TWO COMPARTMENT MODEL-AN APPROACH FOR PHARMACOKINETIC DETERMINATIONS

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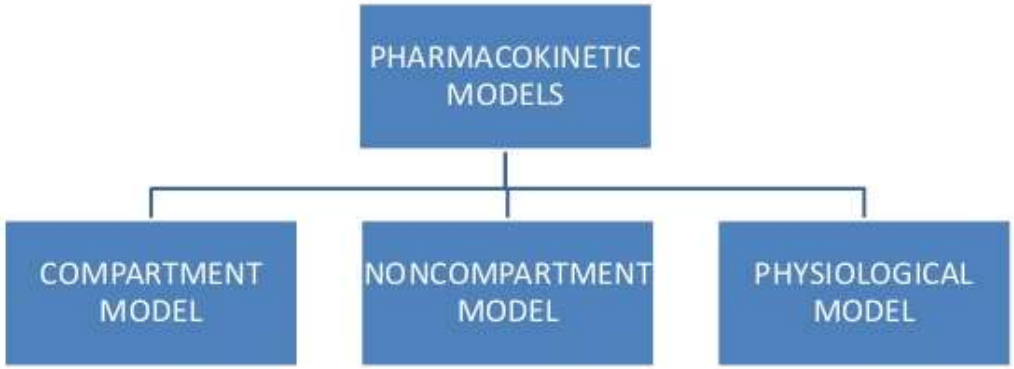
INTRODUCTION

PHARMACOKINETICS:

- **pharmacon:drug**
- **kinesis-motion/change of rate**

pharmacokinetics is the study of kinetics of absorption,distribution,metabolism and excretion(ADME) of drugs and their corresponding pharmacologic,therapeutic or toxic responses in man and animals.

PHARMACOKINETIC MODELS



COMPARTMENT MODELS

Compartment models are classical pharmacokinetic models that simulate the kinetic processes of drug absorption, distribution and elimination with little physiologic detail.

COMPARTMENT MODEL

- A physiological system is described by decomposition into number of interacting substances called compartments.
- Mass of well mixed ,homogenous material.
- Behaves uniformly.
- Exchange material.

OPEN AND CLOSE MODEL

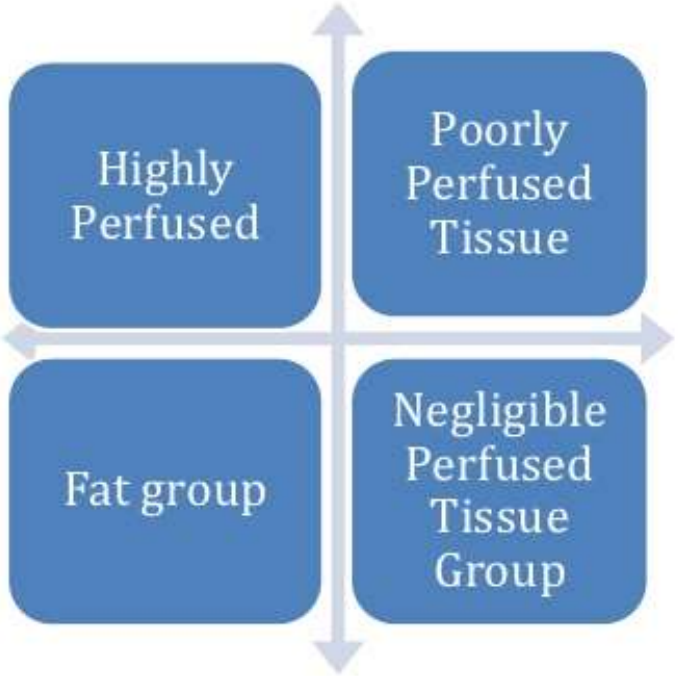
- OPEN MODEL:

  Administered drug dose is eliminated from the body by an excretory mechanism.

- CLOSED MODEL:

  The drug dose is not eliminated from the body.

COMPARTMENTS



(a) Classification of human body into compartments

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TWO COMPARTMENT MODEL

- Many drugs given in single IV bolus dose demonstrate a plasma level time curve that does not decline as single exponential process
- In two compartment model drugs the plasma drug conc. Declines biexponentially as the sum of two first order process, i.e distribution and elimination
- Does not equilibrate throughout the body

- Drug distributes in 2 compartments i.e central compartment & tissue/peripheral compartment.

CENTRAL COMPARTMENT

- Represents the blood ,extracellular fluid and highly perfused tissues
- Drug distributes rapidly and uniformly

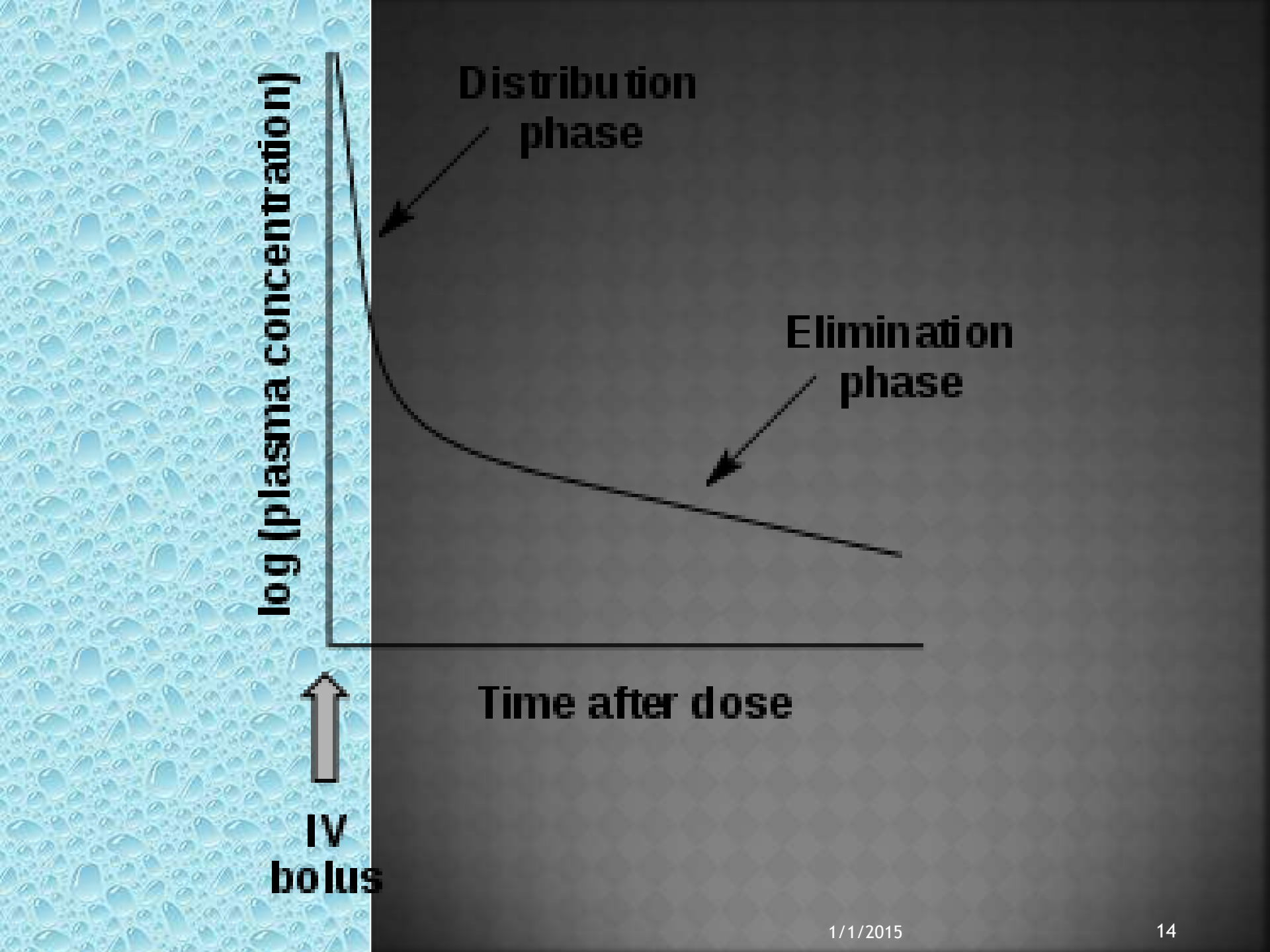
TISSUE OR PERIPHERAL COMPARTMENT

- Contains tissues in which drug equilibrates more slowly

- Drug transfer b/w the two compartments is assumed to be take place by first order processes

GENERAL GROUPING OF TISSUES ACCORDING TO BLOOD SUPPLY

BLOOD SUPPLY	TISSUE GROUP
Highly perfused	Heart, brain, hepatic portal vein, kidney and endocrine glands, skin and muscles
Slowly perfused	Adipose tissue and marrow
	Bone, ligaments, tendons, cartilage, teeth and hair


Distribution phase
Elimination phase
log [plasma concentration]
Time after dose
IV bolus

MODELS OF TWO COMPARTMENT SYSYTEM

- They differ in whether the drug elimination occurs from:
- the central compartment(Model 1)
- the peripheral compartment(Model 2)
- or both(Model 3)

CONTINUED….

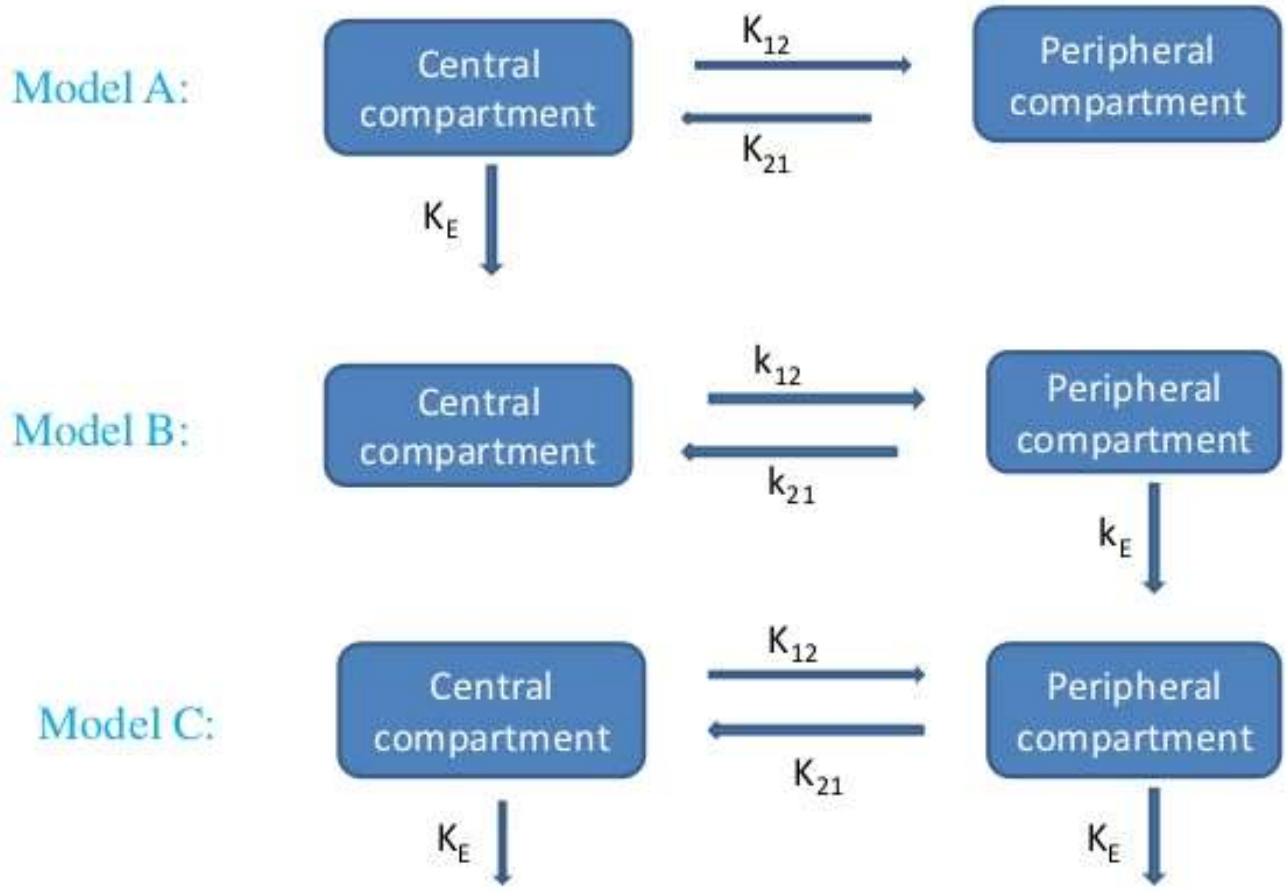
- **MODEL 1:**

  Major sites of drug elimination occurs in organs such as kidney and liver(highly perfused with blood).

- **MODEL 2:**

  Drug is assumed to follow the first order kinetics

TWO-COMPARTMENT OPEN MODEL



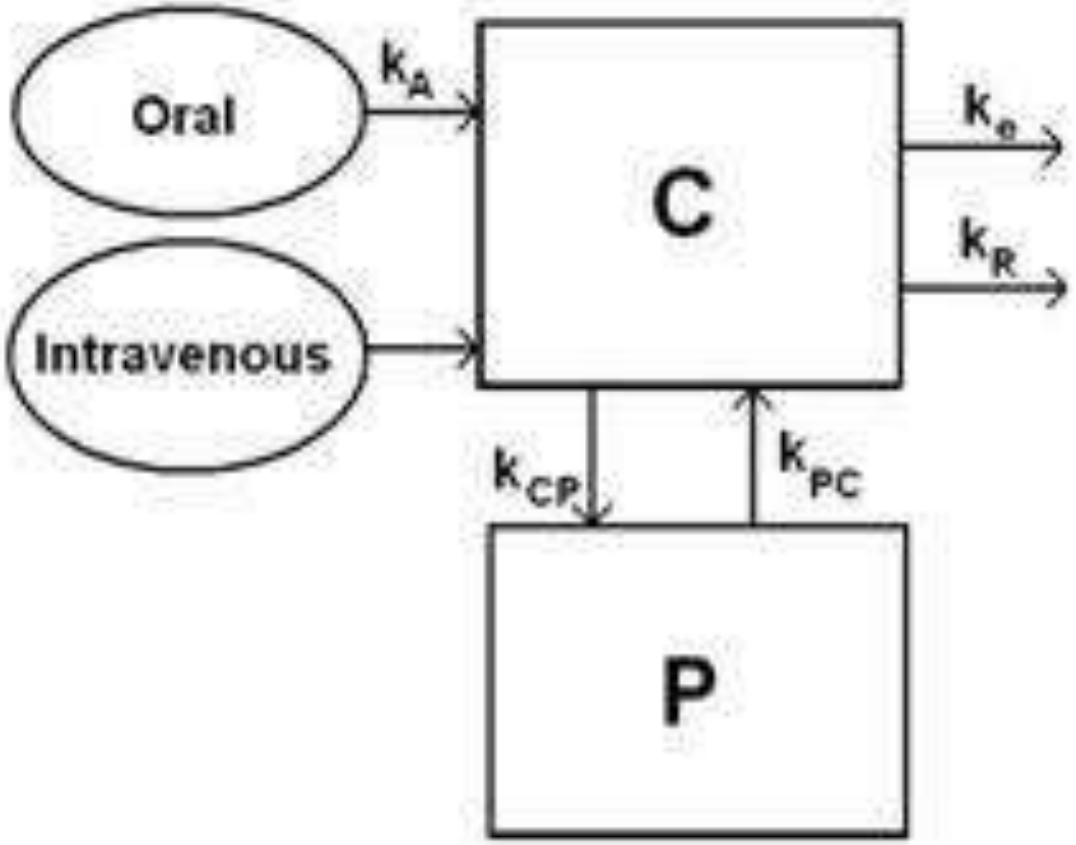


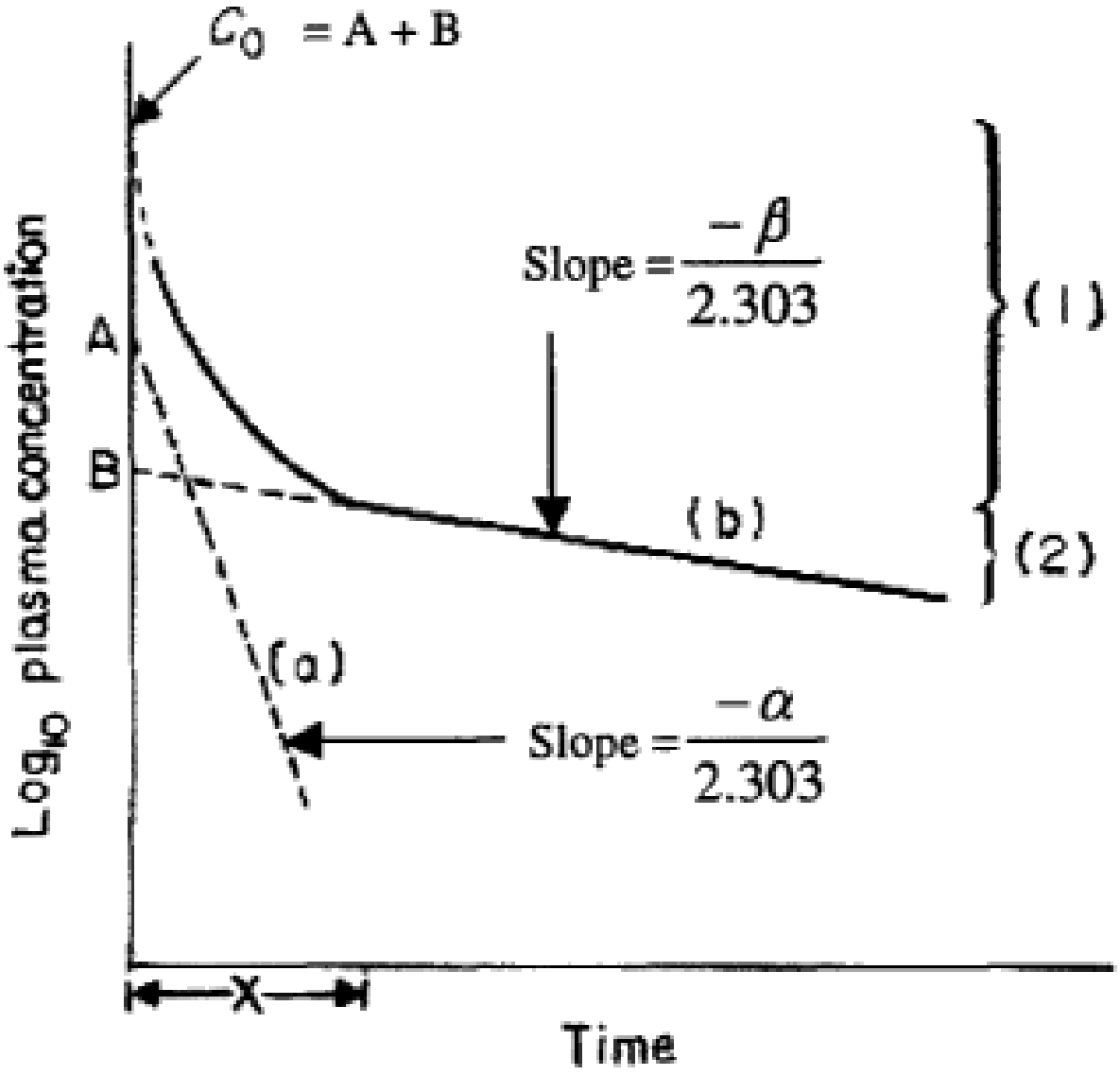
Figure A. Two compartment model

RATE CONSTANTS

- Rate constants k12 and k21 represents the first order rate transfer constants for the movement of drug from compartment 1 to compartment 2 i.e k12
- And from compartment 2 to 1 i.e k21

CURVE OF THE TWO COMPARTMENT MODEL

- Blood sampling
- Analyzed for drug content
- Distributive phase: drug is diffused into peripheral compartment till equillibrium is attained
- Elimination phase


$C_0 = A + B$
Slope $= \frac{-\beta}{2.303}$
A
B
(b)
(1)
(2)
(a)
Slope $= \frac{-\alpha}{2.303}$
Log_{10} plasma concentration
X
Time

BASIC ASSUMPTIONS

- t=0
- After an I.V dose drug levels will first increase,reach maximum and then decline
- tmax
- Distribution equilibrium

BIPHASIC EXPONENTIAL EQUATION

- Values of microconstants cannot be determined by direct method,graphical method is used

$$a+b=k12+k21+k$$

Biphasic equation:

$$Cp=Ae^{-at}+Be^{-bt}$$

$A=D\circ(a-k21)/Vp(a-b)$: $B=D\circ(k21-b)/Vp(a-b)$

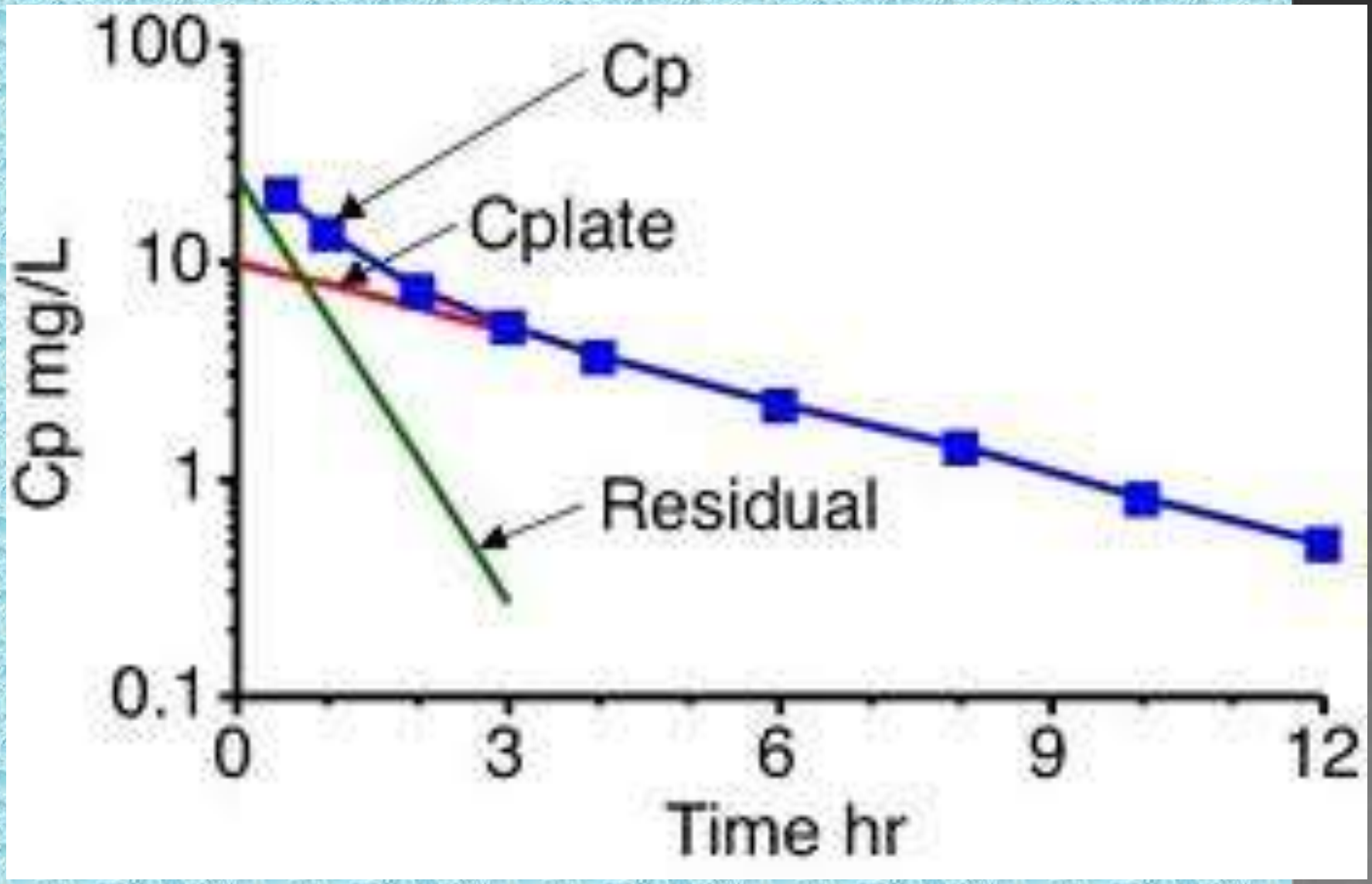
METHOD OF RESIDUAL

- Useful procedure for fitting a curve to the experimental data of a drug when drug does not clearly follow one compartment model
- I.V administration of drug
- Blood sampling
- Assay
- Data is obtained and plotted on semilog graph paper,curve line is obtained

CONTINUED....

- Curve line realationship b/w the log of the plasma conc.and the time indicates that the drug is distributed in more than one compartments
- So from data biexponential equation is derived:

$$Cp=Ae^{-at}+Be^{-bt}$$


100
10
1
0.1
Cp mg/L
Cp
Cplate
Residual
0
3
6
9
12
Time hr

HALF LIFE

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

- From b ,the regression line for the terminal exponential/b phase is extrapolated to y axis
- Y-intercept is equal to B

RESIDUAL VALUES

- Values from the extrapolated line are then subtracted from the original experimenatl values
- Residual plasma conc. Is obtained
- Straight line is obtained
- Residual plasma conc.

PARAMETERS OF THE TWO COMPARTMENT MODEL

- Apparent volume of distribution
- Drug clearance
- Biological half life
- Elimination rate constant
- AUC

APPARENT VOLUME OF DISTRIBUTION

- Relates plasma conc. to the amount of drug in the body
- Drugs with large extravascular distribution,apparent Vd is generally large
- Drugs with high peripheral tissue binding also have large apparent Vd
- For polar drugs,apparent Vd is small
- Reflects the extent of drug distribution

CONTINUED…

Several Vd are calculated as:

- Volume of central compartment
- Apparent Vd at the steady state
- Extrapolated volume of distribution
- volume of distribution by area

VOLUME OF CENTRAL COMPARTMENT

- Useful for determining drug conc.directly after an IV injection into the body
- Also called initial volume of distribution
- Generally smaller than the terminal Vd
- Vp as mass balance factor
- By plasma conc. and from AUC

CONTINUED....

$D_\circ = VpCp$

$Vp = D_\circ / A+B$

$Vp = D_\circ / k[AUC]$

APPARENT VOLUME OF DISTRIBUTION AT STEADY STATE

- The rate of drug entry into the tissue compartment from central compartment is equal to the rate of drug exit from tissue compartment into the central compartment

  Dtk21=Dpk12

  Dt=k12Dp/k21 [Dp=CpVp]

  Dt=k12.CpVp/k21

CONTINUED....

$$V_d = D^\circ / C_p$$

$$(V_d)_{ss} = D_t + D_p / C_p$$

$$(V_d)_{ss} = V_p(1 + k_{12}/k_{21})$$

CONTINUED…

- (VD)ss is a function of transfer constants k12 and k21 which represents rate constants of drug going into and out of time compartment
- Magnitude of (VD)ss is dependent on:

a. hemodynamic factors for drug distribution

b. physical properties of drug

EXTRAPOLATED VOLUME OF DISTRIBUTION

It is calculated by :

$$Vd=D\circ/Cp$$

$$(Vd)exp=D\circ/B$$

$$B=D\circ(k21-b)/Vp(a-b)$$

$$(Vd)exp=Vp(a-b)/(k21-b)$$

- This equation shows that a change in the distribution of drug which is observed by change in the value for vp,will be reflected in change in (Vd)exp

VOLUME OF DISTRIBUTION BY AREA

- reduced drug clearance from the body may increase AUC such that $(Vp)_\beta$ is either reduced or unchanged depending on the value of b.

$$(Vp)_\beta=(Vd)area=Do/b[AUC]_0^\infty$$

$$Cl=Do/[AUC]_0^\infty$$

$$(Vd)_\beta=Cl/b$$

$$(Vd)_\beta=k.Vd/b$$

SIGNIFICANCE OF VOLUME OF DISTRIBUTION

- (VD)b is affected by changes in the overall elimination rate and by the change in the total body clearance of the drugs
- Useful in calculation of clearance
- $(Vd)exp > (Vd)_{\beta} > Vp$

CONTINUED….

- Changes in disease state may not result in different pharmacokinetic parameters.
- Changes in pk parameters should not lead to the physiologic changes.

DRUGS IN TISSUE COMPARTMENT

- Apparent Vt is conceptual volume only and does not represent the true anatomic volume

$$Vt = Vpk12/k21$$

$$Dt = [k12Dp\circ](e^{-bt} \_ e^{-at})/a-b$$

DRUG CLEARANCE

- Clearance is the volume of plasma that is cleared of drug per unit time.

Cl=Vd)b

- Useful in determining average drug conc.

ELIMINATION RATE CONSTANT

- Elimination rate constant of central compartment and tissue compartment
- Because of redistribution of drug out of tissue compartment ,b is smaller than k.
- Three rate constants are associated with two compartment model

$$k21=Ab+Ba/B+A$$

$$k10=ab/k21$$

$$k12=a+b-k21-k10$$

BIOLOGICAL HALF LIFE

- Biological half life can be determined from the rate constant.

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

AREA UNDER CURVE

TWO STEP METHOD:

1. **Trapezoidal method**

   $AUC_{t-\infty} = C_o/ke$

2. **By using equation**

   $AUC_{total} = C_o/k10$

   $AUC = B/b + A/a$

INTRAVENOUS INFUSION OF TWO COMPARTMENT MODEL DRUGS

- I.V infusion requires a distribution and equillibrium of the drug before the stable blood level is reached.
- Distribution equillibrium.
- Constant drug conc. In tissue.
- No net change in the amount in the tissue occurs during steady state.
- Time needed to reach steady state blood level depends entirely on the distribution half life of drug.

- Equation describing plasma drug concentration:

  $Cp=R/Vpk[1-(k-b/a-b)e^{-\alpha t}\_(a-k/a-b)e^{-bt}]$

- At steady state:

  $Css=R/Vpk$

- Infusion rate:

  $R=CssVpk$

LOADING DOSE FOR TWO COMPARTMENT MODEL DRUGS

- Drugs with long half lives require a loading dose to more rapidly attain steady state plasma drug levels
- Rapid therapeutic drug levels can be achieved by using a loading use
- Drugs equilibrate slowly into extravasular tissues,drug equilibrium is not immediate

APPARENT VOLUME OF DISTRIBUTION AT STEADY STATE

Dtk21=Dpk12

Dt=k12Dp/k21

Dt=k12CpVp/k21

- Conc. Of drug in the central compartment at steady state:

(Vd)ss=Dp+Dt/Cp

$$(Vd)ss=CpVp+k12VpCp/k21/Cp$$

$$(Vd)ss=Vp+k12/k21Vp$$

CLINICAL APPLICATIONS

- Hydromorphone studies
- Drug distribution of Loperamide

CONCLUSION

- Pharmacokinetic models predict drug disposition after drug administration.
- Statistical methods are used for the estimation and data interpretation of pharmacokinetic parameters.
- Useful in drug formulation and treatment regimen.

CONTINUED….

- The drug behaviour within the body might be able to fit different compartmental models depending upon the route of drug administration.

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Thank
You
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