

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).

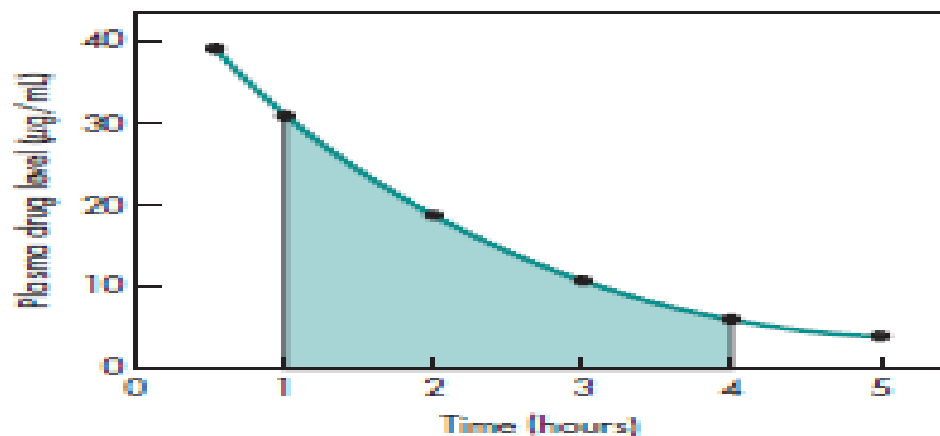


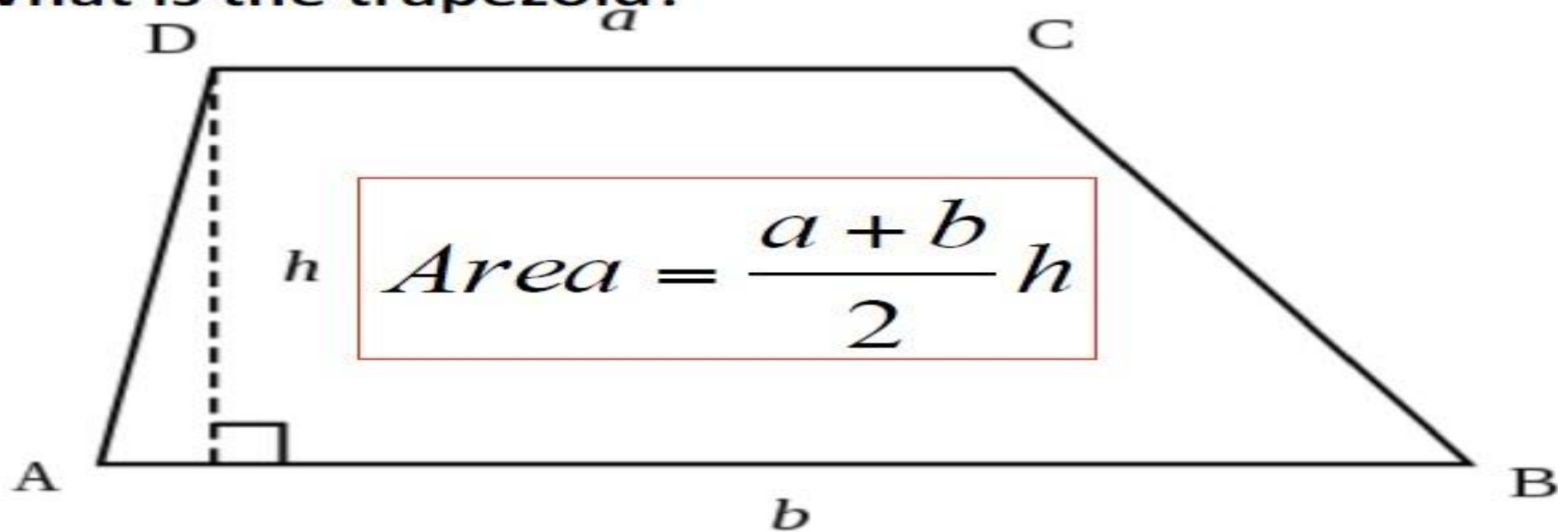
FIGURE 2-2 Graph of the elimination of drug from the plasma after a single IV injection.

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:

Cont,

For sure you know!

- What is the trapezoid?

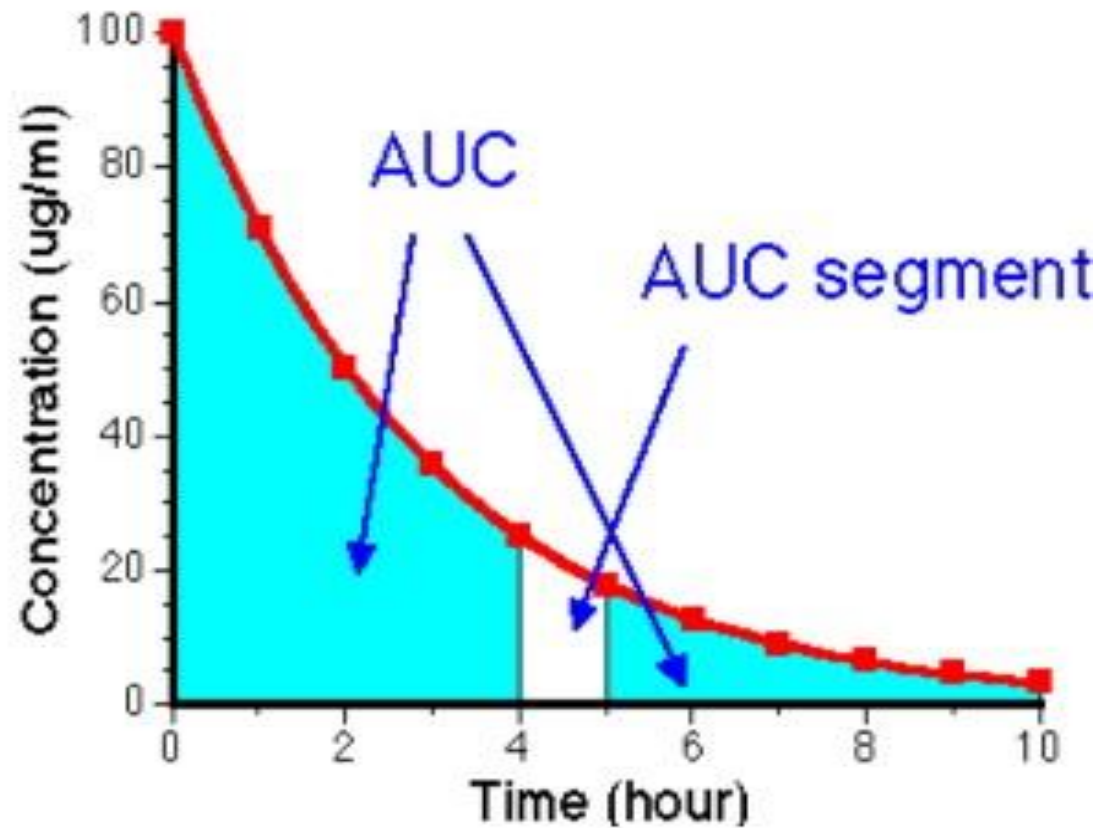


- The area of the trapezoid is equal to what?

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

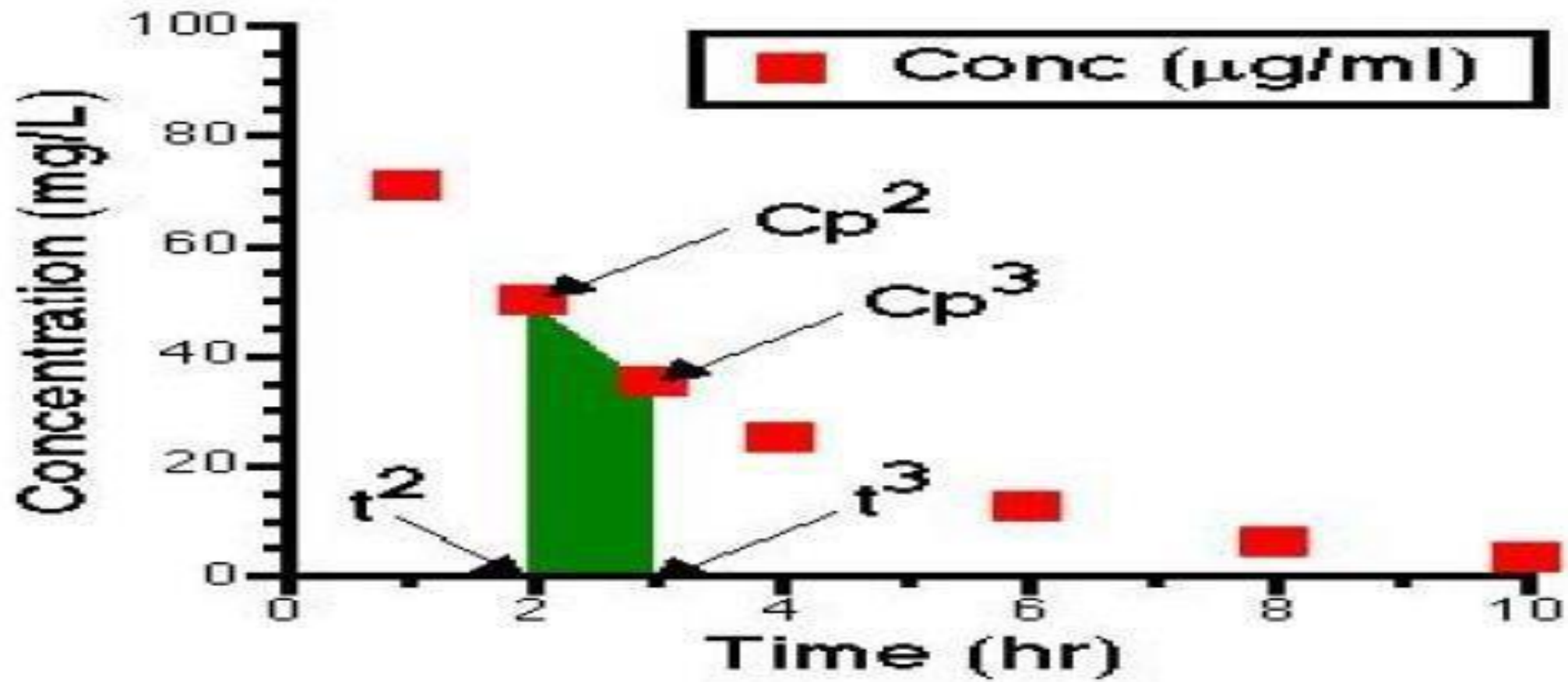
Trapezoidal Rule

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

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

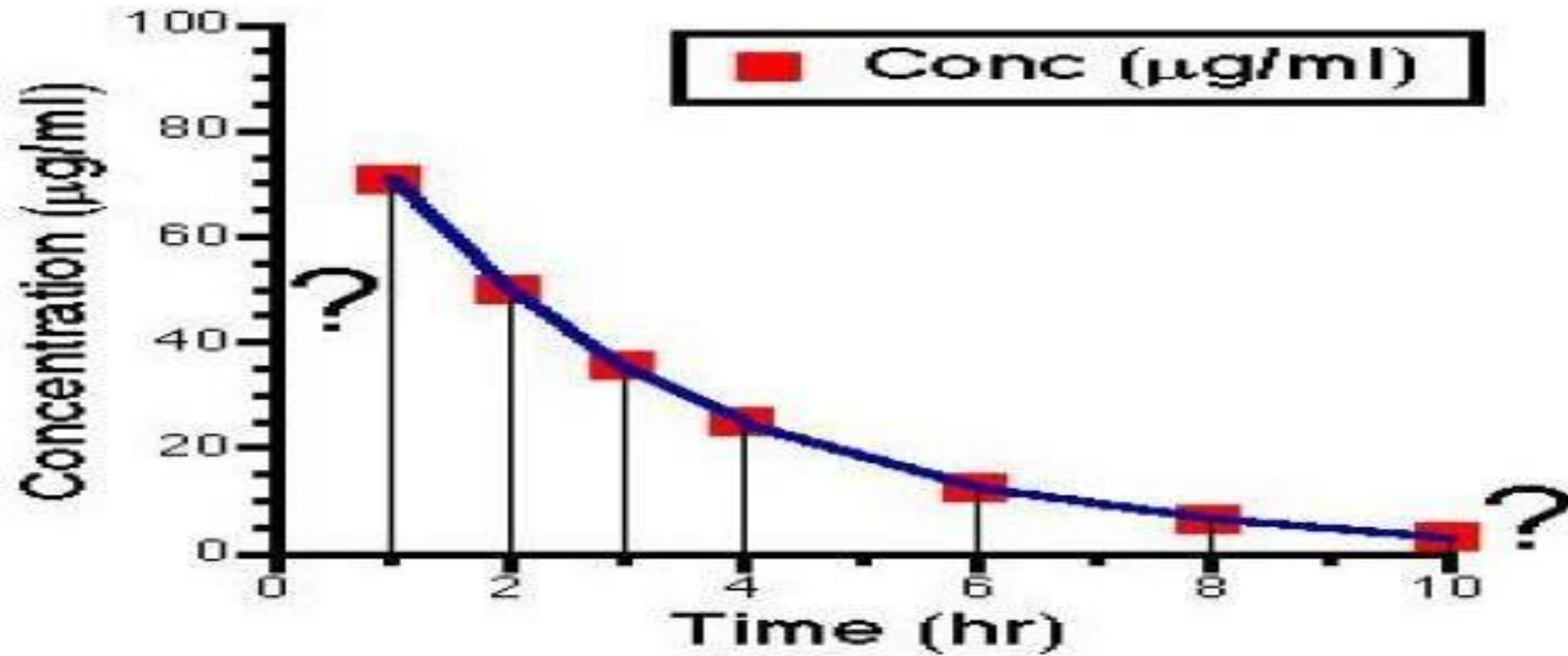
Cont,

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

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

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 $mg \cdot h/mL$, and the AUC between 3 and 4 hours is calculated as 8.94 $mg \cdot h/mL$. 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

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

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

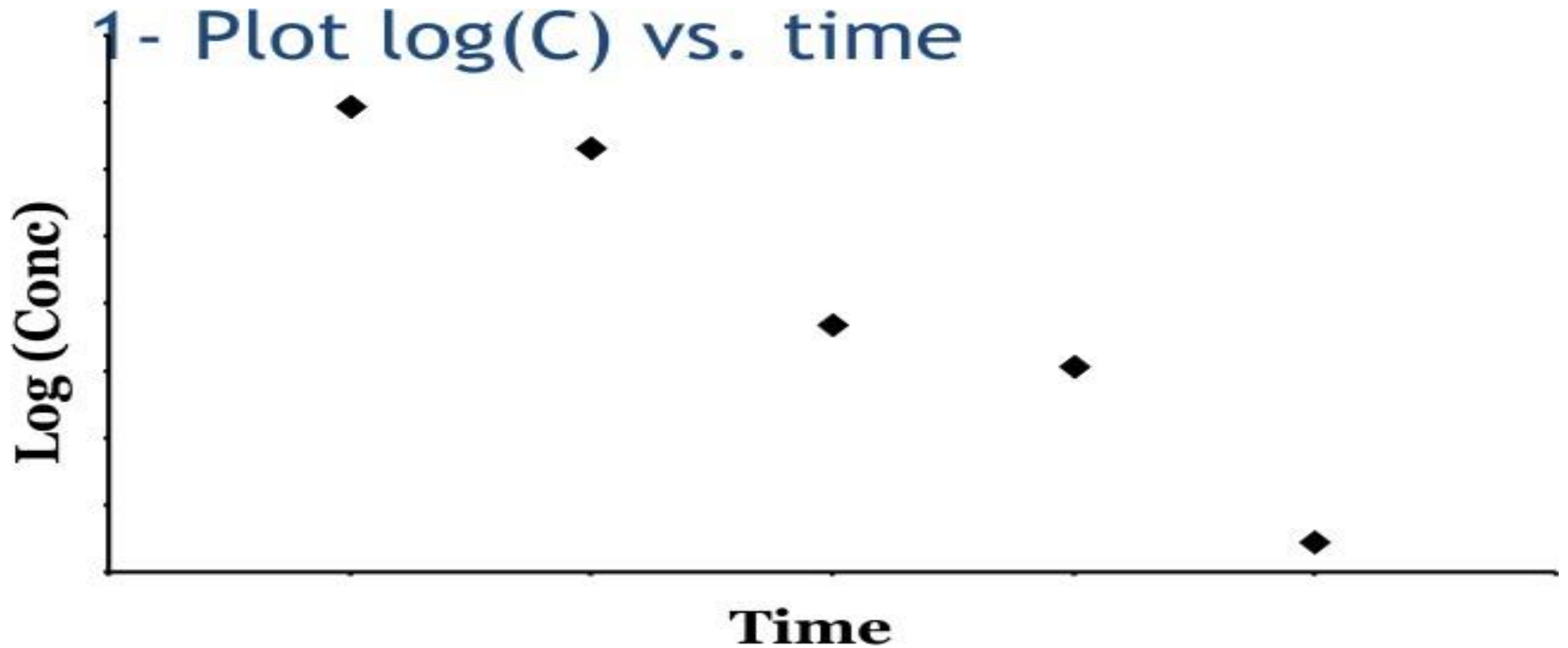
- $K = K_{\text{renal}} + K_{\text{metabolism}} + K_{\text{...}}$
- All are responsible of decline of plasma concentration

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 :

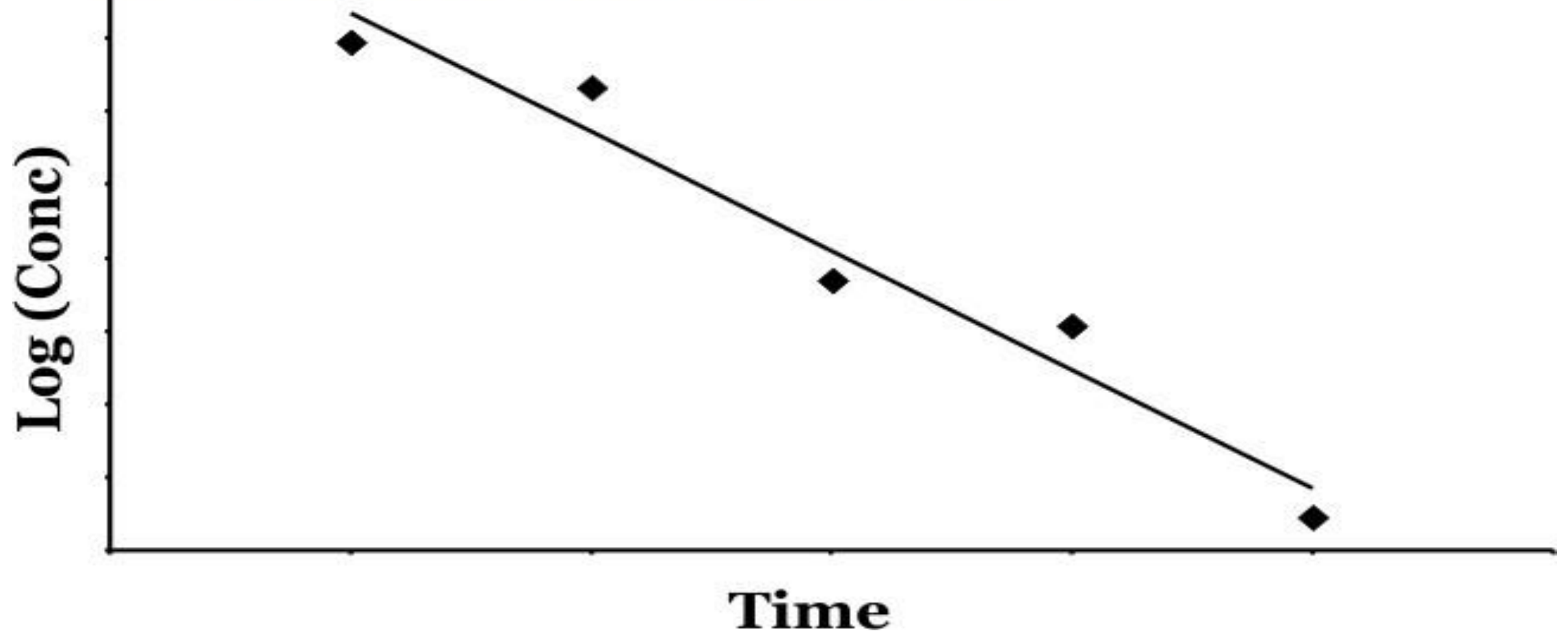
$$K = -\text{Slope} \cdot 2.303$$

Cont,



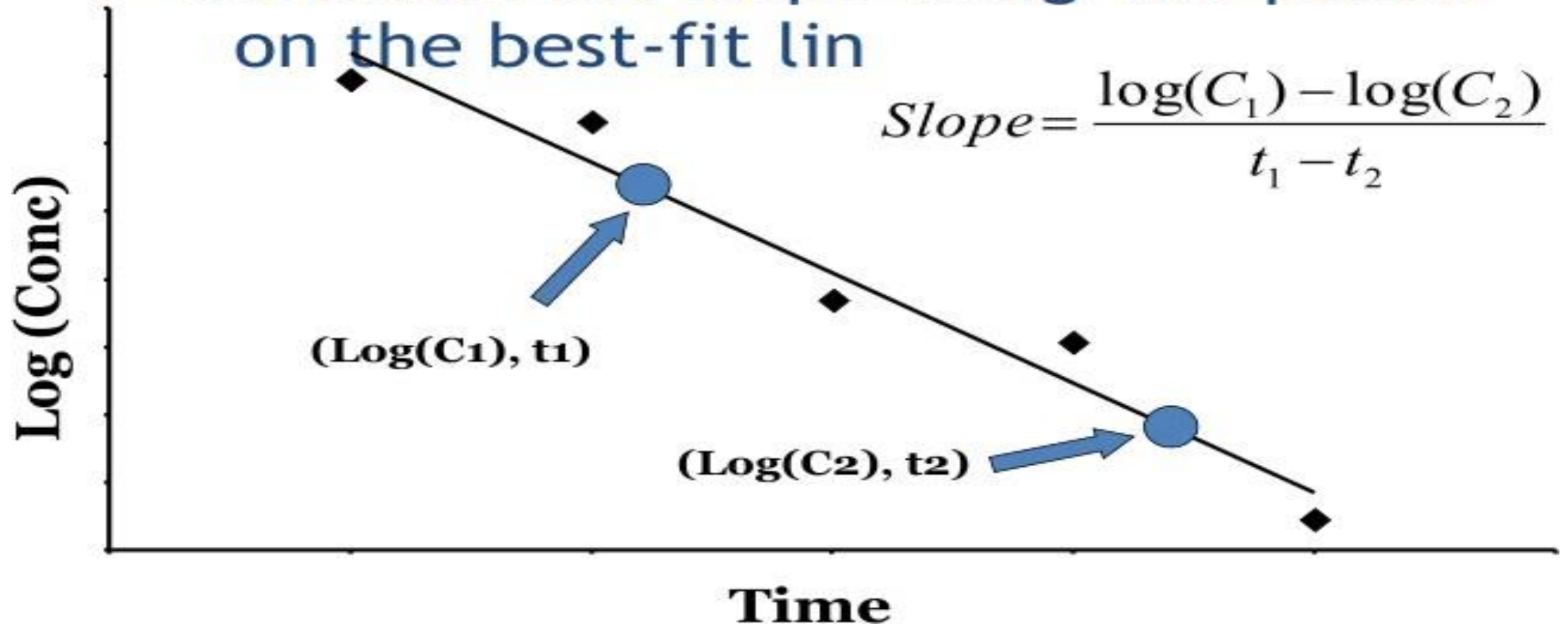
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2- Plot the best-fit line

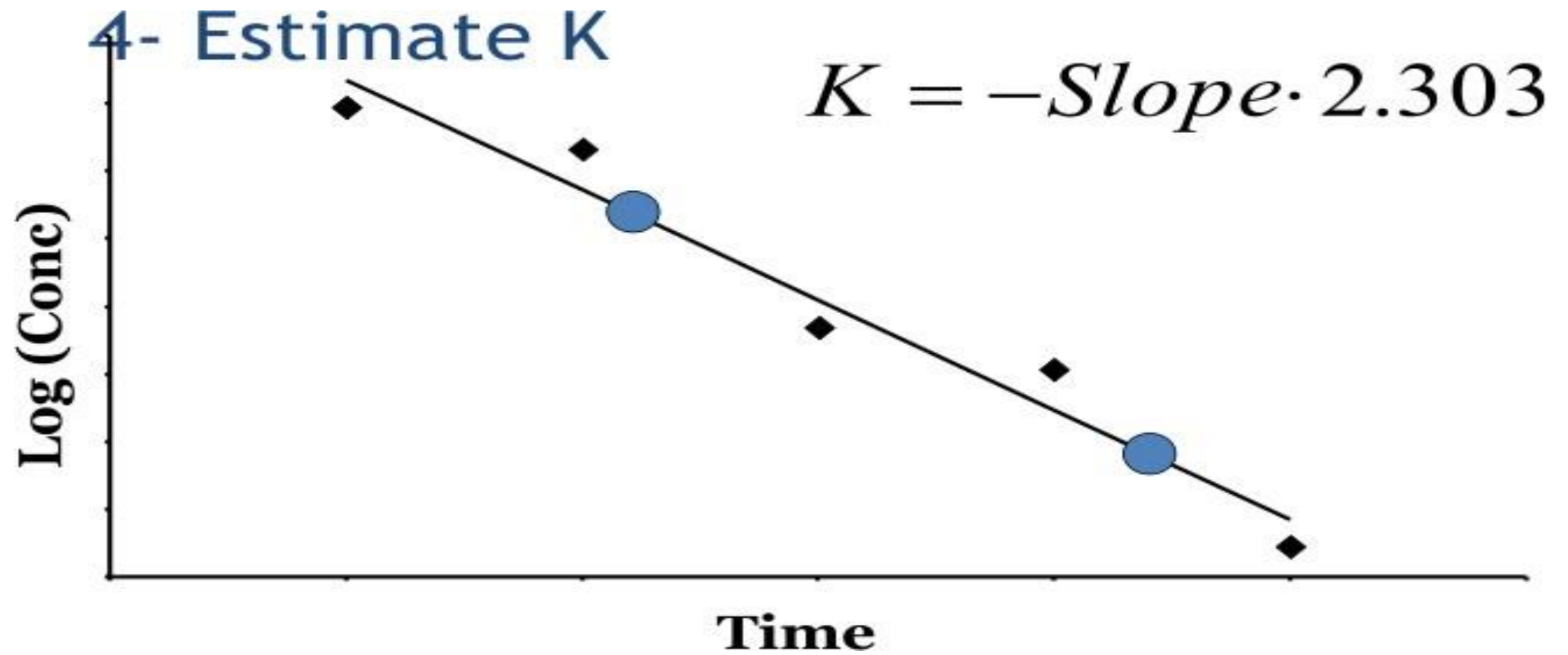


Cont,

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



Cont,



Elimination half life

- **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:
 - 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 (C_1)
 - Look for the time that is needed to get to 50% of C_1
→ **half-life**

Calculation of $t_{1/2}$

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

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

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

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

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.

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.”

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

$C_{\text{in plasma}}$

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 + 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

$$\boxed{Cl = kV_D}$$

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

- 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:
$$Cl = \frac{dose}{AUC}$$

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.

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

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

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

Time to get certain concentration

Time to get to certain conc.

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

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

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

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

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,

Fraction of Dose Remaining (F)

- **F** varies with time and can be easily determined knowing the time passed and **t**_{1/2}

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

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

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

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

(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

example

Case 1

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

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

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

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