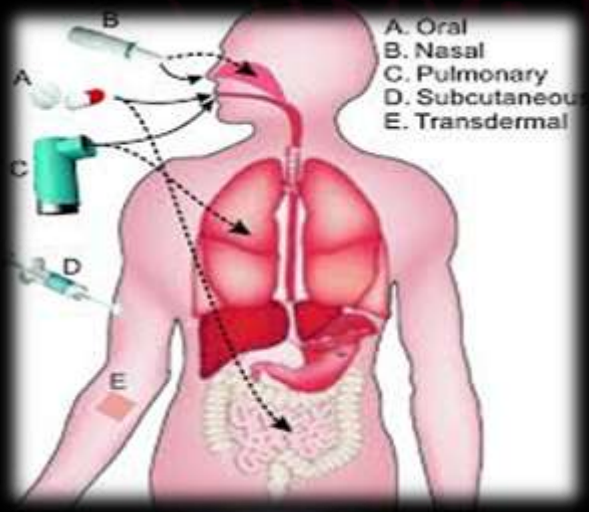
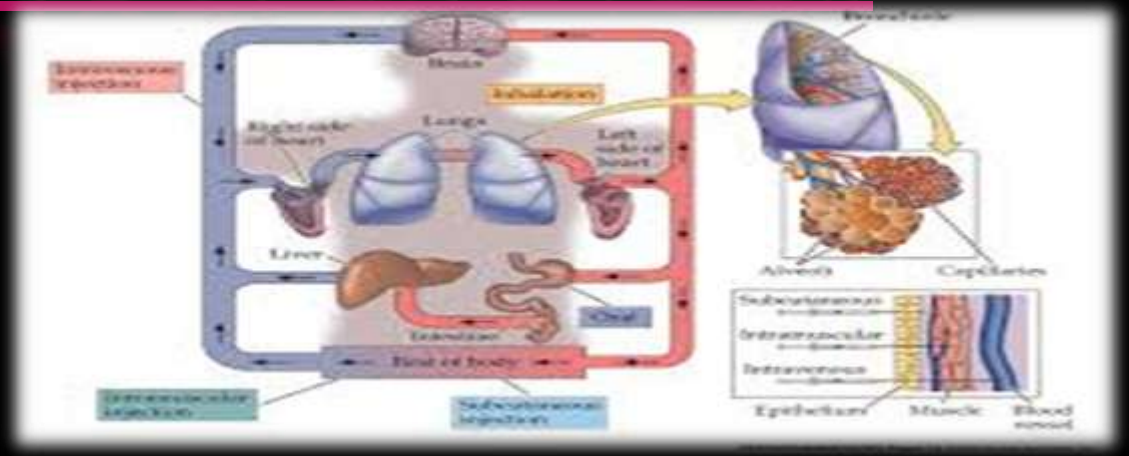
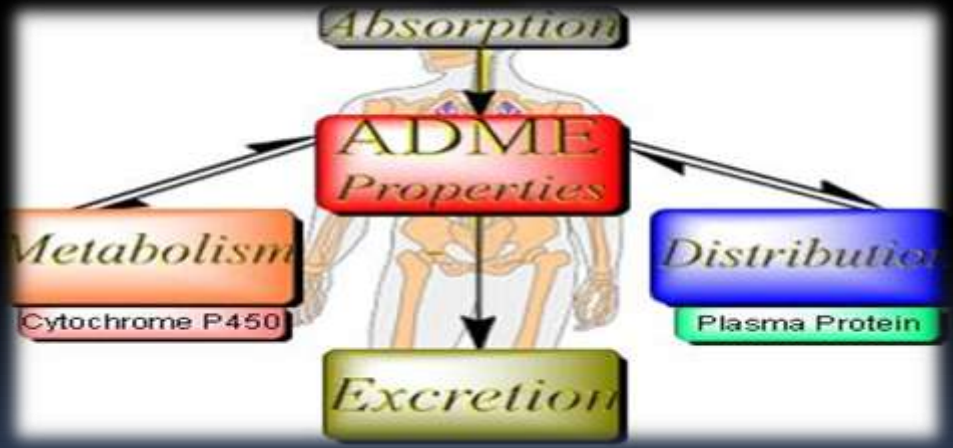
PHARMACOKINETICS







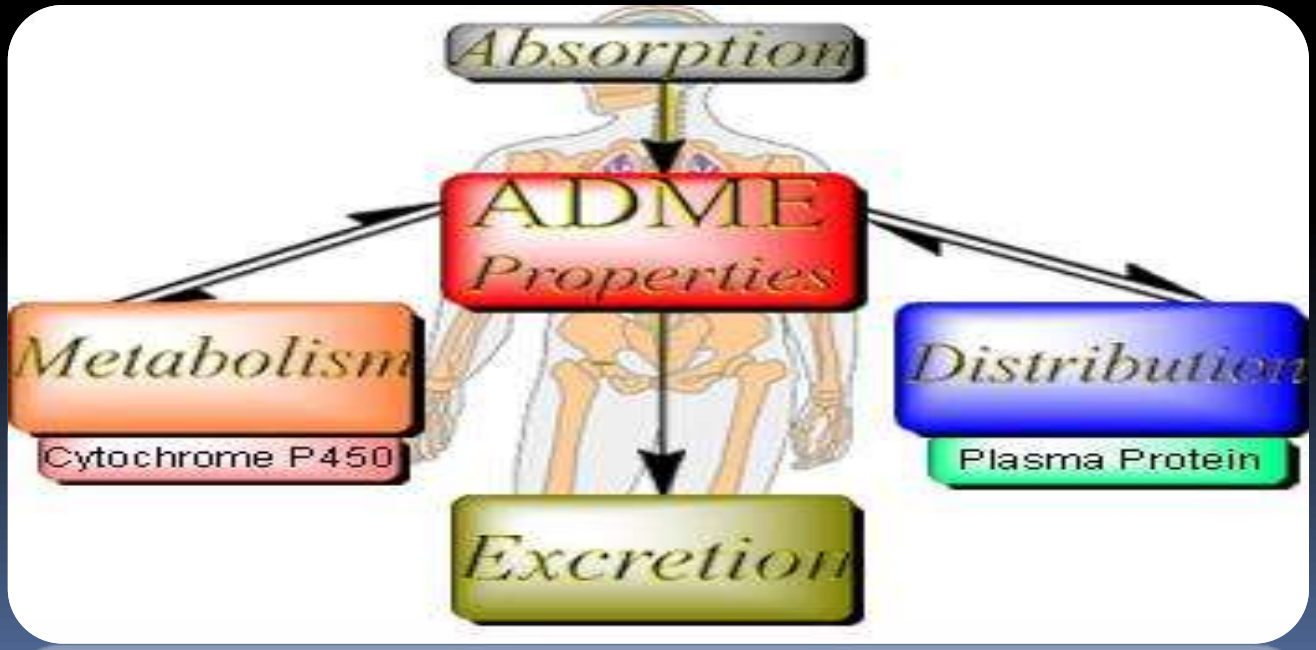
D. Mohammed sherif

pharmacokinetics

- **Definition:**

➢ The study of the time course of absorption, distribution, biotransformation and excretion of drugs and their metabolites in the body.

(kinetic study of ADME).



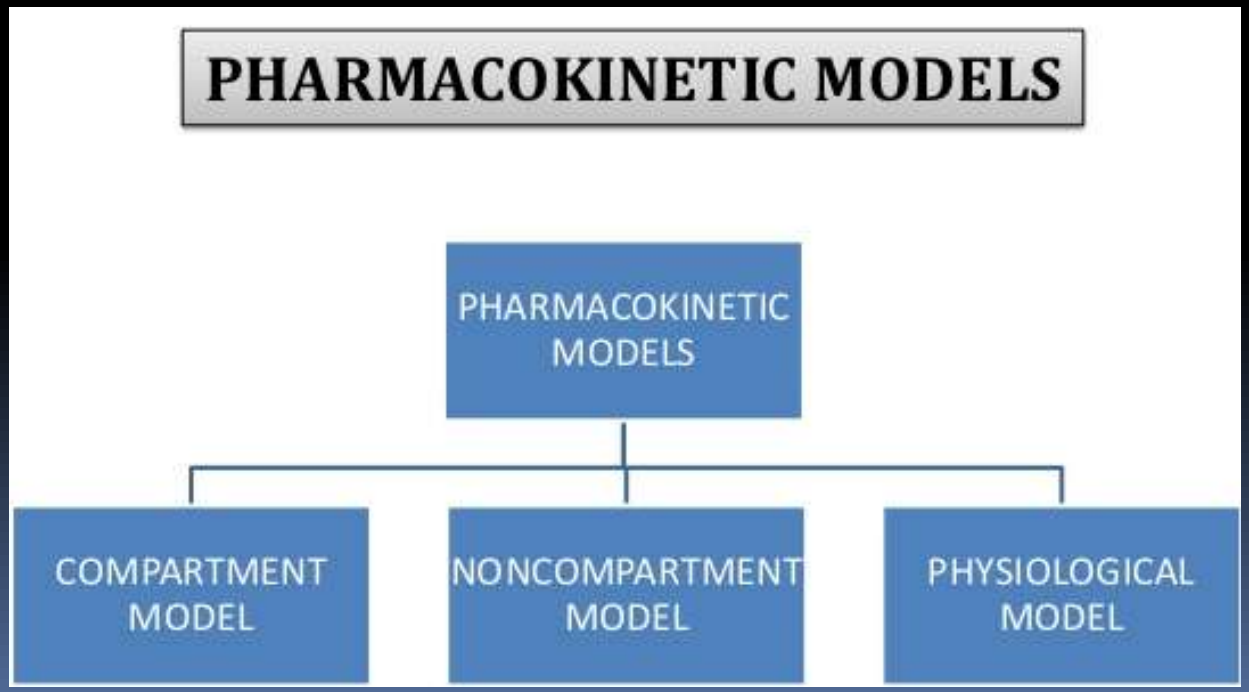
Overview

- Too much of a drug will result into toxic effects & too little will not result into the desired therapeutic effects.

- **Clinical pharmacokinetics**
  - The application of pharmacokinetic data to the most effective and safe therapeutic management of the individual patient.
- **Pharmacodynamics:**
  - The study of the biological and therapeutic effects of drugs
- **Bio-pharmaceutics:**
  - The study of the factors influencing the bioavailability of a drug in man and animals and the use of this information to optimize pharmacological and therapeutic activity of drug products
  - The study of the relationship between dosage formulation and the therapeutic response.

Pharmacokinetic Model

- Is a mathematical model devised to simulate the rate process of drug absorption, distribution and elimination?
- To development of equations descriping drug concentration in the body as a function of time.



- **N.B. There are three different approaches to pharmacokinetic analysis of experimental data;**

1. Compartment modeling
2. Non-compartment modeling
3. Physiological modeling

Compartments:

- is a tissue or a group of tissues that have similar blood flow or drug affinity.
- Anatomic spaces in the body which have the kinetic homogenity within which the drug has distributed.

A compartment in pharmacokinetics

- An entity which can be described by a definite volume and a concentration of drug contained in that volume.

NOTES;

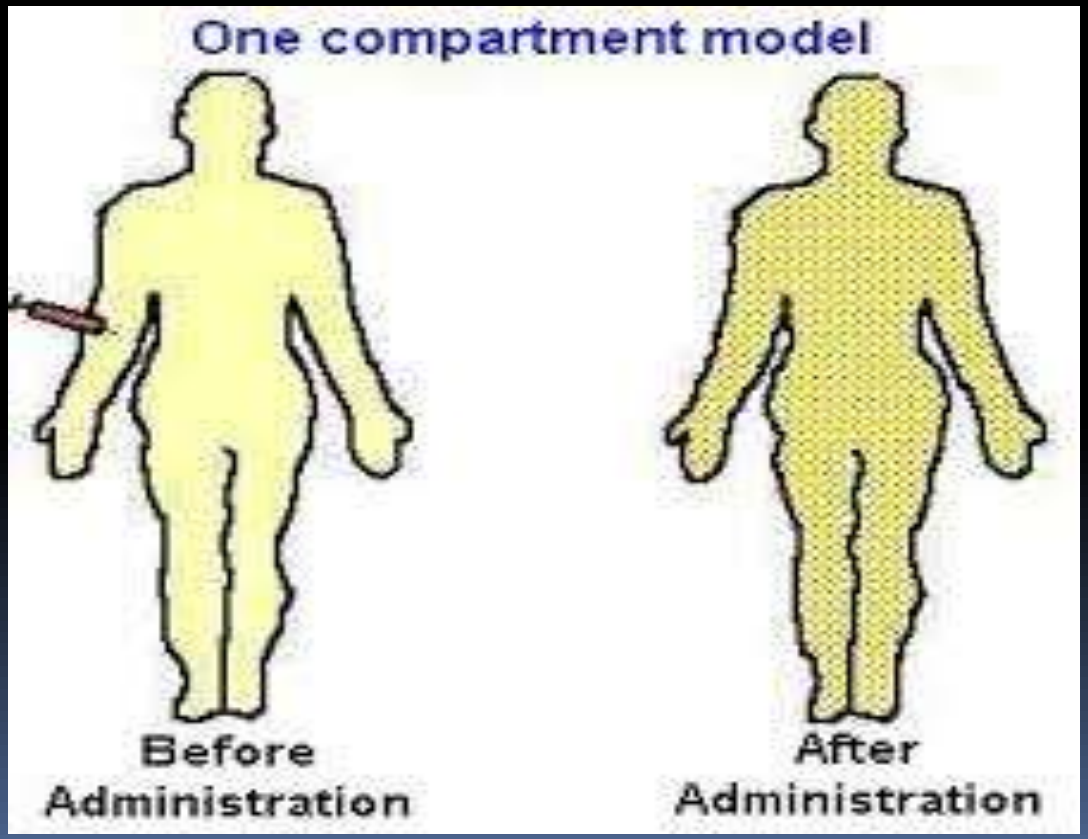
- A compartment is not real physiological or anatomic region.
- The rate constants are used to describe drug movement in and out of the compartments.
- The nature and behavior of the drug determines the number of the compartments
- E.g., some drugs go to 2 places so we have two compartments
- The model is open system because drug can be eliminated from the system

- Compartment models

1- One (single) compartment model:

- The body can be assumed to have homogenous characteristics after the administration of the drug.

- It is expected that after intravenous injection all those tissues are perfused with the drug.



2- Two - compartments model:

- The body is composed of a heterogenous group of tissues, each has a different rate of equilibration (a different affinity for the drug).

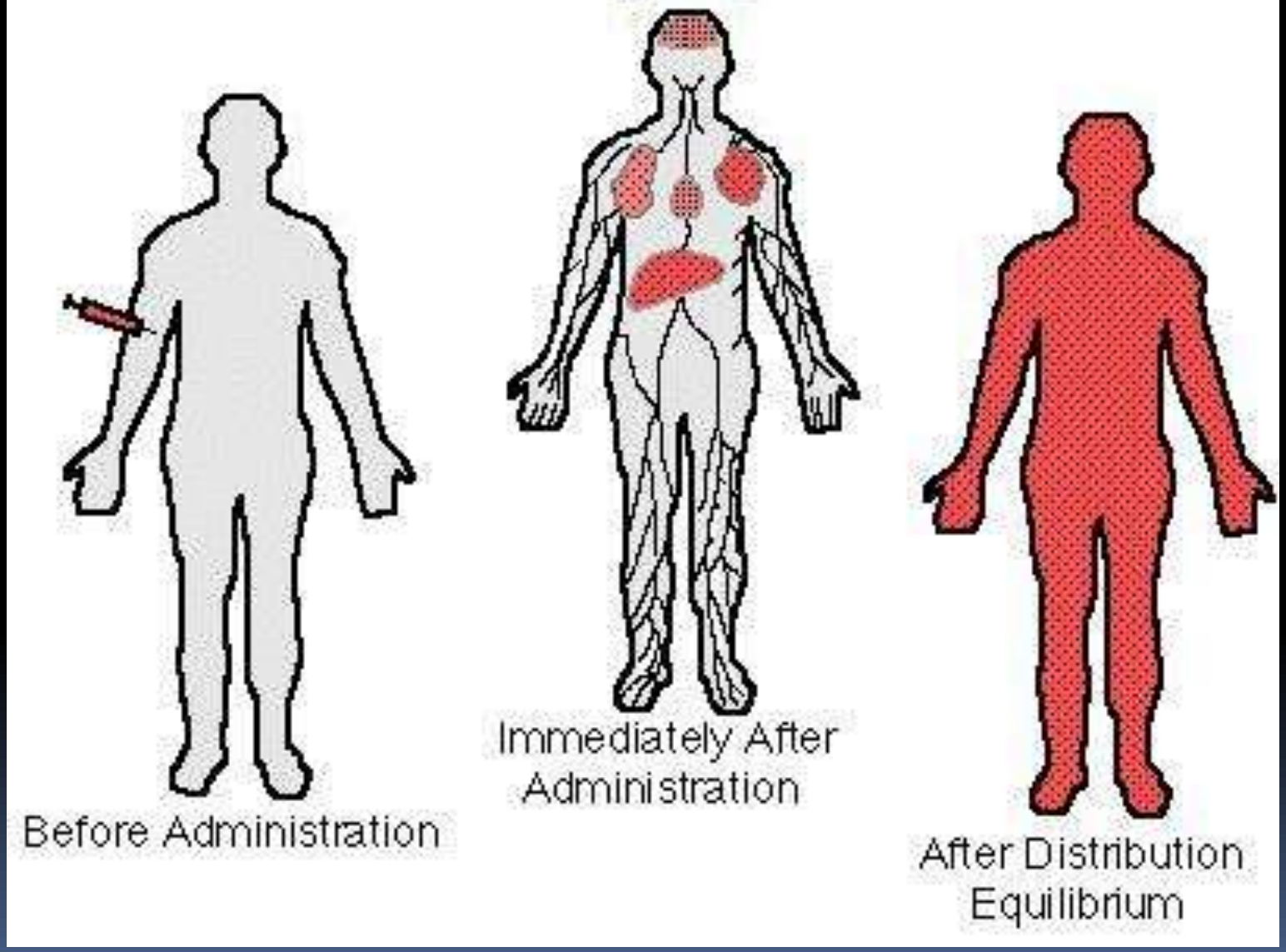
a) Central compartment:

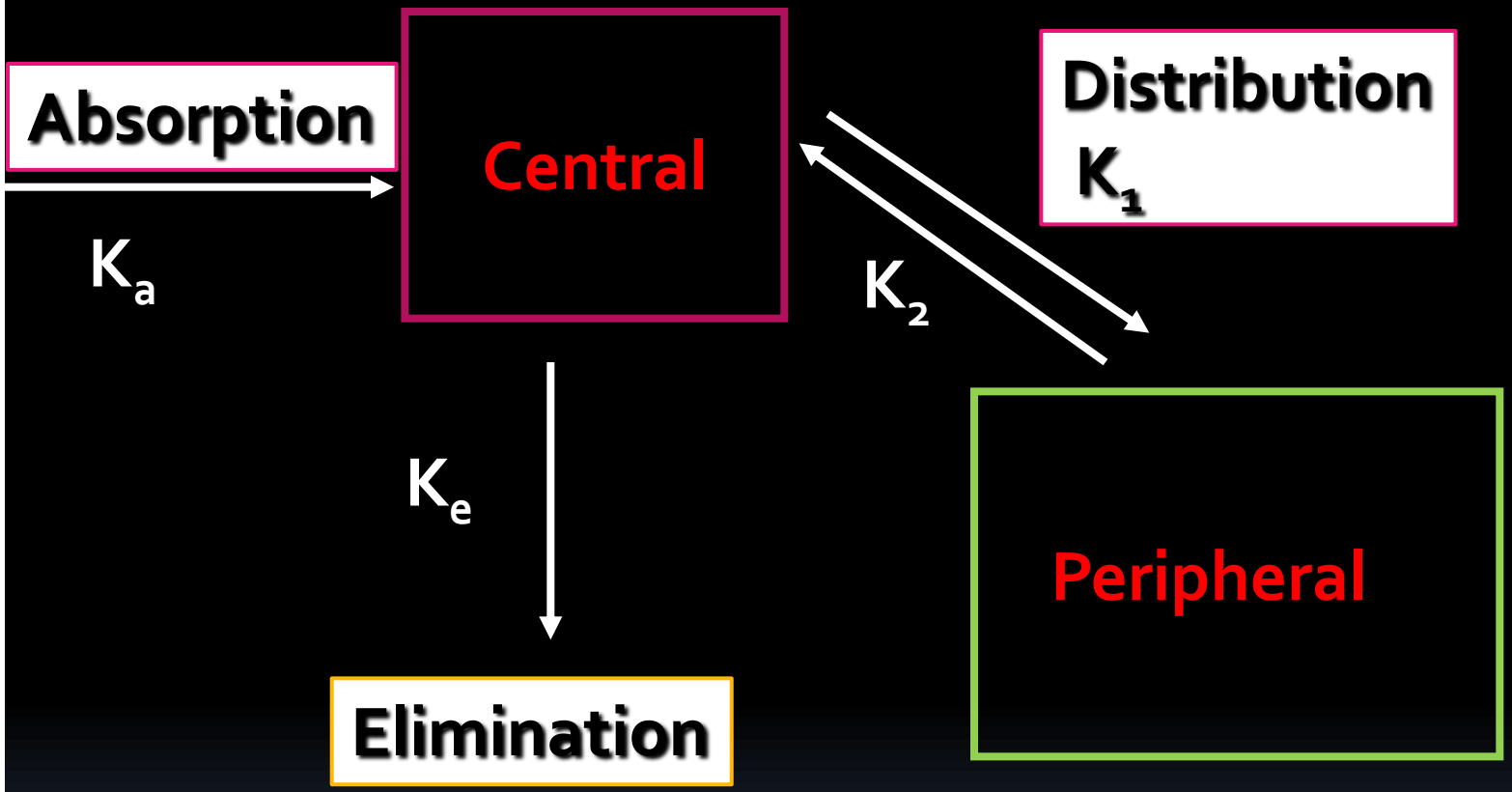
- Those tissues which equilibrate with the drug rapidly such as liver, kidney, heart and brain.

b) Peripheral compartment:

- Those tissues which equilibrate with the drug slowly such as bones, muscles, fats and cartilages.
- It acts as a reservoir compartment.

Two Compartment Model




Absorption
Central
Distribution
K_1
K_a
K_2
K_e
Peripheral
Elimination

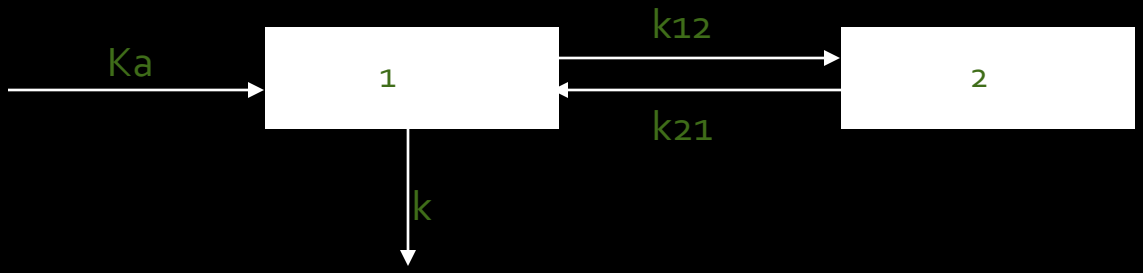
Compartment models;

Model 1: One compartment open model, IV injection;

Model 2: One compartment open model with first order absorption;

Model 3: two compartment open model, IV injection;

Model 4: two compartment open model with first order absorption;



- *N.B.*
- k = Pharmacokinetic rate constant
- Compartment 1 = represent the plasma or the central compartment
- Compartment 2 = represent the tissue compartment.

Uses of pharmacokinetic model

1- To predict plasma, tissue and urine drug levels.

2- To evaluate the bioavailability of different formulations.

3- To calculate the optimum dosage regimen for each patient.

4- To correlate the drug concentration and the pharmacological and toxicological effect.

5- To evaluate drug interactions.

6- To describe the changes in the physiology and the pathology which affect the drug absorption, distribution and elimination.

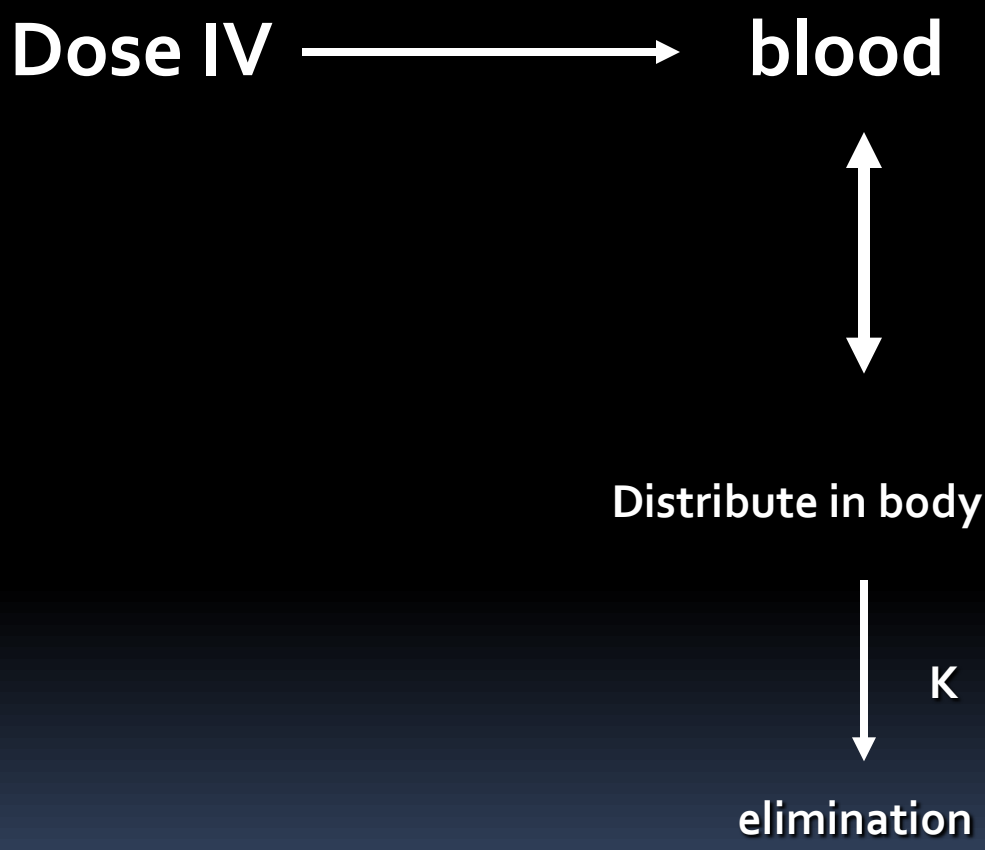
7- To give an idea concerning plasma protein binding.

8- To estimate the accumulation of the drug and its metabolites.

ONE COMPARTMENT MODEL

Intravenous route of administration

The pathway of drug after IV dose



Pharmacokinetic parameters

- **Half life ($t_{1/2}$)**
- **Elimination rate constant (k)**
- **Volume of distribution (v_d)**
- **Clearance (cl)**
- **Initial concentration (C_o)**

Definitions

- **Half life** : it is the time needed for the drug concentration to reach **to half its initial conc**.
- **Rate of elimination**: fraction of drug removed per unit time.

e.g. K= 0.1 min.

this means that **10%** of the drug removed per minute.

Definitions

- **Volume of distribution**: it is the apparent volume in which drug distribute at equilibrium.
- **Clearance**: it is the fraction of volume of distribution cleared of the drug per unit time
- **Initial concentration** : it is the concentration of the drug at zero time

How to calculate the conc. of drug in blood

$$C = C_0 e^{-kt}$$

Where:

C: plasma conc. Of drug at time t

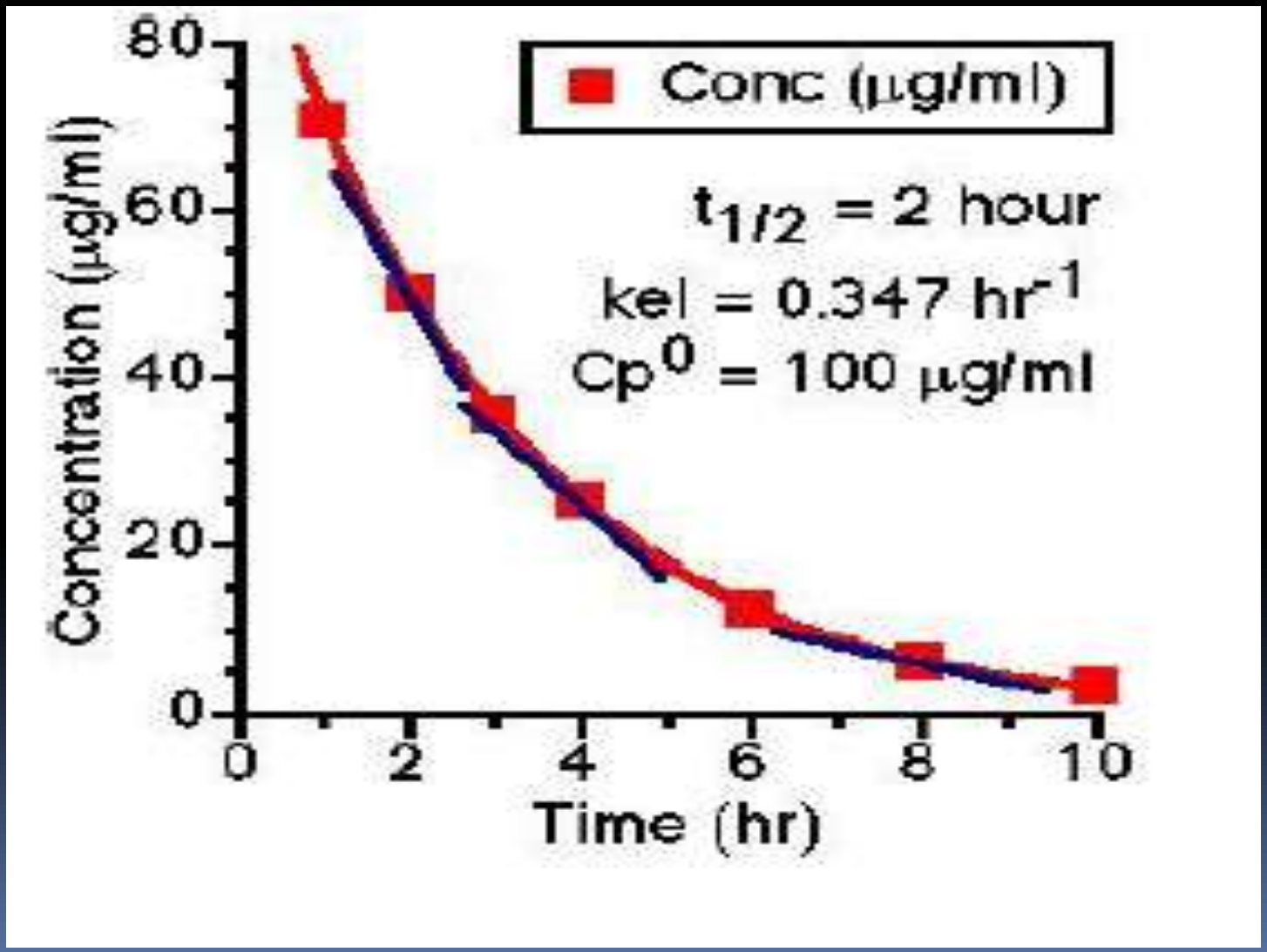
(remaining conc.)

C_0 : initial conc. At zero time

K : elimination rate constant

t : time

$$C = C_0 e^{-kt}$$

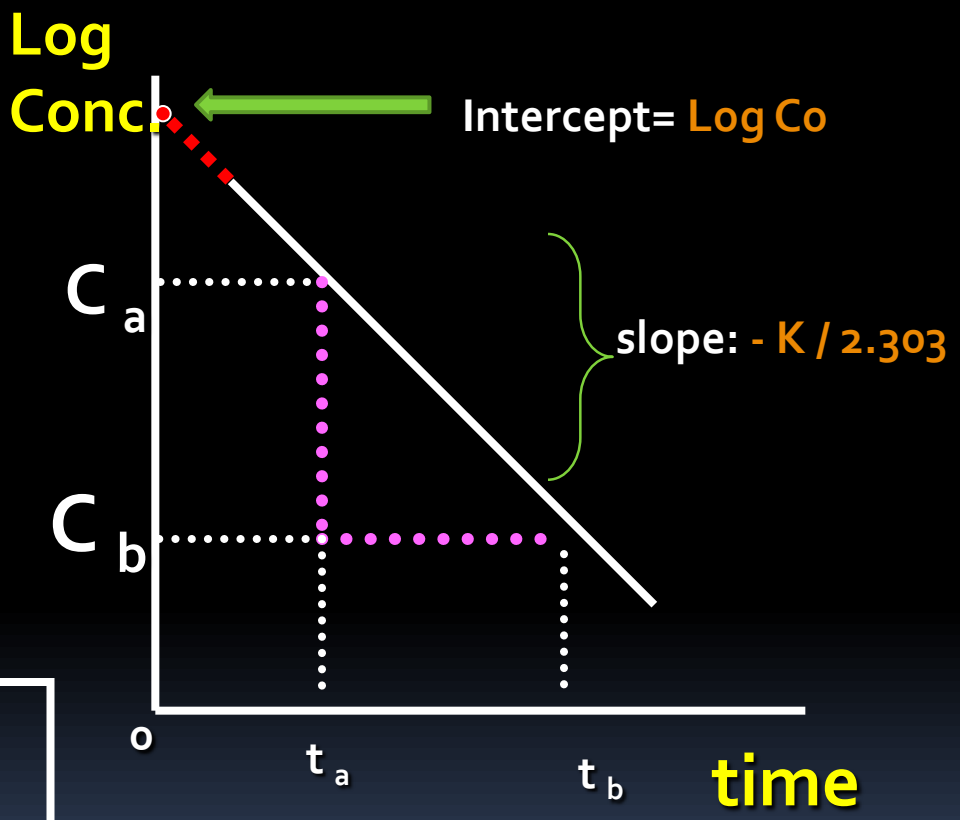

Conc (µg/ml)
$t_{1/2}$ = 2 hour
kel = 0.347 hr^{-1}
Cp^0 = 100 µg/ml
Concentration (µg/ml)
0
20
40
60
80
0
2
4
6
8
10
Time (hr)

$$\text{Log } C = \text{Log } C_o - Kt/2.303$$ (1st order equation)

- At time zero

It gives max conc. or C_o

$$\text{Slope} = \frac{\text{Log } C_a - \text{Log } C_b}{t_a - t_b}$$



Plot a graph between Log C on y-axis &time on x-axis

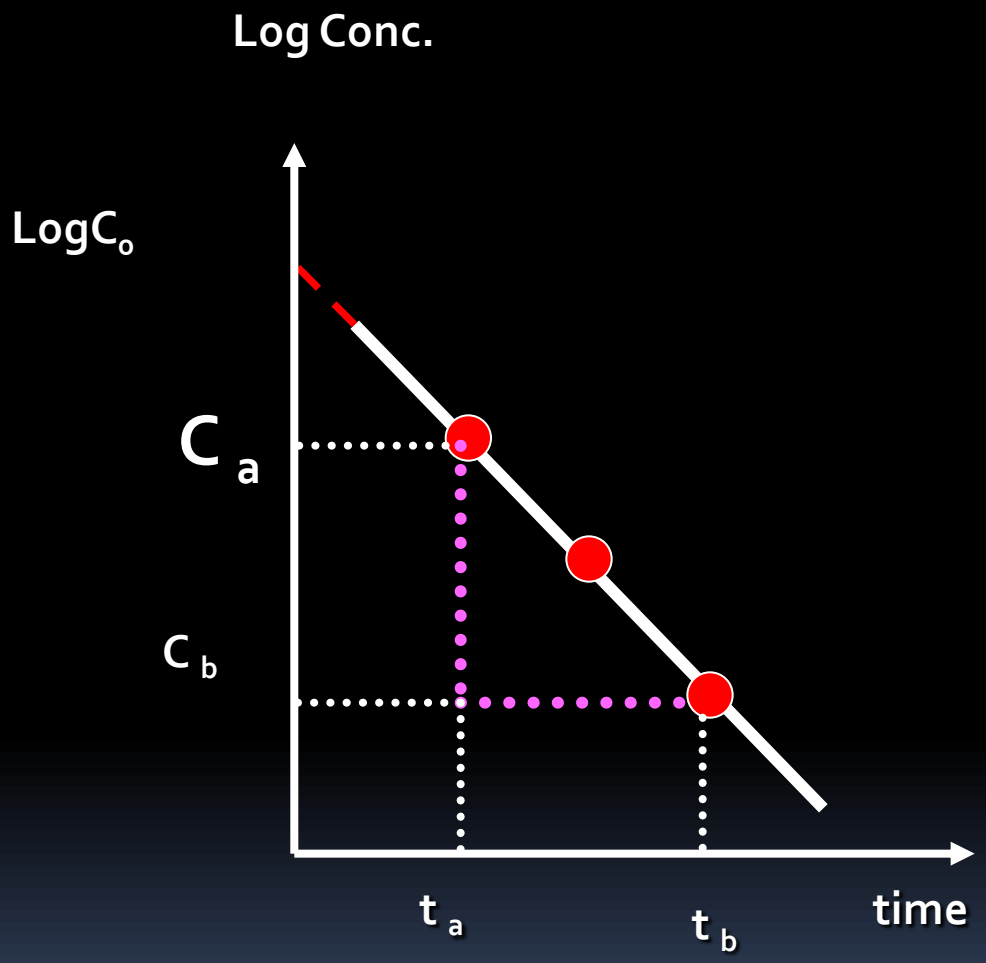
Intercept: Log Co

Slope: - K / 2.303

Notes

Slope will have – ve sign & this means the conc. of the drug decrease with time

How to draw?



Conc.	time
C1	t1
C2	t2
C3	t3

How to calculate pharmacokinetic parameters?

1- elimination rate constant.

Slope= - K / 2.303

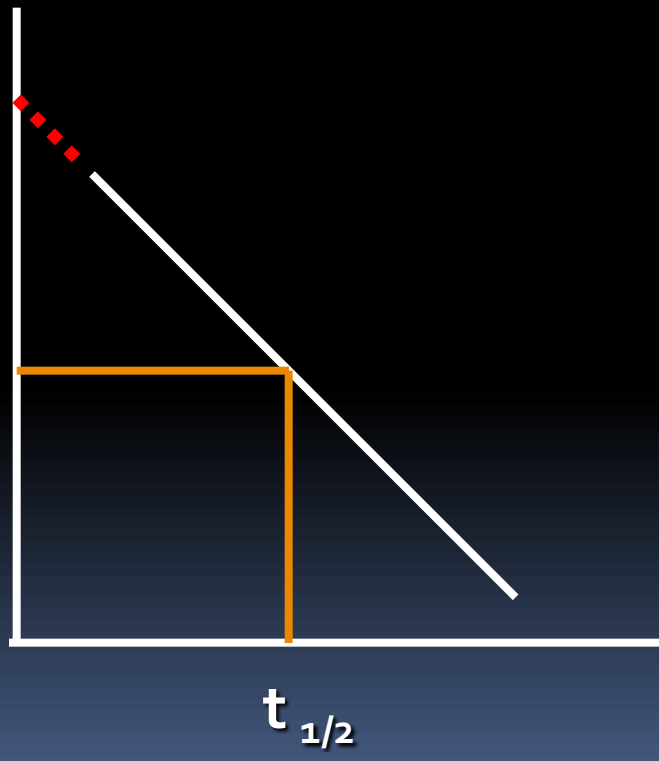
k = - Slope x 2.303

2- Half life

$t_{½} = 0.693 / K$

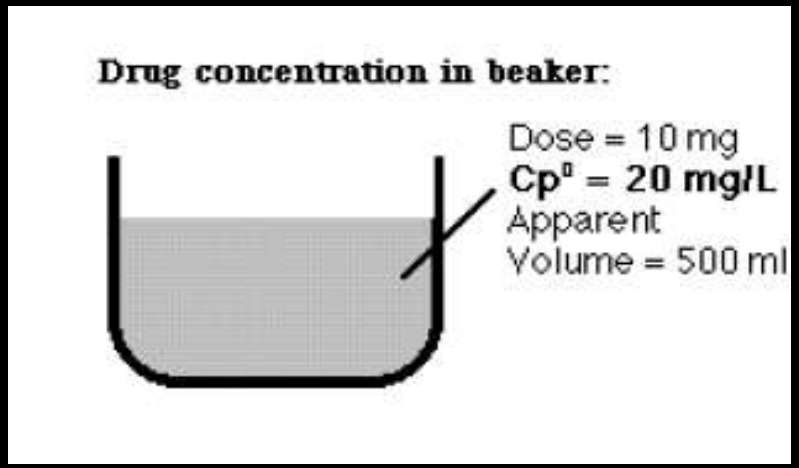
or

from graph $t_{½} = ½ C_o$



3- volume of distribution

$V_d = x_o / c_o$ or



$$V_d = \frac{\text{x at any time}}{\text{C at the same time}}$$

4- clearance (total clearance)

$Cl = K_t \times V_d$

Notes

$$K_t = k_r + k_b + k_{\text{other routes}}$$

Where

K_t : total elimination constant

K_r (K_e) : renal elimination constant

K_b : elimination constant when the drug biotransformed by the liver

Therefore when we need to get the clearance through the kidney. (renal clearance)

$$Cl_r = K_r \times V_d$$

Notes

How to predict the place of the drug distibution?

(predict what body compartment the drug occupy)

Calculate V_d

If $V_d = 4 – 6$ L therefore the drug in the blood only

$V_d > 6$ L therefore the drug in blood and tissues

$V_d = 30$ ml/ kg

Total $V_d = 30$ x wt of the patient

How to calculate Duration of activity?

Duration of activity means

when can the patient take the 2nd dose?

e.g.

Drug is ineffective when conc. < 2 ug ,

what is the time of 2nd dose?

It means we need to calculate the time in which the drug reach 2 ug (MIC) .

as after this time the drug no longer effective.

$$\text{Log } C = \text{Log } C_0 - K\,t / 2.303$$

C = 2 ug

How to know the problem is IV?

- single IV dose
- rapid IV injection
- IV bolus injection

Laws

$$1\text{-}\log C = \log C_0 - \frac{K t}{2.303}$$

Unit of conc. is wt/ vol. (mg / L or ug / ml)

2- k = - Slope x 2.303

Unit of K is time $^{-1}$ (hr $^{-1}$ or min $^{-1}$)

3- t ½ = 0.693 / K

Unit of t ½ is time

Laws

4- $V_d = x_o / c_o$

Unit of V_d is ml or liter

5- $Cl = K_t \times V_d$

Unit of clearance is vol/time (L/hr or ml/min)

Example

- Calculate the dose required by rapid IV bolus of drug (G), to achieve plasma concentration of 2.4 mg/L at 6 hr with a given elimination rate constant(K)=0.17 hr-1 and volume of distribution Vd = 25 L ?????

$\log C = \log C_0 - K t/2.303$

$\log (2.4) = \log C_0 - 0.17 \times 6/2.303$

$C_{0} = 6.65$ $V_d = x_0 / c_0$ $25 = x_{0}/6.65$

$X_0 = 166.3$ mg

Half-Life

- The half-life is the time taken for the plasma concentration to fall to half its original value. Thus if Cp = concentration at the start and Cp/2 is the concentration one half-life later then:

$$\ln\frac{Cp}{2} = \ln Cp - kel \cdot t_{1/2}$$

= ln 2 = kel * t1/2

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

Example

- A 70-kg male patient has been administered a single I.V dose of an antimalarial drug as aprophylactic treatment. If this drug has an elimination half-life of 3 hr and an apparent volume of distribution of 100 mL/kg, assuming that this drug follows a one-compartment kinetic model, determine the drug total body clearance in this patient.

Solution

$k = 0.693 / t \quad = 0.693 / 3 = 0.231\ hr\text{-}1$

Clearnce (Clt) = k VD = 0.231 x 100 = 23.1 ml / kg hr and for 70 kg,
Clt = 23.1 x 70 = 1617 ml / hr

Problems

1. 200 mg dose of drug was rapidly injected IV into an adult . The following blood levels were obtained :

Time(hr.)	2	5	8	12	18	22
Conc.(mg/ml)	15.86	11.2	7.9	4.97	2.5	1.56

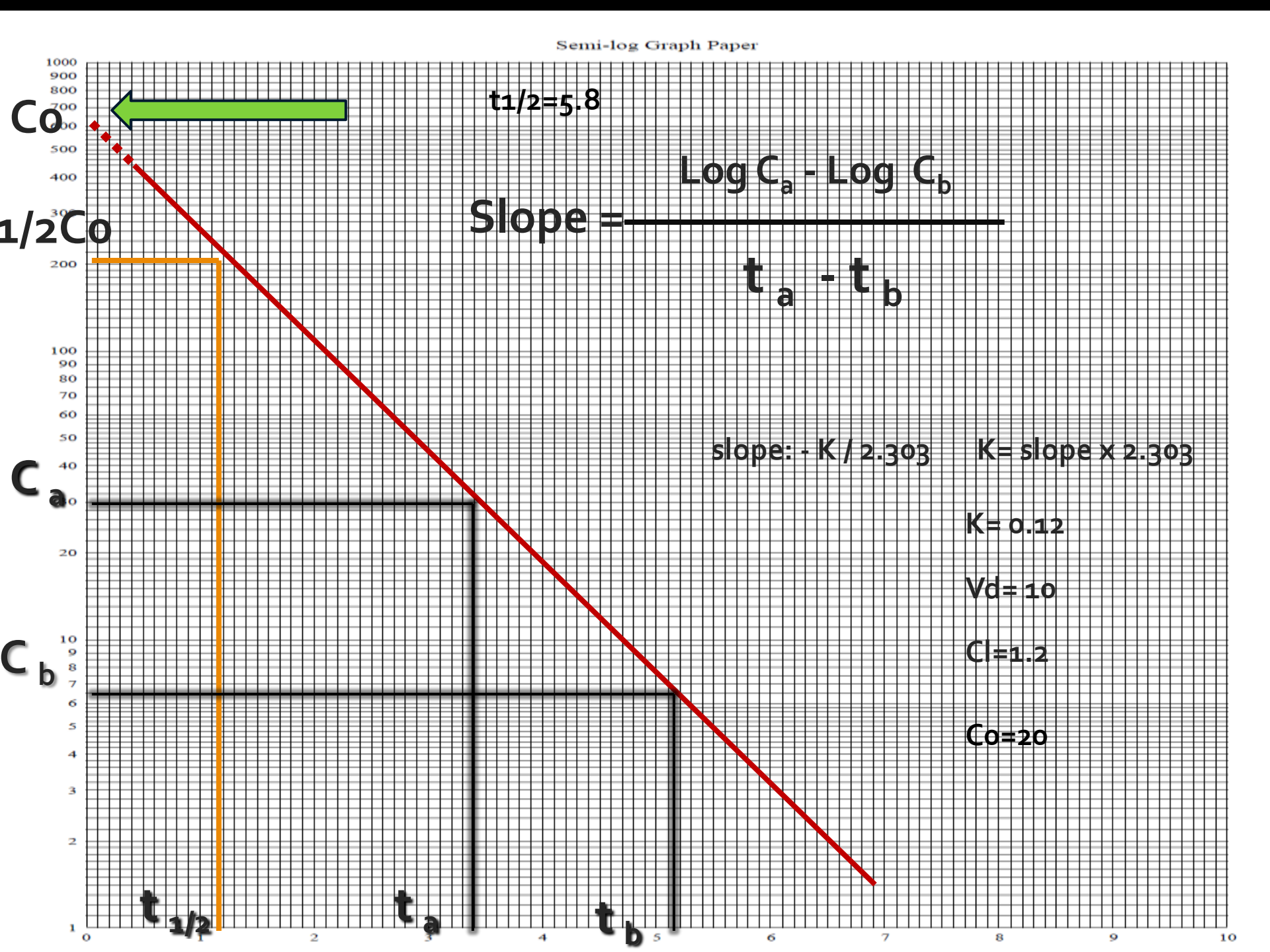
Plot the data on regular & semilog paper & evaluate:

a. $t_{1/2}$.

b. Write down the equation representing the line on the graph.

c. Evaluate the apparent volume of distribution.

d. Calculate the total body clearance.


Semi-log Graph Paper
Co
1/2Co
t1/2=5.8
Slope = (Log Ca - Log Cb) / (ta - tb)
Ca
Cb
slope: - K / 2.303
K= slope x 2.303
K= 0.12
Vd= 10
Cl=1.2
Co=20
t 1/2
ta
tb

2. 140 mg dose of drug was injected by rapid i.v. The following blood levels were obtained :

Time(hr.)	0.5	2	2.5	3	3.5	4.5
Conc.(mcg/ml)	2.85	1	0.7	0.5	0.35	0.17

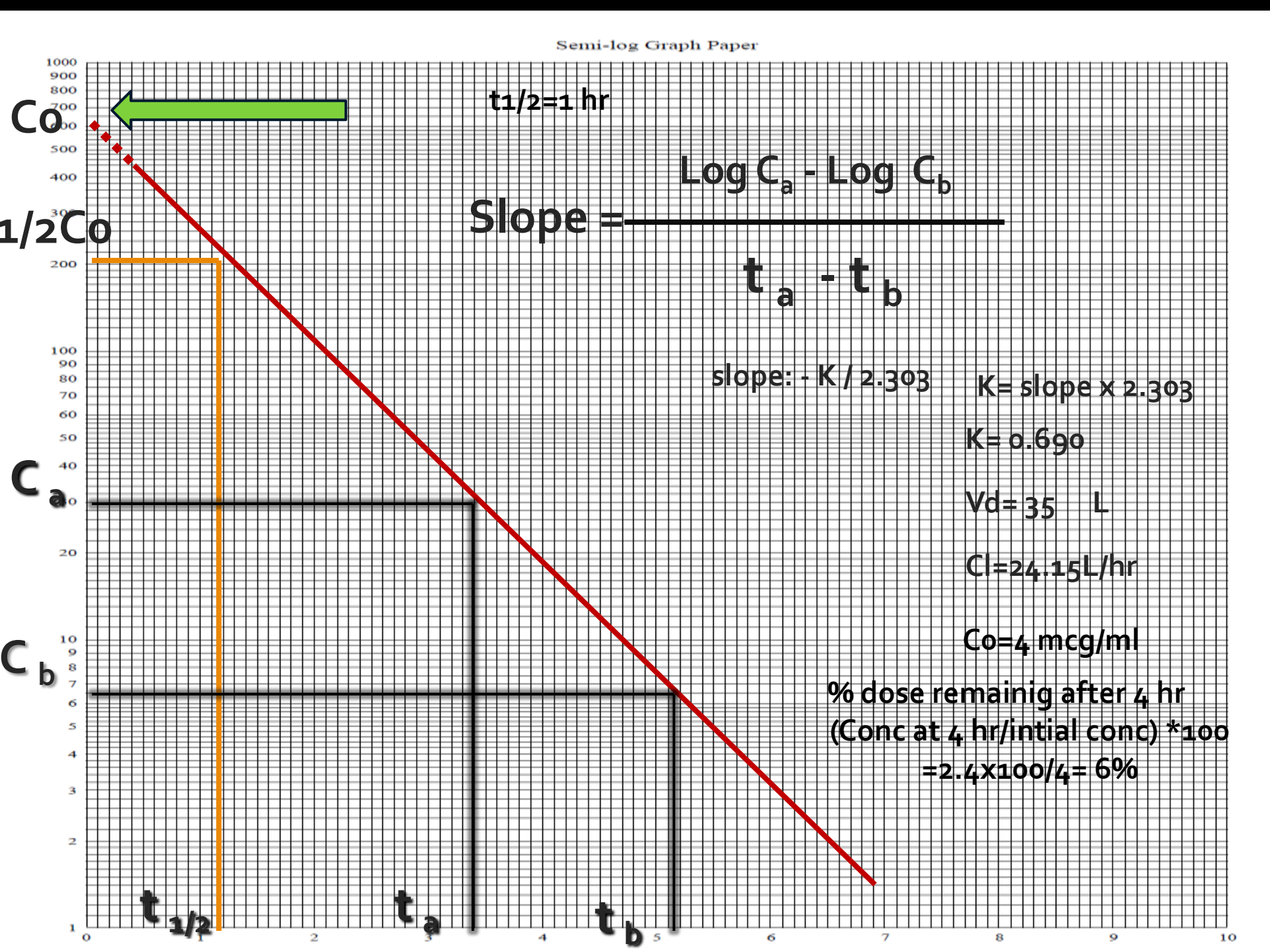
Estimate :

a. $t_{1/2}$ & K.

b. V_d.

c. Total body clearance .

d. % of dose remaining in the body 4 hours post injection .


Semi-log Graph Paper
Co
1/2Co
C_a
C_b
$t_{1/2}$
t_a
t_b
t1/2=1 hr
$\text{Slope} = \frac{\text{Log } C_a - \text{Log } C_b}{t_a - t_b}$
slope: - K / 2.303
K= slope x 2.303
K= 0.690
Vd= 35 L
Cl=24.15L/hr
Co=4 mcg/ml
% dose remainig after 4 hr
(Conc at 4 hr/intial conc) *100
=2.4x100/4= 6%

4) A dose of 2 mg/Kg was injected i.v. to a 75 Kg male. Samples were taken & blood levels versus time was constructed . The curve obtained can be described by the following equation :

$$Cp=20\ e^{-0.25t}$$

Calculate :

a-$t_{1/2}$ in hours

b. V_d.

c.Plasma level 3.5 hours after injection .

d.Percent dose remaining in the body 2.77hours after injection .

e.How long will it take for 99% of the drug to be eliminated &how Many $t_{1/2}$ does this represent? .

Information

- Co=20 mg /ml & K=0.25 hr-1

- t1/2= 0.693/k = 0.693/0.25= 2.77 hr

- Vd= dose/Co = 150/20=7.5 ml

- 99% eliminated this mean the remaining in body =0.1 %

The conc of drug in body which represent 0.1 % = 0.1 x Co =0.1 x 20/100=0.02 mg/ml

- Cp=0.02 mg/ml at what time reach that conc

- Log 0.02 = log 20- 0.25 x t/2.303 t=27.7 hr

- How many t1/2 = 27.7/2.77= 10 t1/2