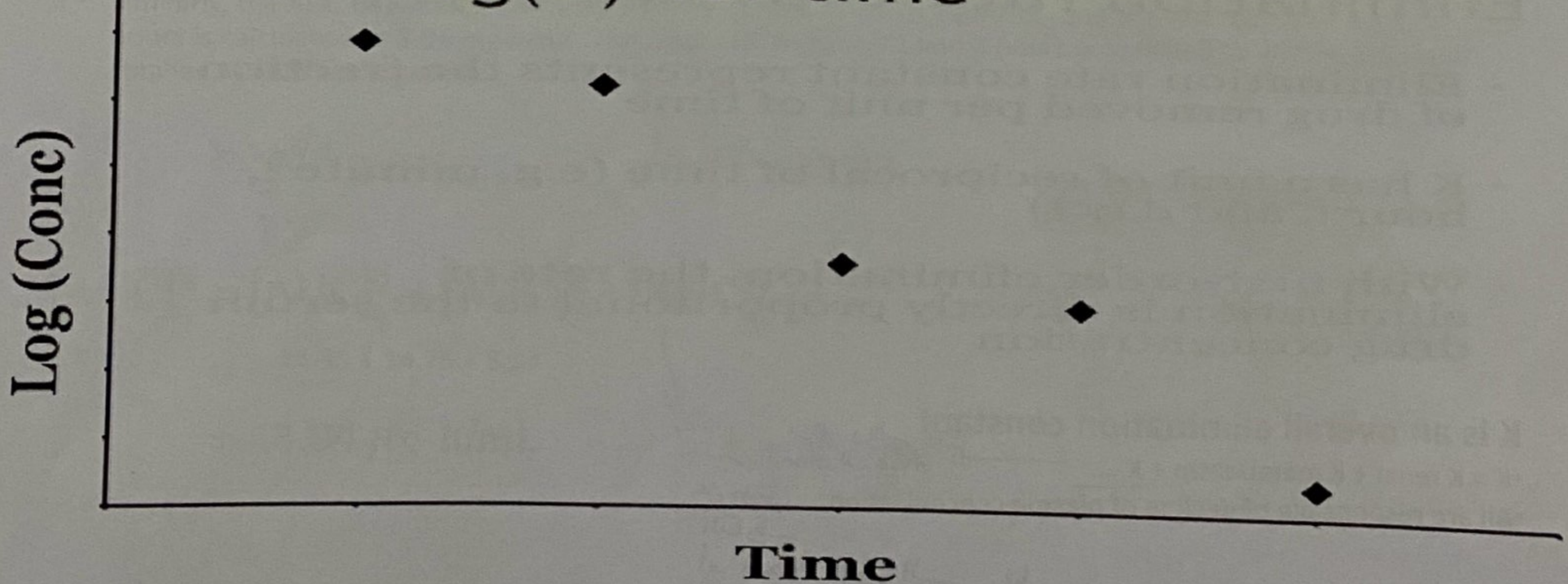
$$\text{Slop} = \frac{-k}{2.303}$$

$$\text{Slop} = -k \times 2.303$$

میری ماہکینا قبل عارفین
ابو کیف اعرفا \log و \ln
بطلو ع (7) ←

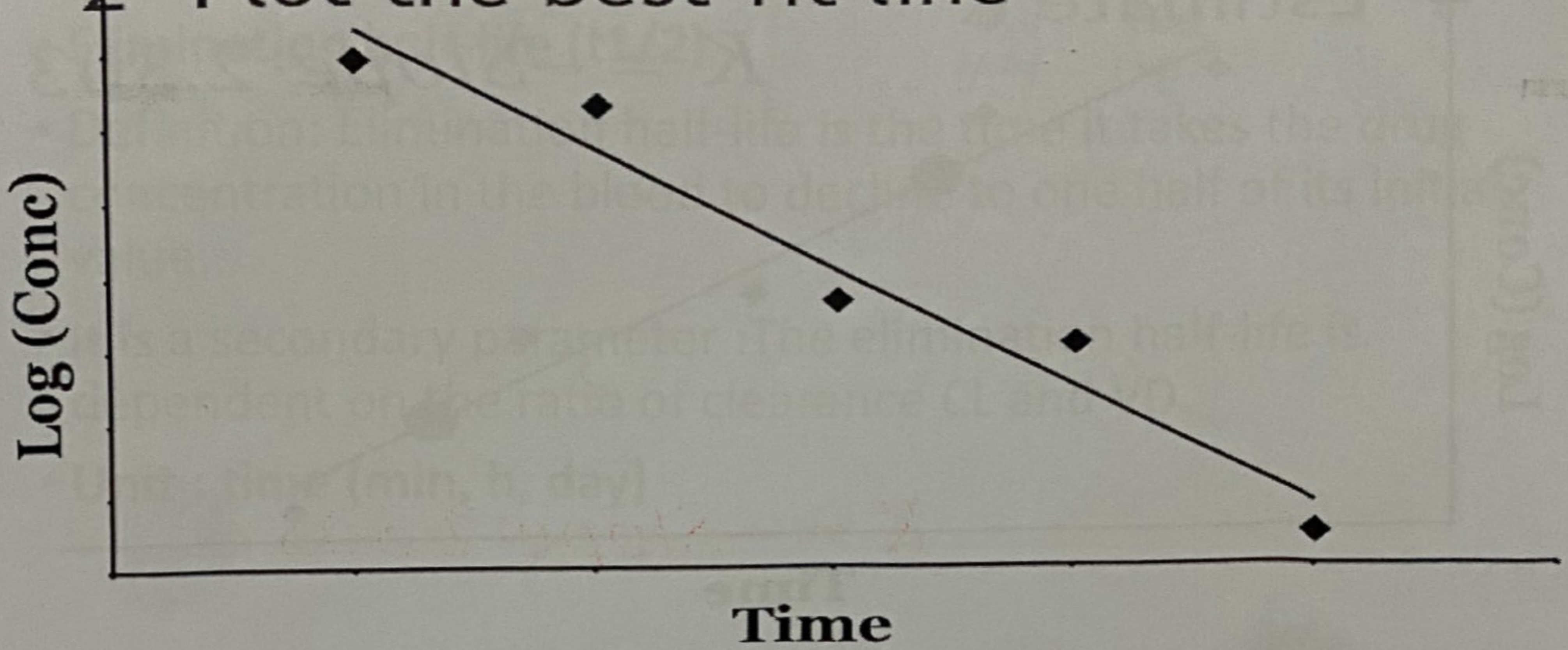
Cont,

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



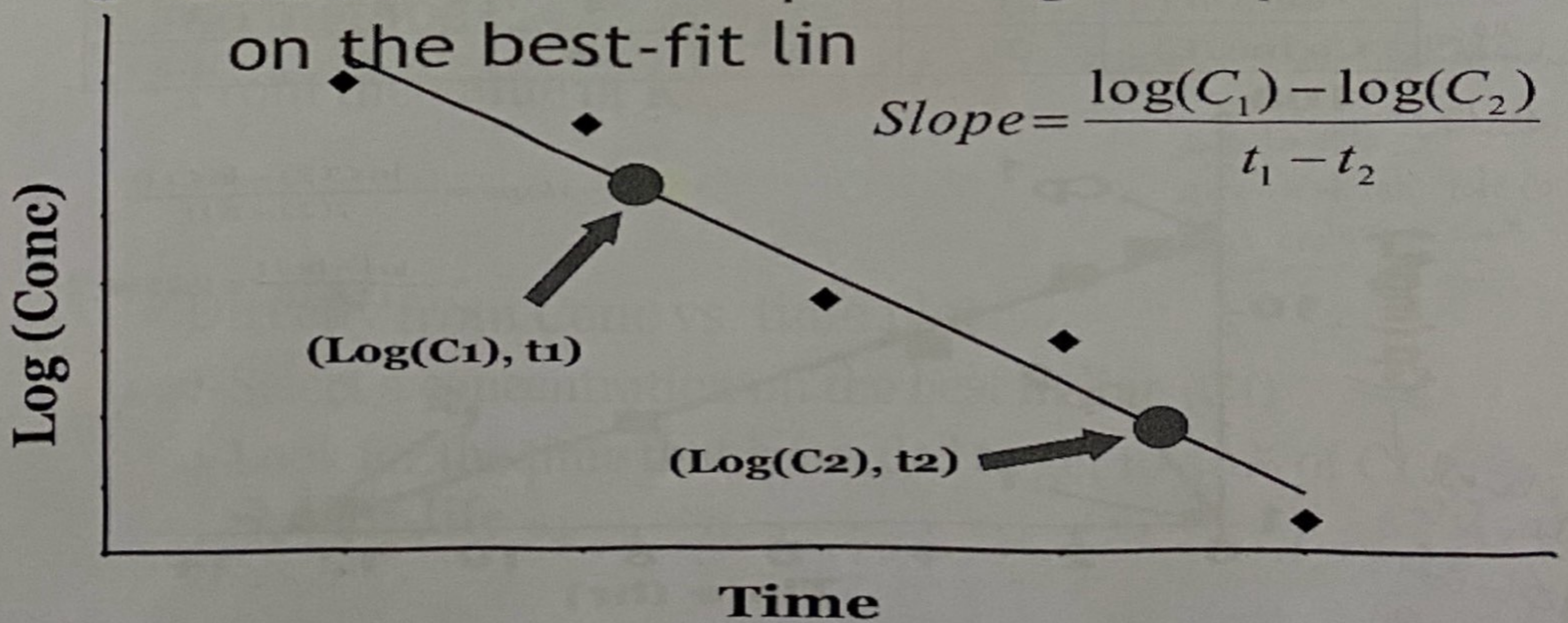
Cont,

2- Plot the best-fit line

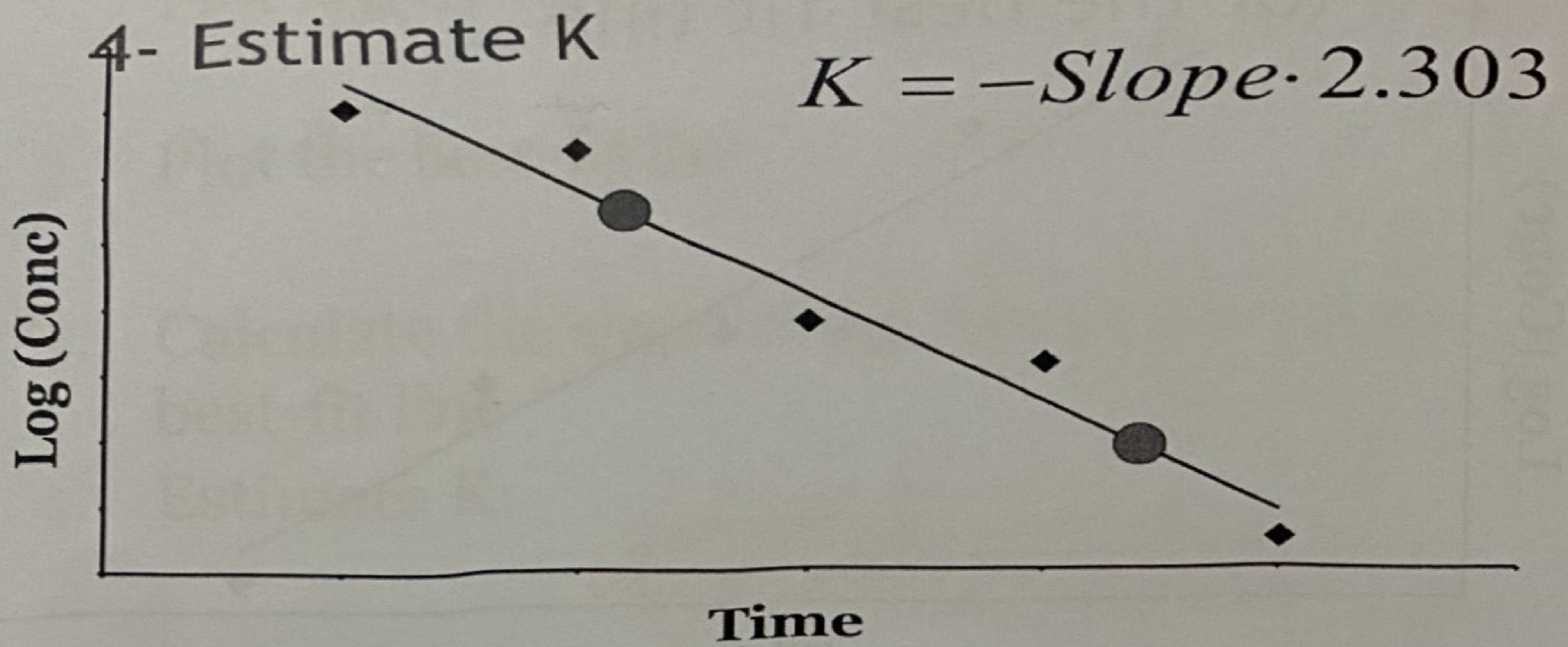


Cont,

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



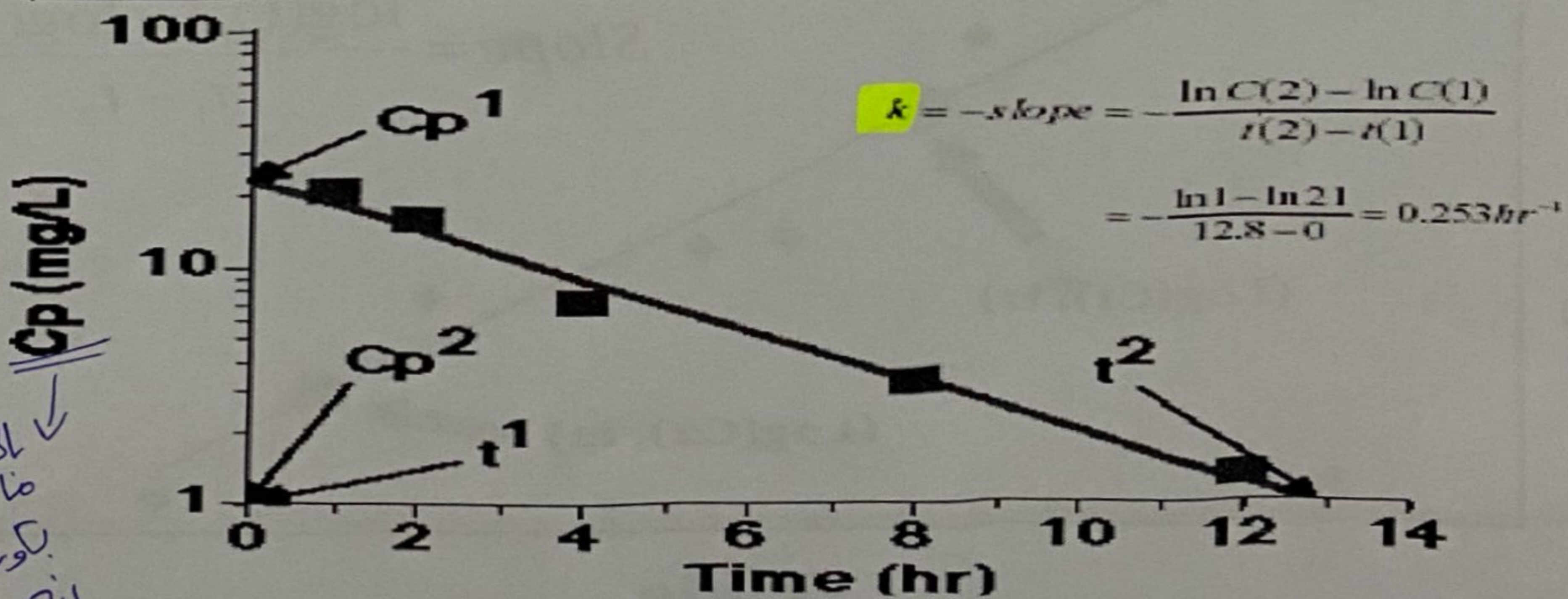
Cont,



example

Concentration

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



الاستجاب
ما يكون هناك
يكون طائفي
انه والاسلوب
او log



Elimination half life

* هلكتنا اذا كان
 First order) انتكون الوحدة
 1/time
 1/min (min)⁻¹
 1/hoer (hoer)⁻¹
 1/day (day)⁻¹

- **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

فنا هاد لقانون
 * لبقدر ادينا t_{1/2} من ك او العكس

- Two methods:
 - From the value of K:

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

مباينه انا تيفاصل
 First order kinetics
 ههناكو t/2
 وهكتنا انو t/2 هانصيد
 elimination rate constant
 First order. في الـ

- Directly from Conc vs. time plot
 - Select a concentration on the best fit line (C₁)
 - Look for the time that is needed to get to 50% of C₁
 → **half-life**

Calculation of $t_{1/2}$

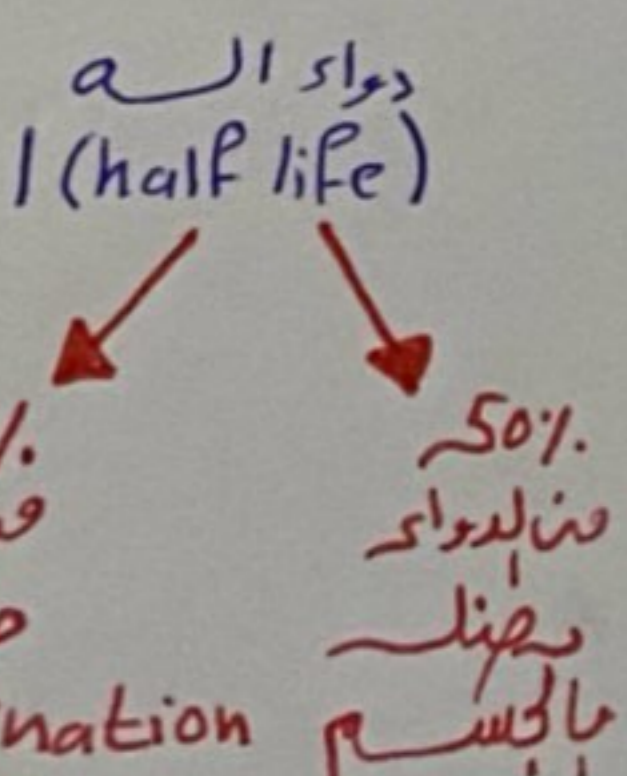
$$\frac{C_0}{2} = C_0 * e^{-k(t_2-t_1)} \quad \rightarrow \quad \frac{C_0}{2} / (C_0) = e^{-k(t_{1/2})}$$

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

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

$$-0.693 = -kt_{1/2}$$

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



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

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.

لأنه :- هيك كليل
بعد مرور 5 ساعات
فقط 3.125% من الدواء تبقى
بعد مرور 7 ساعات
فقط 0.781% من الدواء تبقى
(تعتبر عليه elimination)

* أقيس كمية الدواء التي فقدت من الـ (body) clearance

Clearance

- 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."

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

$C_{\text{in plasma}}$

Plasma drug concentrations

ح يتأثر بتغيرها

① كم أنا الـ (dose) إلى أعطينها، لكنه حكيمة عن (first order) كل ما أعطيت dose أكبر وصلت volume أكبر يعني توصل tissues بكمية أكبر (distribution) ، لكن هو من كونه volume quick distribution يعني أنه صار عندي

Clearance - قده لفقد الدواء من الجسم. ليتفرص في عندي دواء ببطء يكون الـ clearance عالي زي Penicillin

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.

$$CL = CL_{\text{RENAL}} + CL_{\text{HEPATIC}} + CL_{\text{pulmonary}} + \dots + \text{other renal} + \text{nonrenal} \rightarrow CL_{\text{total}}$$

* Clearance is the most important pharmacokinetic parameter

من كونه الـ elimination بتخلصه عن طريق الكلى - liver - الخ... نقل الدواء الـ clearance.

$$C = \frac{X}{V_d}$$

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

$$\frac{dX_t}{dt} = -k(V_D C_t)$$

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

نقسم الطرفين
ع Concentration

Dividing equation on both sides by C_p yields

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

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

$$Cl = k \times V_d \quad \text{--- ② القانون الثاني}$$

$$Cl = k \times \frac{D_0}{k[AUC]_0^\infty}$$

$$Cl = \frac{D_0}{[AUC]_0^\infty} \quad \text{--- ③ القانون الثالث}$$

Cont,

- Thus, elimination of drug with respect to drug concentration =

Clearance

$$Cl = kV_D$$

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

- k is dependent on clearance & V_D

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

$$C_p = \frac{X^0}{V_D} e^{-(Cl/V_D)t} \quad C_t = \frac{C_0}{V_D} e^{-k t}$$

\downarrow \downarrow
 $\frac{X_0}{V_D}$ $\times e^{-(Cl/V_D)t}$

Remember that:

$$k = Cl/V_D$$

Concentration = dose/volume

Cont,

Clearance (Cl) estimation

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

$$Cl = \frac{\text{dose}}{AUC} \rightarrow \text{القانون الثالث}$$

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.

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

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

Units are in L/hr or L/hr/kg
 كاهون لازم
 قسم ع Kg

Time to get certain concentration

Time to get to certain conc.

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

لو كان السؤال
 هايبية C*
 و C₀ و K
 ما التيا كم لورا
 استغرق وقت
 عاشا ينزل ونا
 C₀ = 10
 C* = 5
 (5 → 10)

بد اوهون شال (-)
 و قلب لكر
 هاد لاشي بس
 بالنايمز
 duration
 of action
 درج بيشون عليها
 اسله حد
 lecture (5)

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

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

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

تأخذ ال n اللطرين

$$\frac{5}{10} = \frac{10}{10} \times e^{-7 \times t}$$

$$\frac{5}{10} = e^{-7 \times t}$$

$$\ln\left(\frac{5}{10}\right) = -\frac{7}{1} t$$

$$t = \frac{\ln\left(\frac{5}{10}\right)}{-7}$$

Fraction \leftarrow شوية
 كم هزيت من ال dose صلت
 موجودة بالجسم

في $t = 1/2$ -
 Fraction \leftarrow هاد هو
 in 2 half lives 25% of the drug remains
 in the body . 75.0% of the drug is eliminated

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

شوية
 هين بالساعة
 هار عنك
 10%
 elimination
 للساعة
 هاد هين انه
 30%
 هين
 بالساعة

The remaining drug (un-eliminated) is called fraction of dose remaining (F)

هين هوريب بسالني عن
 Fraction of Dose Remaining
 هاد هين انه قائم بسالني عن
 (Un-eliminated) :- كمية الي ما هار اليا
 (elimination)

او هخلطام عن هاد هين
 احسن
 (Cont)

(طيب ، هون بيضا شوية شوقانون لاد)

Fraction of Dose Remaining (F)

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

First order If

قسمة طرفنا X_0 بهين
 $X_t = X_0 e^{-kt}$
 $\frac{X_t}{X_0} = e^{-kt}$

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

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

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

then $F = e^{-kt}$

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

$F = e^{-0.693n}$

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

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

هين الحكيوم
 ال amount ال
 هلت بالجسم
 عند t هين
 X_0 (dost ال)
 ال هين

تصرفوا هاد عن
First order. $X_t = X_0 e^{-kt}$

تقسم X_0 عن طرفين
 $\frac{X_t}{X_0} = e^{-kt}$

شاي فبر = f

يعني بتكيلي كم ال (amount)

الي دخل بالجسم عند معين

(من ال dose الاصلية) X_0

ف هاد يعني انه لقانون

$f = e^{-kt}$ → number of half life.

لو بدي اكتب كم ال half life ل دواء (n) بتخلي

$n = \frac{t}{t_{1/2}}$ → كل ال drug من ال
اصليه انا ل آخر لحظو
صدر ال (elimination)

ع (وحدة half life) $t_{1/2}$

لو half life = 8 و total = 16 كم $n = 2$

$n = \frac{16}{8} = 2$ هاد ل يقدر با n

تعالوا نفوض
بالقانون في فوق

$f = e^{-kt}$
 $f = e^{-\left(\frac{0.693}{t_{1/2}}\right) \times n \times t_{1/2}}$

تأخذ ال \ln
للا طرفين

$f = e^{-0.693n}$

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

باربي
تأخروا
فاهين
علي
😊

دعني اعرف
فشي عندي رما
ارحمني ابرم مانش

مستكم رما
مستكم

جيباً عادياً بالوال يا ونا مدهيني
 مدهيات انا متا حاجتها برتب افكاريا وكل

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

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

* هون كيلي تم
 half life
 كتاجوا ل اعمل
 elimination
 ل اعمل ل 90%
 فن الدواء

(F)

$$0.1 = \left(\frac{1}{2}\right)^n \rightarrow \log_{0.5} 0.1 = n$$

$$n = \frac{\log_{10} 0.1}{\log_{10} 0.5}$$

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

elimination = 90%

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

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

هنا ال 0.9 ك

$$k = 0.9$$

ف الي فنل بايهم = 10%

$$F = 0.1 \text{ (10\%)}$$

لبس بوجرا
 التي هو تصيف
 مباشر لقانون

example $X_0 = 40 \text{ mg}$

$$k = 0.2$$

Case 1 $V_d = 10 \text{ L}$

- 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 $V_d = 10 \text{ L}$

1. Calculate the initial concentration (C_0) $C_0 = \frac{X_0}{V_d} = \frac{40}{10} = 4 \text{ mg/L}$
2. Calculate the plasma concentration 4h following administration $C_t = C_0 = e^{-kt}$
3. Calculate the time required for the concentration to drop to 1 mg
4. If the initial C_p is unsatisfactory, Calculate the dose required to provide an initial plasma concentration of 6 mg/L

$$1 = 4 \times e^{-0.2t}$$

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• Initial plasma concentration = 6 mg/L →

Cont,

Case 1

1. Calculate the initial concentration (C_0)

$$C_0 = \frac{\text{dose}}{V_d} = \frac{40 \text{ mg}}{10 \text{ L}} = 4 \text{ mg/L}$$

2. Calculate the plasma conc. at 4 h

$$C = C_0 \cdot e^{-K \cdot t} = 4 \cdot e^{-(0.2) \cdot (4)} = 1.79 \text{ mg/L}$$

1. Calculate the time required for the concentration to drop to 1 mg

$$t = \frac{\ln\left(\frac{C_0}{C^*}\right)}{K} = \ln\left(\frac{4}{1}\right) / 0.2 = 6.9 \text{ hr}$$

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

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

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

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