Two Compartment Model

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- Ideally a true pharmacokinetic model should be the one with a rate constant for each tissue undergoing equilibrium.
- Therefore best approach is to pool together tissues on the basis of similarity in their distribution characteristics.
- The drug disposition occurs by first order.
- Multi-compartment characteristics are best described by administration as i.v. bolus and observing the manner in which the plasma conc declines with time.

Multi compartment models (Delayed distribution models)

▸ One compartment is described by mono-exponential term i.e.elimination.

▸ For large class of drugs this terms is not sufficient to describe its disposition.

▸ It needs a bi- or multi- exponential terms.

▸ This is because the body is composed of a heterogeneous group of tissues each with different degree of blood flow and affinity for drug and therefore different rates of elimination.

▸ The no. of exponentials required to describe such a plasma level-time profile determines the no. of kinetically homogeneous compartments into which a drug will distribute.

▸ The simplest and commonest is the two compartment model which classifies the body tissues in two categories :

1. Central compartment or Compartment 1
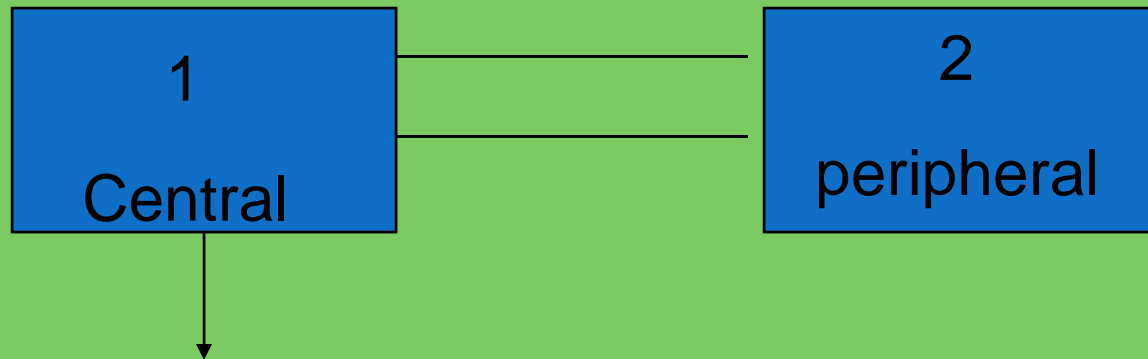2. Peripheral or Tissue Compartment or Compartment 2.

- Compartment 1 comprises of blood and highly perfused tissues like liver, lungs, kidneys, etc. that equilibriate with the body rapidly.
- Elimination usually occurs from this compartment.
- Compartment 2 comprises of poorly perfused and slow equilibriating tissues such as muscles, skin, adipose, etc.
- Considered as a hybrid of several functional physiologic units.

- Depending upon the compartment from which the drug is eliminated, the 2 compartment model can be further categorised into :

- With elimination from Central compartment
- With elimination from peripheral compartment
- With elimination from both the compartments

 In the absence of information, elimination is assumed to occur exclusively from the central compartment.

Two compartment Open model-iv bolus administration: Elimination from central compartment
Fig

```
┌──────────┐          ┌──────────┐
│    1     │──────────│    2     │
│          │          │          │
│ Central  │──────────│peripheral│
└────┬─────┘          └──────────┘
     │
     ▼
```

▸ After the iv bolus of a drug the decline in the plasma conc. is bi-exponential.

▸ Two disposition processes- distribution and elimination.

- These two processes are only evident when a semilog plot of C vs t is made.
- Initially, the conc. of drug in the central compartment declines rapidly, due to the distribution of drug from the central compartment to the peripheral compartment. This is called Distributive phase.
- A pseudo-distribution equilibrium occurs between the two compartments following which the subsequent loss of drug from the central compartment is slow and mainly due to elimination.

- This second, slower rate process, is called as the post-distributive or elimination phase.
- In contrast to this compartment, the conc of drug in the peripheral compartment first increases and reaches its max.
- Following peak, the drug conc declines which corresponds to the post-distributive phase.

$$\frac{dC_c}{dt} = K_{21} \, C_p - K_{12} \, C_c - K_E \, C_c$$

Extending the relationship $X = V_d C$

$$\frac{dC_c}{dt} = \frac{K_{21} X_p}{V_p} - \frac{K_{12} X_c}{V_c} - \frac{K_E X_c}{V_c}$$

X=amt. of drug in the body at any time t remaining to be eliminated

C=drug conc in plasma

V_d =proportionality const app. volume of distribution

X_c and X_p=amt of drug in C1 and C2

V_c and V_p=apparent volumes of C1 and C2

- The rate of change in drug conc in the peripheral component is given by:

- $\dfrac{dC_p}{dt} = K_{12}\, C_c - K_{12}\, C_p$

$$= K_{12}\, \dfrac{X_c}{V_c} - \dfrac{K_{21}\, X_p}{V_p}$$

On integration equation gives conc of drug in central and peripheral compartments at any given time t :

$Cc = X_o\, \dfrac{[(K_{21} - a)\, e^{-at} + (K_{21} - b)\, e^{-bt}]}{b - a \qquad\qquad a - b}$

$$Cp = \frac{Xo}{Vc} \left[\frac{(K_{21} - a)e^{-at}}{b - a} + \frac{(K_{12} - b)e^{-bt}}{a - b} \right]$$

Xo = iv bolus dose

a and b = hybrid first order constants for rapid dissolution phase and slow elimination phase, which depend entirely on 1st order constants K12, K21, KE

The constants K12, and K21 that depict the reversible transfer of drug between the compartments are called micro or transfer constants.

▸ The relation between hybrid and microconstants is given as :

a + b = K12 + K21 + KE

a b = K21 KE

$Cc = A\ e^{-at} + B e^{-bt}$

Cc=distribution exponent + elimination

exponent

A and B are hybrid constants for two exponents and can be resolved by graph by method of residuals.

$$A = \frac{X_0}{V_c} \left[\frac{K_{21} - a}{b - a} \right] = C_o \left[\frac{K_{21} - a}{b - a} \right]$$

$$B = \frac{X_0}{V_c} \left[\frac{K_{21} - b}{a - b} \right] = C_o \left[\frac{K_{21} - b}{a - b} \right]$$

C_o = plasma drug conc immediately after i.v.   injection

- Method of residuals : the biexponential disposition curve obtained after i. v. bolus of a drug that fits two compartment model can be resolved into its individual exponents by the method of residuals.

$$C = A\, e^{-at} + B\, e^{-bt}$$

From graph the initial decline due to distribution is more rapid than the terminal decline due to elimination i.e. the rate constant a >> b and hence the term e^{-at} approaches zero much faster than e^{-bt}

$$C = B\, e^{-bt}$$

$$\log C = \log B - bt/2.303 \quad C = \text{back extrapolated pl.conc}$$

- A semilog plot of C vs t yields the terminal linear phase of the curve having slope $-b/2.303$ and when back extrapolated to time zero, yields y-intercept log B. The $t^{1/2}$ for the elimination phase can be obtained from equation $t^{1/2} = 0.693/b$.

- Residual conc values can be found as-

$$C_r = C - C = \underleftarrow{A}e^{-at}$$

$$\log C_r = \log A \underline{\;-\;at\;}$$

$$2.303$$

A semilog plot Cr vs t gives a straight line.

$$C_0 = A + B$$

$$K_E = \frac{a\ b\ c}{A\ b + B\ a}$$

$$K_{12} = \frac{A\ B\ (b - a)^2}{C_0\ (A\ b + B\ a)}$$

$$K_{21} = \frac{A\ b + B\ a}{C_0}$$

- For two compartment model, KE is the rate constant for elimination of drug from the central compartment and b is the rate constant for elimination from the entire body. Overall elimination t1/2 can be calculated from b.

Area Under (AUC) = $\underline{A}$ + $\underline{B}$
the Curve   a   b

App. volume of Central = $\dfrac{X0}{C0}$ = $\dfrac{X0}{KE\,(AUC)}$
    compartment

App. volume of $= VP = \underline{VC\ K12}$

Peripheral compartment $K21$

Apparent volume of distribution at steady state or equilibrium

$$Vd,ss = VC + VP$$

$$Vd,area = \underline{\ X0\ }$$
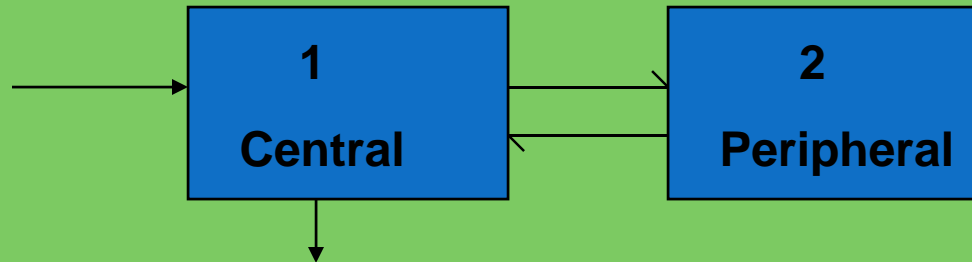
$$b\ AUC$$

Total systemic Clearence $= ClT = b\ Vd$

Renal Clearence $= ClR = KE\ VC$

▸ The rate of excretion of Unchanged drug in urine can be represented by :

$$\frac{dXU}{dt} = KE\ A\ e^{-at} + KE\ B\ e^{-bt}$$

The above equation can be resolved into individual exponents by the method of Residuals.

Two – Compartment open model– I.V. Infusion

The plasma or central compartment conc of a drug when administered as constant rate (0 order) i.v. infusion is given as:

$$C = \frac{R0}{VC\ KE} \left[1 + \frac{(KE - b)}{b - a}e^{-at} + \frac{(KE - a)}{a - b}e^{-bt}\right]$$

At steady state (i.e.at time infinity) the second and the third term in the bracket becomes zero and the equation reduces to:
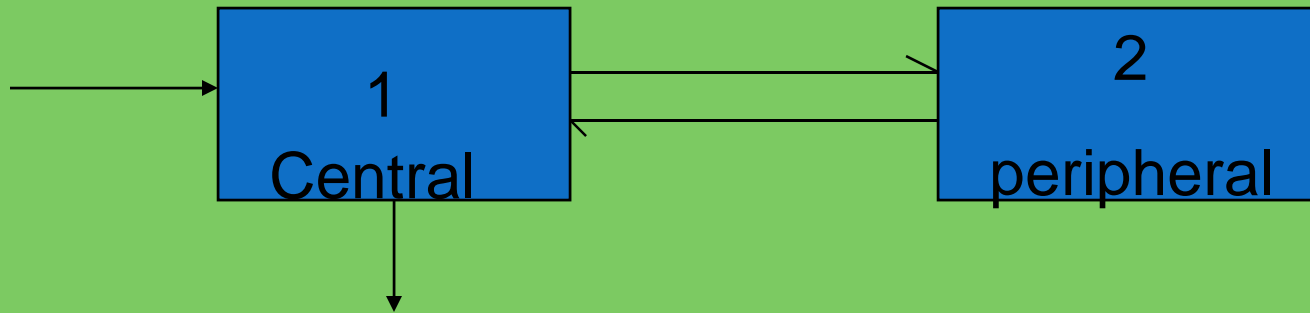
$$Css = \frac{R0}{VC\ KE}$$

Now VC KE = Vd b

$$CSS = \frac{R0}{Vdb} = \frac{R0}{ClT}$$

The loading dose $X0,L = Css\ Vc = \frac{R0}{KE}$

Two-Compartment Open Model— Extravascular administration

‣ First - Order Absorption :

The model can be depicted as follows :

For a drug that enters the body by a first-order absorption process and distributed according to two compartment model, the rate of change in drug conc in the central compartment is described by three exponents :

An absorption exponent, and the two usual exponents that describe drug disposition.

The plasma conc at any time t is

C = N e^{-kat} + L e^{-at} + M e^{-bt}

C = Absorption + Distribution + Elimination
      exponent   exponent   exponent

Besides the method of residuals, Ka can also be found by Loo-Riegelman method for drug that follows two-compartment characteristics.

This method requires plasma drug concentration- time data both after oral and i.v. administration of the drug to the same subject at different times in order to obtain all the necessary kinetic constants.

Despite its complexity, the method can be applied to drugs that distribute in any number of compartments.

Three compartment model and applications of pharmacokinetic parameters in dosage development

THREE COMPARTMENT MODEL

▸ Gibaldi & Feldman described a three compartment open model to explain the influence of route of administration .i.e. intravenous vs. oral, on the area under the plasma concentration vs. time curve.

▸ Portman utilized a three compartment model which included metabolism & excretion of hydroxy nalidixic acid.
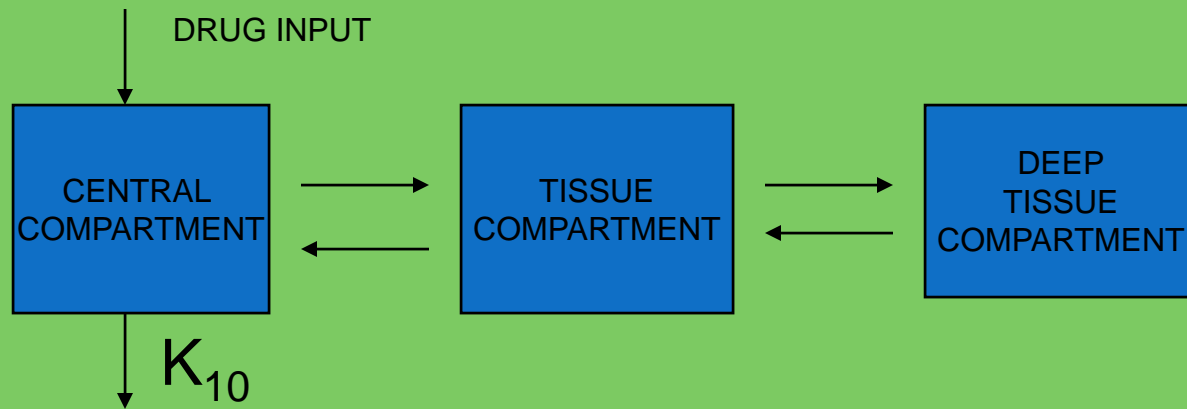
THREE COMPARTMENT CATENARY MODEL
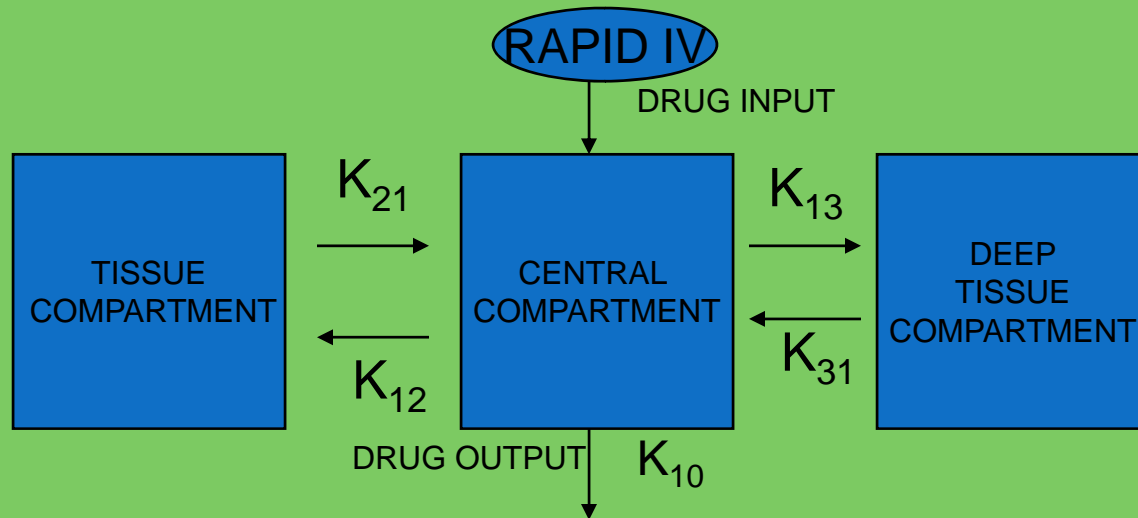
THREE COMPARTMENT MAMMILLARY MODEL

- ➢ Three compartment model consist of the following compartments .
- ✓ Central compartment.
- ✓ Tissue compartment.
- ✓ Deep tissue compartment.

- ➢ In this compartment model drug distributes most rapidly in to first or central compartment.
- ➢ Less rapidly in to second or tissue compartment .
- ➢ Very slowly to the third or deep tissue compartment. The third compartment is poor in tissue such as bone & fat.

- Each compartment independently connected to the central compartment.
- Notari reported the tri exponential equation

$$C = A\,e^{-\alpha t} + B\,e^{-\beta t} + C\,e^{-\gamma t}$$

- A,B,C are the y-Intercept of extrapolated lines.
- α,β,γ are the rate constants.

RAPID I.V BOLUS ADMINISTRATIONS

▸ When the drug is administered by i.v the drug will rapidly distributed in c.c ,less rapidly in to t.c. very slowly in to deep tissue compartment.

PLASMA PROFILE

▸ When the drug is administered by i.v the plasma conc. will increased in c.c this is first order release.

▸ The conc. of drug in c.c. exhibits an initial distribution this is very rapid.

▸ drug in central compartment exhibits an initial distribution this is very rapid .

PHARMACOKINETIC PARAMETERS

BIOLOIGICAL HALF–LIFE

▸ It is defined as the time taken for the amount of drug in the body as well as plasma to decline by one half or 50% its initial value.

▸ Concentration of drug in plasma as a function of time is

$$C = A\, e^{-\alpha t} + B\, e^{-\beta t} + C\, e^{-\gamma t}$$

▸ In this equation $\alpha > \beta > \gamma$ some time after the distributive phase (i.e. when time become large) the two right hand side terms values are equal to zero.

▸ The eq.. is converted in to
$$C = A\, e^{-\alpha t}$$

Taking the natural logarithm on both sides
The rate constant of this straight line is 'α' and biological half life is
$$t_{1/2} = 0.693/\alpha$$

Volume of central compartment

▸ At time=0

$$C = A e^{-\alpha t} + B e^{-\beta t} + C e^{-\gamma t}$$

This equation becomes

$$C_O = A + B + C \quad -----1$$

C_O =conc. of plasma immediately after the i.v administration

▸ When administered the dose is not distributed in tissue compartment.

▸ Therefore the drug is present in c.c only .

▸ If D is dose administered then $C_O = D / V_C$ ---------2

V_C =volume of drug in c.c

- Combining the 1&2 eq..

$$A+B+C=D/V_C$$

or

$$V_C = D/A+B+C=D/C_O$$

$$V_C = D/C_O \qquad C_O----- \text{Conc. Of drug in plasma}$$

ELIMINATION RATE CONSTANT

➤ Drug that follows three compartment kinetics and administered by i.v injection the decline in the plasma drug conc. is due to elimination of drug from the three compartments.

$$K_E=(A+B+C) \ \alpha \ \beta \ \gamma /A \ \beta \ \gamma +B \ \alpha \ \gamma + \ C\alpha \ \beta$$

AREA UNDER CURVE:

$$AUC=A/\alpha+B/\beta+C/\gamma$$

Applications of pharmacokinetics

- To understand process of absorption, distribution and elimination after administration of drug , Which affects onset and intensity of biological response.
- To access drug moiety in terms of plasma drug conc response which is now considered as more appropriate parameter then intrinsic pharmacological activity .
- In design and utilization of invitro model system that can evaluate dissolution characteristics of new compound formulated as new drug formulations and establish meaningful in vivo-in vitro correlationship.
- In design and development of new drug and their appropriate dosage regimen .

- In safe and effective management of patients by improving drug therapy.

- To understand concept of bioavailability which has been used by regulatory authorities to evaluate and monitor in vivo performance of new dosage forms and generic formulations.

- To carry out bioavailability and bioequivalence studies.

- We can used pharmacokinetic principles in the development of N.D.D.S like micro spheres and Nanoparticles .

  e.g. The drug with short half life about 2-6 h can be   formulated as controlled release drugs by using polymers .

- The lower bioavailability of the drugs can be   increased by using several components .
   e.g. β- cyclodextrin

Role of pharmacokinetics in drug design

▸ Many drugs are investigated nowadays the estimation of activity and pharmacokinetics properties are important for knowing the ADME of that particular drug .

▸ By understanding the mechanism of disease the drug design is done .The drug design is based on the mechanism of the particular disease.

▸ Some newly discovered drugs that shows very high activity invitro but in in vivo that drug not shows high activity or showing high toxic activity.

▸ This toxic nature of the drug in in vivo will be explained by studying the pharmacokinetics properties and the toxicity may result from the formation of reactive metabolites.

- Some newly invented drugs showing undesirable p.k properties such as too long or too short $t_{1/2}$, poor absorption and extensive first pass metabolism .

- ABSORPTION

- Two physicochemical factors that effect the both extent and rate of absorption are lipophilicity and solubility .

- Increase in the lipophilicity nature of drug results increase in oral absorption .

1. e.g. Biophosphonates drug with poor lipophilicity will be poorly absorbed after oral administration .

2. absorption of the barbiturates compounds increased with increasing lipophilicity.

- Higher the lipophilicity of a drug the higher its permeability and the greater its metabolic clearance due to first pass effect .

- The effect of the lipophilicity on membrane permeability and first pass metabolism appear to have opposing effect on the bioavailability.

- Solubility is also an important determinant in drug absorption.

- Vavcca successfully developed a novel hydroxyethylene dipeptitide isostere & selective HIV protease inhibitors.

- HIV protease inhibitors are basically lipophilic and poorly soluble resulting in poor bioavailability.

- The solubility of the HIV protease inhibitors can increased by incorporating a basic amine in to the back bone of this series.

- Pro drugs are developed to improve oral absorption .
  Eg pivampicillin, becampicillin are the pro drugs of ampicillin.

Distribution

▸ Lipophilicity of the drug affects the distribution the higher the lipophilicity of a drug the stronger its binding to protein & the greater its distribution.

▸ e.g. Thiopental & polychlorinated insecticides.

▸ These drugs are highly distributed and accumulate   in adipose tissue .

Plasma half-life

▸ Administration of a drug with a short half life requires frequent dosing and often results in a significant in patient compliance.

▸ Half life determined by distribution & elimination clearance.

▸ The prolongation of half life can be achieved by increasing the volume of distribution & decreasing the clearance, latter appear to be easier to modify the chemical structure to slow a drug clearance than to increase its volume of distribution.

- E.g. The addition of an alkyl amine side chain linked to the dihydropyridine 2-methyl group yield amlodipine with a lower clearance which has an improved oral bioavailability and plasma half life without loss of antihypertensive activity.

ROLE OF P.K IN DRUG DEVELOPMENT

- Invitro studies are very useful in studying the factors influencing drug absorption and metabolism.
- These studies are useful for the new drug development .

Invitro studies of drug metabolism

1. **Determination of metabolic pathways**
   - Study of drug metabolic pathways are useful for determining the nature of metabolites.
   - Animals species used for toxicity studies.
   - e.g. The major metabolic pathways of indinavir in human have been identificate as,
   - Glucaronidation at the pyridine nitrogen to yield a quaternary ammonium conjugate
   - Pyridine n-oxidation
   - Para -hydroxylation of the phenyl methyl group
   - 3-hydroxylation of the chain
   - N- depyridomethylation
   - Isolation & cultured hepatocytes also used often as invitro models for identifying metabolic pathways of drug.

IDENTIFICATION OF DRUG METABOLIZING ENZYMES

▸ Metabolism of drugs is usually very complex, involving several pathways and various enzyme system .

▸ In some cases all the metabolic reactions of a drug are catalyzed by a single isozyme, where as in other cases a single metabolic reactions may involve multiple isozymes or different enzyme system…

1. Oxidative metabolic reactions of indinavir are all catalyzed by a single isozyme in human liver microsomes.

2. Two isozymes cyt p-142 & cyt p-344 are involved in human liver microsomes.

▸ Stearns demonstrated that losartan is converted to its active carboxylic acid metabolite in human liver microsomes.

IN-VITRO STUDIES OF PROTEIN BINDING

‣ Drug particles are absorbed from the intestine and bond with the plasma proteins.

‣ Absorbed particles are in two forms bound, unbound

   In vitro - In vivo protein binding:

‣ There are numerous invitro methods for the determination of protein bindings.

e.g. Equilibrium dialysis.

Ultra filtration.

Ultracentrifugation.

‣ Equilibrium dialysis method for measuring the unbound phenytoin fraction in plasma.

- These binding of drug to plasma proteins is an important factor in determining their p.k & pharmacological effects.
- Micro dialysis has been developed for measuring the unbound drug conc. in biological fluid.
- The use of micro dialysis is to determine the plasma protein binding of drugs & evaluated by comparing with ultra filtration and equilibrium dialysis.

Plasma and tissue protein binding

▸ It is generally belived that only the unbound drug can diffuse across membranes.
▸ Therefore drug protein binding in plasma and tissues can affect the distribution of drugs in the body .
▸ Kinetically the simplest quantitative expression relating the volume of distribution to plasma and tissue binding is given as

$$V_d = V_p + \Sigma \, V_t \, f_p \, / \, f_t$$

V_p----Plasma volume

V_t-----Tissue volume

f_t & f_p-----fraction of unbound drug in tissue & plasma.

- This relationship tells that the Vd increase when f p is increased and decrease when ft is increased.
- Several methods have been developed for the study of tissue binding .These include per fused intact organs tissue slices or tissue homogenates.
- In principle these methods allow the direct determination of tissue binding but required removal of tissues from the body.

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