Lab 5
Determination of Pharmacokinetic Parameters from Plasma Data

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Introduction to Pharmacokinetic Parameters

Most pharmacokinetic parameters can be reliably measured from plasma data following either **oral** or **intravenous bolus** administration.
These parameters form the foundation of **drug therapy individualization** and **clinical decision-making** in pharmacy practice.

AUC

Area under the curve - total drug exposure

Clearance (Cl)

Volume of plasma cleared per unit time

Elimination Rate Constant (k)

Rate at which drug leaves the body

Volume of Distribution (Vd)

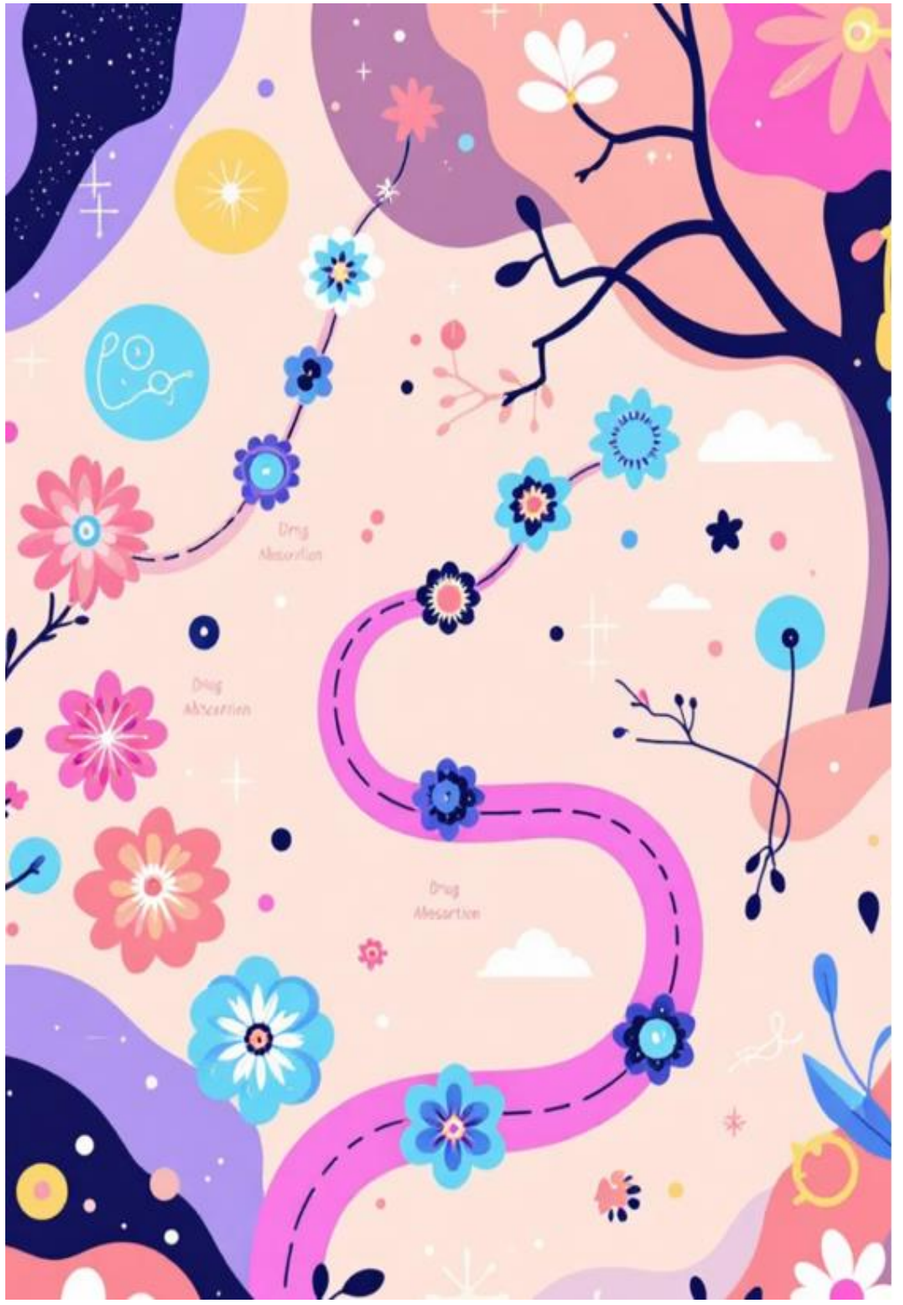
Theoretical volume drug distributes into

Bioavailability (F)

Fraction of dose reaching systemic circulation

Half-Life ($t_{1/2}$)

Time for plasma concentration to decrease by 50%



Understanding Bioavailability

- **Bioavailability** is a critical pharmacokinetic parameter that quantifies both the **rate** and **extent** (absolute amount) of therapeutically active drug that reaches the systemic circulation after administration.
- It reflects the fraction of an administered dose that becomes available in the bloodstream, ranging from **0 to 1** (or 0-100%).
- This parameter is essential for understanding drug absorption differences between routes of administration and for making informed dosing adjustments.

Key Point: Complete bioavailability (F = 1.0) occurs with **IV administration**, making it the **reference standard for comparing other routes**.

Area Under the Curve (AUC): The Complete Picture

The Area Under the Curve (AUC) represents the **total drug exposure over time** and is calculated from time zero to infinity **(0→∞)**.
AUC : captures all plasma concentrations, including **trace amounts** that persist long after initial administration.

1 Why Extend to Infinity?

After each elimination half-life (t½), the remaining concentration is halved: 100 mg → 50 mg → 25 mg → 12.5 mg → 6.25 mg...
The drug never completely leaves the body; trace amounts continue to decline asymptotically toward zero.

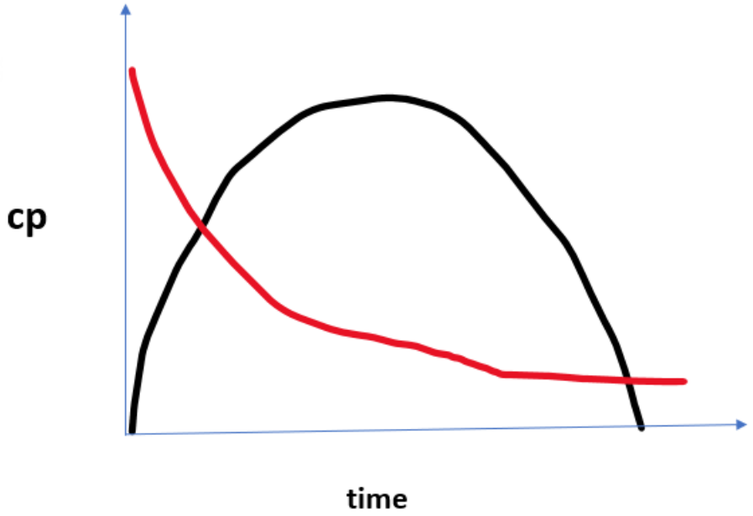
2 Practical Calculation

- **AUC is divided into two components: AUC from 0 to the last measurable time point (using trapezoidal rule),**
- **Plus AUC from the last point to infinity (calculated using the terminal elimination rate constant).**

3 Clinical Significance

- AUC correlates directly with systemic exposure and is essential
- **bioequivalence studies,**
- **dose optimization**
- **and predicting drug-drug interactions.**

Concept Keys: Fundamental Distinctions in Pharmacokinetics



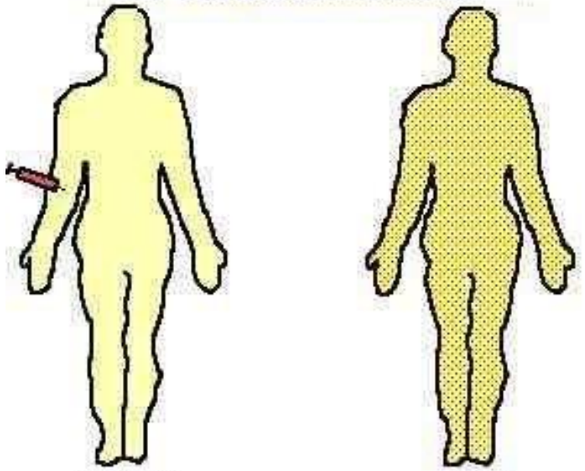
Oral vs. IV Administration: Differences in absorption kinetics and peak concentration patterns affect parameter estimation and clinical outcomes.

One-Compartment Model: Assumes the body acts as a single, homogeneous unit with uniform drug distribution.

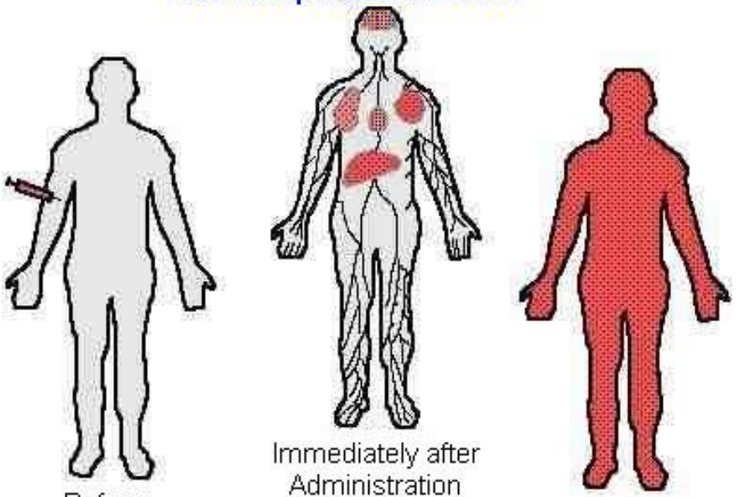
Two-Compartment Model: Recognizes central and peripheral compartments with different drug concentrations and kinetics.

ADME Processes: Absorption, Distribution, Metabolism, and Excretion determine drug behavior and plasma concentrations.

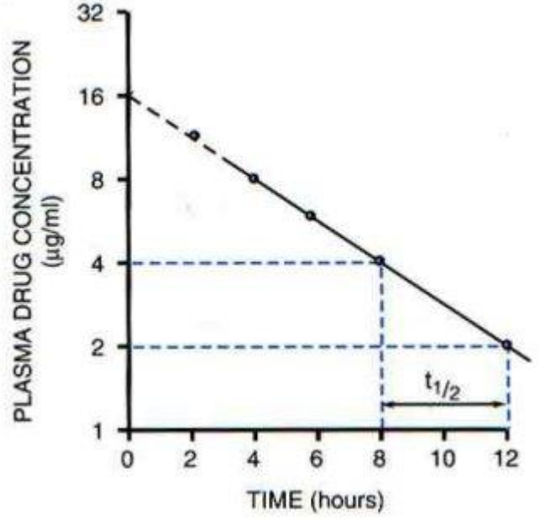
One compartment model

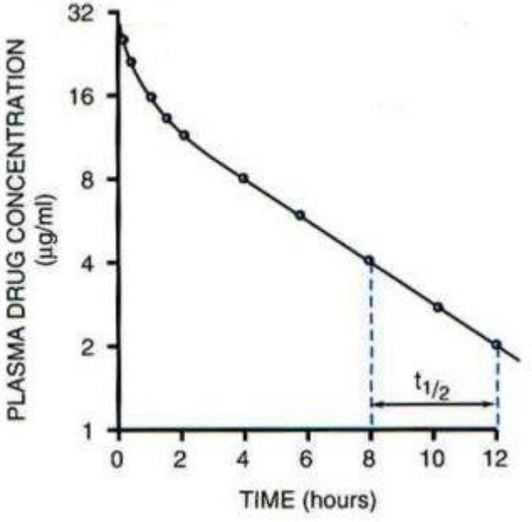


Two compartment model



- A **one-compartment model** may be used for drugs which rapidly equilibrate with the tissue compartment, e.g, aminoglycosides.
- A **two-compartment model** should be used for drugs which slowly equilibrate with the tissue compartment, e.g, vancomycin





Methods for estimation of AUC for IV one compartment model

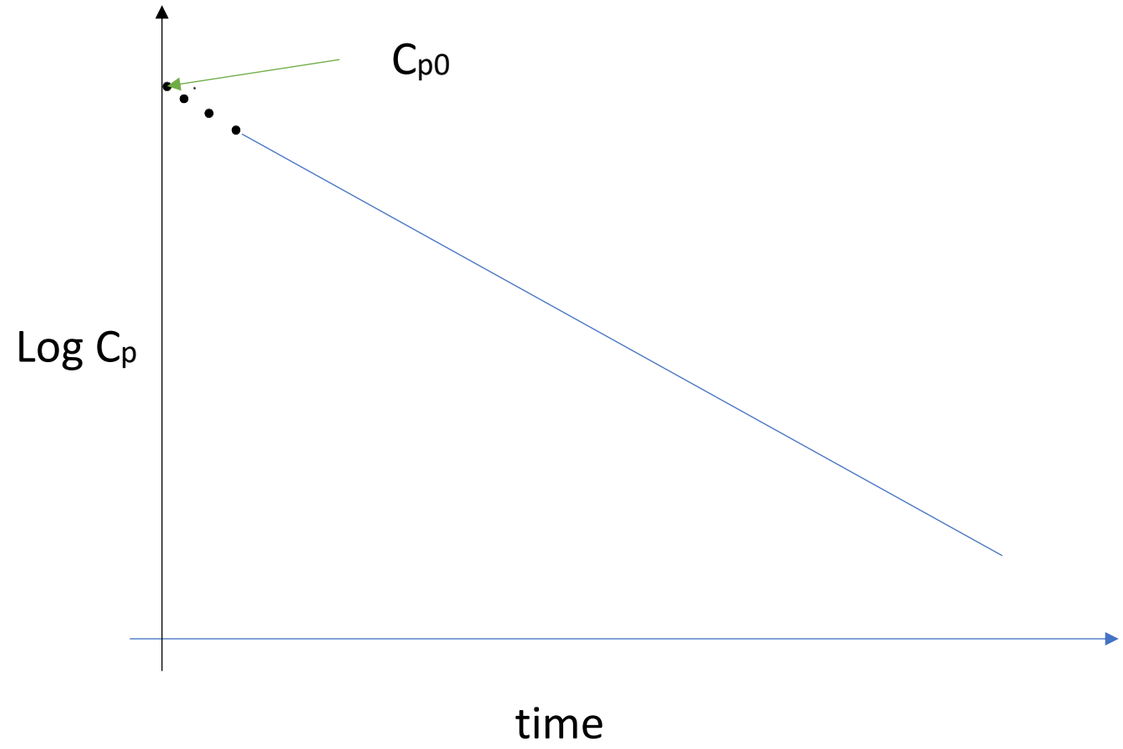
- **1- Residual method** :

It is used for resolving a curve into its various exponential components

i.e. we use the **log** to straighten the curve

Thus AUC $= \frac{Cp0}{K}$

K is equal to slope * -2.303



First order kinetics

$$Y = c + bX$$

$$\text{Log } C = \text{Log } C_0 \pm \frac{K}{2.303} t$$

$$\text{AUC} = \frac{Cpo}{K}$$

$$\underset{t_o \to t_\infty}{AUC} = \int_{t_o}^{t_\infty} c\,dt$$

Since :

$$\log c_t = \log c_o \pm \frac{Kt}{2.303}$$

Or:

$$\ln c = \ln c_t - Kt$$

Then:

$$c = c_o\, e^{-Kt}$$

Thus:

$$\underset{t_o \to t_\infty}{AUC} = \int_{t_o}^{t_\infty} c_o e^{-Kt}\,dt$$

The integration of this yield:

$$AUC = \frac{c_o}{-K}\left[e^{-Kt}\right]_0^\infty$$

$$= -\frac{c_o}{K}[0-1]$$

$$= \frac{c_o}{K} \text{ or } \frac{c_{po}}{K}$$

the previous equations sometimes are written as follows:

$$c_p = A\, e^{-\alpha t} \qquad A = c_{po}$$

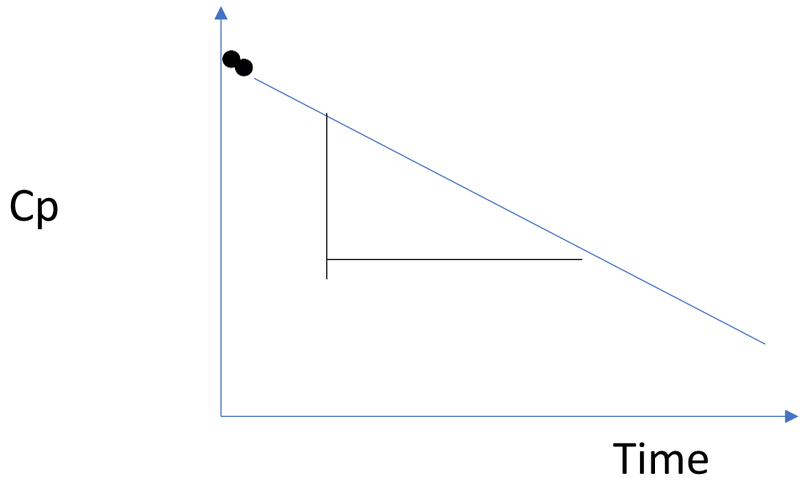
$$AUC = \frac{A}{\alpha} \qquad \alpha = K \text{ (elimination rate constant)}$$

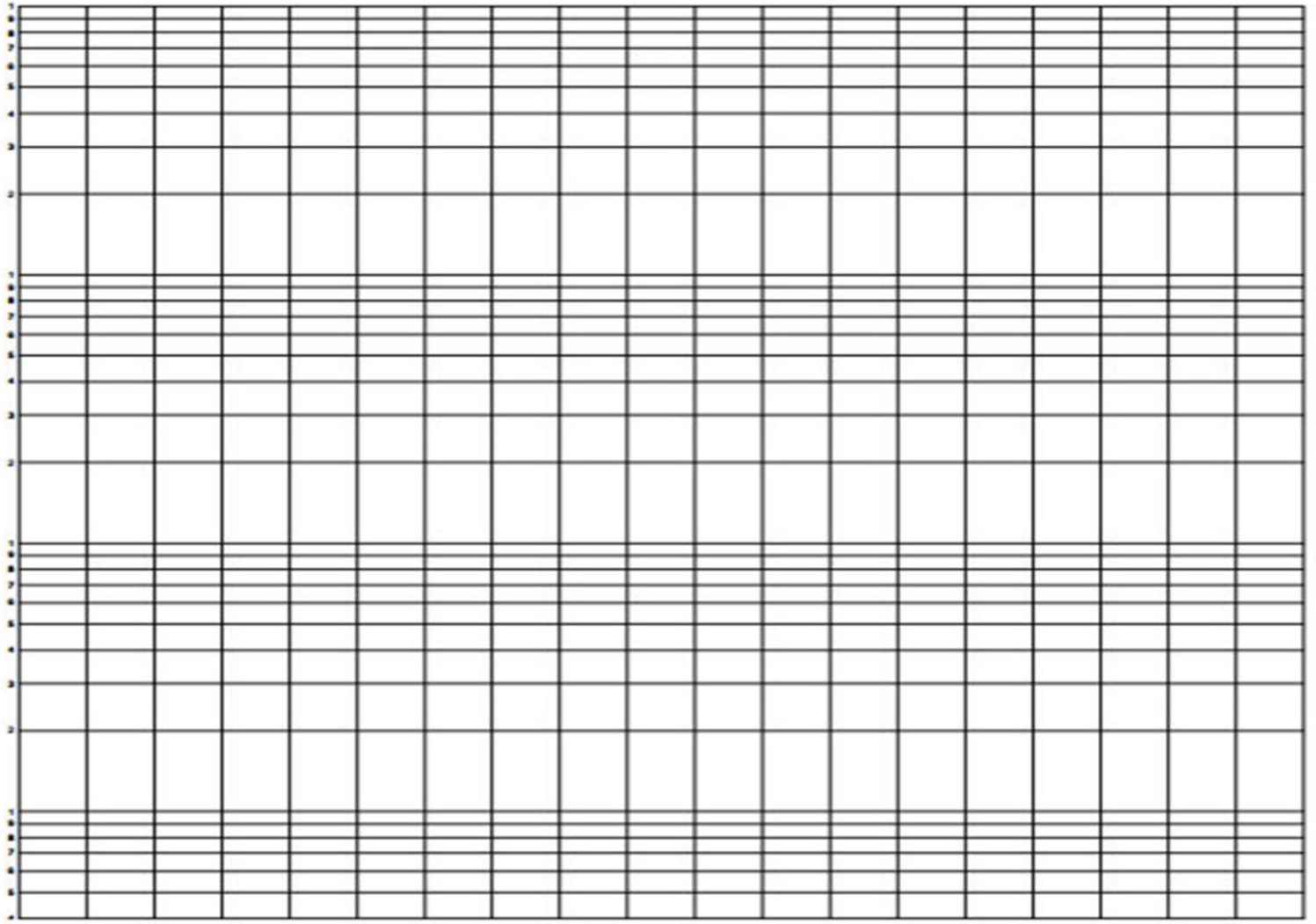
The second method :**Visual method**

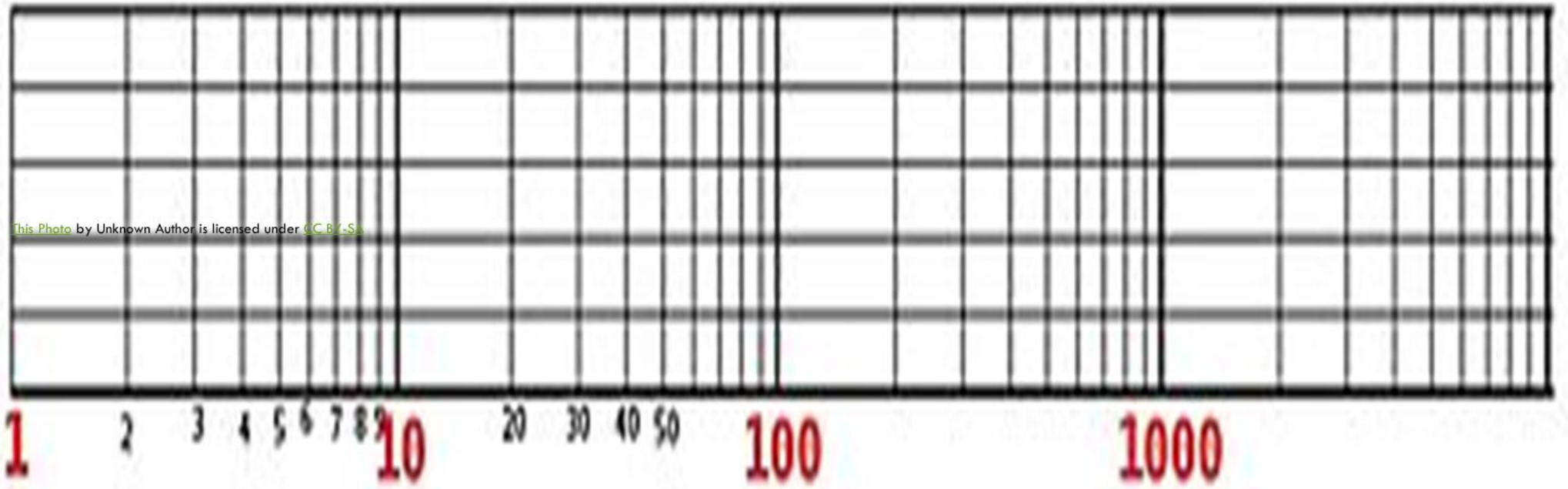
By using **Semilog paper** after curve fitting for the best line , the intercept Is equal to Cpo and to find the slope form the curve we take two points on the straight line as follow

$$\text{slope} = \frac{\log Cp2 - Log\ Cp1}{time\ 2 - time\ 1}$$

K = slop * -2.303







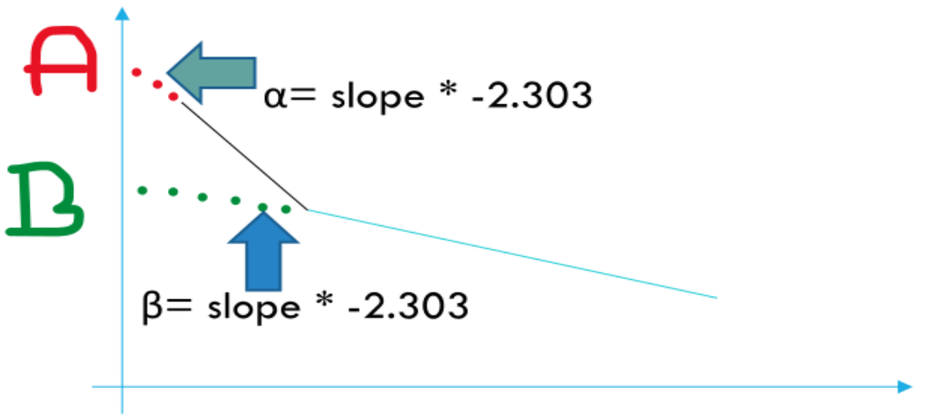
METHODS FOR ESTIMATION OF AUC FOR IV TWO COMPARTMENT MODEL

In IV two compartment model we calculate the AUC by dividing the total area into two parts and estimates the area for each one which are elimination phase and distribution phase area

The biexponential curve shown in the figure is commonly seen after the IV drug administration such curve can be described by the following eq.

$$AUC = \frac{A}{\alpha} + \frac{B}{\beta}$$

A+ B = Cpo



Generally, and commonly after the IV drug administration (apparent first order fat disposition rate constant , AKA distribution rate constant) is much larger than β (apparent first order slow elimination rate constant , AKA elimination rate constant)

$$kel = \frac{-dCp/dt}{Cp}$$

$$\frac{\text{mass}/\text{volume}}{\text{time}} \div \text{mass}/\text{volume} = \frac{1}{\text{time}}$$

1 / hour
Or
Hr^{-1}

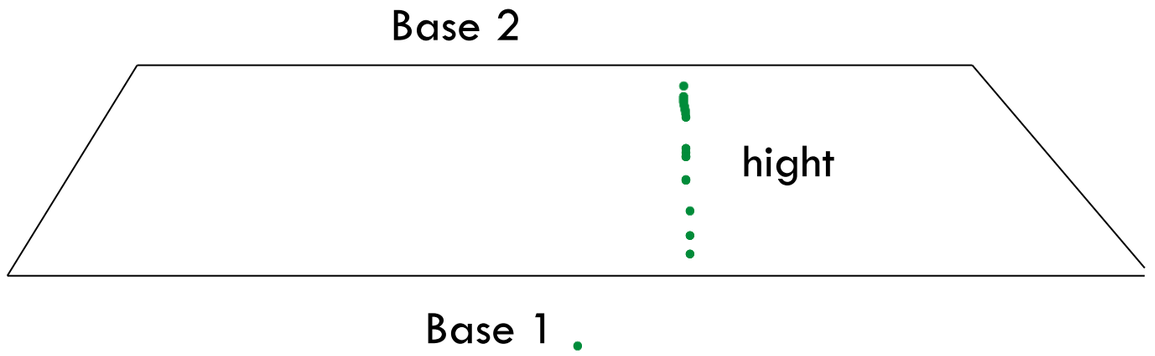
- $t_{1/2} = 0.693/k_{el}$
- **Unit of K of elimination = 1/TIME**

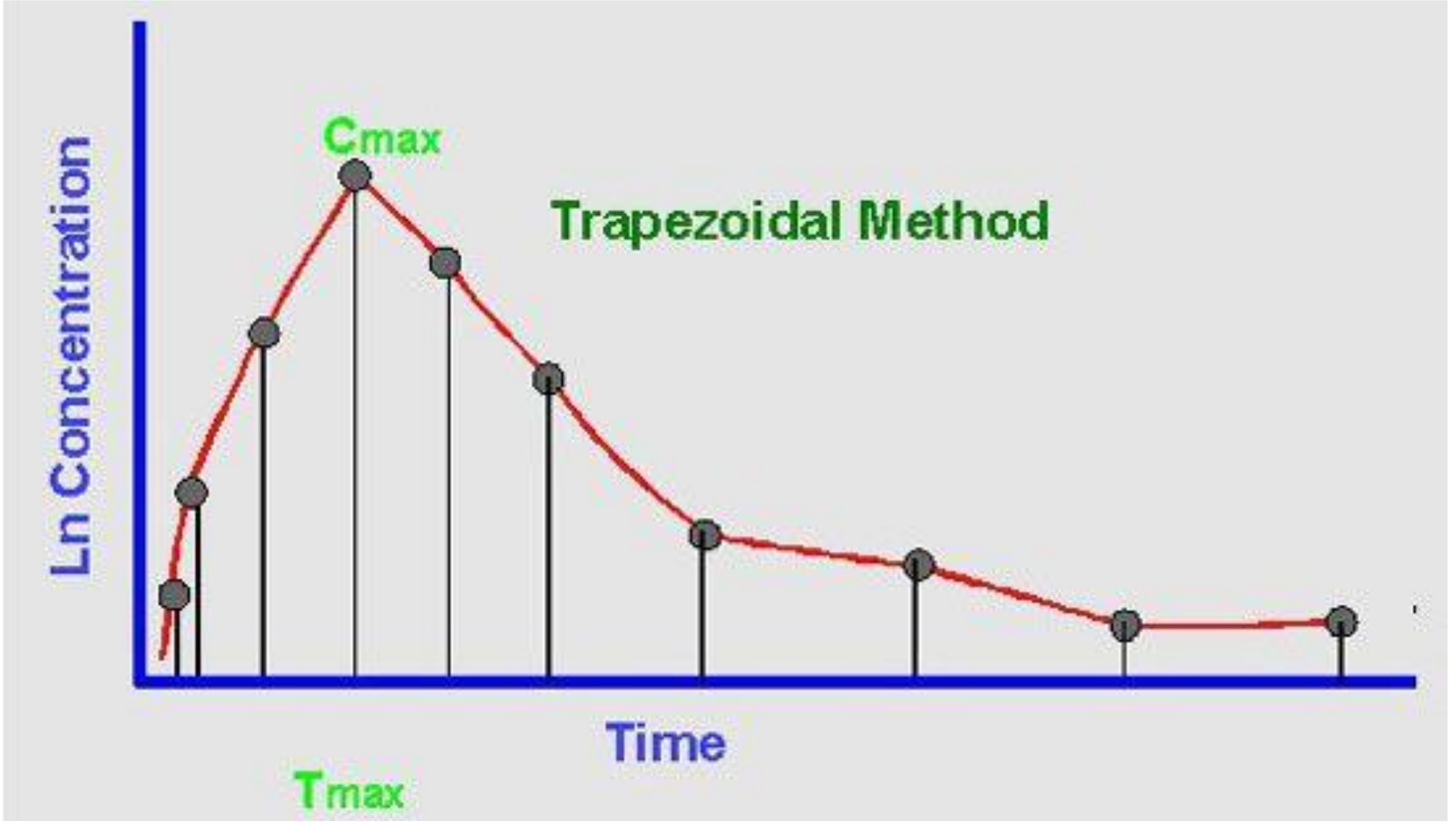
In general, in estimating AUC from time zero to time infinity and to get the best result it should be down the following :

1- sample early enough
2- sampling intervals is short
3- sampling for 6-10 half life

TRAPEZOIDAL METHOD

Area of trapezoid $= \frac{(base\ l + bas\ 2)}{2} . Hight$



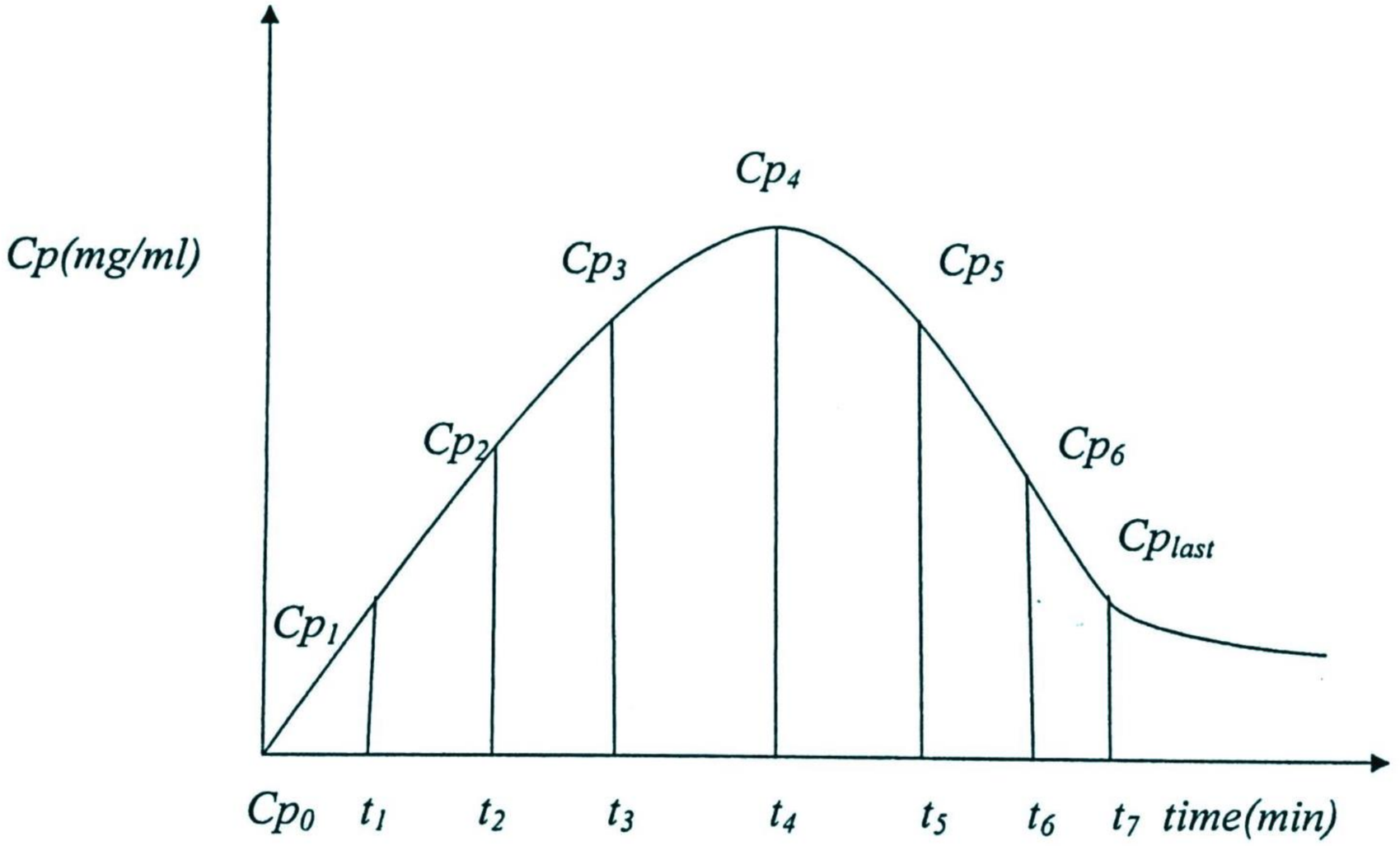

Cmax
Trapezoidal Method
Ln Concentration
Time
Tmax

AREA OF TRAPEZOID

Area of trapezoid $= \frac{(Cp2+Cp1)}{2}.(t2-t1)$

After oral administration the concentration of the drug at zero time is zero thus simply the first area is $= \frac{(Cp2+0)}{2}.(t2-0)$

Usually total AUC means the area under the curve from time zero to time t , therefore the area from the last sampling (concentration) to time infinity (usually called residual area) is measured as the last drug concentration divided by the elimination rate constant


Cp(mg/ml)
Cp4
Cp3
Cp5
Cp2
Cp6
Cplast
Cp1
Cp0
t1
t2
t3
t4
t5
t6
t7
time(min)

$$Auc_{(To\rightarrow\infty)} = Auc_1 + Auc_2 + Auc_3 + \ldots\ldots + Auc_{last}$$

If there is any fluctuation in the curve it should be calculated.

$$Auc_0 \text{ or } Auc_{extrapolated} = \frac{Cp_0 + Cp_1}{2}(t_1 - t_0) = \frac{Cp_1}{2} X\, t_1$$

$$Auc_1 = \frac{Cp_1 + Cp_2}{2}(t_2 - t_1)$$

$$Auc_2 = \frac{Cp_2 + Cp_3}{2}(t_3 - t_2)$$

$$Auc_3 = \frac{Cp_3 + Cp_4}{2}(t_4 - t_3) \ldots\ldots\ldots\ldots$$

$$Auc_{last} = \frac{Cp_{last}}{\beta}$$

UNITS OF AUC

Con. * time

Mg. hr / L


thank you