UNIT 2

PHARMACOKINETICS

COMPARTMENT MODELING

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OVERVIEW

• Basic considerations in pharmacokinetics
• Compartment models
• One compartment model
  – Assumptions
  – Intravenous bolus administration
  – Intravenous infusion
  – Extravascular administration (zero order and first order absorption model)
• References
BASIC CONSIDERATIONS IN PHARMACOKINETICS

- Pharmacokinetic parameters
- Pharmacodynamic parameters
- Zero order kinetic
- First order kinetic
- Mixed order kinetic
- Compartment model
- Non compartment model
- Physiologic model
Pharmacokinetic models

Means of expressing mathematically or quantitatively, time course of drug through out the body and compute meaningful pharmacokinetic parameters.

Useful in:

• Characterize the behavior of drug in patient.
• Predicting conc. of drug in various body fluids with dosage regimen.
• Calculating optimum dosage regimen for individual patient.
• Evaluating bioequivalence between different formulation.
• Explaining drug interaction.
Compartments models
OBJECTIVE

• To understand the assumptions associated with the one compartment model

• To understand the properties of first order kinetics and linear models

• To write the differential equations for a simple pharmacokinetic model

• To derive and use the integrated equations for a one compartment linear model

• To define, use, and calculate the parameters, $K_e$ (elimination rate constant), $t_{1/2}$ (half-life), $Cl$ (clearance), $V$ (apparent volume of distribution), and $AUC$ (area under the concentration versus time curve) as they apply to a one compartment linear model
“OPEN” and “CLOSED” models:

- The term “open” itself means that, the administered drug dose is removed from body by an excretory mechanism (for most drugs, organs of excretion of drug is kidney).

- If the drug is not removed from the body then model refers as “closed” model.
One Compartment

Drug in Body

kel

Drug Eliminated
PHARMACOKINETICS

• **Pharmacokinetics** is the study of drug and/or metabolite **kinetics** in the body.

• The body is a very complex system and a drug undergoes many steps as it is being **absorbed**, **distributed** through the body, **metabolized** or **excreted** (ADME).
Assumptions

1. One compartment

- The drug in the blood is in rapid equilibrium with drug in the extravascular tissues.

- This is not an exact representation however it is useful for a number of drugs to a reasonable approximation.
2. Rapid Mixing

- We also need to assume that the drug is mixed instantaneously in blood or plasma.

3. Linear Model

- We will assume that drug elimination follows first order kinetics.
Linear Model - First Order Kinetics

- First-order kinetics

![Graph showing concentration over time](image)

- $t_{1/2} = 2$ hour
- $k_e = 0.347$ hr$^{-1}$
- $C_p^0 = 100$ µg/ml

![Graph showing concentration change over concentration](image)
This behavior can be expressed mathematically as:

\[
\text{Rate of Change of } C_P \text{ versus time} = -\frac{\Delta C_P}{\Delta t} = kel \cdot C_P
\]
One compartment model

- One compartment model can be defined:
  - One com. open model – i.v. bolus.
  - One com. open model - cont. intravenous infusion.
  - One com. open model - extra vas. administration (zero-order absorption)
  - One com. open model - extra vas. Administration (first-order absorption)
One Compartment Model, Intravenous (IV) Bolus Administration
Rate of drug presentation to body is:

- $dx = \frac{\text{rate in (availability)}}{dt} - \frac{\text{rate out (elimination)}}{dt}$

- Since rate in or absorption is absent, equation becomes $dx = - \frac{\text{rate out}}{dt}$

- If rate out or elimination follows first order kinetic $\frac{dx}{dt} = -k_EX$ (eq.1)
Elimination phase:

- Elimination phase has three parameters:
  - Elimination rate constant
  - Elimination half life
  - Clearance
Elimination rate constant

- Integration of equation (1)

- \( \ln X = \ln X_0 - K_E t \) (eq.2)

\( X_0 = \) amt of drug injected at time \( t = 0 \) i.e. initial amount of drug injected

\( X = X_0 e^{-K_E t} \) (eq.3)

- \( \log X = \log X_0 - K_E t \)

\( 2.303 \) (eq.4)
• Since it is difficult to directly determine amount of drug in body X, we use relationship that exists between drug conc. in plasma C and X; thus

• \[ X = V_d C \] (eq. 5)

• So equation-8 becomes

\[
\log C = \log C_0 - K_E t \quad \frac{2.303}{2.303} 
\] (eq.6)
\[ K_E = K_e + K_m + K_b + K_l + \ldots \]  \hspace{5cm} (eq.7)

\[ K_E \] is overall elimination rate constant

**Fig. 10.2** (a) Cartesian plot of a drug that follows one-compartment kinetics and given by rapid i.v. injection, and (b) Semilogarithmic plot for the rate of elimination in a one-compartment model.
Elimination half life

\[ t_{1/2} = \frac{0.693}{K_E} \]  
(eq.8)

- Elimination half life can be readily obtained from the graph of log C versus t

- Half life is a secondary parameter that depends upon the primary parameters such as clearance and volume of distribution.

\[ t_{1/2} = \frac{0.693 \ V_d}{Cl_T} \]  
(eq.9)
Apparent volume of distribution

- Defined as volume of fluid in which drug appears to be distributed.
- \( V_d = \text{amount of drug in the body} = \frac{X}{\text{plasma drug concentration}} \cdot C \) (eq.10)

\[
V_d = \frac{X_0}{C_0} = \frac{\text{i.v. bolus dose}}{C_0} \quad \text{(eq.11)}
\]

- E.g. 30 mg i.v. bolus, plasma conc. = 0.732 mcg/ml.
- Vol. of dist. = \( \frac{30\text{mg}}{0.732\text{mcg/ml}} \)
  \( = \frac{30000\text{mcg}}{0.732\text{mcg/ml}} \)
  \( = 41 \text{ liter} \).
• For drugs given as i.v. bolus,

\[ V_d \text{ (area)} = \frac{X_0}{K_E \cdot AUC} \]

\[ \ldots \ldots \ldots 12.a \]

• For drugs admins. Extra. Vas.

\[ V_d \text{ (area)} = F \cdot \frac{X_0}{K_E \cdot AUC} \]

\[ \ldots \ldots \ldots 12.b \]
Clearance

Clearance = rate of elimination
plasma drug conc.

- Or Cl = \( \frac{dx}{dt} \)
  
  \( \begin{array}{c}
  C \\
  (\text{eq.13})
  \end{array} \)

Thus

Renal clearance = rate of elimination by kidney
  
  \( \frac{\text{rate of elimination by kidney}}{C} \)

Hepatic clearance = rate of elimination by liver
  
  \( \frac{\text{rate of elimination by liver}}{C} \)

Other organ clearance = rate of elimination by organ
  
  \( \frac{\text{rate of elimination by organ}}{C} \)

- Total body clearance:
  
  \( Cl_T = Cl_R + Cl_H + Cl_{\text{other}} \)  
  (eq.14)
• According to earlier definition
  \[ Cl = \frac{dx}{dt} \]
  \[ C \]
• Submitting eq.1 \( \frac{dx}{dt} = K_E X \), above eq. becomes
  \[ Cl_T = K_E X \frac{1}{C} \quad \text{(eq 15)} \]
• By incorporating equation 1 and equation for vol. of dist. \( V_d = X/C \) We can get
  \[ Cl_T = K_E V_d \quad \text{(eq.16)} \]
• Parallel equations can be written for renal and hepatic clearance.

\[ \text{Cl}_H = \text{Km} \times \text{Vd} \quad \text{(eq.17)} \]
\[ \text{Cl}_R = \text{Ke} \times \text{Vd} \quad \text{(eq.18)} \]

• but \( K_E = \frac{0.693}{t_{1/2}} \)

• so, \[ \text{Cl}_T = \frac{0.693 \times \text{Vd}}{t_{1/2}} \quad \text{(eq.19)} \]
• For non compartmental method which follows one compartmental kinetic is :

• For drug given by i.v. bolus

\[ Cl_T = \frac{X_o}{AUC} \]  .....20.a

• For drug administered by e.v.

\[ Cl_T = F \times X_o \]  .....20.b

\[ AUC \]

• For drug given by i.v. bolus

renal clearance = \[ \frac{X_{u\infty}}{AUC} \]  (eq. 21)
Organ clearance

• Rate of elimination by organ = rate of presentation to the organ – rate of exit from the organ.

• Rate of elimination = $Q \cdot C_{in} - Q \cdot C_{out}$
  (rate of extraction) = $Q \cdot (C_{in} - C_{out})$
  
  $Cl_{organ} = \frac{\text{rate of extraction}}{C_{in}}$
  
  = $Q(C_{in} - C_{out})/C_{in}$
  
  = $Q \cdot ER$  

  ................(eq 22)

• Extraction ratio:
  $ER = (C_{in} - C_{out})/C_{in}$

• ER is an index of how efficiently the eliminating organ clear the blood flowing through it of drug.
According to ER, drugs can be classified as:

- Drugs with high ER (above 0.7)
- Drugs with intermediate ER (between 0.7-0.3)
- Drugs with low ER (below 0.3)
- The fraction of drug that escapes removal by organ is expressed as
  \[ F = 1 - ER \]
- where \( F \) = systemic availability when the eliminating organ is liver.
Hepatic clearance

\[ Cl_H = Cl_T - Cl_R \]

- Can also be written down from eq 22
- \( Cl_H = Q_H \cdot ER_H \)
- \( Q_H = \) hepatic blood flow. \( ER_H = \) hepatic extraction ratio.
- Hepatic clearance of drug can be divided into two groups:
  1. Drugs with hepatic blood flow rate-limited clearance
  2. Drugs with intrinsic capacity-limited clearance
Hepatic blood flow

- \( F = 1 - ER_H \)
  \[ = \frac{AUC_{oral}}{AUC_{i,v}} \]

### Influence of Blood Flow Rate and Protein Binding on Total Clearance of Drugs with High and with Low ER Values.

<table>
<thead>
<tr>
<th>Drugs with ER</th>
<th>Changes in Total Clearance due to</th>
</tr>
</thead>
<tbody>
<tr>
<td>( ER )</td>
<td>( \uparrow ) Blood Flow</td>
</tr>
<tr>
<td>High ER (above 0.7)</td>
<td>( \uparrow )</td>
</tr>
<tr>
<td>Low ER (below 0.3)</td>
<td>No Change</td>
</tr>
</tbody>
</table>

where, \( \uparrow \) = increase, and \( \downarrow \) = decrease.
Intrinsic capacity clearance

- Denoted as $C_{\text{int}}$, it is defined as the inherent ability of an organ to irreversibly remove a drug in the absence of any flow limitation.

<table>
<thead>
<tr>
<th>Hepatic Extraction</th>
<th>Extraction Ratio</th>
<th>Renal Extraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>Aspirin</td>
<td>Some Penicillins</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Codeine</td>
<td>Procainamide</td>
</tr>
<tr>
<td>Nitroglycerine</td>
<td>Nortriptyline</td>
<td>Hydroxide</td>
</tr>
<tr>
<td>Morphine</td>
<td>Quinidine</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Isoprenaline</td>
<td></td>
<td>Cholestyramine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High</th>
<th>Intermediate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>Phenobarbital</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Procainamide</td>
<td>Theophylline</td>
<td>Digoxin</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Esmolol</td>
<td>Esmolol</td>
</tr>
<tr>
<td>Flecainide</td>
<td>Vitamins</td>
<td>Flecainide</td>
</tr>
<tr>
<td>Several Glucuronides</td>
<td></td>
<td>Several Glucuronides</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
One compartment open model: Intravenous infusion

- Model can be represent as: (i.v infusion)

\[ \frac{dX}{dt} = R_0 - K_E X \quad \text{...eq 23} \]

\[ X = \frac{R_0}{K_E} (1 - e^{-K_E t}) \quad \text{...eq 24} \]

Since \( X = V_d C \)

\[ C = \frac{R_0}{K_E} V_d (1 - e^{-K_E t}) \quad \text{...eq 25} \]

\[ = \frac{R_0}{C_l T} (1 - e^{-K_E t}) \quad \text{...eq 26} \]

**Fig. 10.3** Plasma concentration-time profile for a drug given by constant rate i.v. infusion (the two curves indicate different infusion rates \( R_0 \) and \( 2R_0 \) for the same drug)
• At steady state. The rate of change of amount of drug in the body is zero, eq 23 becomes

\[ \text{Zero} = R_o - K_E X_{SS} \quad \ldots 27 \]

\[ K_E X_{SS} = R_o \quad \ldots 28 \]

\[ C_{SS} = \frac{R_o}{K_E V_d} \quad \ldots 29 \]

\[ -\frac{R_o}{Cl_T} \text{ i.e. infusion rate} \quad \ldots 30 \text{ clearance} \]

Substituting eq. 30 in eq. 26

\[ C = C_{SS} (1 - e^{-K_E t}) \quad \ldots 31 \]

Rearrangement yields:

\[ C_{SS} - C = e^{-K_E t} \quad \ldots 32 \]

\[ \log \left( \frac{C_{SS} - C}{C_{SS}} \right) = -K_E t \quad \ldots 33 \]

\[ 2.303 \]
• If \( n \) is the no. of half lives passed since the start of infusion (\( t/t_{1/2} \))
• Eq. can be written as
• \( C = C_{ss} [1-(1/2)^n] \) ...34

<table>
<thead>
<tr>
<th>Half-life</th>
<th>% Remaining</th>
<th>% ( C_{ss} ) Achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>50 + 25 = 75</td>
</tr>
<tr>
<td>3</td>
<td>12.5</td>
<td>75 + 12.5 = 87.5</td>
</tr>
<tr>
<td>4</td>
<td>6.25</td>
<td>87.5 + 6.25 = 93.75</td>
</tr>
<tr>
<td>5</td>
<td>3.125</td>
<td>93.75 + 3.125 = 96.875</td>
</tr>
<tr>
<td>6</td>
<td>1.562</td>
<td>96.875 + 1.562 = 98.437</td>
</tr>
<tr>
<td>7</td>
<td>0.781</td>
<td>98.437 + 0.781 = 99.218</td>
</tr>
</tbody>
</table>
Infusion plus loading dose

- $X_0, L = C_{SS} V_d$  
- Substitution of $C_{SS} = \frac{R_o}{K_E} V_d$
- $X_0, L = \frac{R_o}{K_E}$  
- $C = X_0, L/V_d \, e^{-K_E t} + \frac{R_o}{K_E} V_d(1 - e^{-K_E t})$
Assessment of pharmacokinetic parameter

• $AUC = R_o \frac{T}{K_e} V_d$
  
  $= R_o \frac{T}{\text{Cl}_T}$
  
  $= C_{SS} T$

• Where $T =$ infusion time
One compartment open model: extra vascular administration

- When drug administered by extra vascular route (e.g. oral, i.m, rectal), absorption is prerequisite for its therapeutic activity.

**Fig. 10.6** Distinction between zero-order and first-order absorption processes. *Figure a* is regular plot, and *Figure b* a semilog plot of amount of drug remaining to be absorbed (ARA) versus time t.
• $dX/dt =$ rate of absorption - rate of elimination

\[
dX/dt = dX_{ev}/dt - dX_E/dt \quad \ldots38
\]

\[
dX_{ev}/dt > dX_E/dt
\]

\[
dX_{ev}/dt = dX_E/dt
\]

\[
dX_{ev}/dt < dX_E/dt
\]
One compartment model: extra vascular admin (zero order absorption)

- This model is similar to that for constant rate infusion.

  Rate of drug absorption as in case of CDDS, is constant and continues until the amount of drug at the absorption site (e.g. GIT) is depleted.

- All equations for plasma drug conc. profile for constant rate i.v. infusion are also applicable to this model.
One compartment model: extra vascular admin (first order absorption)

- Drug that enters the body by first order absorption process gets distributed in the body according to one compartment kinetic and is eliminated by first order process.
- The model can be depicted as follows:

- Drug at site

Diagram:

\[ \text{Drug at site} \xrightarrow{K_a} \text{Blood & other Body tissues} \xrightarrow{K_E} \text{elimination} \]

First order absorption
• The differential form if eq. 38 is

\[ \frac{dX}{dt} = k_a X_a - K_E X \] \quad \ldots 39

\[ X = \frac{K_a F X_o}{K_a - K_E} \left[ e^{-K_E t} - e^{-K_E t} \right] \] \quad \ldots 40

\[ C = \frac{K_a F X_o}{V_d} \frac{1}{K_a - K_E} \left[ e^{-K_E t} - e^{-K_E t} \right] \] \quad \ldots 41
Multi-Compartment Models
Contents

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  – Intravenous bolus administration
  – Extravascular administration
• References
• 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 equilibrating 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

- 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.

\[ dC_c = K_{21} C_p - K_{12} C_c - K_E C_c \]

\[ \frac{dt}{dt} \]
Extending the relationship \( X = V_d C \)

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

\( X \) = 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:
• \( \frac{dC_p}{dt} = K_{12} C_c - K_{12} C_p \)

\[
= K_{12} \frac{X_c - K_{21} X_p}{V_c V_p}
\]

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

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

\[ \frac{a}{a - b} \]

\[ Xo = \text{iv bolus dose} \]

\[ a \text{ and } b = \text{hybrid first order constants for rapid dissolution phase and slow elimination phase, which depend entirely on 1}^{\text{st}} \text{order constants} \]

\[ K_{12}, K_{21}, K_E \]

The constants \( K_{12}, \) and \( K_{21} \) 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:

\[ a + b = K_{12} + K_{21} + K_E \]
\[ a \ b = K_{21} K_E \]

\[ C_c = A e^{-at} + B e^{-bt} \]

\( C_c \) = 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[ K_{21} - a \right] = \frac{C_o}{b - a} \left[ K_{21} - a \right]

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

C_o = \text{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 \( a \gg b \) and hence the term \( e^{-at} \) approaches zero much faster than \( e^{-bt} \)

\[ C = B e^{-bt} \]

\[ \log C = \log B - bt/2.303 \]

\( C \) = 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-

\[ C_r = C - C = Ae^{-at} \]

\[ \log Cr = \log A - at \]

\[ 2.303 \]

A semilog plot \(Cr\) vs \(t\) gives a straight line.
\[ C_0 = A + B \]

\[ K_E = \begin{vmatrix} a \\ b \\ c \end{vmatrix} \begin{vmatrix} A \\ b \\ a \end{vmatrix} \]

\[ K_{12} = \begin{vmatrix} A \\ B \end{vmatrix} \begin{vmatrix} (b - a)^2 \end{vmatrix} \begin{vmatrix} C_0 \end{vmatrix} \begin{vmatrix} (A \ b + B \ a) \end{vmatrix} \]

\[ K_{21} = \begin{vmatrix} A \\ b \end{vmatrix} + \begin{vmatrix} B \end{vmatrix} \begin{vmatrix} a \end{vmatrix} \begin{vmatrix} C_0 \end{vmatrix} \]
• For two compartment model, \( K_E \) 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 \( t_{1/2} \) can be calculated from \( b \).

\[
\text{Area Under (AUC)} = A + B
\]

the Curve

\[
\text{App. volume of Central} = X_0 = X_0 \]

\[
\text{compartment} \quad C_0 \quad K_E (\text{AUC})\]

\[
62
\]
App. volume of peripheral compartment

Apparent volume of distribution at steady state or equilibrium

\[ V_{d,ss} = V_C + V_P \]

\[ V_{d,area} = \frac{X_0}{b \cdot AUC} \]

Total systemic Clearance = \( Cl_T = b \cdot V_d \)

Renal Clearance = \( Cl_R = \frac{dX_U}{dt} = K_E \cdot V_C \)
• The rate of excretion of Unchanged drug in urine can be represented by:

\[ \frac{dX_U}{dt} = K_E A \ e^{-at} + K_E B \ e^{-bt} \]

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:

\[ C = R_0 \left[ 1 + \left( K_E - b \right)e^{-at} + \left( K_E - a \right)e^{-bt} \right] \]

\[ V_C K_E \quad b - a \quad a - b \]
At steady state (i.e. at time infinity) the second and the third term in the bracket becomes zero and the equation reduces to:

\[ C_{ss} = \frac{R_0}{V_C K_E} \]

Now \( V_C K_E = V_d b \)

\[ C_{ss} = \frac{R_0}{V_d b} = \frac{R_0}{\text{Cl}_T} \]

The loading dose \( X_{0,L} = C_{ss} V_c = \frac{R_0}{K_E} \)
Two-Compartment Open Model - Extravascular administration

- First-Order Absorption:

The model can be depicted as follows:

1 Central

2 peripheral
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

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

\[ C = \text{Absorption} + \text{Distribution} + \text{Elimination} \]

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 CATERINARY 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.
• \( \alpha, \beta, \gamma \) 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

BIOLOGICAL 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 ‘\( \alpha \)’ and biological half life is
  \[ t_{1/2} = \frac{0.693}{\alpha} \]
Volume of central compartment

- At time=0
  \[ C = A e^{-\alpha t} + B e^{-\beta t} + C e^{-\gamma t} \]

This equation becomes
\[ C_O = A + B + C \quad -----1 \]

- 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 \( C_O = \frac{D}{V_c} \quad ------2 \)

\( V_c = \) 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   C_O----- 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) α β γ/A β γ +B α γ+ Cα β

AREA UNDER CURVE:
  AUC=A/α+B/β+C/γ
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 in vitro but in vivo that drug not shows high activity or showing high toxic activity.

- This toxic nature of the drug 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, and 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 believed 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
  \[ V_d = V_p + \sum V_t \frac{f_p}{f_t} \]
  - \( V_p \)----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 f t 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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