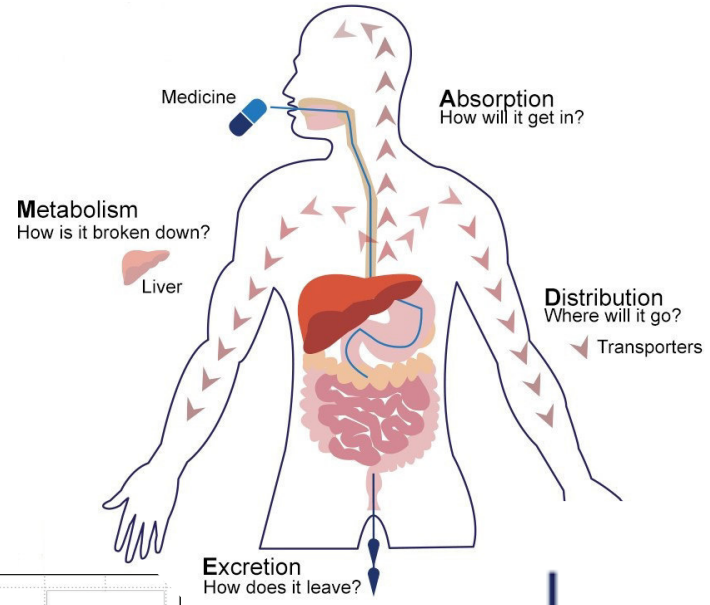
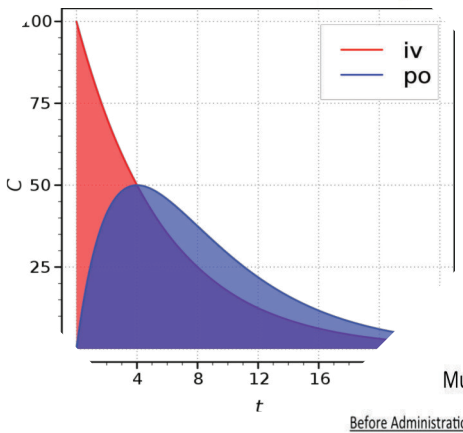
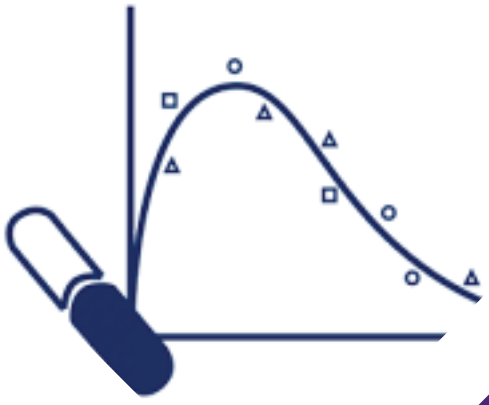
PHARMACOKINETICS

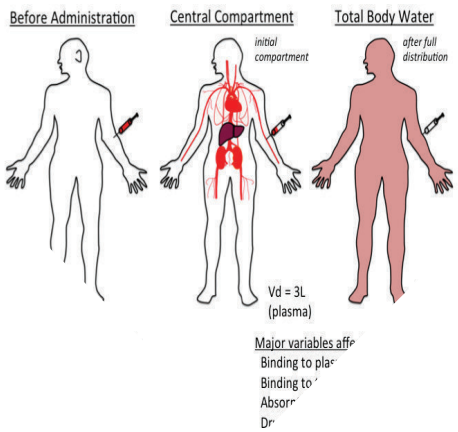
FOR SECOND YEAR STUDENTS







Multiple Drug Compartments



CLINICAL PHARMACY DEPARTMENT

2019/ 2020

Introduction
(basic pharmacokinetics)

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Objectives

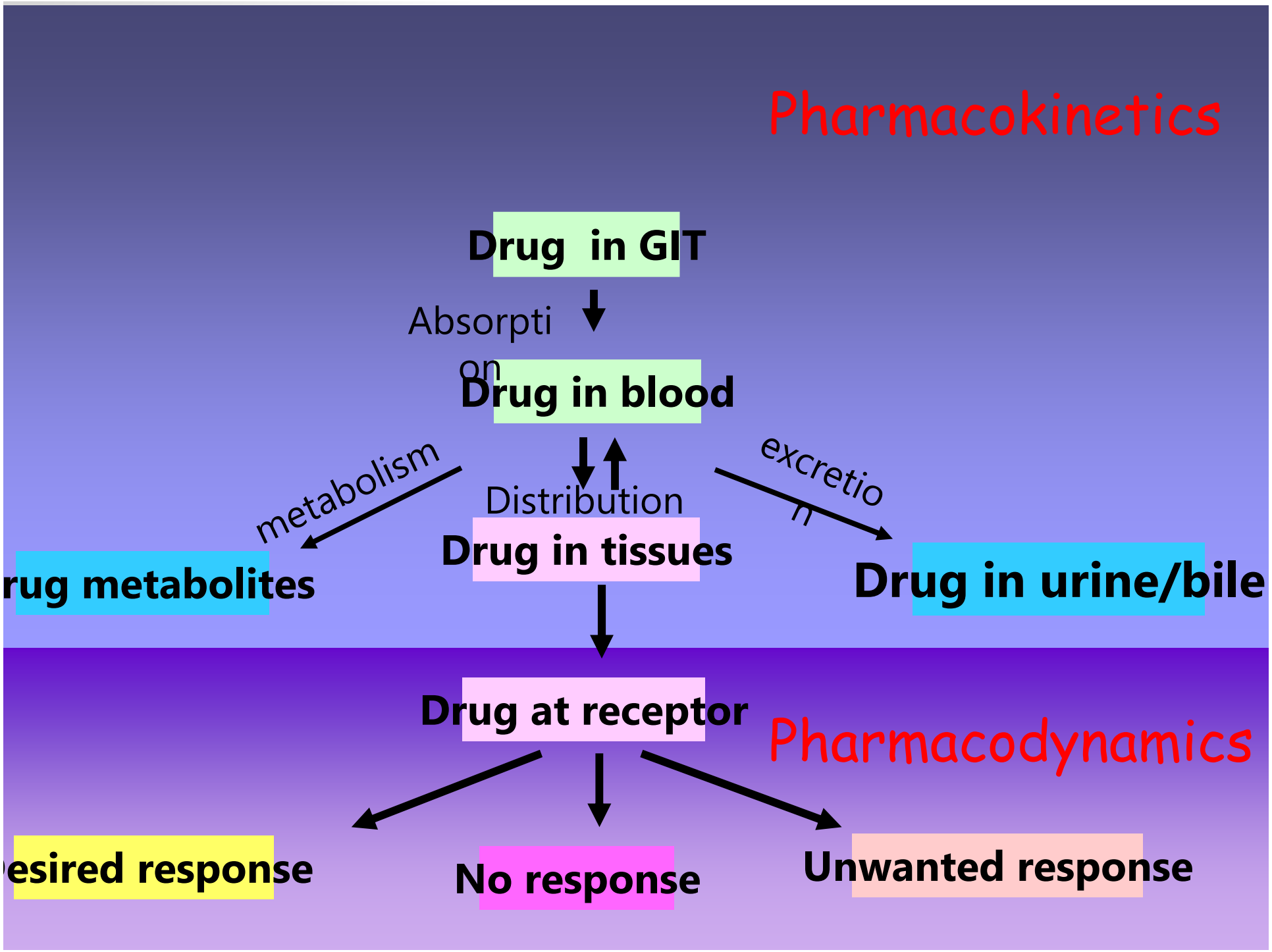
- Define PK
- Importance of PK
- ADME processes
- Plasma concentration curve
- Methods of drug absorption

Pharmacokinetics

- Definition :

the study of the **rates** of the transfer process associated with drug absorption, distribution, metabolism, and excretion (What the body do to the drug).

Pharmacokinetics (PK) involves **four** main process (**ADME**): absorption, distribution, metabolism, and excretion


Pharmacokinetics
Drug in GIT
Absorpti
on
Drug in blood
metabolism
Distribution
excretio
n
rug metabolites
Drug in tissues
Drug in urine/bile
Drug at receptor
Pharmacodynamics
esired response
No response
Unwanted response

Pharmacodynamics

Pharmacodynamics refers to the relationship between the drug at the site of action (receptor) and pharmacologic response

How the drug affect the body

Process affecting drug absorption:

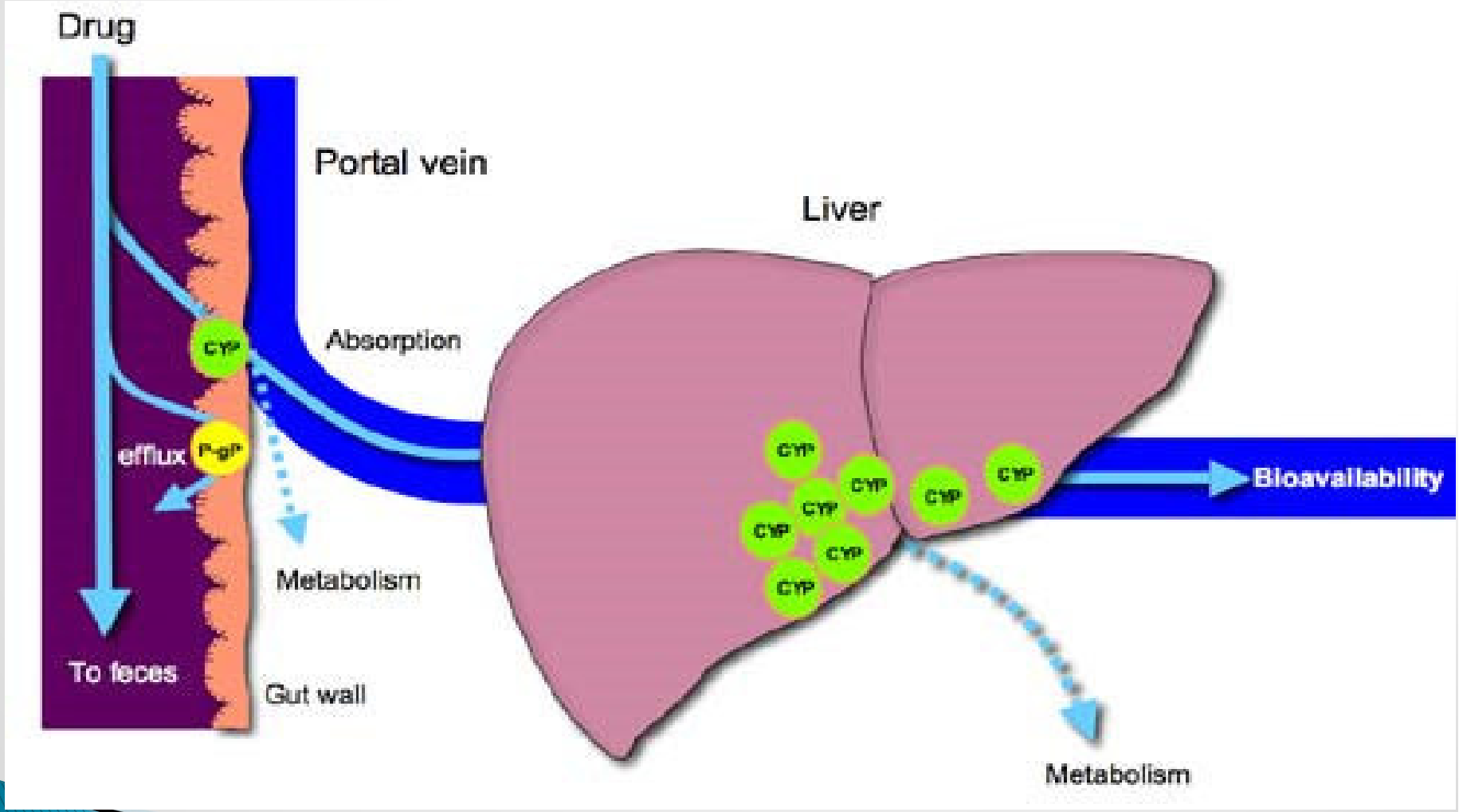
First pass effects

- The phenomena where the concentration of a drug is greatly reduced before it reaches the circulatory system **reducing** drug bioavailability.

- The liver metabolizes many drugs, sometimes to such an extent that only a small amount of active drug reaches the rest of the circulatory system from the liver.

- **Sublingual route shows no first pass effects**

First pass effects:



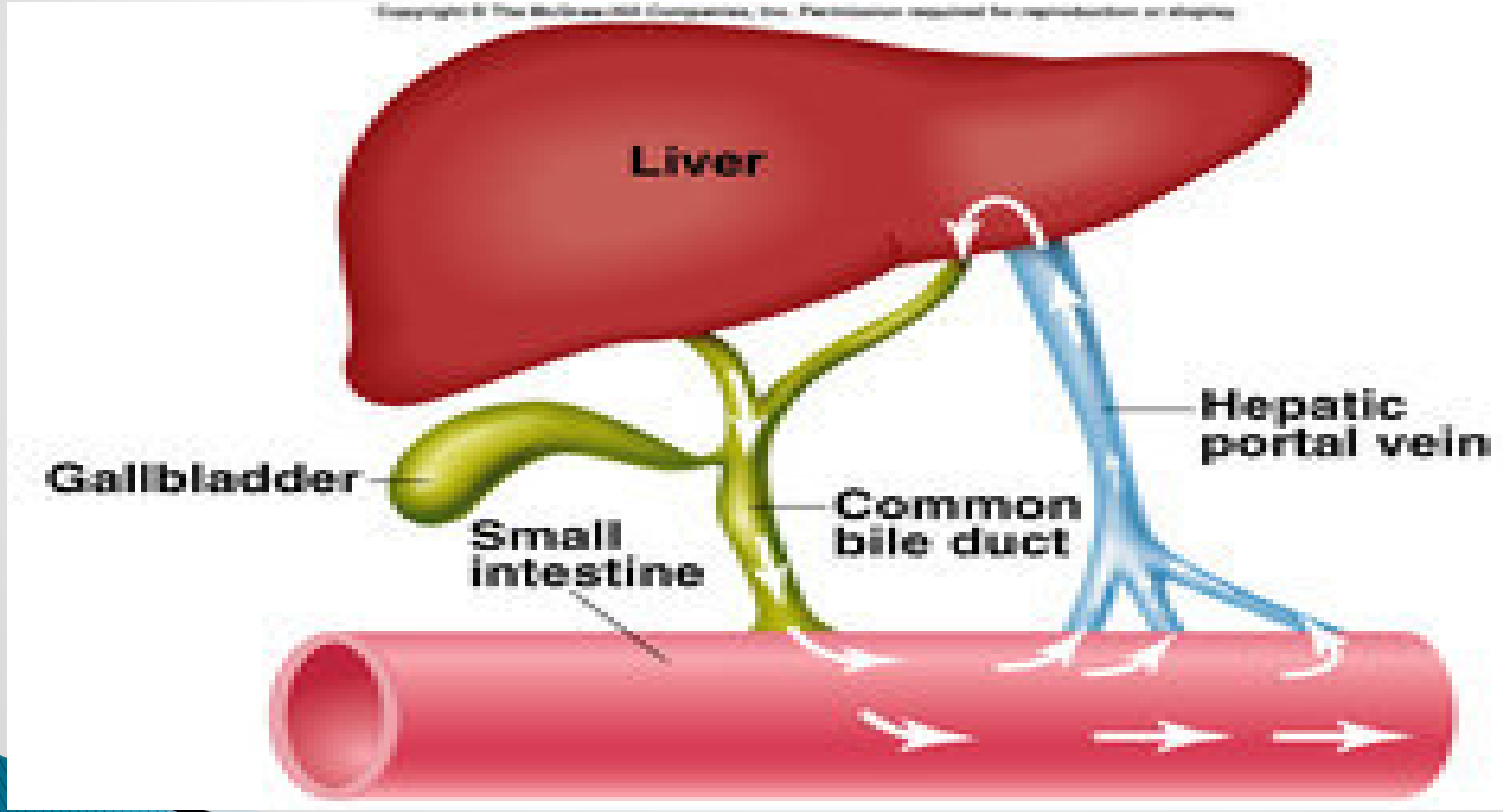
Enterohepatic circulation

This refers to the circulation of **drugs from the liver to the bile, then to the small intestine, followed by reabsorption again through the enterocyte** (often by the bacterial help) and transport back to circulation and liver.

Drugs may be toxic as they reach unexpectedly high concentrations.

Enterohepatic circulation **increase** plasma concentration of drugs like oral **contraceptive**, **estrogen**

Enterohepatic circulation:



P glycoprotein

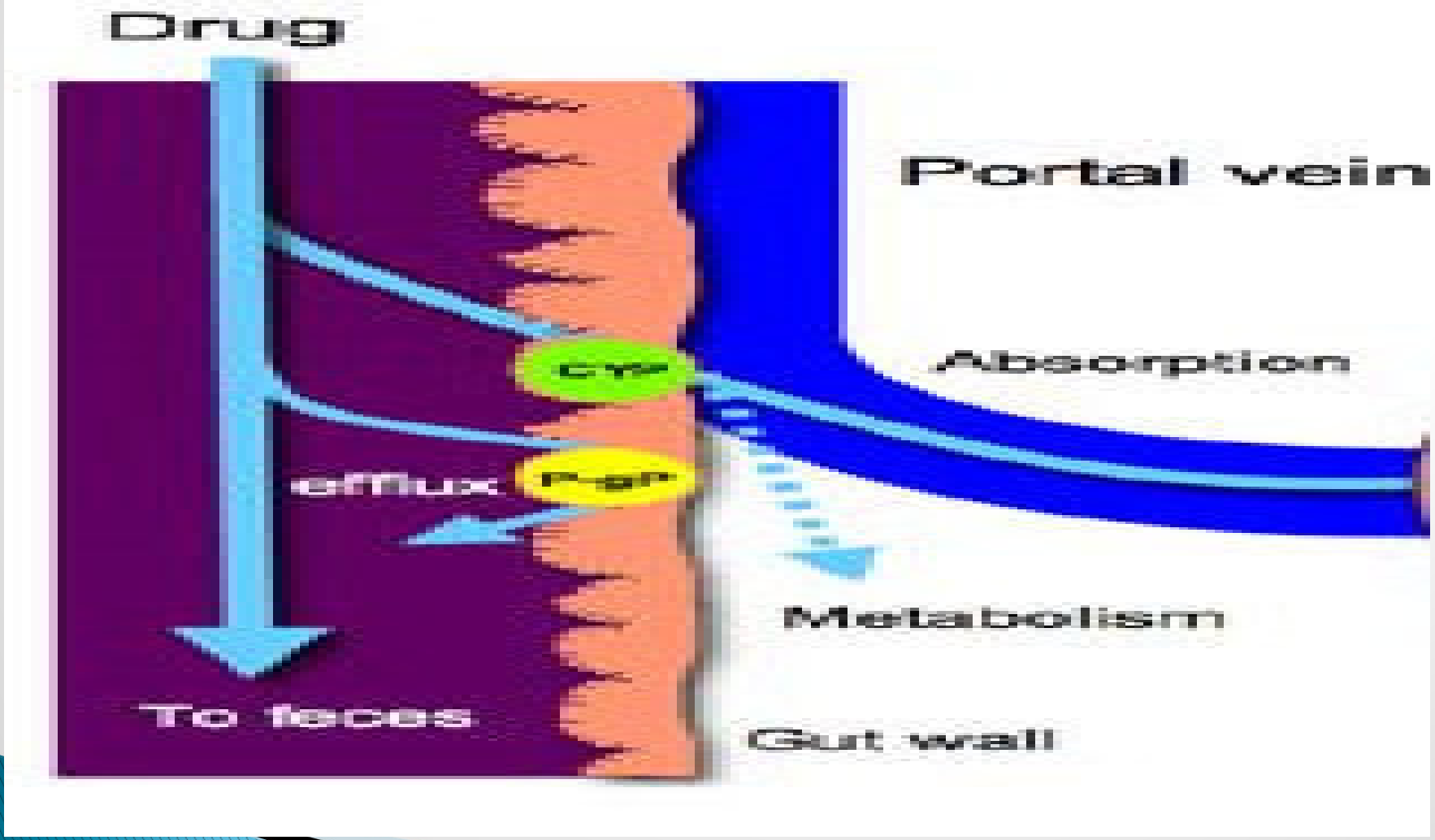
- **Also called multidrug resistance protein 1 (MDR1)**

An important efflux protein of the cell membrane that **pumps many foreign substances out of cells.**

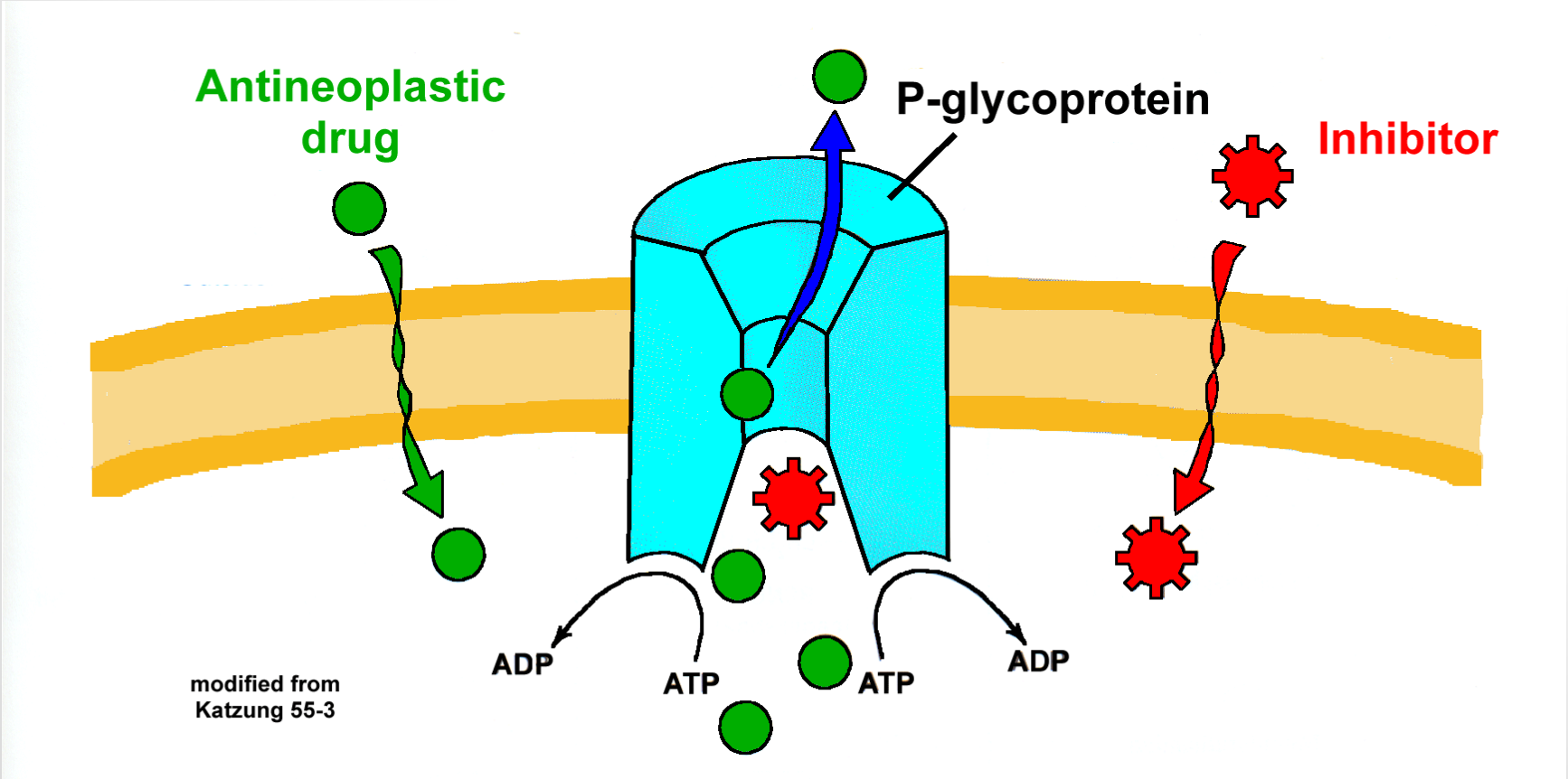
Found in:

- intestinal epithelium (decrease drug bioavailability)
- liver cells (remove drug in bile)
- proximal tubule of the kidney (remove drug in urine)
- endothelial cells composing the blood–brain barrier (preventing entry to the brain)
- Some cancer cells (preventing drug entry causing cancer multi-drug resistant).

P glycoprotein



Inhibiting P glycoprotein improve antineoplastic drug activity on cancer cell



Distribution of drugs

- After absorption to blood stream, drug is rapidly distributed into the interstitial and intercellular fluids

- **Liver, kidney, brain, and other well-perfused organs receive most of the drugs**

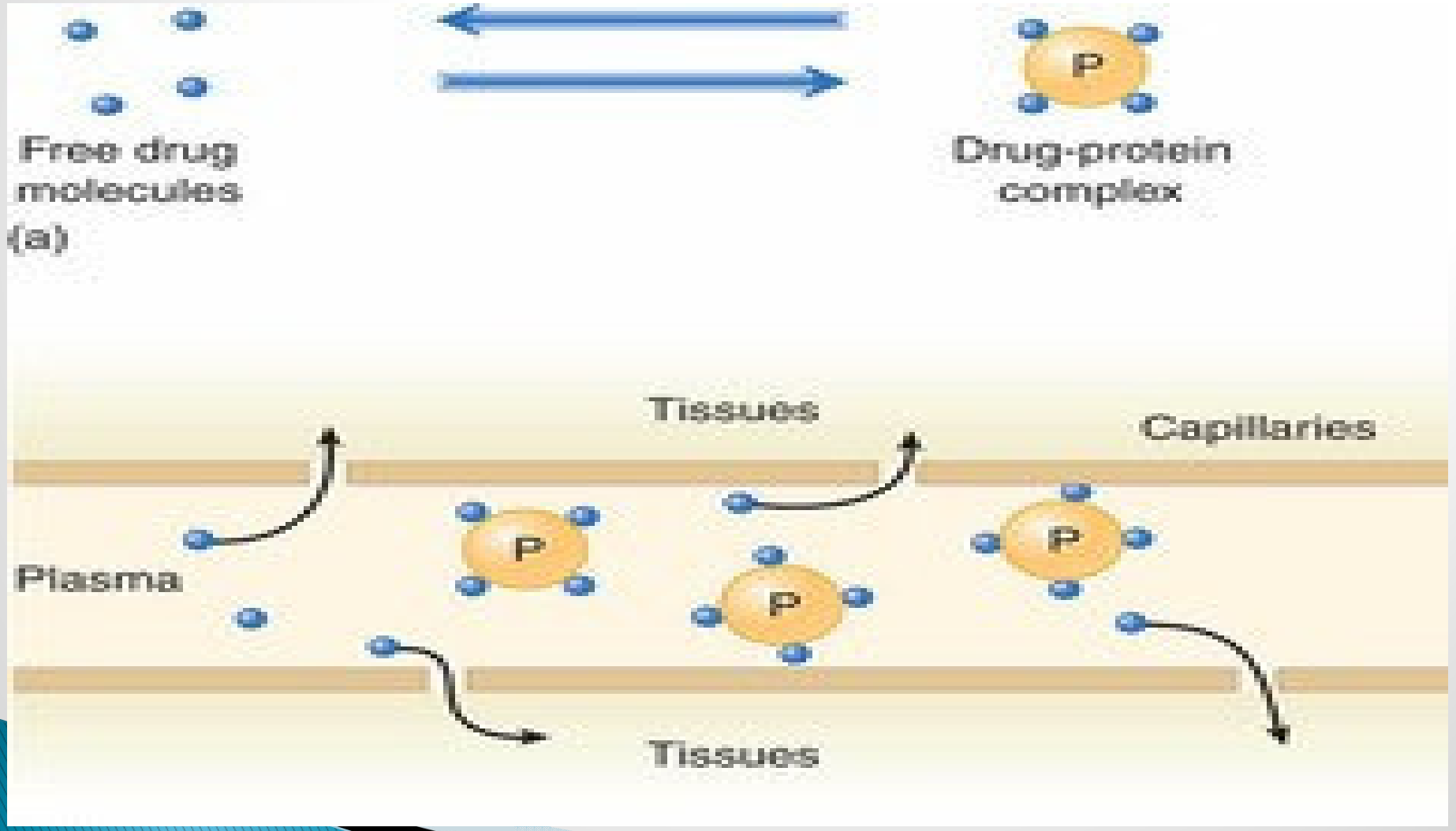
Distribution

- **Plasma proteins bound** to many drugs. This bounded drugs have no action at receptor site and **only unbounded fraction has a pharmacological action**

- **Displacement** of highly bounded drug from plasma protein by other drugs can affect the pharmacological action greatly ex: warfarin

- **Drug distribution determine the model of drug kinetics (one compartment or two compartment)**

Plasma Protein Binding



Metabolism

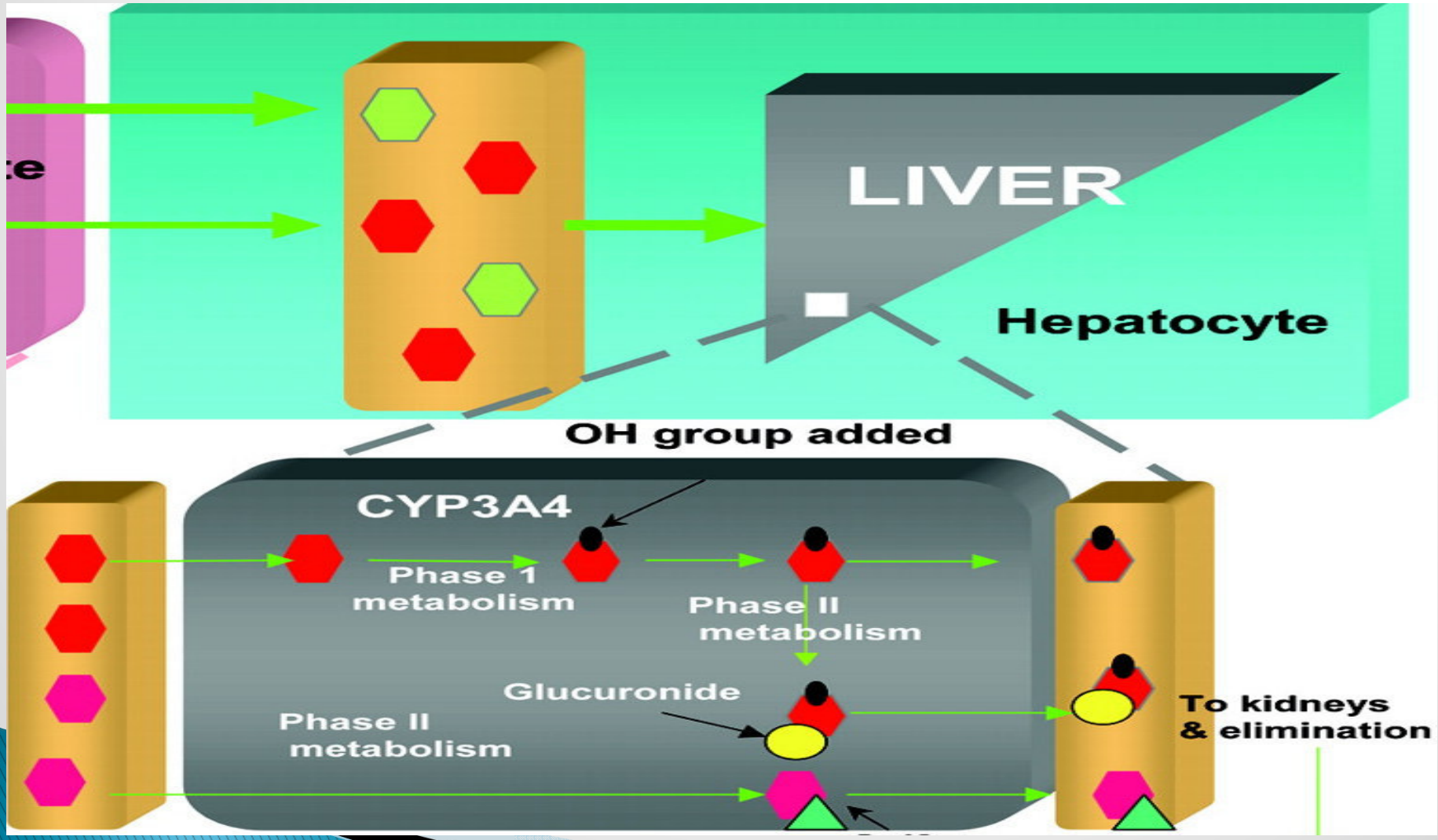
Metabolism of drug occur mainly in the liver

Metabolism involve two main process

1-phase 1 oxidation reaction

2-phase 2(conjugation) reaction

Metabolism


LIVER
Hepatocyte
OH group added
CYP3A4
Phase 1
metabolism
Phase II
metabolism
Glucuronide
Phase II
metabolism
To kidneys
& elimination

Excretion

- Excretion is the **irreversible removal of drug from the body** and commonly occurs via the **kidney** or **biliary** tract.
- Kidney is the main organ for excretion of drugs and their metabolites

- elimination from **lung** is important mainly for the elimination of anesthetic drugs through **sweating**

Clinical pharmacokinetics

- is the **discipline** that applies pharmacokinetic concepts and principles in humans in order to **design individualized dosage** regimens which **optimize** the **therapeutic response** of a medication while **minimizing** the chance of an **adverse** drug reaction.

Receptor sites of drugs

- Receptor sites of drugs are generally **inaccessible** to our observations or are widely distributed in the body, and therefore **direct measurement of drug concentrations at these sites is not practical.**
- we cannot directly sample drug concentration in this tissue. However, we can measure drug concentration in the blood or plasma, urine, saliva, and other easily sampled fluids.

Factors affecting pharmacologic response of a drug

- Differences in an individual's ability to metabolize and eliminate the drug (e.g., genetics)
- Variations in drug absorption
- Disease states or physiologic states (e.g., extremes of age) that alter drug absorption, distribution, or elimination
- Drug interactions

Population pharmacokinetics

- is the **study of the sources of variability** in the drug pharmacokinetic behavior among individuals who are the **target** patient population.
- The effect of each **factor** on the drug pharmacokinetic behavior can be **quantified** and used in recommendations for the **proper use** of the drug in the different patient subpopulations.
- This is because in the presence of high **variability** in the drug pharmacokinetics, the same dose of the drug can produce a wide range of concentrations in different patients. These concentrations can be **high** (toxic), **average (therapeutic), or low (sub therapeutic).**

Toxic kinetics

- It is the field of science that applies the pharmacokinetic principles to determine the relationship between the systemic exposure of a compound and its toxicity.

- **Toxic kinetic studies are pharmacokinetic studies perduring formed to determine the absorption, distribution, metabolism, and elimination of the drug or chemicals the toxicity studies.**

- **The information obtained from these toxic kinetic studies** in **laboratory animals** is extrapolated to establish the drug concentration-toxic effect relationship in humans.

Application of the pharmacokinetic principles in the biomedical fields

1. Design and Evaluation of Dosage Forms
2. Evaluation of Drug Formulation
3. Pharmacological Testing
4. Toxicological Testing
5. Evaluation of Organ Function
6. Dosing Regimen Design

Therapeutic drug monitoring (TDM)

- is defined as the use of **assay** procedures for determination of **drug** concentrations in **plasma**, and the **interpretation** and application of the resulting concentration data to **develop safe and effective drug regimens.**

- If performed properly, this process allows for the **achievement of therapeutic concentrations of a drug more rapidly and safely** than can be attained with empiric dose changes.

- Together with **observations** of the drug's clinical effects, it should provide the safest approach to optimal drug therapy.

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Why need TDM?

1. Some drug have narrow therapeutic window (NTW)
2. Individual variations “Patients usually do not response in a similar way when they are placed on identical dosage regimen”.
3. Some may demonstrate adequate response, others may demonstrate toxicity, and other may not be affected at all by the drug.
4. So, make therapeutic drug monitoring to these drug for each patients.

Therapeutic monitoring using drug concentration data is valuable when:

1.A good correlation exists between the pharmacologic response and plasma concentration.

2.Wide inter subject variation in plasma drug concentrations results from a given dose.

3.The drug has a narrow therapeutic index (i.e., the therapeutic concentration is close to the toxic concentration).

4.The drug's desired pharmacologic effects cannot be assessed readily by other simple means (e.g., blood pressure measurement for antihypertensive).

The value of therapeutic drug monitoring is limited in situations in which:

1.There is no well-defined therapeutic plasma concentration range.

2.The formation of pharmacologically active **metabolites** of a drug **complicates** the application of plasma drug concentration data to clinical effect **unless** metabolite concentrations are also **considered**.

3.There are no significant consequences associated with too high or too low levels.

Plasma concentration curve:

- Plasma concentration is the simplest widely used method to evaluate the therapeutic and toxic effect of the drug.

The changes in drug concentration are as following:

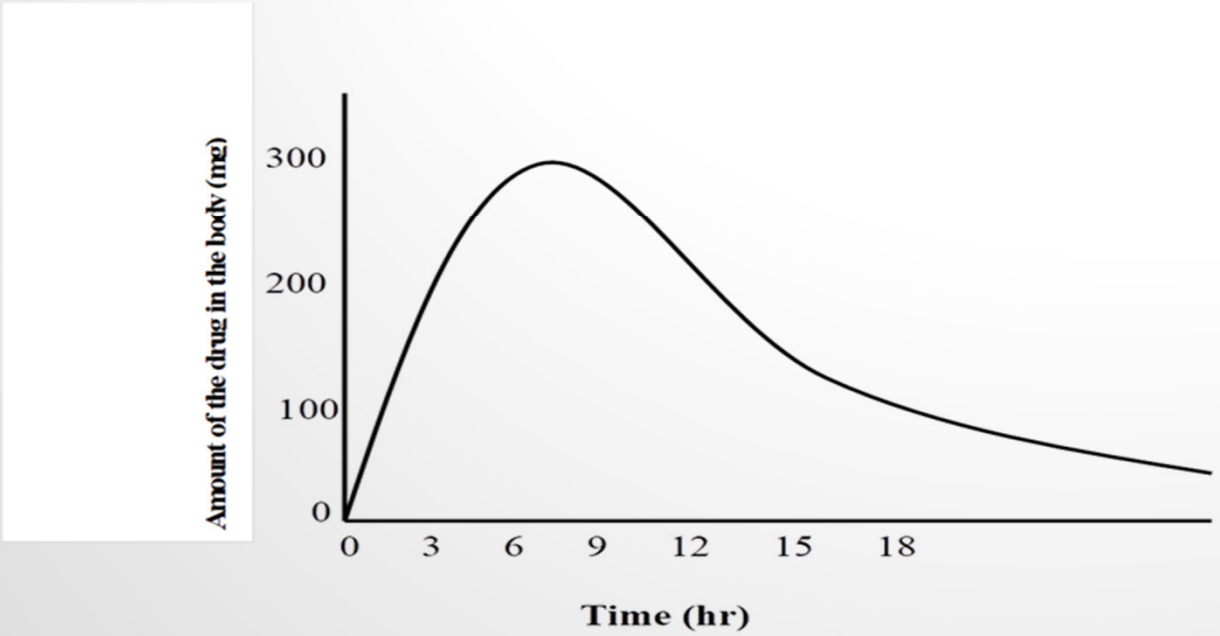
A- An increase in the amount of drug in the body (absorption)

B- A decrease in the amount of drug in the body (metabolism and excretion)

C- No change in the amount of drugs in the body (distribution)

The change in blood amount after oral administration

The drug amount-time profile in the body is an increasing, and then decreasing function as shown below.



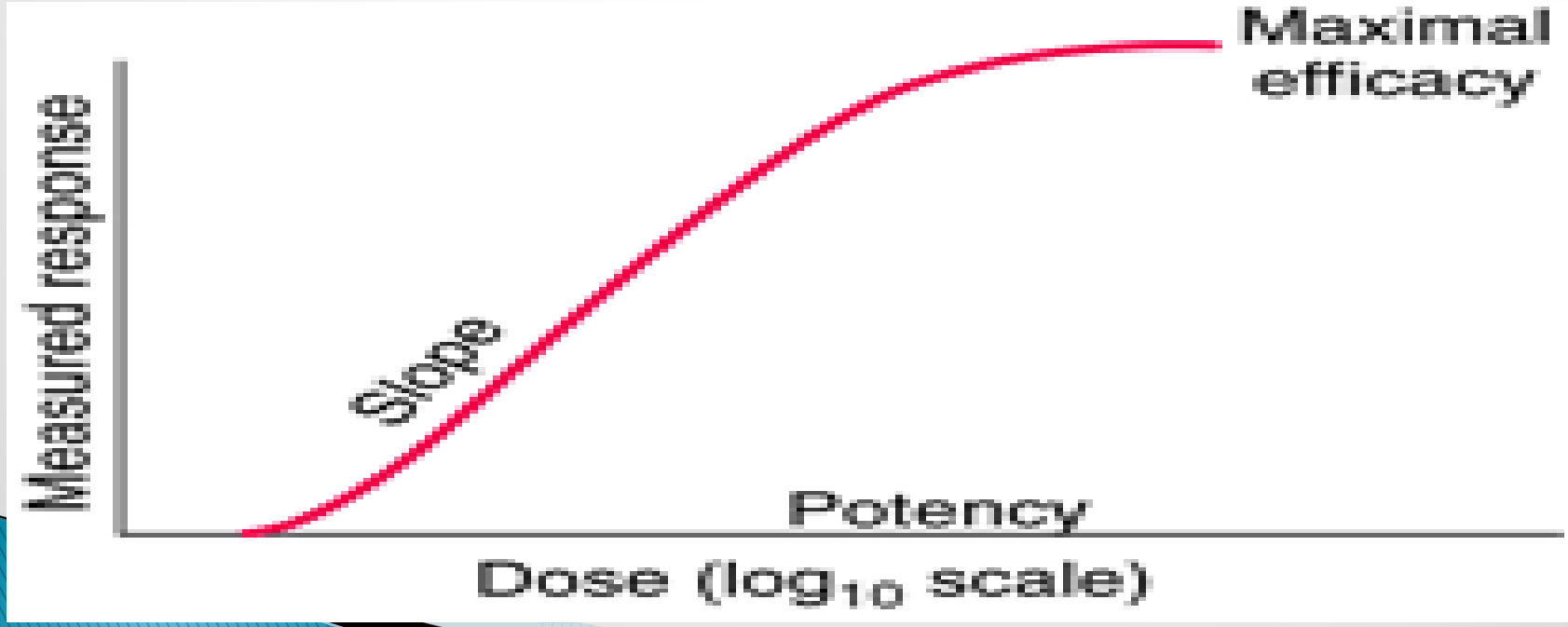
- Some drugs are administered IV, so these agents have no absorptive phase associated with their pharmacokinetic profile.

- IV administration of drugs is followed by distribution and elimination, and thus the time-amount profile of the drug in the body is a **decreasing** function as shown below.

- **The time-amount profile of the drug in the body is a decreasing function**

Pharmacokinetics- pharmacodynamics interface. Plasma concentration and pharmacologic response

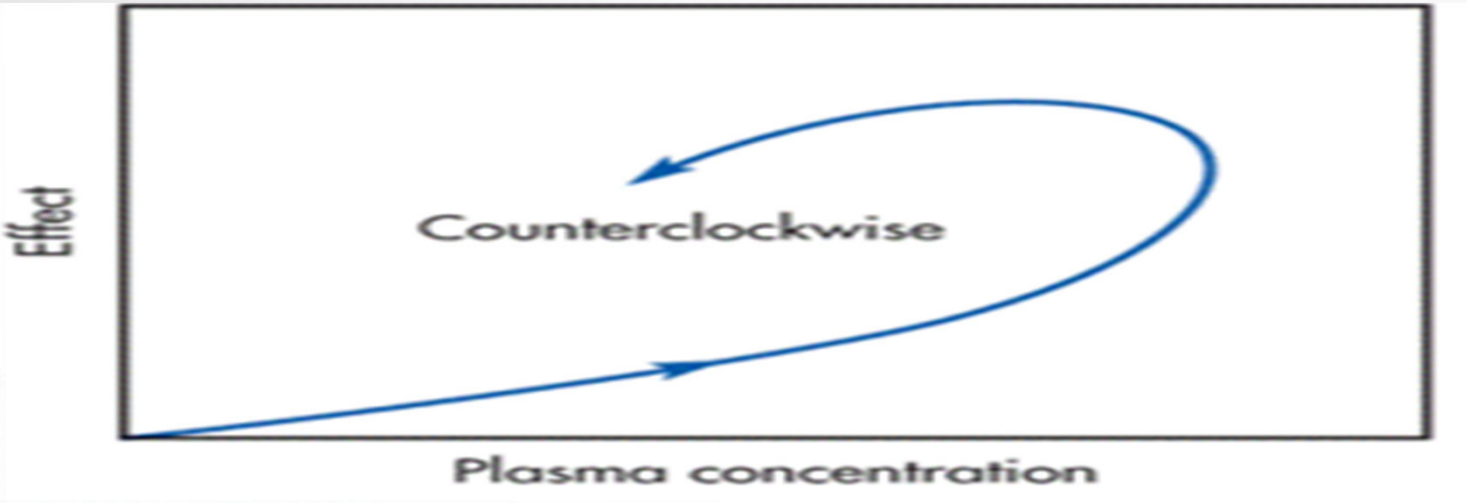
- 1-Concentration response plot: increase concentration increase response till reaching maximal response (Most drugs)



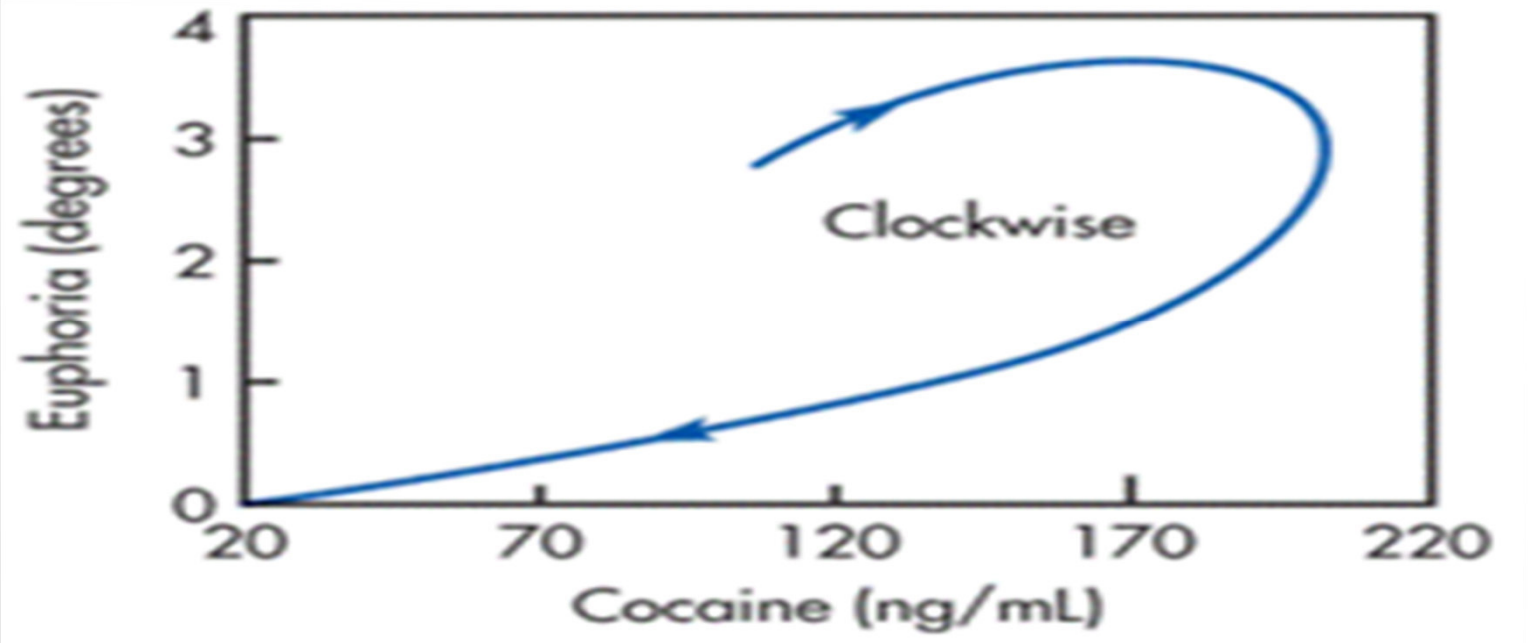
Hysteresis loops

- The response not related to the dose, the cause may be:

a- counterclockwise hysteresis due to increased sensitivity or formation of active metabolite



b- clockwise Hysteresis due to tolerance or formation of inhibitory metabolite



Empirical example

- Three new drug for treating diabetes were introduced in the market. The following table represent the relation between the plasma concentration and the drug effects as indicated by the decrease in blood glucose level
- For each drug determine the pharmacokinetic and pharmacodynamics interface after plotting the concentration effect graph

	drug A	drug B	drug C
Concentration (Mg/dl)	Effect (BG decrease)	Effect (BG decrease)	Effect (BG decrease)
5	2	2	2
10	4	4	4
20	8	8	8
30	16	12	10
20	18	8	6
15	12	6	4
10	10	4	2
5	6	2	1

Rate and orders of reactions

- **Rate**:The velocity with which a reaction or a process occurs is called as its rate.

- **Order of reaction**: The manner in which the concentration of drug (or reactants) influences the rate of reaction or process is called as the order of reaction or order of process.
- Consider the following chemical reaction:

Drug A Drug B

- The rate of forward reaction is expressed as: -dA/dt
- Negative sign indicates that the concentration of drug A **decreases** with time t.

- The rate of forward reaction is expressed as: -dA/dt
- Negative sign indicates that the concentration of drug A decreases with time t. As the reaction proceeds, the concentration of drug B increases and the rate of reaction can also be expressed as: dB/dt

$$dC/dt = -KC^n$$

rate constant = K

order of reaction = n

Zero-Order Kinetics (Constant Rate Processes)

If n = 0, equation becomes:

$dC/dt = -K_o$ where

Ko = zero-order rate constant (in mg/min)

Zero-order process can be **defined as the one whose rate is independent of the concentration of drug** undergoing reaction i.e. the rate of reaction cannot be increased further by increasing the concentration of reactants. Finally

$$\mathbf{C = C_o - K_o\, t}$$

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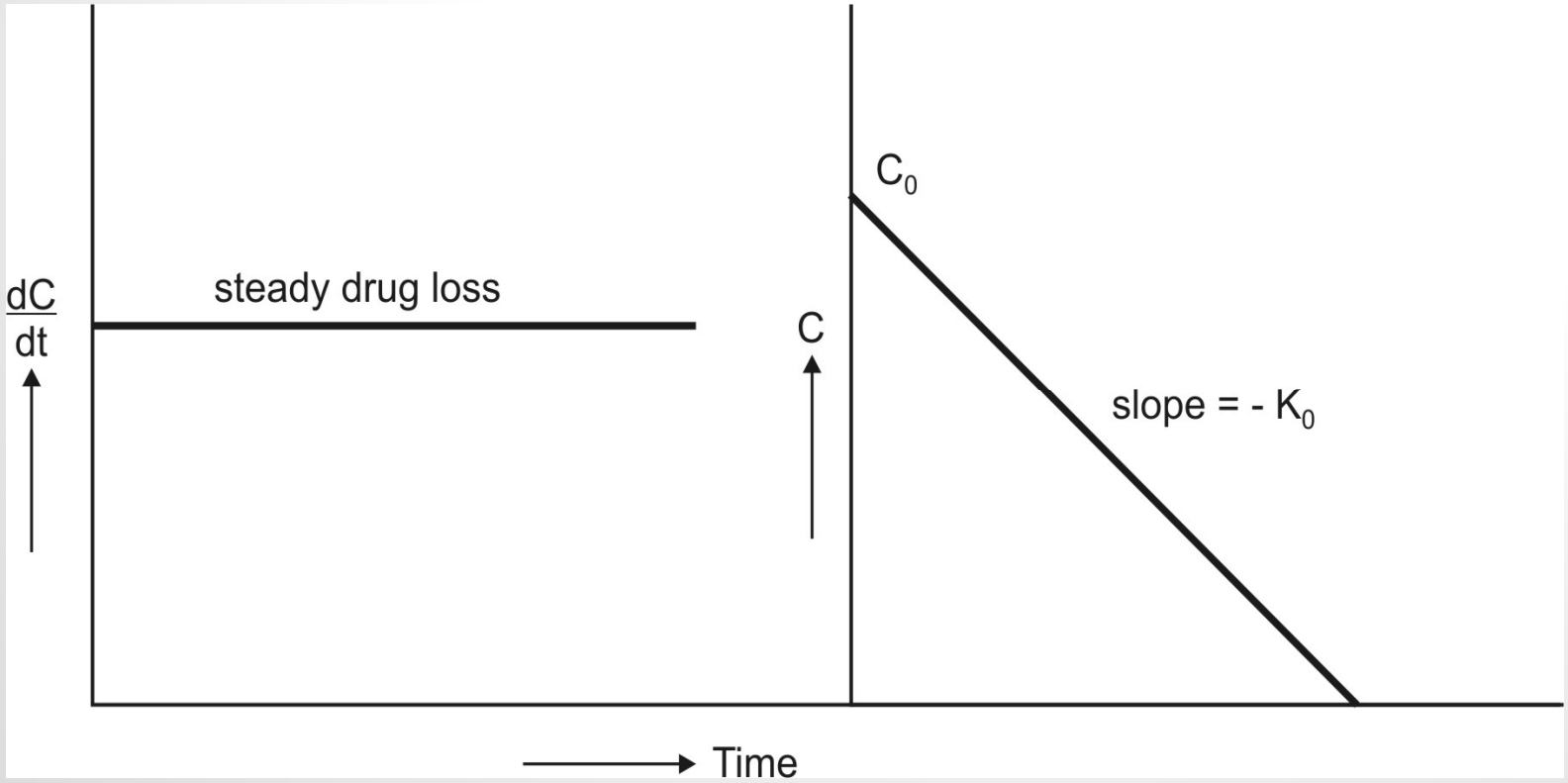
$$C = C_o - K_o t$$

Graph for zero order reaction

- If a graph constructed by plotting the **concentration** of drug versus **time**, it will yield a **straight line**.

- The zero-order rate constant k0 may be obtained from the slope of the line, and the y intercept will be Co


dC
dt
steady drug loss
C
C_0
slope = - K_0
Time

Zero-Order Half-Life

- **Half-life ($t_{½}$) or half-time *is defined as the time period required for the concentration of drug to decrease by one-half.***

$$t_{1/2} = C_o / 2\,K_o$$

- **Half-life ($t_{½}$) is dependent on drug concentration.**

Examples of zero-order processes

1. Metabolism/protein-drug binding/enzyme or carrier-mediated transport under saturated conditions. The **rate of metabolism**, binding or transport of drug remains constant as long as its concentration is in excess of saturating concentration.

2. Administration of a drug as a constant rate **intravenous** (i.V.) infusion.

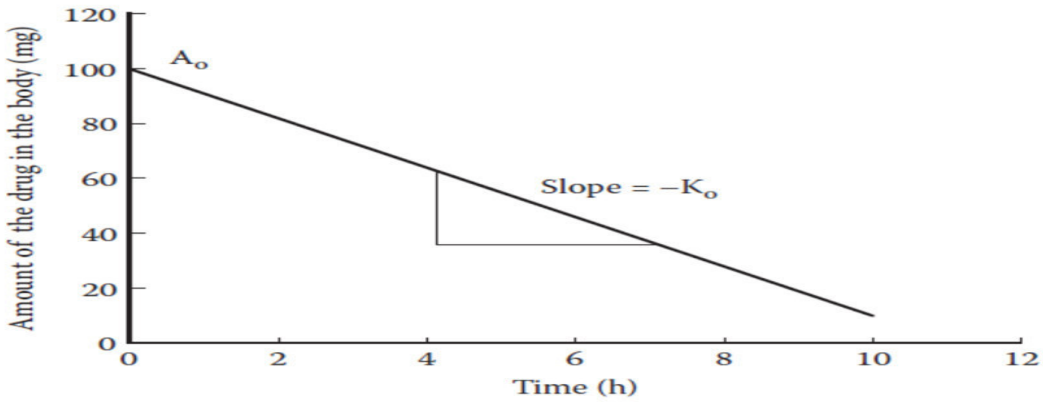
3. Controlled drug delivery such as that from **intramuscular** (I.M.) implants or osmotic pumps.

- Example: The administration of a 1000 mg of drug X resulted in the following concentrations:

Time	Conc. (mg/L)
0	100
4	90
6	85
10	75
12	70

- Zero-Order Reactions: example
- What is the order of the elimination process (zero or first)?
- What is the rate constant?

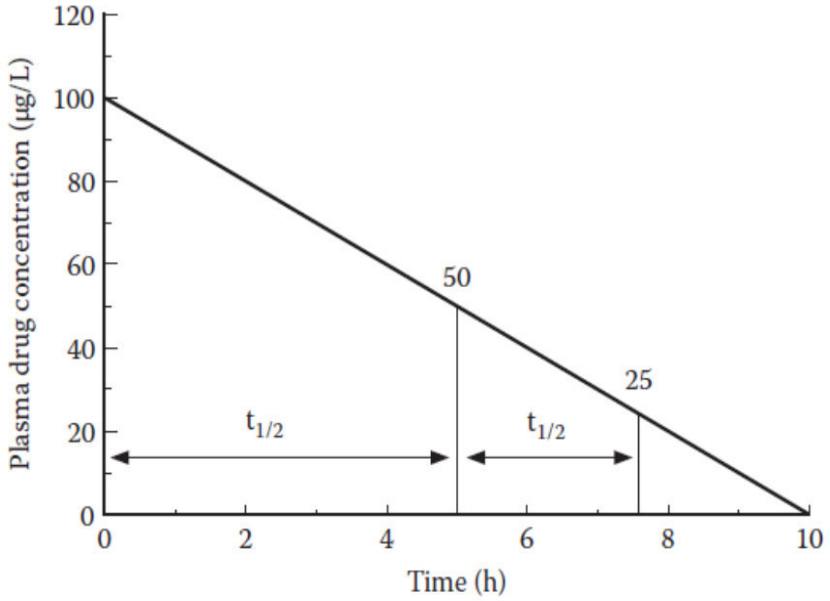
- Since the decline in drug conc. **displayed a linear decline on normal scale, drug X has a zero order decline**.
- The zero-order rate constant k0 may be obtained from the slope of the line, and the y intercept will be Ao



Plot of the amount of the drug versus time on the Cartesian scale when the elimination of the drug follows zero-order kinetics.

- From the equation displayed on the figure (intercept = 100, slope = -2.5)
- Slope = (y2-y1)/(x2-x1)

The elimination rate constant is 2.5 mg/hr



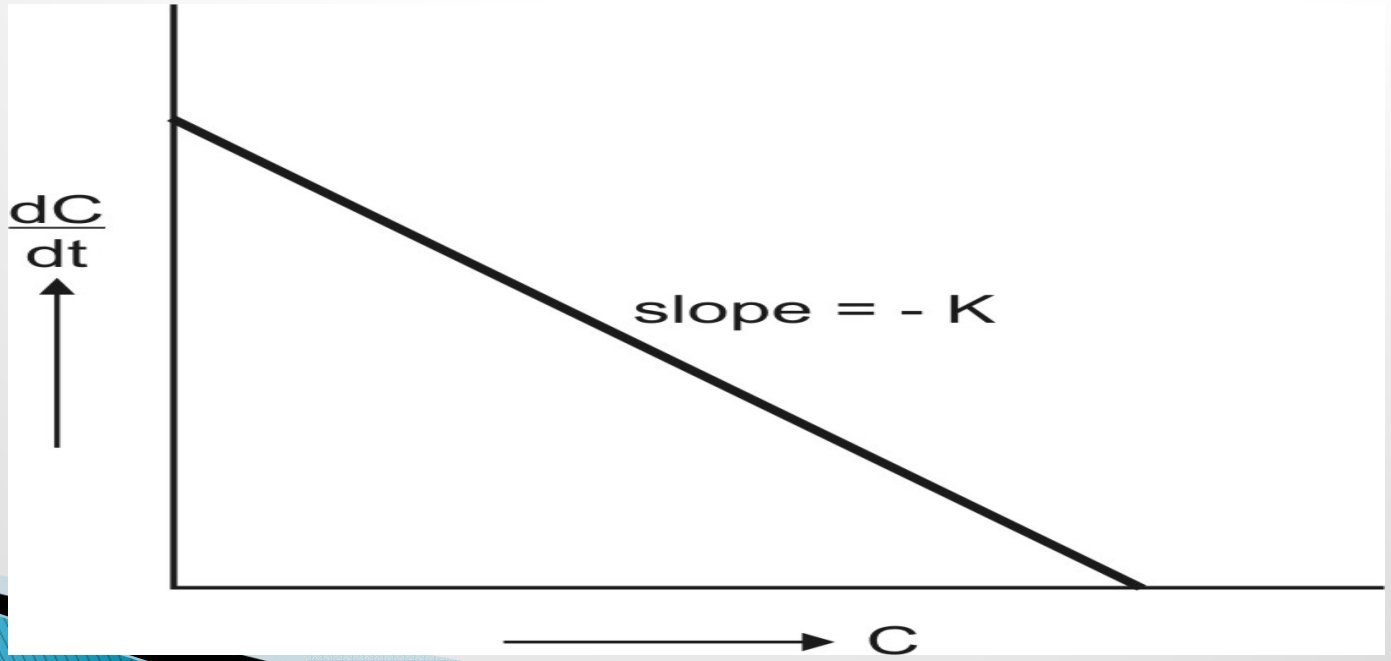
Half-life of the drugs eliminated by zero-order processes is dependent on the drug concentration.

First-Order Kinetics (Linear Kinetics):

- If n = 1, equation becomes:

$$dC/dt = - K C^n$$

- where K = first-order rate constant (in $time^{-1}$ or per hour)



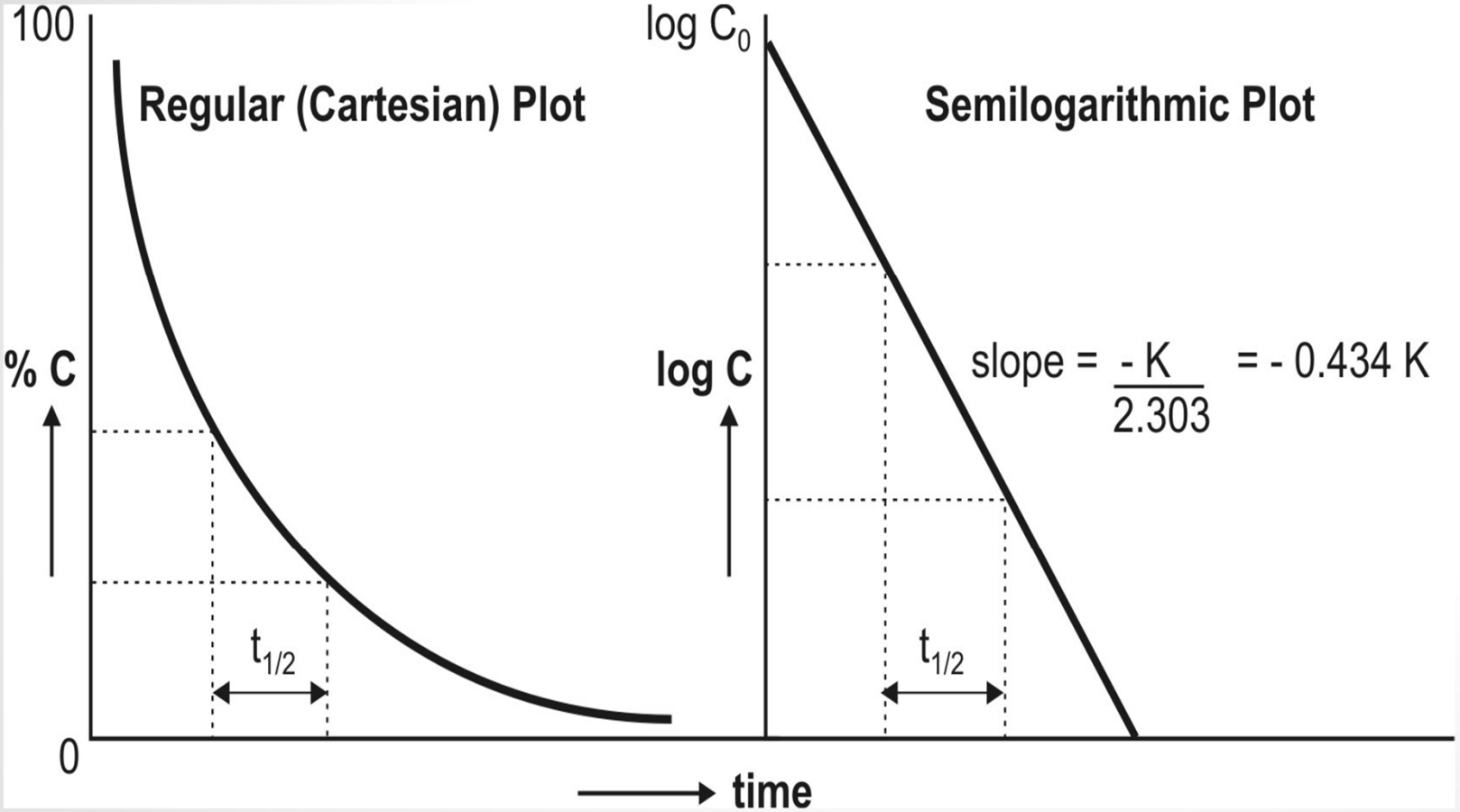
- **By integration:**

$$C = C_o - e^{-Kt}$$

- $\ln C = \ln C_o - K t$

  N.B.: $2.303 \log N = \ln N$

- $\log C = \log Co - Kt / 2.303$
- The first-order process is also called as **monoexponential rate process**. Thus, a first-order process is characterized by logarithmic or exponential kinetics i.e. a **constant fraction of drug undergoes reaction per unit time.**



$$\text{Slope} = \frac{\log y2 - \log y1}{x2 - x1}$$

$t_{1/2} = \ln 2/K$

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

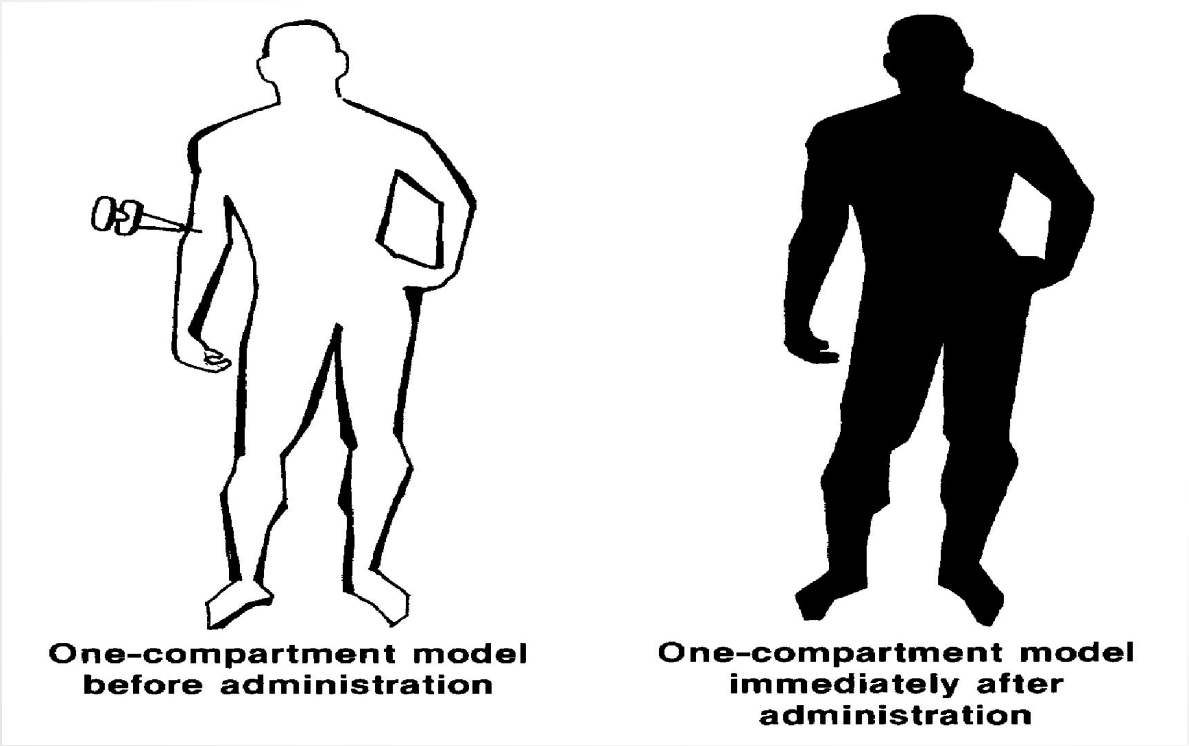
$$Slope = \frac{-K}{2.303}$$

- From equation shows that, in contrast to zero-order process, **the half-life of a first-order process is a constant and independent of initial drug concentration** i.e. irrespective of what the initial drug concentration is, the time required for the concentration to decrease by one-half remains the same.
- **Most pharmacokinetic processes including absorption, distribution and *elimination follow first-order kinetics.**

Difference between zero and first order kinetics:

First order	Zero order
Elimination rate depend on the amount of the drug dA/dt =-KA **Elimination rate constant K (Constant)**	Elimination rate is constant (dA/dt) = -K0 Elimination rate constant K0 (Constant)
Depend on the amount of the drug remaining	Doesn't depend on the amount of the drug
dA/dt = -KA Ln A = ln Ao – Kt	dA/dt = -K A= Ao-Kt
- **Curved** line on the rectangular coordinate graph paper Linear line on semi log paper -	**Linear** line on the rectangular coordinate graph paper
$T_{1/2}$ = ln 2/K = 0.693/K Constant	$T_{1/2}$ = 0.5 Ao/K Depends on the amount remaining
K hr^{-1}	K (mg/hr)
Intercept: Log Ao	Intercept: Ao
K0 & k is constant in zero and 1st order for the same drug and the same patient	

Drug kinetic following an IV dose



One-compartment model before administration

One-compartment model immediately after administration

the drug distributes instantaneously and homogenously throughout the compartment. Drug elimination also occurs from the compartment immediately after injection.

one-compartment model

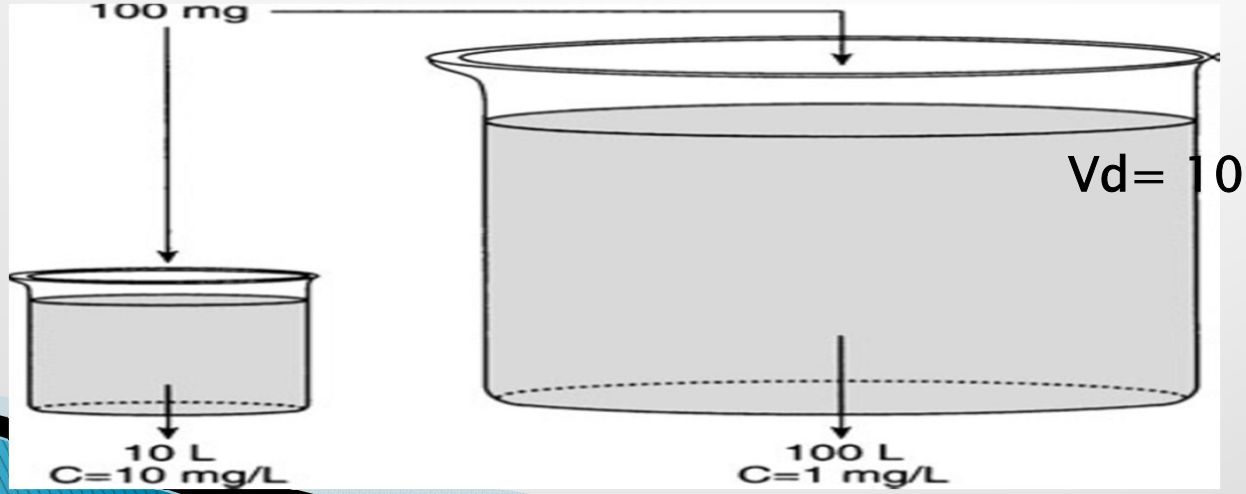
- The **one-compartment** open model offers the **simplest** way to describe the **process** of drug distribution and elimination in the body. This model assumes that the drug can enter or leave the body (ie, the model is "open"), and the **body acts like a single, uniform compartment.**

- The simplest route of drug administration from a modeling perspective is a rapid intravenous injection (IV bolus).

Fundamental parameters in one compartment

1. **Apparent Volume of Distribution (Vd)**
2. **Elimination rate constant (K)**
3. **Elimination half life (t1/2)**
4. **Clearance (Cl)**

- Vd= 10 L



The volume of distribution (Vd)

- is a **hypothetical volume that relates drug serum concentrations to the amount of drug in the body.** Thus, the dimension of volume of distribution is in volume units, such as **L or mL**.
- At any given time after drug has been absorbed from extravascular sites and the serum and tissue drug concentrations are in equilibrium, the serum concentration for a drug (C) is equal to the **quotient** of the amount of drug in the body (A) and the volume of distribution: $C = A/Vd$

- The **volume of distribution** can be: **very small** if the drug is primarily **contained in the blood** (warfarin V = 5–7 L), or **very large** if the drug distributes widely in the body and is mostly bound to **bodily tissues** (digoxin V = 500 L).

Volume of distribution is an **important** pharmacokinetic parameter because it determines the **loading dose** (LD) that is required to achieve a **particular steady-state drug concentration** immediately after the dose is administered:

$$LD = Css \cdot Vd$$

Factors affecting Apparent Volume of Distribution

- - Lipid solubility of drug
- - Degree of plasma protein binding
- - Affinity for different tissue proteins
- - Fat : lean body mass
- - Disease like Congestive Heart Failure (CHF), uremia, cirrhosis

Other Factors that affect VD

- **Demographic data of patient**

age, weight, gender, etc.

- **Medical condition**

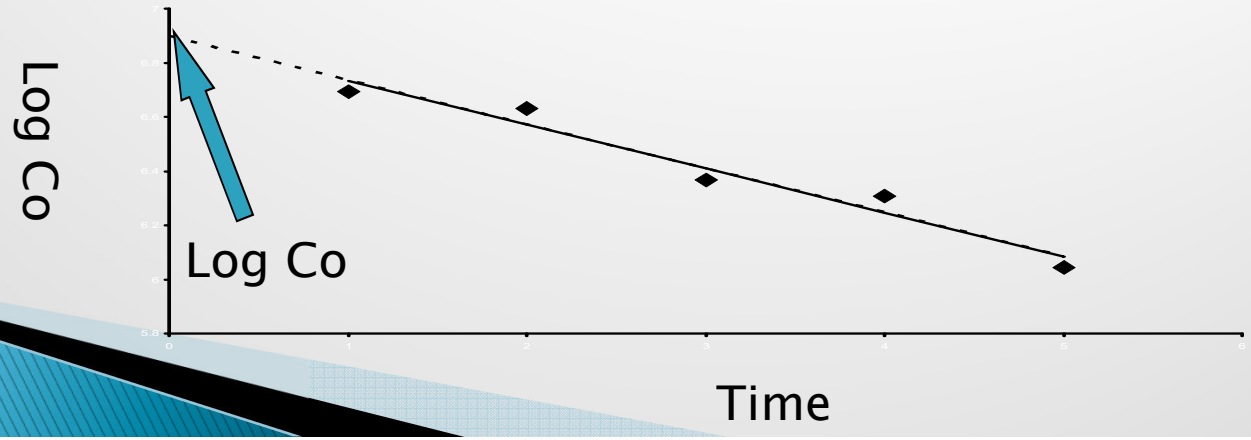
renal failure, liver failure, heart failure, etc.

NB :

most patients will not actually attain steady state after a loading dose, but, hopefully, serum drug concentrations will be high enough so that the patient will experience the pharmacological effect of the drug.

Apparent volume of distribution estimation

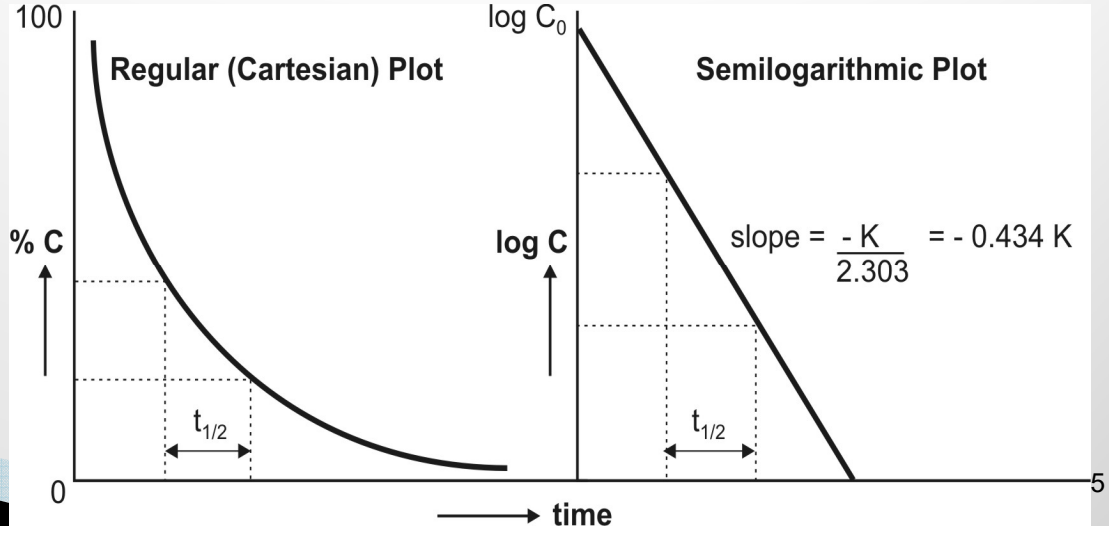
- 1. Plot log(C) vs. time
- 2. Plot the best-fit line
- 3. Extrapolate to the Y-axis intercept (to estimate initial concentration, C0)
- 4. Estimate Vd:
- $Vd = \frac{Dose}{Initial\ conc} = \frac{X0}{Co}$



Half-life (t1/2)and elimination rate constant (K)

- *The half-life describes* how quickly drug serum concentrations decrease in a patient after a medication is administered
- dimension of half-life is time (hour, minute, day, etc.).
- With first-order elimination, the rate of elimination is directly proportional to the serum drug concentration. There is a linear relationship between rate of elimination and serum drug concentration.
- The elimination rate constant (K) represents the fraction of drug eliminated per unit of time.

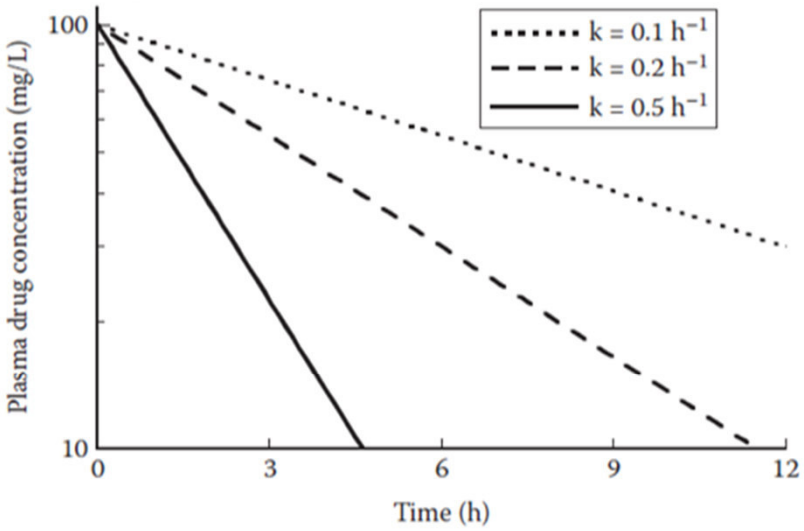
- In first-order elimination, the rate of elimination is directly proportional to the serum drug concentration.
- The elimination rate constant (K) represents the fraction of drug eliminated per unit of time.
- For first-order kinetics:
- $dC/dt = - K C$
- By integration:
- $C = C_o - e^{-Kt}$
- $\ln C = \ln C_o - K t$
- N.B.: $2.303 \log N = \ln N$
- $\log C = \log Co - Kt/2.303$



- $\textbf{Slope} = \frac{\log y2 - \log y1}{x2 - x1}$

- $Slope = \frac{-K}{2.303}$

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



Drugs with larger first-order elimination rate constants are eliminated at faster rate.

- * The half-life and elimination rate constant are known as dependent parameters because their values depend on the clearance (TBC) and volume of distribution (Vd) of the agent:

$t1/2 = (0.693 \cdot Vd)/Cl$ as $K = TBC/Vd$.

- * Because the values for clearance and volume of distribution depend solely on **physiological** parameters and can vary independently of each other, they are known as independent parameters.

Total body clearance:

- Clearance is the volume of serum or blood completely cleared of the drug per unit time.
- **TBC = K . Vd**
- $TBC = Dose/AUC$
- **MD = Css · TBC**
- Clearance (TBC) is the most important pharmacokinetic parameter because it determines the maintenance dose (MD) that is required to obtain a given steady-state serum concentration (Css)
- This range of steady-state concentrations is known as the **therapeutic range for the drug.**

Therapeutic range

an initial guideline for drug concentrations in a specific patient

- For example, the **therapeutic range** for **theophylline** is generally accepted as **10–20** µg/mL for the treatment of asthma. If it were known that the **theophylline clearance for a patient equaled 3 L/h** and the desired steady-state theophylline serum concentration was **10 µg/mL,** the theophylline **maintenance dose** to achieve this concentration would be **30 mg/h**.

Fraction of the dose remaining:

- **Fraction of dose remaining is given by the following equation (F = X(t)/X0), where X(t): the amount at any time & X0: the amount at zero time.**
- One half life later, 1/2 of the dose will remain. After additional half life (1/4 of the dose will remain)… and so on. A simple equation that relates the fraction remaining of **intravenous bolus dose (Q)** which is left after half-lives have elapsed is: $Q = (1/2)^n$

  Where n is the number of half-lives.

Applications of one compartment model:

- 1. Predicting Plasma Concentrations

- Example 1: A 20-mg dose of a drug was administered as an intravenous bolus injection. The drug has the following pharmacokinetic parameters: k = 0.1 h−1 and Vd = 20 L

- 1. Calculate the initial concentration (C0)

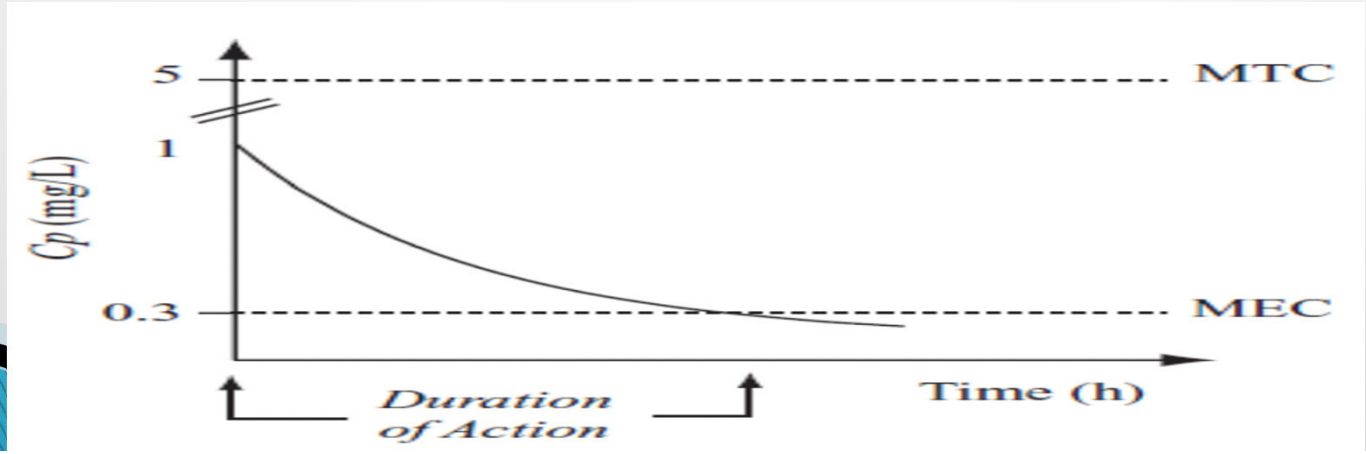
$$C_0 = \frac{\text{dose}}{Vd} = \frac{20\,\text{mg}}{20\,\text{L}} = 1\,\text{mg/L}$$

- Calculate the plasma concentration at 3 h

1. Calculate the plasma concentration at 3 h

$$C = C_0 \cdot e^{-K \cdot t} = 1 \cdot e^{-(0.1)\cdot(3)} = 0.74 \text{ mg/L}$$

- 2. Duration of Action
- Example 2: Continuing with the drug used in Example 1, if the therapeutic range is between 5 and 0.3 mg/L, how long are the plasma concentrations in the therapeutic range?



- As indicated in the diagram C0 =1 mg/L. Thus, at time zero the plasma concentration is in the therapeutic range. The plasma concentration will remain therapeutic until it falls to the MEC (0.3 mg/L). At what time does this occur?

$$t = \frac{\ln\left(\frac{C_0}{C^*}\right)}{K} = \ln\left(\frac{1}{0.3}\right) / 0.1 = 12.0 \text{ hr}$$

- 3. Value of a Dose to Give a Desired Initial Plasma Concentration

  - Example 3: Continuing with the drug used in Examples 1 and 2, If the initial *Cp* of 1 mg/L is unsatisfactory, Calculate a dose to provide an initial plasma concentration of 5 mg/L.

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

$$\text{dose} = 5 \frac{\text{mg}}{\text{L}} \cdot 20 \text{ L} = 100 \text{ mg}$$

- Example 3: Continuing with the drug used in Examples 1 and 2, If the initial *Cp* of 1 mg/L is unsatisfactory, Calculate a dose to provide an initial plasma concentration of 5 mg/L.

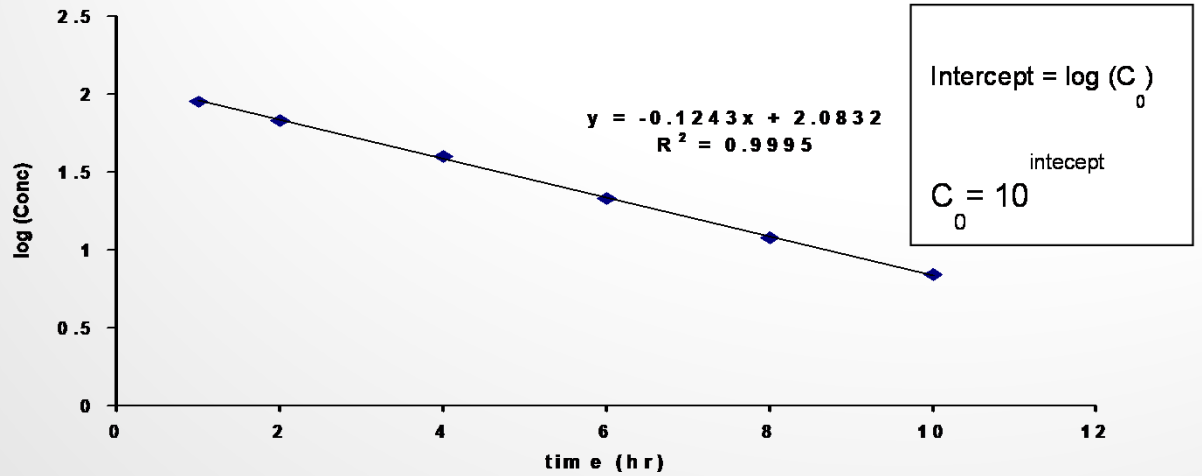
$$C_0 = \frac{\text{dose}}{Vd} \quad \Rightarrow \quad \text{dose} = C_0 \cdot Vd$$

$$\text{dose} = 5\frac{\text{mg}}{\text{L}} \cdot 20\ \text{L} = 100\ \text{mg}$$

- Example 4:
- 10 mg metoclopramide was administered intravenously to a 72 kg patient. The minimum plasma concentration required to cause significant enhancement of gastric emptying is 50 ng/mL. The following plasma concentrations were observed after analysis of the specimen.

Time (hr)	Conc. (ng/ml)
1	90.0
2	68.0
4	40.0
6	21.5
8	12.0
10	7.0

- Calculate the biological half-life of the drug elimination (t½), the overall elimination rate constant (K), the volume (Vd), the coefficient of distribution and the duration of action (td)



- **The elimination rate constant can be obtained from the slope:**

$$\text{Slope} = \frac{\log(C1) - \log(C2)}{t1 - t2}$$

$$\text{Slope} = \frac{\log(40) - \log(21.5)}{4 - 6} = -0.13481$$

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

$$= (0.13481) \cdot (2.303) = 0.286 \text{ hr}^{-1}$$

- the biological half-life of the drug elimination ($t_{½}$):

$$t_{0.5} = \frac{0.693}{K} = \frac{0.693}{0.286} = 2.42 \text{ hr}$$

- The volume of distribution (Vd):

$$Vd = \frac{\text{dose}}{C_0} = \frac{10}{10^{2.0832}} = \frac{10}{121.12}$$

$$= 0.083 \frac{\text{mg}}{\text{ng/ml}} \cdot \frac{10^6 \text{ng}}{\text{mg}} \cdot \frac{\text{L}}{10^3 \text{ml}} = 83 \text{ L}$$

- the coefficient of distribution = Vd/wt =83 L/ 72 kg= 1.15 L/kg
- The duration of action (td). td is the time needed for the concentration to get to 50 ng/ml :

$$t = \ln\left(\frac{C_0}{C^*}\right) \Big/ K = \ln\left(\frac{121.12}{50}\right) \Big/ 0.286 = 3.1\,hr$$

- Example 5:
- An adult male patient was given the first dose of an antibiotic at 6:00 AM. At 12:00 noon the plasma level of the drug was measured and reported as 5 µg/ml. The drug is known to follow the one compartment model with a half-life of 6 hours. The recommended dosage regimen of this drug is 250 mg q.i.d. the minimum inhibitory concentration is 3 µg/ml. Calculate the following:
- • Apparent volume of distribution
- • Duration of action of the first dose
- • Total body clearance
- • Fraction of the dose in the body 5 hours after the injection
- • Total amount in the body 5 hours after the injection
- • Cumulative amount eliminated 5 hours after the injection
- • Total amount in the body immediately after injection of a second dose at 12:00 noon
- • Duration of action of first dose only if dose administered at 6:00 AM was 500 mg.

Answer:

- Elimination rate constant:

$$K = {0.693}/{t_{0.5}} = {0.693}/{6} = 0.116\ hr^{-1}$$

- Initial concentration:

- The conc. at 12:00 noon (6 hrs after the first dose) is 5 µg/ml:

$$C(t=5) = C_0 \cdot e^{-k \cdot t}$$

$$\Rightarrow C_0 = \frac{C(t=5)}{e^{-k \cdot t}} = \frac{5}{e^{(-0.116)\cdot(6)}}\ 10\ ug/ml$$

- Apparent volume of distribution: C(t=6hrs)= 5 ug/ml. Since the half-life is 6 hrs, C_0 = 10 ug/ml.

Duration of action of the first dose

$$V_D = \frac{X_0}{C_0} = \frac{250\,\text{mg}}{10\,\frac{\mu\text{g}}{\text{ml}} \cdot \frac{10^{-3}\,\text{mg}}{\mu\text{g}}} = 25000\,\text{ml} = 25\,\text{L}$$

- Duration of action of the first dose

$$t = \ln\left(\frac{C_0}{C^*}\right) \Big/ K = \ln\left(\frac{10}{3}\right) \Big/ 0.1155 = 10.42\,\text{hr}$$

- Total body clearance
- Fraction of the dose in the body 5 hours after the injection

- Fraction of the dose in the body 5 hours after the injection

- Total amount in the body 5 hours after the injection = (0.56)(250 mg) = 140 mg
- Cumulative amount eliminated 5 hours after the injection = dose – amount in the body = 250 – 140 = 110 mg
- Total amount in the body immediately after injection of a second dose at 12:00 noon

Steady state during constant rate infusion(I.V.infusion)

The main advantage for giving a drug by IV infusion is that

- (1) IV infusion allows precise control of plasma drug concentrations to fit the individual needs of the patient.

- (2) For drugs with a narrow therapeutic window (eg, heparin), IV infusion maintains an **effective constant plasma drug concentration** by eliminating wide fluctuations between the peak (maximum) and trough (minimum) plasma drug concentration.

- (3) The IV infusion of drugs, such as antibiotics, may be given with IV fluids that include electrolytes and nutrients.

- (4) The duration of drug therapy may be **maintained or terminated as needed** using IV infusion.

If the drug is infused slowly through a vein into the plasma, it follow a constant or zero-order rate.

At steady state, the rate of drug leaving the body is equal to the rate of drug (infusion rate) entering the body.

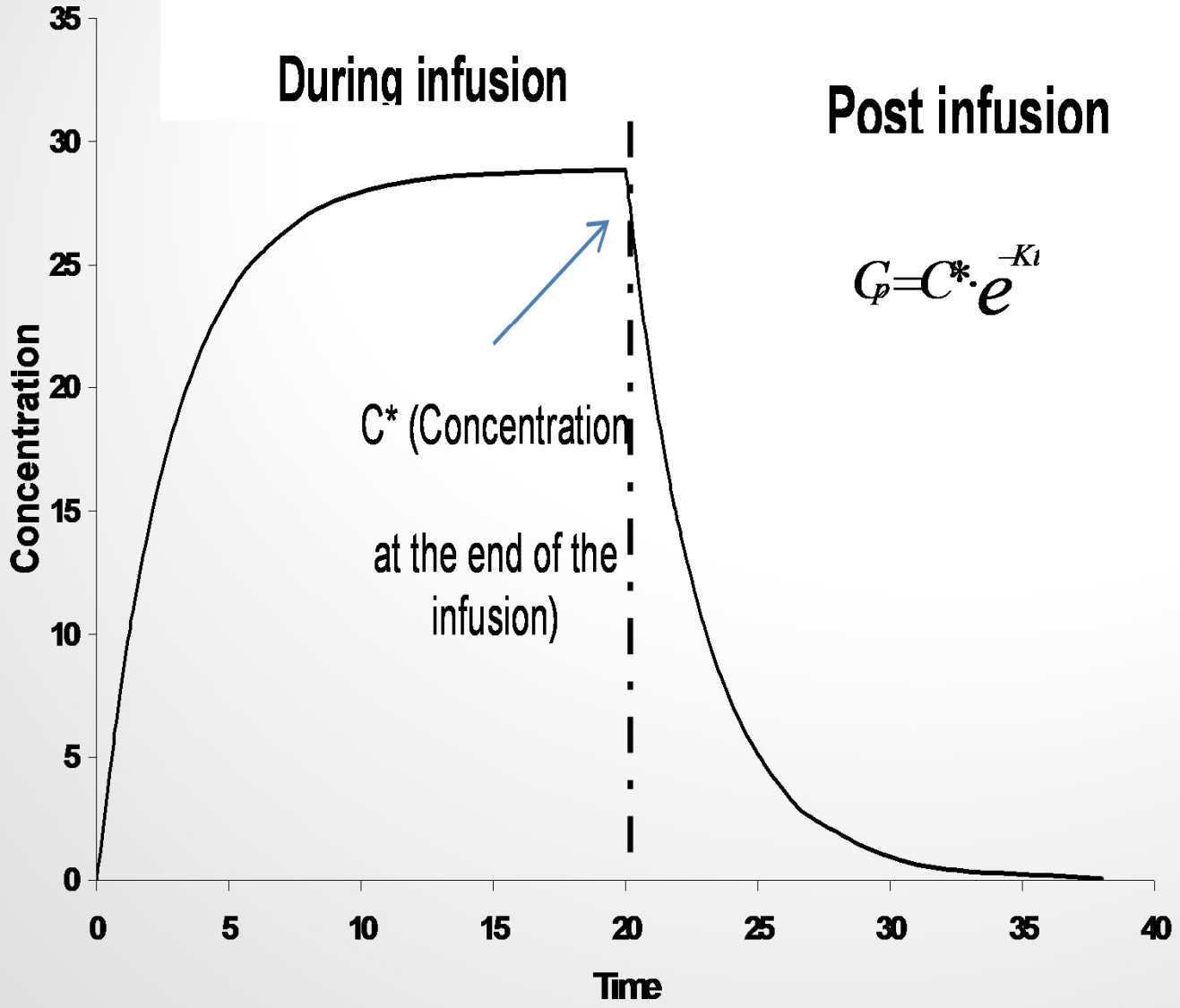
at steady state, the rate of change in the plasma drug concentration, dA/dt = 0, The steady state principle is also known the plateau principle.

Rate of in = rate of out

Infusion rate = elimination rate

R Or K0 = K Ass = K.Vd Css = TBC. Css

This relationship shows that the plasma concentration at **steady** state is proportional to the **rate of infusion** (i.e. the higher the rate of infusion, the higher the SS plasma conc.) and inversely proportional to drug clearance (i.e. the higher the drug clearance, the lower the SS plasma conc.).


During infusion
Post infusion
$C_p = C^* \cdot e^{-Kt}$
C* (Concentration
at the end of the
infusion)
Concentration
Time
0
5
10
15
20
25
30
35
40

During infusion (Before steady state)

$$C_P = \frac{K_0}{K \cdot V_D}\left(1 - e^{-K \cdot t}\right)$$

- During infusion (At steady state)

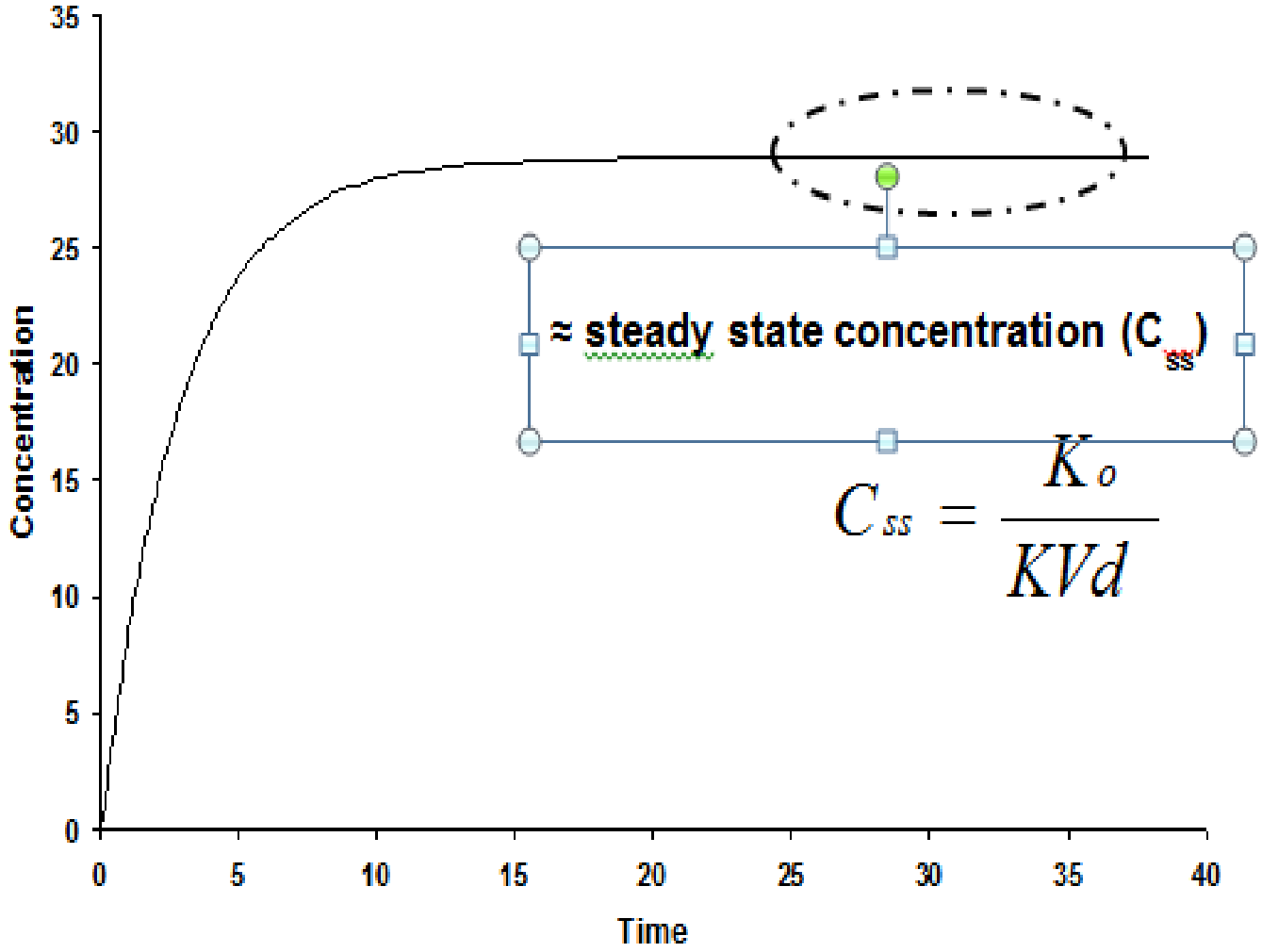
$$C_p = \frac{K_o}{KVd}$$

Or $C_p = K_0/TBC$

where K0 is the infusion rate, K is the elimination rate constant, and Vd is the volume of distribution.

Steady state:

- At steady state the input rate (infusion rate) is equal to the elimination rate.
- The elimination rate must be first order kinetic. This characteristic of steady state is valid for all drugs regardless to the pharmacokinetic behavior or the route of administration.



Fraction achieved of steady state concentration (F_{ss})

$$\left(1 - \right)^{\frac{t}{}}$$

Fraction achieved of steady state concentration (Fss)

Fraction achieved of steady state concentration (F_{ss})

OR $$F_{ss} = 1 - \left(\frac{1}{2}\right)^{\frac{t}{t_{0.5}}}$$ $$F_{ss} = 1 - e^{-Kt}$$

Time needed to achieve steady state: time needed to get to a certain fraction of steady state depends on the half-life of the drug (not the infusion rate)

$$t = (-1.44) \cdot t_{0.5} \cdot \ln(1 - F_{SS})$$

- **Example: What is the minimum number of half-lives needed to achieve at least 95% of steady state?**

$$t = (-1.44) \cdot t_{0.5} \cdot \ln(1 - F_{SS})$$
$$= (-1.44) \cdot t_{0.5} \cdot \ln(1 - 0.95) = (4.3) \cdot t_{0.5} \equiv 5 \ t_{0.5}$$

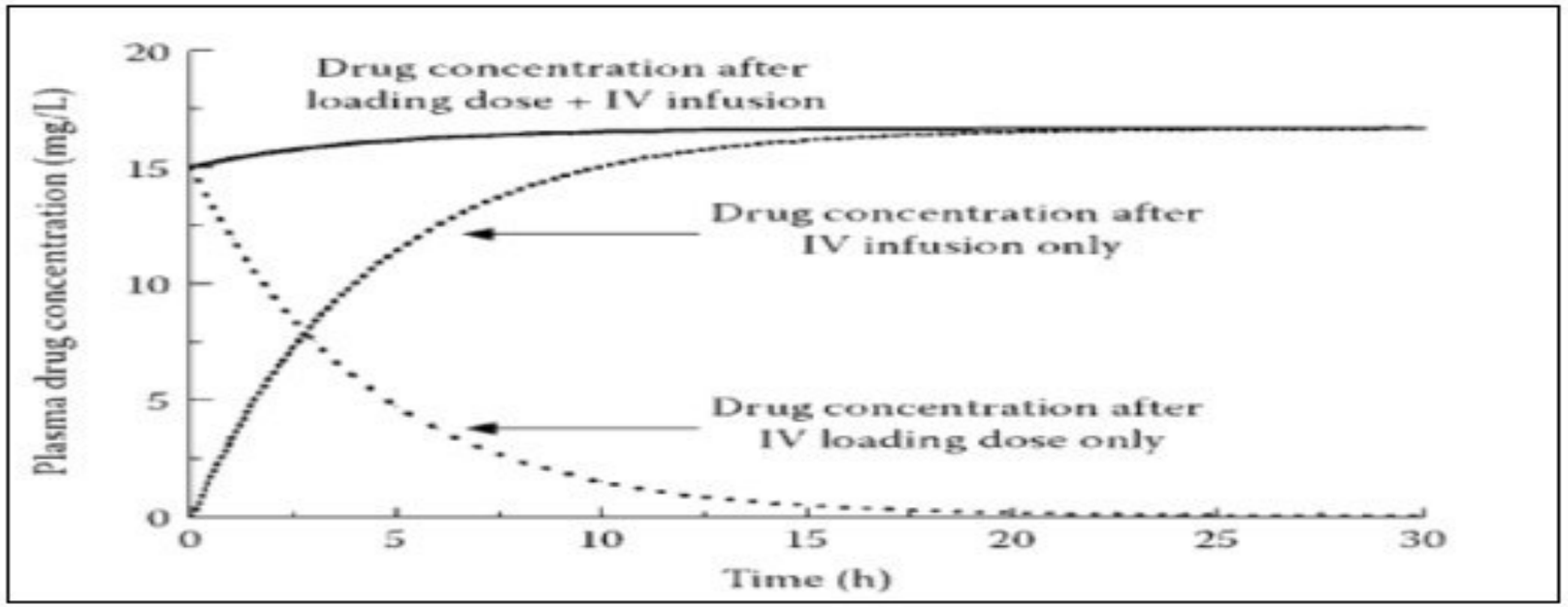
- **At least 5 half-lives are needed to get to 95% of steady state**
  - Mathematically, the time to reach **true steady-state** drug concentration, **C SS, would take an infinite time.** The time required to reach the steady-state drug concentration in the plasma is dependent on the **elimination rate constant of the drug for a constant volume of distribution.**

- • Thus, the time for a drug whose t 1/2 is 6 hours to reach at least 95% of the steady-state plasma drug concentration will be 5t 1/2, or 5 x 6 hours = 30 hours.

- **• *A generally accepted rule is that about 5 half-lives of continuous drug administration at a constant rate are required before plasma concentration reaches its steady state value.***

- ***Because steady state value is the therapeutic value so we need a loading dose to accelerate the reaching to the steady state value at zero time.***

IV infusion + Loading IV bolus:



- when **immediate** drug effect is required and **immediate achievement of therapeutic drug** concentrations is necessary such as in emergency situations
- In this case, administration of a loading dose will be necessary.

- To achieve a target steady state conc (Css) the following equations can be used:
- – For the infusion rate:

$$K_0 = Cl \cdot C_{ss}$$

- – For the loading dose:
- – The loading dose, LD, or initial bolus dose of a drug, is used to obtain desired concentrations (steady state) as rapidly as possible.
-

$$LD = Vd \cdot C_{ss}$$

- The concentration resulting from both the bolus and the infusion can be described as:

- The concentration resulting from both the bolus and the infusion can be described as:

$$C_{total} = C_{infusion} + C_{bolus}$$

Changing Infusion Rates:

- The rate of infusion of a drug is sometimes **changed** during therapy because of **excessive toxicity** or an **inadequate therapeutic response.** If the object of the change is to produce a new plateau, then the **time** to go from one plateau to another whether higher or lower **depends solely on the half-life of the drug.**

Elimination rate constant calculation using post infusion data:

- K can be estimated using post infusion data by:
- – Plotting log(Conc) vs. time
- – From the slope estimate K:

$$Slope = -\frac{k}{2.303}$$

- Volume of distribution calculation using post infusion data:

- If you reached steady state conc (C* = CSS):

$$C_{ss} = \frac{K_0}{K \cdot Vd} \Rightarrow Vd = \frac{K_0}{K \cdot C_{ss}}$$

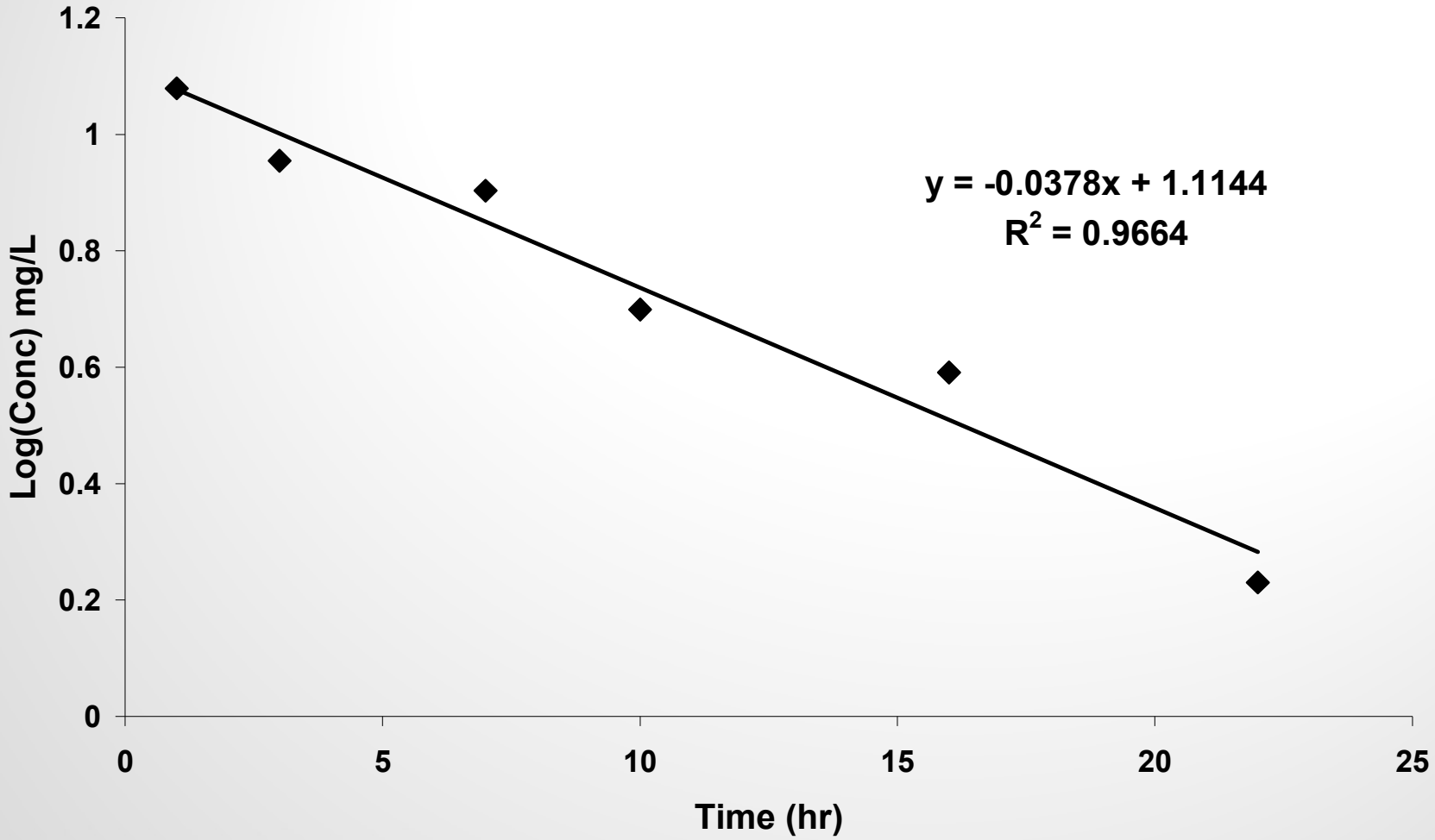
- If you did not reached steady state (C* = CSS(1-e-kT)):

$$C^* = \frac{k_0}{k \cdot Vd}(1 - e^{-kT}) \Rightarrow Vd = \frac{k_0}{k \cdot C^*}(1 - e^{-kT})$$

- Example:
- Following a two-hour infusion of 100 mg/hr plasma was collected and analysed for drug concentration. Calculate k and V.

Time relative to infusion cessation (hr)	1	3	7	10	16	22
Cp (mg/L)	12	9	8	5	3.9	1.7

Post infusion data



- From the slope, K is estimated to be:

$$k = -2.303 \cdot Slope = -2.303 \cdot -0.0378 = 0.087 \ 1/hr$$

- From the intercept, C* is estimated to be:

$$\log(C^*) = \text{intercept} = 1.1144$$

$$C^* = 10^{1.1144} = 13 \ mg/L$$

- Since we did not get to steady state:

$$Vd = \frac{k_0}{k \cdot C^*}(1 - e^{-kT})$$

$$Vd = \frac{100}{(0.087) \cdot (13)}(1 - e^{-0.087^* 2}) = 14.1 \ L$$

Multiple dosing and dosage regimen

- CONTENTS
- • Dosage regimen
- • Objectives of dose regimen
- • Therapeutic drug monitoring
- • Multiple dosage regimen
- • Multiple dosing with respect to I.V.
- • Multiple dosing with respect to Oral route.
- • Concept of loading dose, maintenance dose.
- • Drug accumulation

Dosage regimen

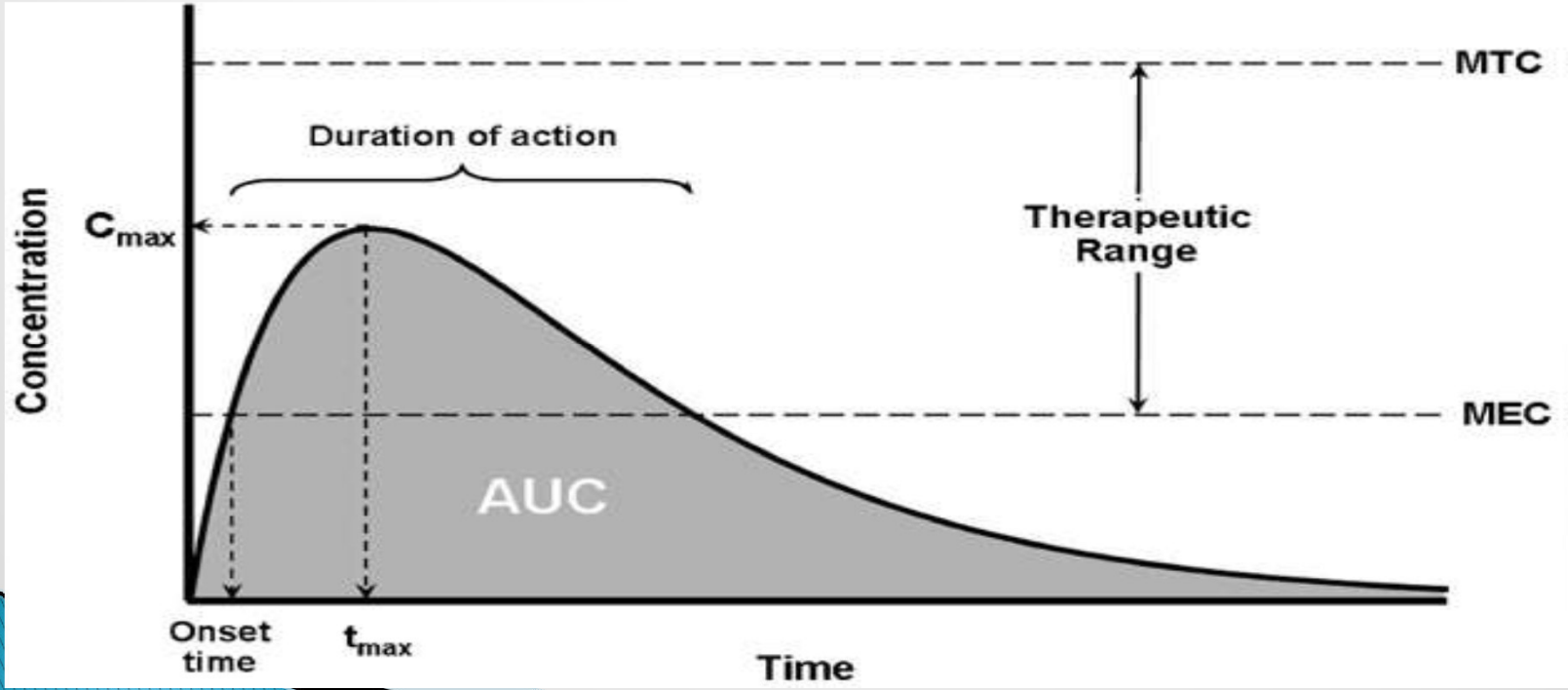
It is defined as the manner in which a drug is taken.

- For certain analgesics, hypnotics, anti-emetics etc. a **single dose** may provide an effective treatment.
- **But the duration of most illness is longer than the therapeutic effect produced by a single dose.**

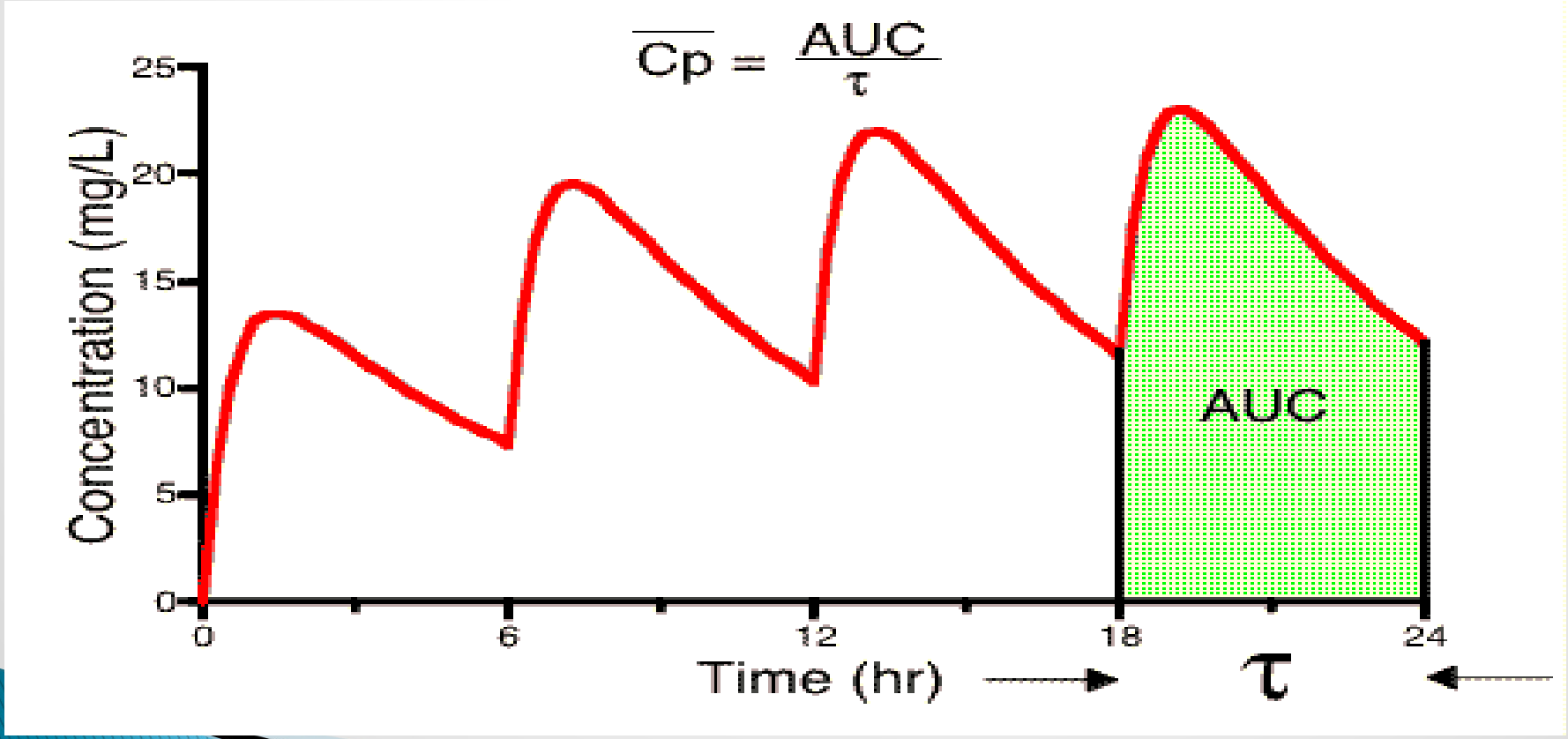
- **In such cases drugs** are required to be taken on a **repetitive basis over a period of time.**

Multiple dosage regimen

- When the duration of treatment of disease is smaller than the therapeutic activity of drug, single dose are given e.g. Aspirin



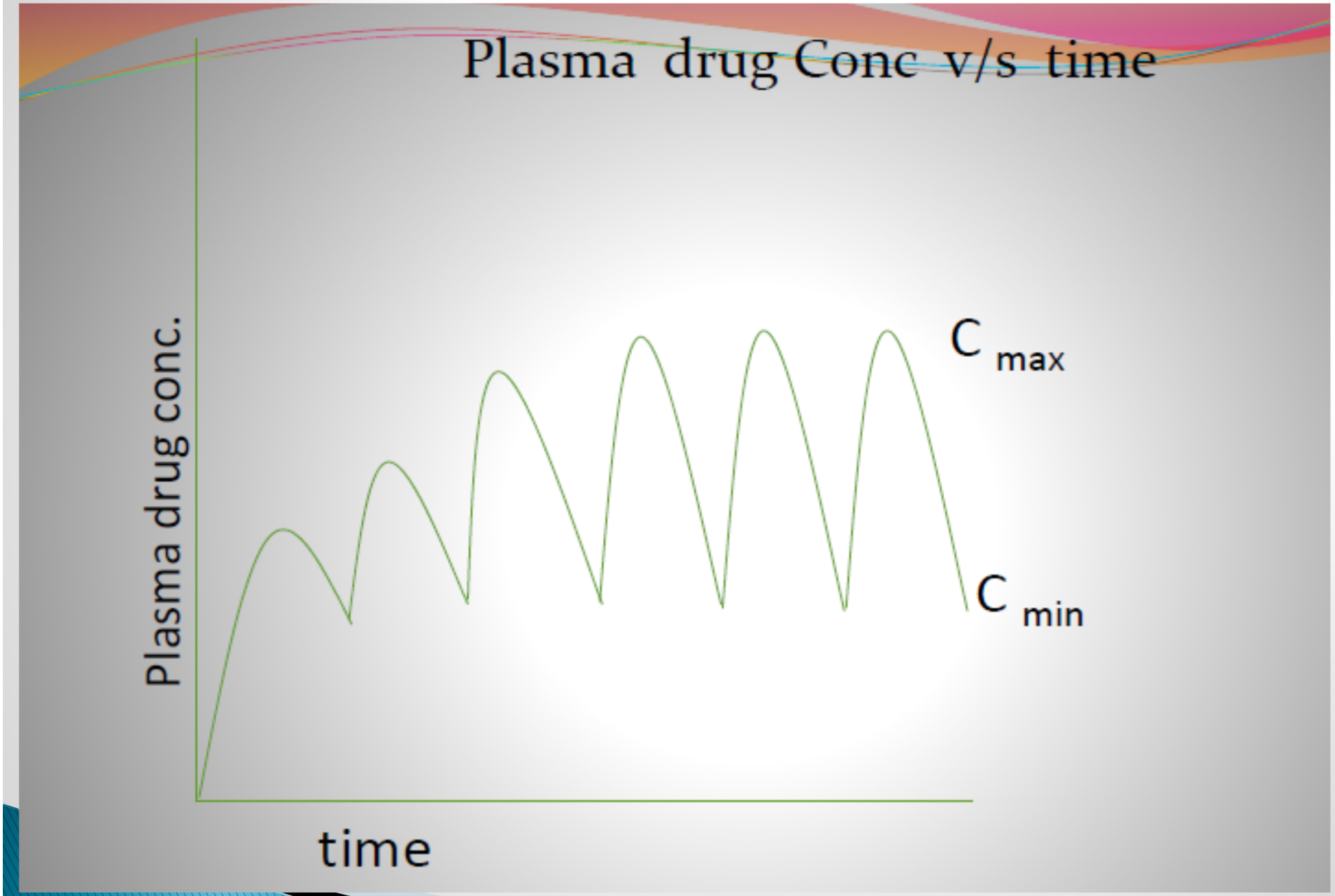
- When the duration of treatment of disease is larger than the therapeutic effect of drug, Multiple dosage regimen are given e.g. antibiotics



Multiple dosing with respect to oral route

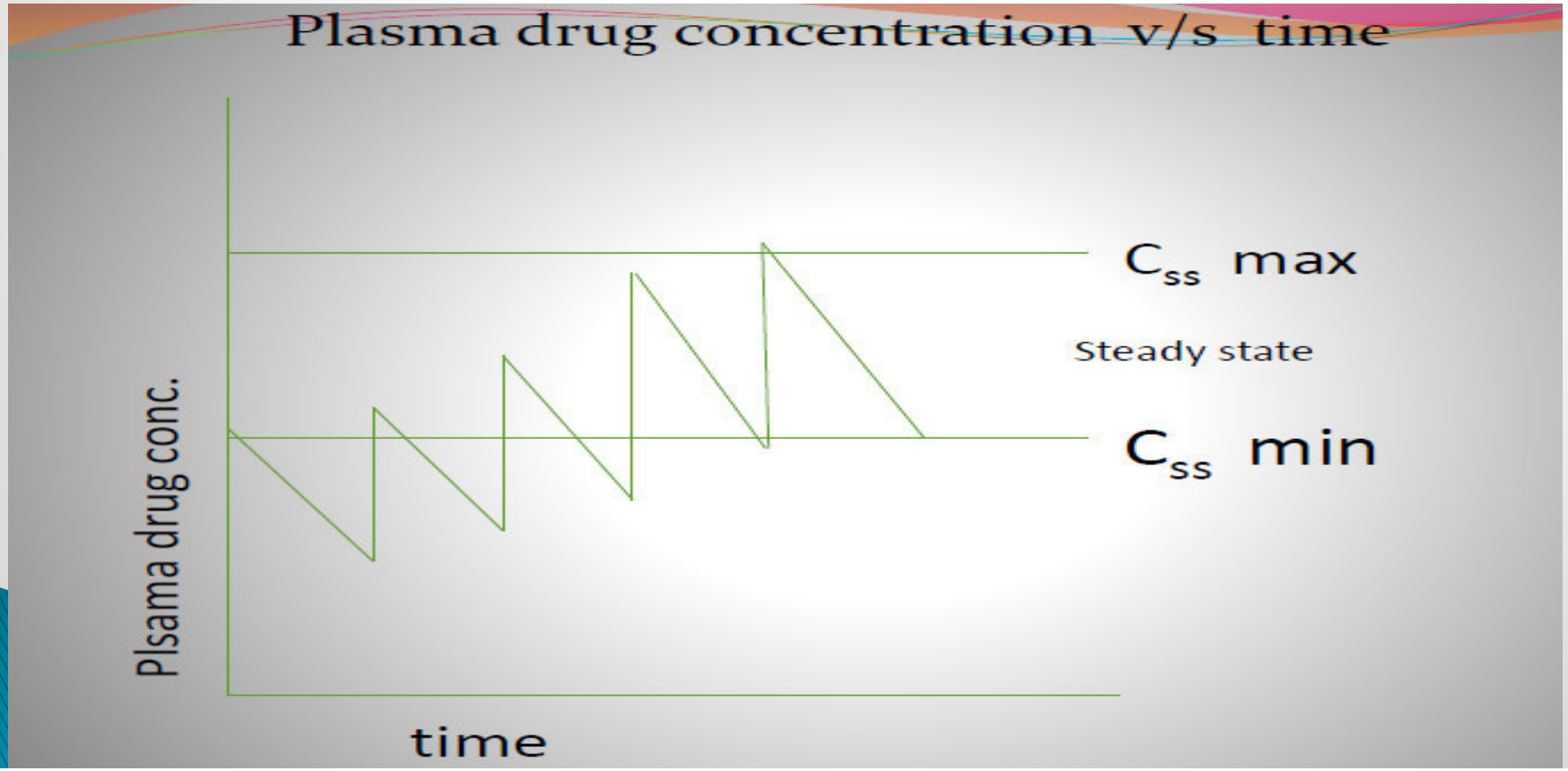
 When an oral multiple dosing regimen is followed, plasma conc. will **increase**, reach a maximum and begin to decline. A 2nd dose will be administered **before** all of the absorbed drug from 1st dose is eliminated.

 Consequently plasma conc. resulting from 2nd dose will be **higher than from 1st dose.** This increase in conc. with dose will continue to occur until a steady state is reach at which rate of drug entry into the body = rate of exit

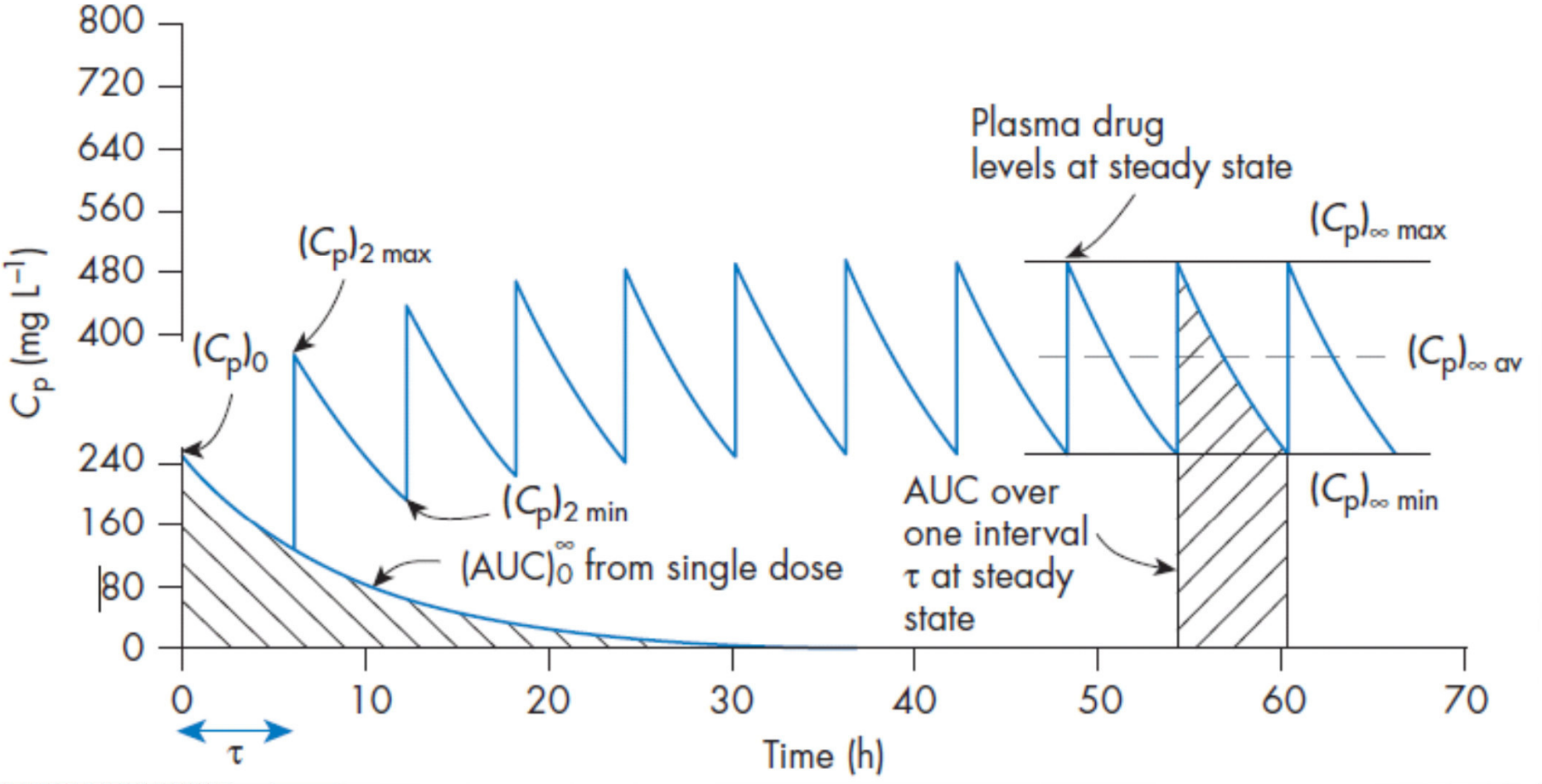

Plasma drug Conc v/s time
Plasma drug conc.
C max
C min
time

Multiple dosing with respect to I.V.

 On repeated drug administration, the plasma conc. will be added upon for each dose interval giving a plateau or steady state with the plasma conc. fluctuating between a minimum and maximum



Plasma drug concentration–time profile during multiple drug administration



- when the drug dose is administered at the beginning of the dosing interval and the drug concentration increases from $Cp_{min\ ss}$ to $Cp_{max\ ss}$, the drug concentration has to return back to Cp_{min} at the end of the dosing interval.

Multiple IV administration:

- For a drug that is eliminated by first-order process during **multiple IV administration** of **similar doses, D**, administered every **fixed dosing interval, τ**, the amount of drug in the body after administration of the first dose is **D**. The amount of the drug in the body before administration of the second dose is **$De^{-k\tau}$.** If this continued, At **steady state** the amount of the drug in the body after drug administration, $A_{\infty\ max} = D(1+e^{-k\tau}+De^{-2k\tau}.+De^{-3k\tau}+De^{-4k\tau}$.

Always Remember

- After single rapid IV injection,

$$DB = D0e^{-k\,t}$$

- If the τ is the dosing interval, then amount of drug
- remaining in the body after several hr,

$$DB = D0e^{-k\,\tau}$$

- The fraction of the Dose remaining in the body

$$f = DB/D0 = e^{-k\,\tau}$$

- This is an infinite series that can be solved as
- $A_\infty \max = \frac{D}{1-e^{-K\tau}}$

- $A_\infty \min = A_\infty \max . e^{-K\tau}$
- $A_\infty \max - A_\infty \min = Dose$
- where k is the first-order elimination rate constant. **Dividing these Equations by Vd, the equation for the maximum plasma drug concentration can be obtained:**

$$\mathbf{Cp_{\infty}\ max} = \frac{D}{Vd(1 - e^{-K\tau})}$$

$$\mathbf{Cp_{\infty}\ min} = \mathbf{Cp_{\infty}\ max}\,.\,e^{-K\tau}$$

$$\mathbf{Cp_{\infty}}\ max - \mathbf{Cp_{\infty}\ min} = \frac{Dose}{Vd}$$

- similar group of expressions can be written to relate the maximum and minimum plasma drug concentration at steady state dur-ing multiple extravascular drug administration when the drug absorption is rapid:
- $\mathbf{Cp_{\infty}\ max} = \frac{FD}{Vd(1-e^{-K\tau})}$

And $Cp_{\infty}\ max - Cp_{\infty}\ min = \frac{FDose}{Vd}$

- There are two main parameters that can be adjusted in developing a dosage regimen:

- (1) The size o f the drug dose

- (2) The frequency of drug administration (ie, the time interval between doses).

- If the drug is administered at a **fixed dose** and a **fixed dosage interval**, as is the case with **multiple-dose regimens**, the amount of drug in the body will **increase** and then **elimination occur**. When the **second dose** is given after a time interval **shorter** than the time required to "**completely" eliminate** the previous dose, drug **accumulation** will occur in the body.

Drug Accumulation –

When the drug is administered at a fixed dose and a fixed dosing interval, "**accumulation occur because drug from previous dose has not been remove.**" **Accumulation** of drug **depend** upon the **dosing** interval and **elimination** half life and is **independent** of the dose size.

$$\text{Accumulation index} = \frac{1}{1 - e^{-K_E \tau}}$$

τ= Dosing interval

K_E = Elimination half life

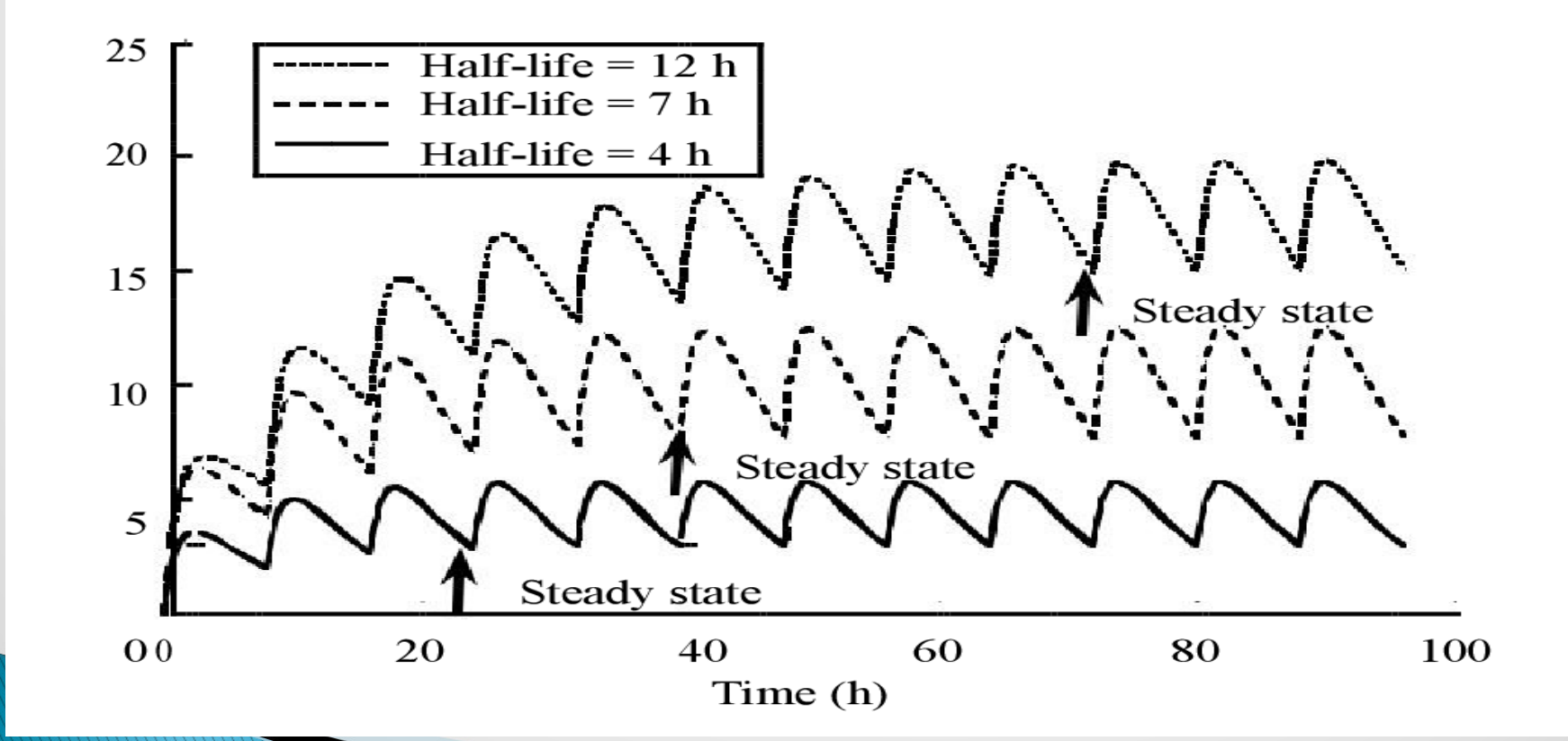
•The degree of **fluctuation** depends on the **dosage size**, the **dosing interval**, the **absorption rate if given IM, or oral, and the disposition rate of the drug**.

Time required to reach steady state

1. The time required to reach steady state is dependent on the half-life of the drug.

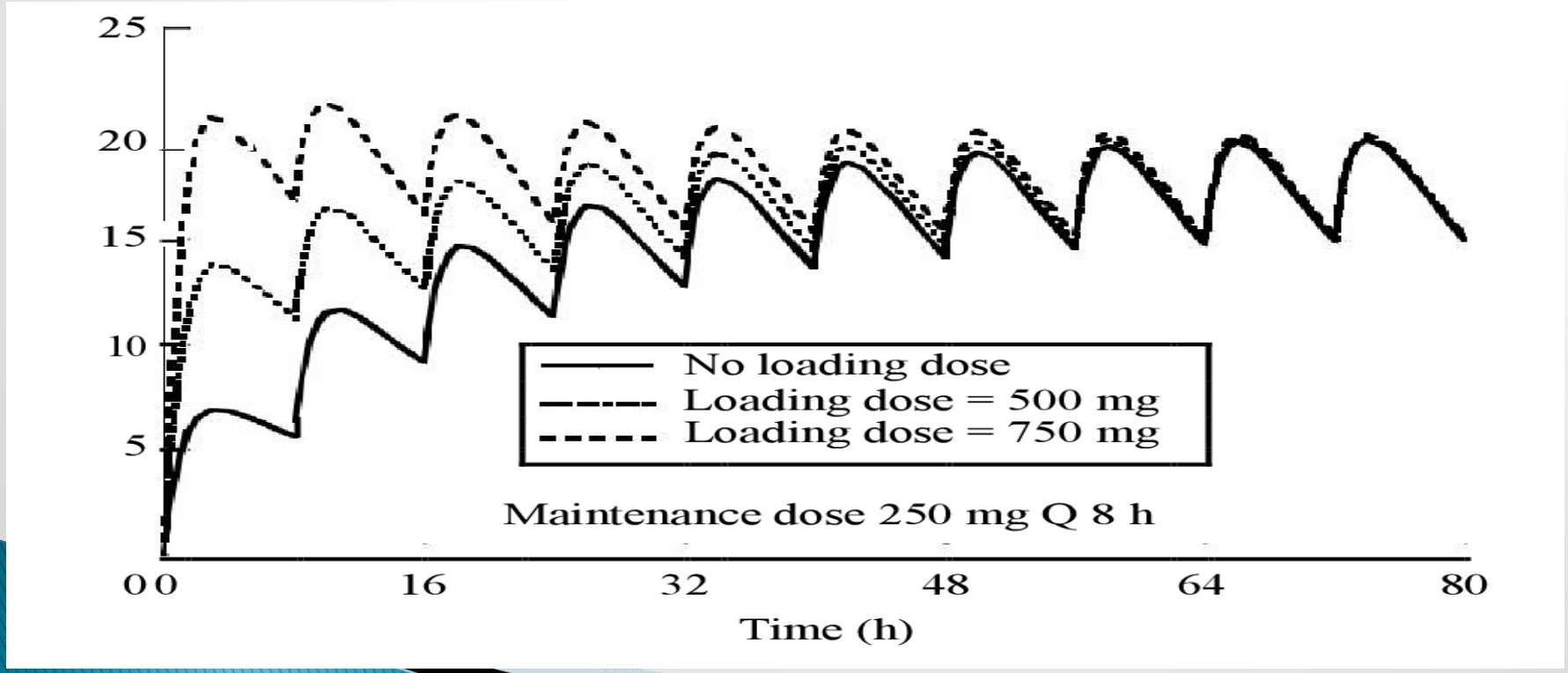
2. Generally, it takes five to six times the elimination half-life of the drug to reach steady state.

3. the drug has to be repeatedly admin-istered for a period equal to five to six half-lives to achieve steady state. The longer the drug half-life the longer it takes to reach steady state.



LOADING DOSE

- The **loading** dose is a dose **larger** than the **maintenance** dose administered at the initiation of therapy to achieve **faster** approach to **steady state**



IV Loading Dose

- The loading dose is calculated from the **desired plasma drug concentration and the Vd of the drug.** The desired drug concentration is usually a drug concentration within the therapeutic range:

Loading dose = Cp desired × Vd

Oral Loading Dose

Loading dose=(Cp desired ×Vd)/F

- The average steady-state plasma drug concentration is dependent on the dosing rate (FD/τ) and the total body clearance of the drug. Again, the loading dose **does not affect** the steady-state concentration.

Dosing regimens:

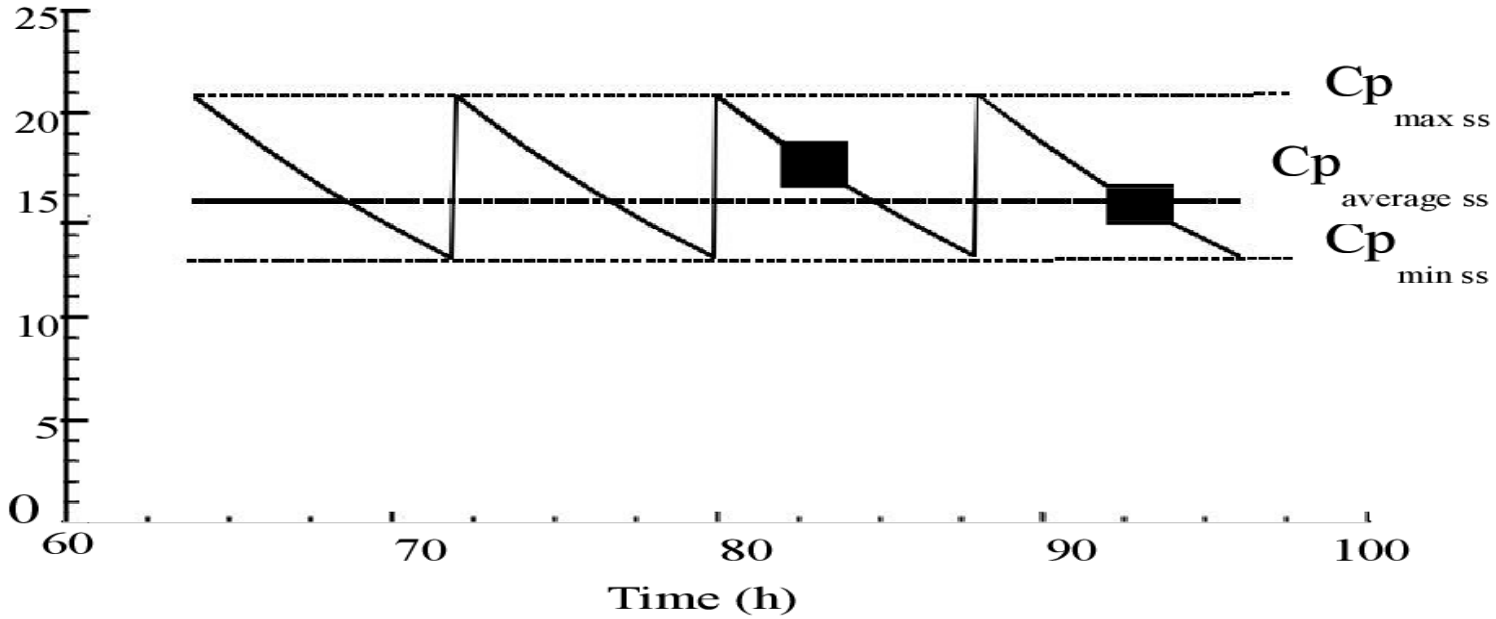
- Is the difference between the MEC and the MTC is large or small (therapeutic index)? (**if small therapeutic index exists, <u>frequent administration of small doses will be necessary to avoid large fluctuation in plasma concentration)</u>**
  - Is there a **compliance problem** with the drug? So, **<u>reducing frequency may be recommended</u>**
- Is there a **delayed response or tolerance** to the action of the drug as therapy progress? This will **<u>require periodic evaluation of the pharmacological response.</u>**

Dosing regimens:

- Is the drug used in situations that require an **immediate effect**? This will require the **administration of loading dose.**
- Does the drug have a **long or short half-life?** This will **determine the frequency of administration (dosing interval T)**
  - Is the **elimination of the drug affected by age or by disease state?** this will determine the **dose according to the patient condition.**

Wagner equation

- this equation represents the relationship between the rate of dosing (FD/τ) and the Average concentration in the body during dosing interval at steady state:



- **Average concentration at steady state:**

$$C_{ss}^{average} = \frac{FD}{KVd\ \tau}$$

- After single dose AUC=FD/KVd Therefore,

$$C_{ss}^{average} = \frac{AUC}{\tau}$$

- It depend on bioavailability , dose & clearance. It is not the mean value of Cpss max & Cpss min.

Time to reach steady state conc.

- The time required to reach to a certain fraction of the steady-state level is given by:

$$n\tau = -1.44 \; t_{0.5} \; \ln(1 - fss)$$

- **Time required to achieve steady-state depends on the half-life** and is **independent of the rate of dosing and the clearance**
- To get to 95% of the steady-state: 5 half-lives are needed
- To get to 99% of the steady-state: 7 half-lives are needed
- **Different doses regimen have the same average steady state conc: The same dosing rate (Dose/ *T*).**

Drug kinetic following single oral dose

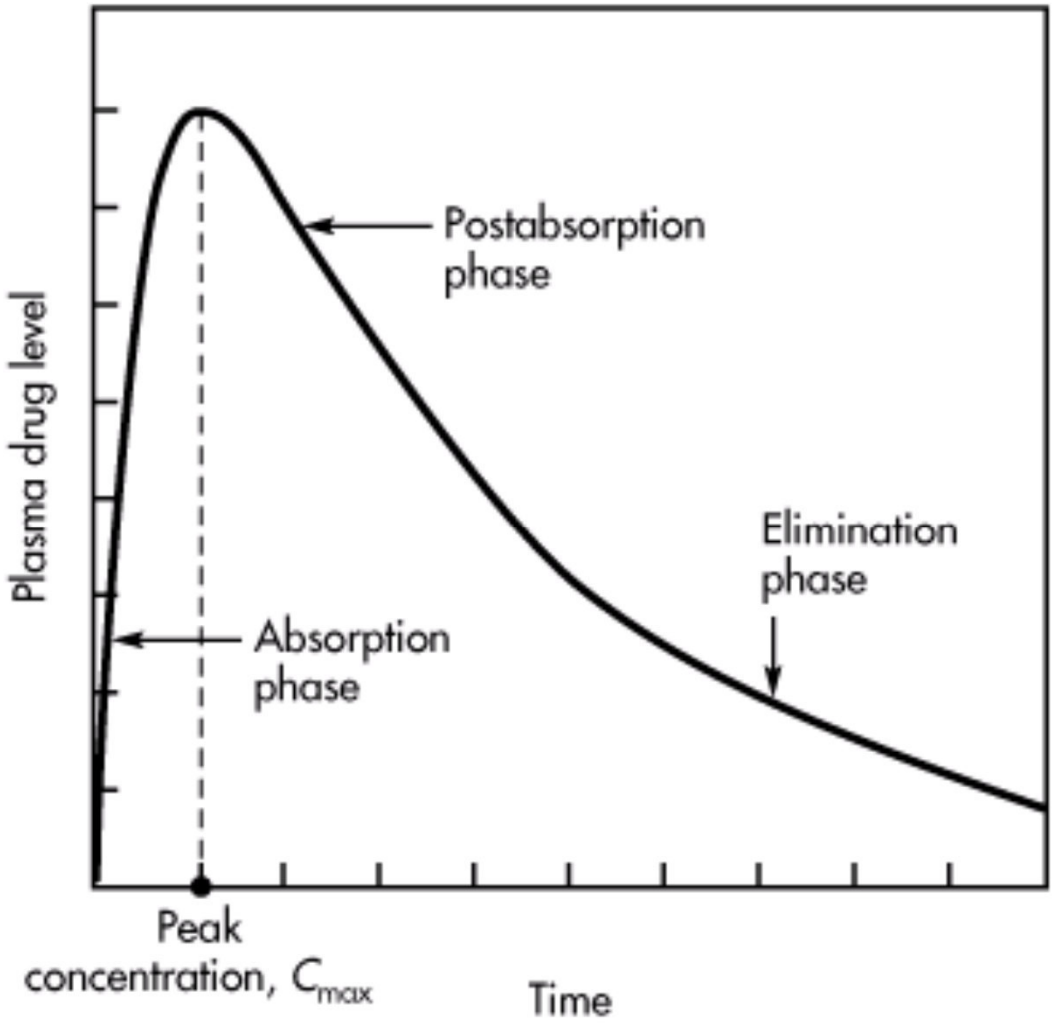
Dr. Mahmoud Samy

Lecturer of Clinical Pharmacy

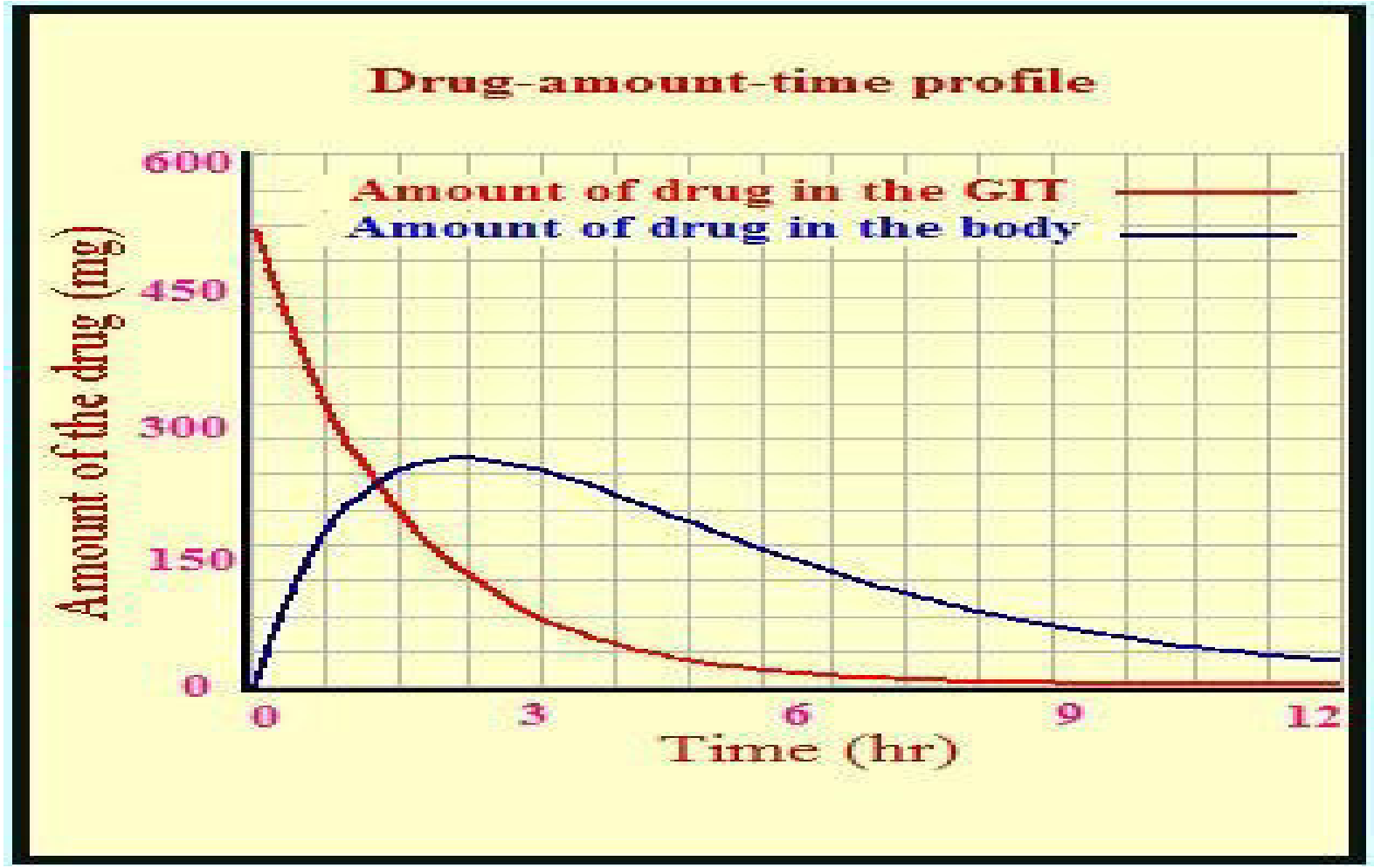
Outlines

- Calculate **plasma drug concentration** at any given time after the administration of **an extravascular dose of drug**.
- Employ **residual method** & extrapolation techniques to characterize the absorption phase
- Calculate peak plasma drug concentration, cp/max, and the time, tmax, at which this occurs
- **Lag time** in a drug's absorption, Onset of action & Duration of response
- **Normal kinetics & Flip-flop kinetics**

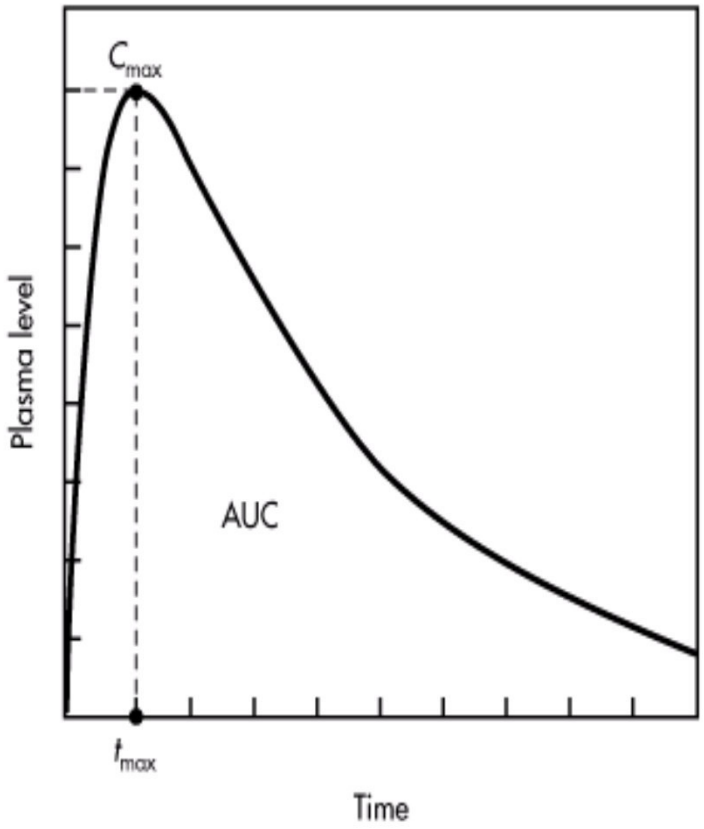
Oral absorption



- **Absorption phase**: absorption rate more than elimination rate
- **Plateau** (elimination rate equal absorption rate)
- **Postabsorption phase**: elimination rate more than absorption rate
- **Elimination phase**: no significant absorption occur (only elimination process)

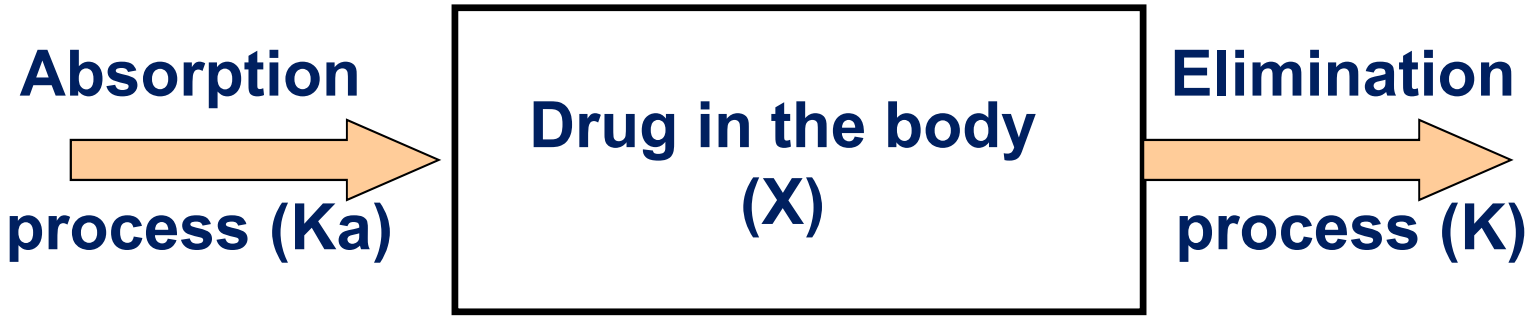

Drug-amount-time profile
Amount of drug in the GIT
Amount of drug in the body
Amount of the drug (mg)
600
450
300
150
0
0
3
6
9
12
Time (hr)

Oral absorption



- **The t_{max}** is independent of dose and is dependent on the rate constants for absorption (*k*a) and elimination (*k*) (**rate of absorption**)
- **At C_{max},** sometimes called *peak concentration*, the rate of drug absorbed is equal to the rate of drug eliminated. Therefore, the net rate of concentration change is equal to zero. (**Intensity of absorption)**
- **AUC** is a measure of the body's exposure to a drug

One-compartment pharmacokinetic model for first-order drug absorption and first-order drug elimination



$$\frac{dX}{dt} = KaXa - KX$$

X: drug amount in the body, **Xa**: drug amount in the GI available for absorption, **K**: elimination rate constant, and **Ka**: absorption rate constant

Mathematical model

- Assuming first-order absorption and first-order elimination, the amount of drug (*Ao or Xo or D*) in the body is described by:

$$Cp = \frac{KaFA}{Vd\,(Ka - K)}\left[e^{-Kt} - e^{-Kat}\right]$$

F (Bioavailability): Fraction of the dose that reach systemic circulation

At time zero, no drug in blood (Cpo= zero)

Determination of the Model Parameters

- K
- Elimination half life
- Ka
- Absorption half life
- t_{max} and C_{max}
- Clearance
- Volume of distribution
- AUC

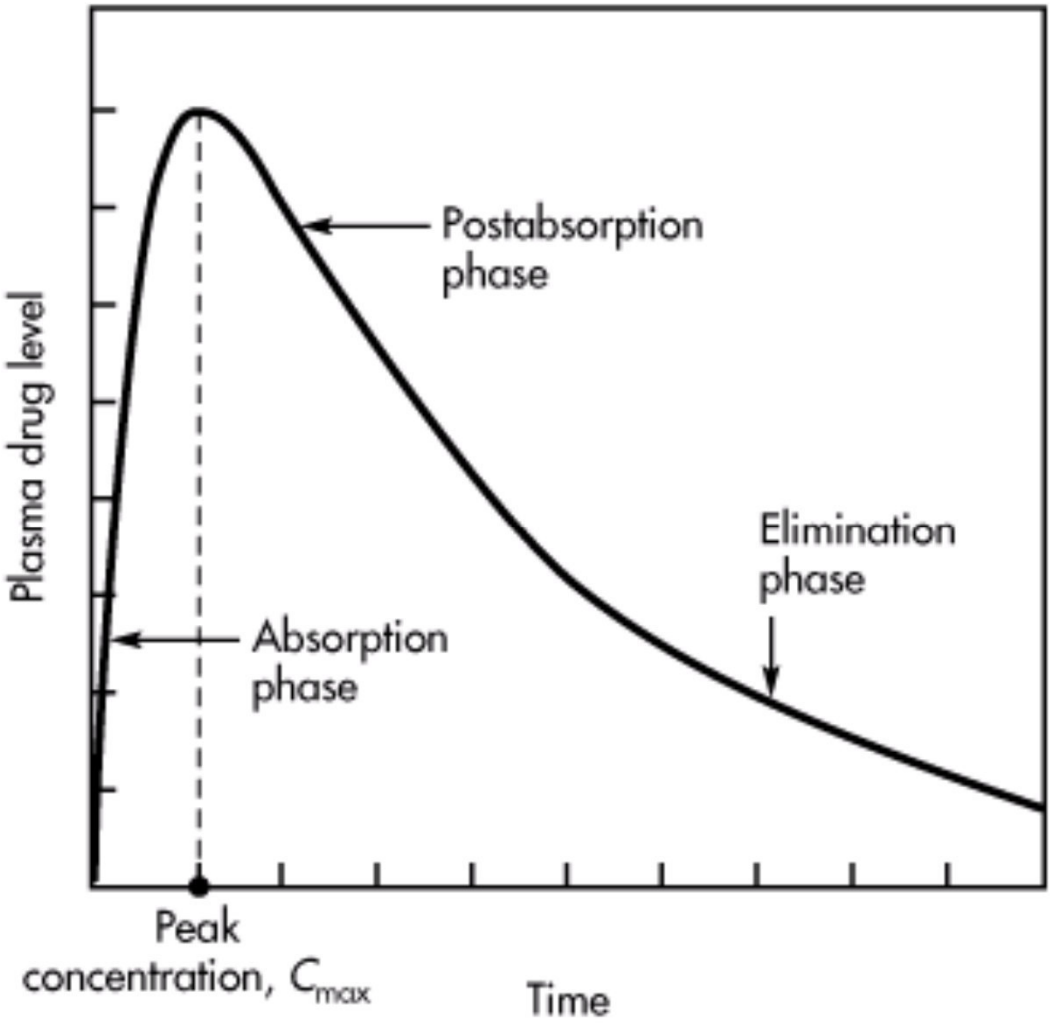
Oral absorption

$$Cp = \frac{KaFXo}{Vd(Ka - K)}\left[e^{-Kt} - e^{-Kat}\right]$$

This portion measure the elimination process

This portion measure the absorption process

Terminal phase (elimination)



- **Because in the Elimination phase** no significant absorption occur (only elimination process), the plasma concentration equation can be simplified into:

$$Cp = \frac{KaFXo}{Vd(Ka - K)}\left[e^{-Kt}\right]$$

Method of residuals

- **The method of residuals is a graphical method used to determine the drug absorption rate constant and has the following assumptions:**
  - The absorption rate constant is larger than the elimination rate constant ,that is, **Ka>K**.
  - Both drug absorption and elimination follow **first-order kinetics**
  - The drug pharmacokinetics follow **one-compartment model**
- The idea of the method of residuals is to characterize the drug elimination rate from the terminal elimination phase of the plasma drug concentration—time profile after a single oral administration.
- Then the contribution of the drug absorption rate and the drug elimination rate during the absorption phase can be separated

Method of residuals

1. The plasma drug concentration is plotted against their corresponding time values on the semi-log scale
2. The slope of the line that represents the elimination phase is calculated. The slope of this line is equal to –k/2.303. The terminal line is back extrapolated to the y-axis
3. At least three Points on the extrapolated line at three different time values during the **absorption Phase** of the drug are taken. Vertical lines from the points on the extrapolated line are dropped to determine the corresponding points (at the same time values) on the plasma drug concentration-time curve
4. The differences between the y-coordinate values of the points on the extrapolated line and corresponding y-coordinate values on the plasma drug concentration-time curve are calculated. The values of these differences are the residuals

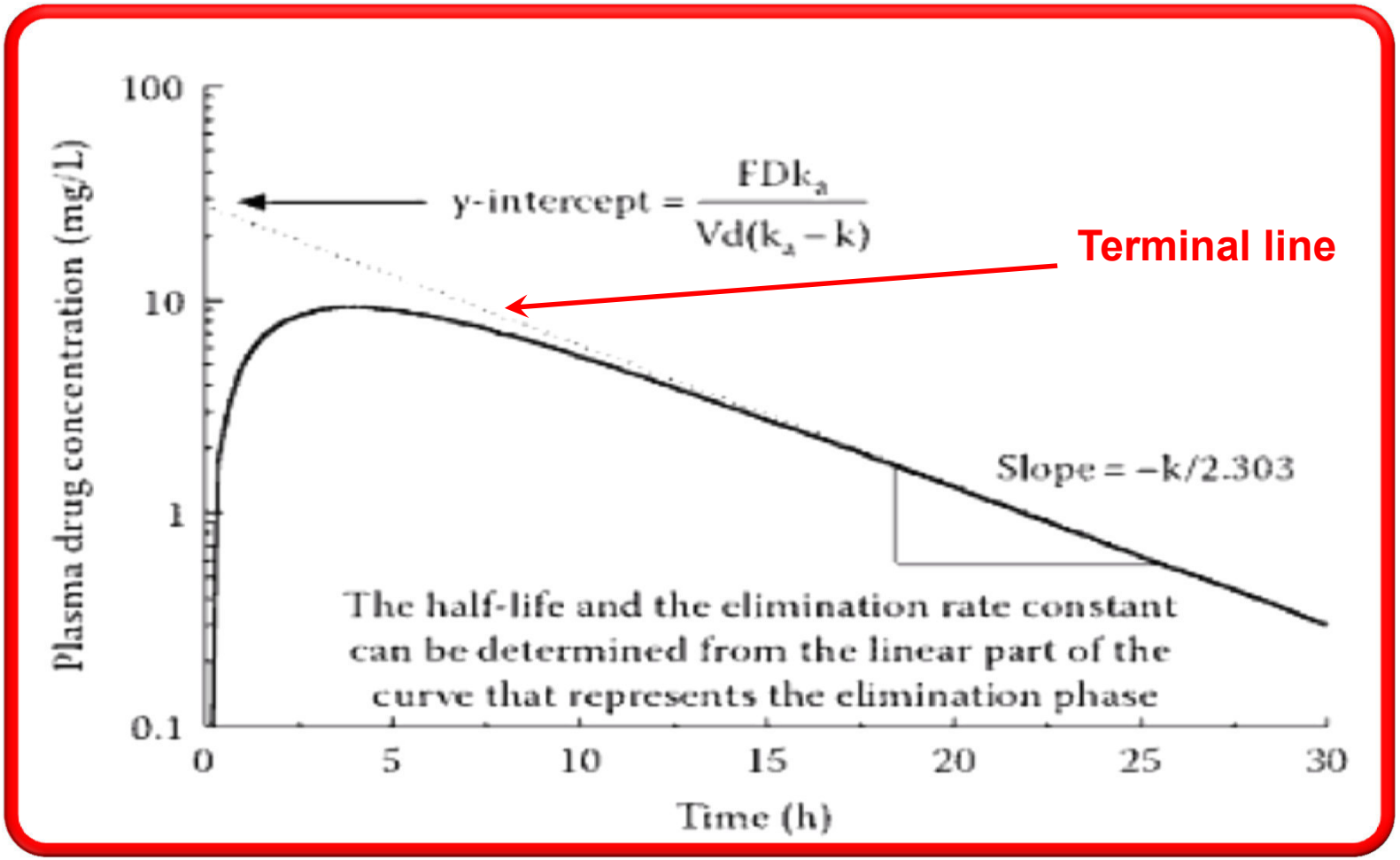
Method of residuals

- The values of the residuals are plotted versus their corresponding time values for each residual on the same graph. A straight line should be obtained with a slope of -ka/2.303.

- The extrapolated line representing the elimination phase and the residuals versus time line should have the same y-intercept. This is because the equations that describe the two lines have the same coefficient, so substituting time by zero in the two equations should give the same term.

Method of residuals

1- From the terminal phase determine the elimination rate constant



نرسم ثلاث اعمدة اقرب ماتكون من محور الصادات تقطع خط ال Elimination مرورا ب curve وحتى محور السينات

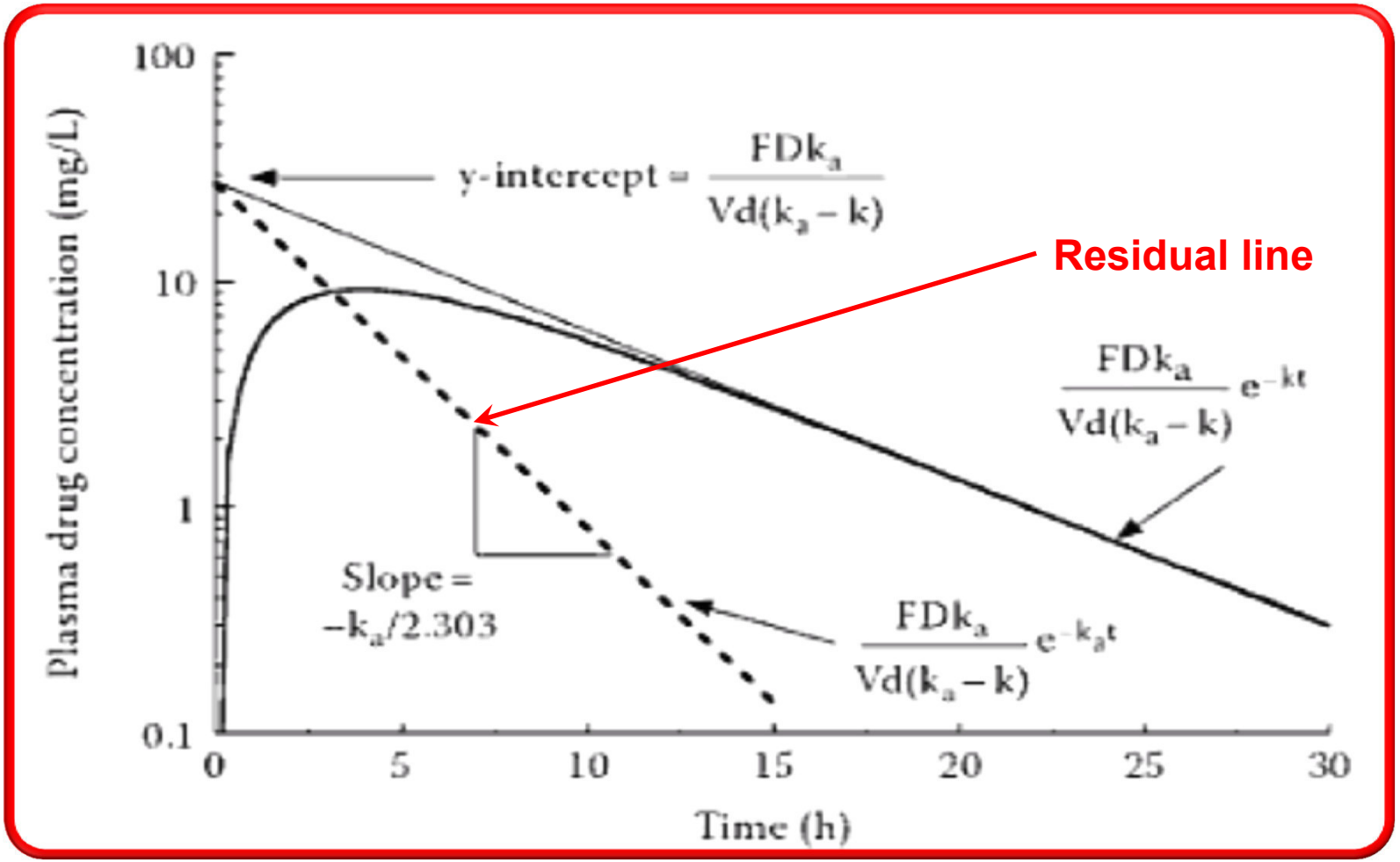
ثم نكون الجدول الاتي:

Time	Line of elimination	Curve	residuals
T1	L1	C1	L1-C1
T2	L2	C2	L2-C2
T3	L3	C3	L3-C3

نرسم خطا جديدا من الجزء الاحمر في الجدول .....امام كل قيمه لل time نحدد ال residual conc. المقابل ...فتتكون ٣ نقاط جديده مع نقطة ال y-intercept of the elimination line فينشأ لدينا خط جديد من ٤ نقاط يمثل خط ال absorption only المبين في الشكل التالي بخط منقط - - - - - -

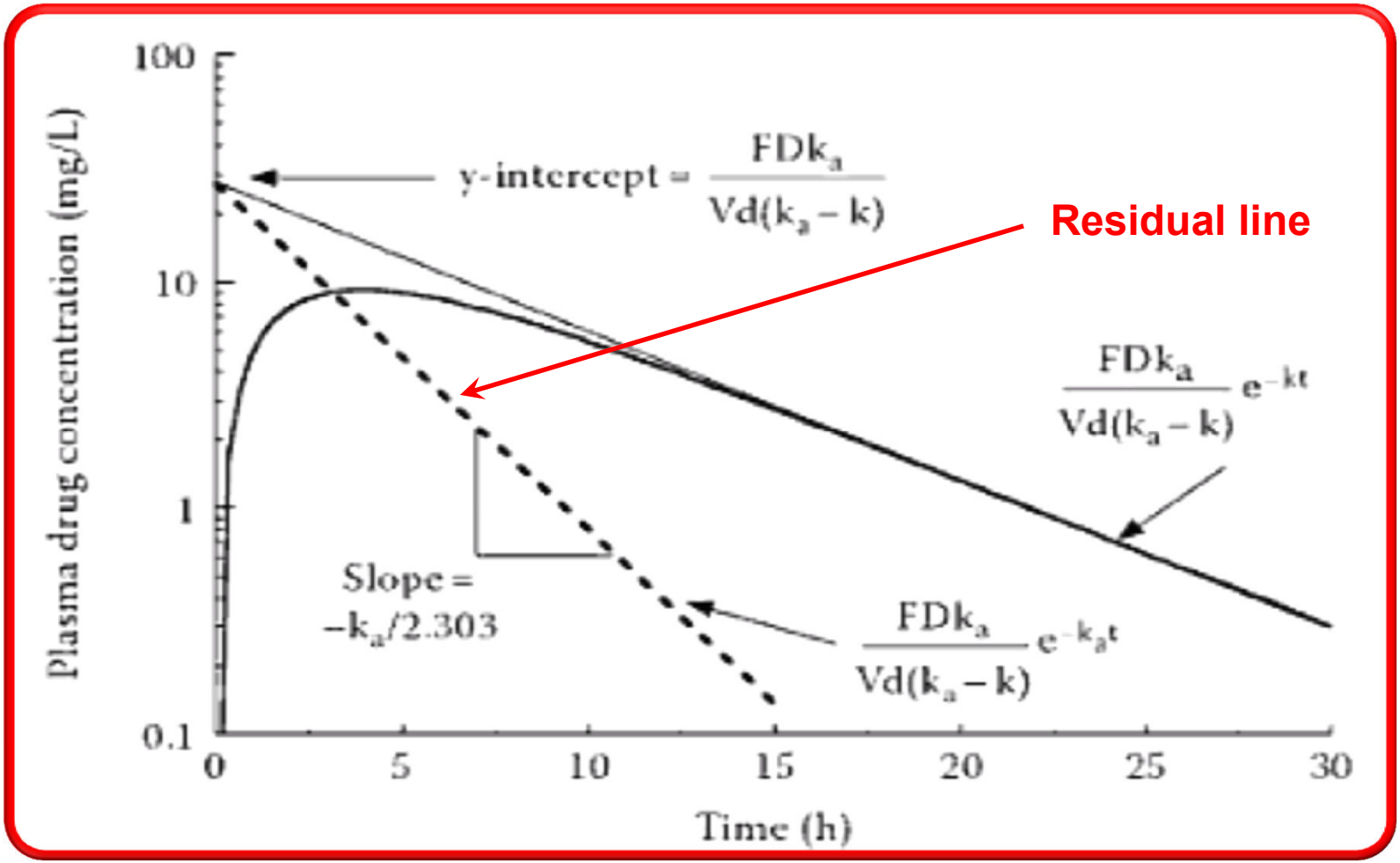
Method of residuals

2- Construct the residual line by taking the difference between the terminal line and the observed conc.



Method of residuals

3- Estimate the absorption rate constant from the slope of the residual line



Example

- After oral administration of a single dose of an antibiotic, the following concentrations were measured:

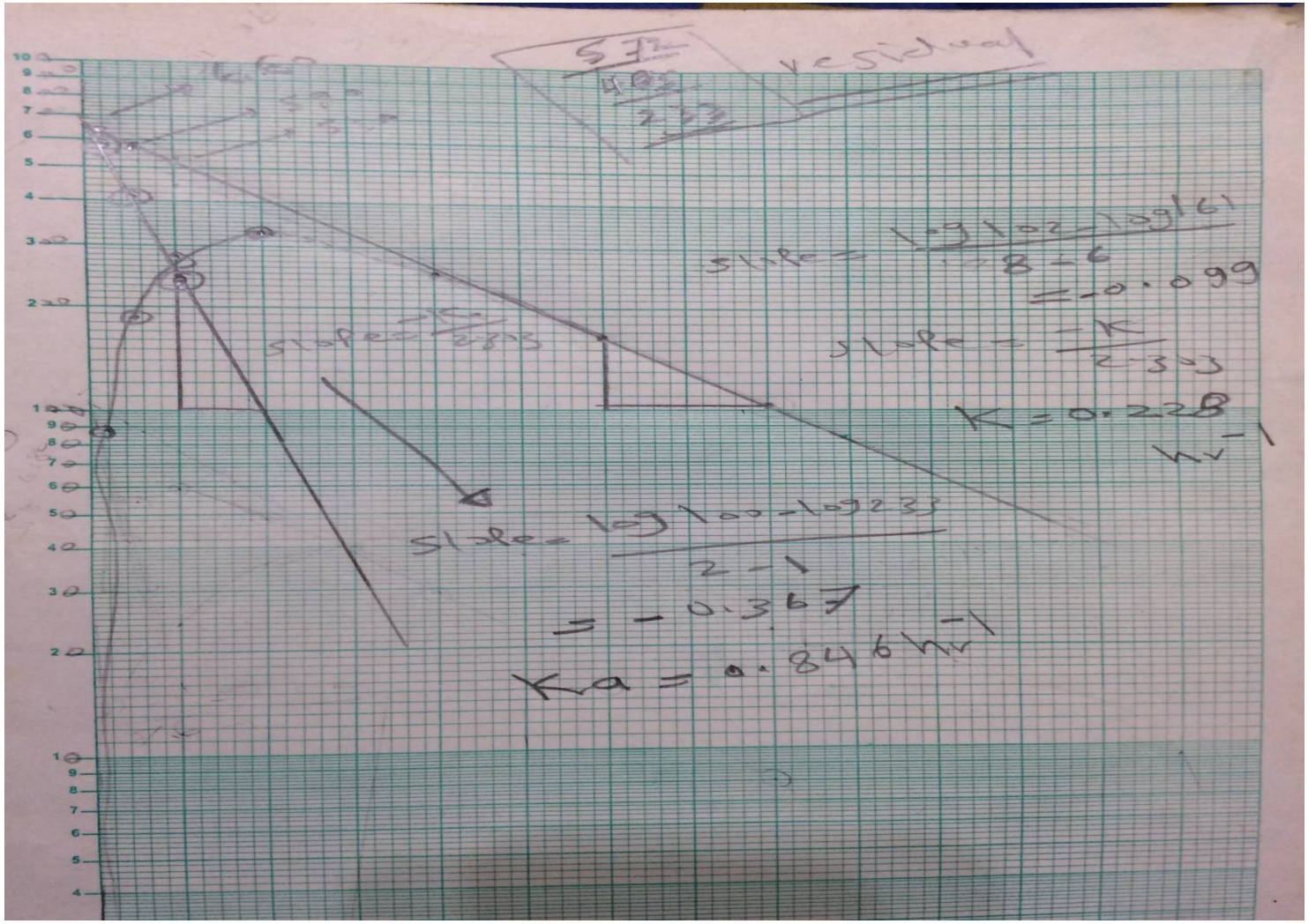
Time (h)	Drug Concentration (mg/L)
0	0
0.2	88
0.5	185
1.0	277
2.0	321
2.5	311
4.0	246
6.0	161
8.0	102

Calculate the first-order absorption rate constant.

Answer

- Plot the plasma concentration–time profile and follow the procedures for the method of residuals as in following Figure. Calculate the residuals.

Time (h)	Line of Elimination	Curve	Residuals (mg/L)
0.2	660	88	660− 88 = 572
0.5	590	185	590− 185 = 405
1.0	510	277	510− 277 = 233



The line resulting from plotting the residuals - 0.367 h^{-1} = Ka/2.303
Ka = 0.846 h^{-1}

Determination of the Model Parameters

- Elimination half life = 0.693/K
- Absorption half life = 0.693/Ka
- t_{max} (or t_p):

$$t_{\max} = \frac{2.303}{(Ka - K)} \log \frac{Ka}{K}$$

- **t_{max} = Ln Ka – LnK / Ka – K = Ln (ka/k)/(Ka-k)**
- **The t_{max}** is independent of dose and is dependent on the rate constants for absorption (*k*a) and elimination (*k*) (**rate of absorption**)

Determination of the Model Parameters

- C_{max} (Conc at t = t_{max})

$$C_{\max} = \frac{KaFD}{Vd(Ka-K)}\left[e^{-Kt_{\max}} - e^{-Kat_{\max}}\right]$$

- At C_{max}, sometimes called *peak concentration*, the rate of drug absorbed is equal to the rate of drug eliminated. Therefore, the net rate of concentration change is equal to zero

Determination of the Model Parameters

- AUC

$$AUC = \frac{FD}{KVd}$$

- Volume of Distribution

$$Vd = \frac{FD}{K.AUC}$$

- Clearance

$$Cl = \frac{FD}{AUC}$$

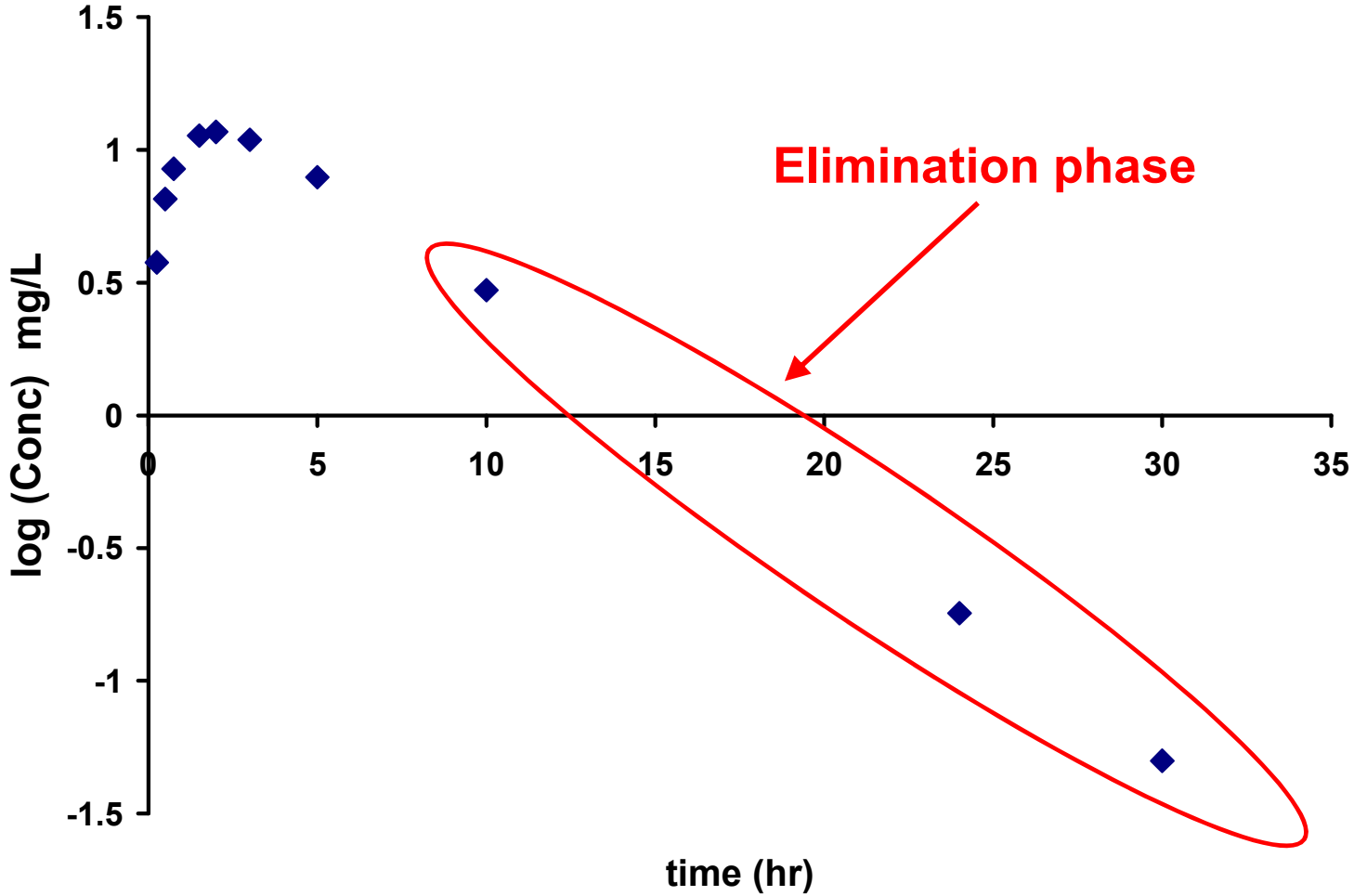
Example 2

- The presented table gives the plasma drug concentrations that were obtained following the oral administration of 500 mg dose of drug X. Assuming that drug X follows normal pharmacokinetics, determine the following:
  - Elimination rate constant
  - Absorption rate constant
  - Volume of distribution (normalized for bioavailability)

Time (hr)	Conc (mg/L)
0.25	3.77
0.5	6.53
0.75	8.49
1.5	11.32
2	11.7
3	10.92
10	2.96
24	0.18
30	0.05

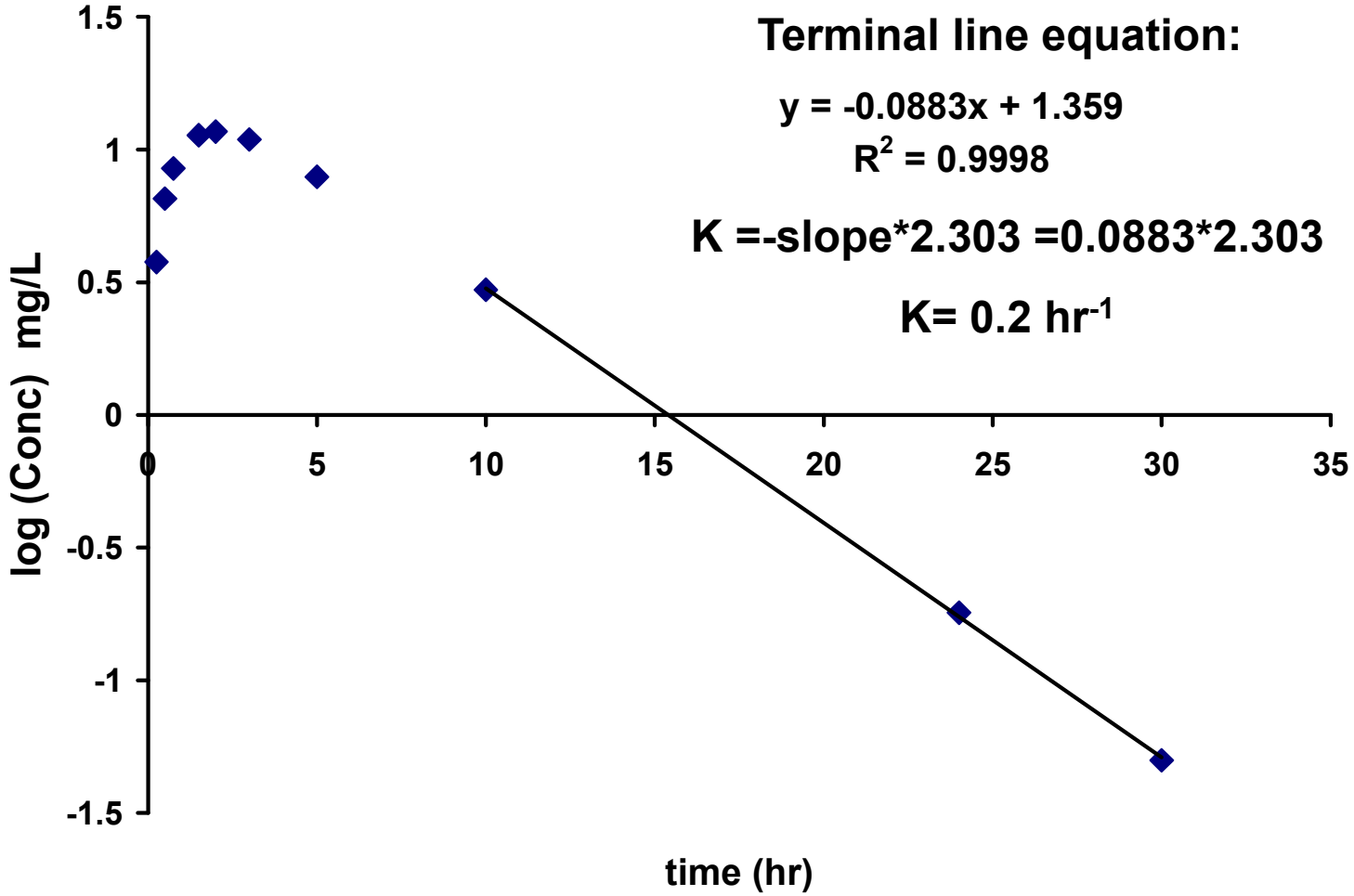
Example 2

Determine elimination phase



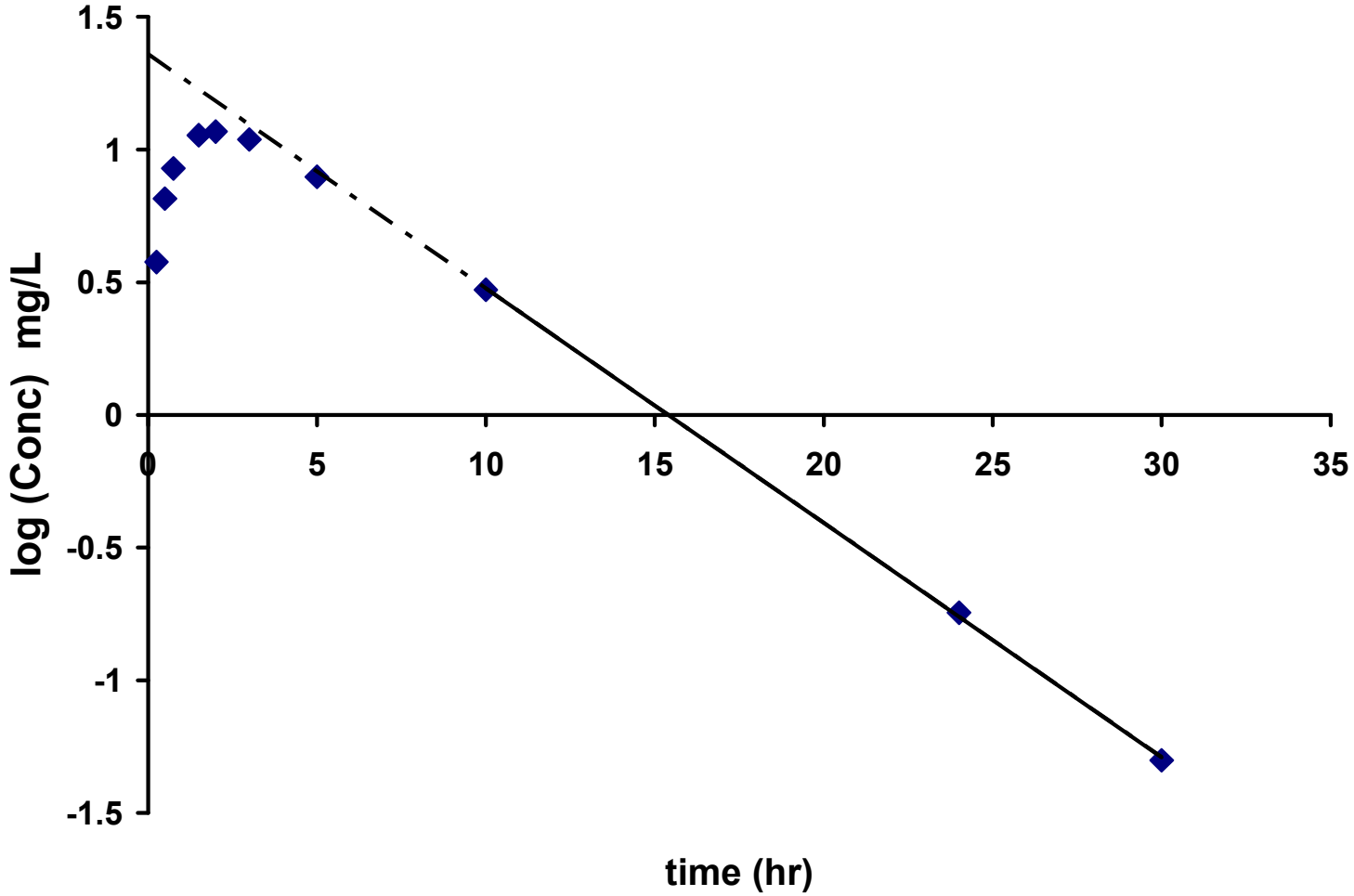
Example 2:

Determine K



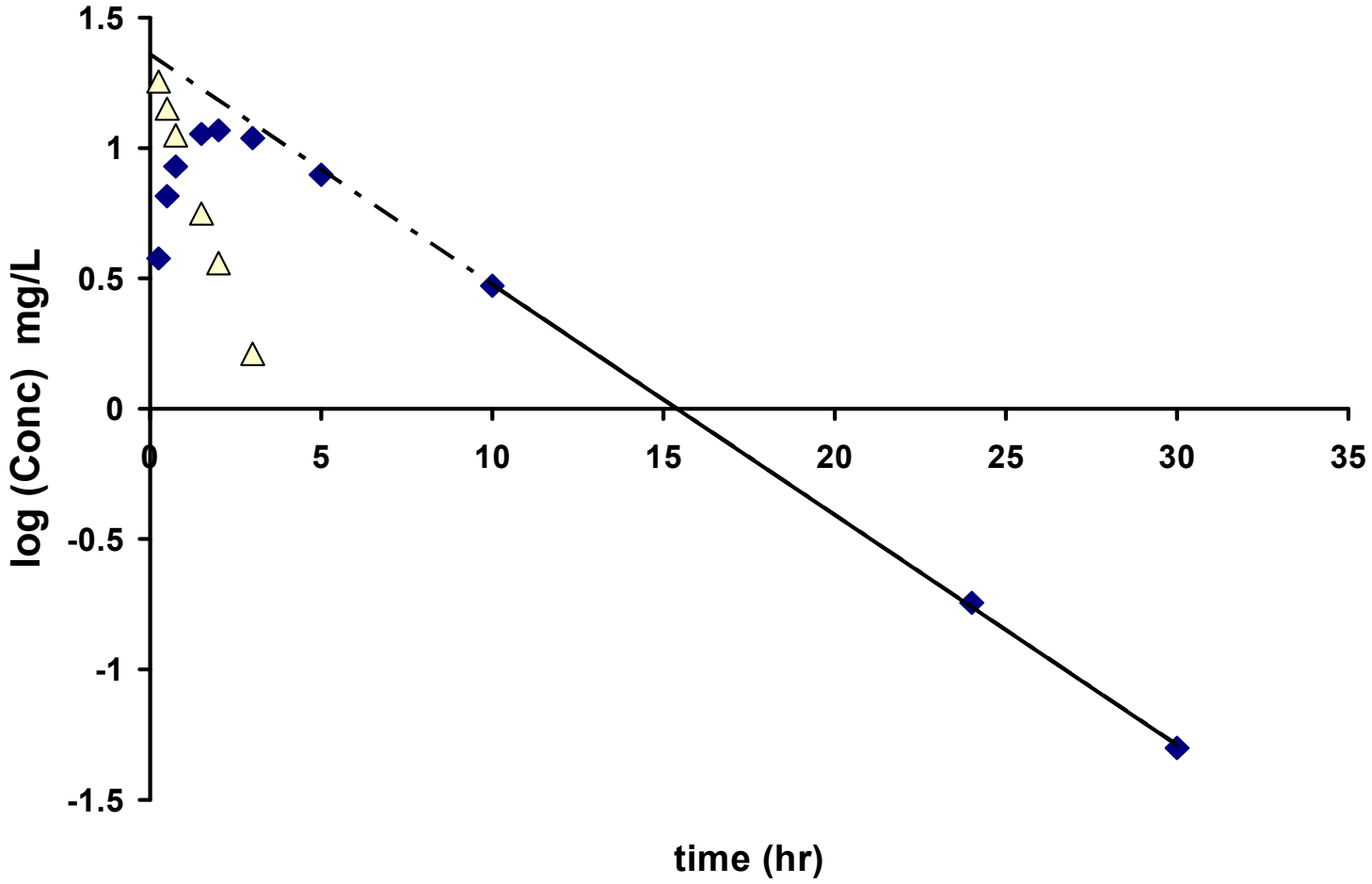
Example 2:

Extrapolate the terminal line to cross the y-axis



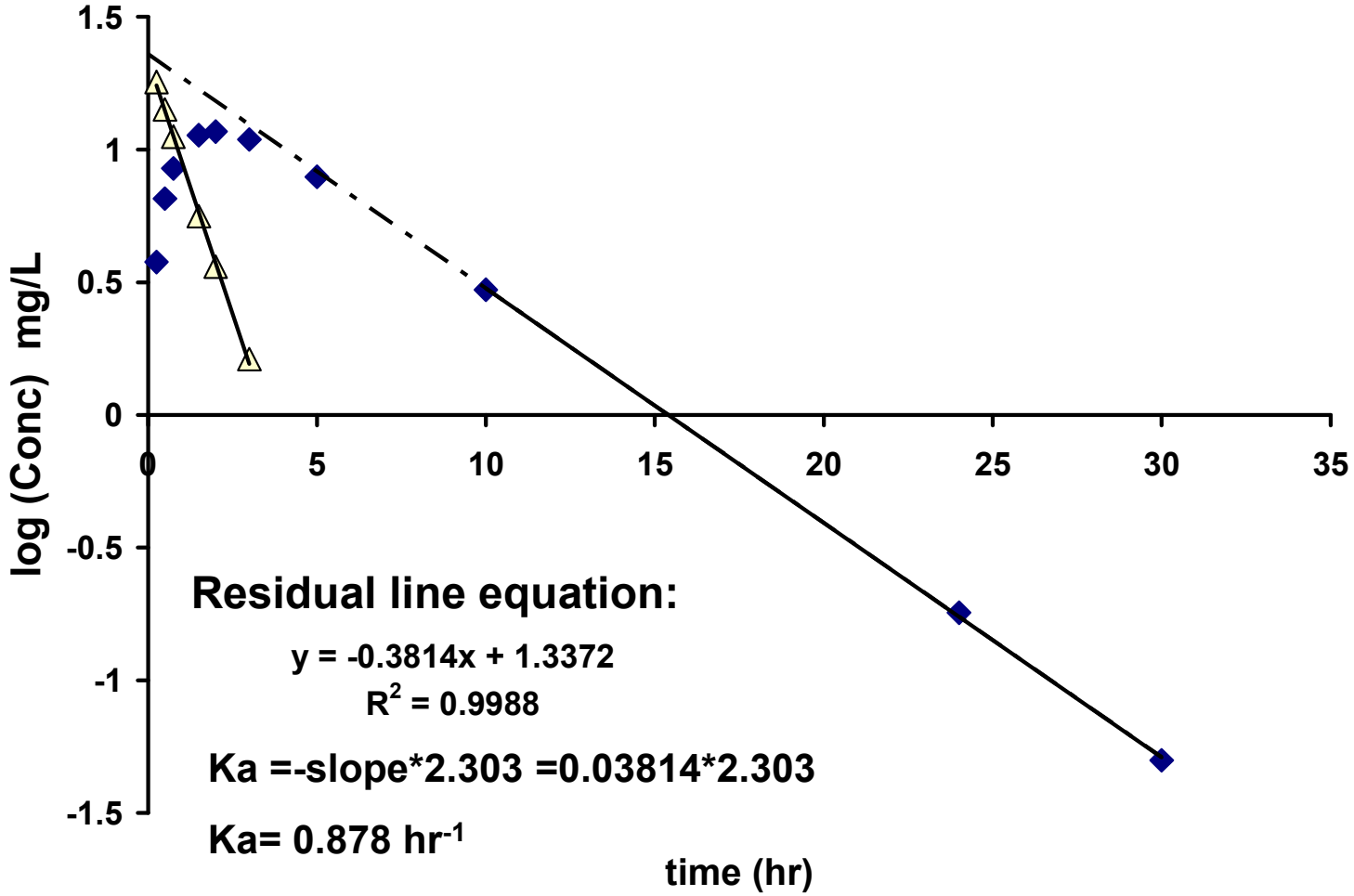
Example 2:

Draw the residual line



Example 2:

Determine Ka



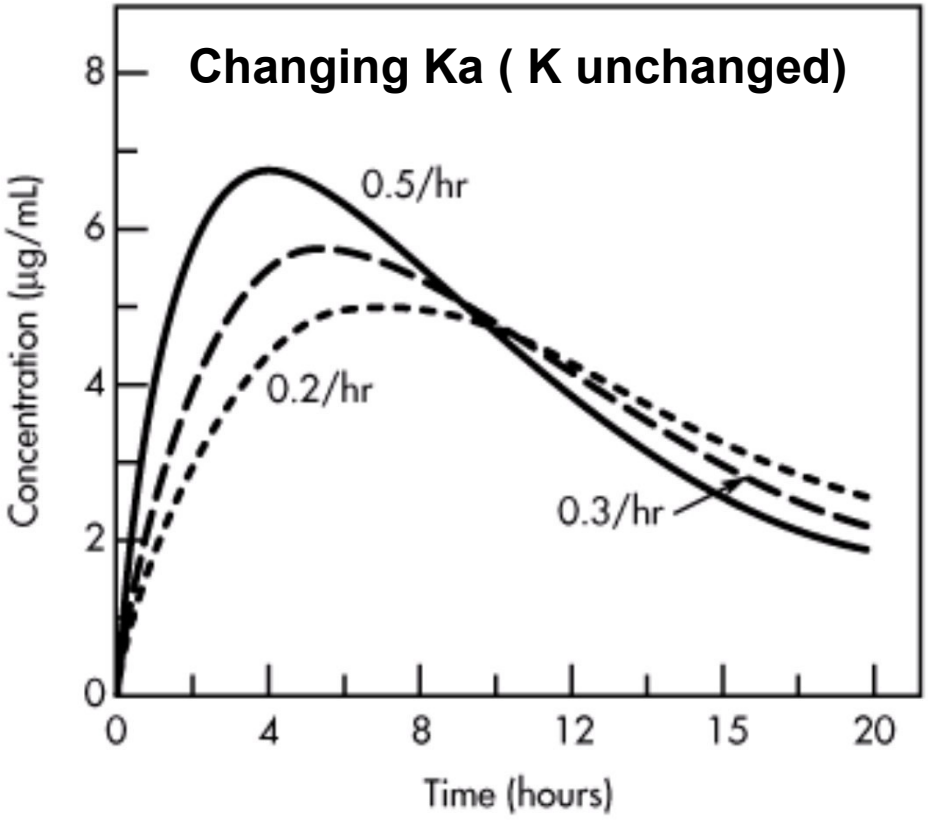
Example 2

- Volume of distribution (normalized for bioavailability):
- From the terminal line best fit line, intercept = 1.359.

$$10^{Intercept} = \frac{Ka \cdot F \cdot D}{Vd(Ka - K)}$$

$$\Rightarrow \frac{Vd}{F} = \frac{Ka \cdot D}{10^{Intercept}(Ka - K)} = \frac{0.878 * 500}{10^{1.359}(0.878 - 0.2)} = 28.3\ L$$

Effect of Ka on t_{max}, C_{max}, and AUC



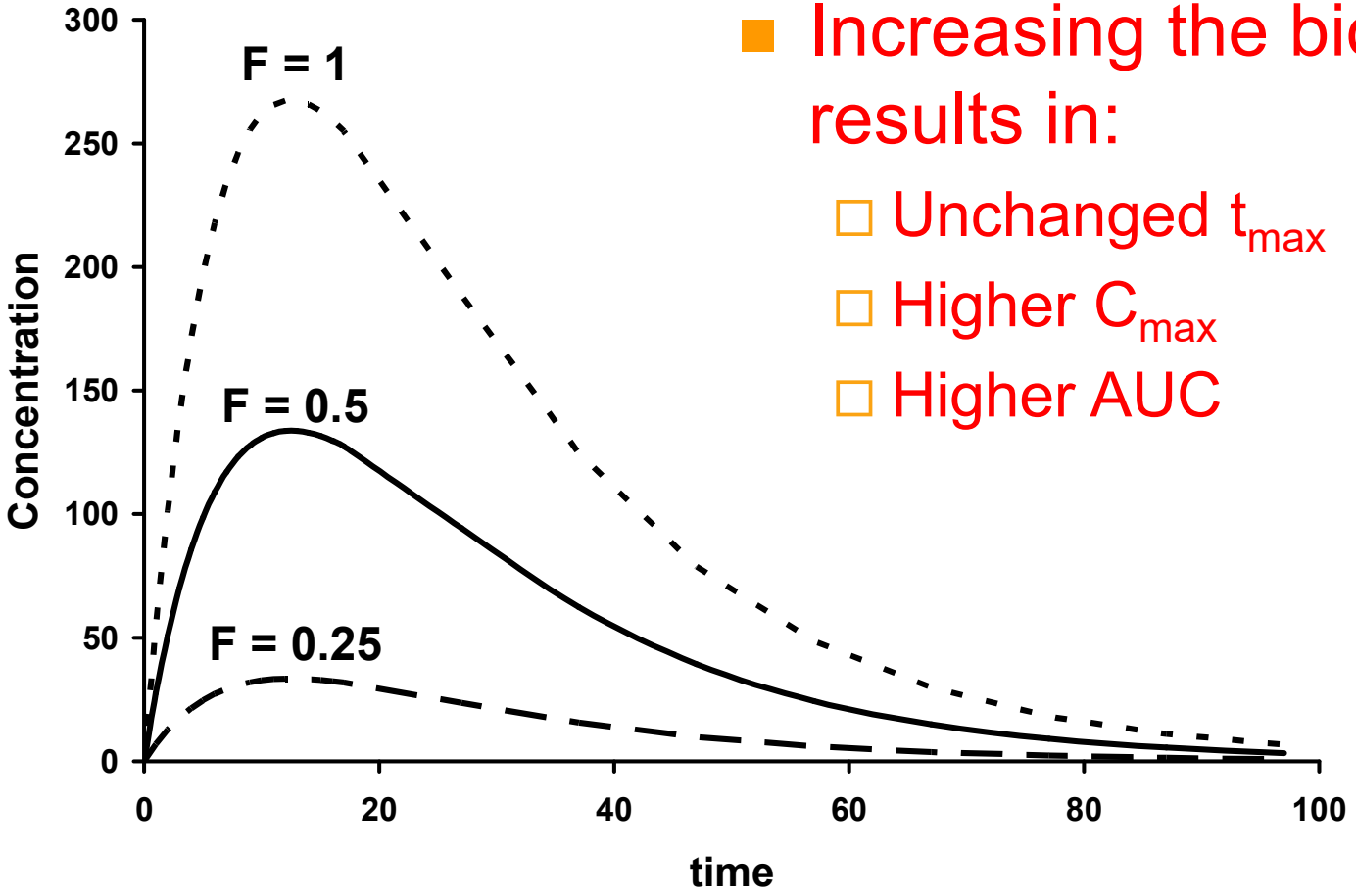
- Increasing the absorption rate constant (Ka) results in:
  - Shorter t_{max}
  - Higher C_{max}
  - Unchanged AUC

Effect of K on t_{max}, C_{max}, and AUC

Changing K (Ka unchanged)

- Increasing the elimination rate constant (K) results in:
  - Shorter t_{max}
  - Lower C_{max}
  - Lower AUC

Effect F on t_{max}, C_{max}, and AUC



- Increasing the bioavailability results in:
  - Unchanged t_{max}
  - Higher C_{max}
  - Higher AUC

Example

- A 500-mg dose of the sulfonamide sulfamethoxazole is administered as an oral tablet to a human subject. Eighty percent of the drug is absorbed, and the balance is excreted unchanged in feces. The drug distributes into an apparently homogeneous body volume of 12 L, and has an absorption half-life of 15 **hr** and overall elimination half-life of 12 h.

1) Calculate the following:

(i) AUC0→∞,(ii) tmax and (iii) C max.

2) Recalculate the values in Problem 1 if all parameter values remained unchanged, but the elimination half-life was increased to 18 h.

Example

- Estimate k and ka:

$$k = 0.693 / t_{1/2}^{elimin} = 0.693/12 = 0.058\ hr^{-1}$$

$$k_a = 0.693 / t_{1/2}^{abs} = 0.693/15 = 0.046\ hr^{-1}$$

- Estimate AUC:

$$AUC = \frac{FD}{KVd} = \frac{0.8 * 500}{0.058 * 12} = 575\ mg \cdot hr/L$$

Example

- Estimate t_{max}:

t_{max} = Ln Ka – LnK / Ka – K

= ((-3.07911- (-2.84731))/ (0.046-0.058)=19.32 hr

$$t_{\max} = \frac{2.303}{(Ka - K)} \log \frac{Ka}{K}$$

$$= \frac{2.303}{(0.046 - 0.058)} \log \frac{0.046}{0.058} = 19.32 \; hr$$

Example

- Estimate C_{max}:

$$C_{\max} = \frac{KaFXo}{Vd(Ka-K)}\left[e^{-Kt_{\max}} - e^{-Kat_{\max}}\right]$$

$$C_{\max} = \frac{0.046*0.8*500}{12(0.046-0.058)}\left[e^{-0.058*19.32} - e^{-0.046*19.32}\right]$$

$$C_{\max} = 10.9\ mg/L$$

Example

Recalculate the values in Problem 1 if all parameter values remained unchanged, but the elimination half-life was increased to 18 h

$$k = 0.039\ hr^{-1}$$

$$t_{\max} = 23.5\ hr$$

$$AUC = 855\ mg \cdot hr/L$$

$$C_{\max} = 13.3\ mg/L$$

Example

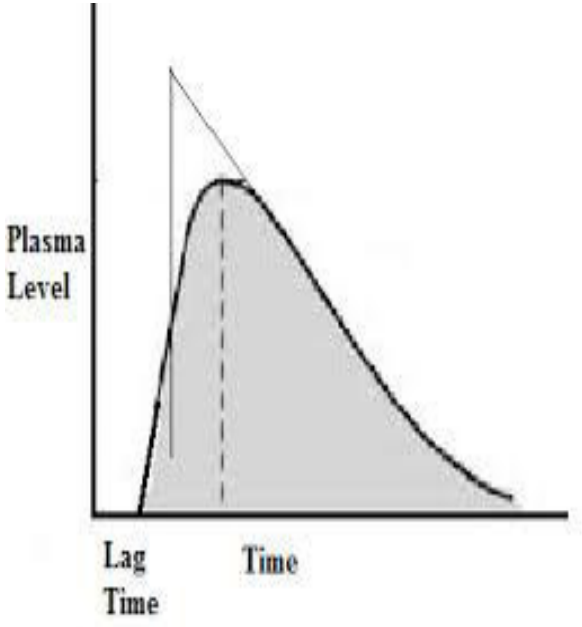
- A single oral dose (100 mg) of an antibiotic was given to an adult male patient (43 years, 72 kg). From the literature, the pharmacokinetics of this drug fit a one-compartment open model. The equation that best fits the pharmacokinetics of the drug is

$$\mathbf{Cp = 45\ (e^{-0.17t} - e^{-1.5t})}$$

- From the equation above, calculate **(a)** t_{max}, **(b)** C_{max}, and **(c)** $t_{1/2}$ for the drug in this patient. Assume C_p is in μg/mL and the first-order rate constants are in hours^{-1}.

Lag Time:

- **This delay time before starting drug absorption is known as the lag time.**
- can be short and does not significantly affect the plasma drug concentration–time profile.
- However, the lag time can be long such as after administration of **enteric coated formulations (formulation factors**)
- **Physiological factors : Gastric emptying rate & intestinal motility**
- In this case, the dosage form disintegration, drug dissolution, and drug absorption start after the dosage form reaches the small intestine, which can take hours, especially if the drug is administered with food.
- **Onset of effect**: Time required to reach MEC.
- **Duration of Response**: The period of time in which plasma conc. is higher than MEC.



Normal kinetics vs. Flip-flop kinetics

- In a series of two consecutive, irreversible first-order rate processes such as absorption of a drug from the intestine and its subsequent systemic elimination, either step can be **rate-limiting in the overall elimination process**
- In general, ka of a drug after oral administration is greater than k so that elimination of the drug from the body after oral administration is governed primarily by how fast it can be removed once it enters the systemic circulation
- In this case (e.g., ka > k), a plasma concentration-time profile after oral dosing exhibits a terminal half-life similar to that after intravenous injection

Normal kinetics vs. Flip-flop kinetics

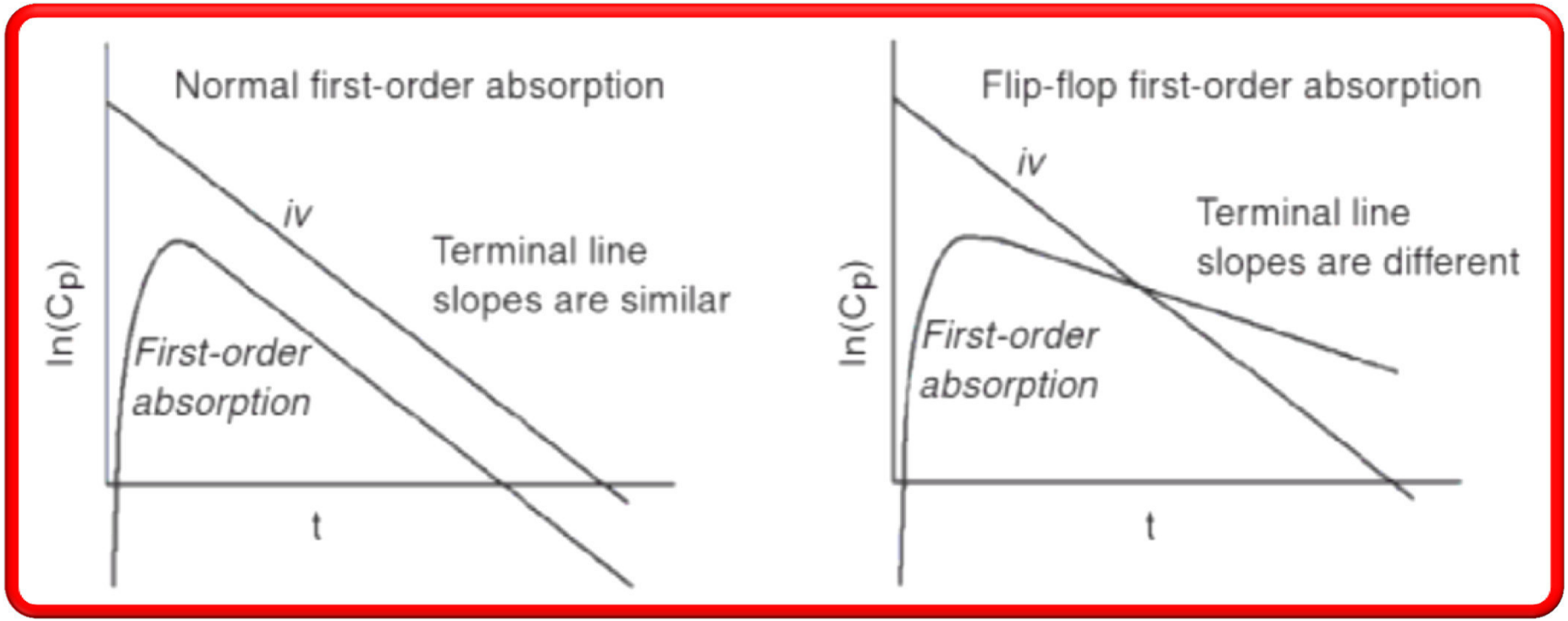
- When ka is much smaller than k (e.g., k > ka) , drug disappearance from the body becomes governed by the rate of absorption rather than by the rate of elimination, and absorption $t_{1/2}$ becomes longer than elimination $t_{1/2}$. This phenomenon is called “flip-flop kinetics”
- **When a drug is released at a sustained rate instead of immediate release**

Summary

Ka > K: Normal Kinetics (the slope of the terminal phase represent K)

K > Ka: Flip-Flop Kinetics (the slope of the terminal phase represent Ka)

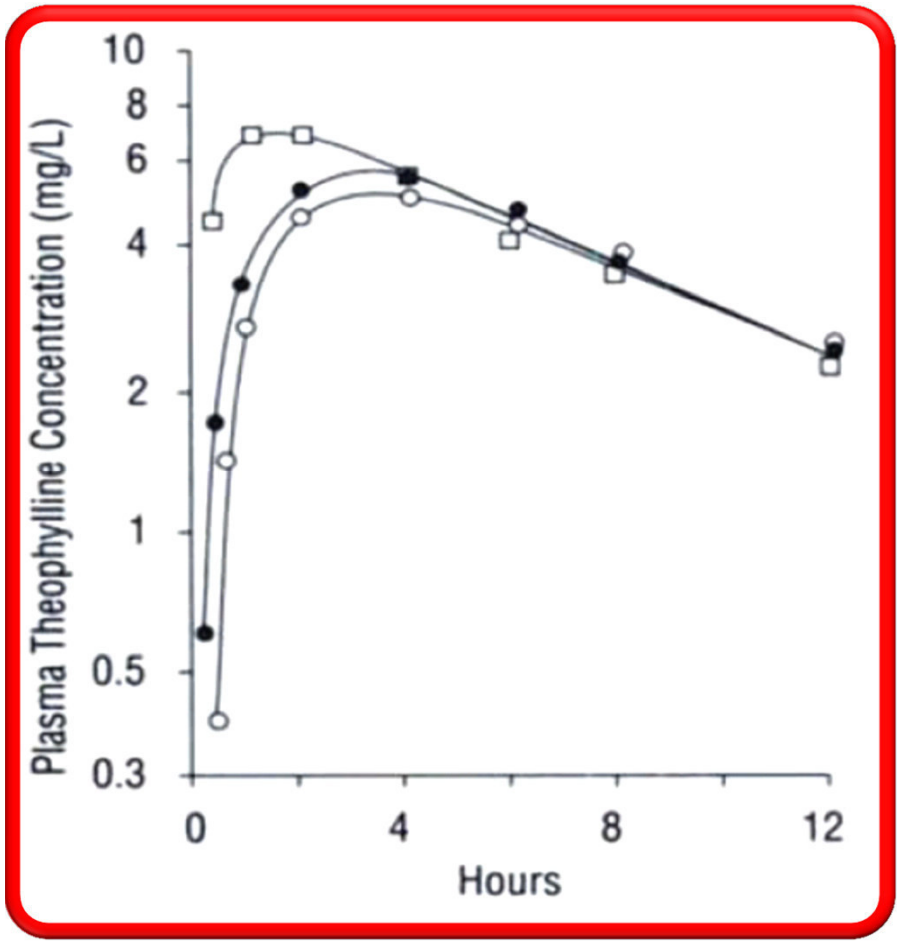
Distinguishing between Normal and Flip-Flop kinetics



IV bolus data is needed to differentiate between Normal and Flip-Flop kinetics

Normal Kinetics example

Difference observed in the absorption phase➔ Normal kinetics



Theophylline conc-time profile resulting from the administration of two 130 mg tablets:

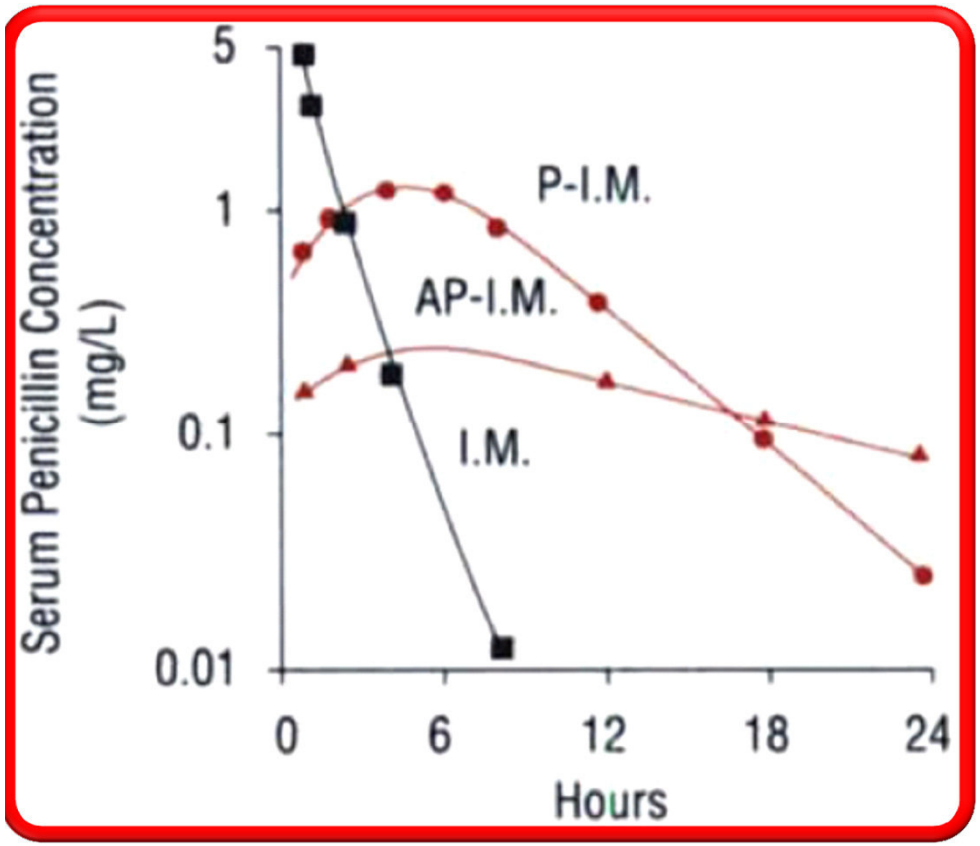
Dissolved in 500 mL water and taken on an empty stomach

Taken on an empty stomach

Taken after meal

Flip-Flop kinetics example

Difference observed in the terminal phase➔ Flip-flop kinetics



Penicillin G was administered IM as an:

Aqueous solution (I.M)

Procaine penicillin in oil (P-I.M)

Procaine penicillin in oil with aluminum monostearate (AP-I.M)

Wagner–Nelson Method

- The Wagner–Nelson method is a method that can be used to determine the absorption rate constant for drugs when their absorption follows zero-order kinetics or first-order kinetics.
- The Wagner–Nelson method uses the relationship between the fractions of the administered dose remaining to be absorbed at different time points to determine the absorption rate constant.


QUESTIONS?

Bioavailability & Bioequivalence

Dr. Mahmoud Samy

Lecturer of Clinical Pharmacy

Outlines

- Bioavailability
- Absolute Bioavailability
- Relative Bioavailability
- **AUC calculation using Trapezoidal rule**
- Bioequivalence

Introduction

- The most important property of any non-intravenous dosage form, intended to treat a systemic condition, is the ability to deliver the active ingredient to the bloodstream in an amount sufficient to cause the desired response
- This property of a dosage form has historically been identified as physiologic availability, biologic availability or bioavailability
- Bioavailability captures two essential features, namely how fast the drug enters the systemic circulation (**rate of absorption**) and how much of the nominal strength enters the body (**extent of absorption**)

Introduction

- Given that the therapeutic effect is a function of the drug concentration in a patient's blood, these two properties of non-intravenous dosage forms are, in principle, important in identifying the response to a drug dose:
  1. **Onset of response is linked to the rate of drug absorption whereas the time-dependent**
  2. **Extent of response is linked to the extent of drug absorption & elimination.**

Bioavailability

- "The relative amount (the extent) of an administered dose that reaches the general circulation and the rate at which this occurs" (American Pharmaceutical Association, 1972)
- **The rate and the extent of drug that reach systemic circulation**

Bioavailability studies importance:

- Bioavailability studies provide an estimate of the fraction of the orally administered dose that is absorbed into the systemic circulation when compared to the bioavailability for an intravenous dosage form that is completely available

- Bioavailability studies provide other useful information that is important to establish dosage regimens.

- Bioavailability studies provide indirect information regarding the presystemic and systemic metabolism of the drug and the role of transporters such as p-glycoproteins

Bioavailability studies importance:

- Bioavailability studies designed to study the food effect on drug absorption
- Such studies when designed appropriately provide information on the linearity or nonlinearity in the pharmacokinetics of the drug and the dose proportionality
- Bioavailability studies provide information regarding the performance of the formulation and subsequently are a means to document product quality

Factors affecting the bioavailability

- Bioavailability following oral doses may vary because of either patient-related or drug & dosage-form-related factors
- Patient factors can include age, disease, genetic, the nature and timing of meals, and gastrointestinal physiology
- The drug & dosage form factors include 1) the chemical form of the drug (e.g. salt vs. acid), 2) its physical properties (e.g. crystal structure, particle size), and 3) an array of formulation (e.g. non-active ingredients) and manufacturing (e.g. tablet hardness) variables

Factors affecting bioavailability

1. Gastric emptying: Although not true in all cases, increased gastric emptying generally enhances bioavailability of orally administered drugs. Gastric emptying depends on the following factors:
   - Volume of liquid & food intake
   - pH of the stomach
   - Intake of other drugs
   - Age and weight of the patients
   - Physical activity of the patients taking drug
   - Various disease states

Factors affecting bioavailability

2. Presystemic and systemic metabolism — Presystemic metabolism, which occurs during first-pass metabolism, can decrease the bioavailability of a drug. The following types of metabolism are commonly seen:
   - First-pass metabolism: First-pass metabolism occurs when an absorbed drug passes directly through the liver before reaching systemic circulation after oral administration.
   - Intestinal metabolism: Drug metabolizes in the intestine itself or during the passage through the intestinal wall.
   - Hydrolysis of the drug in the stomach fluids.
   - Transporters such as p-glycoprotein may influence the bioavailability of a drug.

Factors affecting bioavailability

3. Complexation with other agents in the gastrointestinal tract
4. Formulation factors, such as inert ingredients, the manufacturing process and/or use of surfactants, & dosage form (the bioavailability of the IV >IM > S.C and in case of oral dosage form the bioavailability of the solution > suspension >soft capsule > hard capsule > tablet).
5. Drug related factors: Chemical and physical properties; Lipophilicity & hydrophilicity.

Bioavailability assessment methods

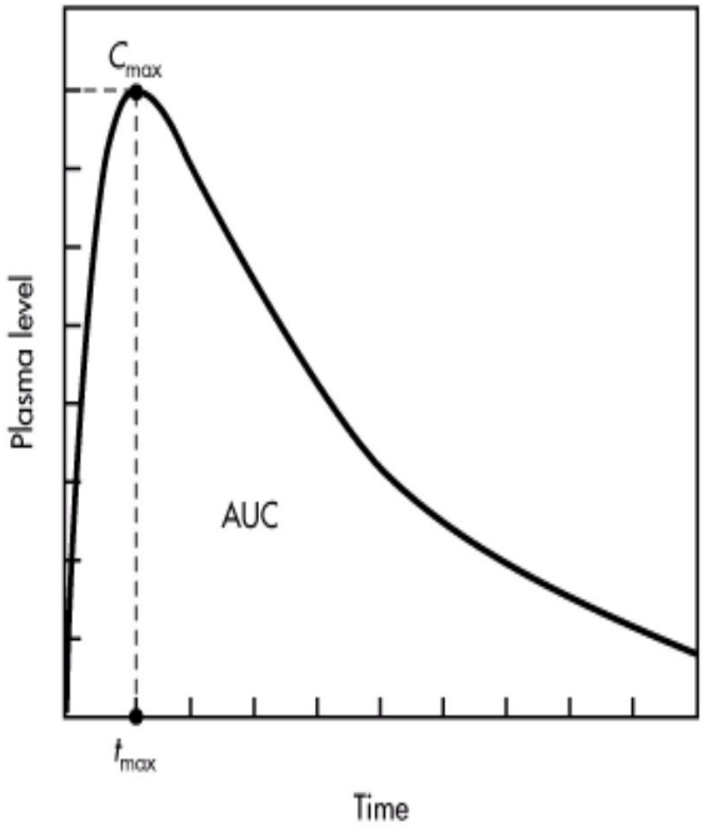
1. **Direct measure of bioavailability:**
   - Based on Plasma Drug Concentrations

2. **Indirect measure of bioavailability:**
   - **Based on Urinary Excretion Data*:*** This method can be used only if urinary excretion of unchanged drug is the main mechanism of elimination of the drug.

   - **Based on Acute Pharmacodynamic Effect*:***

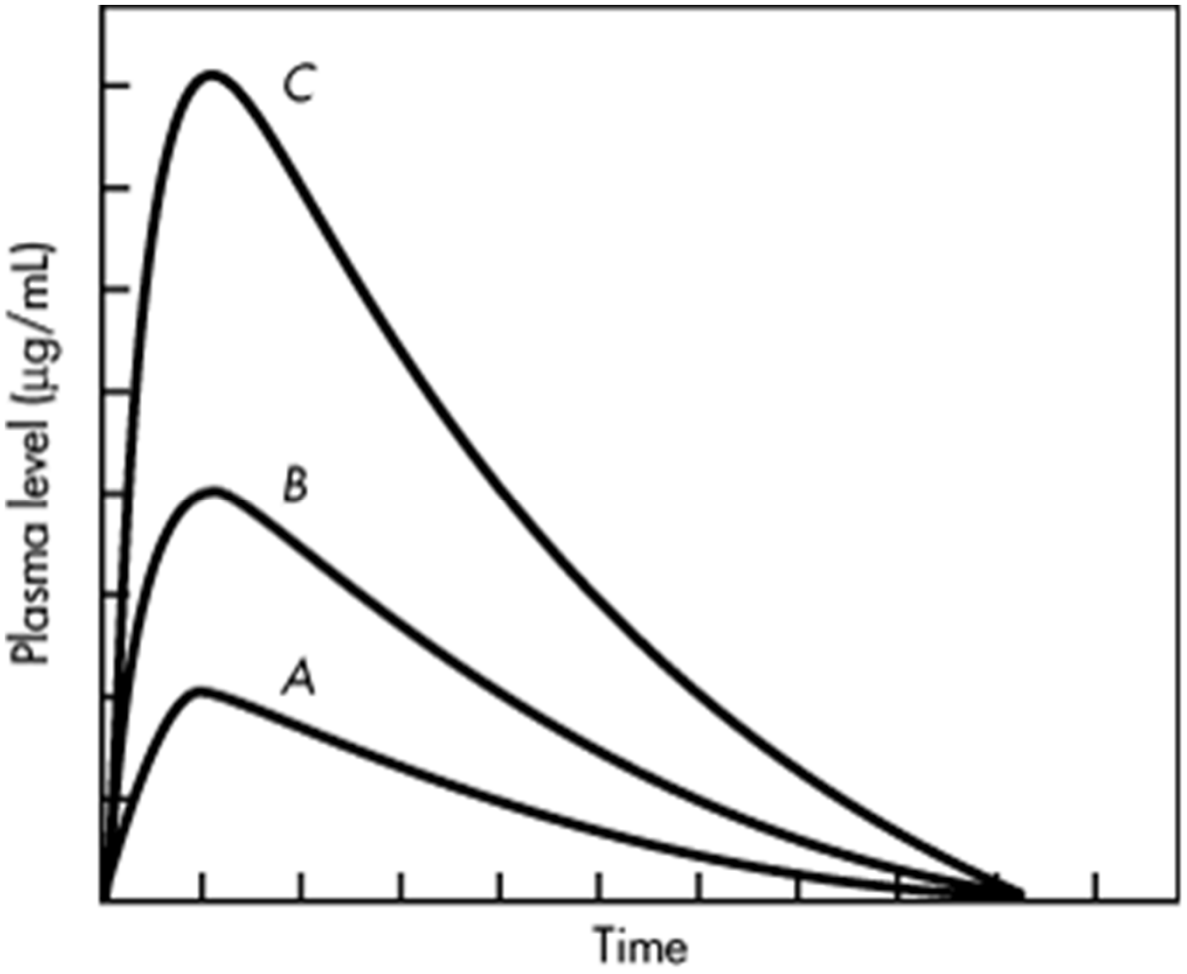
   This approach may be applicable when the drug is not intended to be delivered into the bloodstream for systemic availability. It is an indirect measure of bioavailability in cases where the analytical method for assessing drug concentrations in the plasma or other biological fluids cannot be developed.

To assess the bioavailability



- The t_{max} (**rate of absorption**)
- At C_{max}, (**Intensity of absorption**)
- **AUC** is a measure of the body's exposure to a drug (**The extent of drug absorption and clearance**)

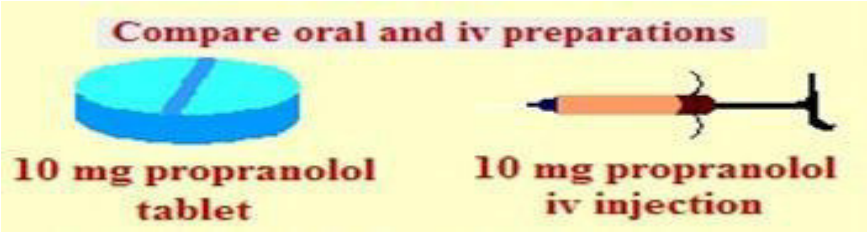
Which formulation has higher bioavailability?



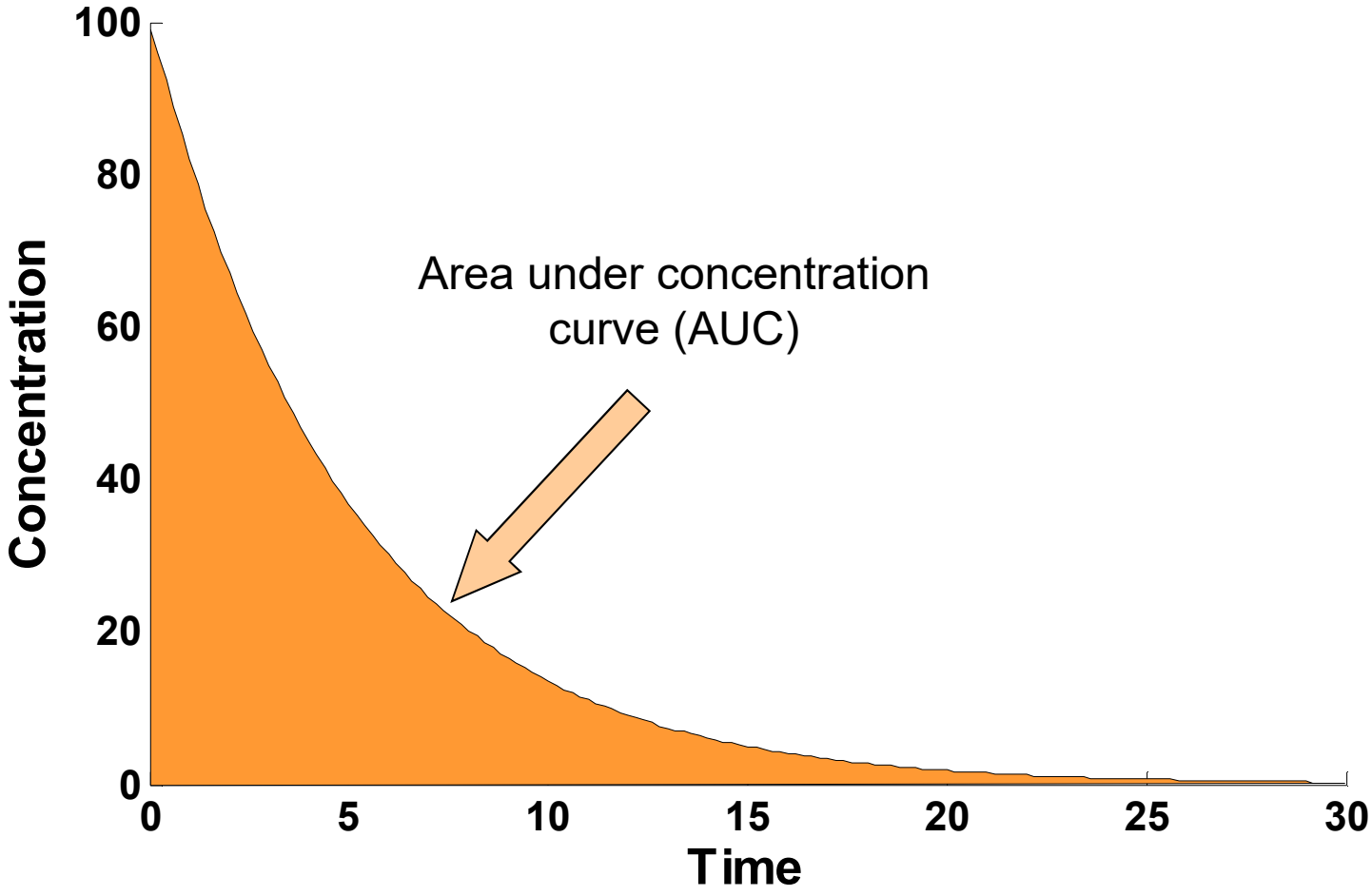
Absolute bioavailability

- The systemic availability of the drug after extravascular administration of the drug and is measured by comparing the area under the drug concentration–time curve after extravascular administration to that after IV administration.

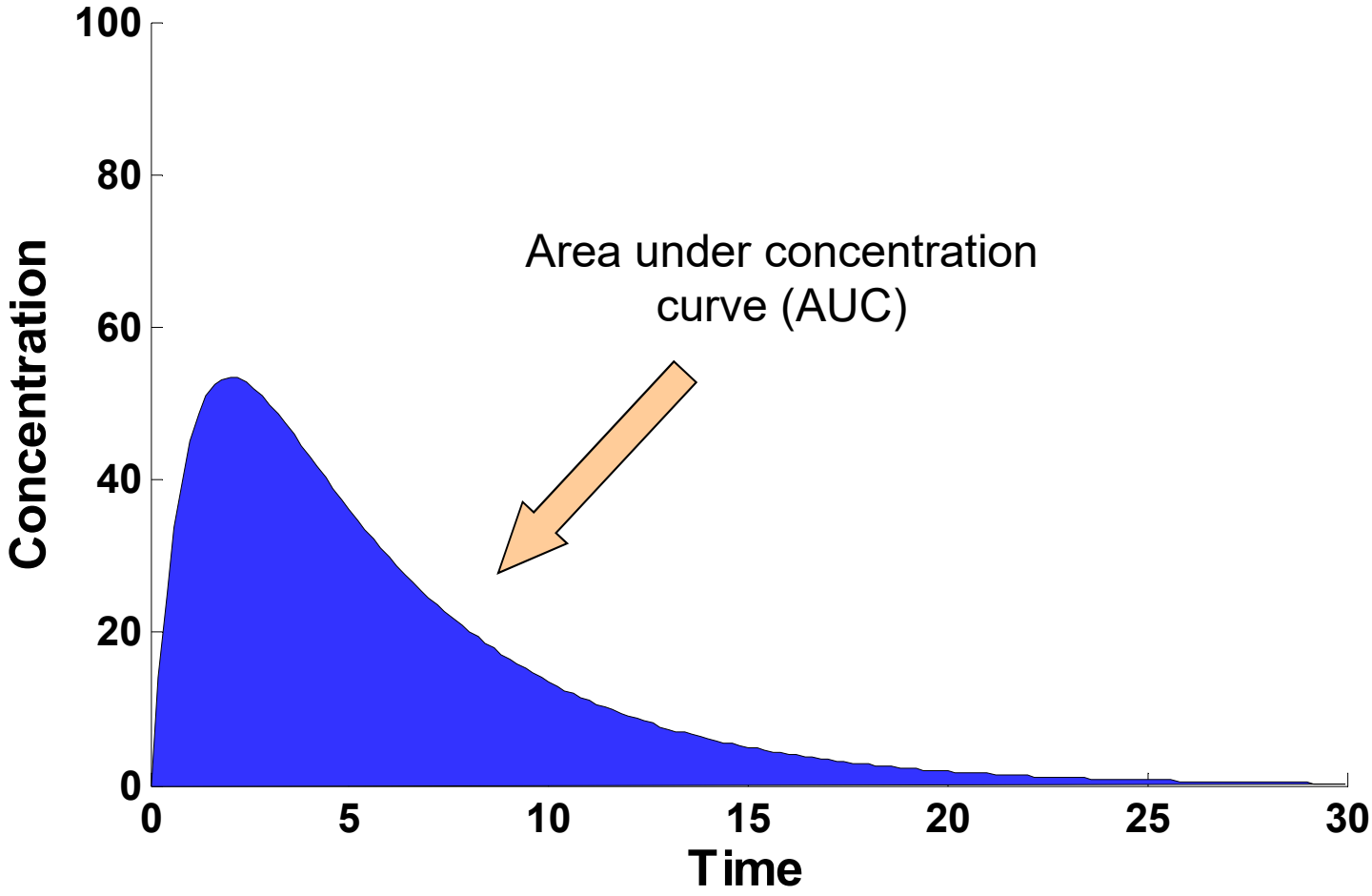
- Extravascular administration of the drug comprises routes such as oral, rectal, subcutaneous, transdermal, nasal, etc.



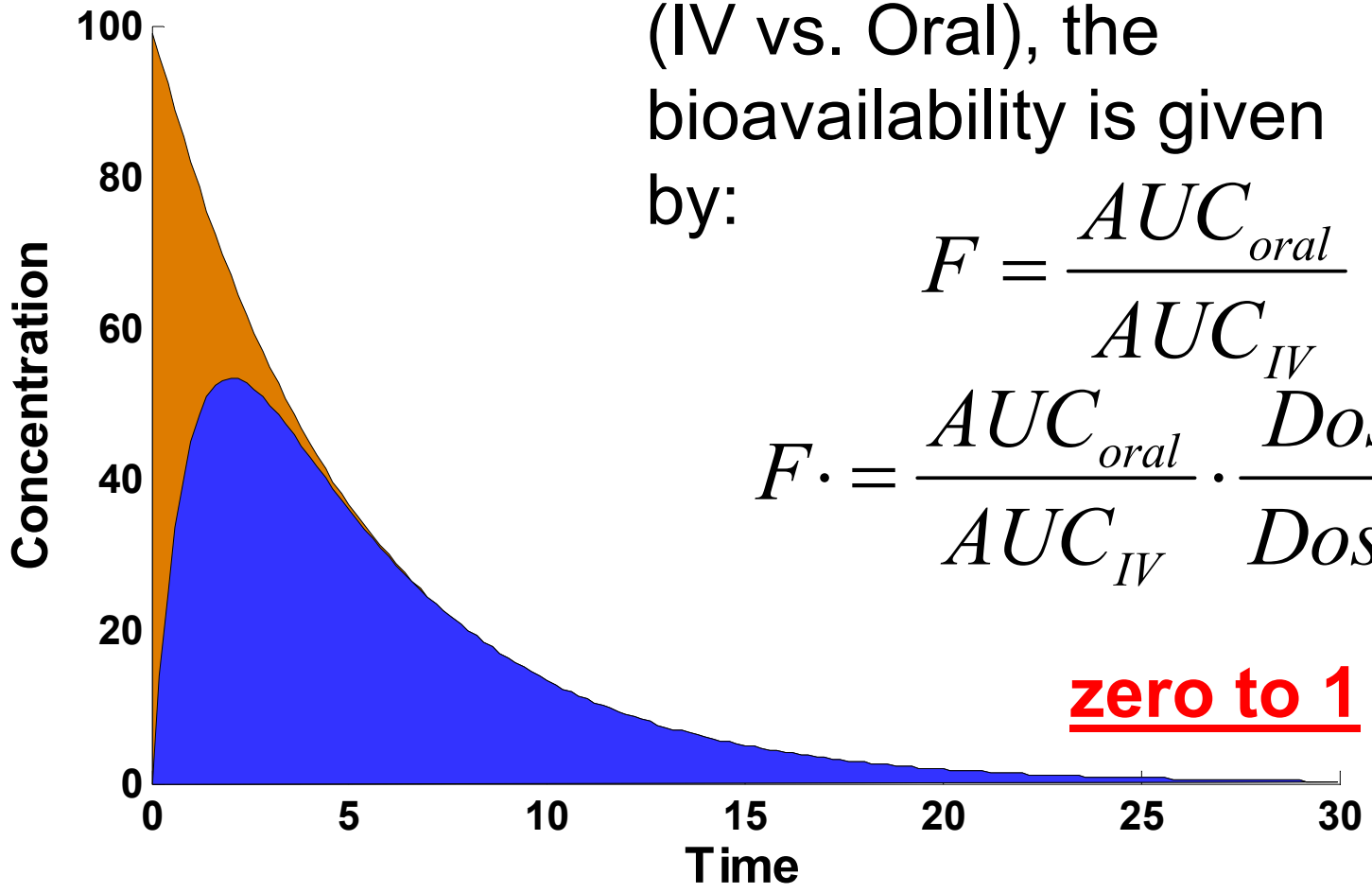
IV bolus


100
80
60
40
20
0
Concentration
Area under concentration curve (AUC)
0
5
10
15
20
25
30
Time

Oral dosage form (product A)



Absolute bioavailability



For the same dose (IV vs. Oral), the bioavailability is given by:

$$F = \frac{AUC_{oral}}{AUC_{IV}}$$

$$F \cdot = \frac{AUC_{oral}}{AUC_{IV}} \cdot \frac{Dose_{IV}}{Dose_{oral}}$$

zero to 1

Example

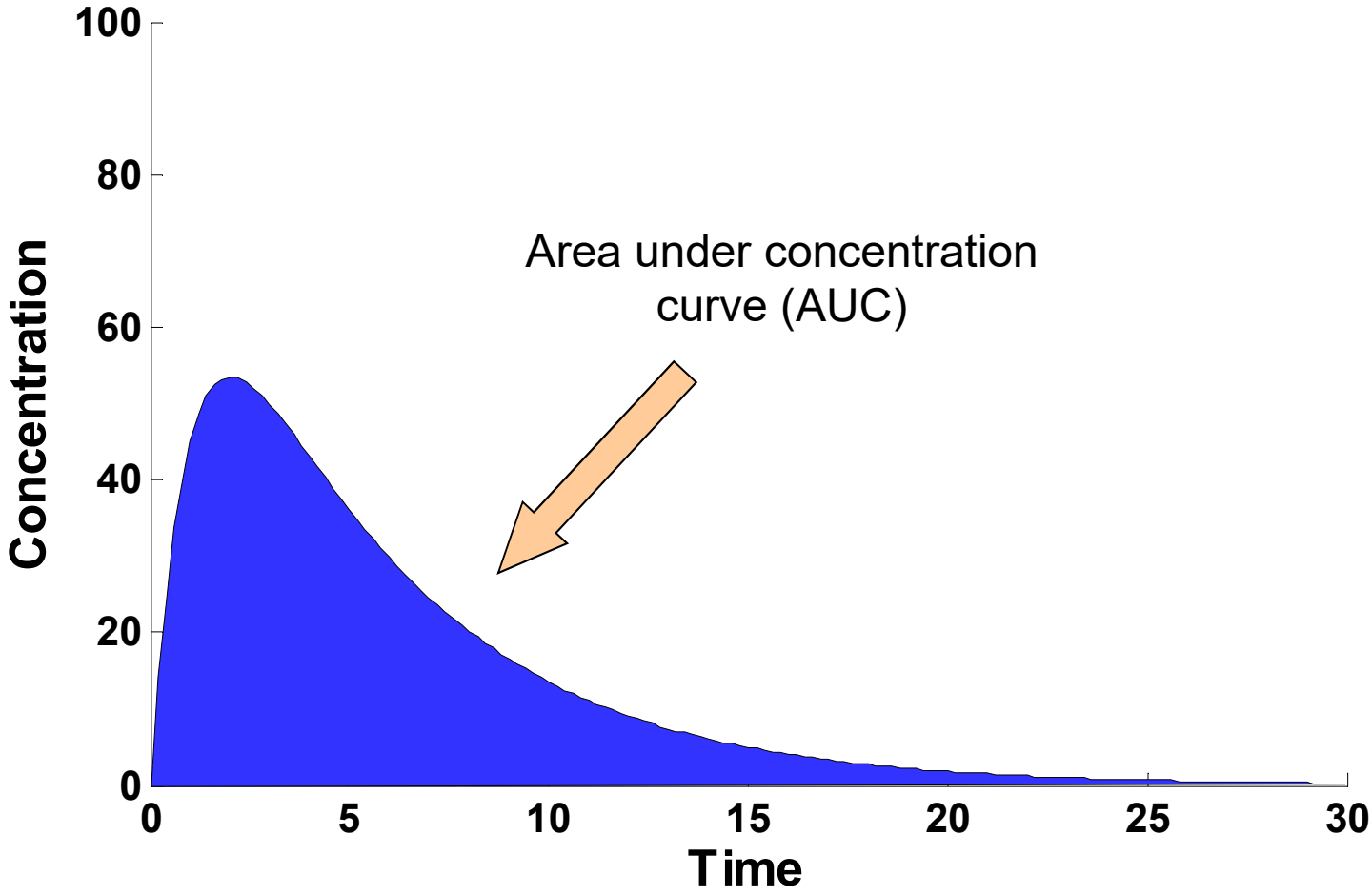
- If the AUC for an oral dose of a drug administered by tablet is 4.5 mg/ml/hr, and the intravenous dose is 11.2 mg/ml/hr, calculate the bioavailability of the oral dose of the drug?

F = 4.5 / 11.2 = 0.4 or 40%

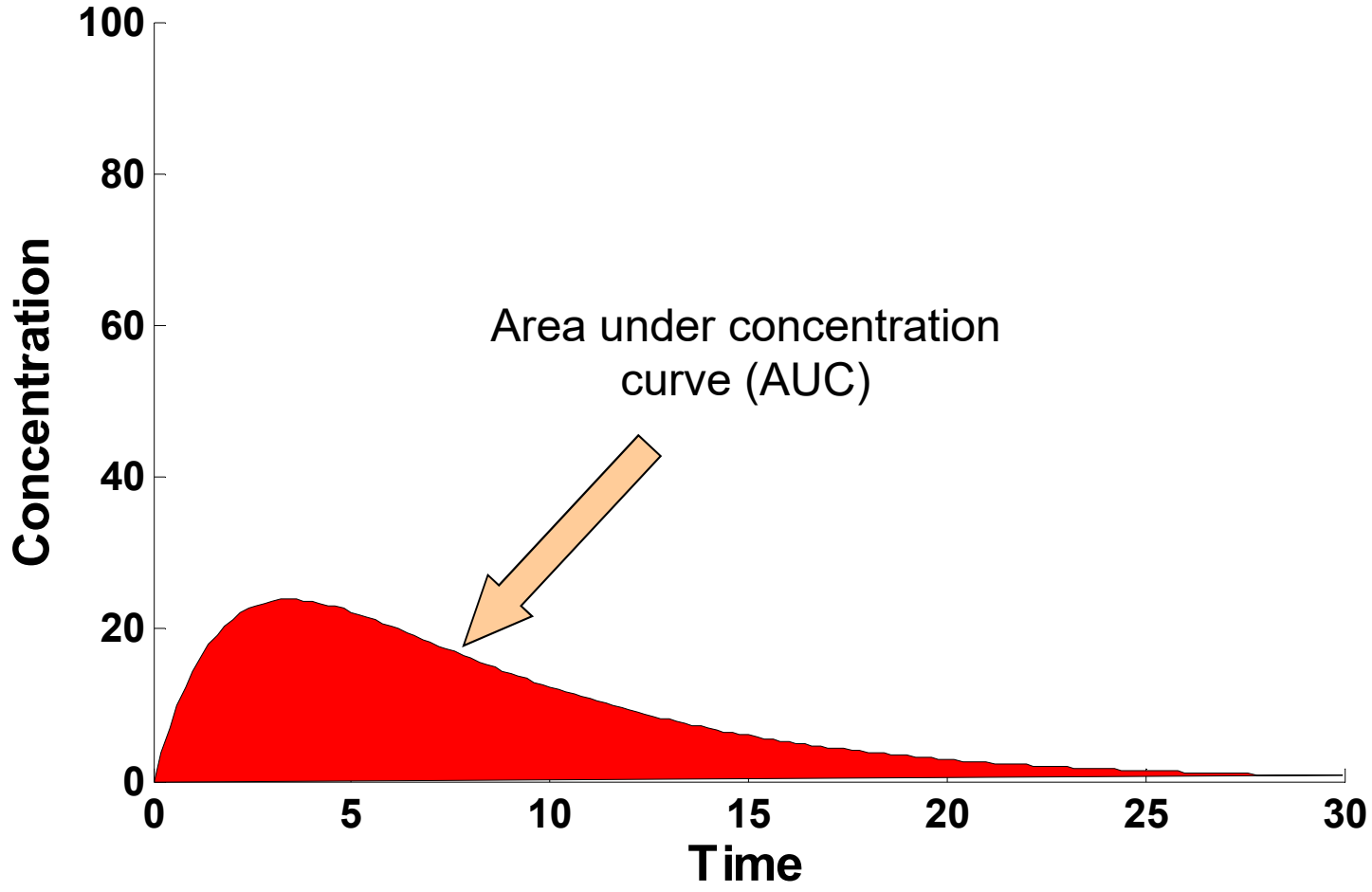
Relative bioavailability

- The systemic availability of a drug from one drug product (*A*) compared to another drug product (*B*).
- It can be more or less than 1.

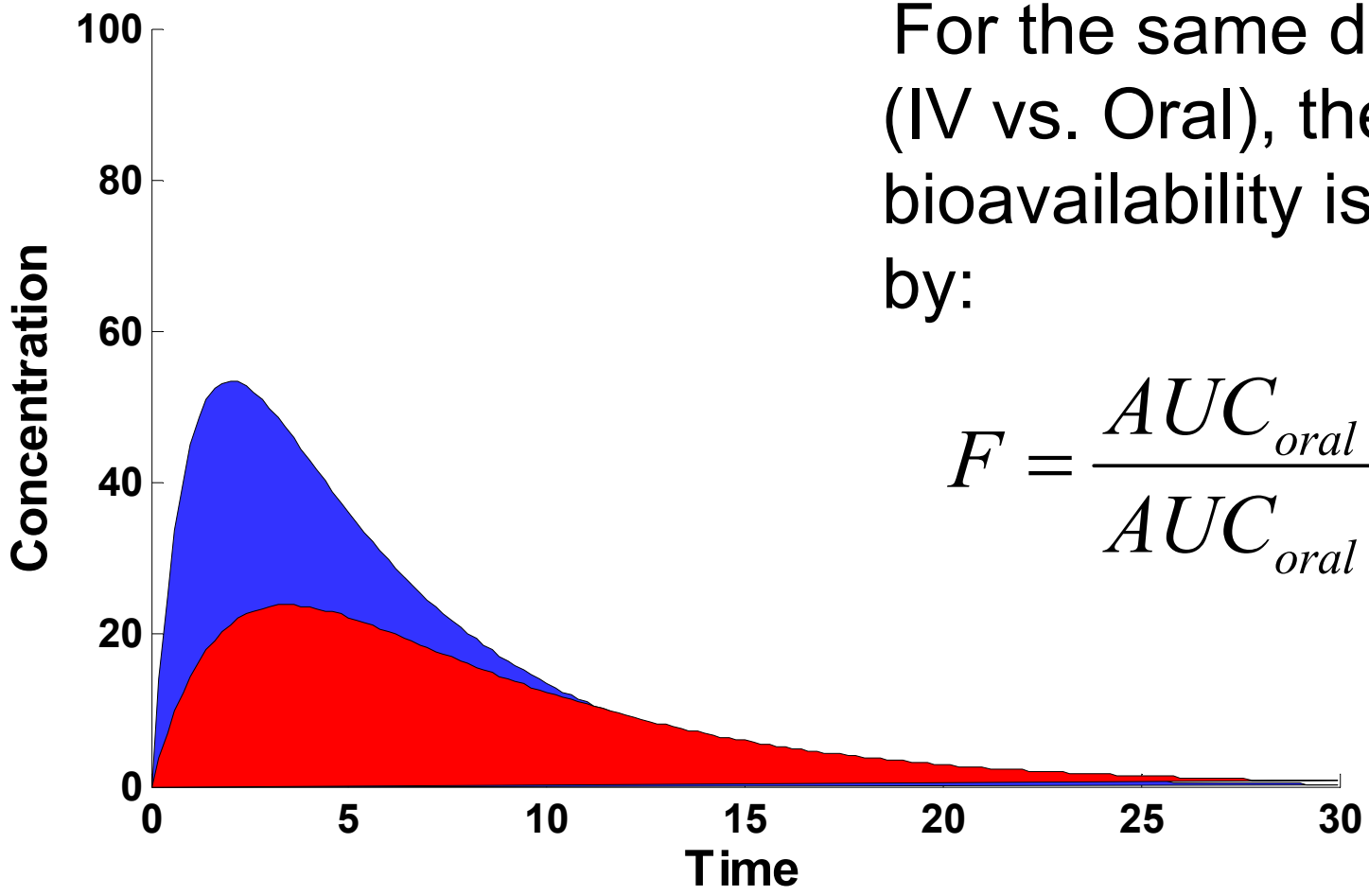
Oral dosage form (product A)



Oral dosage form (product B)



Relative bioavailability



For the same dose (IV vs. Oral), the bioavailability is given by:

$$F = \frac{AUC_{oral}(A)}{AUC_{oral}(B)}$$

Practice Problem

- The bioavailability of a new investigational drug was studied in 12 volunteers. Each volunteer received either a single oral tablet containing 200 mg of the drug, 5 mL of a pure aqueous solution containing 200 mg of the drug, or a single IV bolus injection containing 200 mg of the drug. The average AUC values are given in the table below. From these data, calculate
  - the relative bioavailability of the drug from the tablet compared to the oral solution
  - the absolute bioavailability of the drug from the tablet.

Practice Problem

Drug Product	Dose (mg)	AUC (ug. hr/mL)
Oral tablet	200	50
Oral solution	200	75
IV bolus injection	200	150

Area Under the Conc. Time Curve (AUC) calculation

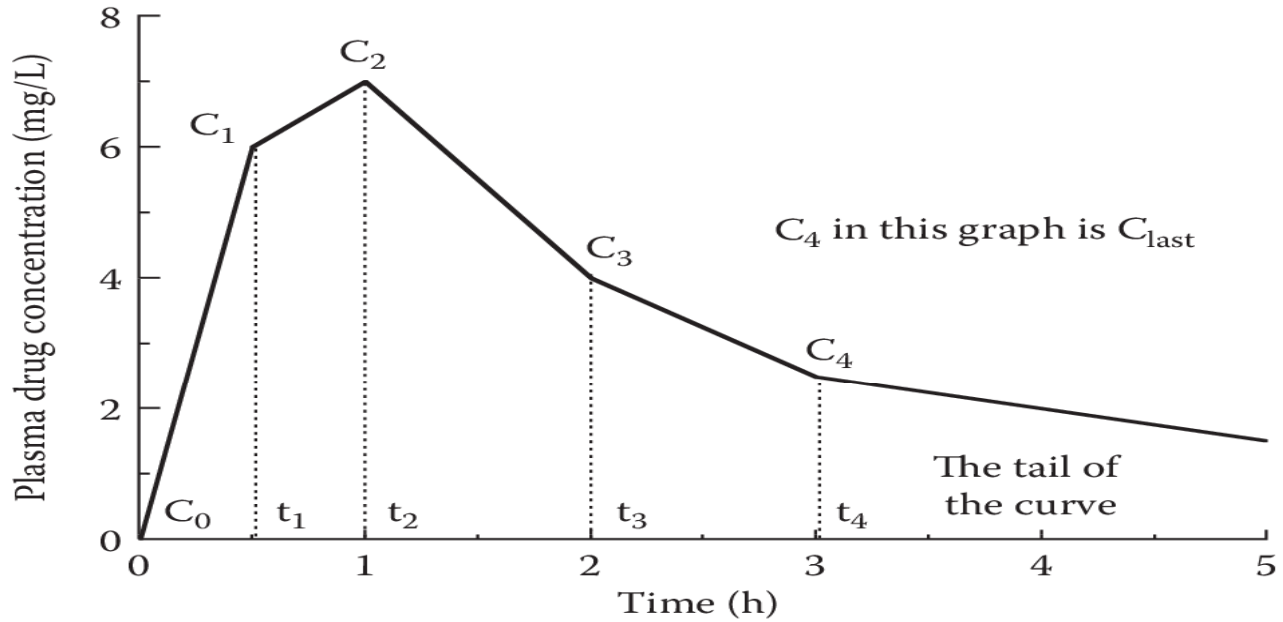
- Two methods:
  - Model dependent: can be used only for one compartment IV bolus
  - Model independent: Can be used for any drug with any route of administration

AUC calculation: Model dependent

- With one compartment model, first-order elimination, and intravenous drug administration, the AUC can be calculated using:

$$AUC = \frac{Dose}{K \cdot Vd} = \frac{C_0}{K}$$

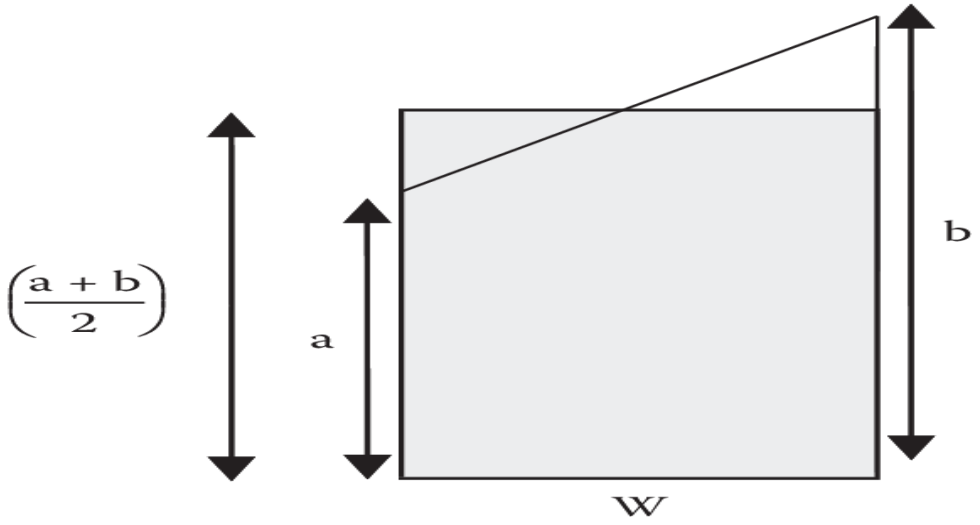
AUC calculation: Model independent



AUC is the sum of the area of all trapezoids and the area under the tail of the curve.

Trapezoidal rule (شبه المنحرف)

مساحة شبه المنحرف=(مجموع القاعدتين/2)×الارتفاع

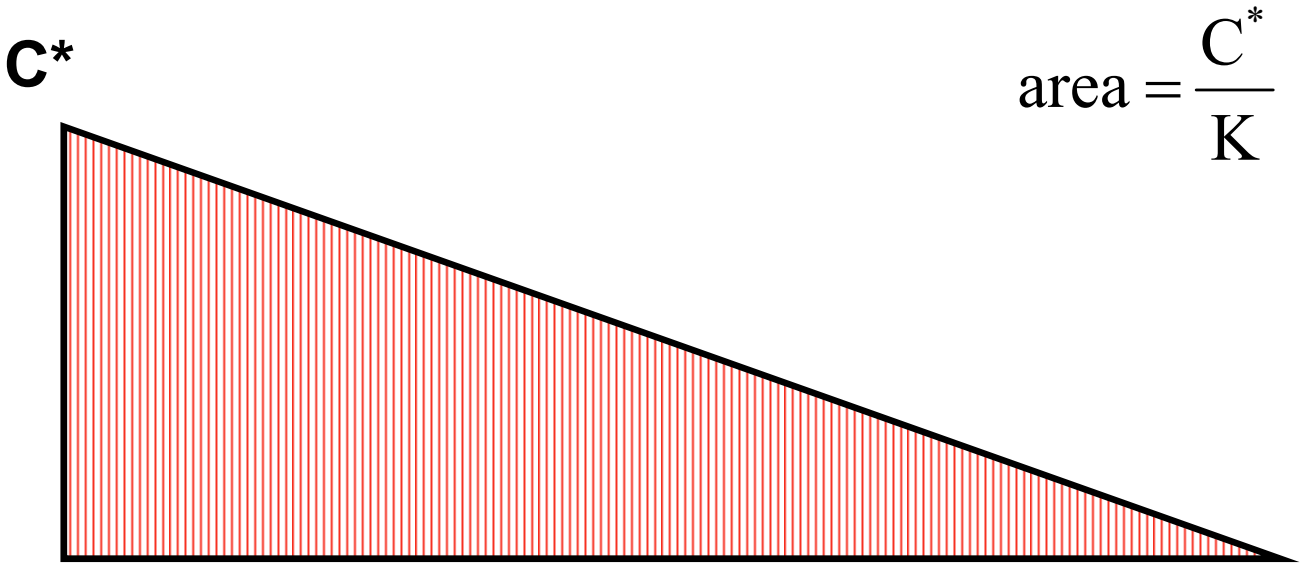


Calculation of the area of a trapezoid.

$$\text{Area} = \left(\frac{C_n + C_{n+1}}{2}\right)(t_{n+1} - t_n)$$

AUC calculation: Model independent

Area under tail (area between the last observed concentration and infinity) use the following equation:



$$\text{area} = \frac{C^*}{K}$$

Trapezoidal rule

- **AUC = Sum of all trapezoids + area under tail**

  - **AUC = 1/2 (C_0+C_1) (t_1-t_0) + 1/2 (C_1+C_2) (t_2-t_1) + 1/2 (C_2+C_3) (t_3-t_2) +1/2 (C_3+C_4) (t_4-t_3) + $C_{4\,(last)}/k$**

Trapezoidal method

Trapezoidal rule (cont'd)

Area of :

$$\text{trapezoid 1} = \left(\frac{0+Cp_1}{2}\right).(t_1 - 0)$$

$$\text{trapezoid 2} = \left(\frac{Cp_1+Cp_2}{2}\right).(t_2-t_1)$$

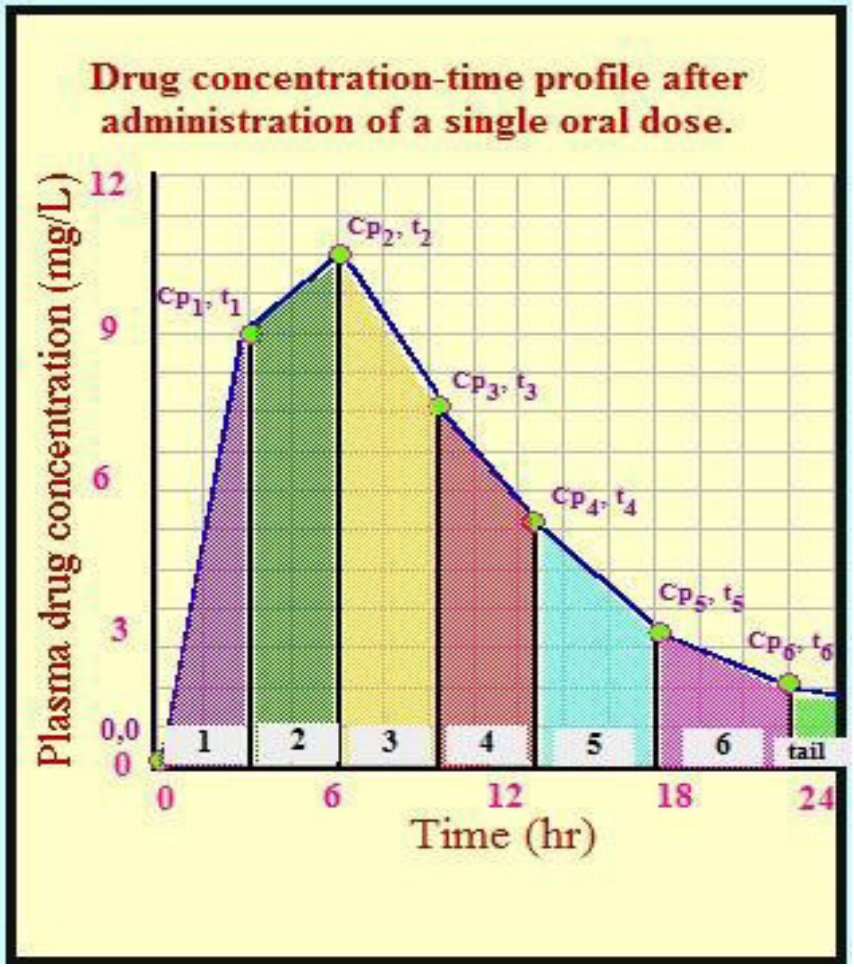
$$\text{trapezoid 3} = \left(\frac{Cp_2+Cp_3}{2}\right).(t_3-t_2)$$

trapezoid 4, 5, and 6 (as above)

Area of the last trapezoid or area under the tail of the curve

$$= \frac{\text{last concentration}}{k} = \frac{Cp_6}{k}$$

AUC = total area of all trapezoids



Example

Time	IV Bolus (250 mg)	Oral Suspension (500 mg)	Oral Capsule (500 mg)
	Conc. (mg/ml)	Conc. (mg/ml)	Conc. (mg/ml)
1	6.3	5.0	3.1
2	5.0	7.0	4.7
3	4.0	7.4	5.2
4	3.2	7.0	5.3
6	2.0	5.4	4.5
8	1.3	3.7	3.4
12	0.5	1.6	1.7

The half-life of this antibiotic is 3 h and the absorption process is complete after 12 h of oral administration.

a. Calculate the absolute BA of the oral suspension and the oral capsule of this antibiotic.

b. Calculate the BA of the oral capsule relative to the oral suspension of this antibiotic.

Answer

- **Calculation of the AUC after administration of 250 mg IV:** Plot the plasma concentration–time profile after IV administration on the semilog scale and back extrapolate the resulting line to calculate the initial plasma concentration Cpo. The Cpo is 8 mg/L and the first-order elimination rate constant (k) is 0.693/3 h = 0.231 h^{-1}.
- **$AUC_{IV} = Cp_0 / k = 8 / 0.231 = 34.63$ mg.h/L**
- **Calculation of the AUC after administration of 500 mg oral suspension by the trapezoidal rule:**

- $AUC = 1/2\ (C_1 t_1) + 1/2(C_1+C_2)\ (t_2-t_1) + 1/2(C_2+C_3)\ (t_3-t_2) + 1/2(C_3+C_4)\ (t_4-t_3) + 1/2(C_4+C_5)\ (t_5-t_4) + 1/2(C_5+C_6)\ (t_6-t_5) + 1/2(C_6+C_7)\ (t_7-t_6) + C_{Last}/k$

Calculation of the AUC after administration of 500 mg oral suspension by the trapezoidal rule:

- Area of trapezoid 1= ½*(0+5) (1-0)=2.5 mg.h/L
- Area of trapezoid 2= ½*(5+7) (2-1)=6 mg.h/L
- Area of trapezoid 3= ½*(7+7.4) (3-2)= 7.2 mg.h/L
- Area of trapezoid 4= ½*(7.4+7) (4-3)= 7.2mg.h/L
- Area of trapezoid 5= ½*(7+5.4) (6-4)= 12.4mg.h/L
- Area of trapezoid 6= ½*(5.4+3.7) (8-6)= 9.1 mg.h/L
- Area of trapezoid 7= ½*(3.7+1.6) (12-8)= 10.6 mg.h/L
- Area of tail= C_{last}/k = 1.6/0.231=6.93 mg.h/L
- **Total AUC =2.5 + 6.0 + 7.2 + 7.2 + 12.4 + 9.1 + 10.6 + 6.93 = 61.93 mg. h/L**

Calculation of the AUC after administration of 500 mg oral capsule by the trapezoidal rule:

- Area of trapezoid 1= ½*(0+3.1) (1-0)=1.55 mg.h/L
- Area of trapezoid 2= ½*(3.1+4.7) (2-1)=3.9 mg.h/L
- Area of trapezoid 3= ½*(4.7+5.2) (3-2)= 4.95 mg.h/L
- Area of trapezoid 4= ½*(5.2+5.3) (4-3)= 5.25 mg.h/L
- Area of trapezoid 5= ½*(5.3+4.5) (6-4)= 9.8 mg.h/L
- Area of trapezoid 6= ½*(4.5+3.4) (8-6)= 7.9 mg.h/L
- Area of trapezoid 7= ½*(3.4+1.7) (12-8)= 10.2 mg.h/L
- Area of tail= C_{last}/k = 1.7/0.231=7.36 mg.h/L
- **Total AUC =1.55 + 3.9 + 4.95 + 5.25 + 9.8 + 7.9 + 10.2 +7.36 = 50.9 mg. h/L**

Answer

- The absolute BA of the suspension (note that the doses for the IV and the oral suspension are different):

$$\text{F susp} = \frac{61.93}{34.63} \times \frac{250}{500} = \mathbf{0.89}$$

- The absolute BA of the capsule (Note that the doses for the IV and the oral capsule are different):

$$\text{F cap} = \frac{50.9}{34.63} \times \frac{250}{500} = \mathbf{0.73}$$

- b. The BA of the capsule relative to the suspension (the dose is similar):

$$\text{F relative} = \frac{50.9}{61.93} \times \frac{500}{500} = \mathbf{0.82}$$

- $$\text{F relative} = \frac{Fcap}{Fsusp} = \frac{0.73}{0.89} = \mathbf{0.82}$$

Bioequivalence

Bioequivalence

- **Pharmaceutical alternatives**: Drug products that contain the same therapeutic moiety but differ in dosage form, strength, salt or ester of the active therapeutic moiety.

- **Pharmaceutical equivalents**: Drug products that contain the exact active ingredient (i.e., the same salt or ester of the therapeutic moiety), identical strength, and the same dosage form for the same route of administration, but differ in shape, release mechanism, labeling, scoring, and excipients including color, flavor, and preservative.

- **Bioequivalent products**: Pharmaceutical equivalent products with no significant difference in the rate and extent to which the active ingredient becomes available at the site of action when administered under similar conditions in an appropriately designed study.
- **Therapeutic equivalents**: Drug products for the same active ingredient that can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product. Drug products are considered to be therapeutically equivalent if they are pharmaceutical equivalents and bioequivalents.
- **Clinical Equivalence:** The drug products provide identical in vivo pharmacological response as measured by control of the disease or symptoms.

Criteria for waiver of the BA or BE

- Parenteral solutions intended solely for administration by injection or ophthalmic or otic solutions that contain the same active and inactive ingredients in the same concentration as an approved drug product.
- Products administered by inhalation as a gas, for example, an inhalation anesthetic, that contain the same active ingredient in the same dosage form as an approved drug product.

Criteria for waiver of the BA or BE

- Solutions for application to the skin (**Topical preparation**), oral solutions, elixirs, syrups, tinctures, solutions for aerosolization or nebulization, nasal solutions, or similar other solubilized form that contain an active drug ingredient in the same concentration and dosage form as an approved drug product and contain no inactive ingredient that can affect the in vivo BA of the active ingredients.
- Drugs with local effect (Not absorbed from GIT) (**Antacids**)

Criteria for waiver of the BA or BE

- For example, immediate-release solid dosage forms of the biopharmaceutics classification system (BCS) **class I drugs (highly soluble, highly permeable**) have rapid and similar in vitro dissolution characteristics.

- Rapid dissolution means at least 85% dissolution in 30 min in 900 mL at pHs 1.2, 4.5, and 6.8, while similar dissolution profile can be evaluated by comparing the similarity factor (f2) at the three pHs. Comparing the dissolution profile is not necessary if the dissolution is 85% in less than 15 min.

Pharmacokinetic approach to demonstrate product bioequivalence:

- **Study Design**
- **Repeated measures, cross-over and carry-over designs:**
- The administration of two or more treatments one after the other in a specified or random order to the same group of patients is called **a crossover design or change-over design**
- **Advantages**
- They provide good precision for comparing treatments because all sources of variability between subjects are excluded from the experimental error. It is economic on subjects. This is particularly important when only a few subjects can be utilized for the experiments.

Washout period

- The time interval between the 2 treatments is called as **WASHOUT PERIOD**.
- It is required for the elimination of the administered dose to avoid the carry over effect
- A washout period of 1 week was usually found suitable in most cases (**5 times half-life of the used drug**).

2. Subjects:

- **Selection of subjects:**
- Aim to minimize variability and permit detection of differences between pharmaceutical products.
- The studies should normally be performed with healthy volunteers 24 volunteers (12 in each group).
- They should be screened for suitability by means of clinical laboratory tests, review of medical history, and medical examination.
- **Standardization of the study:**
- Standardization of the diet, fluid intake and exercise is recommended.
- The subjects should not take other medicines during a suitable period before and during the study.
- **Genetic pheno-typing:**

- **Characteristics to be investigated**
- In most cases evaluation of bioavailability and bioequivalence will be based upon the measured concentrations of the parent compound.
- In some situations, measurements of an active or inactive metabolite are carried out.
- The plasma concentration versus time curves is mostly used to assess extent and rate of absorption.
- The use of urine excretion data may be advantageous in determining the extent of drug input in case of products predominately excreted renally.
- Specificity, accuracy and reproducibility of the methods should be sufficient.

- **Chemical analysis**
- **Reference and test product**
- **Data analysis**
- **Statistical analysis**
- **Acceptance range for pharmacokinetic parameters:**
- **1.AUC-ratio:**
- It should lie within an acceptance interval of 0.80-1.25.
- **2.Cmax-ratio:**
- It should lie within an acceptance interval of 0.80-1.25.
- The wider interval must be 0.75-1.33.
- For t_{max} if there is a clinically relevant claim for rapid release or action or signs related to adverse effects.


QUESTIONS?

Two-compartment Pharmacokinetic Model

Dr. Mahmoud Samy

Lecturer of Clinical Pharmacy

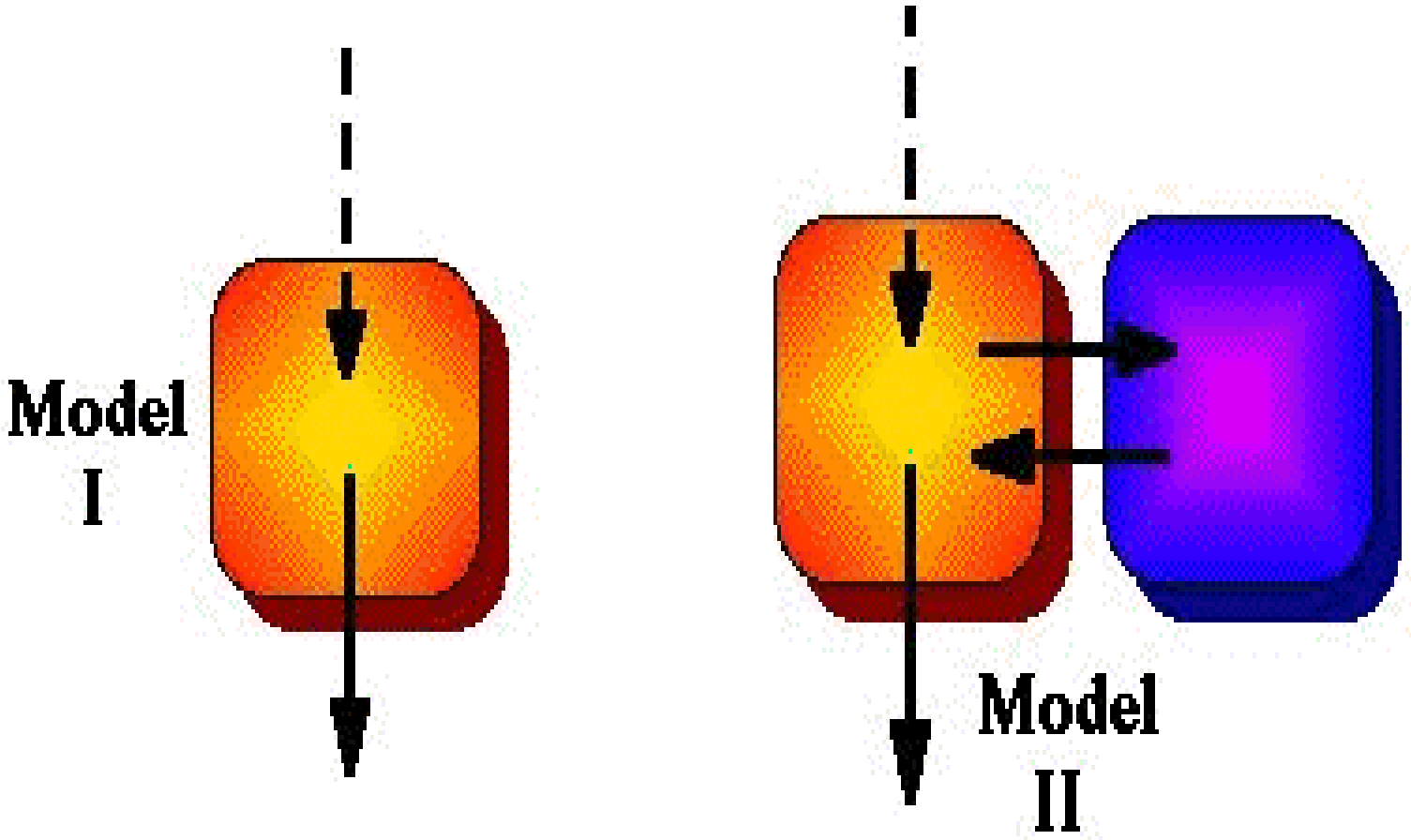
Outlines

- Pharmacokinetic Model
- One Compartment Model
- Two Compartment Model
- Three Compartment Model

Pharmacokinetic Models

- A model is a hypothesis enables using mathematical terms to simulate the rate processes of drug absorption, distribution, and elimination
- Compartment models are based on linear assumptions using linear differential equations
- It enables Predict plasma, tissue, and urine drug levels with any dosage regimen.
- The number of compartments in the model depends on **the rate of drug distribution to the different parts of the body**

Pharmacokinetic Models



one-compartment model

- If the drug in the systemic circulation is distributed rapidly to all parts of the body, the body behaves as a single compartment and the drug pharmacokinetic behavior can be described by one-compartment.

- In this case the plasma and all perfused organs deal as one unit (the central compartment)

- The drug is both added to and eliminated from a central compartment.

One compartment open model

- The one-compartment open model offers the simplest way to describe the process of drug distribution and elimination in the body.

- This model assumes that the drug can enter or leave the body (ie, the model is "open"), and the body acts like a single, uniform compartment.

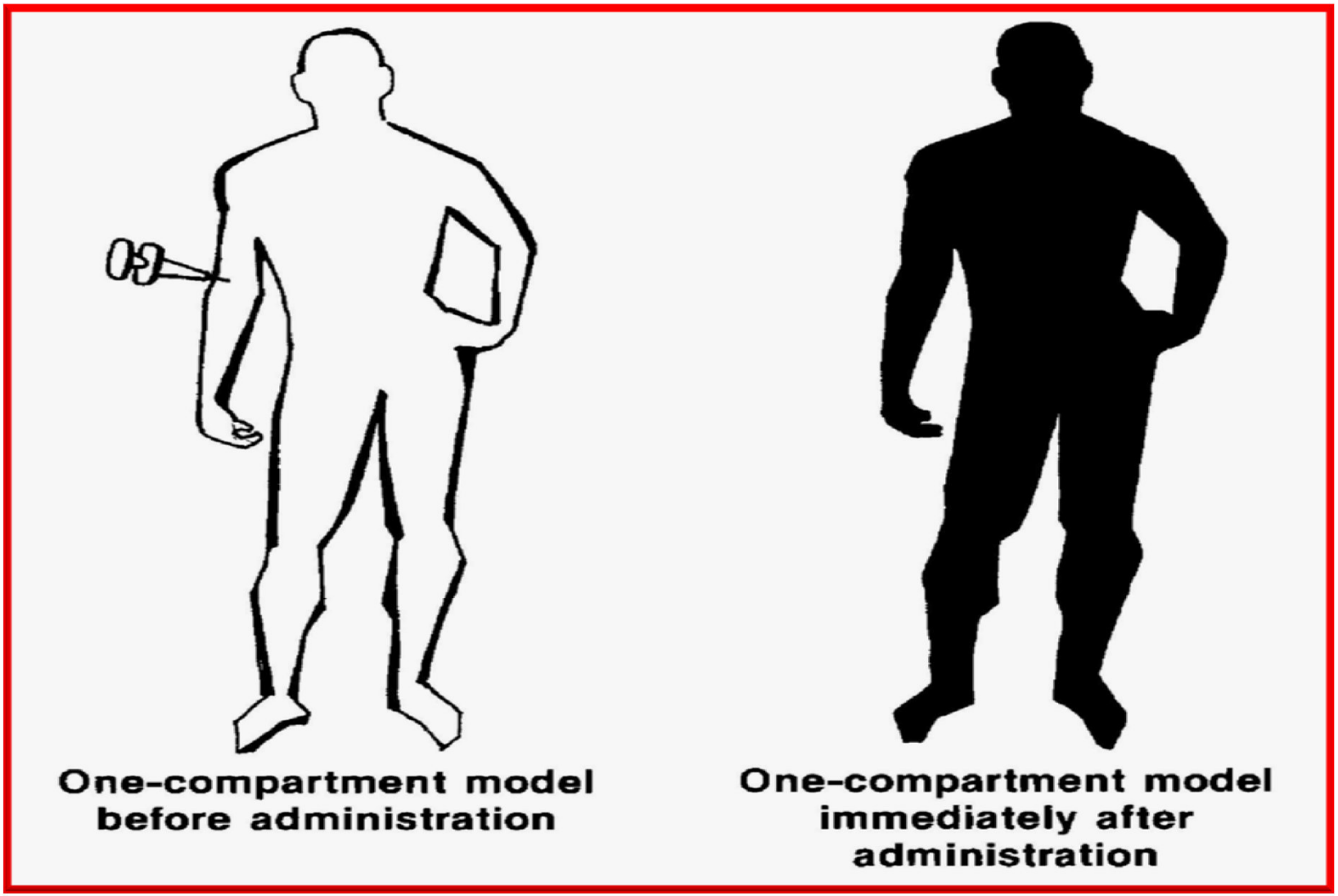
- The simplest route of drug administration from a modeling perspective is a rapid intravenous injection (IV bolus).

One compartment open model

- The simplest kinetic model that describes drug disposition in the body is to consider that the drug is injected all at once into a box, or compartment, and that the drug distributes instantaneously and homogenously throughout the compartment.

- Drug elimination also occurs from the compartment immediately after injection.

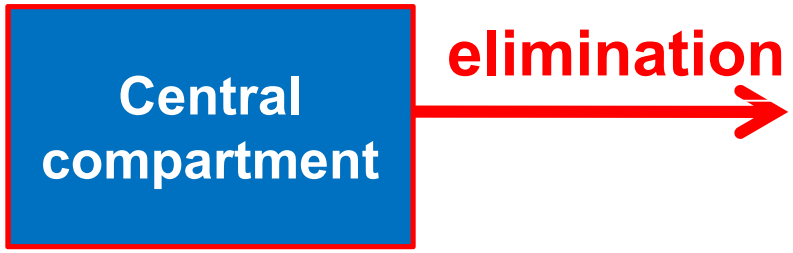
One compartment model



One-compartment model before administration

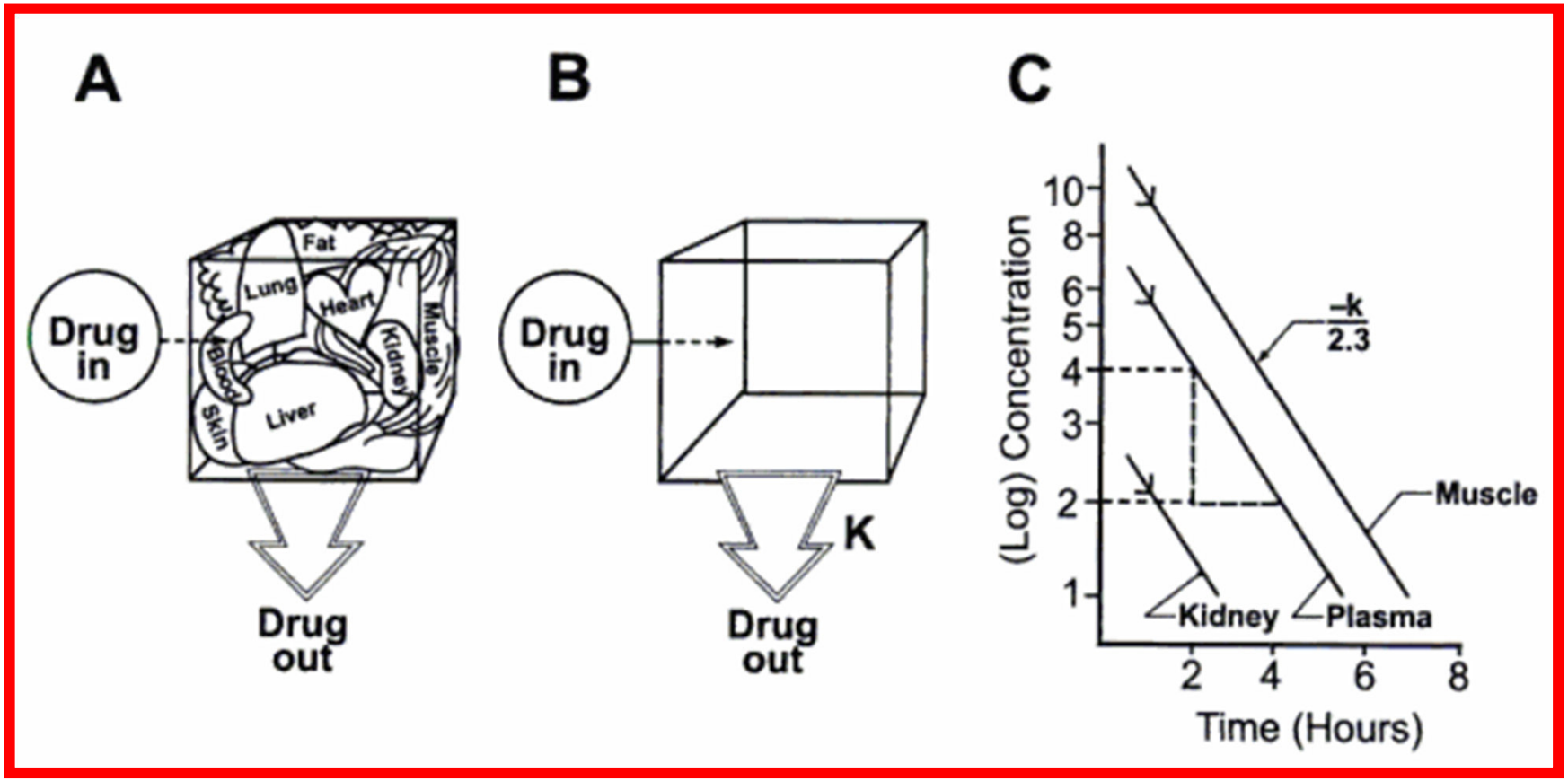
One-compartment model immediately after administration

Oral dose

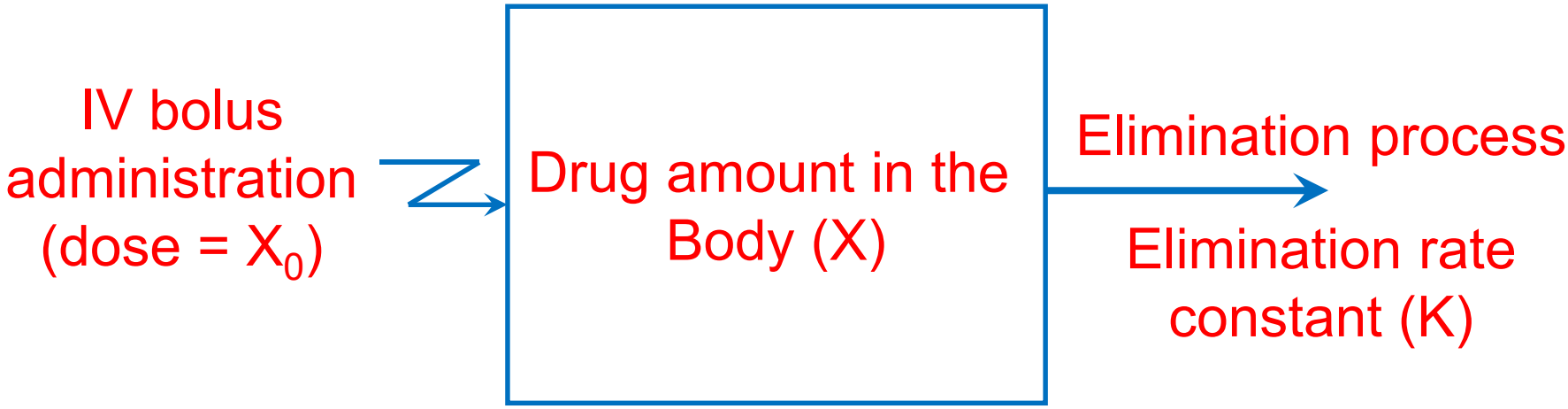


IV dose

One compartment:



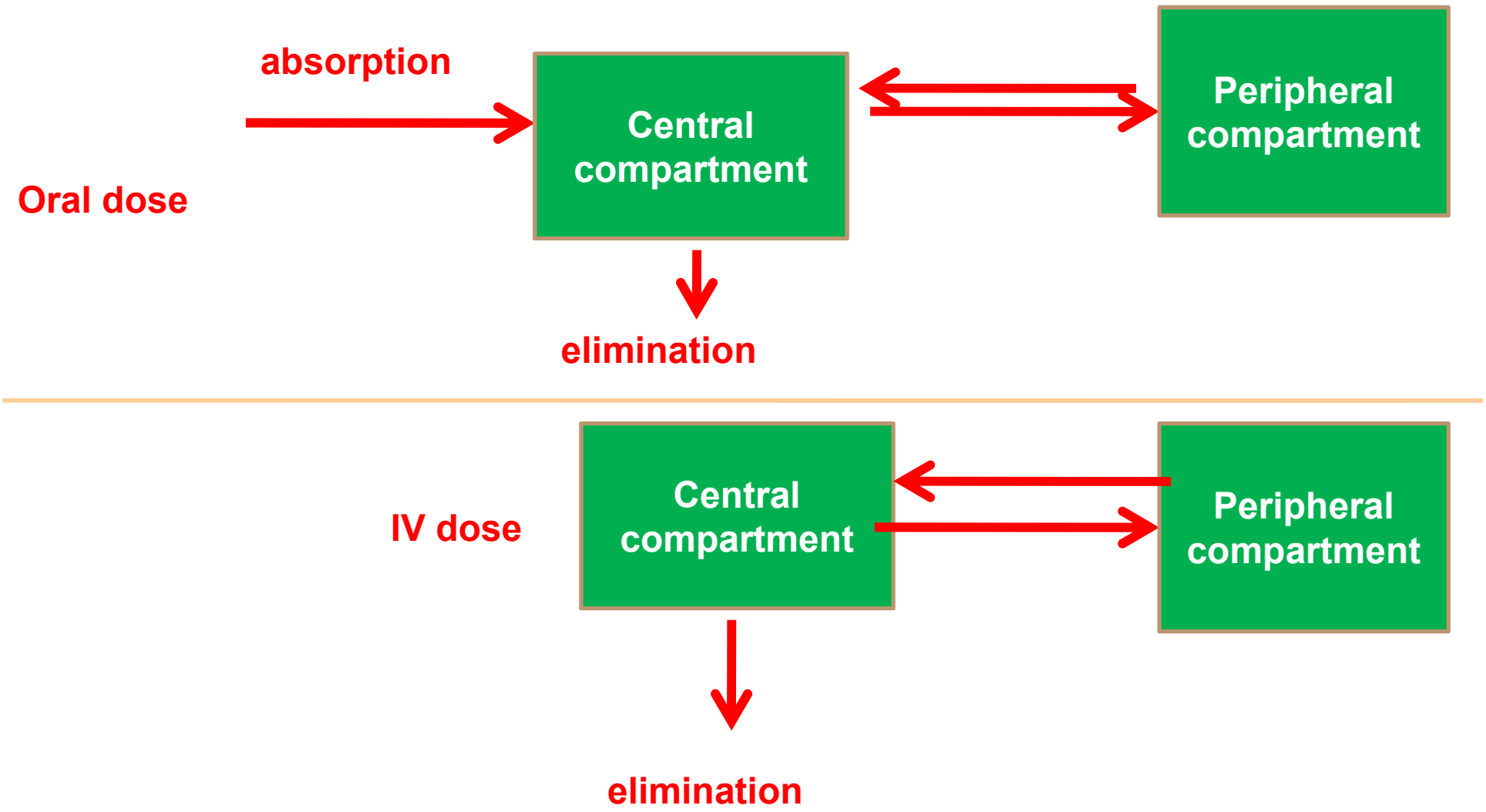
One compartment:



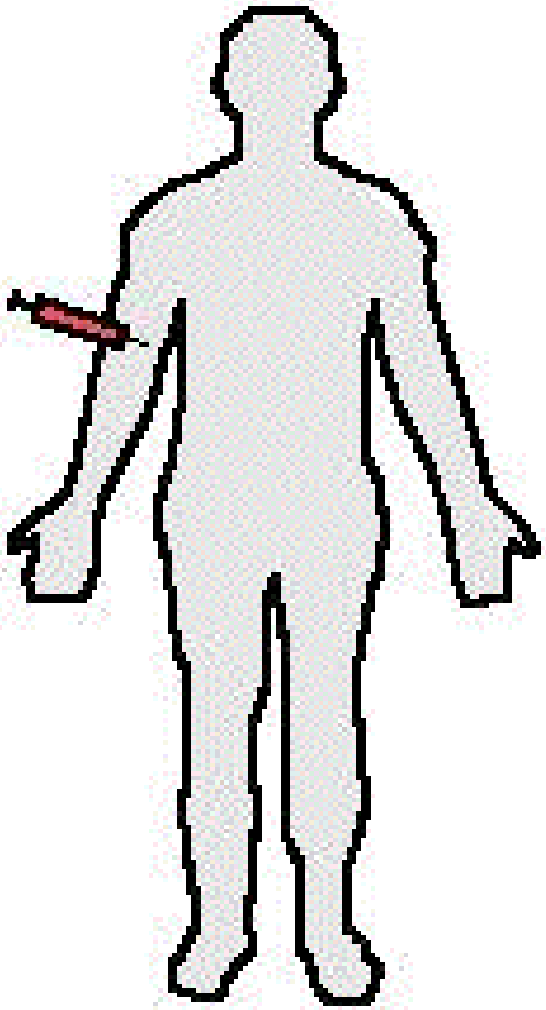
Based on the assumption of first order elimination process

Two-compartment model

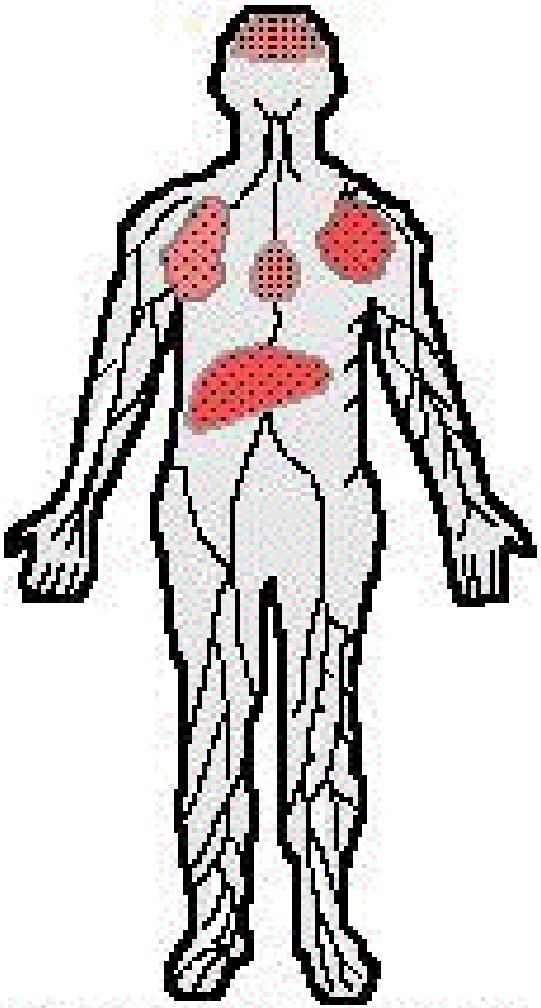
- While if the drug is distributed rapidly to some tissues and organs and slowly to other tissues and organs, the two-compartment pharmacokinetic model can be used to describe the pharmacokinetic behavior of the drug in this case.
- In a two-compartment model, drug can move between the central (plasma compartment and highly perfused organ) to and from the tissue compartment (peripheral compartment).
- In this model, in most cases, there is no elimination from tissue compartment and the drug need to be transported again to the plasma in order to be eliminated


absorption
Central compartment
Peripheral compartment
Oral dose
elimination
IV dose
Central compartment
Peripheral compartment
elimination

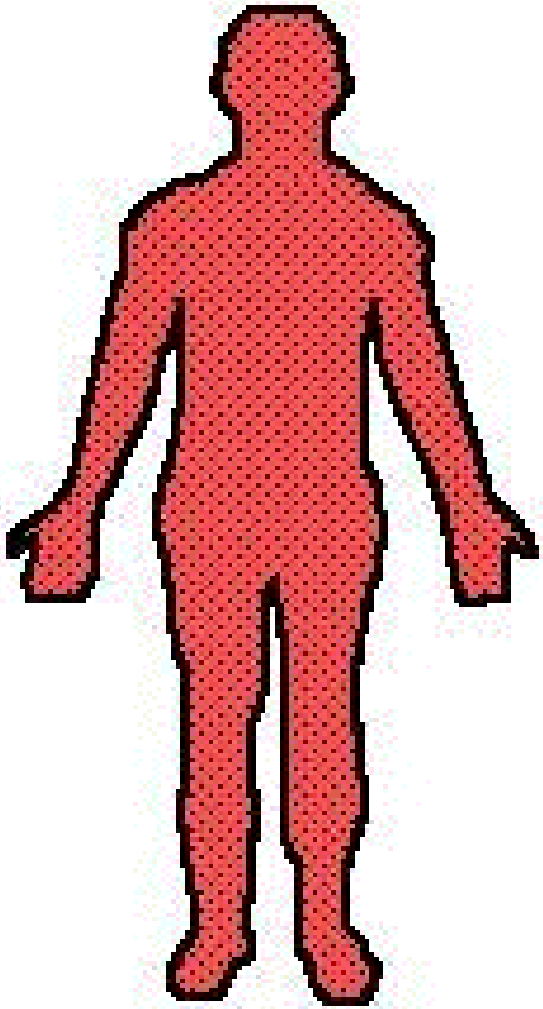
Two Compartment Model



Before Administration

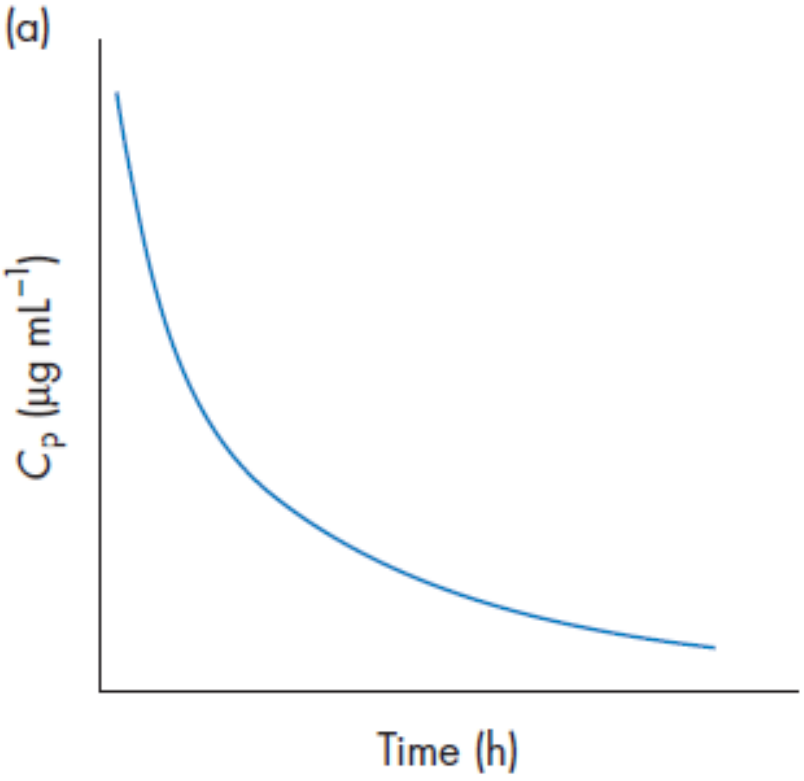


Immediately After Administration

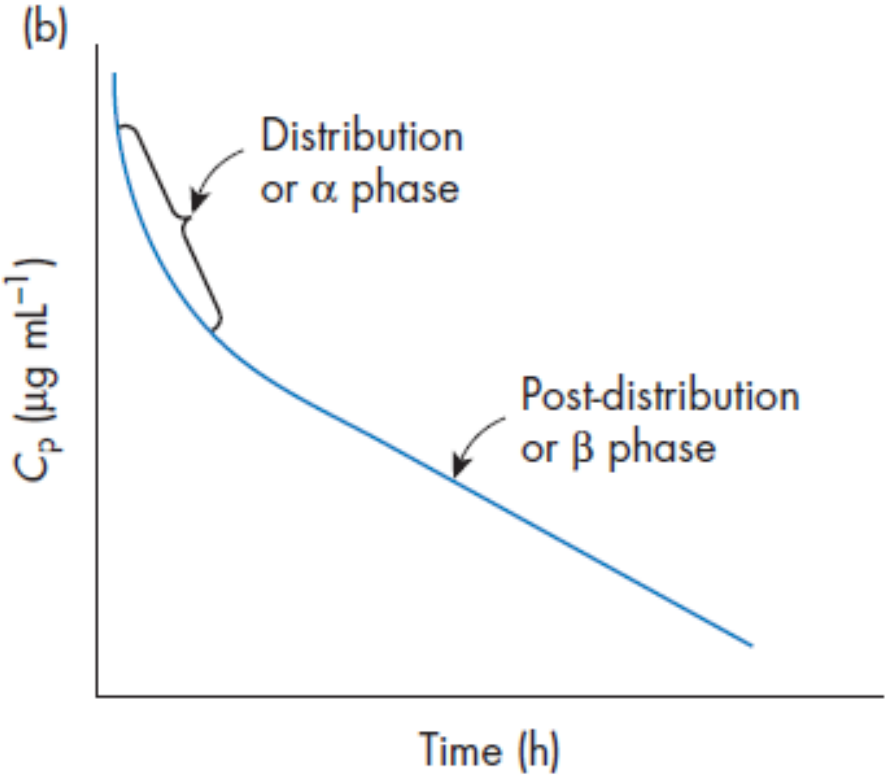


After Distribution Equilibrium

Typical plasma concentration (Cp) versus time profiles for a drug that obeys a two-compartment model following intravenous bolus administration



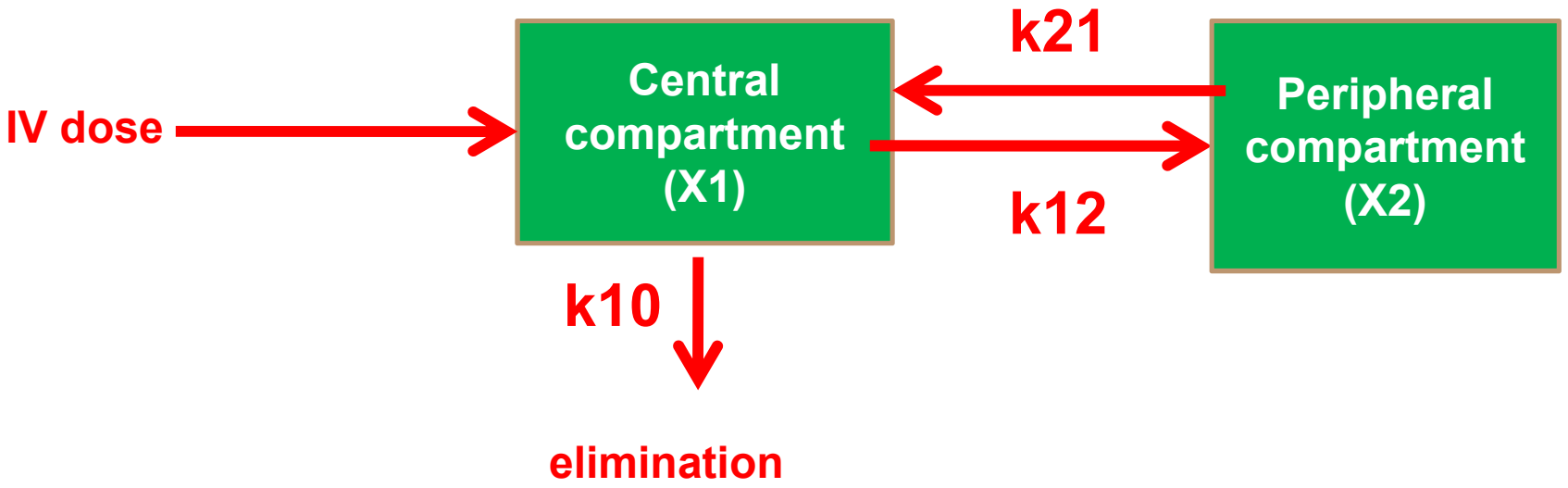
y axis: normal scale



y axis: logarithmic scale

A schematic representation of two-compartment models consisting of a central and a peripheral compartment.

k12 is the first-order **transfer rate constant** from the central compartment to the peripheral compartment and has units of time−1.
k21 is the first-order **transfer rate constant** from the peripheral compartment to the central compartment and has units of time−1.
k10 is the first-order **elimination rate constant** from the central compartment and has units of time−1.

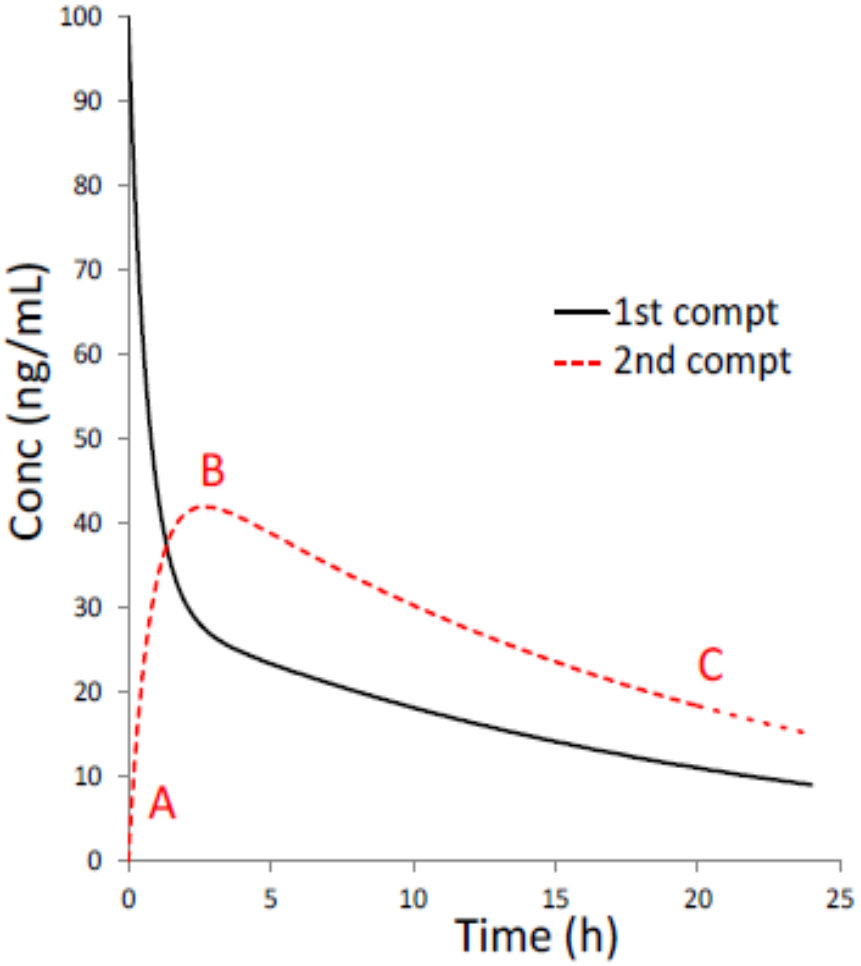


Assumptions of the model

- Upon drug absorption there is instantaneous distribution of drug throughout the central compartment (sampling compartment) having a volume V1 (Vc)
- Transfer of drug from the central compartment to the peripheral compartment is by a first-order process
- Transfer of drug from of drug from the peripheral compartment to the central compartment is by a first-order process

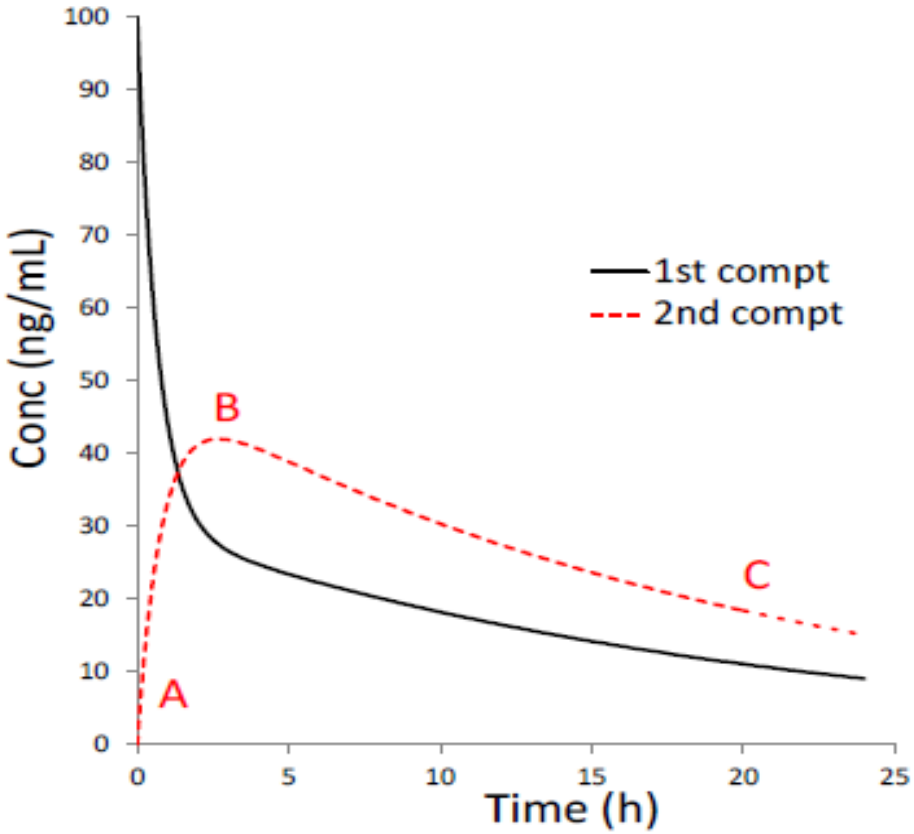
Drug concentrations in the two compartments following a single i.v. bolus injection

A. At zero time, there is no drug in the peripheral compartment
B. The amount of the drug in the central compartment decreases rapidly due to drug distribution and elimination
C. Some drug in peripheral compartment come back to the central compartment but the net transfer from central to the peripheral till equilibrium (maximum conc. In the peripheral compartment)



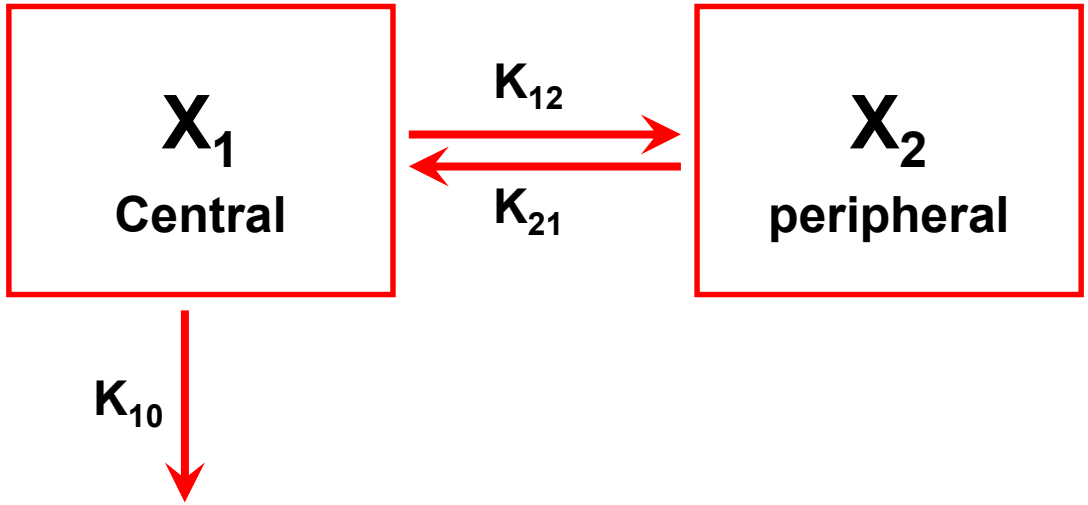
Drug concentrations in the two compartments following a single i.v. bolus injection

D. Elimination occur from central compartment, so amount of drug in it decrease slowly leads to increase the rate of transfer from the peripheral to the central compartment, so the net drug transfer from the peripheral to the central compartment.



Parameters of the two-compartment pharmacokinetic model

- **Vc** is the volume of the central compartment and has units of volume. This term relates the administered dose to the initial plasma drug concentration (central compartment concentration) after administration of a single IV dose: **Cp_0= Dose/Vc**
- **Vdss**: is the volume of distribution of the drug at steady state and has units of volume. This term relates the amount of the drug in the body and the plasma drug concentration at steady state: **Amount of the drug in the body at steady state = Vdss Cpss**
- **Vdβ** : is the volume of distribution during the elimination phase and has units of volume. **This term relates the amount of the drug in the body and the plasma drug concentration during the elimination phase (β-phase):** Amount of the drug in the body during the elimination phase = Vdβ Cpβ-phase.



$$\frac{dX_1}{dt} = K_{21}X_2 - K_{12}X_1 - K_{10}X_1$$

$$\frac{dX_2}{dt} = K_{12}X_1 - K_{21}X_2$$

Distribution rate from X1 to X2 = $K_{12}X_1$

Distribution rate from X2 to X1 = $K_{21}X_2$

Elimination rate = $K_{10}X_1$

$$X_1 = \frac{X_0(\alpha - K_{21})}{\alpha - \beta} e^{-\alpha t} + \frac{X_0(K_{21} - \beta)}{\alpha - \beta} e^{-\beta t}$$

Amount in the central compartment

$$C_1 = \frac{X_0(\alpha - K_{21})}{V_C(\alpha - \beta)} e^{-\alpha t} + \frac{X_0(K_{21} - \beta)}{V_C(\alpha - \beta)} e^{-\beta t}$$

Conc in the central compartment

V_C is the volume of the central compartment

$$Cp = Ae^{-\alpha t} + Be^{-\beta t}$$

biexponential

$$A = \frac{Xo(\alpha - K21)}{Vc(\alpha - \beta)}$$

$$B = \frac{Xo(K21 - \beta)}{Vc(\alpha - \beta)}$$

$$X_2 = \frac{XoK12}{(\alpha - \beta)}(e^{-\beta t} - e^{-\alpha t})$$

Amount in the peripheral compartment

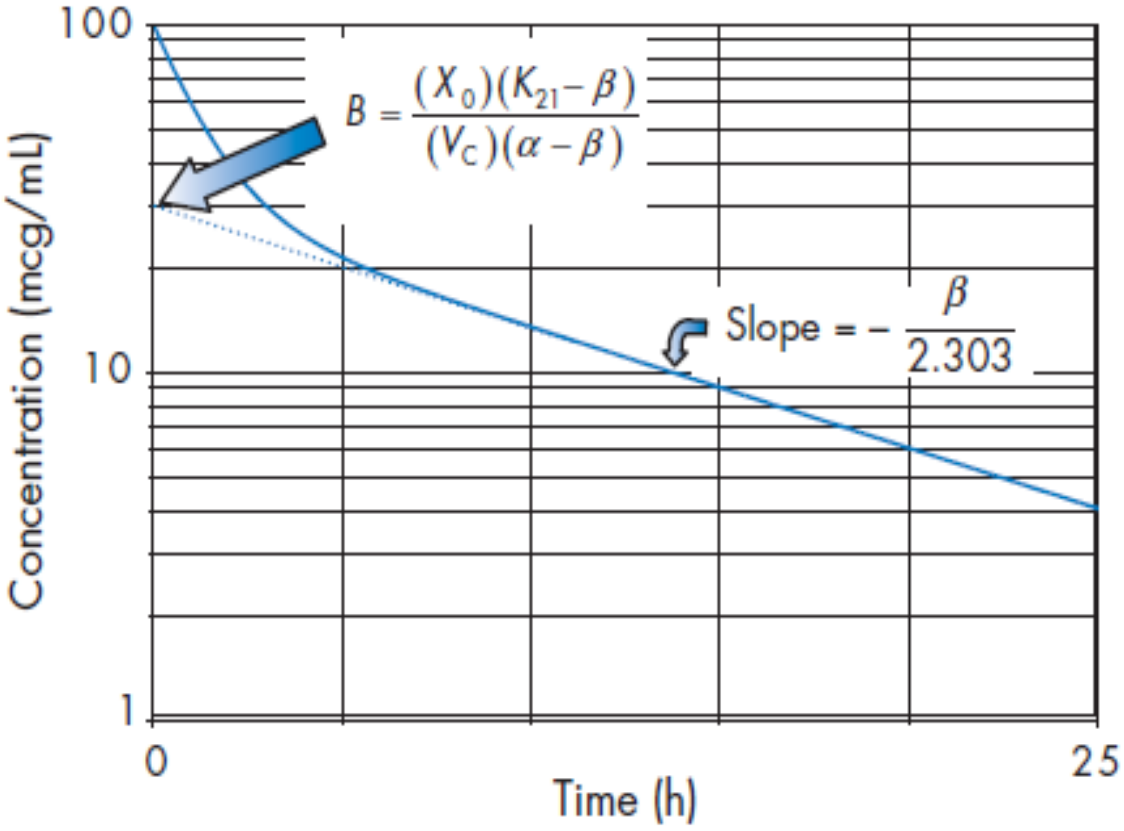
Parameters of the two-compartment pharmacokinetic model

- **A and B** are the hybrid coefficients and have units of concentrations.
- **α** is the hybrid first-order rate constant for the distribution process and has units of time−1.
- **β** is the hybrid first-order rate constant for the elimination process and has units of time−1.
- $\mathbf{t_{1/2}\,\alpha}$ is the half-life for the distribution phase and has units of time.
- $\mathbf{t_{1/2}\,\beta}$ is the half-life for the elimination phase and has units of time.

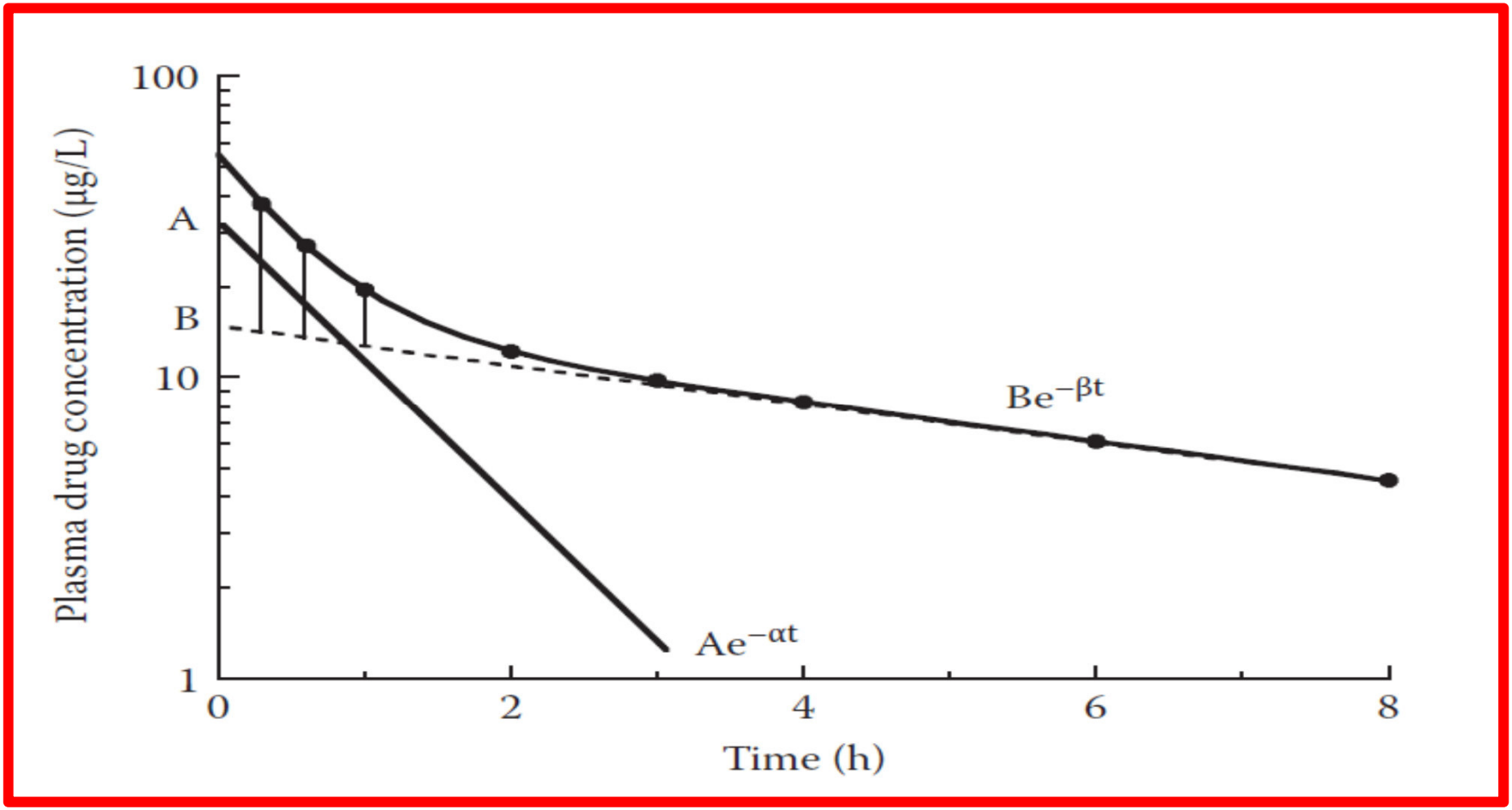
Determination of the postdistribution rate constant (β) and the coefficient (B)

- Postdistribution phase to determine:

1. Determine β from the graph by using the slope
2. The y-axis intercept of the extrapolated line is B



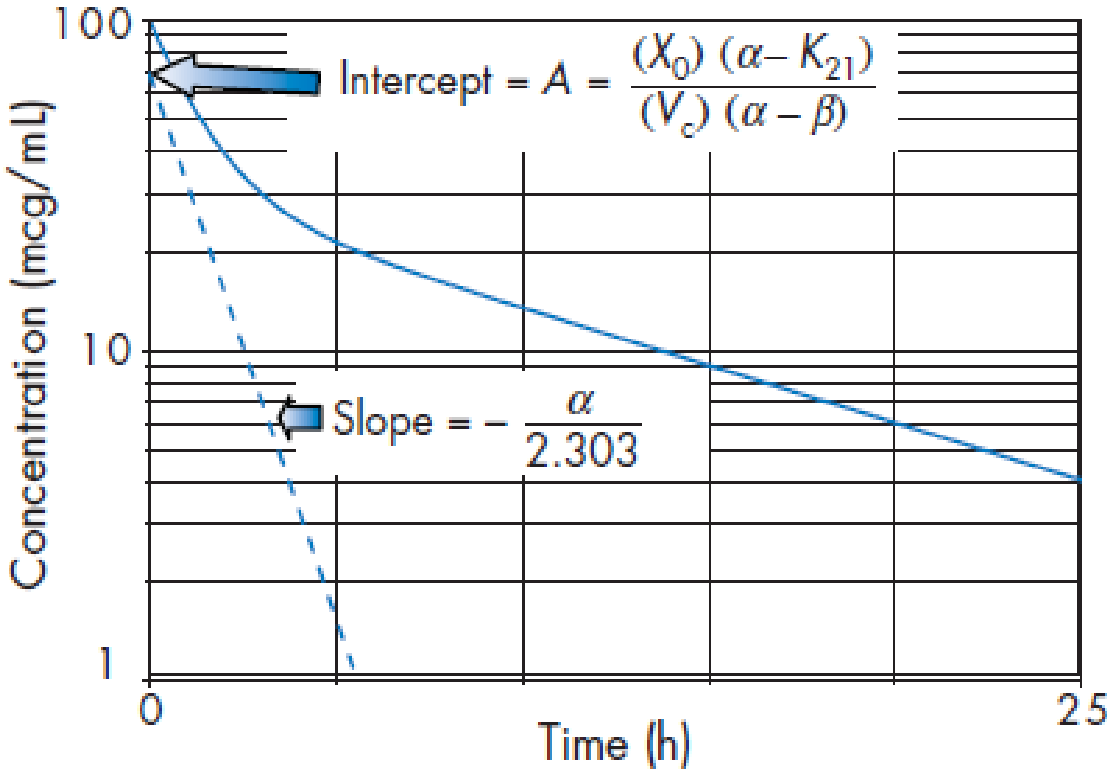
Determination of the distribution rate constant (α) and the coefficient (A)



Determination of the distribution rate constant (α) and the coefficient (A)

- Method of residuals: The difference between measured concentrations and those obtained by extrapolation of the post-distribution line is plotted vs time

1. Determine α from the graph by using the slope
2. The y-axis intercept of the extrapolated line is A



Volume of distribution of the central compartment (V_C)

- Volume of distribution of the central compartment (V_C). This is a proportionality constant that relates the amount of drug and the plasma concentration immediately (i.e. at t=0) following the administration of a drug. **(Cp_0= Dose/Vc)** -------(Cp_0 = A+B)

$$\mathbf{Vc} = \frac{D}{A+B}$$

Determination of micro rate constants: the inter-compartmental rate constants (K21 and K12) and the pure elimination rate constant (K10)

$$\mathbf{K10} = \frac{\boldsymbol{TBC}}{\boldsymbol{Vc}} \qquad K_{10} = \frac{\alpha\beta}{K_{21}}$$

$$\mathbf{K21} = \frac{\boldsymbol{\alpha\beta}}{\boldsymbol{K10}} \qquad K_{21} = \frac{A\beta + B\alpha}{(A+B)}$$

$$\mathbf{K12} = (\boldsymbol{\alpha} + \boldsymbol{\beta}) - (\boldsymbol{K21} + \boldsymbol{K10})$$

Volume of distribution during the terminal phase (Vb or Vβ)

- This is a proportionality constant that relates the plasma concentration and the amount of drug remaining in the body at a time following the attainment of distribution equilibrium, or at a time on the terminal linear portion of the plasma concentration time data.

$$\mathbf{V}\,\boldsymbol{\beta} = \frac{TBC}{\beta} = \frac{K10.VC}{\beta}$$

Volume of distribution at steady state (Vss)

- This is a proportionality constant that relates the plasma concentration and the amount of drug remaining in the body at a time, following the attainment of practical steady state. This volume of distribution is independent of elimination parameters such as K10 or drug clearance.

$$Vss = \frac{Xss}{Css} = \left[\frac{(K_{21} + K_{12})}{K_{21}}\right] Vc$$

$$\mathbf{Vss} = \boldsymbol{Vc}\left(\mathbf{1} + \frac{\boldsymbol{k12}}{\boldsymbol{k21}}\right)$$

The area under the plasma concentration-time curve (AUC)

- Model independent: Trapezoid method
- Model dependent:

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

Total Body Clearance, CL_T

- The CL_T is determined from the dose and the AUC similar to the one-compartment pharmacokinetic model:
  - TBC = Dose/ AUC
  - TBC = $\boldsymbol{K10.VC}$

Problem

- After administration of a single IV bolus dose of 75 mg of a drug to a healthy volunteer, the pharmacokinetics of this drug followed the two-compartment model. The following parameters were obtained:

A = 4.62mg/L	**B = 0.64 mg/L**
$\alpha = 8.94\ h^{-1}$	**$\beta = 0.19\ h^{-1}$**

How to solve

- A , α, B, β دور علي (A > B) & (α > β)
- $t_{1/2\alpha}$, $t_{1/2\beta}$
- AUC, and CL_T.
- V_c
- K_{10}, k_{21}, k_{12}
- $V_{\beta,}$ V_{ss}

Answer

- Calculate $t_{1/2\alpha}$, $t_{1/2\beta}$, k_{12}, k_{21}, k_{10}, V_c, Vd_β, Vd_{ss}, AUC, and CL_T.

$$Cp = Ae^{-\alpha t} + Be^{-\beta t}$$

- $Cp\ (mg/L) = 4.62\ e^{-8.94t} + 0.64\ e^{-0.19t}$
- $t_{1/2\alpha} = 0.693/\alpha = 0.693/\ 8.94 = 0.0775$ h
- $t1/2\beta = 0.693/\ \beta = 0.693/0.19 = 3.65$ h
- $AUC = \frac{A}{\alpha} + \frac{B}{\beta}$
- AUC = 4.62/8.94 + 0.64/0.19 = 3.8 mg.h/L

Answer

- TBC = Dose/ AUC
- CLT= 75/ 3.8 = 19.3 L/h
- **Vc=** $\frac{D}{A+B}$
- Vc= 75/ (4.62+.64) =14.26 L
- k10= TBC/Vc = 19.3/14.2 = 1.353 h^{-1}
- **K21=** $\frac{\alpha\beta}{K10}$ **=** 8.94 × 0.19/1.35 = 1.255 h^{-1}
- k12= $(\alpha+\beta)-(K21+K10)$**=** (8.94 + 0.19) – (1.25+1.35) = 6.52 h^{-1}

- $V\beta = \frac{TBC}{\beta} = \frac{K10.VC}{\beta}$
- Vdβ= 19.3/0.19 = 101.6 L
- $Vss = Vc\left(1 + \frac{k12}{k21}\right)$
- Vdss = 14.25 (1+6.53/1.25) =88.3 L
- **What will be the amount of drug remaining in the body after 8 h?**
  - $Cp(mg/L) = 4.62\ e^{-8.94t} + 0.64\ e^{-0.19t}$
- After 8 hrs. $Cp\ (mg/L) = 4.62\ e^{-8.94(8)} + 0.64\ e^{-0.19(8)} =$ 0.139997 mg/L

Amount = conc. x volume (which volume?? Vdβ)

- Amount = 0.13997 x 101.6 = 14.2 mg

- **C- What will be the plasma concentration when 90% of the administered dose is eliminated?**
- 90 % of the dose is eliminated means that 10 % is still in the body
- 10 % of the dose = $10 \times \frac{75}{100} = 7.5$ mg
- Cp = $\frac{7.5}{101.6} = 0.0738$ mg/L

- **D- Which of the pharmacokinetic parameters above mg will change with the increase in the dose to 150?**
- A, B, (CP0) & AUC. The rest remain constant.
- The equation will be: Cp (mg/L)= $9.24\ e^{-8.94t} + 1.28\ e^{-0.19t}$

Example 2

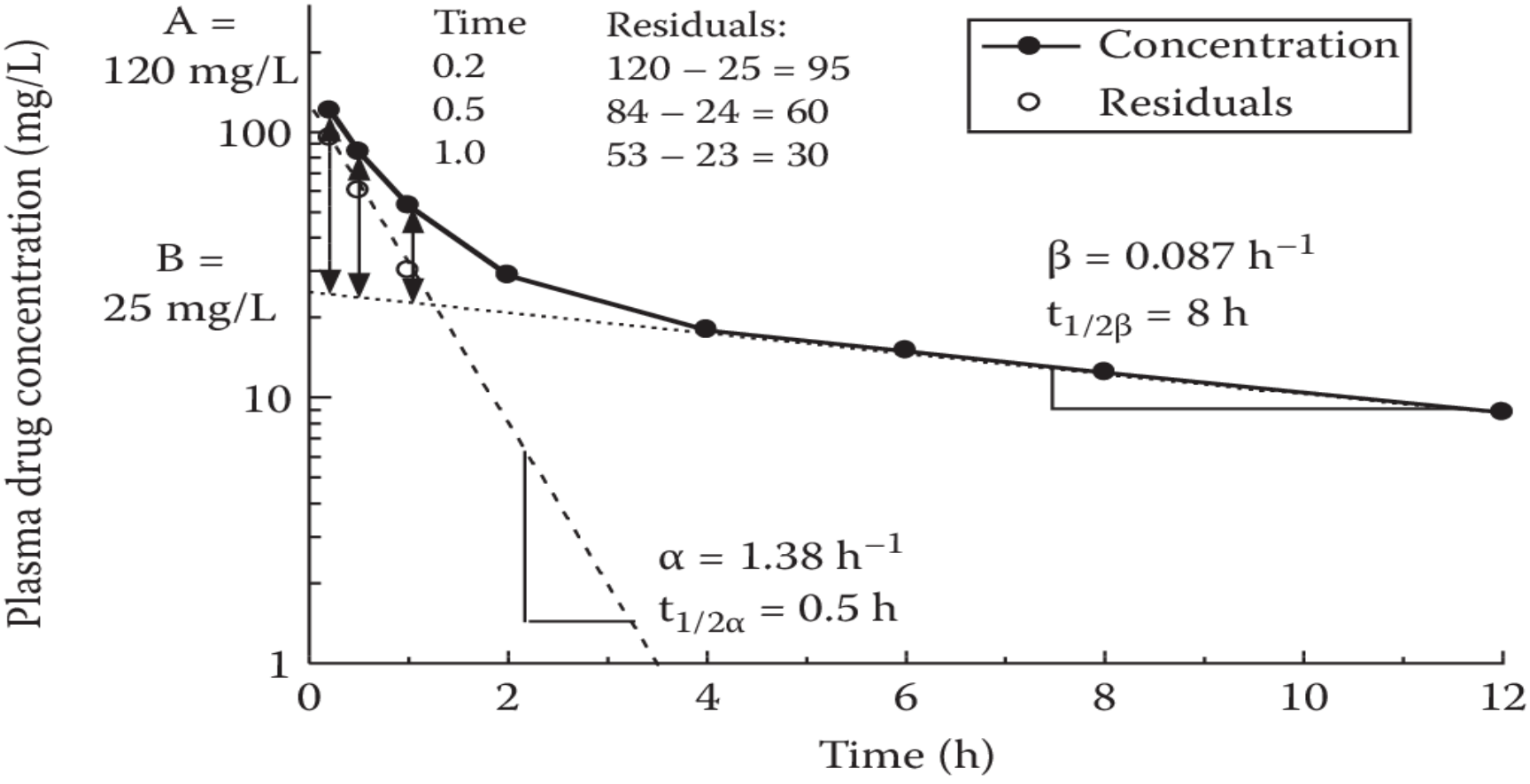
- After a single IV bolus dose of 1000 mg of an antiarrhythmic drug, the following concentrations were obtained:

Time (hr)	Concentration (mg/l)
0.2	120
0.5	84
1	53
2	29
4	18
6	15
8	12.5
12	8.8

Using the method of residual, calculate the following parameters: $\alpha t_{1/2}$, $\beta\ t_{1/2}$, k_1,k_2, k_3, Vc, vd_{β}, vd_{ss}, AUC and CL_T

- Plot the concentration versus time on a semilog scale.
- Identify the best line that represents the drug elimination process.
- The y-intercept is equal to B. The hybrid elimination rate constant (β) and β-half-life can be determined from the line.
- Calculate the residuals from the difference between the plasma drug concentration and the values on the extrapolated line during the distribution phase.
- Plot the residuals versus time, and draw the best line that goes through the points.
- The y-intercept of this line is equal to A. The hybrid distribution rate constant α and α-half-life can be determined from this line.

Application of the method of residuals in solving the example.



Answer

- A = 120 mg/L
- B = 25 mg/L
- $\alpha = 1.38\ hr^{-1}$ $t\alpha_{1/2}$= **0.5 h**
- $\beta = 0.078\ hr^{-1}$ $t\beta_{1/2}$= **8 hr**
- AUC= $\frac{A}{\alpha} + \frac{B}{\beta} = \frac{120}{1.38} + \frac{25}{0.078}$= 374.4 mg.hr/L
- TBC = Dose/ AUC = 1000/374.4= 2.67 L/h
- Vc= D/(A+B) = 1000/(120+25)=6.9 L

Answer

- k10= TBC/Vc = 2.67/6.7 = 0.387 h^{-1}
- **K21**$= \frac{\alpha\beta}{K10}$ **=** 1.38 × 0.087/0.387 = 0.310 h^{-1}
- k12= $(\alpha + \beta) - (K21 + K10)$**=** (1.38+ 0.087) – (0.310+0.387) = 0.77 h^{-1}
- **V** $\beta = \frac{TBC}{\beta}$ **=** $\frac{K10.VC}{\beta}$**=** $\frac{2.67}{0.087}$ **= 30.7 L**
- **Vss**$= Vc\left(1 + \frac{k12}{k21}\right)$
- Vdss = 6.7 (1+0.77/0.310) =88.3 L

What will be the amount of drug remaining in the body after 15 hours?

- $Cp = Ae^{-\alpha t} + Be^{-\beta t}$
- $Cp(mg/L) = 120\ e^{-1.38 * 15} + 25\ e^{-0.087 * 15} = 6.87$ mg/L
- Amount of the drug in the body during the elimination phase = Cp × Vdβ
- Amount15 h = Cp15 h × Vdβ = 6.78 mg/L × 30.7 L = 208 mg

Problem 1

- After the administration of a single IV bolus dose of 100 mg lidocaine, the plasma conc-time profile can be described from the following equation :

$$Cp(mg/l) = 2.6\ e^{-5t} + 0.52\ e^{-0.4t}$$

- Calculate t1/2α, t1/2β, k12, k21, k10, Vc, Vdβ, Vdss, AUC, and CLT.
- Calculate the amount of lidocaine remaining in the body after 4 hours
- What will be the plasma lidocaine concentration when 90 % of the dose is eliminated

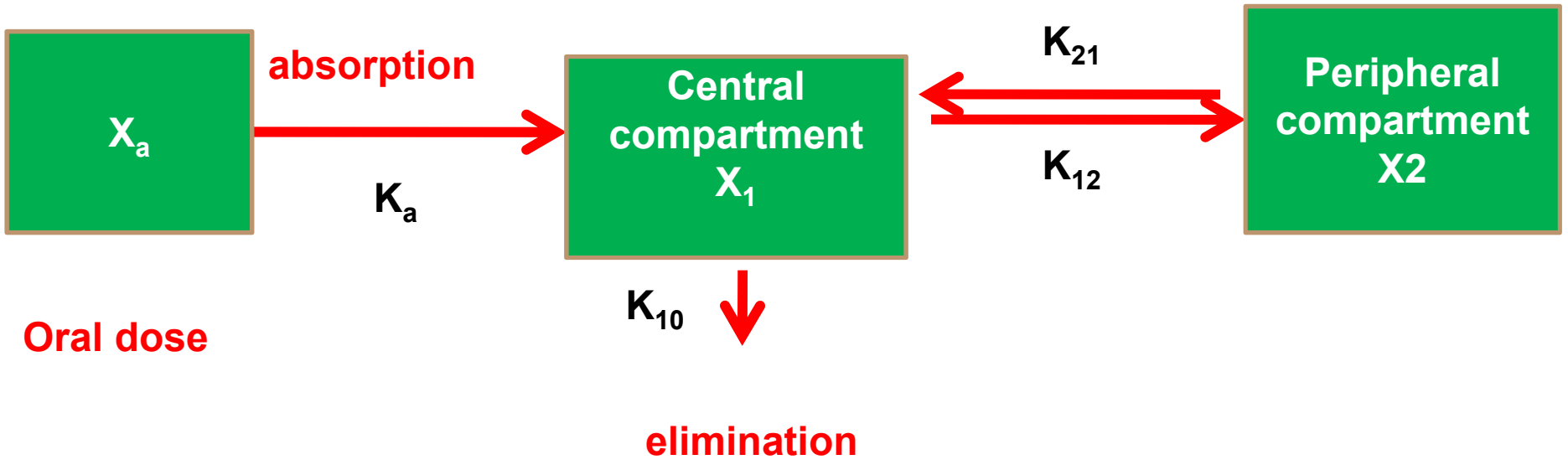
Problem 2

- After an iv bolus dose of 250 mg acyclovir, the plasma conc-time profile can be expressed by the following expression:

$$\mathbf{Cp(mg/L) = 22\ e^{-2t} + 6\ e^{0.23t}}$$

- Which of the PK parameters will change when a dose of 500 acyclovir is administered? And what will be the new equation?

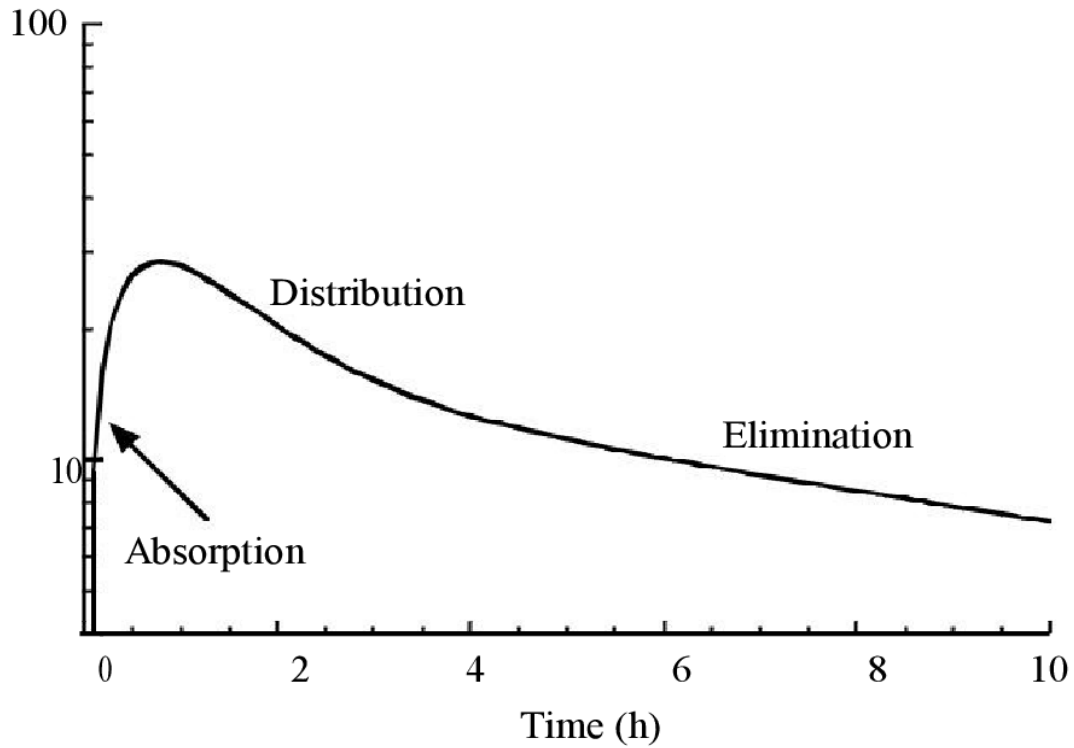
Two Compartment Extravascular



$$\frac{dX_1}{dt} = K_a X_a + K_{21} X_2 - K_{12} X_1 - K_{10} X_1$$

$$\frac{dX_2}{dt} = K_{12} X_1 - K_{21} X_2$$

Two Compartment Extravascular



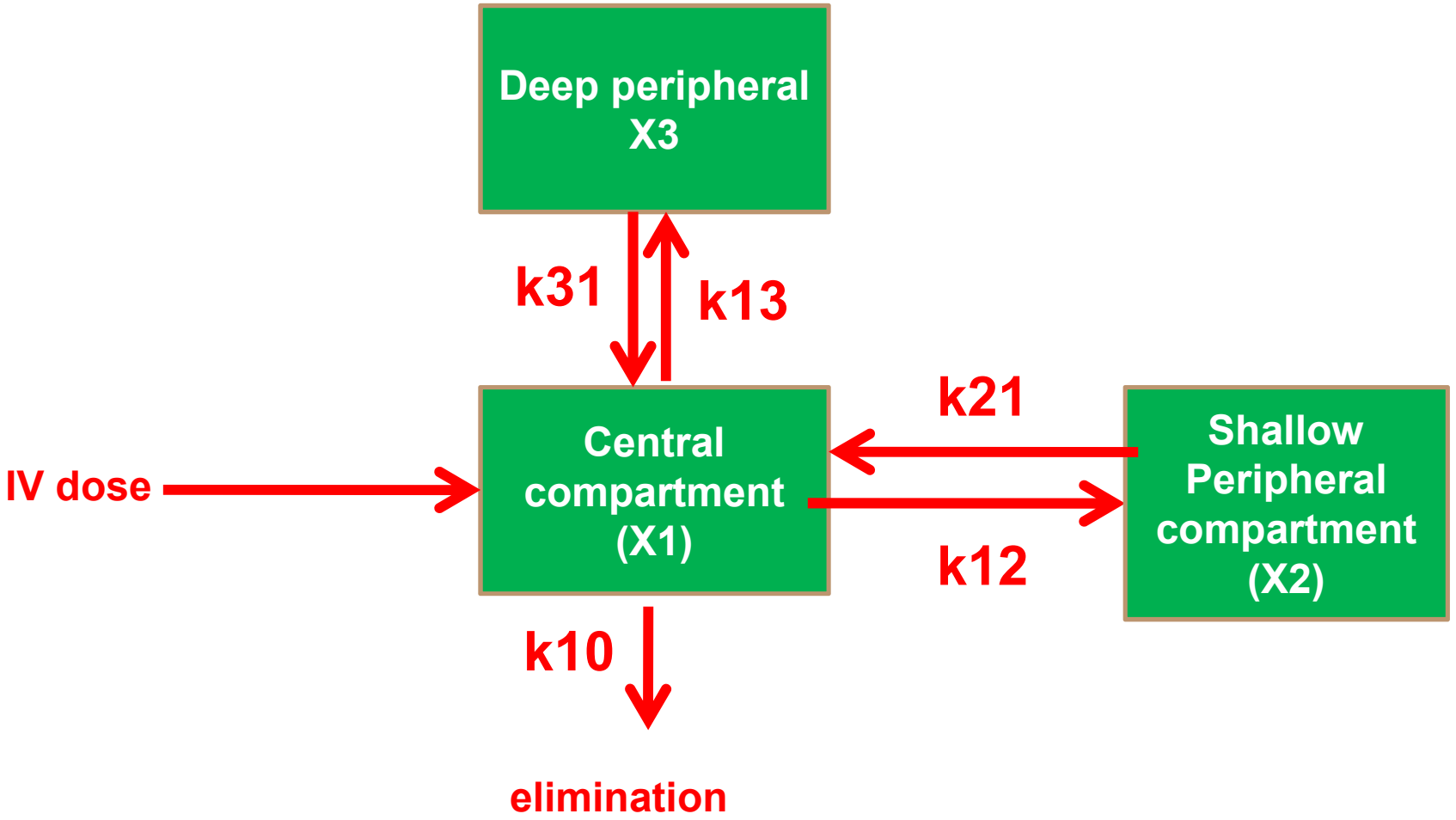
Plasma concentration–time profile for a drug that follows two- compartment pharmacokinetic model after administration of a single oral dose.

Two Compartment Extravascular

- If the drug is rapidly absorbed, the decline in the plasma concentration–time profile after the end of the absorption phase will be **biexponential**, reflecting the distribution and the elimination phases.

- However, if the drug absorption is slow, the plasma drug concentration–time profile after oral administration of drugs that follow two-compartment pharmacokinetic model can be described by a **triexponential equation** that represents the absorption, distribution, and elimination processes.

A schematic representation of Three-compartment models consisting of a central and a peripheral compartments.



Triexponential Equation: $C_1 = Ae^{-\alpha t} + Be^{-\beta t} - Ce^{-\gamma t}$


QUESTIONS?

Metabolites and urinary excretion kinetics

Dr. Mahmoud Samy

Lecturer of Clinical Pharmacy

Outlines

- Metabolite pharmacokinetics
- Renal excretion PK of drugs
- Methods to compute PK parameters from urinary data
- Determination of the Drug Bioavailability from the Cumulative Amount Excreted in Urine

Drug Metabolism

- Drug metabolism, also referred to as drug biotransformation or drug detoxification, usually involves enzymatic modification of the chemical structure of a drug to form one or more metabolites

- This modification of the drug chemical structure causes change (increase or decrease) in the pharmacological and adverse effects of the drugs.

Drug Metabolism

- The metabolites are usually more polar than their parent drugs and are excreted rapidly from the body by the different excretion mechanisms.
- However, there are exceptions to this general rule where the metabolite half-life is longer than that of the parent drug.
- Drug metabolism is usually mediated by specialized enzyme systems that can be induced or inhibited resulting in modification of the rate of the drug metabolic process.

Classification of the Metabolic Reactions:

- **Phase I Metabolic Reactions:**
- These metabolic reactions are also known as functionalization reactions or non-synthetic reactions.
- They involve the introduction of polar function groups such as hydroxyl group, primary amines, carboxylic acids, etc., to form more polar metabolites.
- The most common phase I reactions include oxidation, reduction, and hydrolysis.
- These oxidation reactions are mediated mainly by the **cytochrome P450 (CYP450)** monooxygenase enzyme system in addition to other enzyme systems.

Classification of the Metabolic Reactions:

- **Phase II Metabolic Reactions**
- These metabolic reactions are also known as conjugation reactions or synthetic reactions.
- Phase II reactions usually involve formation of conjugates between the drug and other compounds such as glucuronic acid, glutathione, amino acids, and others.
- The products of phase II metabolic reactions have increased molecular weight and are usually inactive.

Cytochrome P450

- CYP450 is a superfamily of metabolizing enzymes that are responsible for approximately 75% of the total drug metabolism in humans.
- It contains heme cofactors, so it is considered a hemoprotein.

CYP 3 A 4 (Nomenclature)

- CYP: GENE for mammalian cytochrome
- 3: family (> 40% identical in amino acid sequence)
- A: subfamily (> 70% identical in amino acid sequence)
- 4: specific enzyme

Cytochrome P450

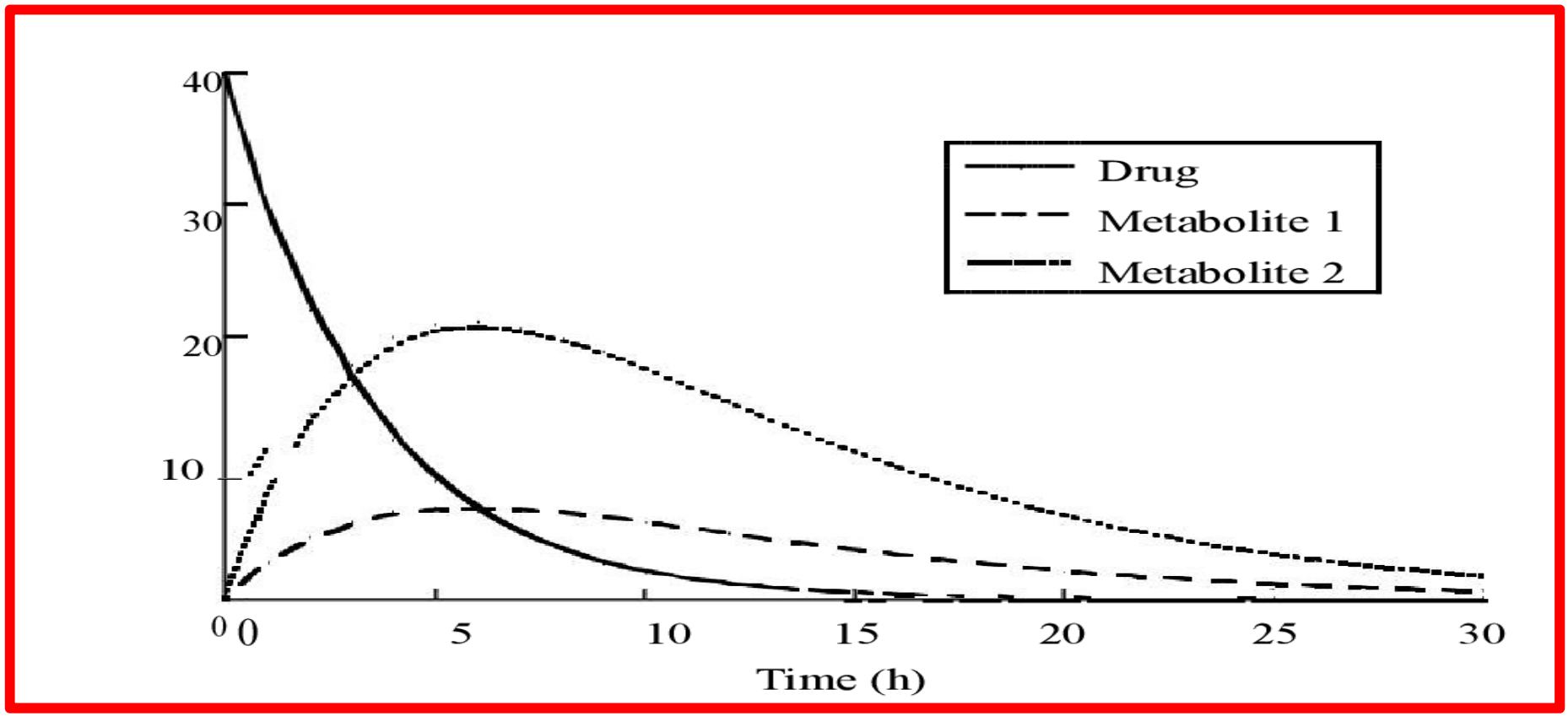
- The CYP metabolizing enzymes are present in many organs including the liver, kidney, lung, gastrointestinal tract, brain, nasal mucosa, and skin.

- However, the special importance of the role of hepatic CYP enzymes in drug metabolism arises from the existence of large amount of enzymes in the liver and the high hepatic blood flow, which exposes large amount of the drug in the systemic circulation to the hepatic CYP enzymes, and also the contribution of the hepatic drug metabolism to the pre-systemic metabolism of orally administered drugs.

Metabolite pharmacokinetics

- Drugs can be metabolized through different metabolic pathways to one or more metabolites, and more than one metabolite can be detected simultaneously in the body.
- Some drugs are metabolized to different metabolites through parallel metabolic pathways. This means that the different metabolites are formed from the parent drug, and the formed metabolites are then eliminated from the body (**parallel metabolism**).
- In some other drugs, the formed metabolite is further metabolized to another metabolite, which is then excreted from the body (**sequential metabolism**).

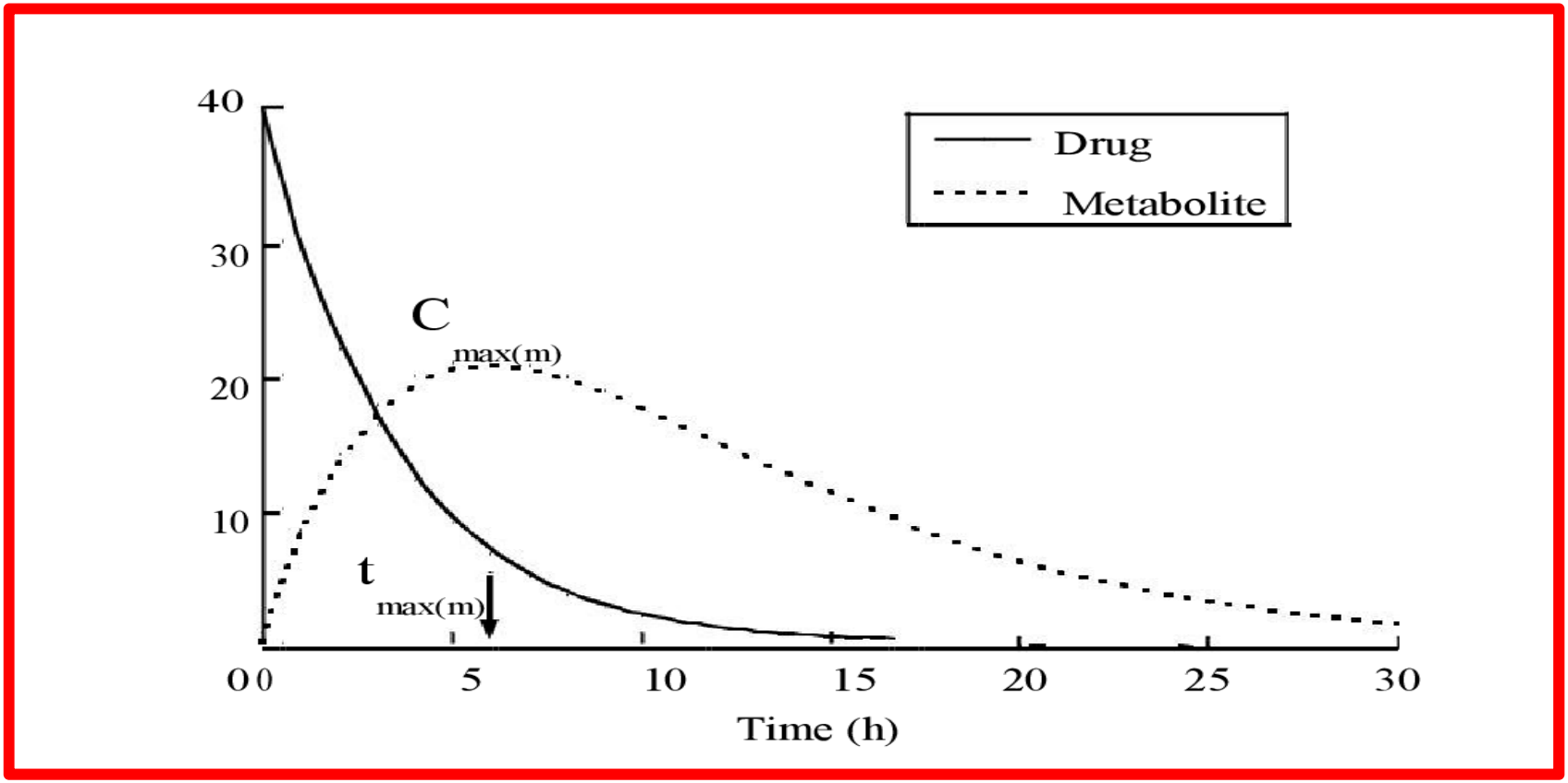
Metabolite pharmacokinetics



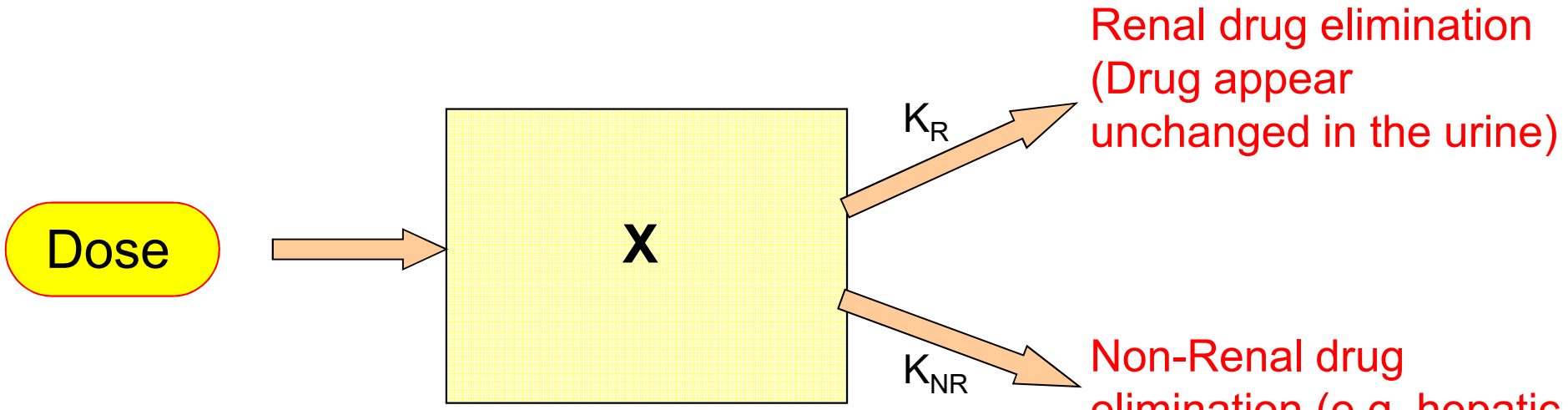
Metabolite pharmacokinetics

- After drug administration, the metabolite formed is a new chemical entity that has pharmacokinetic behavior different from that of the parent drug.
- The elimination rate constant, half-life, volume of distribution, clearance, and area under the curve for the metabolite are different from the parameters of the parent drug.
- So the plasma concentration–time profile for the drug and the metabolite are usually different because of the difference in the pharmacokinetic parameters for the drug and metabolite.

Metabolite pharmacokinetics



Renal and Non-renal elimination pathways



$$CL_T = CL_R + CL_M + CL_L + CL_B$$

Urinary Excretion:

- This means that the first-order elimination rate constant for the overall elimination process is the sum of the rate constants for the different elimination pathways.

$$k = ke + k\,m + kl + kb$$

$$TBC = k.Vd = ke.Vd + k\,m.Vd + kl\,.Vd + kb.Vd$$

<u>So if the drug in excreted in urine only</u>

$$Ke = TBC/Vd = \text{renal clearance}/Vd$$

Renal excretion of drugs

- The renal excretory function starts with the filtration of the blood reaching the glomeruli, which occurs normally at a rate of 120 mL/min.
- The three processes involved in the renal excretion of drugs are the glomerular filtration (GF) (small molecules only), active tubular secretion, and tubular reabsorption.

Renal excretion rate = Rate of filtration + Rate of active secretion - Rate of reabsorption

Renal excretion of drugs

- If the renal clearance equal zero, this mean that the drug is completely metabolized.
- If the renal clearance equal 120 ml/min, this mean that the drug is completely excreted by GF.
- If the renal clearance more than 120 ml/min, this means that the drug is excreted by GF & Active secretion.
- If the renal clearance less than 120 ml/min, this means that some of the drug is reabsorbed.

Methods to compute PK parameters from urinary data

1. the “amount remaining to be excreted” method (ARE); also known as the sigma-minus method

2. The rate of excretion method.

Determination of the renal excretion rate

- Consider a drug that is eliminated by first-order processes, including renal excretion. The renal excretion rate of the drug at any time is equal to

$$\frac{dAe}{dt} = \mathbf{Ke\ A} = \frac{\Delta Ae}{\Delta t}$$

- where
- A_e is the amount of the drug excreted in urine
- K_e is the first-order renal excretion rate constant
- A is the amount of the drug in the body

Determination of the renal excretion rate

- To construct the drug renal excretion rate versus time plot, the experimentally determined renal excretion rate for the drug during each urine collection interval is plotted against the time corresponding to the middle of the urine collection interval (tmid).
- This is because the calculated drug renal excretion rate represents the average rate of renal drug excretion during the urine collection interval.

Determination of the renal *Clearence*

- **Therefore,**

$$\frac{\Delta Ae}{\Delta t} = \mathbf{Ke\ A}_{\mathbf{tmid}} = \mathbf{Ke.Vd.Cp}\ \boldsymbol{tmid}$$

- here At-mid is the amount of drug in the body at the midpoint of the urine collection interval, which is approximately equal to the average amount of the drug during the urine collection interval.

Therefore,

$$\frac{\Delta Ae/\Delta t}{\mathbf{Cp}\ \boldsymbol{tmid}} = \mathbf{Ke.Vd} = \boldsymbol{Renal\ Clearence}$$

Determination of the renal clearance

- Cp tmid is the drug plasma concentration at the midpoint of the urine collection interval.

- This means that the drug renal clearance (CLR) can be determined by collecting urine over a certain interval and also obtaining a plasma sample at the middle of the urine collection interval

$$\frac{\Delta Ae/\Delta t}{\mathrm{Cp}\ tmid} = \mathrm{Ke.Vd} = Renal\ Clearence$$

Determination of the renal excretion rate

- The renal excretion rate versus time profile is parallel to the blood drug amount-time profile and the blood drug concentration–time profile after a single IV administration when the drug elimination follows first-order kinetics
- Since the drug renal excretion rate at any time is the product of ke and the amount of the drug in the body, the drug renal excretion rate–time profile is always parallel to the blooddrug amount-time profile and drug concentration–time profile.

$$\frac{\Delta Ae}{\Delta t} = Ke\, A_{tmid} = Ke.Vd.Cp\ tmid$$

Determination of the renal excretion rate

- Slope of the drug renal excretion rate versus time plot on the semilog scale is equal to −k/2.303 and the y-intercept is equal to ke Dose.

- The elimination rate constant, k, can be determined from the slope of the plot, the elimination half-life can be calculated from k or estimated graphically by determining the time required for any value on the line to decrease by 50%, and ke can be determined from the y-intercept.

Cumulative amount of the drug excreted in urine

- The drug renal excretion rate–time profile can be described by following Equation.
- $$\frac{\Delta Ae}{\Delta t} = \mathbf{Ke.A} = \mathbf{Ke.Ao.}\, e^{-Kt}$$
- Where A_O: the total amount of the drug in the body at time zero.
- The total amount of the drug excreted in urine is determined by integrating this equation and substituting time by infinity:

Upon integration,

$$\mathrm{Ae} = \frac{Ke}{K} Ao(1 - e^{-Kt})$$

- At time ∞

$$\mathrm{A_{e\,\infty}} = \frac{Ke}{K} Ao = \frac{Ke}{K} Dose$$

where $A_{e\,\infty}$ is the total amount of the drug excreted in urine when all the drug is eliminated from the body.

Therefore

$$\boldsymbol{Ke = \frac{K.\mathrm{Ae}_{\infty}}{Dose}}$$

$$\boldsymbol{Renal\ clearance = Ke.Vd = \frac{K.Vd.A_{e\,\infty}}{Dose} = \frac{A_{e\,\infty}}{AUC\ iv \int 0 - \infty}}$$

Determination of the pharmacokinetic parameters from the renal excretion rate data

- Elimination Rate Constant and Half-Life:
- Renal Excretion Rate Constant:

The fraction of dose excreted unchanged in urine after IV administration, f and k, are known (**f = ke/k**) or **from the y-intercept (ke*D)**.

- Volume of Distribution: **CLR = keVd**
- Renal Clearance:

CLR = keVd OR CLR = Ae∞/AUC OR f = CLR/CLT

Determination of the Drug Bioavailability from the Cumulative Amount Excreted in Urine

- Fraction of Dose Excreted Unchanged in Urine: **ke/k, CLR/CLT, or Ae∞/FDose**.

- F absolute =(Ae ∞ (oral))/(Ae ∞ (iv))

- F relative =(Ae ∞ (test))/(Ae ∞ (reference))

Example

- After an IV injection of 500 mg of a new drug to a patient, the following data were obtained:

Collection Interval (h)	Urine Volume (mL)	Urine Concentration (mg/mL)	$C_{pt\text{-mid}}$ (mg/L)
0–2	119	0.60	22.3
2–4	81	0.70	17.7
4–8	160	0.50	12.5
8–12	220	0.23	7.88
12–18	284	0.15	4.42
18–24	212	0.10	2.21

Estimate the biological half-life of this drug in this patient using the urinary excretion data.
Estimate the renal clearance of this drug in this patient & Calculate TBC
Calculate the fraction of the administered dose excreted unchanged in the urine from the available data.
Assume that the unexcreted portion of drug is metabolized determine the metabolic rate constant.
Estimate how much drug is in the body 5 days after the dose was administered.

The rate method (Example)

Time interval (h)	Volume (mL)	Concentration (mg/mL)
0–2	119	0.60
2–4	81	0.70
4–8	160	0.50
8–12	220	0.23
12–18	284	0.15
18–24	212	0.10

The rate method:

1- Calculate amount of drug eliminated

Time interval (h)	Volume (mL)	Concentration (mg/mL)	Drug amount in the urine (mg) ΔAe
0–2	119	0.60	71.4
2–4	81	0.70	56.7
4–8	160	0.50	80.0
8–12	220	0.23	50.6
12–18	284	0.15	42.6
18–24	212	0.10	21.2

Amount = volume*conc

The rate method:

2- Calculate the change in time

Time interval (h)	Volume (mL)	Concentration (mg/mL)	Drug amount in the urine (mg)	Δt (hr)
0–2	119	0.60	71.4	2
2–4	81	0.70	56.7	2
4–8	160	0.50	80.0	4
8–12	220	0.23	50.6	4
12–18	284	0.15	42.6	6
18–24	212	0.10	21.2	6

The rate method:

3- Calculate the rate of urinary excretion

Time interval (h)	Volume (mL)	Concentration (mg/mL)	Drug amount in the urine (mg)	Δt (hr)	
0–2	119	0.60	71.4	2	35.7
2–4	81	0.70	56.7	2	28.35
4–8	160	0.50	80.0	4	20.00
8–12	220	0.23	50.6	4	12.65
12–18	284	0.15	42.6	6	7.10
18–24	212	0.10	21.2	6	3.53

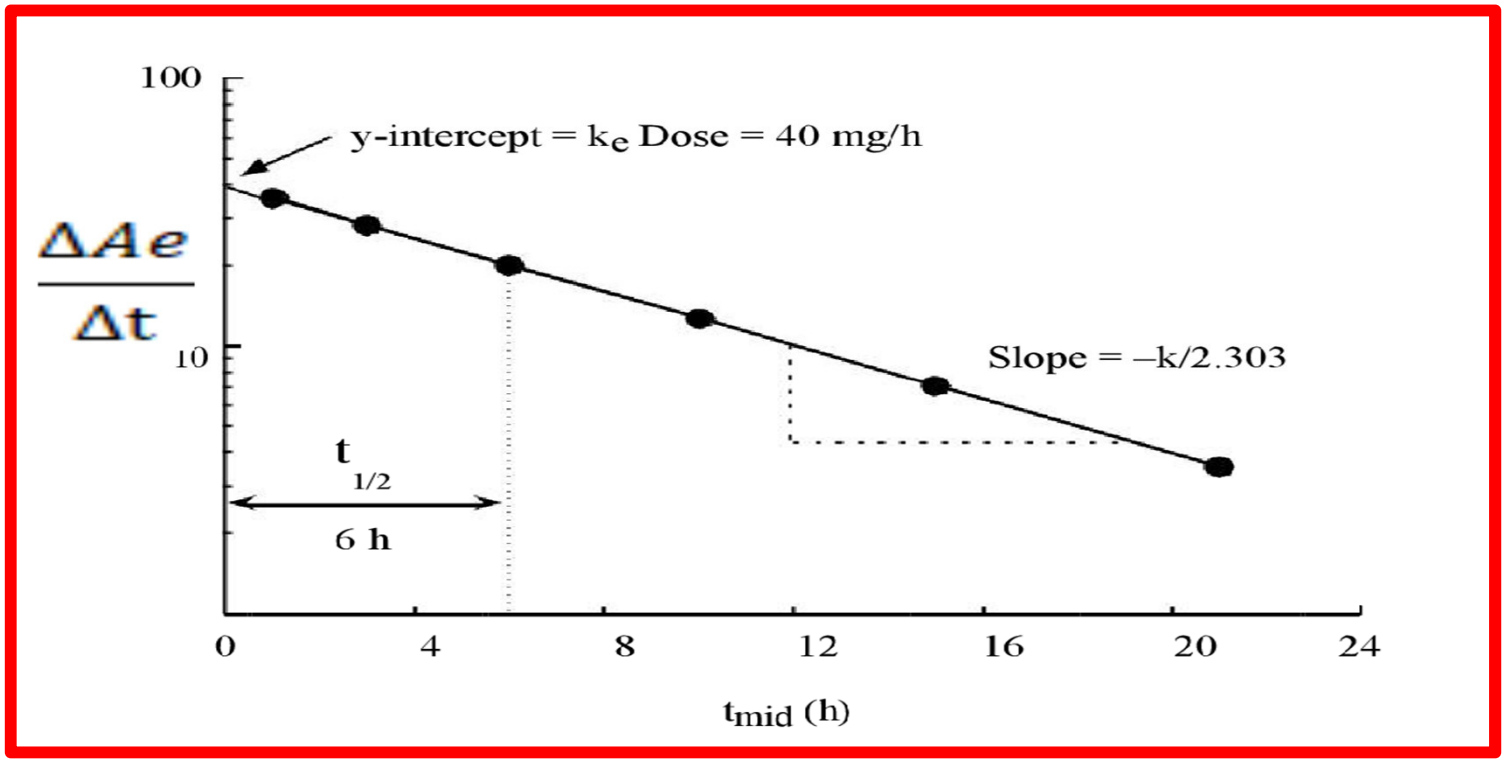
The rate method:

3- Calculate the rate of urinary excretion

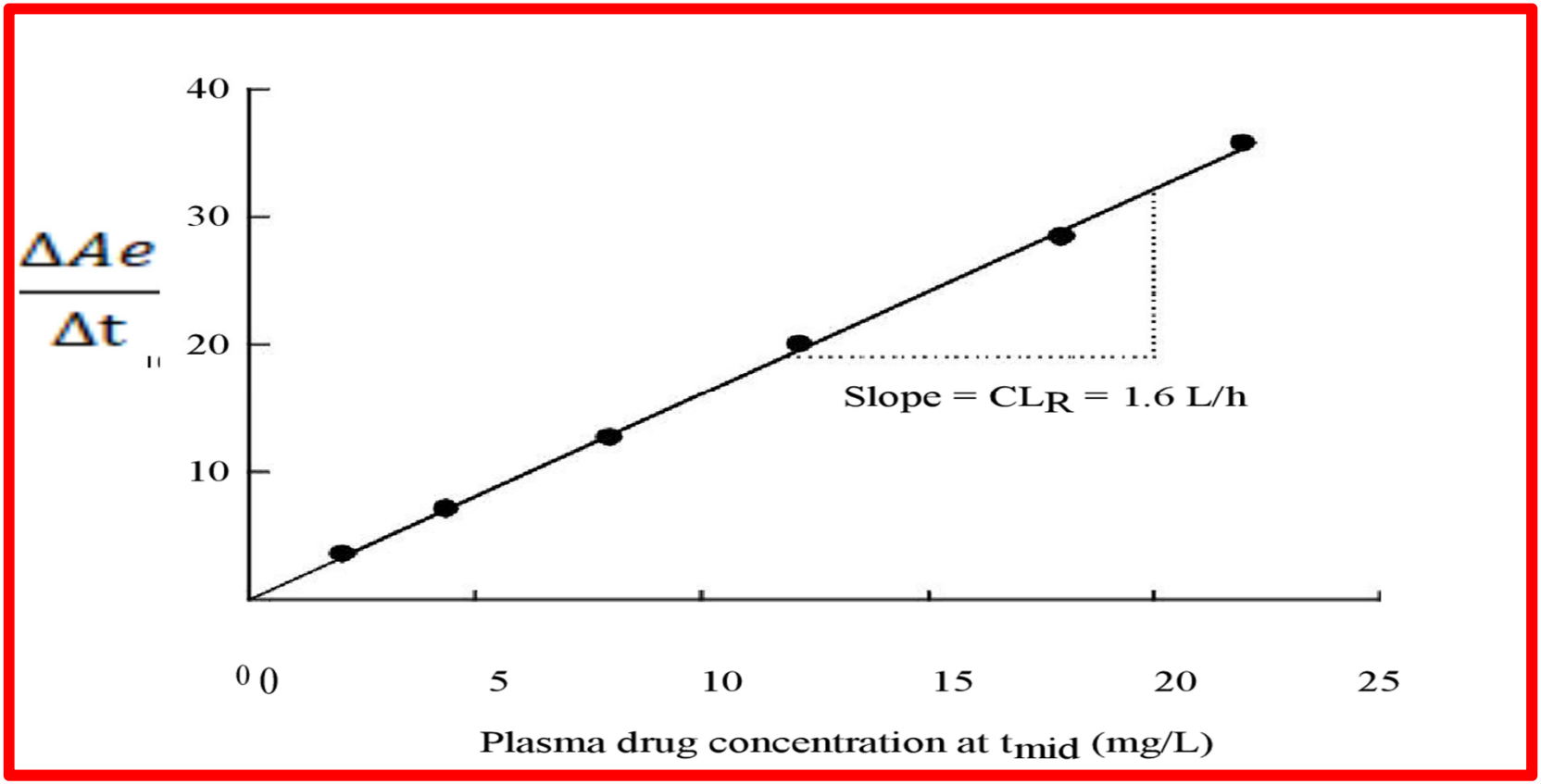
Time interval (h)	Volume (mL)	Concentration (mg/mL)	Drug amount in the urine (mg)	Δt (hr)		Cpt-mid (mg/L)	t-mid (hr)
0–2	119	0.60	71.4	2	35.7	22.3	1
2–4	81	0.70	56.7	2	28.35	17.7	3
4–8	160	0.50	80.0	4	20.00	12.5	6
8–12	220	0.23	50.6	4	12.65	7.88	12
12–18	284	0.15	42.6	6	7.10	4.42	15
18–24	212	0.10	21.2	6	3.53	2.21	21

The half-life can be estimated from the renal excretion rate versus time plot as in Figure.

The half-life is = 6 h, k = 0.1155 h^{-1}. The elimination rate constant can also be determined from the slope of the line.



The CLR can be estimated from the slope of the renal excretion rate versus plasma concentration plot. The renal clearance = 1.6 L/h



Calculate the fraction of the administered dose excreted unchanged in the urine from the available data.

- The fraction excreted unchanged in urine can be calculated from the ratio of the (ke/k) or (CLR/CLT).

- y-intercept = ke Dose = k"e 500mg = 40mg/h So, ke = $0.08h^{-1}$
- f = Ke /k = 0.08/0.1155= 0.69
- TBC = CLR/f = 1.6 / 0.69 = 2.32 L/ hr

Answer

- Assume that the unexcreted portion of drug is metabolized determine the metabolic rate constant.
- $K = ke + km$
- $Km = k - ke = 0.1155 - 0.08 = 0.0355\ hr^{-1}$
- Estimate how much drug is in the body 5 days after the dose was administered.

$$A = A_o \cdot e^{-Kt}$$

$$A = 500 \cdot e^{-0.1155 \times 5}$$

Example

- After an IV injection of 8 mg/kg of a new drug in 24 kg, 10 years patient, the following data were obtained:

Collection Interval (days)	Urine Volume (mL)	Urine Concentration (mg/L)
0–1	600	43.3
1–2	450	46.4
2–4	1340	23.6
4–6	1420	14.4
8–10	1280	7.34
12–14	1300	3.38

Estimate the biological half-life of this drug in this patient using the urinary excretion data.
Estimate the renal excretion rate constant.
If the initial drug conc. In plasma was 9.2 mg/L, what is the renal clearance?

The rate method (Example)

Time interval (h)	Volume (mL)	Concentration (mg/L)
0–1	0.6	43.3
1–2	0.45	46.4
2–4	1.34	23.6
4–6	1.42	14.4
8–10	1.28	7.34
12–14	1.30	3.38

The rate method:

1- Calculate amount of drug eliminated

Amount = volume*conc

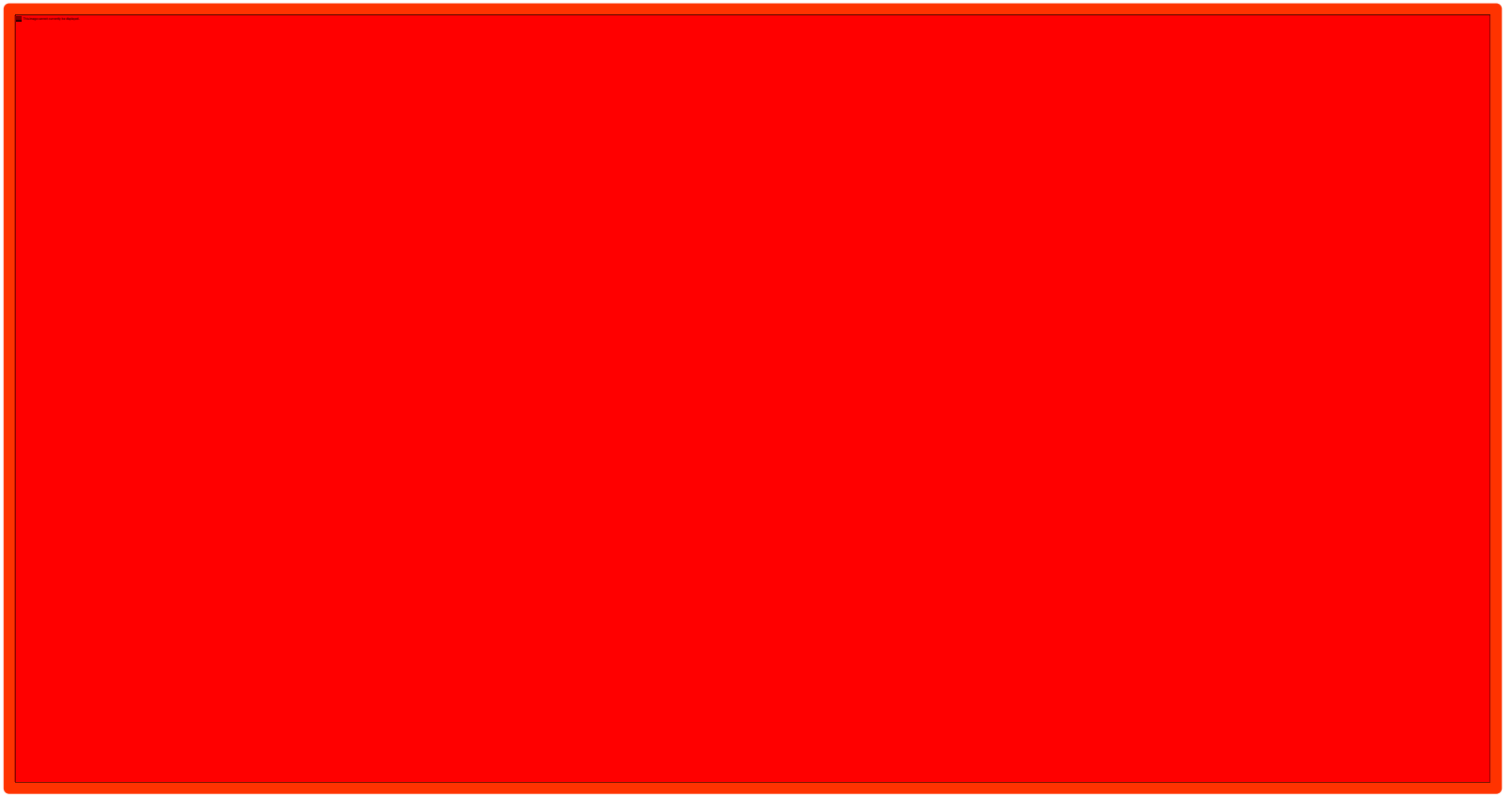
Time interval (h)	Volume (L)	Concentration (mg/L)	Drug amount in the urine (mg) ΔAe
0–1	0.6	43.3	25.9
1–2	0.45	46.4	20.8
2–4	1.34	23.6	15.8
4–6	1.42	14.4	10.2
8–10	1.28	7.34	4.6
12–14	1.30	3.38	2.1

The rate method:

2- Calculate the change in time

Time interval (h)	Volume (L)	Concentration (mg/L)	Drug amount in the urine (mg)	Δt (hr)
0–1	0.6	43.3	25.9	1
1–2	0.45	46.4	20.8	1
2–4	1.34	23.6	15.8	2
4–6	1.42	14.4	10.2	2
8–10	1.28	7.34	4.6	2
12–14	1.30	3.38	2.1	2

The half-life can be estimated from the renal excretion rate versus time plot as in Figure. The half-life is = 3.3 day



Answer

- Estimate Ke
- y-intercept = ke Dose = k"e (8 * 24) = 29 mg/h
  So, ke = 0.15 h^{-1}
- If the initial drug conc. In plasma was 9.2 mg/L, what is the renal clearance?
- Cpo= 9.2 mg/L, Vd = D/Cpo=(8 *24)/9=20.86 L
- **CLR = keVd = 0.15 * 20.86 = 3.15 L/Day**

Example

- If a drug was administered in a dose of 1 gm and the total amount excreted by the kidney was 910 mg & the renal clearance was 4.5 L/hr. Calculate the TBC?
- $$\boldsymbol{Renal\ clearence} = \frac{K.Vd.A_{e\infty}}{Dose} = \frac{TBC.A_{e\infty}}{Dose}$$
- TBC = 4.5*1000/910 = 4.94 **L/hr**

Practical 7.1

- A patient received a single 1000 mg IV dose of an antibiotic. Urine and plasma samples were collected and the following results were obtained:

Collection Interval (h)	Urine Volume (mL)	Urine Concentration (ug/mL)	^{Cp}t-mid (ug/mL)
0–1	67	2.1	Not determined
1–2	70	1.01	Not determined
2–4	100	0.50	0.5 ug/ml at time 3
4–8	250	0.05	Not determined

Calculate the average renal execretion rate of the drug during the first urine collection interval (0-1 hr).
Calculate the average renal execration rate of the drug during the third urine collection interval (2-4 hr).
Calculate the renal clearance of this drug in this patient.
The half life of this drug is 1 hr. what is the elimination rate constant of this drug?
The slope of renal excretion rate vs time plot on a semilog graph paper?

The rate method (Example)

Time interval (h)	Volume (mL)	Concentration (ug/mL)
0–1	67	2.1
1–2	70	1.01
2–4	100	0.50
4–8	250	0.05

The rate method:

1- Calculate amount of drug eliminated

Amount = volume*conc

Time interval (h)	Volume (mL)	Concentration (ug/mL)	Drug amount in the urine (ug) ΔAe
0–1	67	2.1	140.7
1–2	70	1.01	70.7
2–4	100	0.50	50
4–8	250	0.05	12.5

The rate method:

2- Calculate the change in time

Time interval (h)	Volume (mL)	Concentration (ug/mL)	Drug amount in the urine (ug)	Δt (hr)
0–1	67	2.1	140.7	1
1–2	70	1.01	70.7	1
2–4	100	0.50	50	2
4–8	250	0.05	12.5	4

The rate method:

3- Calculate the rate of urinary excretion

Time interval (h)	Volume (mL)	Concentration (ug/mL)	Drug amount in the urine (ug)	Δt (hr)	
0–1	67	2.1	140.7	1	140.7
1–2	70	1.01	70.7	1	70.7
2–4	100	0.50	50	2	25
4–8	250	0.05	12.5	4	3.125

The rate method:

3- Calculate the rate of urinary excretion

Time interval (h)	Volume (mL)	Concentration (ug/mL)	Drug amount in the urine (ug)	Δt (hr)		Cpt-mid (ug/mL)	t-mid (hr)
0–1	67	2.1	140.7	1	140.7	ND	0.5
1–2	70	1.01	70.7	1	70.7	ND	1.5
2–4	100	0.50	50	2	25	0.5	3
4–8	250	0.05	12.5	4	3.125	ND	6

Calculate the renal clearance of this drug in this patient.

$$\frac{\Delta Ae}{\Delta t} = Ke\ A_{tmid} = Ke.Vd.Cp\ tmid$$

- Cl R= Ke.Vd = $rate\ of\ excretion$/ $Cp\ tmid$ =25/0.5 = 50 mL/hr

Answer

- The half life of this drug is 1 hr. what is the elimination rate constant of this drug?
- T1/2= 1hr k= 0.693/1= 0.693 hr^{-1}

- The slope of renal excretion rate vs time plot on a semilog graph paper?
- Slope = - k/ 2.303 = 0.693/2.303 = - 0.3 hr^{-1}

Problem 7.2 (Practice problem)

- After IV injection of 10 mg of a new drug to a patient, the following data were obtained:

Collection Interval (h)	Urine Volume (mL)	Urine Concentration (ug/mL)	$C_{pt\text{-mid}}$ (ug/L)
0–1	1250	1.8	16
1–2	1500	0.984	10.4
2–3	1750	0.544	6.8
3–4	1380	0.488	4.4
4–5	1630	0.248	2.9
5–7	3130	0.136	1.5

1- Using a graphical method, estimate the biological half-life of this drug in this patient.
2- Calculate the renal clearance and total body clearance of this drug in this patient.
3- Calculate the fraction of the administered dose execrated unchanged in the urine from the above data.
4- Estimate how much drug in the body 5 days after the dose was administered.
5- Assuming that the unexcreted portion of this drug is metabolized, determine its metabolic rate constant (km) in this patient.

General comment on rate method

- The method tends to give overestimate of intercept.
- The overestimation can be minimized by collecting urine samples more frequently (which is not always easy from practical consideration)

General comments on the use of urinary data in PK analysis

- Urine collection is a non-invasive technique
- It is, perhaps, a more convenient method of sample collection, and sample size is generally not a problem. The sampling time, however, reflects drug in urine collected over a period of time, rather than a drug concentration at a discrete time
- Urinary data allows direct measurement of bioavailability, both absolute and relative, without the need of fitting the data to a mathematical model.

Nonlinear pharmacokinetics

Dr. Mahmoud Samy

Lecturer of Clinical Pharmacy

Outlines

- Linear pharmacokinetics
- Nonlinear pharmacokinetics
- Example of Nonlinear PK (**Phenytoin**)
  - M-M equation
  - Orbit graph method
  - Direct linear plot
  - Linear transformation method

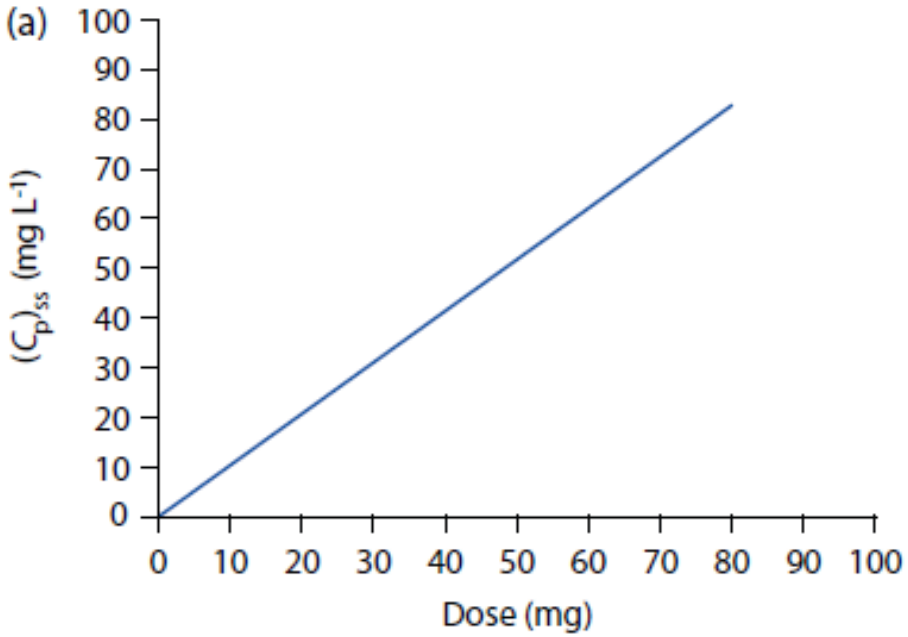
Linear Pk

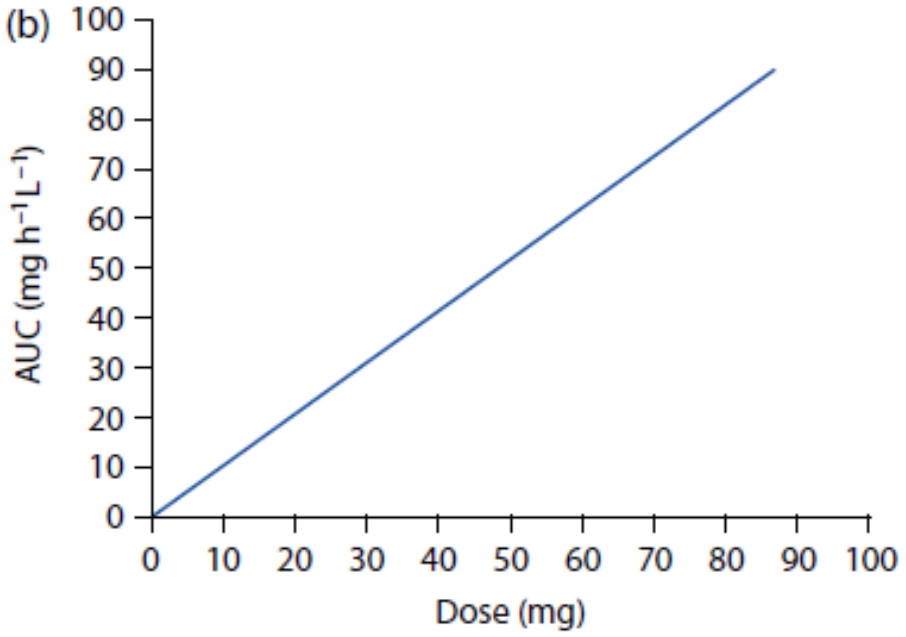
- Pharmacokinetic parameters, such as elimination half life (t1/2), the elimination rate constant (K), the apparent volume of distribution (V), and the systemic clearance (Cl) of most drugs are not expected to change when different doses are administered and/or when the drug is administered via different routes as a single dose or multiple doses

- The kinetics of these drugs is described as **linear, or dose-independent**, pharmacokinetics and is characterized by the first-order process

- The term linear simply means that plasma concentration at a given time at steady state and the area under the plasma concentration versus time curve (AUC) will both be directly proportional to the dose administered

Linear Pk


(a)
100
90
80
70
60
50
40
30
20
10
0
$(C_p)_{ss}$ (mg L^{-1})
0 10 20 30 40 50 60 70 80 90 100
Dose (mg)


(b)
100
90
80
70
60
50
40
30
20
10
0
AUC (mg $h^{-1}L^{-1}$)
0 10 20 30 40 50 60 70 80 90 100
Dose (mg)

Linear Pk

- In this situation, steady-state serum concentrations increase or decrease proportionally with dose.

- Therefore, if a patient has a steady-state drug concentration of 10 µg/mL at a dosage rate of 100 mg/h, the steady-state serum concentration will increase to 15 µg/mL if the dosage rate is increased to 150 mg/h (e.g., a 50% increase in dose yields a 50% increase in steady-state concentration).

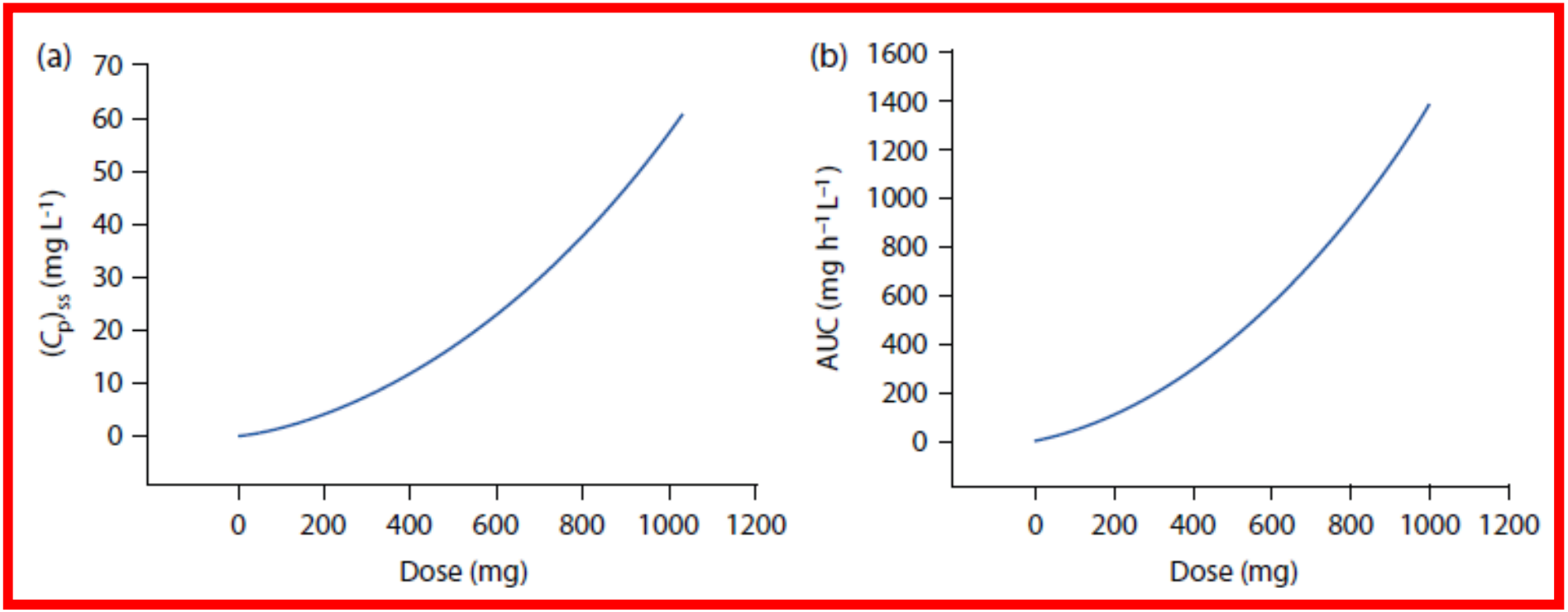
Nonlinear Pk

- For drugs that exhibit **nonlinear or dose dependent kinetics or concentration dependent**, the fundamental pharmacokinetic parameters such as clearance, the apparent volume of distribution, and the elimination half life may vary depending on the administered dose.

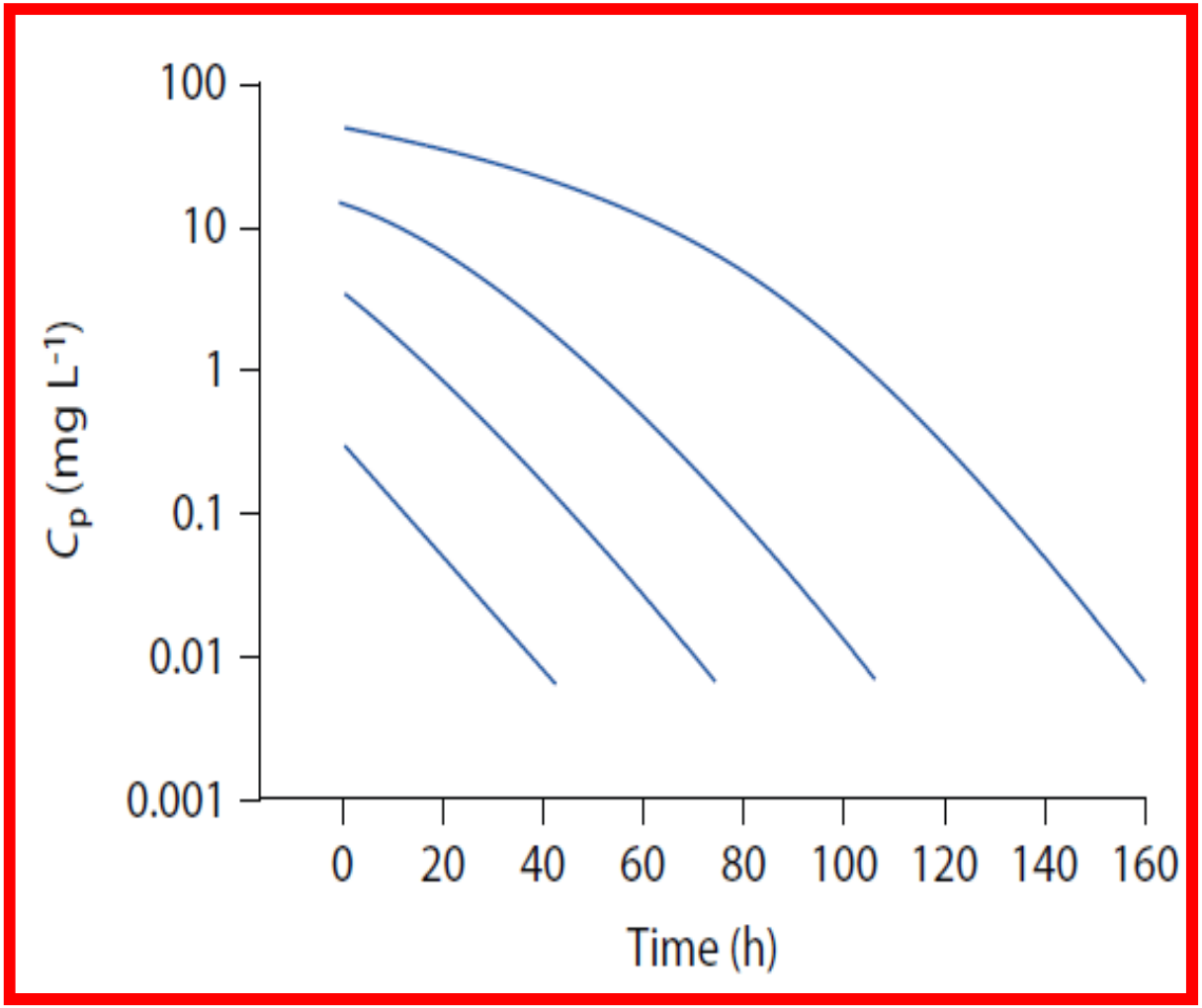
- For these drugs, therefore, the relationship between the AUC or the plasma concentration at a given time at steady state and the administered dose is not linear (not directly proportional)

- Most drugs follow linear kinetics at therapeutic doses. However, Some drugs follow non linear kinetics including phenytoin.

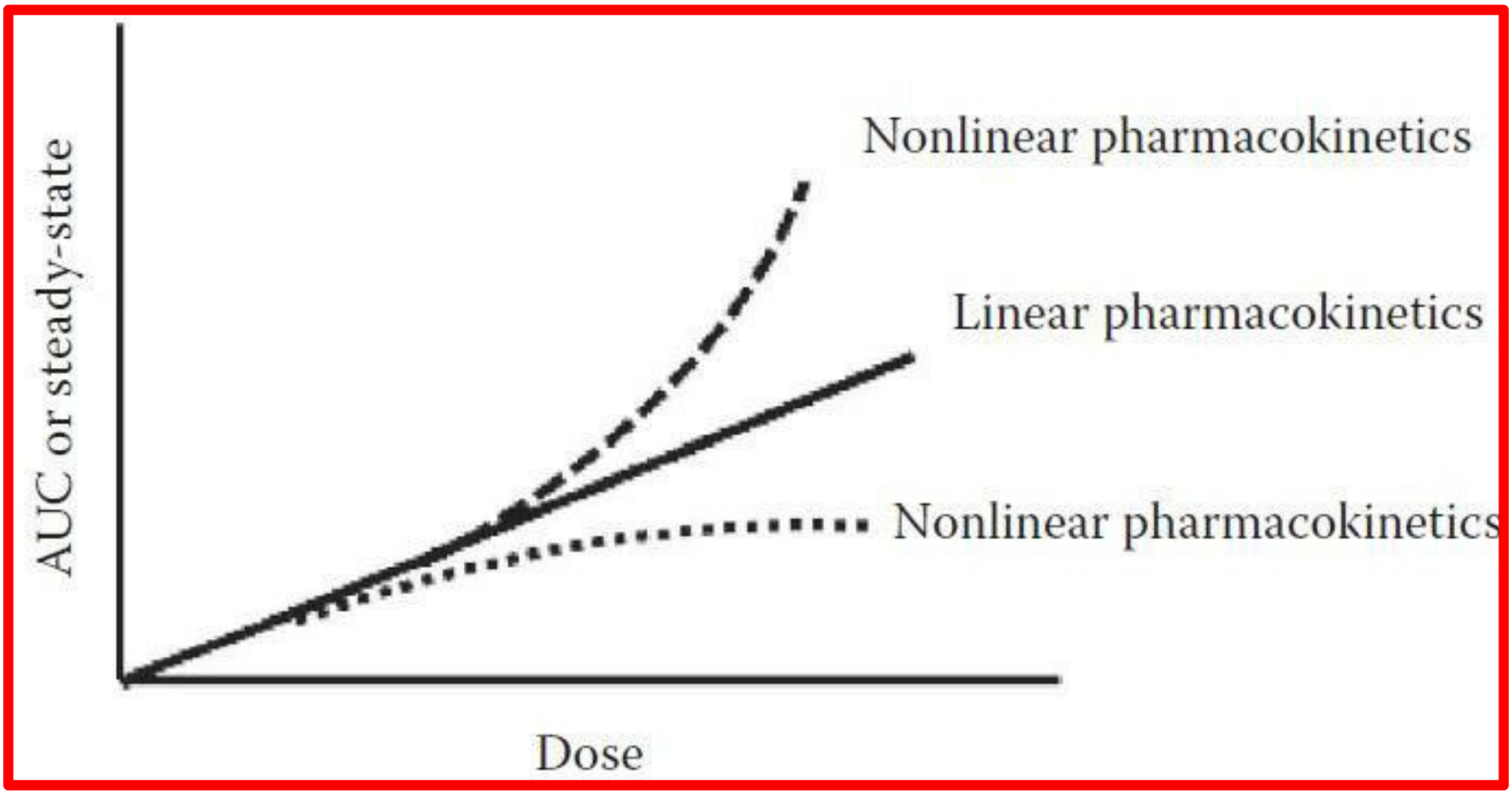
Nonlinear Pk



Nonlinear Pk



Administration of different doses of drugs with nonlinear kinetics may not result in parallel plasma concentration versus time profiles expected for drugs with linear pharmacokinetics


AUC or steady-state
Nonlinear pharmacokinetics
Linear pharmacokinetics
Nonlinear pharmacokinetics
Dose

Nonlinear Pk Causes

- This is because one or more of the kinetic processes (absorption, distribution and/or elimination) of the drug may be occurring via a mechanism other than simple first-order kinetics.
  - Saturable absorption: For example, the extent of absorption of amoxicillin decreases with an increase in dose
  - Saturable binding: plasma protein binding of disopyramide is saturable at the therapeutic concentration, the fraction of disopyramide bound varies between 35% at high doses & 95% at low doses. This means that small increase in doses result in disproportionally increase in the effect

Nonlinear Pk Causes

- Saturable Active secretion: As for nonlinearity in renal excretion, it has been shown that the antibacterial agent dicloxacillin has saturable active secretion in the kidneys, resulting in a decrease in renal clearance as dose is increased

- Saturable metabolism: Both phenytoin and ethanol have saturable metabolism, which means that an increase in dose results in a decrease in hepatic clearance and a more than proportional increase in AUC

Nonlinear Pk

- When steady-state concentrations increase less than expected after a dosage increase, there are two typical explanations:

- Some drugs, such as valproic acid and disopyramide, saturate plasma protein binding sites so that as the dosage is increased, steady-state serum concentrations increase less than expected till complete saturation.

- Other drugs, such as carbamazepine, increase their own rate of metabolism from the body as dose is increased so steady-state serum concentrations increase less than anticipated. This process is known as **autoinduction of drug metabolism**.

Nonlinear PK

- In either case, the relationship between steady-state concentration and dose for drugs that follow nonlinear pharmacokinetics is associated with significant intersubject variability.
- Drugs that exhibit nonlinear pharmacokinetics are oftentimes very difficult to dose correctly.
- Theoretically, all metabolic pathways can be saturated at very high drug concentration. However, saturable drug metabolism is of clinical significance when saturation occurs after administration of therapeutic doses of the drug.
- Steady-state serum concentrations/dose plots for medications are determined in humans early during the drug development process.

Difference between linear & nonlinear PK:

Linear PK (first order kinetic)	Nonlinear PK (zero order kinetic)
1-Known as dose-independent or concentration-independent PK.	1-Known as dose-dependent or concentration-dependent PK.
2-The absorption, distribution and elimination of the drug follow first-order kinetics	2-At least one of the PK processes (absorption, distribution or elimination) is saturable (zero order kinetic).
3-The pharmacokinetic parameters such as the half-life, total body clearance and volume of distribution are constant and do not depend on the drug conc	3-The pharmacokinetic parameters such as the half-life, volume of distribution, total body clearance are conc-dependant
4-The change in drug dose results in proportional change in the drug concentration.	4-The change in drug dose results in more than proportional or less than proportional change in the drug conc.

Difference between linear & nonlinear PK:

Linear PK (first order kinetic)	Nonlinear PK (zero order kinetic)
Proportional dose response relationship (Cp, AUC)	disproportional dose response relationship (unpredictable) Increase in dose resulted in more than proportional increase in Cp & AUC
Constant proportion (fraction) eliminated per unit time	Constant amount eliminated per unit time
T1/2 & Cl (constant) (useful)	T1/2 & Cl are variable (not useful)
Superimposable Terminal parts of plasma conc. Curve after oral & iv are superimposed	Not superimposable Terminal parts of plasma conc. Curve after oral & iv are not parallel or superimposed

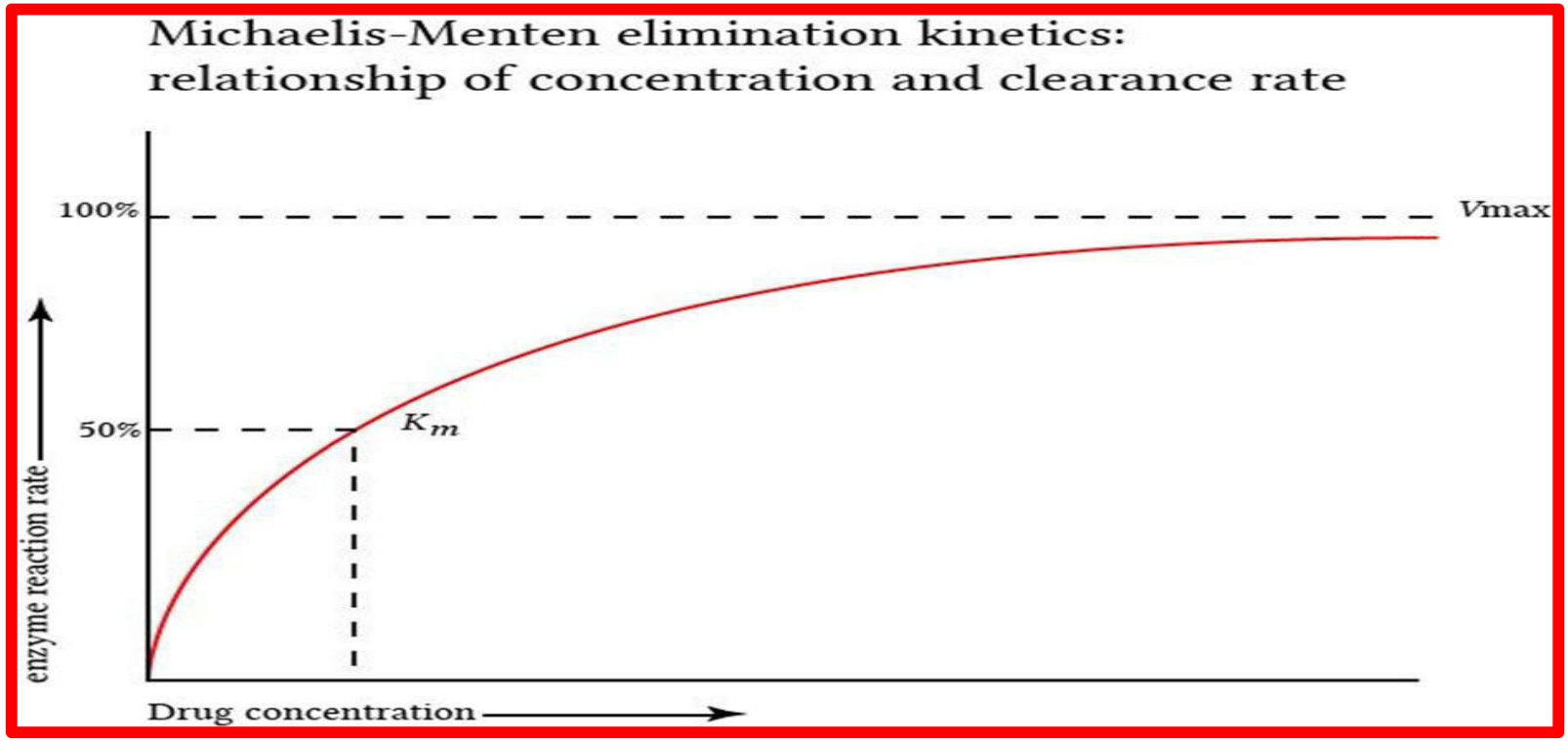
Nonlinearity in metabolism
Capacity-limited metabolism

- Capacity-limited metabolism is also called saturable metabolism, Michaelis–Menten kinetics
- Nonlinearity in metabolism, is one of the most common sources of nonlinearity
- Phenytoin, ethanol, and salicylic acid follow Michaelis-Menten pharmacokinetics

Michaelis–Menten kinetics

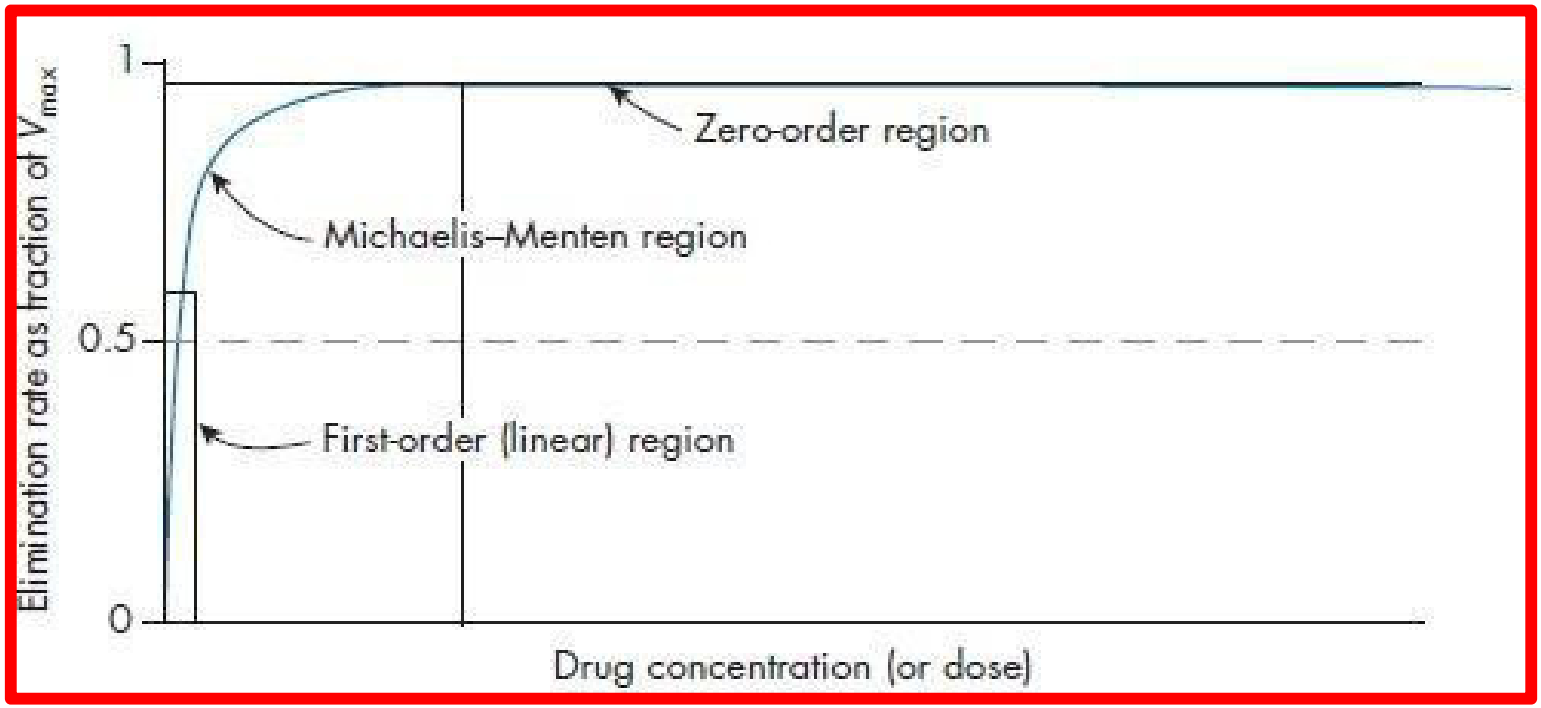
- Michaelis-Menten kinetics model that describe saturable enzyme system
- Used to predict Cp resulting from administration of drug with saturable metabolism where a drug at low concentration is cleared by first-order kinetics and at high concentrations by zero order kinetics
- Conditions that alter M-M parameters
  - Enzyme Induction or inhibition (**Vm**)
  - Hepatic disease

Michaelis- Menten kinetics



Vm is the maximum metabolic rate (unit: amount/time)
Km :Substrate concentration at 50% Vm (mg / L), the Michaelis–Menten constant (unit: same as the concentration [amount/volume]),

Michaelis- Menten kinetics



a drug at low concentration is cleared by first-order kinetics and at high concentrations by zero order kinetics

Michaelis- Menten kinetics

- The rate of metabolism, or the rate of elimination **if metabolism is the only pathway of elimination**, is defined by the Michaelis–Menten equation:

$$\mathbf{R}\left(\frac{mg}{day}\right) = \frac{Vm * Css}{Km + Css}$$

- where **R** is the rate of drug administration or the metabolic rate;

$$Rate\ of\ administration(RA) = \left(\frac{FD}{\tau}\right) S = \mathbf{DD.S}$$

- **Vm** is the maximum metabolic rate (unit: amount/time)
- **Km** :Substrate concentration at 50% Vm (mg / L), the Michaelis–Menten constant (unit: same as the concentration [amount/volume]), and **Css** plasma conc at steady state .

$$\mathbf{t1/2} = \frac{0.693\ Vd}{Vm}\ (Km + Css) \qquad \mathbf{TBC} = \frac{Vm}{Km + Css}$$

Phenytoin & its key pharmacokinetic parameters

Phenytoin is antiepileptic drug that follow **EXCLUSIVE** non-linear kinetic

Therapeutic concentration	**20- 10mg / L**
F (bioavailability)	1.0
S (salt form)	0.92
Vd	0.7 L/ kg
Cl (clearance), t1/2	Dose dependant
Vm	7mg / kg / day
Km	4mg /L (average) Constant
PPB	%95-90

Plasma concentration below 5 mg/L not effective

Phenytoin

Phenytoin side effect is concentration dependent	Other long term side effect
➢ **20 – 30 mg/L (Nystgmus)** ➢ **> 30 m/L (Ataxia)** ➢ **>40 m/L (mental capacity diminished)**	➢ Acne, hirsutism, folate deficiency, neuropathy, gingival hyperplasia

Phenytoin dosage forms

Phenytoin acid	Phenytoin Na (s=.92)
Chewable tablet	Capsules
Suspension	Parenteral solution

N.B:

- Change between different brands should consider the difference in bioavailability.
- Poor solubility, so it is formulated in microcrystal form

Rationale for TDM

- Saturable elimination at therapeutic range
- Lack of predictability
- Narrow therapeutic index
- Significant drug interaction
- Large intersubject variability

- Time to take blood sample: 2- 3 days after intitation, second level in 3- 5 days, if Ok, it should be monitored everey 3-12 months)

Phenytoin dosing to patient

- **Three situations**
  - Patient 1st visit : no dose, no serum level
  - Patient 2nd visit : a dose is present, serum level determined
  - Patient 3rd visit : 2 doses & 2 serum levels

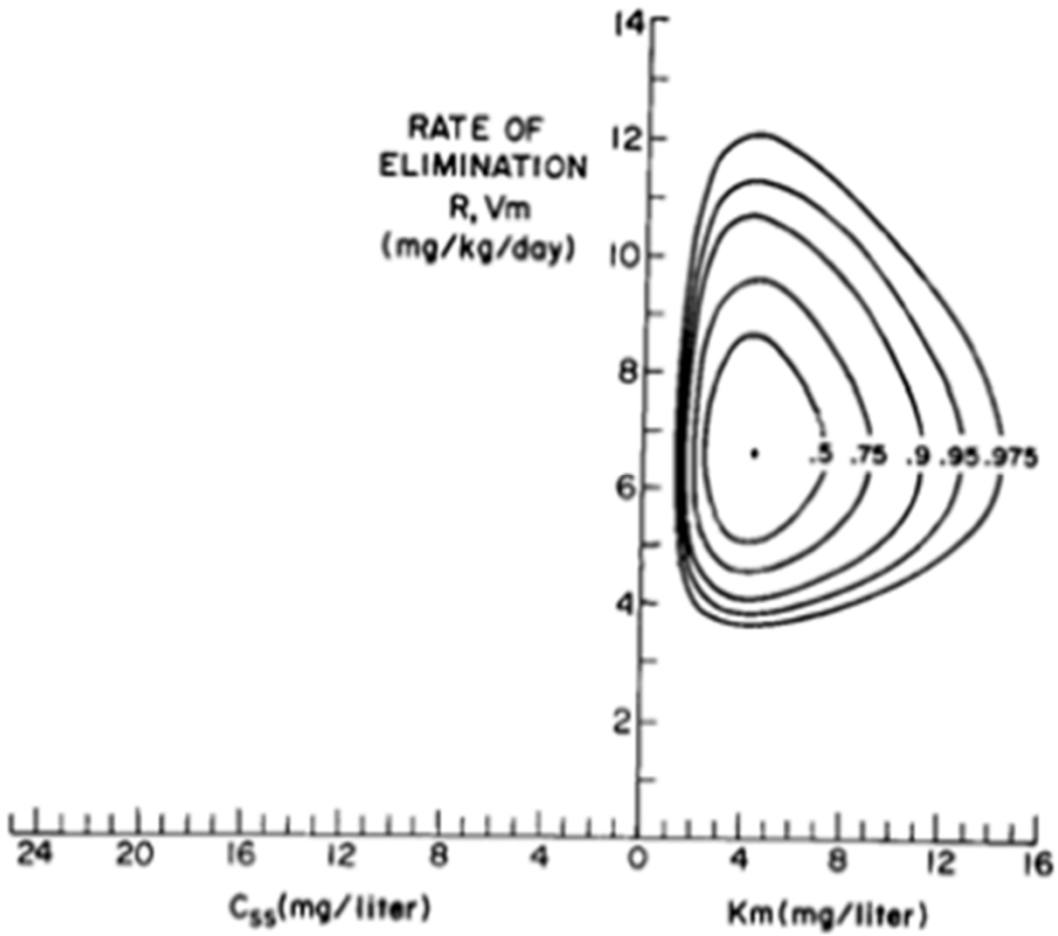
Patient 1st visit : no individualized data available

Patient 1st visit : no individualized data available

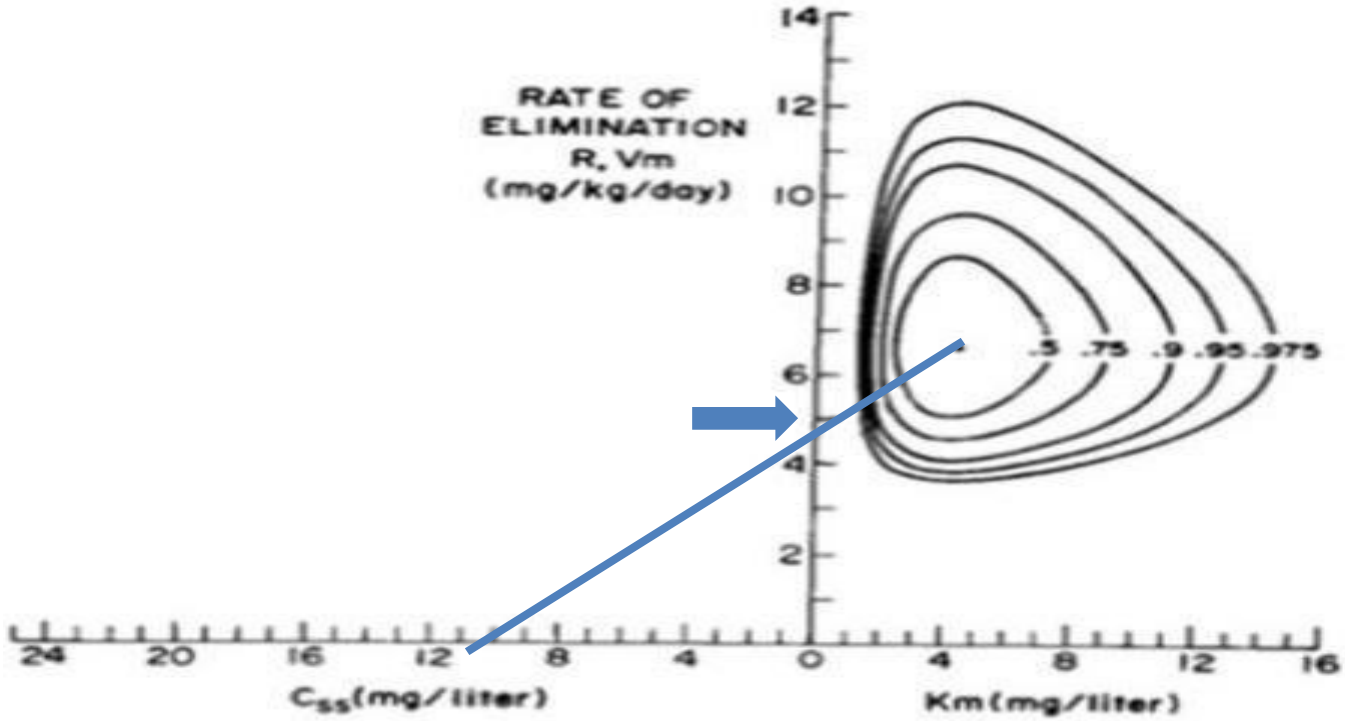
- **Use population date Km= 4 mg/L, Vm=7 mg/kg/day & Vd = 0.7 L/Kg/day**
- Mathematically: M-M Equation
- $R\left(\frac{mg}{day}\right) = \frac{Vm * desired\ Css}{Km + desired\ Css}$
- $Rate\ of\ administration(RA) = \left(\frac{FD}{\tau}\right) S$=DD.S
- D/τ= **daily** dose

Graphically using Orbit graph method

- The orbit graph is a plot of Vmax vs. km with probability contours drawn on it.
- x-axis is labeled Km & the extension of the x-axis in the negative direction labeled Css.
- The y-axis labeled both Vmax and dose.
- Dose is plotted as mg/kg/d of phenytoin.
- This method uses data previously derived from a patient population to construct shapes, orbit representing 50, 75, 90,95 and 97.5%



Graphically: Orbit graph method (phenytoin nomogram)



Patient 2nd visit : one dose & one level available

Patient 2nd visit : one dose & one level available

- Use the given dosing rate & the measured serum level to calculate Vm Michaelis Menten equation assume Km = 4 mg / L
- R $(\frac{mg}{day})$= DD.S = $\frac{Vm*desired\ Css}{Km+desired\ Css}$

Example 1

- S.B. is a 70 kg , 37 Y.O. male with seizure disorder that only partially been controlled with 300mg / day capsules of phenytoin. His plasma phenytoin conc. has been measured twice over the past year & both times it was 8 mg / l. Calculate a daily dose which will achieve a steady state concentration of 15 mg / l.

Answer

- R = 300 mg / day , Cpss = 8 mg/L , S = 0.92 F = 1
- R $(\frac{mg}{day})$= DD.S = $\frac{Vm*desired\ Css}{Km+desired\ Css}$
- 300 $*$ 0.92 = $\frac{Vm*8}{4+8}$
- Vm = (12 * 300 * 0.92)/ 8 = 414 mg / day
- DD $*$ 0.92 = $\frac{414*15}{4+15}$ =355 mg/day

Example 2

- B.U. is a 9 Y.O. 30 kg male who has been admitted to the emergency dep. for treatment of uncontrolled seizure activity. His friend relates that he has been taking 180 mg chewable tablet of phenytoin QD for 6 weeks, serum levels of phenytoin was found to be 3 mg / l . Assume that this is a steady state level. Calculate Vmax for this patient.
- In the above case, what is the new dose of phenytoin required to yield a steady state plasma concentration of 15 mg / l ?

Answer

- R =180 mg / day , Cpss = 3 mg/L S = 1.0 F = 1.0
- R $(\frac{mg}{day})$= DD.S = $\frac{Vm*desired\ Css}{Km+desired\ Css}$
- 180 ∗ 1 = $\frac{Vm*3}{4+3}$
- Vm = (7 * 180 * 1) / 3 = 420 mg / day
- DD∗ 1 = $\frac{420*15}{4+15}$ **= 332 mg / day**

Orbit graph

1. On the left side of the x-axis, a steady-state total phenytoin concentration is plotted.
2. On the y-axis, the phenytoin dosage rate (in mg/kg/d) is plotted.
3. A straight line is drawn between these two points, extended into the right sector, and through the orbs contained in the right sector.
4. If the line intersects more than one orb, the innermost orb is selected, and the midpoint of the line contained within that orb is found and marked with a point.
5. The midpoint within the orb and the desired steady-state phenytoin total concentration (on the left portion of the x-axis) are connected by a straight line.

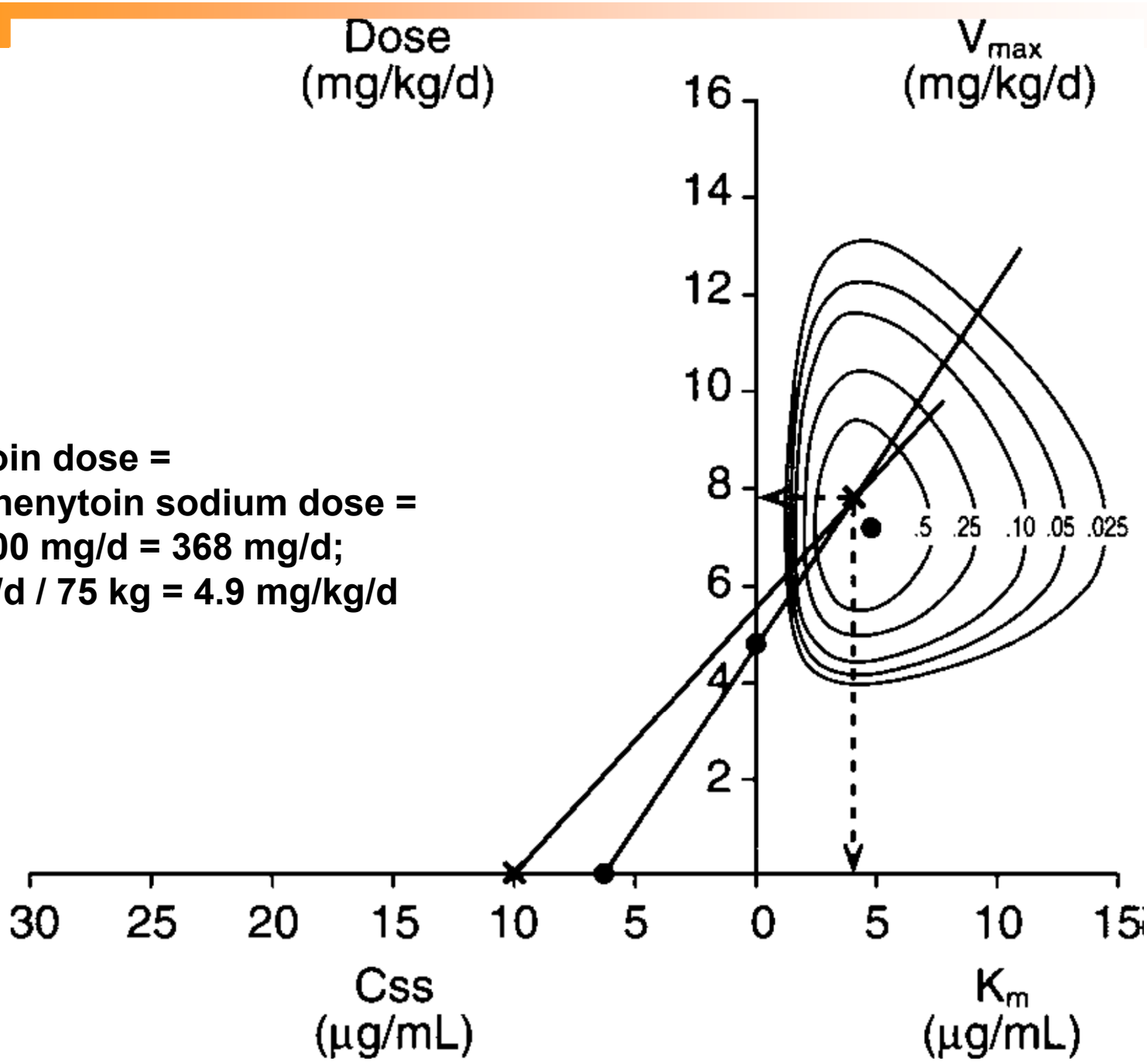
Orbit graph

6. The intersection of this line with the y-axis is the new phenytoin dose required to achieve the new phenytoin concentration.
7. If a line parallel to the y-axis is drawn down to the x-axis from the midpoint of the line contained within the orb, an estimate of Km (in μg/mL) is obtained.
8. Similarly, if a line parallel to the x-axis is drawn to the left to the y-axis from the midpoint of the line contained within the orb, an estimate of Vmax (in mg/kg/d) is obtained.

Example

- TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function. The patient was prescribed 400 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 6.2 μg/mL. The patient is assessed to be compliant with his dosage regimen. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration within the therapeutic range.

phenytoin dose =
0.92 · phenytoin sodium dose =
0.92 · 400 mg/d = 368 mg/d;
368 mg/d / 75 kg = 4.9 mg/kg/d



Patient 3rd visit : two doses & two levels available

Patient 3rd visit : two doses & two levels available

- Use the two dosing rate & the two measured serum levels to calculate the new Vm & Km by Michaelis-Menten equation

$$R\left(\frac{mg}{day}\right) = DD.S = \frac{Vm * Css}{Km + Css}$$

Example 3

- RM is a 32 year old, 80kg male who is being seen in the Neurology Clinic. Prior to his last visit he had been taking 300mg of Phenytoin daily; however, because his seizures were poorly controlled and because his plasma concentration was only 8mg/L, his dose was increased to 350mg daily. Now he complains of minor CNS side effects and his reported plasma Phenytoin concentration is 20mg/L. Renal and hepatic function are normal. Assume that both of the reported plasma concentrations represent steady state and that the patient has compiled with the prescribed dosing regimens. Calculate RM's apparent Vm and Km and a new daily dose of Phenytoin that will result in a steady state level of about 15mg/L.

Answer

$$R1 * Km + R1 * C_{SS}(1) = Vm * C_{SS}(1)$$
$$R2 * Km + R2 * C_{SS}(2) = Vm * C_{SS}(2)$$

$$R1 = 300\, mg/day,\ \ C_{SS}(1) = 8\, mg/L$$
$$R2 = 350\, mg/day,\ \ C_{SS}(2) = 20\, mg/L$$

$$\left.\begin{aligned} 300 * Km + 300 * 8 &= Vm * 8 \\ 350 * Km + 350 * 20 &= Vm * 20 \end{aligned}\right\} \Rightarrow \begin{cases} 37.5 * Km + 300 = Vm & (1) \\ 17.5 * Km + 350 = Vm & (2) \end{cases}$$

Eqn (1)- Eqn(2):

$$20 * Km - 50 = 0 \qquad Km = \frac{50}{20} = 2.5\, mg/L$$

Eqn (1):

$$Vm = 37.5 * Km + 300 = 37.5 * 2.5 + 300 = 393.75\, mg/day$$

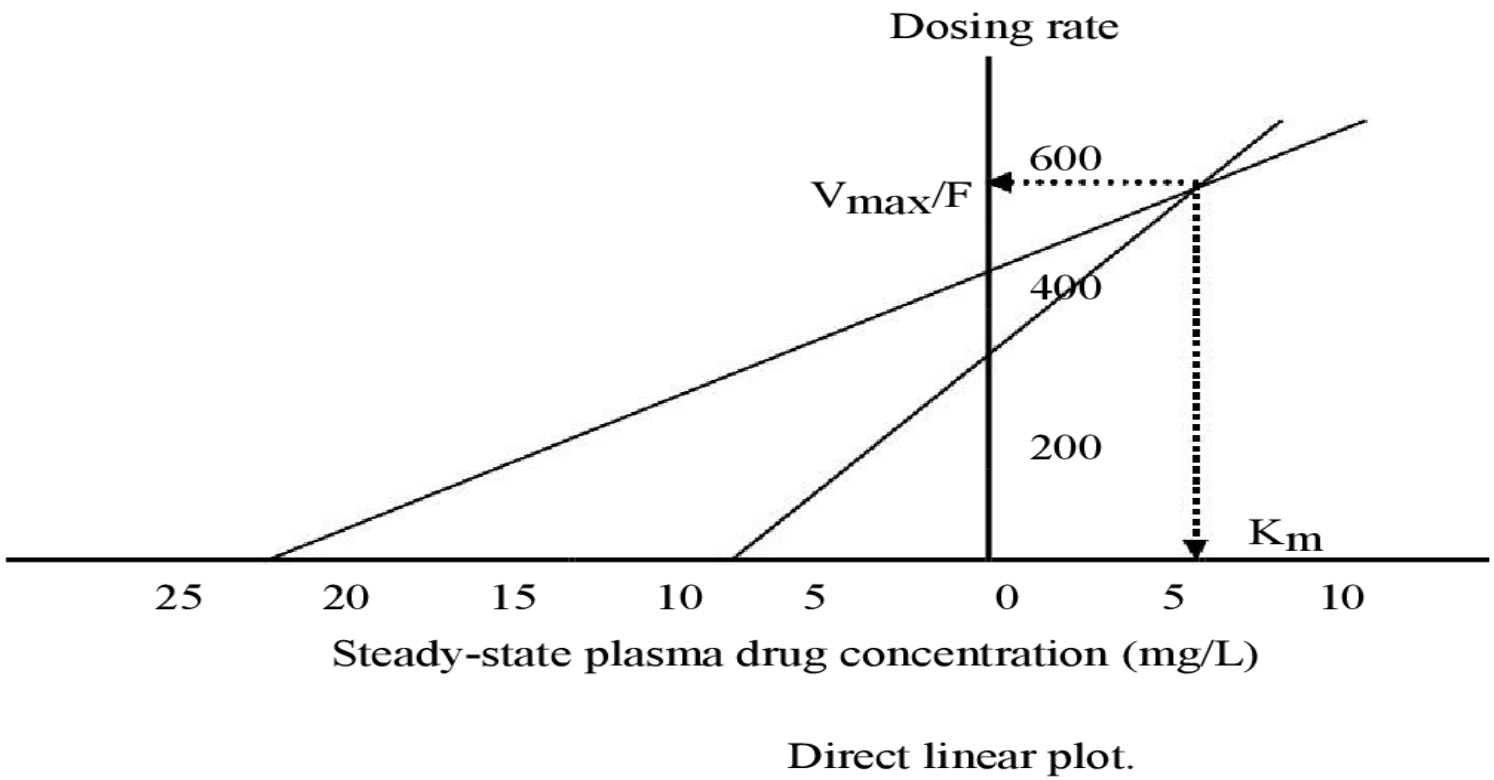
- Calculate RM's a new daily dose of Phenytoin that will result in a steady state level of about 15mg/L

$$\text{Dosing rate} = \frac{\text{VmC}_{SS}}{Km + C_{SS}} = \frac{393.75 * 15}{2.5 + 15} = 337.5\, mg / day$$

Direct Linear Plot

- Direct linear plot is a linear transformation method that is used to estimate V_{max} and K_m.
- This method requires knowledge of two different dosing rates and their corresponding steady-state plasma drug concentrations.
- The plot is constructed by plotting the dosing rate in the y-axis and the steady-state drug concentration on the left side of the x-axis. A line is drawn between each dosing rate and its corresponding steady-state concentration.
- The two lines for the two dosing rates are extrapolated until they intersect.
- The x-coordinate of the point of intersection corresponds to K_m, while the y-coordinate of the point of intersection corresponds to V_{max}/F as presented in following Figure.

Direct Linear Plot

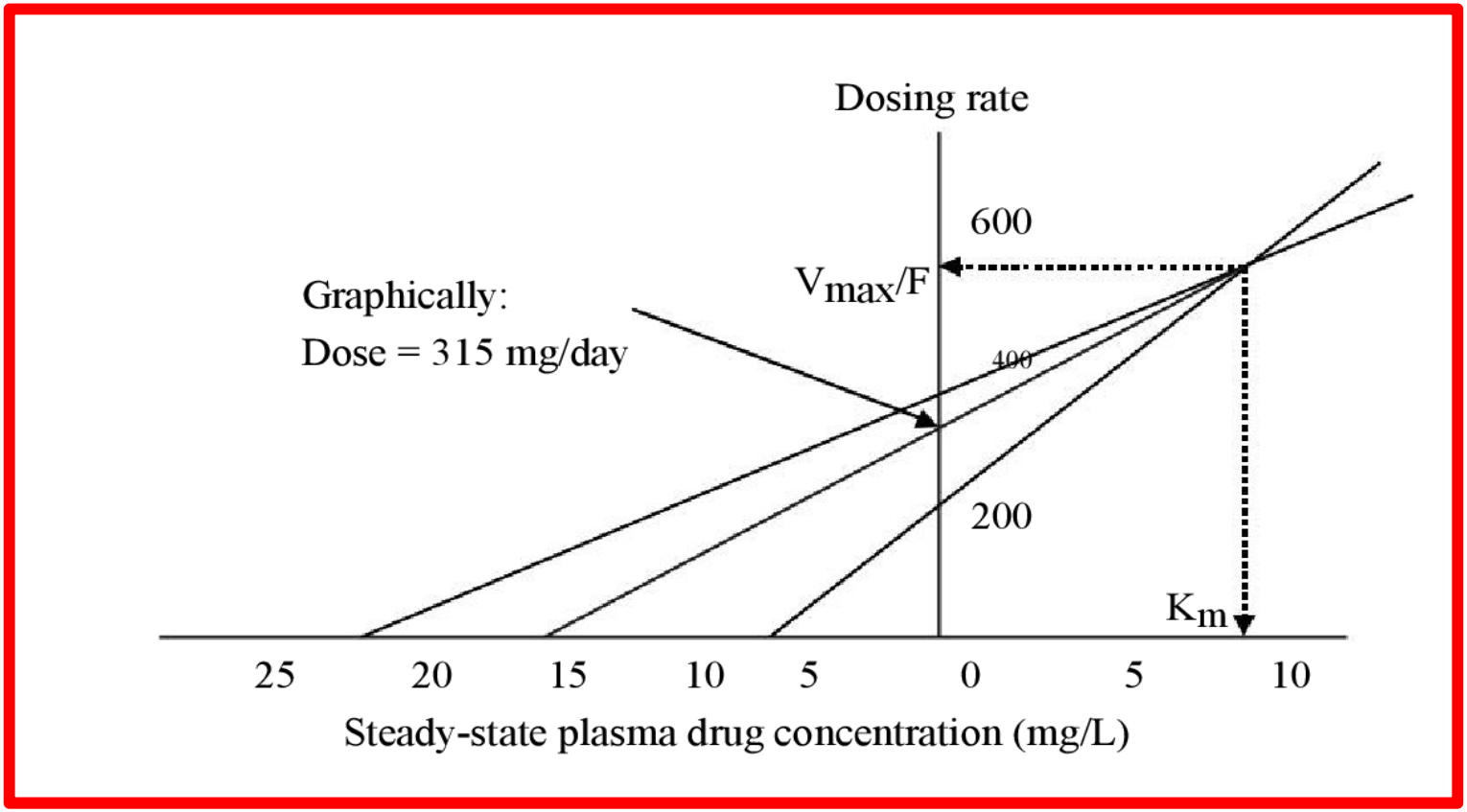


Direct linear plot.

Example 3

- A 32-year-old, 75 kg female has been taking 200 mg of phenytoin daily. Because her average phenytoin plasma concentration was only 6 mg/L, her phenytoin dose was increased to 350 mg/day. The steady-state average phenytoin concentration was 21 mg/L (Vd of phenytoin is 0.75 L/kg and F = 1).
- a. Using the direct linear plot, calculate the phenytoin Vmax and Km in this patient.
- b. Calculate the dose required to achieve an average steady-state phenytoin plasma concentration around 15 mg/L.
- c. Calculate phenytoin half-life & TBC at steady state while the patient was taking 350 mg/day.
- d. Because of poor seizure control, phenobarbitone (enzyme inducer) was added to the patient's medications. After several weeks, phenytoin plasma concentration was 14 mg/L while taking 360 mg/day phenytoin. Comment on the decrease in phenytoin plasma concentration.

Answer


Dosing rate
600
Vmax/F
Graphically:
Dose = 315 mg/day
400
200
Km
25
20
15
10
5
0
5
10
Steady-state plasma drug concentration (mg/L)

Answer

- From the direct linear plot V_{max} = 500 mg/day; K_m 9 mg/L
- The dose required to achieve a steady-state concentration of 15 mg/L can be determined graphically and mathematically.
- Graphically from Figure, the dose is approximately 315 mg/day (Approximately 350 mg). Mathematically,
- Dosing rate= $\frac{Vm*Css}{Km+Css} = \frac{500*15}{9+15}$=312.5 mg/day

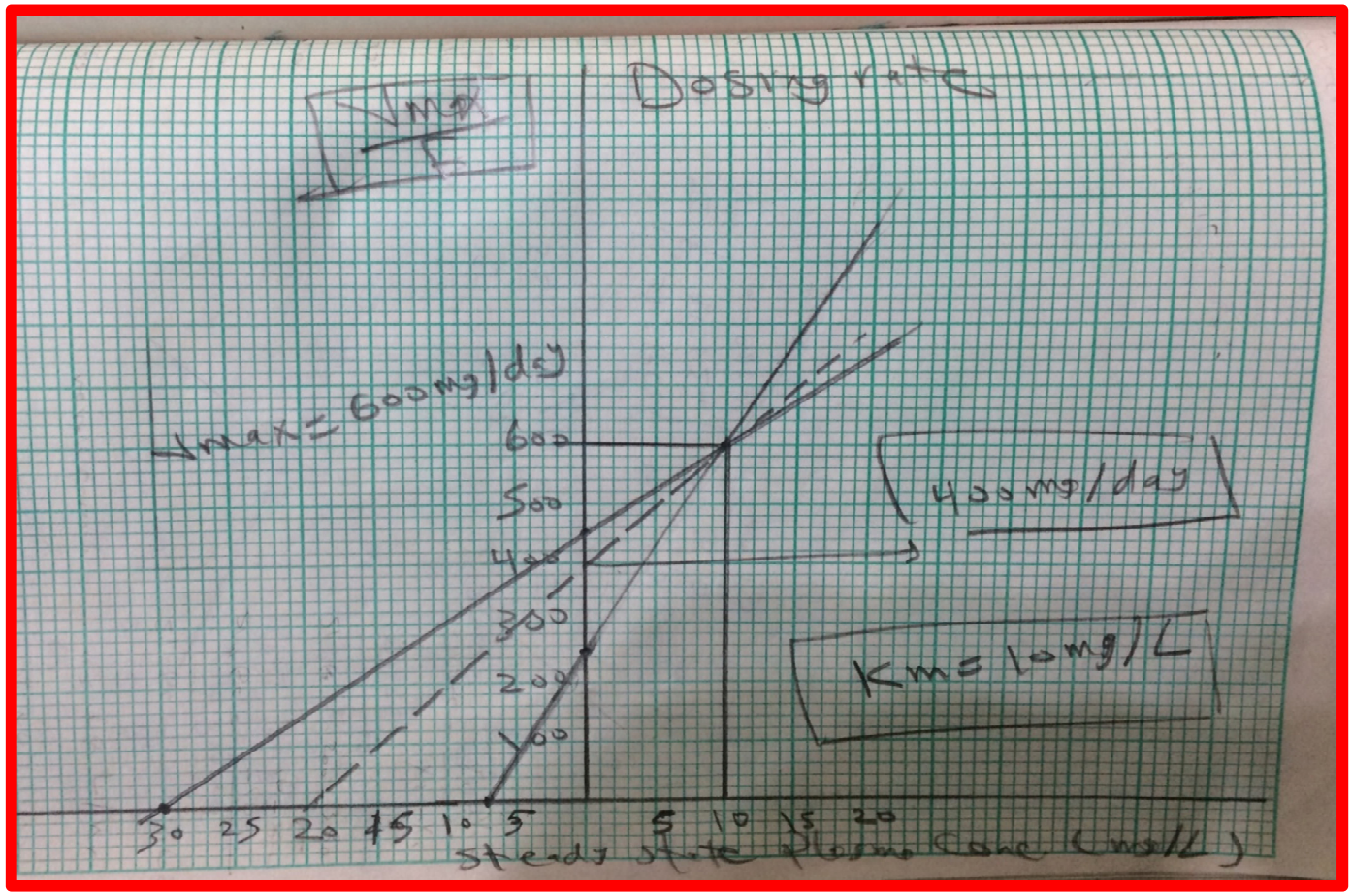
- C- Steady state when the dose was 350 mg/day = 21 mg/L.
- **t1/2=** $\frac{0.693\ Vd}{Vm}\ (Km + Css)$
- **t1/2=** $\frac{0.693\ (0.7\ L * 75\ Kg)}{500}\ (9 + 21)$ **= 2.18 days**
- **TBC =** $\frac{Vm}{Km+Css}$ **=** $\frac{500}{9+21}$ **=16.67 L/Day**

- D- Phenobarbitone is an enzyme inducer that can increase the rate of phenytoin metabolism (increase Vmax) and decrease its steady-state concentration.

Practical Problem 1

- A 78 kg, 28-year-old man is receiving phenytoin for the treatment of seizures. When this patient was taking a daily oral dose of 250 mg phenytoin, his steady-state plasma concentration was 7.2 mg/L. Because phenytoin plasma concentration was well below the therapeutic range, the patient's daily dose was increased to 450 mg phenytoin, which resulted in a steady-state plasma concentration of 30 mg/L. (Assume that the absolute bioavailability of oral phenytoin is 100%, and that the volume of distribution of phenytoin is 50 L.)
- a. Graphically calculate the patient's Vmax and Km.
- b. Calculate phenytoin half-life in this patient at steady state while taking 450 mg daily.
- c. What is the steady-state concentration that should be achieved if the dose was 300 mg daily?
- d. What is the daily phenytoin dose that should achieve a steady-state phenytoin plasma concentration of 20 mg/L in this patient?

Answer



a. Vmax = 600 mg/day, Km = 10 mg/L

Answer

- b. Calculate phenytoin half-life in this patient at steady state while taking 450 mg daily.
- **t1/2=** $\frac{0.693\ Vd}{V\ max}\ (Km + Css)$
- **t1/2=** $\frac{0.693\ *50}{600}\ (10 + 30)$ **= 2.31 days**
- c. What is the steady-state concentration that should be achieved if the dose was 300 mg daily?
- Dosing rate= $\frac{Vm*Css}{Km+Css}$
- $300 = \frac{600*Css}{10+Css}$ =10 mg/L

Answer

- d. What is the daily phenytoin dose that should achieve a steady-state phenytoin plasma concentration of 20 mg/L in this patient?
- Dosing rate$= \frac{Vm*Css}{Km+Css}$
- Dosing rate $= \frac{600*20}{10+20}$ =400 mg/day

Linear Transformation method

- This method is based on a linear transformation of M-M Equation that relates the dosing rate and the achieved steady-state drug concentration and includes the Michaelis-Menten parameters, Vmax and Km:

- $R\left(\frac{mg}{day}\right) = \left(\frac{FD}{\tau}\right) = \frac{Vm*Css}{Km+Css}$

- $\left(\frac{FD}{\tau}\right) km + \left(\frac{FD}{\tau}\right) Css = Vm * Css$

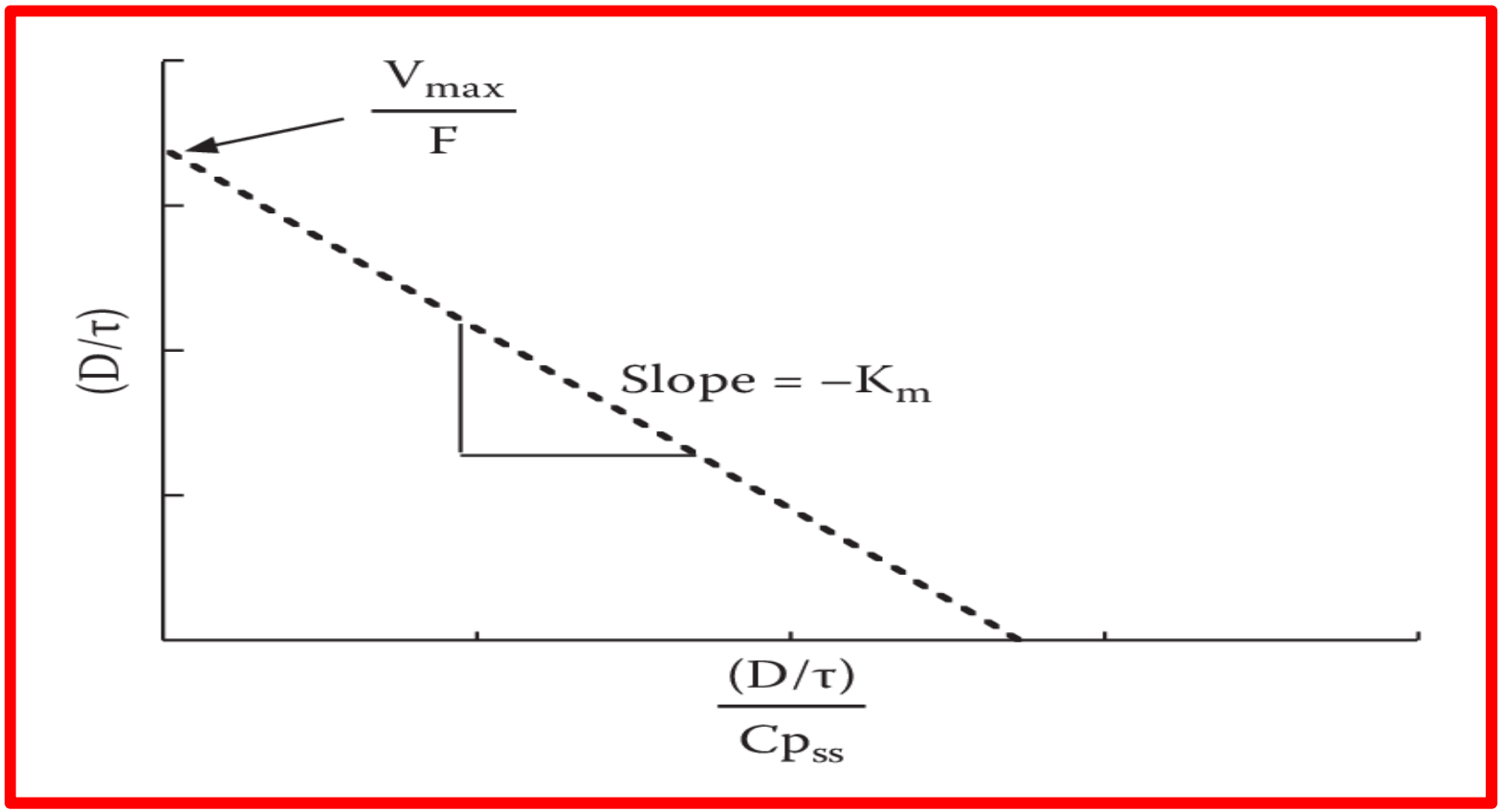
- Rearrangement and dividing by F Css

- $\left(\frac{D}{\tau}\right) = -Km\left(\frac{\frac{D}{\tau}}{Css}\right) + \left(\frac{Vm}{F}\right)$

Linear Transformation method:

- This is a straight-line equation.
- A plot of the dosing rate (D/τ) versus the dosing rate divided by the average steady-state concentration yields a straight line with a slope equal to −Km and y-intercept equal to Vmax/F.
- The parameters Vmax and Km estimated from the slope and the y-intercept of the plot can be used to calculate the dosing rate required to achieve a certain Cpss or, conversely, to calculate the expected Cpss from administration of a given dosing rate.

Linear Transformation method:



Practical problem 2

- A 25 kg, 14-year-old female was admitted to the hospital because of frequent episodes of seizures. She was diagnosed as having epileptic seizures and she was started on IV phenytoin. She received a loading dose of 5 mg/kg followed by 80 mg phenytoin IV given every 12 h. At steady state, the average plasma phenytoin concentration was found to be 8 mg/L. The phenytoin dose was increased to 100 mg phenytoin IV given every 12 h. At steady state, the plasma phenytoin concentration was 13.3 mg/L. Because the patient's condition was stable, the IV phenytoin was replaced with phenytoin oral suspension, which is known to have 100% bioavailability. The patient went home with a prescription for 225 mg phenytoin suspension at bed time every day. (The volume of distribution of phenytoin is 0.8 L/kg.)
- a. Graphically estimate phenytoin Vmax and Km in this patient.
- b. What is the expected average steady-state phenytoin concentration in this patient while taking the 225 mg phenytoin suspension at night?
- c. Calculate phenytoin CLT and half-life in this patient while taking the phenytoin suspension (225 mg phenytoin at bed time) at steady state.

Answer

- a. Vmax = 340 mg/day Km = 8.8 mg/L
- b. Cpss = 17.2 mg/L
- c. Half-life = 1.1 day CLT = 13.0 L/day


QUESTIONS?

Drug Distribution
&
Protein binding

Dr. Mahmoud Samy

Lecturer of Clinical Pharmacy

Outlines

- **Drug Distribution & Protein binding**

- **Dosing regimen - Disease state in special populations**
  - Dosing Regimens in Renal Dysfunction Patients Based on Creatinine Clearance
  - Dose Adjustment in Hepatic Dysfunction:
  - Alteration in Drug Pharmacokinetics in Obese Patients

Drug Distribution & Protein binding

- The distribution of drugs in the body depends on their lipophilicity & protein binding.
- **Factors affecting drug distribution:**
- **A. Rate of distribution**
- 1- Membrane permeability
- 2- Blood perfusion rate

Drug Distribution & Protein binding

- **B. Extent of Distribution**
- **1. Lipid Solubility:**
- Very high lipid solubility can result in a drug partitioning into highly vascular lipid-rich areas. Subsequently these drugs slowly redistribute into body fat where they may remain for long periods of time.
- **2. Effects of pH:**
- The rate of movement of a drug out of circulation will depend on its degree of ionization and therefore its pKa.
- **3.Plasma protein binding:**

➢ **Extensive plasma protein binding will cause more drug to stay in the central blood compartment. Therefore drugs which bind strongly to plasma protein tend to have lower volumes of distribution. (↑ protein binding = ↓ V)**

➢ **Albumin comprises 50 % of the total proteins binds the widest range of drugs.**

➢ **Acidic drugs commonly bind to albumin, while basic drugs often bind to α1-acid glycoproteins and lipoproteins.**

General rules

- **Rule 1**: Plasma proteins represent silent binding site (depot) for drugs: the BOUND drug is inactive; the FREE, UNBOUND drug can leave the blood and act and can be acted upon. As long as a drug is bound to plasma protein, it cannot act (as it cannot reach the site of action), it cannot be eliminated (as it can not reach enzymes and transporters, and cannot be filtered at the glomeruli).

- **Rule 2**: Only for extensively bound drugs (>90%) can changes in the FREE (active) drug fraction be significant. Drug with intermediate plasma protein binding: Decreased binding causes insignificant increase in free concentration.

The percentage of protein binding

- The percentage of protein binding of a drug in plasma can be determined experimentally as follows:
- $\%\ \text{Protein binding} = \frac{(TOTAL - Unbounded) \times 100}{total}$

- The fraction of unbound drug in the plasma (F_p) is determined by the following relationship:

$$F_p = \frac{(Unbounded)}{total}$$

Dosing regimen
&
Disease state in special populations

Dr. Mahmoud Samy

Lecturer of Clinical Pharmacy

Introduction

- The design of a dosing regimen involves selection of the appropriate dose and dosing interval for each individual patient.
- Few factors have to be considered before calculating the dosing regimen:

- Therapeutic Range of the Drug
- Required Onset of Effect
- Drug Product (availability of modified-release products for the drug of interest)
- Progression of the Patient's Disease State
- Estimation of the Patient Pharmacokinetic Parameters

Variables that can affect total body clearance (TBC) within individual

- Changes in eliminating organ function leads to changes in total body clearance

TBC = Rcl + Mcl + Other organ clearance

- Factors affecting metabolic clearance including: Age, Genetics, Liver disease, Plasma protein binding & other drug that induce or inhibit metabolic enzymes.
- Factors affecting renal clearance including: it is related to glomerular filtration rate (GFR) which measured by creatinine clearance.

Effect of age on volume of distribution (Vd):

- In very young infant, hydrophilic drugs have large Vd as infant has higher proportion of their body weight as water (80 %)

- In elderly person, hydrophilic drugs have reduced Vd due to reduced extracellular fluids, tissue mass and decreased tissue perfusion.

- In older patients, the body fat increased so lipid soluble drugs have larger Vd and longer $t_{1/2}$

Effect of age on drug metabolism & renal function

- **Effect of age on drug metabolism**
- In neonates (**<** 1 months), they have slow metabolic rate so drugs have longer t1/2
- In Children (3 – 12 y), they have normal metabolic rate
- In elderly (**>** 65 y), they have slow metabolic rate so drugs have longer t1/2

- **Effect of age on renal function:**
- Average adult value of GFR (120 ml/min)
- Premature infants have 1/10 of normal GFR
- Neonates have 1/2 or 1/4 of normal GFR

The general approach for dose adjustment in renal dysfunction patients has the following assumptions:

- The kidney dysfunction does not affect the concentration-effect relationship, that is, the therapeutic range does not change due to the change in kidney function (Linear PK).

- The decrease in kidney function results in a proportional decrease in the rate of renal drug elimination.

- The decrease in kidney function does not affect the nonrenal drug elimination.

- The decrease in kidney function does not affect drug absorption or distribution.

General Requirements

- This approach requires knowledge of:
- The average drug dose in patients with normal kidney function (Normal Dose).
- the kidney function of the patient (KF)
- The fraction of the IV drug dose excreted unchanged in urine in patient with normal kidney function (F).
- This information can be used to calculate the dose required for patients with kidney dysfunction to achieve an average steady-state concentration similar to that achieved in patients with normal kidney function when they use the average dose of the drug.

Dose failure

- The fraction of the dose normally excreted unchanged in the urine, the kidney function, and the average dose used in patients with normal kidney function can be used to calculate the dose required in patients with renal dysfunction as follows:

$$\textbf{Dose failure} = \textbf{Dose normal } [f\ (\text{KF} - 1) + 1]$$

- Also, the half-life in patients with renal dysfunction patients can be determined from the following relationship:

$$\mathbf{t1/2\ failure} = \frac{t\ 1/2\ normal}{[f(KF - 1) + 1]}$$

Fraction (f)

- The fraction of the IV dose excreted unchanged in urine (f) can be determined from the ratio of the total amount of the drug excreted in urine and the IV dose or the bioavailable oral dose:

$$\textbf{Fraction (f)} = \frac{Ae}{Dose\ (iv)}$$

$$\textbf{Fraction (f)} = \frac{Ae}{F\ Dose\ (Oral)}$$

- Also, the fraction excreted unchanged in urine can be determined from the ratio of the renal excretion rate constant to the elimination rate constant or the ratio of the renal clearance to the total body clearance as follows:

$$\textbf{Fraction (f)} = \frac{Ke}{K} = \frac{CLR}{TBC}$$

Kidney function (KF)

- The initial dose estimation for renally eliminated drugs in renal dysfunction patients is usually based on the patient's creatinine clearance.
- This is because the decrease in kidney function, which is reflected by the decrease in creatinine clearance, results in the decrease in renal clearance of the drug.
- The kidney function (KF) is expressed as the fraction remaining of the normal kidney function and is determined from the ratio of creatinine clearance in the patient to normal creatinine clearance:

$$\mathbf{KF} = \frac{CrCL\ failure}{CrCL\ normal}$$

Creatinine Clearance from urine collection

- The creatinine clearance can be determined from the 24 h urine collection and calculation of the average creatinine excretion rate.
  - **$CrCl\ (in\ mL/min) = (U_{Cr} \cdot V_{urine}) / (S_{Cr} \cdot T)$**

where:

- U_{Cr} is the urine creatinine concentration in mg/dL,
- V_{urine} is the volume of urine collected in mL,
- S_{Cr} is the serum creatinine collected at the midpoint of the urine collection in mg/dL,
- T is the time in minutes of the urine collection.
- **Disadvantages: Tedious method, Time consuming, Affected by diet & muscle mass, Not accurate**

Cockroft and Gault method

- The Cockoroft and Gault method can be used to estimate the creatinine clearance in adults from 18 years and older with stable serum creatinine.
- **Male:**

$$\textbf{Creatinine clearance (ml/min)} = \frac{(140 - \text{age}) \times \text{weight } (kg)}{\text{serum creatinine} \times 72}$$

- **Female:**

$$\textbf{Creatinine clearance (ml/min)} = 0.85 \times \frac{(140 - \text{age}) \times \text{weight } (kg)}{\text{serum creatinine} \times 72}$$

- **1 kg = 2.2 pound, for example 132 pound = 60 kg**

Problem 8.1

- A patient admitted to the hospital because of acute myocardial infarction was started on oral antiarrhythmic medication. He was given 600 mg every 12 h from an oral formulation that is known to be rapidly absorbed but only 80% bioavailable. At steady state, the maximum and minimum plasma concentrations were 30 and 10.5 μg/mL, respectively
- a. Calculate mathematically the half-life and the volume of distribution of this drug in this patient.
- b. The patient suddenly developed acute renal failure and the kidney function dropped to 30% of its normal value. If the renal clearance of this drug is 75% of the total body clearance, recommend an appropriate dose for this patient after developing the renal failure.
- c. Calculate the maximum and minimum plasma concentration achieved at steady state from the regimen you recommended in part (b).

A) Normal renal function

- $Cp_{max\ ss} - Cp_{min\ ss} = \frac{FDose}{Vd}$
- $30-10.5 = \frac{0.8 \times 600}{Vd}$
- $Vd = 480/19.5 = 24.6\ L$

- $Cp_{min\ ss} = Cp_{max\ ss}\ e^{-k\tau}$
- $\ln Cp_{min\ ss} = \ln Cp_{max\ ss} - \ln e^{-k\tau}$

$$Ln\left(\frac{Cp_{max\ ss}}{Cp_{min\ ss}}\right) = K\tau$$

- $Ln\ (30/10.5) = 12\ K$
- $K = 0.0875\ hr^{-1}$
- $t_{1/2} = .693/\ 0.0875 = 7.9$ hrs.

B) At renal dysfunction

- Fraction (f) = $\frac{Ke}{K} = \frac{CLr}{TBC} = \frac{75}{100} = 0.75$
- KF= $\frac{CrClfailure}{CrCl\ normal} = 0.3$
- Dose $_{failure}$ =Dose $_{normal}$ [f(KF-1)+1]
- Dose $_{failure}$ =600mg/12 h [0.75(0.3-1)+1]
- Dose $_{failure}$ =600mg/12 h [0.75(-0.7)+1]
- Dose $_{failure}$ =600mg/12 h [-0.525+1]
- Dose $_{failure}$ =600mg/12 h [0.475]
- Dose $_{failure}$ =285 mg/12 h

B) At renal dysfunction

- $$T_{1/2failure} = \frac{t\ 1/2\ normal}{[f\ (KF-1) + 1]}$$
- $$T_{1/2failure} = \frac{7.9}{0.475} = 16.6\ hr$$

- **K=0.693/16.6= 0.0416 hr-1**

C) Calculate the maximum and minimum plasma concentration achieved at steady state from the regimen you recommended in part (b).

- Regimen 285/12h

$$Cp_{\infty}\ max = \frac{FD}{Vd(1-e^{-K\tau})}$$

- $Cp_{max\ ss} = \frac{0.8x285}{24.6(1-e^{-.0416x\ 12})} = 23.58$ mg/l

$$Cp_{\infty}\ min = Cp_{\infty}\ max\ .\ e^{-K\tau}$$

- $Cp_{min\ ss} = 23.58e^{-.0416\ x12}$
- $Cp_{min\ ss} = 14.2$ mg /L

Problem 8.2

- A patient was admitted to the hospital because of severe pneumonia. An IV loading dose of an antibiotic followed by IV maintenance doses of 300 mg q12 h were prescribed. The creatinine clearance was 120 mL/min, which is considered normal for this patient. After 7 days of therapy (300 mg q12 h), the maximum and minimum plasma concentrations were 38 and 12.5 mg/L, respectively.
- A- Calculate mathematically the half-life and the volume of distribution of this drug in this patient.
- At steady state (while receiving 300 mg q12 hr) 180 mg of the drug is excreted unchanged in urine during one dosing interval. What is the renal clearance of this drug?
- After 15 day of antibiotic therapy, the kidney function of this patient deteriorated and his creatinine clearance was found to be 40 ml/min. what is the new half-life of the drug after this change in the patient's kidney functions?
- What will be the steady state maximum and minimum plasma concentrations if this patient continues taking 300mg q12 hr despite the change in his kidney functions?

A) Normal renal function

- $Cp_{max\ ss} - Cp_{min\ ss} = \frac{FDose}{Vd}$
- $38\text{-}12.5 = \frac{300}{Vd}$
- $Vd = 300/25.5 = 11.76\ L$

- $Cp_{min\ ss} = Cp_{max\ ss}\ e^{-k\tau}$
- $\ln Cp_{min\ ss} = \ln Cp_{max\ ss} - \ln e^{-k\tau}$

$$\text{Ln}\left(\frac{Cp_{max\ ss}}{Cp_{min\ ss}}\right) = K\tau$$

- $\text{Ln}\ (38/12.5) = 12\ K$
- $K = 0.09265\ hr^{-1}$
- $t_{1/2} = .693/\ 0.09265 = 7.47\ hrs.$

At steady state (while receiving 300 mg q12 h), 180 mg of the drug is excreted unchanged in urine during one dosing interval. What is the renal clearance of this drug?

- **Fraction (f) = $\frac{\text{Ke}}{\text{K}} = \frac{\text{CLrenal}}{\text{TBC}} = \frac{Ae}{Dose\ (iv)}$**
- **Fraction (f) = $\frac{Ae}{Dose\ (iv)} = \frac{180}{300} = 0.6$**
- **TBC = K Vd= 0.09265 x 11.76= 1.089 L/hr**
- **Renal clearance = f TBC= 0.6 x 1.089= .653 L/hr**

After 15 days of antibiotic therapy, the kidney function of this patient deteriorated and his creatinine clearance was found to be 40 mL/min. What is the new half-life of the drug after this change in the patient's kidney function?

- $KF = \frac{\text{CrClfailure}}{\text{CrCl normal}} = 40/120 = 0.3333$
- $f = 0.6$
- $\mathbf{T_{1/2failure} = \frac{t\ 1/2\ normal}{[f\ (KF-1)+1]}}$
- $\mathbf{T_{1/2failure} = \frac{7.5}{[0.6(.333-1)+1]}} = 12.5hr$
- $K = 0.693/12.5 = 0.05544\ hr^{-1}$

What will be the steady-state maximum and minimum plasma concentrations if this patient continues taking 300 mg q12 h IV despite the change in his kidney function?

- $Cp_{\infty}\ max = \frac{FD}{Vd(1-e^{-K\tau})}$

- $\mathbf{Cp_{max\ ss} = \frac{300}{11.76(1-e^{-.05544x\ 12})}} = 52.5$ mg/l

$\mathbf{Cp_{\infty}\ min = Cp_{\infty}\ max\ .\ e^{-K\tau}}$

- $\mathbf{Cp_{min\ ss} = 52.5e^{-.05544x12}}$

- $\mathbf{Cp_{min\ ss} = 26.9\ mg\ /L}$

Dose Adjustment in Hepatic Dysfunction

- Dose adjustment in patients with hepatic dysfunction is not an easy task. This is because there is no single clinical test that can be used for the assessment of liver function. Also, different metabolic enzyme systems are affected to different degrees by the reduction in liver function.
- **The Child-Pugh classification** has been used in clinical practice for categorizing patients according to the severity of their liver function impairment.
- This classification utilizes five different laboratory tests and clinical conditions to assess the severity of liver disease: serum albumin, total bilirubin, prothrombin time, ascites, and encephalopathy.
- Each of these parameters is classified and is given a score of 1, 2, or 3 depending on the value of the parameter
- The total Child-Pugh score is calculated from the sum of the scores for all the five parameters.

Child-Pugh's Classification for Patients with Liver Diseases

Parameters	Score		
	1	2	3
Serum albumin (g/dL)	>3.5	2.8–3.5	< 2.8
Total bilirubin (mg/dL)	< 2.0	2.0–3.0	> 3.0
Prothrombin time (seconds over control)	<4	4–6	>6
Ascites	Absent	Mild	Moderate
Encephalopathy	None	Moderate	Severe

- Patients having a score of 6–7 points classified as group A (mild) (No adjustment)
- Patients having a score of 8–9 group B (moderate) (25 % reduction of initial dose) (>60% metabolized)
- Patients having a score of 10–15 group C (severe) (50 % reduction of initial dose).

Example:

- A 55-year-old female was admitted to the hospital after developing an episode of ventricular arrhythmia. The patient had history of multiple medical problems including liver cirrhosis, hypertension, and ischemic heart disease. Her laboratory values upon admission were serum creatinine 1.1 mg/dL, serum albumin 3.2 g/dL, total bilirubin 4.5 mg/dL, and prothrombin time 8 s more than control. Physical examination showed that the patient is alert without any signs of encephalopathy, and the patient has mild ascites. The physician wanted to start the patient on lidocaine and asked you to recommend an average starting dose of lidocaine.

Answer

Lidocaine is an antiarrhythmic drug that is completely metabolized. So the patient's liver condition may affect the clearance of lidocaine. It is wise to calculate the Child-Pugh score for his patient to determine if dose reduction is necessary.

Serum albumin	**3.2 g/dL**	**Score = 2**
Bilirubin	**4.5 mg/dL**	**Score = 3**
Prothrombin time	**8 s > control**	**Score = 3**
Ascites	**Mild**	**Score = 2**
Encephalopathy	**Absent**	**Score = 1**
Total	**Child-Pugh score = 11**	

According to the Child-Pugh score, the starting dose of lidocaine in this patient should be 50% of the average recommended dose of lidocaine. Lidocaine dose can be adjusted after the start of therapy according to the therapeutic and the adverse effects of lidocaine.

Alteration in Drug Pharmacokinetics in Obese Patients

- Medications that have high lipid solubility tend to partition into adipose tissue, and the volume of distribution in obese patients for these drugs can be dramatically larger than in normal weight patients.
- Examples of lipophilic drugs with larger volume of distribution values in obese individuals are diazepam, carbamazepine, and trazodone.
- However, hydrophilic drugs tend to not distribute into adipose tissue so that the volume of distribution for many water-soluble drugs is not significantly different in obese and normal weight patients with some exceptions.

Ideal body weight (IBW)

- Ideal body weight (IBW) were preferred in moderate to highly lipophilic drugs when used.in obese patients.
- IBW (male) = 50 + 2.3 X height in inches > 60 inches
- IBW (Female) = 45 + 2.3 X height in inches > 60 inches
- **Obese: if > 130% IBW.**
- Inch = 2.54 cm; Foot = 12 inch.

Example of Hydrophilic drugs

- The aminoglycoside antibiotics (gentamicin) are hydrophilic drugs that are mainly distributed in the extracellular fluid (ECF) and usually have an average Vd of about 0.26.L/kg.
- It is recommended that in obese patients (patients whose TBW is >130% of the IBW) the Vd for aminoglycosides should be calculated based on following Equation.
- In this equation, the difference between TBW and IBW that represents the adipose tissues is multiplied by a factor of 0.4 to account for the lower extracellular fluids in adipose tissues:

$$Vd\ (L) = 0.26\ (L/kg)[IBW + 0.4\ (TBW - IBW)]$$

Example of Lipophilic drugs

- Also, lipophilic drugs such as phenytoin usually have high affinity to fat and are distributed to adipose tissues more than their distribution to lean tissues.

- The Vd for phenytoin is usually calculated in obese patients using following Equation. In this equation, the difference between TBW and IBW, which represents the adipose tissues, is multiplied by a factor of 1.33 to account for the higher affinity of this lipophilic drug to the adipose tissues:

$$Vd\ (L) = 0.7(L/kg)[IBW + 1.33(TBW - IBW)]$$


QUESTIONS?