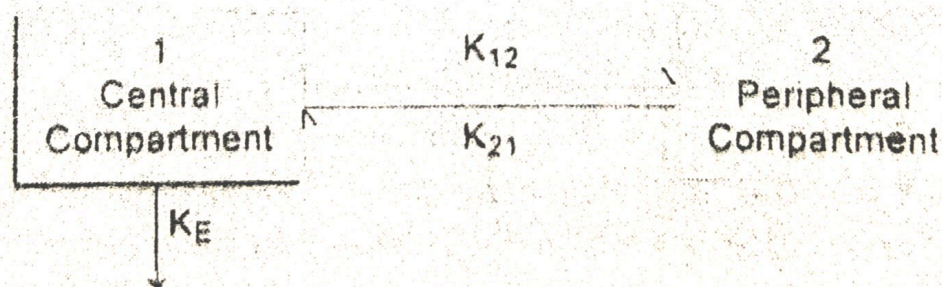


One Compartment	Two Compartments
Rapid or prompt equilibrium is attained.	Distribution equilibrium is slow (takes finite time).
There is a single disposition phase	Distribution and post-distribution are two distinct phases.
Linear: drug elimination follows first order kinetics	Linear: distribution and elimination both follow first order

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 pres-

ence 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. 10.12). 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.10.12).

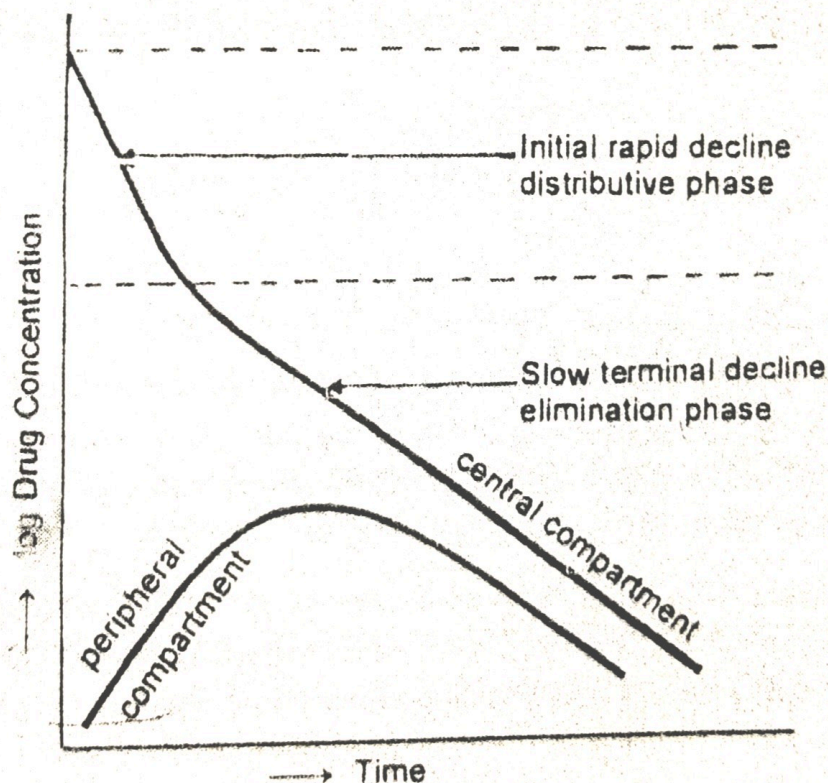


Fig. 10.12 Changes in drug concentration in the central (plasma) and the peripheral compartment after i.v. bolus of a drug that fits two-compartment model.

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:

$$\frac{dC_c}{dt} = K_{21} C_p - K_{12} C_c - K_E C_c \quad (10.84)$$

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

$$\frac{dC_c}{dt} = \frac{K_{21} X_p}{V_p} - \frac{K_{12} X_c}{V_c} - \frac{K_E X_c}{V_c} \quad (10.85)$$

where X_c and X_p are the amounts of drug in the central and peripheral compartments respectively and V_c and V_p 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:

$$\frac{dC_p}{dt} = K_{12} C_c - K_{21} C_p \quad (10.86)$$

$$= \frac{K_{12} X_c}{V_c} - \frac{K_{21} X_p}{V_p} \quad (10.87)$$

Integration of equations 10.85 and 10.87 yields equations that describe the concentration of drug in the central and peripheral compartments at any given time t :

$$C_c = \frac{X_0}{V_c} \left[\left(\frac{K_{21} - \alpha}{\beta - \alpha} \right) e^{-\alpha t} + \left(\frac{K_{21} - \beta}{\alpha - \beta} \right) e^{-\beta t} \right] \quad (10.88)$$

$$C_p = \frac{X_0}{V_p} \left[\left(\frac{K_{12}}{\beta - \alpha} \right) e^{-\alpha t} + \left(\frac{K_{12}}{\alpha - \beta} \right) e^{-\beta t} \right] \quad (10.89)$$

where X_0 = 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:

$$\alpha + \beta = K_{12} + K_{21} + K_E \quad (10.90)$$

$$\alpha \beta = K_{21} K_E \quad (10.91)$$

Equation 10.88 can be written in simplified form as:

$$C_c = A e^{-\alpha t} + B e^{-\beta t} \quad (10.92)$$

$$C_c = \frac{\text{Distribution}}{\text{exponent}} + \frac{\text{Elimination}}{\text{exponent}}$$

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

COMPARTMENT MODELING

$$A = \frac{X_0}{V_c} \left[\frac{K_{21} - \alpha}{\beta - \alpha} \right] = C_0 \left[\frac{K_{21} - \alpha}{\beta - \alpha} \right] \quad (10.93)$$

$$B = \frac{X_0}{V_c} \left[\frac{K_{21} - \beta}{\alpha - \beta} \right] = C_0 \left[\frac{K_{21} - \beta}{\alpha - \beta} \right] \quad (10.94)$$

where C_0 = plasma drug concentration immediately after i.v. injection.

Assessment of Pharmacokinetic Parameters : All the parameters of equation 10.92 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.

$$C_0 = A + B \quad (10.99)$$

$$K_E = \frac{\alpha \beta C_0}{A \beta + B \alpha} \quad (10.100)$$

$$K_{12} = \frac{A B (\beta - \alpha)^2}{C_0 (A \beta + B \alpha)} \quad (10.101)$$

$$K_{21} = \frac{A \beta + B \alpha}{C_0} \quad (10.102)$$

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:

$$AUC = \frac{A}{\alpha} + \frac{B}{\beta} \quad (10.103)$$

The apparent volume of central compartment V_c is given as:

$$V_c = \frac{X_0}{C_0} = \frac{X_0}{K_E AUC} \quad (10.104)$$

Apparent volume of peripheral compartment can be obtained from equation:

$$V_p = \frac{V_c K_{12}}{K_{21}} \quad (10.105)$$

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

$$V_{d,ss} = V_c + V_p \quad (10.106)$$

It is also given as:

$$V_{d,area} = \frac{X_0}{\beta AUC} \quad (10.107)$$

Total systemic clearance is given as:

$$Cl_T = \beta V_d \quad (10.108)$$

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

$$\frac{dX_u}{dt} = K_e V_c \quad (10.109)$$

An equation identical to equation 10.92 can be derived for rate of excretion of unchanged drug in urine:

$$\frac{dX_u}{dt} = K_e A e^{-\alpha t} + K_e B e^{-\beta t} \quad (10.110)$$

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:

$$Cl_R = K_e V_c \quad (10.111)$$

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 10.92:

$$C = A e^{-\alpha t} + B e^{-\beta t} \quad (10.92)$$

As apparent from the biexponential curve given in Fig. 10.12., the initial decline due to distribution is more rapid than the terminal decline due to elimination i.e. the rate constant $\alpha \gg \beta$ and hence the term $e^{-\alpha t}$ approaches zero much faster than does $e^{-\beta t}$. Thus, equation 10.92 reduces to:

$$\overleftarrow{C} = B e^{-\beta t} \quad (10.95)$$

In log form, the equation becomes:

$$\log \overleftarrow{C} = \log B - \frac{\beta t}{2.303} \quad (10.96)$$

where $\overleftarrow{C}$ = back extrapolated plasma concentration values. A semilog plot of $\overleftarrow{C}$ versus 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. 10.13.). 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 10.95) from the corresponding true plasma concentration values (equation 10.92) yields a series of residual concentration values C_r .

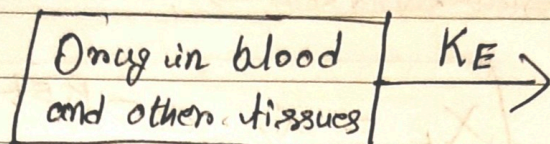
$$C_r = C - \overleftarrow{C} = A e^{-\alpha t} \quad (10.97)$$

In log form, the equation becomes.

$$\log C_r = \log A - \frac{\alpha t}{2.303} \quad (10.98)$$

A semilog plot of C_r versus t yields a straight line with slope $-\alpha/2.303$ and y-intercept $\log A$ (Fig. 10.13).

One compartment open model IV Bolus $\rightarrow$



$$\frac{dx}{dt} = \text{Rate in} - \text{Rate out Elimination.} \quad \text{--- (1)}$$

(Availability on absorption)

Where, $\frac{dx}{dt}$ = Rate of change of drug concn in the body with respect to time.

For IV absorption with respect to time Nil so eq (1) becomes.

$$\frac{dx}{dt} = - \text{Rate out} \quad \text{--- (2)}$$

$$\frac{dx}{dt} = -K_E X \quad \text{--- (3)}$$

Where, K_E = Elimination constant.

X = Amount of drug in the body at time. 't'

ie remaining amount to be eliminated.

Elimination phase 1. (elimination rate constant)

2. (Elimination half life)

3. clearance.

Elimination rate constant $\rightarrow$ Integrating the eq (3) yield.

$$\int \frac{dx}{dt} = -K_E \int X \quad \text{--- (4)}$$

$$\int_0^t \frac{dx}{X} = -K_E \int dt \quad \text{--- (5)}$$

$$\frac{X_t}{X_0} = e^{-K_E t} \quad \text{--- (6)}$$

cannabis

Amotivational Syndrome →

$$X_t = X_0 \cdot e^{-KEt} \quad \text{--- (7)}$$

By applying logarithms.

$$\log X_t = \log X_0 - \frac{KEt}{2.303} \quad \text{--- (8)}$$

difficult to determine directly the amount of drug in the body i.e. X

amount of drug in the body at time t

$$X = V_d c \quad \text{where, } V_d = \text{vol of distrib'n}$$

$c = \text{plasma drug conc'n}$

→ (9)

Substituting eq (9) in (8) will yield.

$$\log V_d c = \log V_d c_0 - \frac{KEt}{2.303} \quad \text{--- (10)}$$

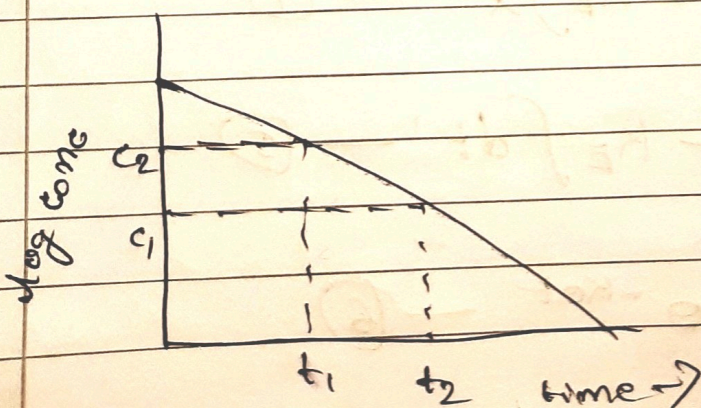
$$\log \frac{V_d c}{V_d c_0} = - \frac{KEt}{2.303}$$

$$\log c = \log c_0 - \frac{KEt}{2.303} \quad \text{--- (11)}$$

c_0 = plasma drug conc'n. immediately

after IV injection,

i.e. plasma drug conc at zero hours.



$$\text{Slope} = \frac{Y_2 - Y_1}{X_2 - X_1} \quad \text{or,}$$

$$\begin{aligned} \text{Slope} &= \frac{\log Y_2 - \log Y_1}{X_2 - X_1} \\ &= \frac{\log c_2 - \log c_1}{t_2 - t_1} \end{aligned}$$

$$K_E = \text{slope} = -K_E / 2.303$$

$$K_E = -\text{slope} \times 2.303 \quad \text{--- (12)}$$

Elimination half life (Biological half life)

$$\log c = \log c_0 - \frac{K_E t}{2.303} \quad \text{--- (11)}$$

$$\text{If } X = 1/2 X_0, \quad t = t_{0.5}$$

$$\text{So, } \log 1/2 c = \log c_0 - \frac{K_E t_{0.5}}{2.303} \quad \text{--- (13)}$$

$$\log 1/2 c - \log c_0 = \frac{-K_E t_{0.5}}{2.303} \quad \text{--- (14)}$$

c and c_0 are same at zero hours.

$$\log 1/2 c = -K_E t_{0.5} / 2.303 \quad \text{--- (15)}$$

$$\begin{aligned} \log 1/2 &= -K_E t_{0.5} / 2.303 \quad (\text{or}) \quad \text{--- (16)} \\ -K_E t_{0.5} / 2.303 &= \log 1/2 \end{aligned}$$

$$\log 1 = 0$$

$$\log 2 = 0.3010$$

$$\log 1/2 = 0 - 0.3010$$

$$\log 1/2 = -0.3010$$

$$\frac{-K_E t_{0.5}}{2.303} = -0.3010 \quad \text{--- (17)}$$

$$\text{--- (18)} \quad \leftarrow t_{0.5} = \frac{0.3010 \times 2.303}{K_E} \quad \left| \quad t_{0.5} = \frac{0.693}{K_E} \quad \text{--- (19)}$$

Half life is based on the volume of distribution and body clearance.

$$K_E = cl / V_d \rightarrow (20)$$

Substitute this value in eq $\rightarrow (19)$

$$t_{0.5} = 0.693 / \frac{cl}{V_d} \text{ or } \boxed{t_{0.5} = \frac{0.693 \times V_d}{cl}} \rightarrow (21)$$

Apparent volume of distribution.

$$\boxed{V_d = X_0 / C_0} \rightarrow (22)$$

Where, X_0 = Amount of drug in the body at zero hrs i.e initial dose.

C_0 = plasma drug conc at zero hours.

$$V_d = X_0 / C_0$$

$$V_d = \frac{IV \text{ bolus dose}}{C_0}$$

V_d is also calculated from clearance.

$$V_d = cl / K_E \rightarrow (23)$$

clearance

from

$$K_E = cl / V_d \rightarrow (20)$$

$$\boxed{cl = K_E \times V_d} \rightarrow (24)$$

In equation (23)

$$V_d = X_0 / C_0$$

Substitute ~~(23)~~ (22) in eq (24)

$$cl = K_E \frac{X_0}{C_0} \rightarrow (25)$$

$$Cl_T = Cl_R + Cl_H + Cl_b + Cl_p + Cl_u \rightarrow (26)$$

Total (Renal) (hepatic) (blood) (plasma) (urinary)

$$Cl_T = K_E \cdot \frac{X_0}{C_0} \rightarrow (25)$$

$$\frac{X_0}{C_0} = V_d \rightarrow \text{given}$$

So the equation (25) become.

$$Cl_T = K_E \cdot V_d \rightarrow (27)$$

Renal clearance

$$Cl_R = K_e \cdot V_d \rightarrow (28)$$

Hepatic clearance

$$Cl_H = K_m \cdot V_d \rightarrow (29)$$

$$t_{1/2} = 0.693 / K_E \quad \text{From (19)}$$

$$\text{So, } K_E = 0.693 / t_{1/2} \rightarrow (30)$$

Substitute the above equation in (30) into

$$Cl = K_E \cdot V_d \quad \text{From (24)}$$

$$Cl = \frac{0.693 \cdot V_d}{t_{1/2}} \rightarrow (31)$$

Biotransformation of Drugs

The onset of pharmacologic response depends upon two pharmacokinetic processes—drug absorption, and drug distribution (since most sites of action are in the extravascular tissues). The duration and intensity of action depend upon the rate of drug removal from the body/site of action or simply speaking, on the rate of elimination and tissue redistribution of drug. Elimination is the major process for removal of a drug from the body and termination of its action. It is defined as the irreversible loss of drug from the body. Elimination occurs by two processes viz. biotransformation and excretion.

✓ **Biotransformation of drugs is defined as the conversion from one chemical form to another.** The term is used synonymously with **metabolism**. The chemical changes are usually affected enzymically in the body and thus, the definition excludes chemical instability of a drug within the body; for e.g. conversion of penicillin to penicilloic acid by the bacterial penicillinase and mammalian enzymes is metabolism but its degradation by the stomach acid to penicillenic acid is chemical instability.



FACTORS AFFECTING BIOTRANSFORMATION OF DRUGS

The therapeutic efficacy, toxicity and biological half-life of a drug greatly depend upon its metabolic rate. A number of factors may influence the rate of drug metabolism; they are:

1. Physicochemical properties of the drug
2. Chemical factors:
 - a. Induction of drug metabolizing enzymes
 - b. Inhibition of drug metabolizing enzymes
 - c. Environmental chemicals
3. Biological factors:
 - a. Species differences
 - b. Strain differences
 - c. Sex differences
 - d. Age
 - e. Diet
 - f. Altered physiologic factors:
 - i. Pregnancy
 - ii. Hormonal imbalance
 - iii. Disease states
 - g. Temporal factors:
 - i. Circadian rhythm
 - ii. Circannual rhythm

✓ PHYSICOCHEMICAL PROPERTIES OF THE DRUG

Just as the absorption and distribution of a drug are influenced by its physicochemical properties, so is its interaction with the drug metabolizing enzymes. Molecular size and shape, pK_a , acidity/basicity, lipophilicity

and steric and electronic characteristics of a drug influence its interaction with the active sites of enzymes and the biotransformation processes to which it is subjected. However, such an interrelationship is not clearly understood.

✓ CHEMICAL FACTORS

Induction of Drug Metabolizing Enzymes

The phenomenon of increased drug metabolizing ability of the enzymes (especially of microsomal monooxygenase system) by several drugs and chemicals is called as enzyme induction and the agents which bring about such an effect are known as inducers. Most inducers are in general lipophilic compounds with long elimination half-lives.

✓ Two categories of inducers have been defined:

1. Phenobarbital type inducers : includes several drugs and pesticides which increase the rate of metabolism of a large number of drugs.
2. Polycyclic hydrocarbon type inducers : such as 3-methylcholanthrene and cigarette smoke which stimulate the metabolic rate of few drugs.

Some drugs such as carbamazepine, meprobamate, cyclophosphamide, rifampicin, etc. stimulate their own metabolism, the phenomenon being called as auto-induction or self-induction.

Mechanisms involved in enzyme induction may be increased enzyme synthesis, decreased rate of enzyme degradation, enzyme stabilization or enzyme activation.

TABLE 5.3
Inducers of Drug Metabolizing Enzyme System
and Drugs Commonly Affected by them

<i>Inducers</i>	<i>Drugs with Enhanced Metabolism</i>
Barbiturates	Coumarins, Phenytoin, Cortisol, Testosterone, Oral Contraceptives
Alcohol	Pentobarbital, Coumarins, Phenytoin
Phenytoin	Cortisol, Coumarins, Oral Contraceptives, Tolbutamide
Rifampicin	Coumarins, Oral Contraceptives, Tolbutamide, Rifampicin
Cigarette Smoke	Nicotine, Amino Azo Dyes

Enzyme induction results in decreased pharmacologic activity of most drugs, increased activity where the metabolites are active and altered physiologic status due to enhanced metabolism of endogenous compounds such as sex hormones. Some examples of inducers and drugs affected by them are given in Table 5.3.

Inhibition of Drug Metabolizing Enzymes

A decrease in the drug metabolizing ability of an enzyme is called as enzyme inhibition. The process of inhibition may be direct or indirect.

✓ 1. **Direct Inhibition** : may result from interaction at the enzymic site, the net outcome being a change in enzyme activity. Direct enzyme inhibition may be competitive or noncompetitive.

a. Competitive Inhibition : results when structurally similar compounds compete for the same site on an enzyme. Such an inhibition due to substrate competition is *reversible* and can be overcome by high concentration of one of the substrates, e.g. methacholine inhibits metabolism of acetyl choline by competing with it for cholinesterase.

b. Noncompetitive Inhibition : arises when a structurally unrelated agent interacts with the enzyme and prevents the metabolism of drugs. Since the interaction is not structure-specific, metals like lead, mercury and arsenic and organophosphorus insecticides inhibit the enzymes noncompetitively. Isoniazid inhibits the metabolism of phenytoin by the same mechanism.

Direct inhibition also results *when the metabolic product competes with the substrate for the same enzyme (called as product inhibition)*. Certain specific inhibitors such as xanthine oxidase inhibitors (e.g. allopurinol) and MAO inhibitors (e.g. phenelzine) also inhibit the enzyme activity directly.

✓ 2. **Indirect Inhibition** : is brought about by one of the two mechanisms:

a. Repression : is defined as the decrease in enzyme content. It may be due to a fall in the rate of enzyme synthesis as affected by ethionine, puromycin and actinomycin D or because of rise in the rate of enzyme degradation such as by carbon tetrachloride, carbon disulfide, disulfiram, etc.

b. Altered Physiology : due to nutritional deficiency or hormonal imbalance.

Direct enzyme inhibition is usually rapid (a single dose of inhibitor may be sufficient) and therefore more important than enzyme induction.

Enzyme inhibition generally results in prolonged pharmacologic action of a drug. Some examples of inhibitors and drugs affected by them are given in Table 5.4.

TABLE 5.4
Enzyme Inhibitors and Drugs Affected by them

<i>Inhibitors</i>	<i>Drugs with Decreased Metabolism</i>
MAO Inhibitors	Barbiturates, Tyramine
Coumarins	Phenytoin
Allopurinol	6-Mercaptopurine
PAS	Phenytoin, Hexobarbital

Environmental Chemicals

Several environmental agents influence the drug metabolizing ability of enzymes. Halogenated pesticides such as DDT and polycyclic aromatic hydrocarbons contained in cigarette smoke have enzyme induction effect. Organophosphate insecticides and heavy metals such as mercury, tin, nickel, cobalt and arsenic inhibit drug metabolizing ability of enzymes.

Other environmental factors that may influence drug metabolism are temperature, altitude, pressure, atmosphere, etc.

BIOLOGICAL FACTORS

Species Differences

Screening of new therapeutic molecules to ascertain their activity and toxicity requires study in several laboratory animal species. Differences in drug response due to species differences are taken into account while extrapolating the data to man.

Species differences have been observed in both phase I and phase II reactions. In phase I reactions, both qualitative and quantitative variations in the enzyme and their activity have been observed. An example of this is the metabolism of amphetamine and ephedrine. In men and rabbit, these drugs are predominantly metabolized by oxidative deamination whereas in rats the aromatic oxidation is the major route. In phase II reactions, the variations are mainly qualitative and characterized either by the presence of, or complete lack of certain conjugating enzymes; for example, in pigs, the phenol is excreted mainly as glucuronide whereas its sulfate conjugate dominates in cats. Certain birds utilize ornithine for conjugating aromatic acids instead of glycine.

✓ Strain Differences/Pharmacogenetics

Enzymes influencing metabolic reactions are under the genetic control. Just as the differences in drug metabolizing ability between different species are attributed to genetics, so also are the differences observed between strains of the same animal species. A study of intersubject variability in drug response (due to differences in, for example, rate of biotransformation) is called as pharmacogenetics. The intersubject variations in drug biotransformation may either be monogenically or polygenically controlled. A polygenic control has been observed in studies in twins. In identical twins (monozygotic), very little or no difference in the metabolism of phenylbutazone, dicoumarol and antipyrine was detected but large variations were apparent in fraternal twins (dizygotic; twins developed from two different eggs) for the same drugs.

Differences observed in the metabolism of a drug among different races are called as ethnic variations. Such a variation may be monomorphic or polymorphic. When a unimodal frequency distribution is observed in the entire population, the variations are called as continuous or monomorphic; for example, the entire human race acetylate PABA and PAS to only a small extent. A polymodal distribution is indicative of discontinuous variation (polymorphism). An example of polymorphism is the acetylation of isoniazid (INH) in humans. A bimodal population distribution was observed comprising of slow acetylators or inactivator phenotypes (metabolize INH slowly) and rapid acetylators or inactivator phenotypes (metabolize INH rapidly) (see Table 5.5.).

TABLE 5.5
Ethnic Variations in the N-Acetylation of Isoniazid

<i>Ethnic Group</i>	<i>% Slow Acetylators</i>	<i>% Rapid Acetylators</i>
Whites (USA and Canada)	45	55
Blacks (USA)	48	52
Latin Americans	67	33
American Indians	79	21
Japanese	87	13
Eskimos	95	05

Source : Kalow, W. *Pharmacogenetics: Heredity and the Response to Drugs*. Saunders, Philadelphia, 1962

Approximately equal percent of slow and rapid acetylators are found among whites and blacks whereas the slow acetylators dominate Japanese and Eskimo populations. Dose adjustments are therefore necessary in the

latter groups since high levels of INH may cause peripheral neuritis. Other drugs known to exhibit pharmacogenetic differences in metabolism are debrisoquine, succinyl choline, phenytoin, dapsone and sulfadimidine.

✓ Sex Differences

Sex related differences in the rate of metabolism can be attributed to regulation of such processes by sex hormones since variations among male and female are generally observed following puberty. Such sex differences are widely studied in rats; the male rats have greater drug metabolizing capacity. In humans, women metabolize benzodiazepines slowly than men and several studies show that women on contraceptive pills metabolize a number of drugs at a slow rate.

✓ Age

Differences in the drug metabolic rate in different age groups is mainly due to variations in the enzyme content, enzyme activity and hemodynamics. In neonates (upto 2 months), the microsomal enzyme system is not fully developed and many drugs are biotransformed slowly; for example, caffeine has a half-life of 4 days in neonates in comparison to 4 hours in adults. A major portion of this drug is excreted unchanged in urine by the neonates. Conjugation with sulfate is well developed (paracetamol is excreted mainly as sulfate) but glucuronidation occurs to a very small extent. As a result, hyperbilirubinemia precipitates kernicterus and chloramphenicol leads to cyanosis or Gray baby syndrome in new born. Similarly, sulfonamides cause renal toxicity and paracetamol causes hepatotoxicity. Infants (between 2 months and one year) show almost a similar profile as neonates in metabolizing drugs with improvement in the capacity as age advances and enzyme activity increases. Children (between one year and 12 years) and older infants metabolize several drugs much more rapidly than adults as the rate of metabolism reaches a maximum somewhere between 6 months and 12 years of age. As a result, they require large mg/Kg doses in comparison to adults; for example, the theophylline half-life in children is two-third of that in adults. In very elderly persons, the liver size is reduced, the microsomal enzyme activity is decreased and hepatic blood flow also declines as a result of reduced cardiac output all of which contribute to decreased metabolism of drugs. Drug conjugation however remains unaffected.

Diet

The enzyme content and activity is altered by a number of dietary components. In general, low protein diet decreases and high protein diet increases the drug metabolizing ability. This is because the enzyme

synthesis is promoted by protein diet which also raises the level of amino acids for conjugation with drugs. The protein-carbohydrate ratio in the diet is also important; a high ratio increases the microsomal mixed function oxidase activity. Fat free diet depresses cytochrome P-450 levels since phospholipids, which are important components of microsomes, become deficient. Dietary deficiency of vitamins (e.g. vitamin A, B₂, B₃, C and E) and minerals such as Fe, Ca, Mg, Cu and Zn retard the metabolic activity of enzymes. Starvation results in decreased amount of glucuronides formed than under normal conditions. Malnutrition in women results in enhanced metabolism of sex hormones. Alcohol ingestion results in a short term decrease followed by an increase in the enzyme activity.

Altered Physiologic Factors

Pregnancy : Studies in animals have shown that the maternal drug metabolizing ability (of both phase I and phase II reactions) is reduced during the later stages of pregnancy. This was suggested as due to high levels of steroid hormones in circulation during pregnancy. In women, the metabolism of promazine and pethidine is reduced during pregnancy or when receiving oral contraceptives. Higher rate of hepatic metabolism of anticonvulsants during pregnancy is thought to be due to induction of drug metabolizing enzymes by the circulating progesterone.

Hormonal Imbalance : The influence of sex hormones on drug metabolism has already been discussed. The effect of other hormones is equally complex. Higher levels of one hormone may inhibit the activity of few enzymes while inducing that of others. Adrenalectomy, thyroidectomy and alloxan induced diabetes in animals showed an impairment in the enzyme activity with a subsequent fall in the rate of metabolism. A similar effect was observed with pituitary growth hormone. Stress related changes in ACTH levels also influence drug biotransformation.

Disease States : (As liver is the primary site for metabolism of most drugs, all pathologic conditions associated with it result in enhanced half-lives of almost all drugs.) Thus, a reduction in hepatic drug metabolizing ability is apparent in conditions such as hepatic carcinoma, hepatitis, cirrhosis, obstructive jaundice, etc. (Biotransformations such as glycine conjugation of salicylates, oxidation of vitamin D and hydrolysis of procaine which occur in kidney, are impaired in renal diseases.) Congestive cardiac failure and myocardial infarction which result in a decrease in the blood flow to the liver, impair metabolism of drugs having high hepatic extraction ratio e.g. propranolol and lidocaine. In diabetes, glucuronidation is reduced due to decreased availability of UDPGA.

Temporal Factors

Circadian Rhythm : Diurnal variations or variations in the enzyme activity with light cycle is called as circadian rhythm in drug metabolism. It has been observed that the enzyme activity is maximum during early morning (6 to 9 a.m.) and minimum in late afternoon (2 to 5 p.m.) which was suggested to correspond with the high and low serum levels of corticosterone (the serum corticosterone level is dependent upon the light-dark sequence of the day). Clinical variation in therapeutic effect of a drug at different times of the day is therefore apparent. The study of variations in drug response as influenced by time is called as chronopharmacology. Time dependent change in drug kinetics is known as chronokinetics. Drugs such as aminopyrine, hexobarbital and imipramine showed diurnal variations in rats. The half-life of metyrapone was shown to be 2.5 times longer during the night than in the day, in rats.

BIOACTIVATION AND TISSUE TOXICITY

Formation of highly reactive metabolites (from relatively inert chemical compounds) which interact with the tissues to precipitate one or more of the several forms of toxicities such as carcinogenesis and teratogenesis is called as bioactivation or toxicological activation. The reactive, chemically unstable species, capable of toxication, are broadly divided into two categories—electrophiles and free radicals (Fig. 5.3.).

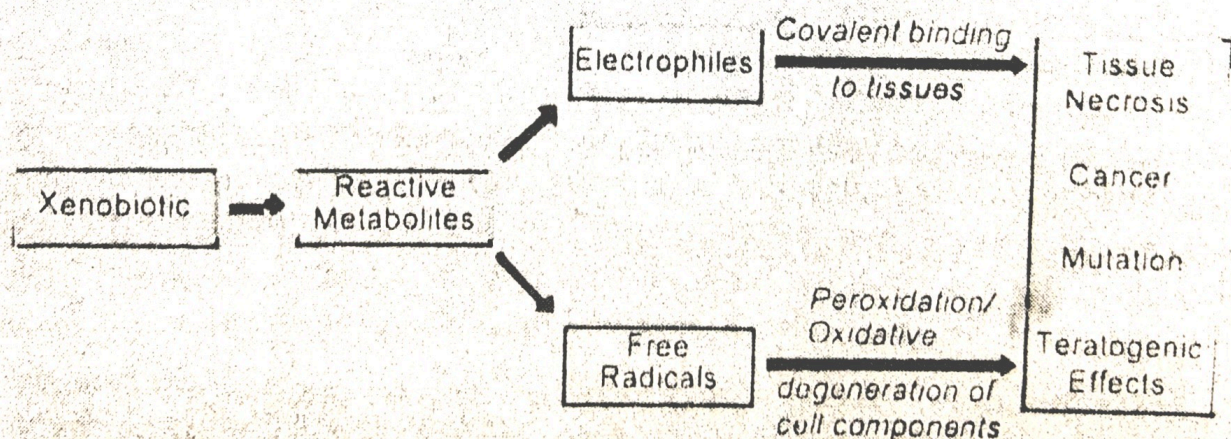


Fig. 5.3 Mechanisms of tissue toxicity by bioactivation of drugs

Electrophiles are species deficient in electron pair. The enzyme system through which they are generated is cytochrome P-450. Carbon, nitrogen or sulfur-containing compounds can be metabolically activated to yield electrophiles. Important electrophiles are epoxides (e.g. epoxide of benzo(a)pyrene present in cigarette smoke which causes cancer), hydroxylamines, nitroso and azoxy derivatives, nitrenium ions and elemental sulfur. The mechanism by which electrophiles precipitate toxicity is through

CONCEPT OF CLEARANCE

The clearance concept was first introduced to describe renal excretion of endogenous compounds in order to measure the kidney function. The term is now applied to all organs involved in drug elimination such as liver, lungs, the biliary system, etc. and referred to as hepatic clearance, pulmonary clearance, biliary clearance and so on. *The sum of individual clearances by all eliminating organs is called as total body clearance or total systemic clearance.* It is sometimes expressed as a sum of renal clearance and nonrenal clearance.

Clearance is defined as the hypothetical volume of body fluids containing drug from which the drug is removed or cleared completely in a specific period of time. It is expressed in ml/min and is a constant for any given plasma drug concentration. In comparison to apparent volume of distribution which relates plasma drug concentration to the amount of drug in the body, clearance relates plasma concentration to the rate of drug elimination.

$$* \text{ Clearance (Cl)} = \frac{\text{Elimination rate}}{\text{Plasma drug concentration}} \quad (7.9)$$

Renal Clearance (Cl_R) : It can be defined as the volume of blood or plasma which is completely cleared of the unchanged drug by the kidney per unit time. It is expressed mathematically as:

$$* Cl_R = \frac{\text{Rate of urinary excretion}}{\text{Plasma drug concentration}} \quad (7.10)$$

Physiologically speaking, **renal clearance** is the ratio of "sum of rate of glomerular filtration and active secretion minus rate of reabsorption" to "plasma drug concentration C ".

$$* Cl_R = \frac{\text{Rate of filtration} + \text{Rate of secretion} - \text{Rate of reabsorption}}{C} \quad (7.11)$$

TABLE 7.2
Relationship between Renal Clearance Values
and Mechanism of Clearance

Renal Clearance (ml/min)	Renal Clearance Ratio	Mechanism of Renal Clearance	Example(s)
0 (least value)	0	Drug filtered and reabsorbed completely	Glucose
< 130	Above 0, Below 1	Drug filtered and reabsorbed partially	Lipophilic drugs
130 (GFR)	1	Drug is filtered only	Creatinine, Inulin
> 130	> 1	Drug filtered as well as secreted actively	Polar, ionic drugs
650 (Highest value)	5	Clearance equal to renal plasma flow rate	Iodopyracet, PAH

The contribution of each of the above physiologic processes in clearing a drug cannot be determined by direct measurement. It can however be determined by comparing the clearance values obtained for a drug with that of an agent such as creatinine or inulin which is cleared by glomerular filtration only. The ratio of these two values is called as renal clearance ratio or excretion ratio.

$$\text{* Renal Clearance Ratio} = \frac{\text{Cl}_R \text{ of drug}}{\text{Cl}_R \text{ of creatinine}} \quad (7.12)$$

Thus, depending upon whether the drug is only filtered, filtered and secreted or filtered and reabsorbed, the clearance ratio will vary (Table 7.2). The renal clearance values range from zero to 650 ml/min and the clearance ratio from zero to five.

[5, 10 marks]

FACTORS AFFECTING RENAL EXCRETION OR RENAL CLEARANCE

Apart from the three physiologic processes that govern the urinary excretion, other factors influencing renal clearance of drugs and metabolites are:

1. Physicochemical properties of the drug
2. Plasma concentration of the drug
3. Distribution and binding characteristics of the drug
4. Urine pH
5. Blood flow to the kidneys
6. Biological factors
7. Drug interactions
8. Disease states

* Physicochemical Properties of the Drug

Important physicochemical factors affecting renal excretion of a drug are - molecular size, pK_a and lipid solubility. The molecular weight of a drug is very critical in its urinary elimination. An agent of small molecular size can be easily filtered through the glomerulus. Compounds of weights below 300 daltons, if water soluble, are readily excreted by the kidneys. Drugs in the molecular weight range 300 to 500 daltons can be excreted both in urine and bile. Molecules of size greater than 500 daltons are excreted in urine to a lesser extent.

The influence of drug pK_a on excretion has already been discussed. Urinary excretion of an unchanged drug is inversely related to its lipophilicity. This is because, a lipophilic drug is passively reabsorbed to a large extent.

Plasma Drug Concentration-Time Profile

A direct relationship exists between the concentration of drug at the biophase (site of action) and the concentration of drug in plasma. A typical plasma drug concentration-time curve obtained after a single oral dose of a drug and showing various pharmacokinetic and pharmacodynamic parameters is depicted in Fig. 9.1. Such a profile can be obtained by measuring the concentration of drug in plasma samples taken at various intervals of time after administration of a dosage form and plotting the concentration of drug in plasma (Y-axis) versus the corresponding time at which the plasma sample was collected (X-axis).

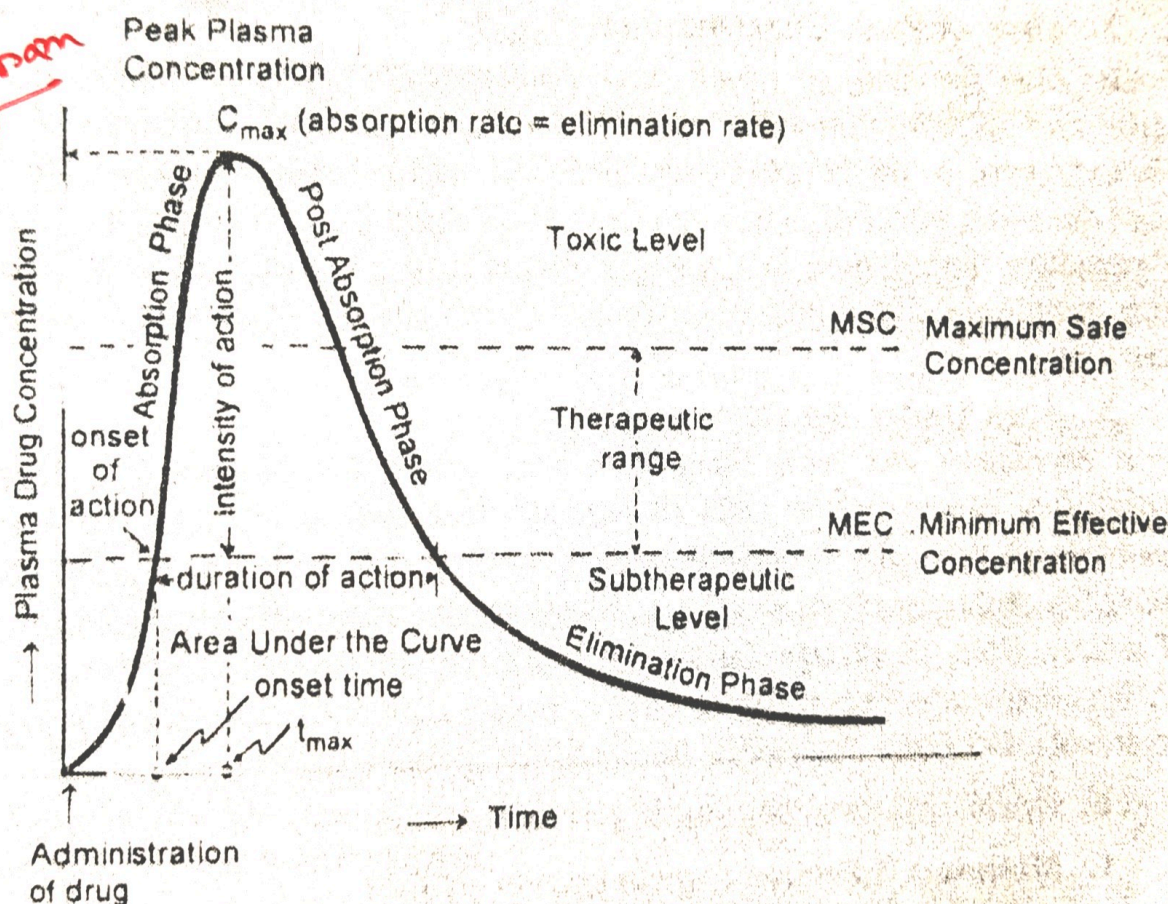


Fig. 9.1 A typical plasma concentration-time profile showing pharmacokinetic and pharmacodynamic parameters obtained after oral administration of single dose of a drug.

The three important pharmacokinetic parameters that describe the plasma level-time curve and useful in assessing the bioavailability of a drug from its formulation are:

1. Peak Plasma Concentration (C_{max})

The point of maximum concentration of drug in plasma is called as the peak and the concentration of drug at peak is known as peak plasma concentration. It is also called as peak height concentration and maximum drug concentration. C_{max} is expressed in mcg/mL. The peak

level depends upon the administered dose and rate of absorption and elimination. The peak represents the point of time when absorption rate equals elimination rate of drug. The portion of curve to the left of peak represents absorption phase i.e. when the rate of absorption is greater than the rate of elimination. The section of curve to the right of peak generally represents elimination phase i.e. when the rate of elimination exceeds rate of absorption. Peak concentration is often related to the intensity of pharmacologic response and should ideally be above minimum effective concentration (MEC) but less than the maximum safe concentration (MSC).

2. Time of Peak Concentration (t_{max})

The time for drug to reach peak concentration in plasma (after extravascular administration) is called as the **time of peak concentration**. It is expressed in hours and is useful in estimating the rate of absorption. Onset time and onset of action are dependent upon t_{max} . The parameter is of particular importance in assessing the efficacy of drugs used to treat acute conditions like pain and insomnia which can be treated by a single dose.

3. Area Under the Curve (AUC)

It represents the total integrated area under the plasma level-time profile and expresses the total amount of drug that comes into the systemic circulation after its administration. AUC is expressed in mcg/mL X hours. It is the most important parameter in evaluating the bioavailability of a drug from its dosage form as it represents the extent of absorption. AUC is also important for drugs that are administered repetitively for the treatment of chronic conditions like asthma or epilepsy.

The various pharmacodynamic parameters are:

1. Minimum Effective Concentration (MEC)

It is defined as the minimum concentration of drug in plasma required to produce the therapeutic effect. It reflects the minimum concentration of drug at the receptor site to elicit the desired pharmacologic response. The concentration of drug below MEC is said to be in the **subtherapeutic level**.

In case of antibiotics, the term **minimum inhibitory concentration (MIC)** is used. It describes the minimum concentration of antibiotic in plasma required to kill or inhibit the growth of microorganisms.

2. Maximum Safe Concentration (MSC)

Also called as **minimum toxic concentration (MTC)**, it is the concentration of drug in plasma above which adverse or unwanted effects are

precipitated. Concentration of drug above MSC is said to be in the toxic level.

3. Onset of Action

The beginning of pharmacologic response is called as onset of action. It occurs when the plasma drug concentration just exceeds the required MEC.

4. Onset Time

It is the time required for the drug to start producing pharmacologic response. It corresponds to the time for the plasma concentration to reach MEC after administration of drug.

5. Duration of Action

The time period for which the plasma concentration of drug remains above the MEC level is called as duration of drug action.

6. Intensity of Action

It is the maximum pharmacologic response produced by the peak plasma concentration of drug. It is also called as peak response.

7. Therapeutic Range

The drug concentration between MEC and MSC represents the therapeutic range.

PHARMACOKINETIC MODELS

Drug movement within the body is a complex process. The major objective is therefore to develop a generalized and simple approach to describe, analyze and interpret the data obtained during *in vivo* drug disposition studies. This involves development of pharmacokinetic models which provide concise means of expressing mathematically or quantitatively, the time course of drug(s) throughout the body and compute meaningful pharmacokinetic parameters.

Pharmacokinetic models are useful in—

1. Characterizing the behavior of drugs in patients
2. Predicting the concentration of drug in various body fluids with any dosage regimen
3. Predicting the multiple-dose concentration curves from single dose experiments
4. Calculating the optimum dosage regimen for individual patients
5. Evaluating the risk of toxicity with certain dosage regimens
6. Correlating plasma drug concentration with pharmacologic response
7. Evaluating the bioequivalence/bioinequivalence between different formulations of the same drug
8. Estimating the possible drug and/or metabolite(s) accumulation in the body
9. Determining the influence of altered physiology/disease state on drug ADME
10. Explaining drug interactions

Caution must however be exercised in ensuring that the model fits the experimental data; otherwise, a new, more complex and suitable model may be proposed and tested.