PK fundamental parameters

PK theory lec.4

Area under the curve (AUC)

from parameters but not fundamental parameters

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

بهاي الطريقة بتقدر نحسب المساحة تحت المنحنى لاي شكل من الاشكال الدوائية عن طريق قانون شبه المنحرف

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).

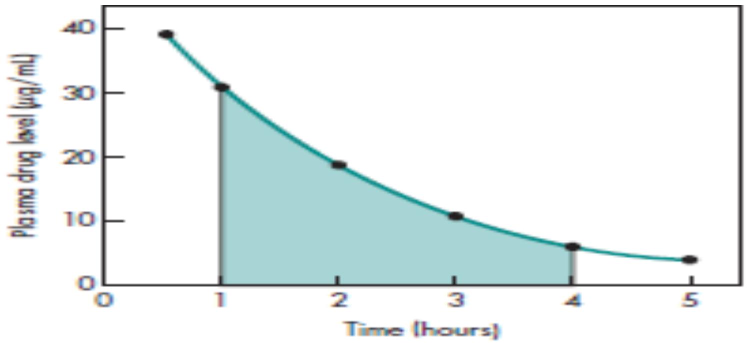


FIGURE 2-2 Graph of the elimination of drug from the plasma after a single IV injection.

شبه منحرف ؟

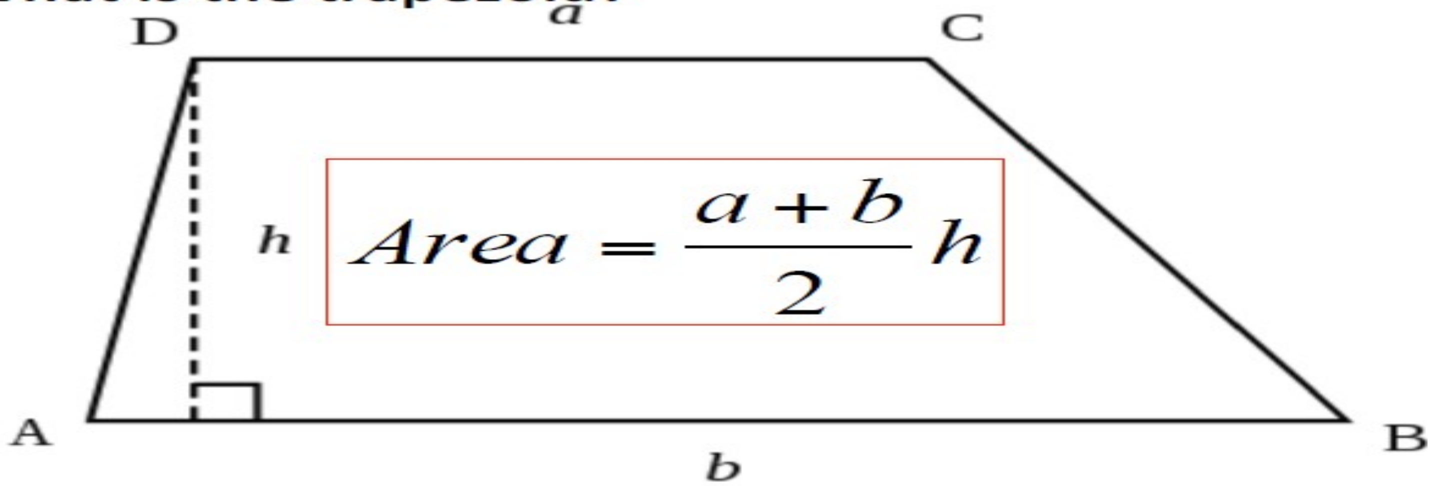
$A = \frac{1}{2}$ (مجموع القاعدتين) (الارتفاع)

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!

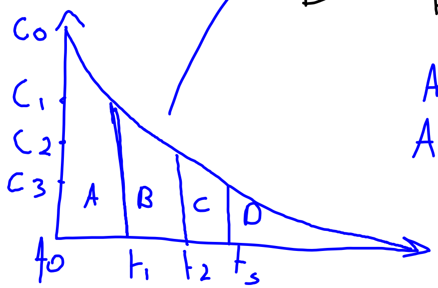
- **What is the trapezoid?**



$$Area = \frac{a+b}{2}h$$

- **The area of the trapezoid is equal to what?**

$$\frac{\Delta y}{\Delta x} = \frac{\ln C_2 - \ln C_3}{t_2 - t_3} \quad \text{or} \quad \frac{\log C_2 - \log C_3}{t_2 - t_2} * 2.303$$



$$AUC_A = \frac{1}{2}(C_0 + C_1) * (t_0 - 0)$$

$$AUC_B = \frac{1}{2}(C_1 + C_2) * (t_2 - t_1)$$

$$AUC_C = \frac{1}{2}(C_2 + C_3)(t_3 - t_2)$$

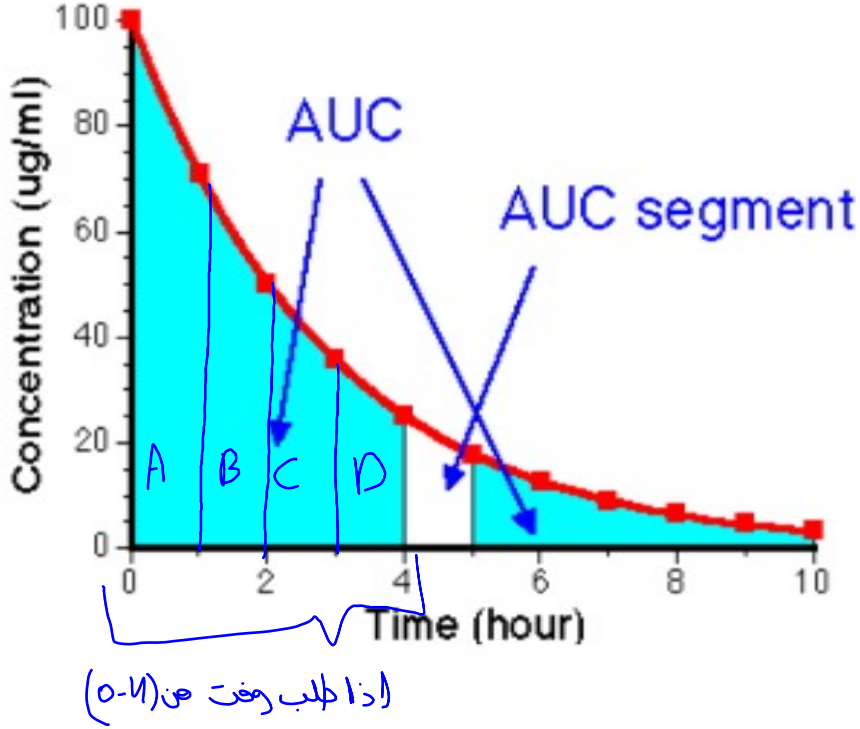
$$AUC_D = \frac{1}{2}(C_3 + 0)(t_\infty - t_3) = \frac{C_3}{K}$$

$$AUC_{tot} = AUC_A + AUC_B + AUC_C + AUC_D$$

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:

هون بس بوضح طريقة حساب المساحة تحت المنحنى وانه بقسم المنحنى
لاكثر من شبه منحرف مثلا عشرة وبحسبهم عن طريق القانون اللي بالسلايد

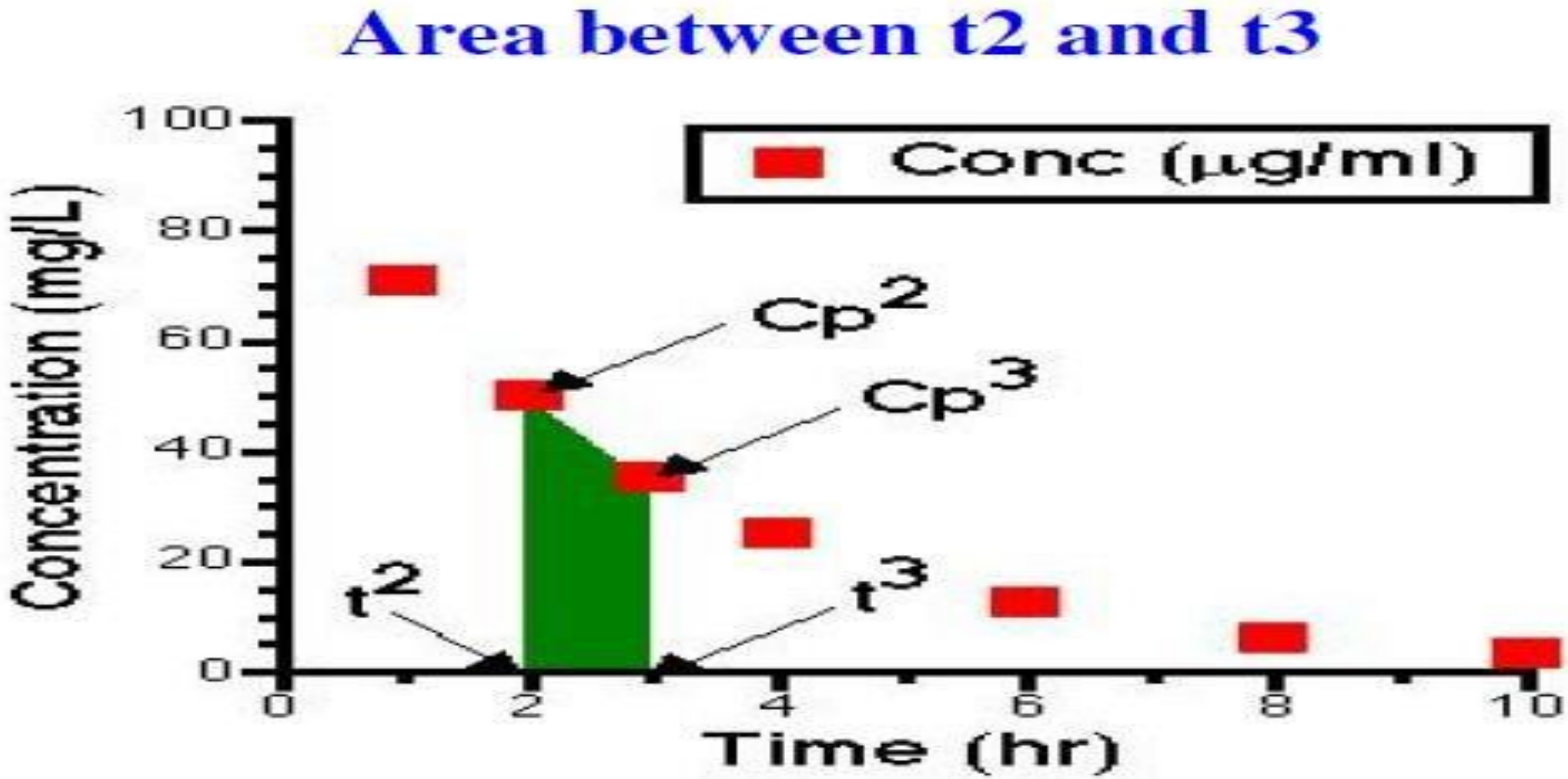
$$\text{area} = \frac{C_2 + C_1}{2} \cdot (t_2 - t_1)$$

Model-independent Approach Trapezoidal Rule

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

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

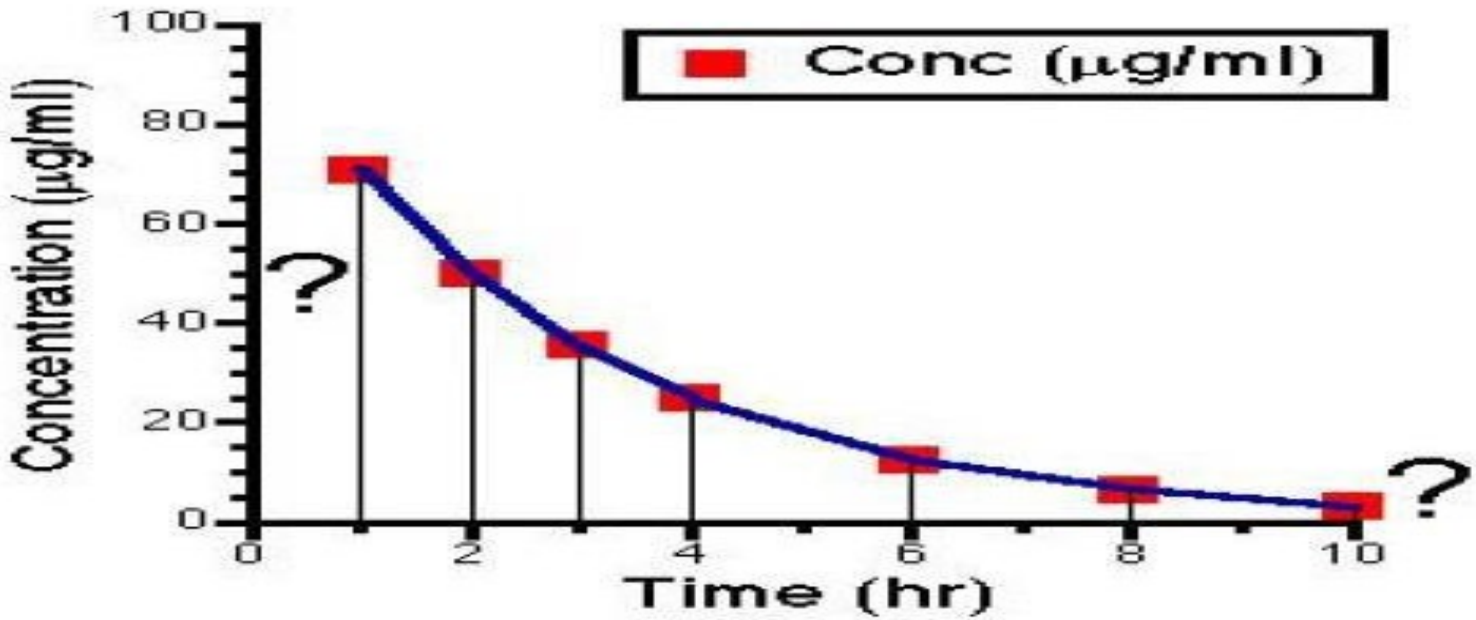
Cont,



Area between t2 and t3
Conc (µg/ml)
Concentration (mg/L)
Time (hr)
Cp2
Cp3
t2
t3
0
20
40
60
80
100
0
2
4
6
8
10

Cont,

Total Area



Cont,

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

$$AUC_{0-1} = \left\{ \frac{Cp_0 + Cp_1}{2} \bullet (t_1) \right\}$$

- The last segment:

$$AUC^{t_{last}-\infty} = \int_{t=t_{last}}^{t=\infty} Cp \bullet dt = \frac{Cp_{last}}{k}$$

- Then:

$$AUC^{0-\infty} = \; ??$$

AUC unit: Conc. * time

Ex: mg*ml^{-1} *h = mg*h/ml

exampl
e

- 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

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

Time (hours)	Plasma Drug Level (μg/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 *m*g·h/mL, and the AUC between 3 and 4 hours is calculated as 8.94 *m*g·h/mL. The total AUC between 1 and 4 hours is obtained by adding the three smaller AUC values together. :

$$[AUC]_{t_1}^{t_4} = [AUC]_{t_1}^{t_2} + [AUC]_{t_2}^{t_3} + [AUC]_{t_3}^{t_4}$$

$$= 24.35 + 14.75 + 8.94$$

$$= 48.04\ \mu g \cdot h/mL$$

Time (hours)	Plasma Drug Level (μg/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

exampl
e

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

calculate $t_{\frac{1}{2}}$?! $t_{\frac{1}{2}} = \frac{0.693}{K} = \frac{0.693}{0.35} = 1.98$ hour

calculate the concentration after two hour ?! $\ln A = -Kt + \ln 125$

$\ln A = -0.35(2) + \ln 125$

$\ln A = 4.1283 \Rightarrow A = 62.07$

calculate the rate after two hour ?!

$\frac{dA}{dt} = -KA = -0.35 * 62.07 = -21.72$ mg/L hr

Elimination rate

Elimination rate constant (K) → (percentage)

- 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 renal + K metabolism + K.....
- All are responsible of decline of plasma concentration

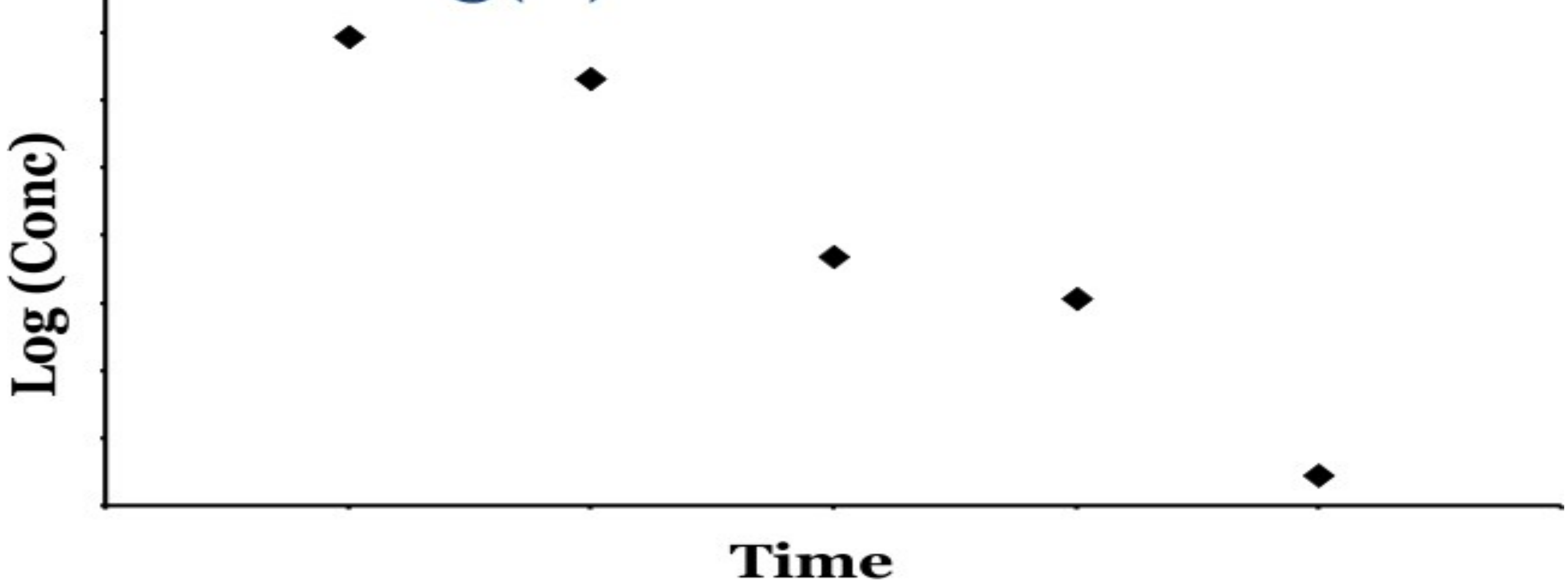
Elimination rate constant estimation

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:

$$K = -Slope \cdot 2.303$$

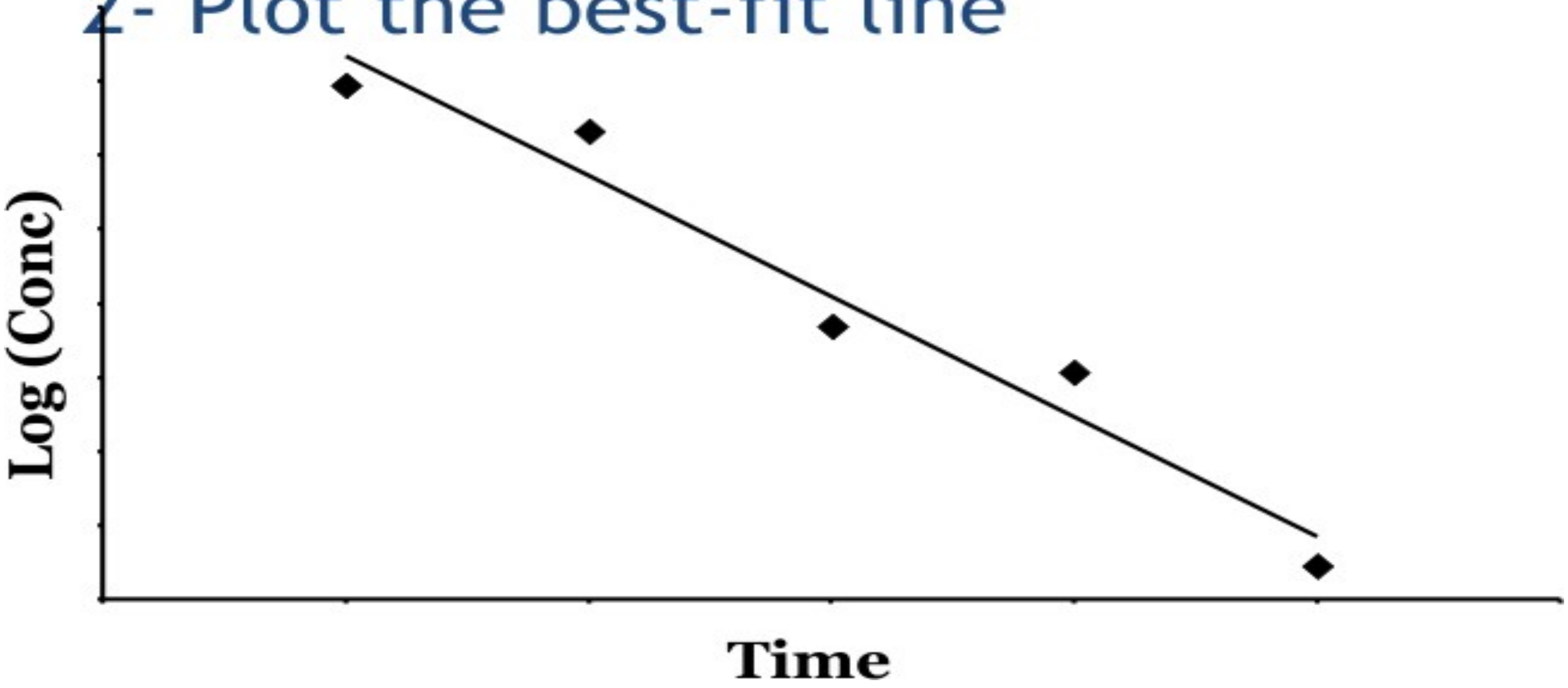
Cont,

1- Plot log(C) vs. time



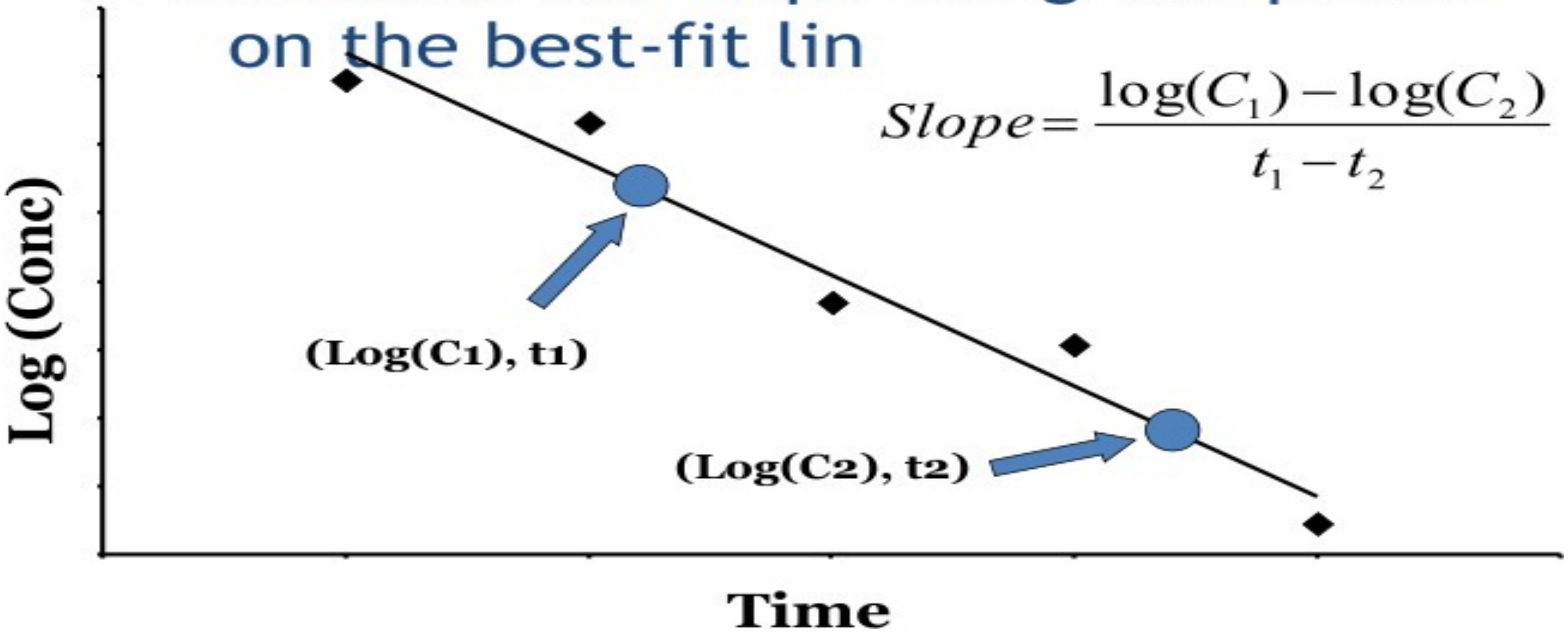
Cont,

2- Plot the best-fit line



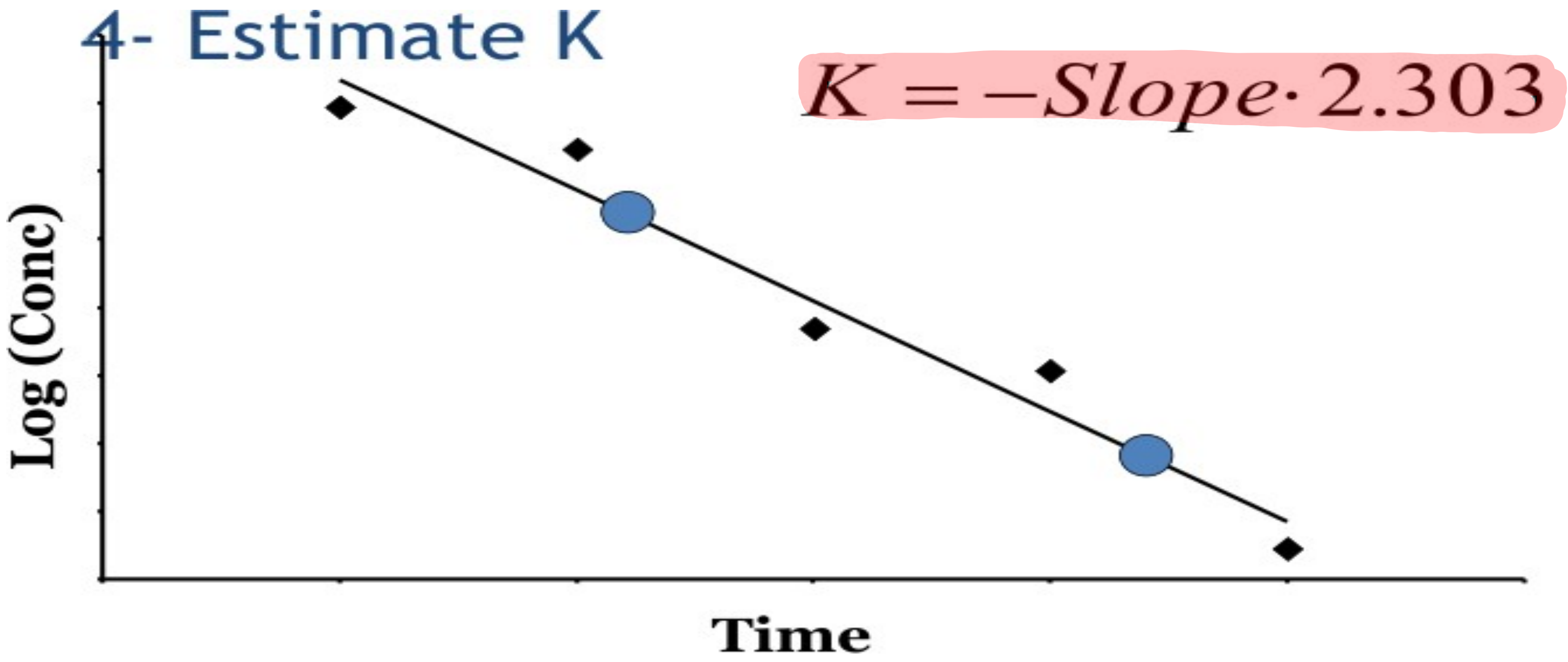
Cont,

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



$$Slope = \frac{\log(C_1) - \log(C_2)}{t_1 - t_2}$$

Cont,



Elimination half life

- **Elimination half-life (t1/2)**
- Definition: Elimination half-life is the time it takes the drug concentration in the blood to decline to one half of its initial value.

مثلا تم حقن ٥٠ ملغ من الدوا كم الوقت اللازم لحتى
يصير الدوا بالدم ٢٥ ملغ هاد بنسميه عمر النصف للدوا

- It is a secondary parameter :The elimination half-life is dependent on the ratio of clearance CL and VD.
- **Unit : time (min, h, day)**

كل ما زاد حجم التوزيع يعني الدوا بروح للانسجة اكثر وهذا يعني
انه بظل وقت اكثر بالجسم يعني رح يحتاج وقت اكثر حتى يتم
طرح نصف هذا الدوا من الجسم بالتالي رح يزيد عمر النصف للدوا

بينما كل ما زاد الكليرنس رح يزيد طرح الادوية
من الجسم بالتالي رح يقل عمر النصف للدوا

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

- Two methods:
  - From the value of K:

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

  - 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** بتشوف وين خلصت نص كمية الدوا عندها بكون عمر النصف للدوا

Calculation of t ½

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

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

$$\rightarrow$$

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

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

Cont,

لو كان عنا ..امغ وعنا ...امغ هل عدول الادوية بخاصة او بصير وجودهم بالجسم صفر عند نفس الوقت؟
نعم لانه احنا بنتعامل مع معدل ازالة الدواء ك نسبة فشو ما كان كمية الدوا رح يصير وجوده صفر عند نفس الوقت

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

لما عند هاي بنحسب انه الدوا طلع بشكل كامل من الجسم

- 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

* Cl = Q * E
blood flow → V/t
$\frac{V_{in} - V_{out}}{V_{in}}$ %

Clearance

most important parameter, volume/time = mL/hr

- 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."

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

Rate of elimination → spicific time; $C_{\text{in plasma}}$ → that time

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

* clearance = $\frac{\text{rate of elemination}}{C}$ = K Vd = $\frac{Vd}{T}$

rate of elemination = KA

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.

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

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,

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

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

- 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 <u>ALL LINEAR pharmacokinetics (including one compartment)</u> , clearance is calculated using: $$Cl = \frac{dose}{AUC}$$

  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.

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

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

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

Time to get certain concentration

Time to get to certain conc.

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

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

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

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

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 hr^{-1}, it means that 10% of the drug is eliminated by the end of 1 hour. If ***k*** = 0.3 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,

less than one — eliminated or

Fraction of Dose Remaining (F)

- ***F*** varies with time and can be easily determined knowing the time passed and **t** ½

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

and $F = \frac{X_t}{D^0}$ and $n = t / t_{1/2}$ $\qquad t = n * t_{1/2}$

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

$F = e^{-0.693n}$ $\qquad F = (\frac{1}{2})^n$ → for fraction remaing

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

عدد وليس ساعات

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?

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

↳ Fraction of dose remaining = 10%

- This means that 10% is remaining (*F*)
- $0.1 = (1/2)^n \rightarrow \log_{0.5} 0.1 = n$
- $n = \log_{10}0.1/\log_{10}0.5$
- $n = -1/-0.3 = 3.333$ half-lives

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

$\Rightarrow n = \frac{\ln 0.1}{\ln 0.5} = 3.323$ half-lives

example

Case 1

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

1. Calculate the initial concentration (C_0)
2. Calculate the plasma concentration 4h following administration
3. Calculate the time required for the concentration to drop to 1 mg
4. If the initial Cp is unsatisfactory, Calculate the dose required to provide an initial plasma concentration of 6 mg/L

Cont,

Case 1

1. **Calculate the initial concentration (C_o)**

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

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**

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

Cont,

Example 1

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

$$C_0 = \frac{\text{dose}}{\text{Vd}} \quad \Rightarrow \quad \text{dose} = C_0 \cdot Vd$$

$$\text{dose} = 6\,\frac{\text{mg}}{\text{L}} \cdot 10\ \text{L} = 60\ \text{mg}$$

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

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