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PHARMACOKINETIC MODELS

Introduction

Pharmacokinetics

(The Pharmacokinetics term derives from the Greek words *pharmakon* "drug"& *kinetikos* "moving, put in motion"; see chemical kinetics), and concerns the application of kinetics in the study of absorption, distribution, metabolism and elimination of drugs. The purpose of pharmacokinetics is to study the time course of the techniques and concentration of the drug sas well as its metabolism in different tissues of the body and to build appropriate models to interpret the data.

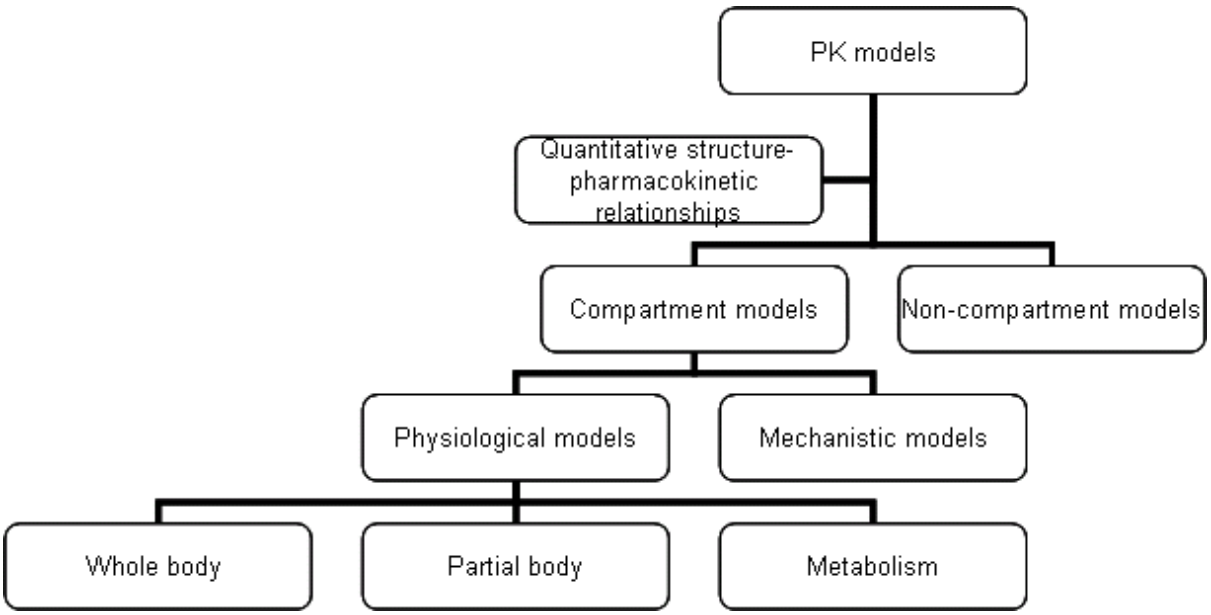
Overview

Pharmacokinetics describes how the body affects a specific xenobiotic/chemical after administration through the mechanisms of absorption and distribution, as well as the metabolic changes of the substance in the body (e.g. by metabolic enzymes such as cytochrome P450 or glucuronosyltransferase enzymes), and the effects and routes of excretion of the metabolites of the drug.[2] Pharmacokinetic properties of chemicals are affected by the route of administration and the dose of administered drug. These may affect the absorption rate.[3]

Models have been developed to simplify conceptualization of the many processes that take place in the interaction between an organism and a chemical substance. One of these, the multi-compartmental model, is the most commonly used approximations to reality; however, the complexity involved in adding parameters with that modelling approach means that *monocompartmental models* and above all *two compartmental models* are the most-frequently used. The various compartments that the model is divided into are commonly referred to as the ADME scheme (also referred to as LADME if liberation is included as a separate step from absorption):

- **L**iberation – the process of release of a drug from the pharmaceutical formulation.[4][5] See also IVIVC.
- **A**bsorption – the process of a substance entering the blood circulation.
- **D**istribution – the dispersion or dissemination of substances throughout the fluids and tissues of the body.
- **M**etabolism (or biotransformation, or inactivation) – the recognition by the organism that a foreign substance is present and the irreversible transformation of parent compounds into daughter metabolites.
- **E**xcretion – the removal of the substances from the body. In rare cases, some drugs irreversibly accumulate in body tissue.[*citation needed*]

Types of Pharmacokinetics models



Non-compartmental Modeling

Non-compartmental model thinks of an organism as only one homogenous compartment. It presumes that a drug's blood-plasma concentration is a

true reflection of the concentration in other tissues and that the elimination of the drug is directly proportional to the drug's concentration in the organism. Non-compartmental methods are often more versatile, and it is acceptable for bioequivalence studies.

Creative Biolabs provides non-compartmental modeling analysis to calculate PK parameters. For instance, the area under the concentration (AUC) is calculated by the trapezoidal rule; clearance (CL) is calculated from drug dose and AUC; C_{max} and T_{max} are calculated from concentrations and time points; half-life is usually calculated from the last two to four sampling time-points directly. The closer time points are, the more accurate noncompartmental model reflects the actual shape of the concentration-time curve.

Compartmental Modeling

Compartmental modeling of pharmacokinetics describes the fate of a drug in the body by dividing the whole body into one or more compartments (Figure 1). A compartment involves several organs or tissues and is kinetically homogenous. Different compartments do not have a direct anatomical or physiological signification. In compartmental methods, drug concentration changes over time are estimated using kinetic models.

Applications of Pharmacokinetic models

The pharmacokinetics models are useful in:

1. Predict plasma, tissue and urine drug levels with any dosage regimen
2. Calculate the optimum dosage regimen for individual patient
3. Establish a relation between drug concentration and pharmacologic or toxicology activity.
4. Estimate the possible accumulation of drugs and metabolism.
5. Establish bioequivalence between various formulations.
6. Describe effect of altered physiology on ADME.
7. Explain the drug interaction.

RGPV QUESTIONS

S.No	Questions	Year	M.Marks
1.	Define Pharmacokinetic models?	2017	03
2.	Give the classification of pharmacokinetic model	2018	07

COMPARTMENT MODELS

INTRODUCTION

The time course of drug concentration determined after its administration can be statisfactorily explained by assuming the body as a single, well mixed compartment with first –order desposition processes. In case of other drugs, two or more body compartments may be postulated to decscribe mathematically the data colloected.

ONE-COMPARTMENT OPEN MODEL

(Instantaneous Distribution Model)

The one-compartment open model is the simplest model which depicts the body as a single, kinetically homogenous unit that has no barriers to the movement of drug and final distribution equilibrium between the drug the plasma and other body fluids is attained instantaneously and maintained at all times. This model thus applies only to those drugs that distribute rapidly throughout the body. The anatomical **reference compartment** is the plasma and concentration of drug in plasma is representative of drug concentration in all body tissues. i.e. any change in plasma drug concentration reflects a proportional change in drug concentration thorught out the body. However, the model does not assume that the drug concentration in plasma is equal to that in other body tissue. *The term* **open***indicates that the input (availability) and output (elimination) are unidirectional and that the drug can be eliminated from the body.* Fig. 5.1 shows such a one-compartment model.

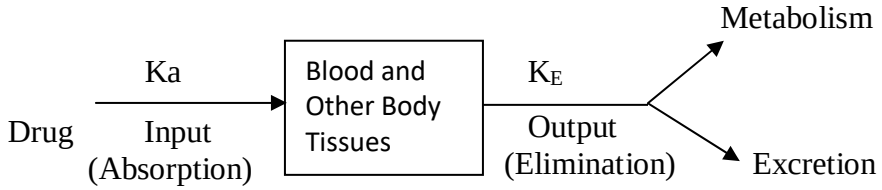


Fig. 5.1 Representation of one-compartment open model showing input and output processes.

One-compartment open model is generally used to describe plasma levels following administration of a single dose of a drug. Depending upon the input, several one-compartment open models can be defined.

One – compartment open model, intravenous bolus administration

One –Compartment open model, continuous intravenous infusion

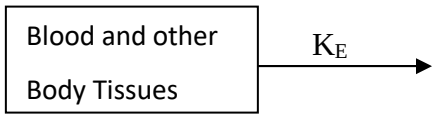
One-compatmtment open model, extravascular administration, zero-order absorption, and

One-Compartment open model, extravascular administration, first-order absorption.

One – Compartment Open Model;

Intravenous Bolus Administration

when a drug that distributes rapidly in the body is given in the form of a rapid intravenous injection (i.e. i.v. bolus or slug), it takes about one to three minutes for complete circulation and therefore the rate of absorption is neglected in calculations. The model can be depicted as follows:



The general expression for **rate of drug presentation** to the body is :

$$\frac{dX}{dt} = \text{Rate in (availability)} - \text{Rate out (elimination)} \qquad (5.1)$$

Since **rate in** or absorption is absent, the equation b ecomes;

$$\frac{dX}{dt} = -\text{Rate out} \qquad (5.2)$$

If the **rate out** or elimination follows first-order kinetics, then:

$$\frac{dX}{dt} = -K_E X \qquad (5.3)$$

Where K_E = first-order elimination rate constant, and

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

Negative sign indicates that the drug is being lost from the body. The various releted pharmacokinetic parameters can now be estimated.

Elimination Rate Constant: For a drug that follows one-compartment kinetics and administered as rapid. i.v. injection, the decline in plasma drug concentration is only due to elimination of drug from the body (and not due to distribution), the phase being called as elimination phase. **Elimination phase** can be characterized by 3 parameters – elimination rate constant, elimination half-life and clearance.

Integration of equation 5.3 yields:

$$\text{Ln } X = \ln X_0 - K_E t \qquad (5.4)$$

Where X_o = amount of drug at time t = zero i.e. the initial amount of drug injected.

Equation 5.4 can also be written in the exponential form as :

$$X = X_o e^{-K_E t} \qquad (5.5)$$

The above equation shows that *disposition of a drug that follows one-compartment kinetics* is **monoexponential.**

Transforming equation 4.4 into common logarithms (log base 10), we get:

$$\log \frac{X}{X_0} = -\frac{K_E t}{2.303} \qquad (5.6)$$

Since is difficult to determine directly the amount of drug in the body X, advantage is taken of the fact that a constant relationship exists between drug concentration in plasma C (easily measurable) and X; thus:

$$X = V_d C \qquad (5.7)$$

Where V_d = proportionality constant popularly known as the apparent volume of distribution. It is a pharmacokinetic parameter that permits the use of drug concentration in place of amount of drug in the body. The equation 5.6 therefore becomes:

$$\log C = \log C_o - \frac{K_E t}{2.303} \qquad (5.8)$$

Where C_o = plasma drug concentration immediately after i.v. injection

Equation 5.8 is that of a straight line and indicates that a semilogarithmic plot of log C versus t will be linear with *Y*-intercept $\log C_o$. The elimination rate constant is directly obtained

from the slope of the line (Fig. 5.3). It has units of min^{-1}.

Thus, a linear plot is easier to handle mathematically than a curve which in this case will be obtained from a plot of C versus t on regular (Certesian) graph paper (Fig. 5.2).

Thus, C_o, K_E (and 1/2) can be readily obtained from log C versus t graph. The elimination or removal of the drug from the body is the sum or urinary excretion, metabolism, biliary excretion, pulmonary excretion, and other mechanisms involved therein. Thus K_E is an additive property of rate constants for each of these processes and better called as **overall elimination rate constant.**

$$K_E = K_e + Km + K_b + K_l + \ldots\ldots\ldots\ldots \quad (5.9)$$

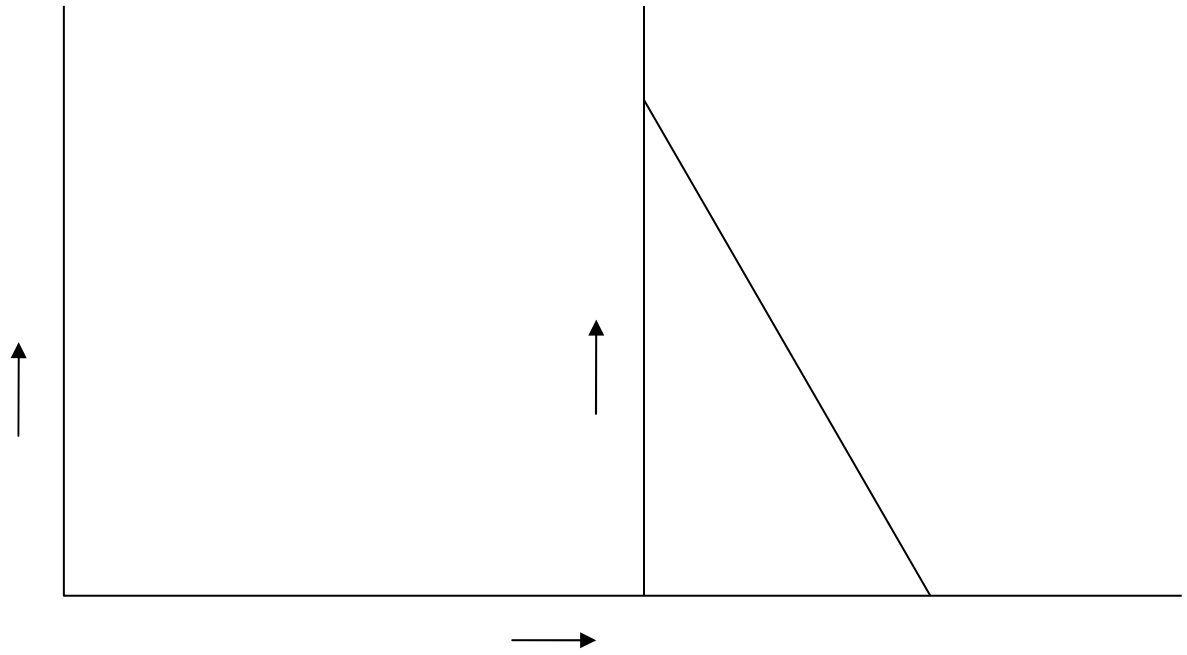


Fig. 5.2 Cartesian plot of a drug that follows one-compartment kinetics and given by rapidi.iv. injection and

Fig 5.3 Semilogarithmic plot for the rate of elimination in a one-compartment model.

The fraction of drug eliminated by a particular route can be evaluated if the number of rate constants involved by and their values are known. For example, if a drug is eliminated by

urinary excretion and metabolism only, them, the fraction of drug excreted unchanged in urine F_e and fraction of drug metabolized F_m can be given as :

$$F_e = \frac{K^e}{K_E} \qquad (5.10)$$

$$F_m = \frac{K^e}{K_E} \qquad (5.11)$$

Elimination Half-Life : Also called as **biological half-life.** It is the oldest and the best known of all pharmacokinetic parameters and was once considered as the most important characteristic of drug. *It is defined as the time taken for the amount of drug in the body as well as plasma concentration to decline by one-half or 50% its initial value.* It is expressed in hours or minutes. Half-life is related to elimination rate constant by the following equation:

$$t\,½ = F_e = \frac{0.693}{K_E} \qquad (5.12)$$

elimination half-life can be readily obtained from the graph of log C versus t as shown in Fig. 5.2

Today , increased physiologic understanding of pharmacokinetics shows that *half-life is a secondary parameter that depends upon the primary parameters* clearance and apprent volume of distribution according to following equation :

$$t_{1/2} = \frac{0.693\,V_d}{CS_T} \qquad (5.13)$$

Apparent volume of distribution : Clearance and apparent volume of distribution are two separate and independent pharmacokinetic characteristics of a drug. *Since they are closely related with the physiologic mechyanisms in the body. They are called as* **primary parameters.**

Modification of equation 5.7 defines apparent volume of distribution:

$$V_d = \frac{\text{Amount of drug in the body}}{\text{Plasma drug concentration}} = \frac{X}{C} \qquad (5.14)$$

V_d is a measure of the extent of distribution of drug and is expressed in liters. The best and the simplest way of estimating V_d of a drug is administering it by rapid i.v. injection and using the following equation:

$$V_d = \frac{X_0}{C_0} = \frac{\text{i.v. bolus dose}}{C_0} \qquad (5.15)$$

Equation 5.15 can only be used for drugs that obey one-compartment kinetics. This is because the V_d can only be estiamted when distribution equilibrium is achieved between drug in plasma and that in tissues and such an equilibrium is established instantaneosuly for a drug that follows one-comapartment kinetics. A more general, more useful non-compartmental method that can be applied to many compartment models for estimating the V_d is:

For drugs given as i.v. bolus.

$$V_{d(area)} = \frac{X_o}{K_E \text{-AUC}} \qquad (5.16)$$

For drugs administred extravascularly (e.v.)

$$V_{d(area)} = \frac{F\,X_o}{K_E \text{-AUC}} \qquad (5.17)$$

Where X_0 = dose administered. And F = fraction of drug absorbed into the systemic circulation. F is eual to *one* i.e. complete availability when the drug is administered intravenously.

Clearance: Difficulties arise when one applies elimination rate constant and half-life as pharmacokinetic parameters in an anatomical /physiological context and as a measure of drug elimination mechanisms. A much more valuable alternative appraoch for such applications is use of clearance parameters to characterize drug disposition. *Clearance* is the most important parameter in clinical drug applications and is useful in evaluating the mechanism by which a drug is eliminated by the whole organism or by a particular organ.

Just as V_d is needed to relate plasma drug concentration with amount of drug in the body, clearance is a parameter to relate plasma drug concentration with the rate of drgu elimination according to following equation:

$$\text{Clearance} = \frac{\text{Rate of elimination}}{\text{Plasma drug concentration}} \qquad (5.17)$$

$$\text{or} \qquad Cl = \frac{dX/dt}{C} \qquad (5.18)$$

Clearance is defined as the theoretical volume of body fluid containing drug. (i.e. that fraction of apparent volume of distribution) from which the drug is completely removed in a given period of time. It is expressed in m1/min or liters/hour. Clearance is usually further defined as **blood clearance** (Cl_b), **plasma clearance** (Cl_p) or clearance based on unbound or free drug concentration (Cl_u) depending upon the concentration C measured for the right side of the equation 5.17.

Total Body Clearance : Elimination of a drug from the body involves processes occuring in kidney, liver, lungs, and other eliminating organs. Clearance at an individual organ level is called as **organ clearacne.** It can be estimated by dividing the rate of elimination by each organ with the concentration of drug presented to it. Thus,

$$\text{Renal Clearance} \qquad Cl_R = \frac{\text{Rate of elimination by Kidney}}{C} \qquad (5.19)$$

$$\text{Hepatic Clearance} \qquad Cl_H = \frac{\text{Rate of elimination by liver}}{C} \qquad (5.20)$$

Other organ Clearance

$$Cl_{others} = \frac{\text{Rate of elimination by other organs}}{C} \qquad (5.21)$$

The total body clearance. Cl_T also called as total systemic clearance, is an additivie property of individual organ clearances. Hence,

Total Systemic Clearance $Cl_T = Cl_R + Cl_H + Cl_{others}$ (5.22)

Because of the additivity of clearance, the relative contribution by any organ in eliminating a drug can be easily calcualted. Clearance by all organs other than kidney is sometimes known as **nonrenal clearance** Cl_{NR}. It is the difference between total clearance and renal clearance.

According to an earlier definition (equation 5.18),

$$Cl_T = \frac{dX/dt}{C} \quad (5.18)$$

Substituting $dX/dt = K_E X$ from equation 5.3 in above equation, we get:

$$Cl_T = \frac{K_E\ X}{C} \quad (5.23)$$

Since $X/C = V_d$ (from equation 5.13), the equation 5.19 can be written as:

$$Cl_T = K_E\ V_d \quad (5.19)$$

Parallel equations can be written for renal and hepatic clearances as :

$$Cl_R = K_E\ V_d \quad (5.20)$$

$$Cl_H = K_m\ V_d \quad (5.21)$$

Since $K_E = 0.693/\ t_{1/2}$ (from equation 5.12), clearance can be related to half-life by the following equation :

$$Cl_T = \frac{0.693\ V_d}{t_{½}} \quad (5.22)$$

identical equations can be written for ClR and ClH in which cases the $t_{½}$ will be urinary excretion half-life for unchanged drug and metabolism half-life respectively. Equation 5.22 shows that as ClT decreases, as in renal insufficiency, $t_{1/2}$ of the drug increases. As the Cl_T takes into account V_d, changes in V_d as in obesity or edematous condition will reflect changes in Cl_T.

The noncompartmental method of computing total clearance for a drug that follows one-compartment kinetics is:

For drgus given as i.v. bolus,

$$Cl_T = \frac{X_o}{AUC} \qquad (10.24)$$

For drugs administred e.v.

$$Cl_T = \frac{F\ X_o}{AUC} \qquad (5.25)$$

For a drug given by i.v. bolus, th renal clearance Cl_R may be estimated by determing the toal amount of unchanged drug excretred in urine, X_u and AUC

$$Cl_R = \frac{X_u^{\infty}}{AUC} \qquad (5.26)$$

Organ Clearance : the best way of understading clearnce is at individual organ level. Such a physiologic approach is advantageous in predicting and evaluating and influence of pathology, blood flow, P-D binding, enzyme activity, etc. on drug elimination. At an organ level, the rate of elimination can be written as :

Rate of elimiation = Rate of presentation – Rate of exit (5.27)
By an organ to the organ from the organ

Rate of presentation = Organ blood flow x Entering concentration
(input) = $Q.C_{in}$ (5.28)

Rate of exit (output) = Organ blood flow x Exiting concentration
= $Q.C_{out}$ (5.29)

Substitution of equation 5.28 nad 5.29 in equation 5.27 yields:

Rate of elimination = $Q.C_{in} - Q.C_{out}$
(also called as rate of extraction) = $Q (C_{in} - C_{out})$ (5.30)

Division of above equation by concentration of drug that enters the organ of elimination C_{in} yields an expressions for clearance of drug by the organ under consideration. Thus:

$$\frac{\text{Rate of extraction}}{C_{in}} = Cl_{oran} = \frac{Q (C_{in} - C_{out})}{C_{in}} = Q.ER \qquad (5.31)$$

Where **ER** = (C_{in} -Q. C_{out}) /C_{in} is called as **extraction ratio**. It has no units and its value range from zero (no elimination) to one (complete elimination). Based on ER values, drugs can be classified into 3 groups;

- Drugs with **high ER** (above).
- Drugs with **intermediate ER** (between to 0.3), and
- Drugs with **low ER** (below 0.3).

ER is an index of how efficiently the eliminating organ clears the blood following through it of drug. For example, an ER of 0.6 tells that 60% of the blood flowing through the organ will be completely cleared of drug. The fraction of drug that escapes removal by the organ is expressed as :

$$F = 1- ER \quad (5.32)$$

Where, **F = systemic availability** when the eliminating organ is liver.

Hepatic Clearance: For certain drugs, the nonrenal clearance can be assumed as equal to hepatic

clearance Cl_H. It is given as:

$$Cl_H = Cl_T - Cl_R \quad (5.33)$$

An equation parallel to equation 5.31 can also be written for hepatic clearance:

$$Cl_H = Q_H.ER_H \quad (5.34)$$

Where, QH = hepatic blood flow (about 1.5 liters/min), and

ER_H= hepatic extraction ratio.

The hepatic clearance of drugs can be divided into two groups:

-drugs with hepatic blood flow rate-limited clearance, and

-drugs with intrinsic capacity-limited clearance.

1. **Hepatic Blood Flow** : When ERH is one, ClH approaches its maximum value i.e. hepatic blood flow. In such a situation , hepaicclearance is said to be **perfusion rate-limited or flow-dependent**. Alteraction in hepatic blood flow significantly affects the elimination of drugs with high ERH e.g. propranolod, lidocaine, etc. Such drugs are removed from the blood as rapodly as they are presented to the liver (high first-pass hepatic metabolism). Indocyanine green

is so rapodly eliminated by the human liver that its clearance is often used as an indicator of hepatic blood flow rate. First-pass hepatic extraction is suspected when there is lack of unchanges drug in systemic circulation after oral administration. **Maximum oral availability F** or such drugs can be computed from equation 5.32 an extension of the same equation is the noncompartmental method of estimating F:

$$F = 1 - ER_H = \frac{AUC_{oral}}{AUC_{i.v.}} \qquad (5.35)$$

Table 5.1
Influence of Blood Flow Rate and Protein Binding on Total Clearance of Drugs with High and with Low ER Values.

Drugs with	Changes in Total Clearance due to			
	T Blood Flow	† Blood Flow	T Binding	† Binding
High ER (above 0.7)	T	†	No Change	No Change
Low ER (below 0.3)	No Change	No Change	T	†

Where,T = increase and † = decrease

On the contrary, hepatic blood flow has very little or no effect on drgus with low ER_H .e.g theophyline. For such drugs, whatever concentration of drug present in the blood perfuses liver, is more than what the liver can eliminate (low first-pass hepatic metabolism). Similar discussion can be extended to the influence of blood flow on renal clearance of drugs. This is illustrated in Table 10.1. Hepatic clearance of a drug with high ER is independent of protein binding.

2. **Instrinsic Capacity Clearance :** Denoted as Cl_{int}. it is defined as the inherent ability of an organ to irreversibly remove a drug in the absence of any flow limitation. It depends, in this case, upon the hepatic enzyme activity. Drugs with low ER_H and with elimination primarily by metabolism are greatly affected by changes in enzyme activity. Hepatic clearance of such drugs is said to be capacity-limited e.g. theopnyllirc. The $t_{1/2}$ of such drugs show great intersubject variability Hepatic clearance of drugs with low ER is indepndent of blood flow rate but sensitive to changes in protein binding.

The heptatic and renal extraction rations of some drugs and metabolites are given in Table 5.2.

Table 5.2

Hepatic and Renal Extraction Ratio of Some Drugs and Metabolites

	Extraction Ratio		
	High	Intermediate	Low
Hepatic Extraction	Propranolol Lodicaine Nitroglycerine Morphine Isoprenaline	Aspirin Codeine Nortripty line Quinidine	Diazepam Phenobarbital Phenytoin Procainmide Theophyline
Renal Extraction	Some Penicillins Hippuric acid Several Sulfates Several Glucuronides	Some Penicillins Procainamide Cimetidine	Digoxin Furosemide Atenolol Tetracyclilne

One-Compartment Open Model

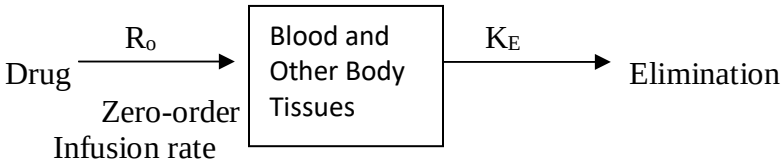
-Intravenous Infusion

Rapid i.v. injection is unsuitable when the drug has potential to precipitate toxicity or when maintainance of a stable concentration or amount of drug in the body is desired. In such a situation, the drug (for example, several antibiotics, theophyline, procainmide, etc.) is administered at a constant rate (zero-order) by i.v. infusion. In contrast to the short duration of infusion of an i.v. bolus (few seconds), the duration of constant rate infusion is usually much longer than the half-life of the drug. Advantages of such a zero-order infusion of such a zero order infusion of drugss include –

1. Ease of control of rate of infusion to fit individual patient needs.
2. Prevents fluctuating maxima and minima (peak and valley) plasma level, desired especially when the drug has a narrow therapeutic index.

3. Other drugs, electrolytes and nutrients can be conveniently administered simultaneously by the same infusion line in critically ill patients.

The model can be represented as follows:



At any time during infusion, the rate of change in the amount of drug in the body. dX/dt is the difference between the zero-order rate of drug infusion R_o and first-order rate of elimination, $-K_E X$:

$$\frac{ds}{dt} = R_o - K_E X \qquad (5.36)$$

Integration and rearrangement of above equation yields:

$$X = \frac{R^0}{K_E}(1 - e^{-K_E t}) \qquad (5.37)$$

Since $X = V_d C$, the equation 5.37 can be transformed into concentration terms as follows:

$$C = \frac{R^0}{K_E V_d}(1 - e^{-K_E t}) = \frac{R^0}{CS_T}(1 - e^{-K_E t}) \qquad (5.38)$$

At the start of constant rate infusion, the amount of drug in the body is zero and hence, there is no elimination. As time passes, the amount of drug in the body rises gradually (elimination rate less than the rate of infusion) until a point after which the rate of elimination equals the rate of infusion i.e. the concentration of drug in plama appraches a constant value called as steady-state, plateau or equilibrium (Fig. 5.4).

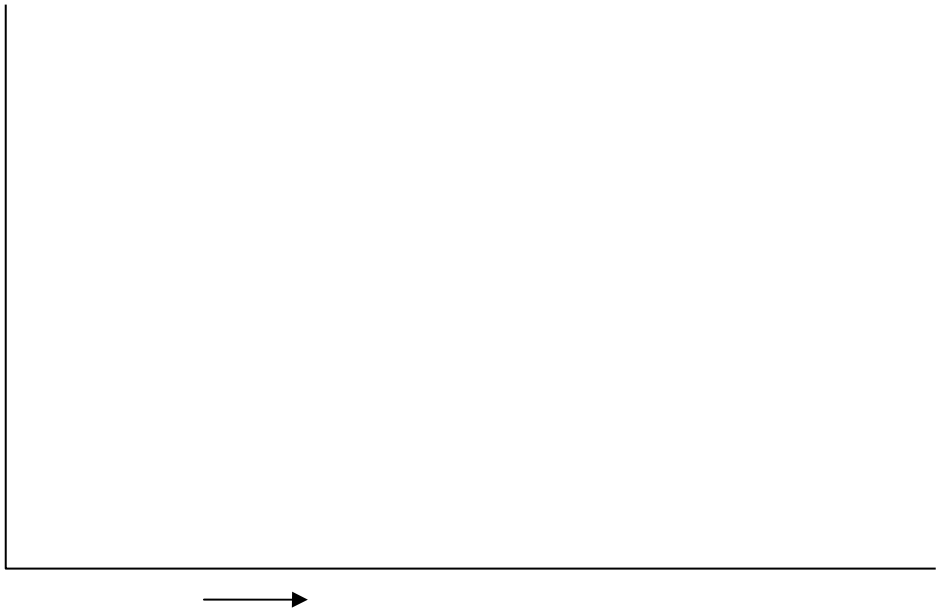


Fig. 5.4 Plasama concentration time profile for a drug given by constant rate i.v. infusion (the two curves indicate different infusion rates Ro and $2R_0$ for the same drug)

At steady-state, the rate of change of amount of drug in the body is zero, hence the equation 5.36 becomes:

$$\text{Zero} = R_0 - K_E X_{ss}$$

or

$$K_E X_{ss} = R_0 \qquad (5.39)$$

Transforming to concentration terms and rearranging the equation:

R_0 R_0 Infusion

$$C_{ss} = \frac{\text{rate}}{K_E V_d} = \frac{R_0}{Cl_T} \text{ i.e } \frac{R_0}{\text{Clearance}} \quad (5.40)$$

Where X_{ss} and C_{ss} are amount of drug in the body and concentration of drug in plasma at steady –state repectively. The value of K_E (and hence $t_{1/2}$) can be obtained from the slope of straight line obtained after a semilogarithmic plot (log C versus t) of the plasma concentration-time data generated from the time when infusion is stopped (Fig. 5.4). Alternatively, K_E can be calculated from the data collected during infusion to steady-state as follows:

Substituting R_0/C_{ss} = C_{ss} from equation 5.40 in equation 5.38 we get:

$$C = C_{ss}(1 - e^{-K_E t}) \qquad (5.41)$$

Rearrangement yields:

$$\frac{C_{ss} - C}{C_{ss}} = e^{-K_E t} \qquad (5.42)$$

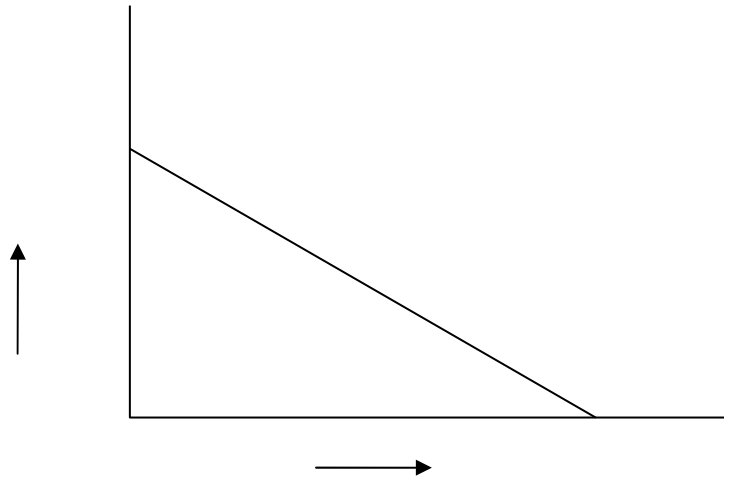
Transforming into log form, the equation becomes:

$$\log \frac{C_{ss} - C}{C_{ss}} = \frac{-K_E t}{2.303} \qquad (10.40)$$

A semilog plot of $(C_{ss} - C) / C_{ss}$ versus t results in a straight line with slope $-K_E / 2.303$ (Fig. 5.5)

Fig. 5.5 **S**emilog plot to compute K_E from infusion data upon steady-state

The time to reach steady-state concentration is dependent upon the elimination half-life and not infusion rate. An increase rate will merely increase the plasma concentration at steady-



state (Fig.5.4). If n is the number of half-lives passed since the start of infusion (t/t1/2), equation

5.41 can be written as:

The percent of Css achieved at the end of each t1/2 is the sum of Css at previous t1/2 and the concentration of drug remaining after a given t1/2 (Table 5.3).

TABLE 5.3 Percent of Css attained at the end of a given t1/2

Half-Life	% Remaining	%	Css	Achieved
1	50	50		
2	25	25	+ 25	= 75
3	12.5	75	+ 12.5	= 87.5
4	6.25	87.5	+ 6.25	= 93.75
5	3.125	93.75	+ 3.125	= 96.875
6	1.562	96.875	+ 1.562	= 98.437
7	0.781	98.437	+ 0.781	= 99.218

For therapeutic purpose, more than 90% of the steady-state drug concentration in the blood is desired which is reached in 3.3 half-lives. It take 6.6 half-lives for the concentration to reach 99% of the steady-state. Thus, the shorter the half-life (e.g. penicillin G, 30 min), sooner is the steady-state reached.

Infusion Plus Loading Dose : It takas a very long time for the drugs having longer half-lives before the plateau concentration is reached (e.g. phenobarbital, 5 days). Thus, initially, such drugs have subtherapeutic concentrations. This can be overcome by asministering an i.v. loading dose large enough to yield the desired steady-state immediately upon injection prior to starting the infusion. It should then be followed immediately by i.v. infusion at a rate enough maintain this concentration (Fig. 5.6).

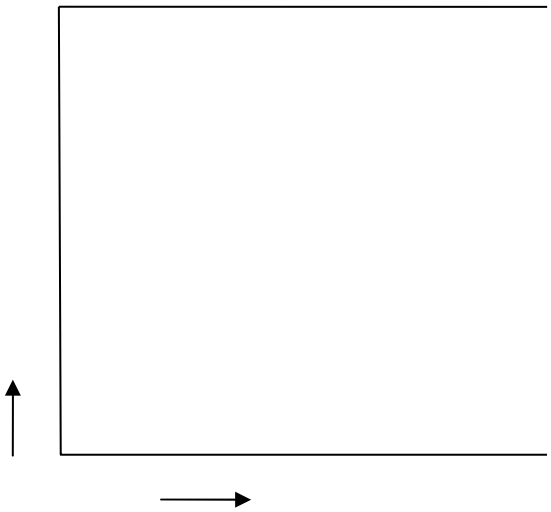


Fig. 5.6 Intravenous infusion with loading dose.

As the amount of bolus dose remaining in the body falls, there is a complementary rise Resulting from the infusion

Recalling once again the ralationship $X = V_dC$, the equation for computing the loading dose $X_{o,L}$ can be given:

$$X_{o,L} = C_{ss}V_d \qquad (5.45)$$

Substitution of $C_{ss} = R_o/K_EV_d$ from equation 5.40 in above equation yields another expression for loading dose in terms of infusion rate:

$$X_{o,L} = \frac{R_o}{K_E} \qquad (5.46)$$

The equation describing the plasma concentration-time profile following simultaneous i.v. loading dose (i.v. bolus) and constant rate i.v. infusion is the sum of two equations describing each process (i.e. modified equation 5.38):

$$C = \frac{X_0L}{V_d} e^{-K_Et} + \frac{R_0}{K_EV_d} (1 - e^{-K_Et}) \qquad (5.47)$$

If we substitute $C_{ss}V_d$ for $X_{o,L}$ (from equation5.45) and $C_{ss}K_EV_d$ for R_o (from equation 5.40) in above equation and simplify it, it reduces to $C = C_{ss}$ indicating that the concentration of drug in plasma remains constant (steady) throughout the infusion time.

Assessment of Pharmacokinetic Parameters

The first-order elimination rate constant and elimination half-life can be computed from a semilog plot of post-infusion concentration-time data. Equation 5.43 can also be used for the asme purpose. Apparent volume of distribution and total systemic clearance can be estimated from steadystate concentration and infusion rate (equation 5.40). These two perameters can also be computed from the total area under the curve (Fig 5.4) till the end of infusion:

$$AUC = \frac{R_0 T}{K_E V_d} = \frac{R_0 T}{Cl_T} = C_{ss} T \qquad (5.48)$$

Where, T = infusion time.

The adove equation is a general exprssion which can be appllied to several pharmacokinetic models.

One-Compartment Open Model

--Extravascular Asministration

The rate of absorption may be described mathematically as a zeroorder or first-order process. A large number of plasma concentration-time profiles can be described by a one-compartment model with first-order absorption and elimination. However, under certain conditions, the absorption of some drugs may be better described by assuming zero-order(constant rate) kinetics. Differences between zero-order and first-order kinetics are illustrated in Fig. 5.7.

Zero-order absorption is characterized by a constant rate of absorption. It is independent of amount remaining to be absorbed (ARA), and its regular ARA versus t plot is linear with slope equal to tate of absorption while the semilog plot is described by an ever-increasing gradient with time. In contrast, the first –order absorption process is distinguished by a decline in the rate with ARA i.e. absorption rate is dependent upon ARA ; its regular plot is curvilinear and semilog plot a straight line with absorption rate as its slope.

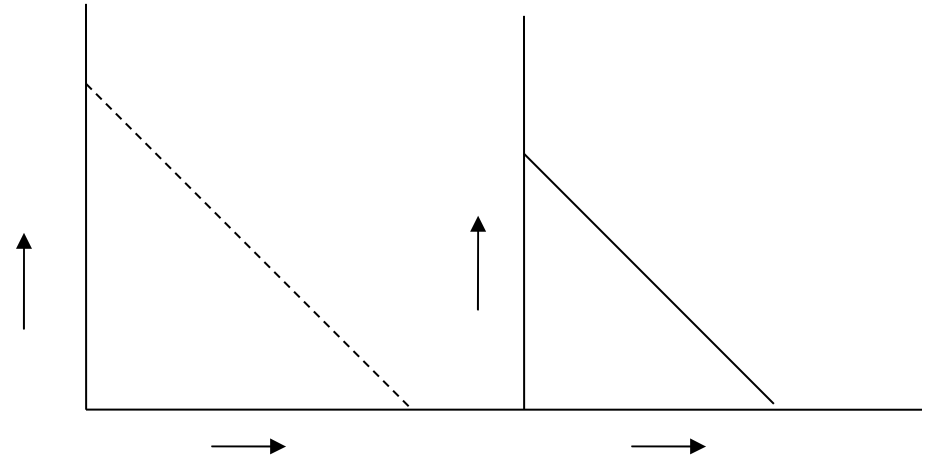


Fig. 5.7 Distinction between zero-order and first-order absorption processes.
Figure a is regular plot, and Figure b a semilog plot of amount of drug remaining to be Absorbed (ARA) versus time t.

After e.v. administration, the rate of change in the amount of drug in the body dX/dt is the difference between the rate of input (absorption) dX_{ev}/dt and rate of output (elimination).

dX/dt = Rate of absorption – Rate of elimination

$$\frac{dX}{dt} = \frac{dX_{ev}}{dt} - \frac{dX_E}{dt} \qquad (10.49)$$

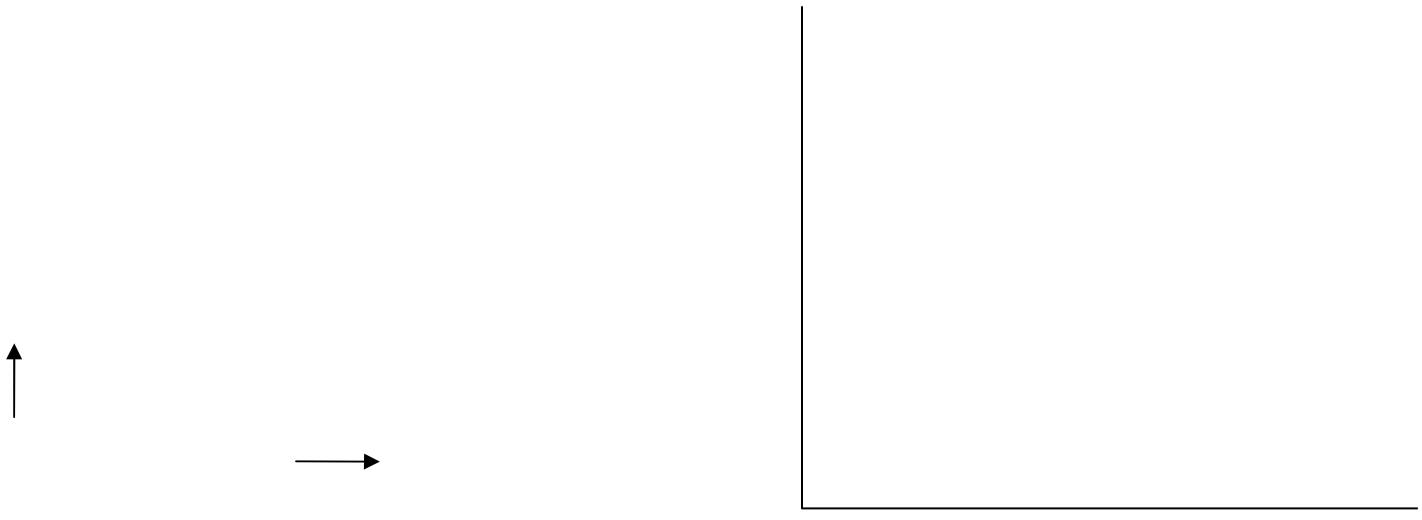


Fig. 5.8 The absorption and elimination phases of the plasma concentration – time profile obtained after extravascular administration of a single dose of a drug.

For a drug that follows one-compartment kinetics, the plasma concentration profile is characterized by absorption phase, post-absorption phase and elimination phase (Fig . 5.8) During the **absorption phase,** the rate of absorption is greater than the rate of elimination

$$\frac{dX_{ev}}{dt} > \frac{dX_E}{dt} \qquad (5.50)$$

At peak plasma concentration, the rate of absorption equals the rate of elimination and the change in amount of drug in the body is zero.

$$\frac{dX_{ev}}{dt} = \frac{dX_E}{dt} \qquad (5.51)$$

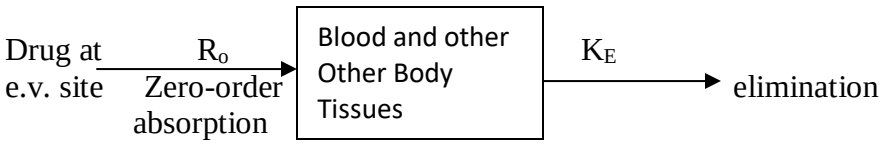
During the post-absorption phase, there is some drug at the extravascular site still remaining to be absorbed and the rate of elimination at this stage is greater than the absorption rate.

$$\frac{dX_{ev}}{dt} < \frac{dX_E}{dt} \qquad (5.52)$$

After completion of drug absorption, its rate becomes zero and the plasma level time curve is characterized only by the elimination phase.

Zero-order Absorption model

The model is similar to that for constant rate infusion.

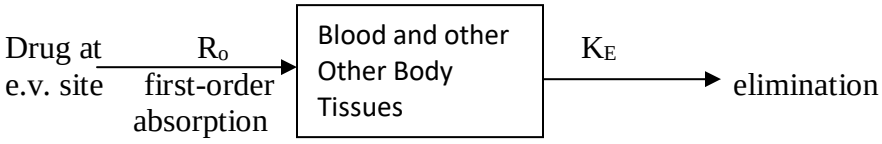


The rate of drug absorption, as in the case of several controlled drug delivery systems, is constant and continues until the amount of drug at the absorption site (e.g. GIT) is depleted. All

equation that explains the plasma concentration-time profile for constant rate i.v. infusiion are also applicable to this model.

First –Absorption Model

For a drug that enters the body by a first –order absorption process, gets distributed in the body according to one-compartment kinetics, and is eliminated by a first-order process, the model can be depicted as follows:



The differential form of the equation 5.49 is

$$\frac{ds}{dt} = K_a X_a - K_E X \qquad (5.53)$$

Where K_a = first-order absorption rate constant, and

X_a = amount of drug at the absorption site remaining to be absorbed i.e. A.R.A

Integration of equation 5.53 yields:

$$X = \frac{K_a F X_0}{(K_a - K_E)} \left(e^{-K_E t} - e^{-Kat} \right) \qquad (5.54)$$

Transforming into concentration terms, the equation becomes:

$$C = \frac{K_a F X_0}{V_d(K_a - K_E)} \left(e^{-K_E t} - e^{-Kat} \right) \qquad (5.55)$$

Where F = fraction of drug absorption systemically after e.v. administration. A typical plasma concentration-time profile of a drug administered e.v. is shown in Fig. 5.8

Assessment of Pharmacokinetic Parameters

C_{max} and t_{max} : At peak plasma concentration, the rate of absorption equals rate of elimination i.e. $K_a X_a = K_E X$ and the rate of change in plasma drug concentration dC/dt = zero. This rate can be obtained by differentiating equation 5.55

$$\frac{dc}{dt} = \frac{K_a F X_0}{(K_a - K_E)} \left(-K_E e^{-KEt} + K_a e^{-Kat}\right) = \text{zero} \qquad (5.56)$$

On simplifying the above equation becomes:

$$K_E e^{-KEt} + K_a e^{-Kat} \qquad (5.57)$$

Converting to logarithmic form,

$$\log K_E - \frac{K_E t}{2.303} = \log K_a - \frac{K^a t}{2.303} \qquad (5.58)$$

Where t is t_{max} Rearrangement of above equation yields:

$$t_{max} = \frac{2.303 \log (k_a/K_E)}{K_a - K_E} \qquad (5.59)$$

The above equation shows that as K_a becomes larger than K_E, t_{max} becomes smaller since $(K_a - K_E)$ increases much faster than $\log K_a / K_E$. C_{max} can be obtained by substituting equation 5.55. However, a simpler expression for the same is:

$$C_{max} = \frac{F X_0}{V_d} e^{-K_{Etmax}} \qquad (5.60)$$

It has been shown that at C_{max}, when $K_a = K_E$, $t_{max} = 1/ K_E$. Hence, the above equation further reduces to:

$$C_{max} = \frac{F X_0}{V_d} e^{-1} = \frac{0.37 F X_o}{V_d} \qquad (5.61)$$

Since FX_o/V_d represents C_o following i.v. bolus, the maximum plasma concentration that can be attained afetr e.v. administration is just 37% of the maximum level attainable with i.v. bolus in the same dose. If bioavailability is less than 100% still lower concentration will be attained.

Elimination Rate Constant: This parameter can be computed from the elimination phase of the plasma level time profile. For most drugs administered e.v., absorption rate is significantly greater than the elimination rate i.e. $K_at > K_Et$. Hence, one can say that e^{-Kat} approaches zero

much faster than does $e^{-K_{Et}}$. At such a stage, when absorption is complete, the change in plasma concentration is dependent only on elimination rate and equation 5.55 reduces to:

$$C_{max} = \frac{K_a F X_0}{V_d(K_a - K_E)} e^{-K_{Et}} \qquad (5.62)$$

Transforming into log form, the equation becomes:

$$\log C = \log \frac{K_a F X_0}{V_d(K_a - K_E)} - \frac{K_{Et}}{2.303} \qquad (5.63)$$

A plot of log C versus t yields a straight line with slope $-K_E/2.303$ (half-life can then be computed from K_E). K_E can also be estimated from urinary excretion data (see the section on urinary excretion data).

Absorption Rate Constant: it can be calculated by the method of residuals. The technique is also known as feathering peeling and stripping. It is commonly used in pharmacokinetics to resolve a multiexponential curve into its individual components. For a drug that follows one-compartment kinetics and administered e.v. the concentration of drug in plasma is expressed by a biexponential equation 5.55.

$$C = \frac{K_a F X_0}{V_d(K_a - K_E)} e^{-K_E t} - e^{-Kat} \qquad (5.55)$$

If $KaFX_0 / V_d(Ka - K_E) = A$, a hybrid constant, then:

$$C = A e^{-K_{Et}} - e^{-Kat} \qquad (5.64)$$

During the elimination phase, when absorption is almost over, $K_a >> K_E$ and the value of second exponential $e^{-K_E t}$ retains some finite value. At this time, the equation 5.64 reduces to:

$$\dot{C} = A e^{-K_E t} \qquad (5.65)$$

In log form, the above equation is:

$$\log \dot{C} = \log A = \frac{K^{Et}}{2.303} \qquad (5.66)$$

Where $\dot{C}$ represents the back extrapolated plasma concentration values. A plot of log C versus t yields a biexponential curve with a terminal linear phase having slope $-K_E/2.303$ (Fig. 5.9). Back extrapolation of this straight line to time zero yields y-intercept equal to log A.

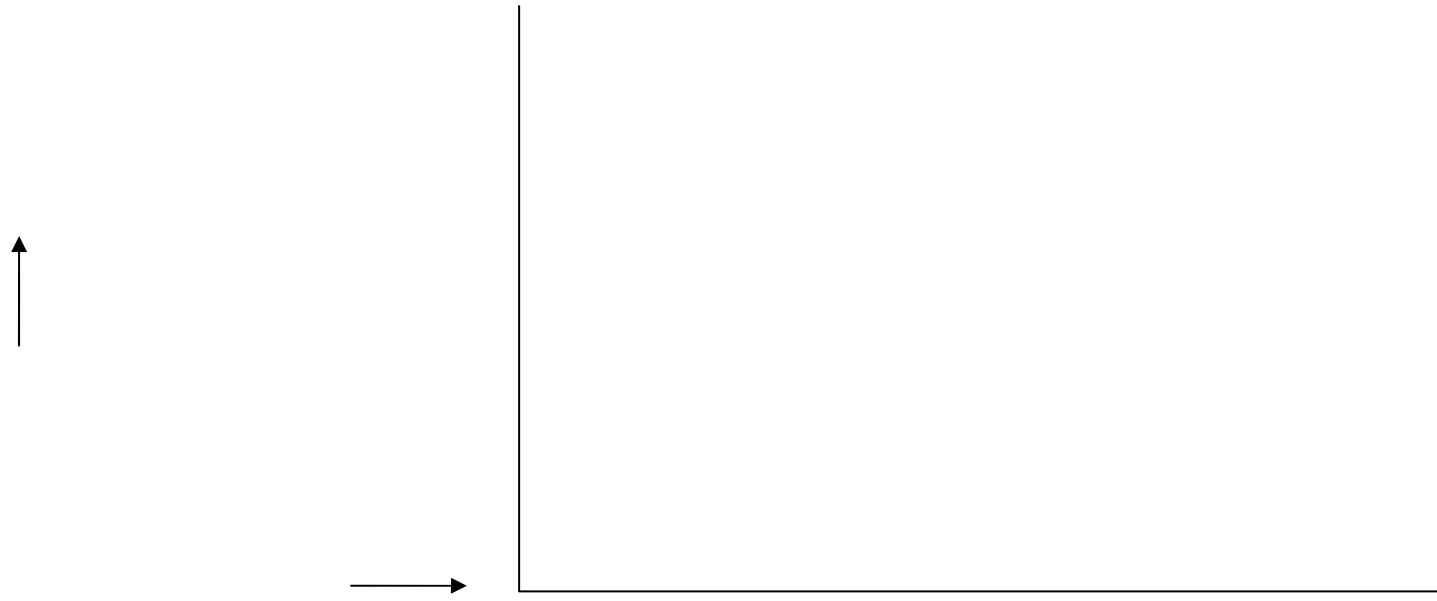


Fig. 5.9 Plasma concentration-time profile after oral administration of single dose of a drug. The biexponential curve has been resolved into its two components- absorption and elimination.

Subtraction of true plasma concentration values i.e. equation 5.64 from the extrapolated plasma concentration values i.e. equation 5.65 yields a series of residual concentration values C_r :

$$(\dot{C} - C) = C_r = A\, e^{-Kat} \qquad (5.67)$$

Ln log form, the equation is:

$$\log C_r = \log A - \frac{K_a t}{2.303} \qquad (5.68)$$

A plot of log C_r versus t yielys a straight line with slope – $K_a/2.303$ and y-intercept log A (Fig. 5.9). Absorption half-life can then be computed from K_a using the relation $0.693/K_a$. Thus, the method of residuals enables resolution of the biexponential plasma level-time curve into its two exponential components. The technique works best when the difference between K_a and K_E is large ($K_a/K_E \geq 3$). In some instances, the K_E obtained after i.v. bolus of the same drug is very large, much larger than the K_a obtained by the method of residuals (e.g. isoprenaline) and if $K_E/K_a \geq 3$, the terminal slope estimates K_a and not K_E whereas the slope of residual line gives K_E and not K_a. This is called as **flip-flop** *phenomenon since the slopes of the two lines have exchanged their meanings*.

Ideally, the extrapolated and the residual lines intersect each other on y-axis i.e. at time t = zero and there is no lag in absorption. However, if such an intersection occurs at a time greater than zero, it indicates **timelag**. *It is defined as the time difference between drug administration and start of absorption*. It is denoted by symbol t_o and represents the beginning of absorption process. Lag time should not be confused with onset time.

The method for the estimation of K_a is a curve-fitting method. The method is best suited for drugs for drugs which are rapidly and completely absorbed and follow one-compartment kinetic even given i.v. However, if the absorption of the drug is affectexc in some way such as Gl motility or enzymatic degradation and if the drug shows multicompartment characteristics after i.v. administration (which is true for virtually all drugs), then K_a computed by curve-fitting method is incorrect even if the drug were truly absorbed by first-order kinetics. The K_a so obtained is at best, estimate of first-order disappearance of drug from the GIT rather than of first-order appearance in the systemic circulation.

Wagner-Nelson Method for Estimation of K_a

One of the better alternatives to curve-fitting method in the estimation of Ka is Wagner-Nelson method. The method involves determination of Ka from percent unabsorbed-time plots and does not require the assumption of zero-or-first-order absorption.

After oral administration of a single dose of a drug, at any given time, the amount of drug absorbed into the systemic circulation X_A, is the sum of amount of drug in the body X and the amount of drug eliminated from the body X_E. Thus:

$$X_A = X + X_E \tag{5.69}$$

The amount of drug in the body is X = VdC. The amount of drug eliminated at any time t can be calculated as follows:

$$X_E = K_E V_d [AUC]_0^t \tag{5.70}$$

Substitution of values of X and X_E in equation 10.63 yields:

$$X_A = V_d C + K_E V_d [AUC]_0^t \tag{5.71}$$

The total amount of drug absorbed into the systemic circulation from time zero to infinity X_A^∞ can be given as:

$$X_A^\infty = V_d C^\infty + K_E V_d [AUC]_0^\infty \tag{5.72}$$

Since at $t = \infty$, $C^\infty = 0$, the above equation reduces to:

$$X_A^\infty = K_E V_d [AUC]_0^\infty \tag{5.73}$$

The fraction of drug absorbed at any time t is given as:

$$\frac{X_A}{X_A^\infty} = \frac{V_d C + K_E V_d [AUC]_0^t}{K_E V_d [AUC]_0^\infty}$$

$$= \frac{C + K_E [AUC]_0^t}{K_E [AUC]_0^\infty} \tag{5.74}$$

Percent drug unabsorbed at any time is therefore:

$$\%ARA = 1 - \frac{X_A}{X_A^\infty} 100 = 1 - \frac{C + K_E V_d [AUC]_0^t}{K_E [AUC]_0^\infty} 100 \tag{5.75}$$

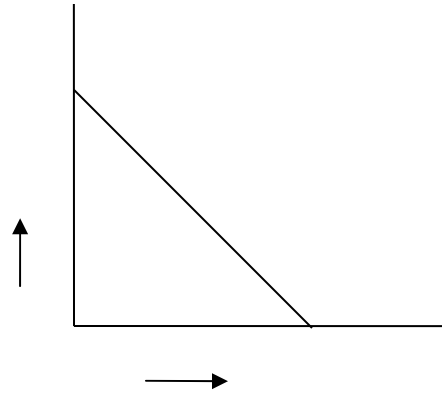


Fig. 5.10 Semilog plot of percent ARA versus t according to Wagner – Nelson method

The method requires collection of blood samples after single oral dose at regular intervals of time till the entire amount of drug is eliminated from the body. K_E is obtained from log C versus t plot and $[AUC]_0^t$ and $[AUC]_0^\infty$ are obtained from plot of C versus t. A semilog plot of percent of unabsorbed (i.e. percent ARA) versus t yields a straight line whose slope is $-K_a/2.303$ (Fig. 5.10). If a regular plot of the same is a straight line, then absorption is zero-order.

K_a can similarly be estimated from urinary excretion data (see the relevant section). The biggest disadvantage of Wagner-Nelson method is that it applies only to drugs with one-compartment characteristics. Problem arises when a drug that obeys one-compartment model after e.v. administration shows multicompartment characteristics on i.v. injection.

Effect of K_a And K_E on C_{max}, and t_{max} and AUC

A summary of the influence of change in K_a at constant K_E and of K_E at constant Ka on C_{max}, t_{max} and AUC of a drug administered e.v. is shown in Table 5.4

Table 5.4
Influence of Ka and K_E on C_{max}, t_{max} and AUC

Parameters Affected	Influence when K_E is Constant		Influence when K_a is Constant	
	Smaller K_a	Large K_a	Smaller K_E	Larger K_E
C_{max}	†	T	†	T
t_{max}	Long	Short	Long	Short
AUC	No Change	No Change	T	†

Where, T = increase and † = decrease

Apparent Volume of Distribution and Clearance : For a drug that follows one-compartment kinetics after e.v. administration. V_d and Cl_T can be computed from equation 5.16 and 5.17 respectively Where F is the fraction absorbed into the systemic circulation.

$$V_d = \frac{F X_0}{K_E \, AUC} \qquad (5.16)$$

$$Cl_T = \frac{F X_0}{AUC} \qquad (5.17)$$

URINARY EXCRETION DATA

(Disposition Viewed from Urine only)

In the absence of plasma level-time data, useful information can still be obtained from urine data regarding elimination kinetics of a drug. The method has several advantages in the analysis of a pharmacokinetic system:

1. The method is useful when there is lack of sufficiently sensitive analytic techniques to measure concentration of drugs in plasma with accuracy.
2. The method is noninvasive and therefore better subject compliance is assured.
3. Convenience of collecting urine samples in comparison to drawing of blood periodically.
4. Often, a less sensitive analytic method is required for determining urine drug concentration as compared to plasma concentrations; if the urine drug concentration are low, assaying of larger sample volumes is relatively easy.

5. First – order elimination, excretion and absorption rate constants and fraction excreted unchanged can be computed from such data; first order metabolism or extrarenal excretion rate constant can also be calculated subsequently from the difference $(K_E - K_e) = K_m$.
6. Direct measurement of bioavailability, both absolute and relative, is possible without the necessity of fitting the data to a mathematical model.
7. When coupled with plasma level-time data it can also be used to estimate renal clearance of unchanged drug according to following equation:

$$Cl_R = \frac{\text{Total amount of drug excreted unchanged}}{\text{Area under the plasma level-time curve}} \qquad (5.76)$$

If V_d is known, total systemic clearance and nonrenal clearance can also be calculated.

One cannot however compute V_d and Cl_T from urine data alone. One must also remember that urinary excretion data is not an accurate substitute for the plasma level data. At best, the data can be employed as a rough estimate of the pharmacokinetic parameters. Moreover, if the drug product provides a very slow drug release or if the drug has a very long biological half-life, the resulting low urinary drug concentration may be too dilute to be assessed with accuracy. In the latter case, i.e. for drugs with $t_{1/2}$, urine may have to be collected for several days to account for total drug excreted.

Criteria for Obtaining Valid Urinary Excretion Data

1. A significant amount of drug must be excreted unchanged in the urine (at least 10%).
2. The analytical method must be specific for the unchanged drug; metabolites should not interfere.
3. Water-loading should be done by taking 400 ml of water after fasting overnight, to promote diuresis and enable collection of sufficient urine samples.
4. Before administration of drug, the bladder must be emptied completely after 1 hour from water-loading and the urine sample taken as blank; the drug should then be administered with 200 ml of water and should be followed by 200 ml given at hourly intervals for the next 4 hours.

5. Volunteers must be instructed to completely empty their bladder while collecting urine samples.
6. Frequent sampling should be done in order to obtain a good curve.

Table 5.5

Urinary Excretion Data following i.v. Bolus of 100 mg of a drug

Observation					Treatment of Data				
Sample	**Time of urine collection t (hours)**	**Volume of urine collected (ml)**	**Concentration of unchanged drug in urine (mcg/ml)**	**Urine collection interval Dt (or Δt)**	**Mid-point of urine collection t^***	**Amount excreted in time interval (mg) dXu (or ΔX_U**	***Excretion rate (mg/H) dXu/dt***	**Cummulative amount Excreted (mg) Xu^t**	**Amount remaining to be excreted $Xu^\infty - Xu^t$**
0	0	-	-	-	-	-	-	0	66.7
1	0-2	140	250	2	1	35.0	17.5	35.0	31.7
2	2-4	150	100	2	3	15.0	7.5	50.0	16.7
3	4-6	90	80	2	5	7.2	3.6	57.2	9.5
4	6-8	200	20	2	7	4.0	2.0	61.2	5.5
5	8-12	310	10	4	10	3.1	0.8	64.3	2.4
6	12-24	600	04	12	18	2.4	0.2	66.7 † Xu^∞	-

7. During sampling, the exact time and volume of urine excreted should be noted.
8. An individual collection period should not exceed one biologic half-life tof the drug and ideally should be considerably less.
9. Urine samples must be collected for at least 7 biological half-lives in order to ensure collection of more than 99% of excreted drug.
10. Changes in urine pH and urine volume may after the urinary excretion rate.

The urine data can be set as shown in the table 5.5. Observations include times of urine collection, volumes collected and concentration of unchanged drug in each sample. These data are treated to derive further information.

Determination of K_E from Urinary Excretion Data

The first-order elimination (and excretion) rate constants can be computed from urine data by two methods:

1. Rate of excretion method, and
2. Sigma-minus method.

Rate of Excretion Method: The rate of urinary drug excretion dX_u/dt is proportional to the amount of drug in the body X and written as:

$$\frac{dX_u}{dt} = K_e X \qquad (5.77)$$

Where K_e = first order urinary excretion rate constant. According to first-order disposition kinetics, $X = X_o\, e^{-K_E t}$ (equation 5.5). Substituting it in above equation yields:

$$\frac{dX_u}{dt} = K_e X_0\, e^{-K_E t} \qquad (5.78)$$

Where X_0 = dose administered (i.v. bolus). Transforming to log form the equation becomes:

$$\log \frac{dX_u}{dt} = \log K_e X_0 - \frac{K_E t}{2.303} \qquad (5.79)$$

The above equation states that a semilog plot of rate of excretion versus time yields a straight line with slope $-K_E/2.303$ (Fig. 5.11). It must therefore be remembered that the slope of such an excretion rate versus time plot is related to elimination rate constant K_E and not to excretion rate constant K_e. The excretion rate constant can be obtained from the *Y*-intercept (log K_e X_o). Elimination half-life and nonrenal elimination rate constant can then the computed from K_E and K_e.

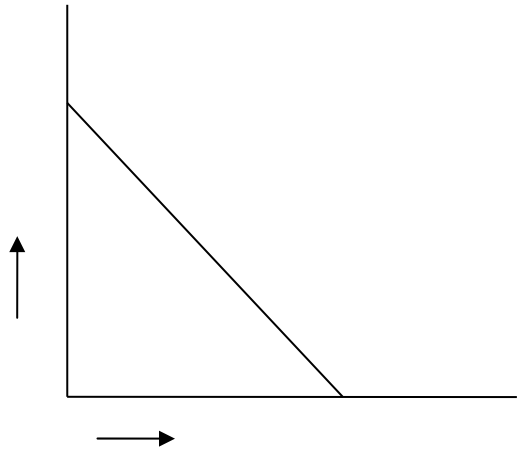


Fig. 5.11 Semilog plot of excretion rate versus midpoint time of urine collection period for computing elimination rate constant after i.v. bolus administration.

An advantage of excretion rate method is that for drugs having long half-lives, urine may be collected for only 3 to 4 half-lives. Moreover, there is no need to collect all urine samples since collection of any two consecutive urine samples yields points on the rate plot from which a straight line can be constructed.

Sigma-Minus Method: A disadvantage of rate of excretion method is estimating K_E is that fluctuations in the rate of drug elimination are observation to a high degree and in most instances, the data are so scattered that an estimate of half-life is difficult. These problems can be minimized by using the alternative approach called as sigma-minus method.

From an earlier equation:

$$\frac{dX_u}{dt} = K_e X_0 e^{-K_E t} \qquad (5.80)$$

Integration of equation 5.80 yields:

$$X_u = \frac{K_e X_0}{K_E} = (1 - e^{-K_E t}) \qquad (5.81)$$

Where X_u = cumulative amount of drug excreted unchanged in urine at anay time t. As time apprroaches infinity i.e. after 6 to 7 half-lives, the value $e^{-K_E \infty}$ becomes zero and therefore the cumulative amount excreted at infinite time X_u^{∞} can be given by equation:

$$X_u^{\infty} = \frac{K_e X_0}{K_E} \quad (5.82)$$

Substitution of equation 5.82 in equation 5.81 and rearrangement yields:

$$X_u^{\infty} - Xu = X_u^{\infty} e^{-K_E t} \quad (5.83)$$

Converting to logarithms, we get:

$$\text{Log}(X_u^{\infty} - X_u) = \text{Log}X_u^{\infty} - \frac{K^E t}{2.303}$$

Where $(X_u^{\infty} - X_u)$ = amount remaining to be excreted i.e. ARE at any given time. A semilog plot of ARE versus t yields a straight line with slope $-K_E / 2.303$. The method is, therefore, also called as ARE plot method. A disadvantage of this method is that total urine collection has to be carried out until no unchanged drug can be detected in the urine i.e. upon 7 half-lives, which may be tedious for drugs having long $t_{1/2}$.

The equations until now for computing KE from the urinary excretion data apply to a drug that fits one – compartment model and given as i.v. bolus. Similarly, data obtained during constant rate i.v. infusion can be used to evaluate the elimination rate constant. The equation that descrides the urinary excretion rate of unchanged drug when administered as i.v. bolus also applies when it is administered as i.v. infusion. Thus:

$$\frac{dXu}{dt} = K_e X \quad (5.77)$$

For a drug given as i.v. infusion, the amount of drug in the boby X is given by equation(described earlier)

$$X = \frac{R_0}{K_E}(1 - e^{-K_E t}) \quad (5.37)$$

Substitution of equation 5.37 in equation 5.77 and integration of the same yields:

$$X_u = \frac{K_e R_0}{K_E} - \frac{K_e R_0}{K_E^2}(1 - e^{-K_E t}) \quad (5.84)$$

When the drug has been infused for a period long enough to attain steady-state in the plasma, the term e^{-KEt} approaches zero and the above equation reduces to:

$$X_u = \frac{K_e R_0 t}{K_E} - \frac{K_e R_0}{K_E^2} \qquad (5.85)$$

A regular plot of cumulative amount of drug excreted Xu versus t yields a curvilinear plot the linear portion of which has a slope K_eR_o/K_E.

Extrapolation of linear segment to time axis yields x-intercept equal to 1/KE since when Xu = 0, t = 1/KE (Fig. 5.12).

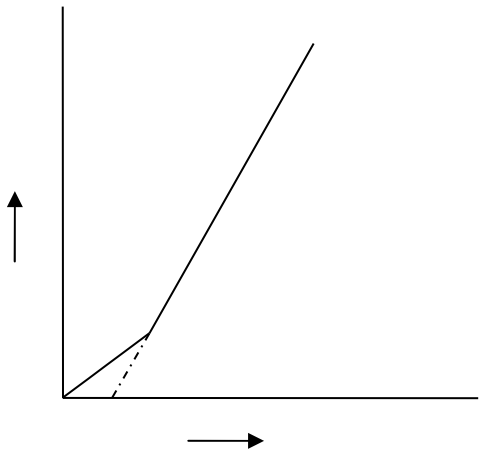


Fig. 5.12 Regular plot of X_u versus t during constant rate i.v. infusion

Relationships for rate of excretion when the drug is administered e.v. can also be given similarly. Thus:

$$\frac{dXu}{dt} = K_e X \qquad (5.77)$$

For a drug given e.v. and absorbed by a first-order process, X is given as:

$$X = \frac{K_a F X_0}{(K_a - K_E)} e^{-K_E t} - e^{-Kat} \qquad (5.54)$$

Substitution of equation 5.54 in equation 5.77 and integration of the same yields:

$$X_u = \frac{K_e K_a F X_0}{K_E}\left[\frac{1}{K_a} + \frac{e^{-K_E t}}{(K_E - K_a)} - \frac{K_E e^{-K_E t}}{K_a(K_E - K_a)}\right] \quad (5.86)$$

At time infinity, the equation 5.86 reduces to:

$$ARE = (Xu^{\infty} - X_u) = \frac{Xu^{\infty}}{(K_a - K_E)}(K_a e^{-K_E t} - K_E e^{-K_E t}) \quad (5.87)$$

Substitution of equation 5.86 in equation 5.87 and subsequent rearrangement yields:

A semilog plot of (Xu - Xu) versus t results in a biexponential curve and if Ka > KE, the slope of the terminal linear portion of the curve will define KE of the drug. The adsorption rate constant Ka can be estimated by the method of residuals using the same data i.e. equation 5.87.

Urinary excretion data after oral administration can also be treated according to Wagner-Nelson method to calculate Ka by construction of % ARA plots. The method requires urine collection for sufficiently long time to ensure accurate estimation of KE but need not be collected to time infinity. The equation derived to relate % ARA with urinary excretion rate is:

$$\%ARA = 1 - \frac{XA}{Xu^{\infty}} 100 = 1 - \frac{dX_u/dt + K_E X_u}{K_E Xu^{\infty}} 100 \quad (5.88)$$

A semilog plot of % ARA versus t yields a straight line with slope –Ka/2.303.

Accurate determination of Ka from urinary excretion data is possible only for drugs with slow rate of absorption since for drugs with rapid absorption; collection of urine samples at very short intervals of time is difficult.

RGPV QUESTIONS

S.No	Questions	Year	M.Marks
1.	Explain One compartment model following extravascular administration.	2017	07
2.	Discss one compartment model following intraveneous injection (bolous)	2018	14
3.	How to estimate the Ka & Ke from urinary excretion data.	2018	14

MULTICOMPARTMENT MODELS (Delayed Distribution Models)

Introduction

The one – compartment model adequately describes pharmacokinetics of many drugs. Instantaneous distribution equilibrium is assumed in such cases and decline in the amount of drug in the body with time is expressed by an equation with a monoexponential term (i.e.

elimination). However, instantaneous distribution is not truly possible for an even larger number of drugs and drug disposition is not monoexponential but bi-or multi-exponential. 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 rate of equilibration. Ideally, a true pharmacokinetic model should be the one with a rate constant for each tissue undergoing equilibrium, which is difficult mathematically. The best approach is therefore to pool together tissues on the basis of similarity in their distribution characteristics. As for one-compartment models, drug disposition in multicompartment systems is also assumed to occur by first-order. Multicompartment characteristics of a drug are best understood by giving it as i.v. bolus and observing the manner in which the plasma concentration declines with time. The number of exponentials required to describe such a plasma level-time profile determines the number of kinetically homogenous compartments into which a drug will distribute.

TWO-COMPARTMENT OPEN MODEL

The commonest of multicompartment model is two compartment model. In such a model, the body tissues are broadly classified into 2 categories.

1. Central Compartment or Compartment 1. Comprising of blood and highly perfused tissues like liver, lungs, kidneys, etc. that equilibrate with the drug rapidly. Elimination usually occurs from this compartment.]
2. Peripheral or Tissue Compartment or Compartment 2 comprising of poorly perfused and slow equilibrating tissues such as muscles, skin, adipose, etc. and considered as a hybrid of several functional physiological units.

Classification of particular tissue, for example brain, into central or peripheral compartment depends upon the physicochemical properties of the drug. A highly lipophilic drug can cross the BBB and brain would then be included in the central compartment. In contrast, a polar drug cannot penetrate the BBB and brain in this case will be a part of peripheral compartment despite the fact that it is a highly perfused organ.

Depending upon the compartment from which the drug is eliminated, the two-compartment model can be categorized into 3 types:

1. Two –compartment model with elimination from central compartment.

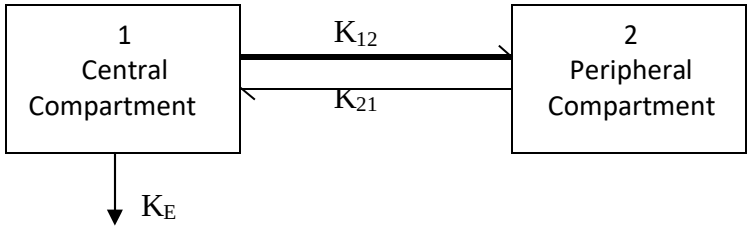
2. Two – compartment model with elimination from peripheral compartment.
3. Two- compartment model with elimination from both the compartments.

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

Two-Compartment Open Model-Intravenous

Bolus Administration

The model can be depicted as shown below with elimination from the central compartment.



After the i.v. bolus of a drug that follows two-compartment kinetics, the decline in plasma concentration is biexponential indicating the presence of two disposition processes viz. distribution and elimination. These two processes are not evident to the eyes in a regular arithmetic plot but when a semilog plot of C versus t is made, they can be identified (Fig. 5.13). Initially, the concentration of drug in the central compartment declines rapidly, this is due to the distribution of drug from the central compartment to the peripheral compartment. The phase during which this occurs is therefore called as the distributive phase. After sometime, a pseudo-distribution equilibrium is achieved 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 the central compartment, the drug concentration in the peripheral compartment first increases and reaches a maximum. This corresponds with the distribution phase. Following peak, the drug concentration declines which corresponds to the post-distributive phase (Fig. 5.13).

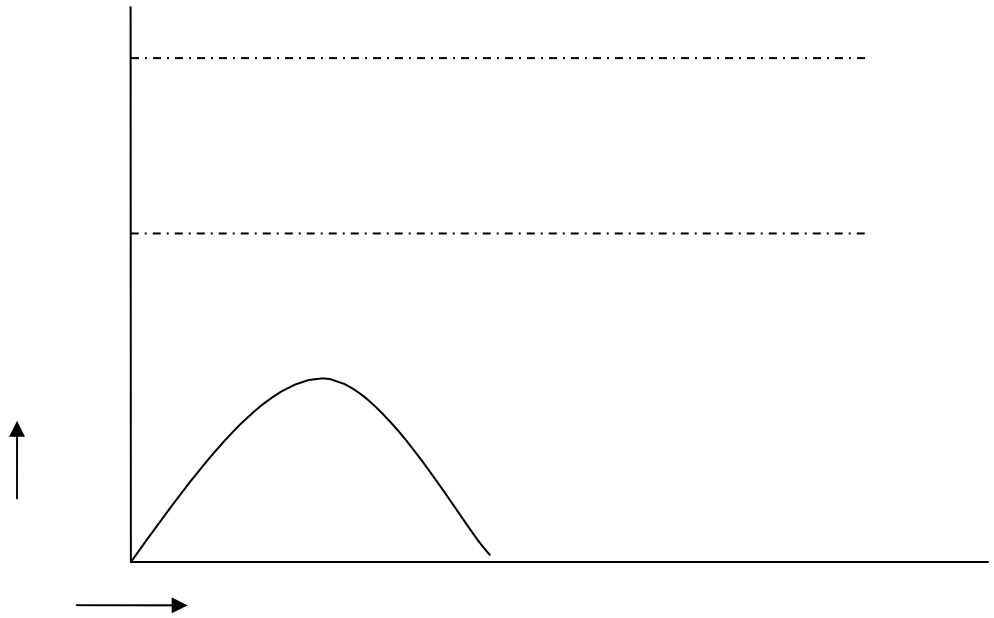


Fig. 5.13. Changes in drug concentration in the central (plasma) and the peripheral compartment after i.v. bolus of a drug that fits two-compartment model.

Let K_{12} and K_{21} be the first-order distribution rate constants depicting drug transfer between the central and the peripheral compartments and let subscript c and p define central and peripheral compartment respectively. The rate of change in drug concentration in the central compartment is given by

$$\frac{dC_c}{dt} = K_{21}\, C_p - K_{12}\, Cc - K_E\, C_C \qquad (5.89)$$

Extending the relationship $X = V_dC$ to the above equation, we have

$$\frac{dC_c}{dt} = \frac{K_{21}\, X_p}{Vp} - \frac{K_{12}\, Xc}{Vc} - \frac{K_E X_c}{Vc} \qquad (5.90)$$

Where Xc and Xp are the amounts of drug in the central and peripheral compartment respectively and Vc and Vp are the apparent volumes of the central and the peripheral compartment respectively. The rate of change in drug concentration in the peripheral compartment is given by :

$$\frac{dC_c}{dt} = K_{12}\, C_c - K_{21}\, C_p \qquad (5.91)$$

$$= \frac{K_{12}\,C_c}{V_c} - \frac{K_{21}\,C_p}{V_p} \qquad (5.92)$$

Integration of equation 5.90 and 5.91 yields equations that describe the concentration of drug in the central and peripheral compartment at given time t:

$$Cc = \frac{X_0}{Vc}\left| \frac{K_{21}-\alpha}{\beta-\alpha} e^{-\alpha t} + \frac{K_{21}-\beta}{(\alpha-\beta)} e^{-\beta t} \right| \qquad (5.93)$$

$$Cp = \frac{X_0}{Vc}\left| \frac{K_{12}}{\beta-\alpha} e^{-\alpha t} + \frac{K_{12}}{(\alpha-\beta)} e^{-\beta t} \right| \qquad (5.94)$$

Where X_o = i.v. bolus dose, α and β are hybrid first-order constants for the rapid distribution phase and the slow elimination phase respectively which depend entirely upon the first-order constants K_{12}, K_{21} and K_E.

The constants K_{12} and K_{21} that depict reversible transfer of drug between compartments are called as microconstants or transfer constants. The mathematical relationships between hybrid and microconstants are given as:

$$\alpha + \beta = K_{12} + K_{21} + K_E \qquad (5.95)$$

$$\alpha\,\beta = K_{21}\,K_E \qquad (5.96)$$

Equation 5.93 can be written in simplified form as:

$$C_C = Ae^{-\alpha t} + Be^{-\beta t} \qquad (5.97)$$

Cc = Distribution exponent + Elimination exponent

Where A and B are also hybrid constants fro the two exponents and can be resolved graphically by the method of residuals.

$$A = \frac{X_0}{Vc}\left|\frac{K_{21} - \alpha}{\beta - \alpha}\right| = C_0\left|\frac{K_{21} - \alpha}{\beta - \alpha}\right| \qquad (5.98)$$

$$B = \frac{X_0}{Vc}\left|\frac{K_{21} - \alpha}{\alpha - \beta}\right| = C_0\left|\frac{K_{21} - \alpha}{\alpha - \beta}\right| \qquad (5.99)$$

Where C_o = Plasma drug concentration 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. Rewriting the equation 5.97:

$$C = A\, e^{-\alpha t} + \beta\, e^{-\beta t} \qquad (5.97)$$

As apparent from the biexponential curve given in Fig. 5.14., the initial due to distribution is more rapid than the terminal decline due to elimination i.e. the rate constant $\alpha > > \beta$ and hence the term $e^{-\alpha t}$ approaches zero much faster than does $e^{-\beta t}$. Thus, equation 5.97 reduces to:

$$\dot{C} = B\, e^{-\beta t} \qquad (5.100)$$

In log form, the equation becomes:

$$\log \dot{C} = \log B - \frac{\beta t}{2.303} \qquad (5.101)$$

Where $\dot{C}$= back extrapolated plasma concentration values. A semilog plot of C versus t yields t yields the terminal linear phase of the curve having slope $-\beta/2.303$ and when back extrapolated to time zero, yields y-intercept log B (Fig. 5.14). The $t_{1/2}$ for the elimination phase can be obtained from equation $t_{1/2} = 0.693/\beta$.

Subtraction of extrapolated plasma concentration values of the elimination phase (equation 5.100) from the corresponding true plasma concentration values (equation 5.97) yields a series of residual concentration values C_r.

$$C_r = C - \dot{C} = A\, e^{-\alpha t} \qquad (5.102)$$

ln log form, the equation becomes:

$$\log C_r = \log A - \frac{\alpha t}{2.303} \quad (5.103)$$

A semilog plot of C_r versus t yields a straight line with slope $-\alpha/2.303$ and *Y* –intercept log A (Fig. 5.14).

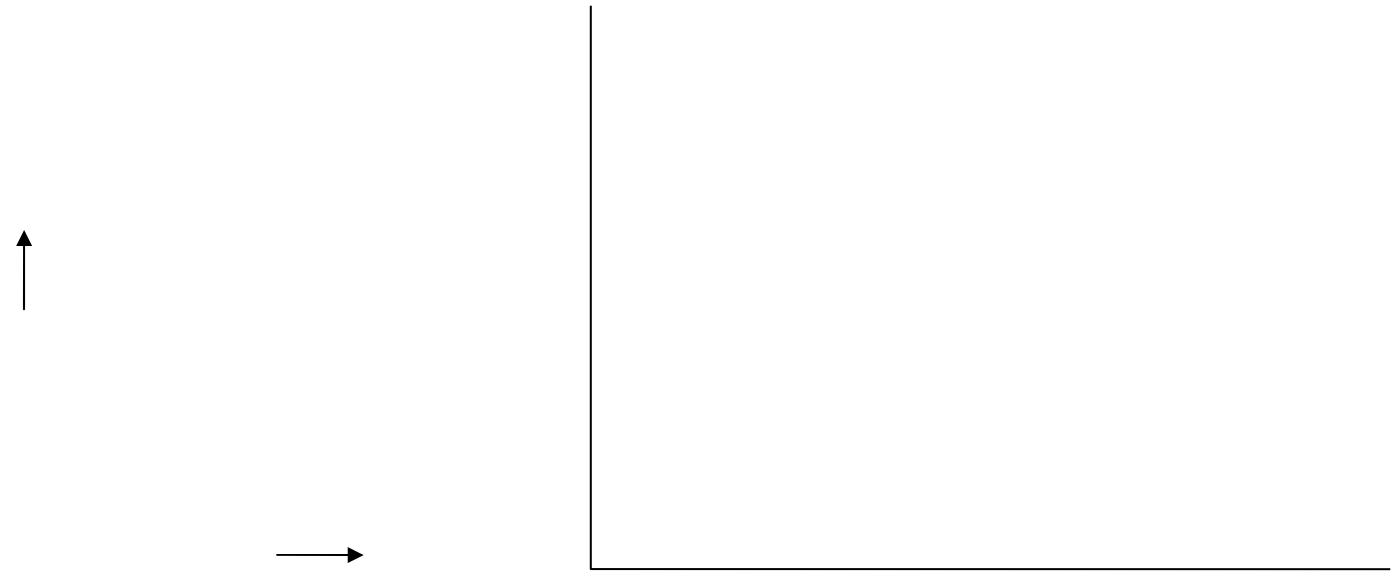


Fig. 5.14. Resolution of biexponential plasma concentration-time curve by the method of residuals for a drug that follows two-compartment kinetics on i.v. bolus administration.

Assessment of Pharmacokinetic Parameters: All the parameters of equation 5.97 can be resolved by the method of residuals as described above. Other parameters of the model viz. K_{12}, K_{21}, K_E, etc. can now be derived by proper substitution of these values.

$$C_0 = A + B \quad (5.104)$$

$$K_E = \frac{\alpha \beta C_0}{A\beta + B\alpha} \quad (5.105)$$

$$K_{12} = \frac{A B (\beta - \alpha)^2}{C_0 (A\beta + B\alpha)} \quad (5.106)$$

$$K_{21} = \frac{(A\beta + B\alpha)}{C_0} \quad (5.107)$$

It must be noted that for two-compartment model K_E is the rate constant for elimination of drug from the central compartment and β is the rate constant for elimination from the entire body. Overall elimination $t_{1/2}$ should therefore be calculated from β.

Area under the plasma concentration-time curve can be obtained by the following equation:

$$AUC = \frac{A}{\alpha} + \frac{B}{\beta} \quad (5.108)$$

The apparent volume of central compartment V_C is given as:

$$V_C = \frac{X_0}{C_0} = \frac{X_0}{K_E AUC} \quad (5.109)$$

Apparent volume of peripheral compartment can be obtained from equation:

$$Vp = V_c K_{12}/K_{21} \quad (5.110)$$

The apparent volume of distribution at steady-state or equilibrium can now be defined as:

$$V_{d,ss} = V_c + V_p \quad (5.111)$$

It is also given as:

$$V_{d,\ area} = \frac{X_0}{\beta\ AUC} \quad (5.112)$$

Total systemic clearance is given as:

$$Cl_T = \beta\ V_d \quad (5.113)$$

The pharmacokinetic parameters can also be calculated by using urinary excretion data:

$$\frac{dX_u}{dt} = K_e V_c \quad (5.114)$$

An equation identical to equation 5.97 can be derived for rate of excretion of unchanged drug in urine.

$$\frac{dX_u}{dt} = K_e A e^{-\alpha t} + K_e B e^{-\beta t} \qquad (5.115)$$

The above equation can be resolved into individual exponents by the method of residuals as described for plasma concentration-time data.

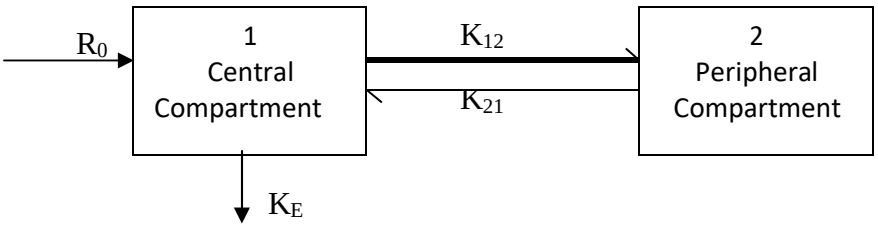
Renal clearance is given as :

$$Cl_R = K_e V_c \qquad (5.116)$$

Two-Compartment Open Model

-Intravenous Infusion

The model can be depicted as shown below with elimination from the central compartment.



The plasma or central compartment concentration of a drug that fits two-compartment model when administered as constant rate (zero-order) i.v. infusion is given by equation.

$$C = \frac{R_0}{V_c K_E}\left| 1 + \frac{K_E - \beta}{(\beta - \alpha)} e^{-\alpha t} + \frac{K_E - \alpha}{(\alpha - \beta)} e^{-\beta t} \right| \qquad (5.117)$$

At steady-state (i.e. at time infinity), the second and the third term in the bracket becomes zero and the equation reduces to:

$$C_{ss} = \frac{R_0}{V_c K_E} \qquad (5.118)$$

Now $V_c K_E = V_d \beta$ Substituting this in equation 5.118, we get:

$$C_{ss} = \frac{R_0}{V_d \beta} = \frac{R_0}{Cl_T} \qquad (5.119)$$

The loading dose $X_{o,\,L}$ to obtain C_{ss} immediately at the start of infusion can be calculated from equation:

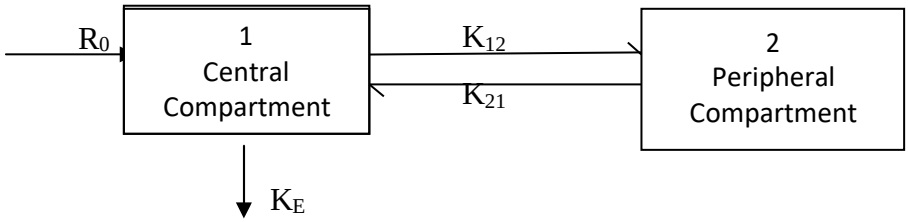
$$X_{o,\,L} = C_{ss}\ V_c = \frac{R_0}{K_E} \qquad (5.120)$$

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 concentration in the central compartment is described by 3 exponents –an absorption exponent, and the two usual exponents that describe drug disposition.

The plasma concentration at any time t is given by equation:

$$C = N\, e^{-kat} + L\, e^{-\alpha t} + M\, e^{-\beta t} \qquad (5.121)$$

C = **Absorption exponent + Distribution exponent + Elimination exponent**

Where Ka, α and β have meanings, L, M and N are coefficients.

The 3 exponents can be resolved by stepwise application of method of residuals assuming $K_a > \alpha > \beta >$ as shown in Fig. 5.15. The various pharmacokinetic parameters can then be estimated.

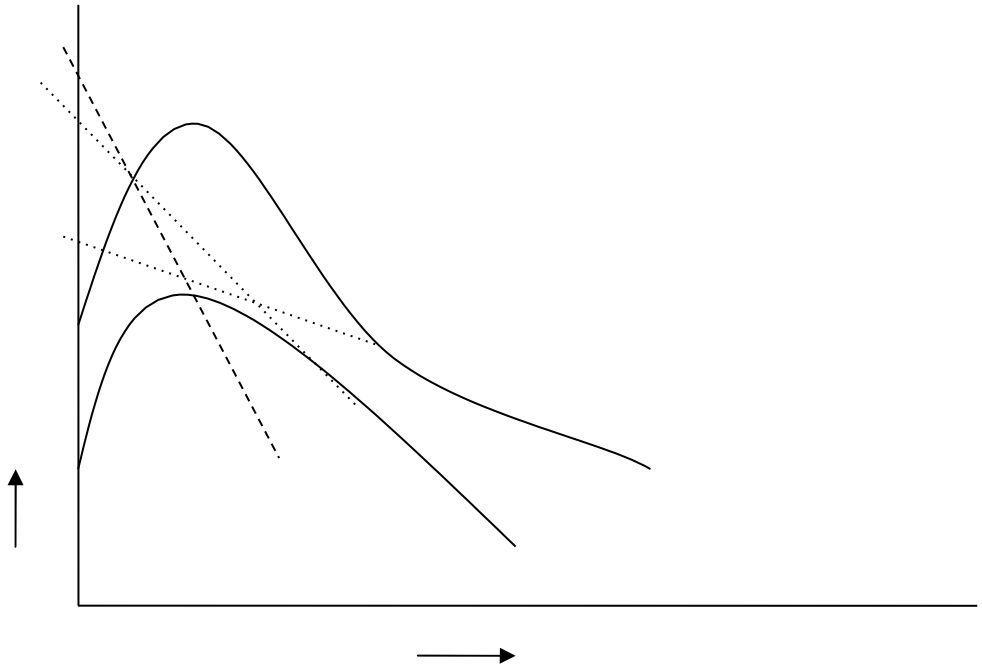


Fig. 5.15 Semilog plot of C versus of a drug with two-compartment characteristics when administered extravascularly. The various exponents have been resolved by the method of residuals.

Besides the method of residuals, K_a can also be estimated by Loo-Riegelman method for a drug that follows two-compartment characteristics. This method is in contrast to the Wagner-Nelson method for determination of K_a of a drug with one-compartment characteristic. The Loo-Riegelman method requires plasma drug concentration-time data 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.

RGPV QUESTIONS

S.No	Questions	Year	M.Marks
1.	Discuss non-compartment model in detail along with its advantages.	2016	07
2.	What is the significance of distributed parameter model?	2018	14
3.	Why are first-order processes said to follow linear kinetics?	2019	14