1

Introduction

Pharmacokinetics and pharmacodynamics are the important fields of pharmaceutical sciences for investigating disposition profiles and the pharmacological efficacy of drugs in the body under various experimental and clinical conditions (Caldwell *et al.,* 1995 and Cocchetto and Wargin, 1980).

Pharmacokinetics (PK) is the study of the way drug molecules behave in the body after administration. Four distinctive yet somewhat interrelated processes occur between the administration and the elimination of a drug from the body: after oral administration, drug molecules are absorbed into the portal vein via the enterocytes from the gastrointestinal lumen, pass through the liver and the lungs, reach the systemic circulation, and then further distribute into various tissues and organs via blood vessels, some of which may have metabolic or excretory activity for eliminating the drug. These sequential events are called the ADME processes of the drug after administration, i.e., absorption, distribution, metabolism, and excretion, as illustrated in Fig. 1.1.

The purpose of pharmacokinetics is to study ADME processes of drugs in the body by examining the time course of drug concentration profiles in readily accessible body fluids such as blood, plasma, urine, and/or bile. Basically, all of a drug's pharmacokinetic parameters, such as clearance, volume of distribution, mean residence time, and half-life, can be estimated from its concentration-vs.-time profiles in plasma (or blood). It is important to realize that pharmacokinetic interpretations of drug exposure profiles are simply descriptions of the phenomenology of the ADME processes, and, thus, there might possibly be many different interpretations of the pharmacokinetic properties of a drug based on the same plasma drug concentration profiles.

Pharmacodynamics (PD) is the study of the relationships between the concentration of a drug at the effect site(s), where target enzymes or receptors are located, and the magnitude of its pharmacological efficacy. Let us consider an anticoagulant drug as an example. As the drug's effect site is the systemic circulation, its pharmacodynamics elucidates the relationship between its concentration in blood (the effect site) and the extent of its anticoagulant effect (pharmacological effect).

When the effect site is not in plasma and the drug concentration in the plasma (or blood) is different from that in the effect site, the kinetic relationship between pharmacokinetics and pharmacodynamics becomes an important component in

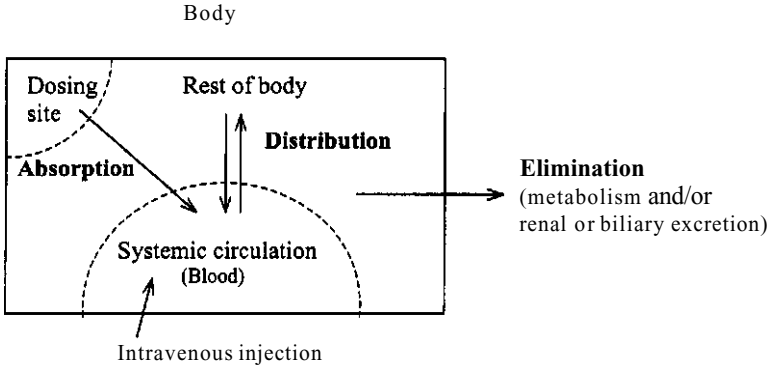


Figure 1.1. A schematic description of the pharmacokinetic behavior of a drug. Distribution and elimination processes are often referred as to disposition processes.

correlating the drug's concentration in plasma and the pharmacological endpoints observed. The kinetic relationship between drug concentrations in plasma and in the effect site can be arrived at by exploring various pharmacokinetic/pharmacodynamic (PK/PD) models (Fig. 1.2). For reasonable PK and PD studies, one must have a

Figure 1.2. A schematic description of the pharmacokinetics (PK), the pharmacodynamics (PD), and the pharmacokinetic/pharmacodynamic (PK/PD) relationships of a drug. $C_p(t)$ and $C_e(t)$ are the concentrations of the drug in the plasma (sampling site) and the effect site, respectively.

thorough understanding of the conditions and assumptions under which the experiments are carried out as well as of PK and PD models employed, as the validity of virtually all the PK and PD data interpretations depends on the scientific soundness and physiological relevance of those assumptions and conditions.

REFERENCES

Caldwell J. *et al.,* An introduction to drug disposition: the basic principles of absorption, distribution, metabolism and excretion, *Toxicol. Pathol.* **23**: 102–114, 1995.

Cocchetto D. M. and Wargin W. A., A bibliography for selected pharmacokinetic topics, *Drug Intel. Clin. Pharmacol.* **14**: 769–776, 1980.

2

Pharmacokinetic Study Design and Data Interpretation

Pharmacokinetic data interpretation can be viewed primarily as an effort to deduce what has happened to a drug in the body after administration based on the time course of its exposure in biological fluids such as plasma or blood. Reliability of data obtained from *in vivo* pharmacokinetic studies depends on the validity of study design and execution and on sample collection, handling, and assay. Selection of proper data analysis methods is equally important in understanding pharmacokinetic characteristics of a drug. In this chapter, useful information and guidelines for intravenous and oral administration studies in animals as well as data interpretation are discussed.

2.1. INTRAVENOUS ADMINISTRATION OF DRUGS

2.1.1. Utility of Intravenous Administration Studies

The plasma exposure profiles of a drug after intravenous dosing provide critical information on its pharmacokinetic properties including:

(i) Systemic clearance and volume of distribution at steady state. And estimate of the systemic clearance of a drug can be obtained from plasma (or blood) concentration–time profiles after *intravenous* injection. It can also be estimated after dosing the drug by a route other than intravenous injection, as long as its bioavailability is complete. However, an estimate of the volume of distribution of the drug at steady state cannot be obtained from exposure data after administration by any route other than intravenous injection.

(ii) Terminal half-life of a drug. The terminal half-life of a drug following intravenous injection is governed by disposition (distribution and elimination) processes of the drug in the body. The terminal half-life estimated after administration by the route other than intravenous injection can be affected not only by disposition but also by absorption (or input) processes from the site of administration.

(iii) Reference exposure levels for estimates of bioavailability. The area under the plasma concentration *vs.* time curve (AUC) after intravenous injection is commonly used as a reference for estimating the bioavailability of a drug by a route other than intravenous injection.

2.1.2. General Considerations for Intravenous Administration Studies

Important considerations and suggestions for intravenous dosing studies are summarized below.

(i) Bolus injection vs. short infusion. In general, intravenous (or intraarterial) injection of a drug is assumed to be bolus administration completed within a few seconds, unless otherwise indicated. If injection takes more than 1 min, it should be considered a short infusion.

(ii) Dosing solution. In general, isotonic sterile water at pH 6.8 is the most desirable dosing vehicle for intravenous injection. Although an aqueous vehicle is generally preferred, because of the limited water solubility of some compounds or their chemical instability in water the use of various organic cosolvents is not uncommon. Nonaqueous vehicles such as, e.g., dimethyl sulfoxide (DMSO), ethanol, polyethylene glycol (PEG) 400, and vegetable oil or solubilizing agents such as β-cyclodextrin are often used with sterile water to enhance compound solubility in a dosing vehicle, especially during drug discovery. In this case, the effects of organic vehicles or solubilizing agents on pharmacokinetic profiles of a compound (such as inhibition of metabolism and hemolysis of blood) and on its pharmacological and toxicological responses should be considered. In general, the amount of organic cosolvent should not exceed 20% of the total injection volume. The pH of a dosing vehicle can be slightly acidic or basic to optimize aqueous solubility. However, caution should be taken to adjust pH to enhance aqueous solubility of a compound, because the alteration of pH may result in chemical instability. The viscosity of a dosing vehicle should be maintained such that it allows ease of injection (syringe-ability) and optimal fluidity.

(iii) Dosing volume. In case of bolus injection, it is important to have a suitable dosing volume. If the dosing volume is too large, it may take more time to inject, and if it is too small, there can be difficulties in preparation and administration of the dosing solution. The maximum volume for single bolus injection is approximately 1 ml/kg body weight for laboratory animals such as rabbits, monkeys, and dogs. In small animals such as mice and rats, larger volumes of up to 0.3 and 0.5 ml, respectively, per animal can be used. In small laboratory animals, continuous 24-hr intravenous infusion should not exceed 4 ml/kg body weight/hr (see Chapter 13).

2.1.3. Sample Collection after Intravenous Administration

(ii) Blood-Sampling time points (Fig. 2.1).

- The entire concentration-us.-time curve. Seven (at least five) time points are recommended.

- The early distribution phase. At least two time points within a short period of time after injection, typically less than 15 min after administration, are recommended for reliable estimation of imaginary plasma concentration at time zero [$C_p(0)$].

- The terminal phase. At least three time points during the terminal phase have to be obtained for reliable estimation of the terminal half-life of a drug. As a rule of thumb, three or four time points during the terminal phase are selected such that the interval between the first and the last is more than twice the estimated terminal half-life based on them.

(*ii*) *Blood— Volume*. In general, no more than 10% of the total blood volume in the body can be drawn as an acceptable weekly maximum in small laboratory animals; 20% is the maximum that can be taken acutely without serious hemorrhagic shock and tissue anoxia. In the latter case 3–4 weeks should be allowed for recovery and/or a proper quantity of blood should be infused.

NOTE: IMAGINARY PLASMA CONCENTRATION AT TIME ZERO AFTER INTRAVENOUS INJECTION [$C_p(0)$]. The $C_p(0)$ of a drug can be estimated by connecting the first two data points after intravenous injection and extrapolating back to the y-axis on a semilog scale (Fig. 2.1). There is, of course, no drug in the plasma at the sampling site at time zero because at the moment of injection, the drug has not yet been delivered to the sampling site. However, an estimate of $C_p(0)$ is a useful value for calculating the area under the concentration–time curve from time zero to the first sampling time point and the apparent volume of distribution of the drug in the central compartment (V_c; see Multicompartment model). V_c, an imaginary space in the body where drug molecules in plasma reach rapid equilibrium upon injection,

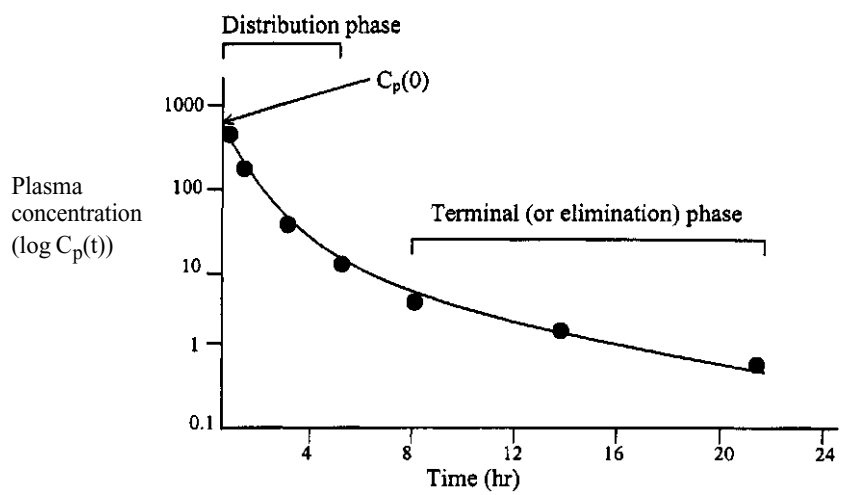


Figure 2.1. Example of a plasma drug concentration-*vs.*-time profile after intravenous injection of a drug. In general, the first two time points shortly after injection are used to estimate $C_p(0)$, and at least three time points during the terminal phase are needed to calculate of the terminal half-life of a drug.

can be estimated by dividing an intravenous dose by $C_p(0)$. In small laboratory animals it may take only a few seconds before the distributional equilibrium of the drug between the plasma and the central compartment is achieved.

(ii) Urine. Collection of urine from laboratory animals over an extended period of time (usually up to 24 hr in small animals) can also provide useful pharmacokinetic information, such as renal clearance and metabolic profiles of a drug. In general, it is easier to identify metabolites in urine than in blood owing to their higher concentrations in the former.

Renal clearance (Cl_r) can be calculated by dividing the amount of the parent drug excreted in the urine by AUC, regardless of the route of administration. The difference between the systemic clearance (Cl_s; see Chapter 6) and Cl_r is nonrenal clearance (Cl_{nr}):

$$Cl_{nr} = Cl_s - Cl_r \tag{2.1}$$

where Cl_{nr} represents clearances of a drug in the body other than by the kidney, such as elimination by, e.g., the liver, lung, intestine, blood, or brain. In general, Cl_{nr} is assumed to be similar or equal to hepatic clearance because the liver is the major eliminating organ for most drugs.

2.2. ORAL ADMINISTRATION OF DRUGS

2.2.1. Utility of Oral Administration Studies

Oral administration is the most popular and acceptable route for drug administration. Important pharmacokinetic parameters estimated from plasma exposure profiles after oral administration of drug are given below.

(i) C_{max} *and* t_{max}. C_{max} is the highest drug concentration observed after oral administration, and t_{max} is the time at which C_{max} is observed.

(ii) Terminal half-life. The terminal half-life of a drug after oral administration can be affected by both its absorption and disposition rates, and it is usually similar to or longer than that following intravenous injection.

(iii) Bioavailability. Bioavailability of a drug after oral administration is determined by dose-normalized AUC from time zero to infinity ($AUC_{0-\infty}$) after oral administration compared to that after administration of the drug via a reference route, usually intravenous injection.

2.2.2. General Considerations for Oral Administration Studies

(i) Dosing volume. Drug solution or suspension can be administered by oral gavage. In small laboratory animals such as rats, up to 10 ml/kg body weight can be dosed in a fasted condition. Approximately 5 ml/kg is considered acceptable for

oral administration in small animals under a fed condition. A solution formulation of a compound is most desirable for oral administration, but suspension can also be given when necessary (see Chapter 13).

(ii) Food intake. Concomitant food intake can alter the rate and extent of absorption of orally dosed drugs. In addition, when the drug is subject to enterohepatic circulation, its exposure profiles in animals with restricted food intake can be significantly different from those in animals with free access to food.

(iii) Water intake. Restrictions on water intake are sometimes required to reduce variability in exposure levels, especially when nonaqueous dosing vehicles such as polyethylene glycol (PEG) 400 are used to increase solubility of water-insoluble drugs in a dosing vehicle. In such cases, water intake may cause precipitation of the drug and subsequently reduce the extent of its absorption.

(iv) Coprophagy. In rodents, coprophagy (feeding on their own feces) can have significant effects on drug absorption profiles. Coprophagy can be avoided either by using tail caps or by conducting the experiments in metabolism cages, where the feces can be separated from the animals.

(ii) Dose levels. At least three different dose levels have to be examined over the intended therapeutic range to test for the presence of potential nonlinear pharmacokinetics. In most cases, however, one or two dose levels may be sufficient to determine preliminary pharmacokinetic profiles of a compound during drug discovery.

2.2.3. Sample Collection after Oral Administration —Blood

(i) Sampling time points (Fig. 2.2).

- The entire concentration *vs.* time curve. Seven (at least five) time points are recommended.

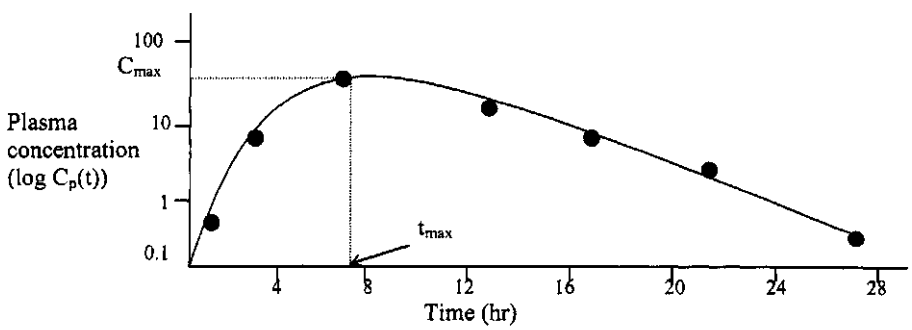


Figure 2.2. Example of a plasma drug concentration *vs.* time profile after oral administration of a drug. In general, at least one time point before and three time points after t_{max} are desirable for reliable characterization of oral exposure profiles of a drug.

- Before and after t_{max}. At least one time point before and three time points after t_{max}.

- The terminal phase. At least three time points during the terminal phase for half-life estimation, of which the interval is greater than twice the estimated terminal half-life.

- Estimate of AUC_{0-x}. Preferably, select time points over three half-lives beyond t_{max} for reliable $AUC_{0-\infty}$ estimation.

(ii) Volume. Less than 10% of the total blood volume from small laboratory animals within a week. Refer to the suggestions for intravenous administration.

2.3. DATA INTERPRETATION

There are basically two different approaches— compartmental and noncompartmental— to analyzing plasma drug concentration-*vs*.-time profiles for estimating pharmacokinetic parameters (Balant and Gex-Fabry, 1990; Gerlowke and Jain, 1983; Gillespie, 1991; Zierler, 1981). The noncompartmental approach is more commonly used for simple pharmacokinetic data interpretation in the pharmaceutical industry.

2.3.1. Compartmental Approach

The compartmental approach (or compartmental model) views the body as being composed of a number of pharmacokinetically distinct compartments. Each compartment can be thought of as an imaginary space in the body representing a combination of various tissues and organs, among which concentrations of a drug are in rapid equilibrium. Anatomical composition of the compartment is unknown and in most cases its analysis is of little value. The number of compartments in a model is empirically determined depending on plasma drug concentration time profiles. The compartmental model is designed to:

1. Provide a conceptual understanding of distributional behaviors of a drug between the plasma (or blood) and other tissues or organs in the body.
2. Empirically assess the changes in physiological processes such as membrane transport or metabolism without thorough mechanistic investigations.
3. Estimate various pharmacokinetic parameters such as rate constants, clearance, and apparent volumes of distribution.

The compartmental approach requires mathematical data analysis, usually nonlinear regression methods, to estimate the parameters used in models by fitting the model to the plasma concentration–time profile. Several computer programs for nonlinear regression are commercially available (e.g., PCNONLIN). The first step in the compartmental approach to data analysis is to determine the number of compartments required for the model.

2.3.1.1. One- vs. Multicompartment Models

When drug molecules are administered, the drug is initially localized at the administration site before further distribution into different regions of the body. For instance, if upon intravenous injection the distribution of drug molecules from the injection site, i.e., venous blood, throughout the body occurs instantaneously, the body may behave as if it is one pharmacokinetically homogeneous compartment for the drug. In this case, the plasma drug concentration–time profile exhibits a monophasic decline on a semilogarithmic scale (plasma drug concentrations on a log scale and time on a linear scale), and can be readily described with a one-compartment model.

When the distribution of a drug from the plasma into certain organs or tissues is substantially slower than to the rest of the body, multicompartment models, i.e., a central compartment and one or more peripheral (or tissue) compartments, should be considered. In general, it is expected that the distribution of a drug from the plasma into the highly perfused organs or tissues such as the liver, kidneys, or spleen is much faster than to those organs with a limited blood supply such as fat, muscle, skin, or bone. The central compartment represents the systemic circulation and those highly perfused organs and tissues, whereas the peripheral compartment(s) represents the poorly perfused organs and tissues. In a multicompartment system, the plasma drug concentration-*vs*.-time profile exhibits a multiphasic decline on a semilogarithmic scale. The intercompartmental distribution of a drug can be conceptually viewed as a pharmacokinetic expression of drug transport actually occurring between tissues and organs via blood vessels and/or membranes, and is generally assumed to follow first-order kinetics.

NOTE: FIRST-ORDER PHARMACOKINETICS. A first-order pharmacokinetic process is one in which the rate of change of concentration of a drug in biological fluids is directly proportional to its concentration. For instance, under a first-order kinetic condition, the rate of change in plasma drug concentration can be described as a function of the concentration $[C_p(t)]$, i.e., $dC_p(t)/dt = k \cdot C_p(t)$, where k is a first-order rate constant. First-order pharmacokinetics is often called linear pharmacokinetics (see Chapter 10).

2.3.1.2. One-Compartment Model Analysis

The simplest compartment model is a one-compartment model, in which the entire body is viewed as a single kinetically homogeneous compartment. A schematic description of the one-compartment model with first-order elimination of a drug after intravenous dosing is shown in Fig. 2.3.

The amount of drug present in the body at any given time t [A(t)] in a one-compartment model is described in Eq. (2.2):

$$A(t) = Cp(t) \cdot V \tag{2.2}$$

where $C_p(t)$ and V are the drug concentration in the plasma and the apparent volume of distribution (see Chapter 5), respectively. The equation describing the

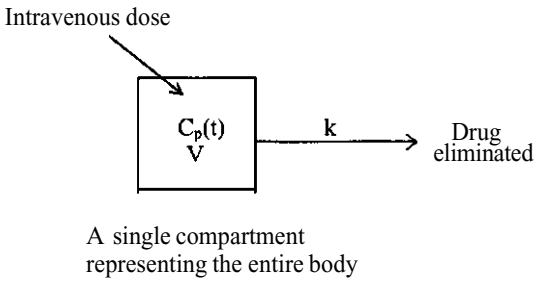


Figure 2.3. One-compartment model with first-order elimination after intravenous administration of a drug. $C_p(t)$ is the drug concentration in plasma at time t, k is a first-order elimination rate constant, and V is the apparent volume of distribution of the compartment.

plasma drug concentration $[C_p(t)]$ at time t in a one-compartment model after intravenous bolus injection is

(2.3)
$$C_p(t) = \underbrace{\frac{D_{iv}}{V} \cdot e^{-k \cdot t}}_{C_p(0)}$$

where $C_p(0)$ is an imaginary drug concentration at time zero (Fig. 2.1) and k is a first-order elimination rate constant. Equation (2.3) can be fitted to the plasma drug concentration–time data for estimates of V and k. The systemic clearance (Cl_s, see Chapter 6) and half-life ($t_{1/2}$) of a drug can be estimated from these parameters through the following equations:

(2.4)
$$Cl_s = k \cdot V$$

(2.5)
$$t_{1/2} = \frac{0.693}{k}$$

(a) Drug Concentration in Plasma and Tissues. It is important to note that one-compartment behavior of plasma drug concentrations does not necessarily imply that the drug is at the same concentration in all the tissues and organs in the body. It means rather that the drug concentrations in different tissues or organs are in instantaneous equilibrium with those in the plasma upon drug administration into the systemic circulation, establishing the constant concentration ratios between the plasma and the various tissues. When this occurs, the rate of change of drug concentration in the plasma can directly reflect the change in drug concentration in tissues with differences in concentrations corresponding to the magnitude of the accumulation between plasma and tissues (Fig. 2.4).

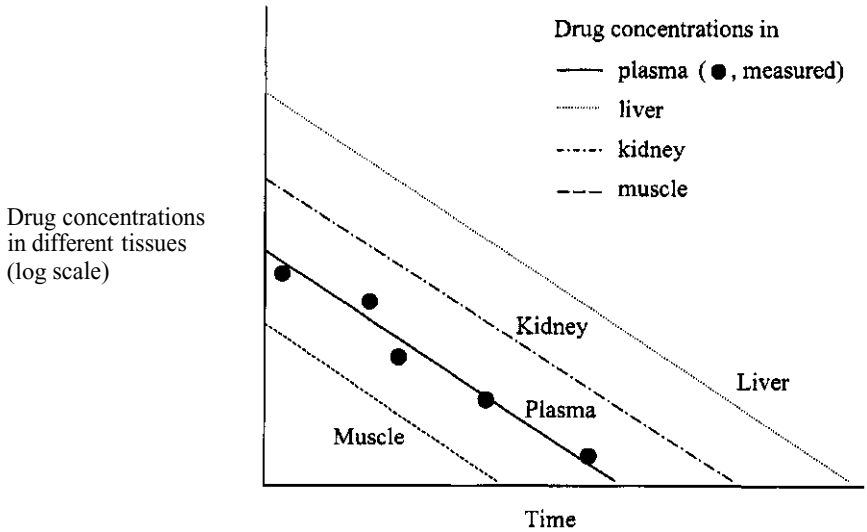


Figure 2.4. Hypothetical concentration–time profiles of a drug in plasma and various tissues when its plasma drug concentration–time profile shows a monophasic decline on a semilog scale and thus can be readily described by a one-compartment model. Drug concentrations in plasma are experimentally determined, whereas those in tissues are assumed.

(b) Relationships among Monophasic Decline, the Monoexponential Equation, and the One-compartment Model. In a one-compartment system, a monoexponential equation for a plasma drug concentration–time profile and a monophasic decline on a semilog scale after intravenous injection are necessary and sufficient conditions for each other (Fig. 2.5).

(c) Plasma Concentration–Time Plot on a Linear or a Semilogarithmic Scale. When the disposition of a drug after intravenous injection follows linear kinetics with a one-compartment system, a concentration–time profile [$C_p(t)$ *vs.* t] will be curvilinear on a linear scale. If the same data are plotted on a semilog scale, the plot of log $C_p(t)$ *vs.* t becomes a straight line and shows a monophasic decline (Fig. 2.6). When two- or three-compartment models are required for drug disposition after intravenous injection, the concentration–time profile on a semilog scale shows a bi- or triphasic decline, respectively, with a straight line during the terminal phase. On a linear scale, however, the plasma drug concentration–time plots will be curvilinear with little distinction between two- and three-compartment models. Conversion of the linear scale of plasma concentration–time data to a semilogarithmic scale thus makes it possible to determine the number of compartments needed for data analysis based on a visual inspection of the plots.

NOTE: NATURAL LOG *VS.* COMMON LOG. The base of a natural logarithm is e (= 2.718), whereas the base of the common logarithm is 10. The relationship between the natural log and the common log is

$$\ln C_p(t) = 2.303 \log C_p(t) \tag{2.6}$$

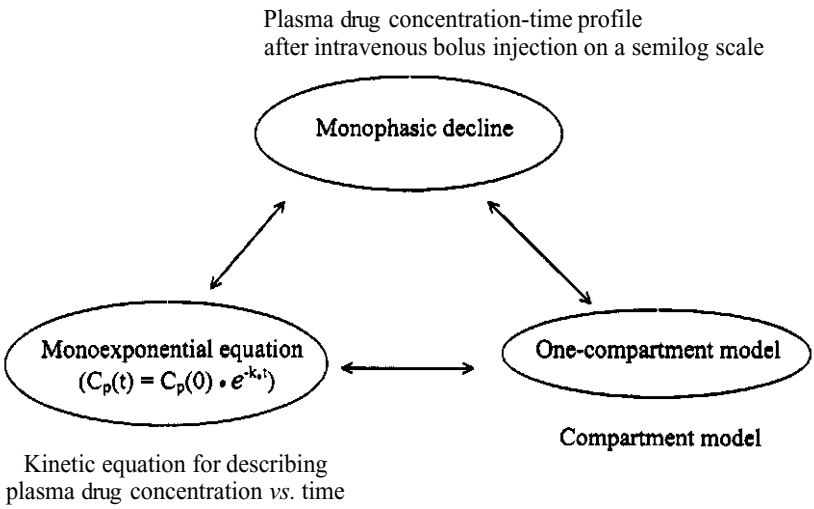


Figure 2.5. Relationships among a monophasic decline of a plasma drug concentration–time profile after intravenous injection on a semilog scale, a monoexponential equation, and a one-compartment model.

Taking the natural or common logarithms of both sides of Eq. (2.3), gives

(2.7) $$\ln C_p(t) = \ln C_p(0) - k \cdot t$$

or

(2.8) $$\log C_p(t) = \log C_p(0) - \frac{k}{2.303} \cdot t$$

2.3.1.3. Multicompartment Model Analysis

The number of compartments required to describe drug disposition profiles can vary depending on how often samples are collected and how fast after administration the drug is distributed throughout the body. Let us consider a drug for which the initial distribution into the blood pool and highly perfused organs takes place within 5 min after intravenous injection, followed by slower distribution into the rest of the body, and the first plasma sample is collected more than 5 min after injection. In this case, the drug exposure profile will show a monophasic decline so that a one-compartment model may be considered suitable for model-fitting. However, if several additional blood samples are obtained within the first 5 min, the entire plasma drug concentration–time profile may exhibit a biphasic decline on a semilog scale, and a two-compartment rather than a one-compartment model would be more suitable.

There are three different types of two-compartment models and seven three-compartment models, depending on the compartment(s) responsible for drug elim-

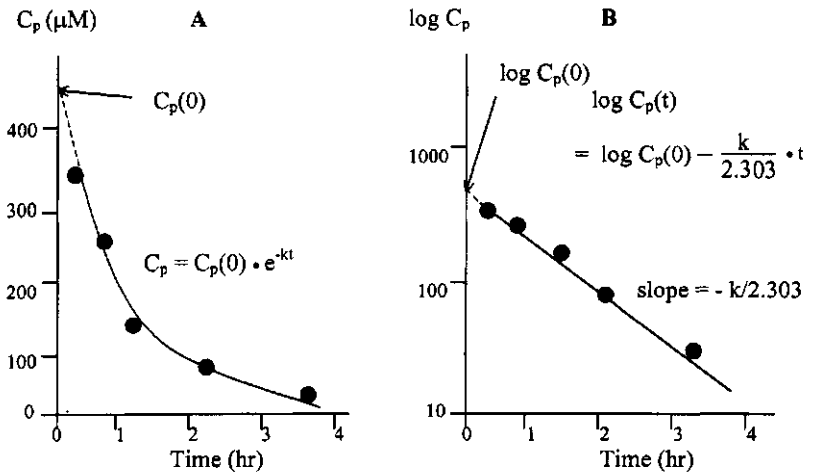
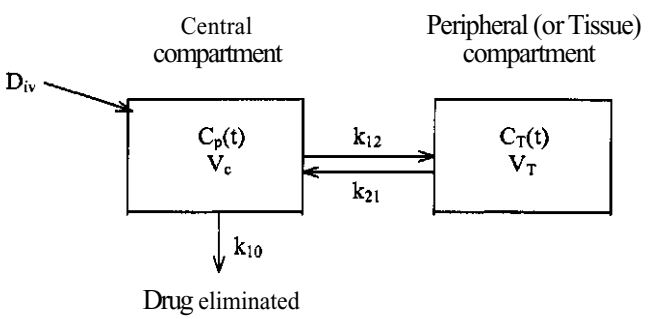


Figure 2.6. Plasma drug concentration *vs.* time profiles after intravenous injection of a hypothetical drug on linear (A) or semilogarithm (B) scales, with plasma drug concentration–time data being describable with a monoexponential equation.

ination. In the absence of any experimental evidence, it is usually assumed that drug elimination takes place exclusively from the central compartment. This is because in most drugs, the major sites of elimination are the liver (metabolism and biliary excretion) and the kidney (urinary excretion), both of which are well perfused with blood and thus readily accessible to a drug in plasma. The most commonly used two-compartment model for drug disposition after intravenous administration is shown in Fig. 2.7.



Two-compartment model representing the body

Figure 2.7. Two-compartment model with first-order elimination of a drug from the central compartment after intravenous administration. $C_p(t)$ and $C_T(t)$ are drug concentrations in the plasma and the peripheral compartment at time t, respectively; D_{iv} is an intravenous drug dose; k_{12} and k_{21} are the first-order rate constants for distribution of the drug from the central to the peripheral compartments, and vice versa, respectively; k_{10} is the first-order elimination rate constant from the central compartment; and V_c and V_T are the volumes of distribution of the central and the peripheral compartments, respectively.

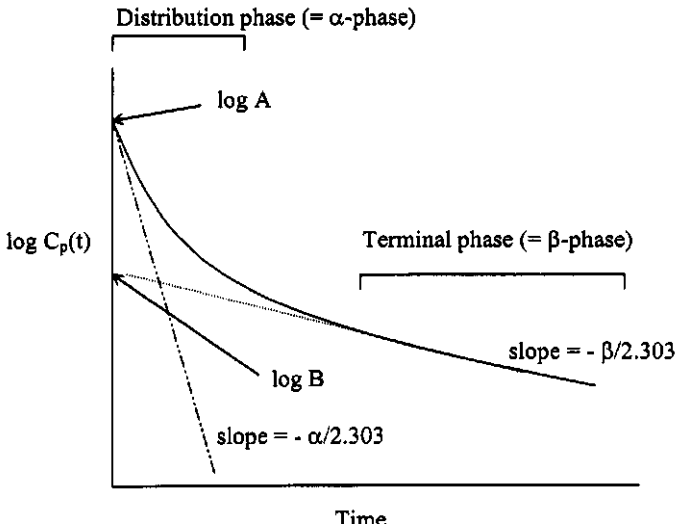


Figure 2.8. Biexponential decline of a log $C_p(t)$ *vs.* t plot after intravenous bolus injection when drug disposition can be described using a two-compartment model.

In a two-compartment model under linear conditions, plasma drug concentration–time data after intravenous injection exhibiting a biphasic curve on a semilog scale (Jusko and Gibaldi, 1972) can be described by the following biexponential equation:

(2.9) $$C_p(t) = A \cdot e^{-\alpha \cdot t} + B \cdot e^{-\beta \cdot t}$$

Estimates of A, B, α, and β can be obtained from the intercepts and slopes of a plasma concentration–time plot after intravenous administration of a drug by curve-fitting with the method of residuals or nonlinear regression using a computer program (Fig. 2.8). Those parameters can be used to estimate $C_p(0)$, V_c, and microconstants such as k_{12}, k_{21}, and k_{10}.

At time zero,

(2.10) $$C_p(0) = A + B$$

Therefore,

(2.11) $$V_c = \frac{D_{iv}}{C_p(0)} = \frac{D_{iv}}{A+B}$$

The relationships between the microconstants, i.e., k_{12}, k_{21}, and k_{10}, and A, B, α, and β are as follows:

(2.12) $$k_{21} = \frac{A \cdot \beta + B\alpha}{A + B}$$

(2.13) $$k_{10} = \frac{\alpha \cdot \beta}{k21}$$

(2.14) $$k_{12} = \alpha + \beta - k_{21} - k_{10}$$

From k_{12}, k_{21}, k_{10}, and V_c, the systemic clearance (Cl_s, see Chapter 6) and the volume of distribution at steady state (V_{ss}, see Chapter 5) can be also calculated:.

(2.15) $$Cl_s = k_{10} V_c$$

and

(2.16) $$V_{ss} = V_c(1 + k_{12}/k_{21})$$

(a) Distribution and Terminal Phases. When the disposition of a drug can be described using a two-compartment model under linear conditions, the plasma drug concentration–time profile after intravenous injection will show a biphasic decline on a semilog scale (Fig. 2.8). The initial sharply declining phase of the exposure profile is often called the "distribution or α-phase" and the later phase, shown as a shallower straight line, is called "terminal or β-phase" (also known as the postdistribution, pseudodistribution equilibrium, or elimination phase) (Riegelman *et al.,* 1968). During the distribution phase, the decrease in the plasma drug concentration is due mainly to the initial rapid distribution of the drug from the plasma into well-perfused organs and tissues. The pseudodistribution equilibrium is achieved at some time after drug administration when the ratios of the amounts of drug between the plasma pool and all other body tissues become constant. During this phase, the decrease in the plasma drug concentration is due primarily to the elimination of the drug from the body, and exhibits a straight line on a semilog scale (Fig. 2.8).

(b) Drug Levels in a Peripheral Compartment. Concentrations of a drug in a peripheral compartment increase rapidly during the distributional phase following intravenous injection and decrease gradually in parallel with drug concentrations in the plasma during the terminal phase (Fig. 2.9). The shape of the curve can vary depending on drug distribution and elimination rates (Gibaldi et *al.,* 1969).

(c) Relationships among Biphasic Decline, the Biexponential Equation, and the Two-Compartment Model. If the fall in the plasma drug concentrations on a semilog scale after intravenous injection of a drug is biphasic (an initial rapid decline followed by a slower decrease) or triphasic, two- or three-compartment models respectively, may be suitable (Fig. 2.10). However, a multiphasic decline of the plasma drug concentration profile does not necessarily mean that the body behaves

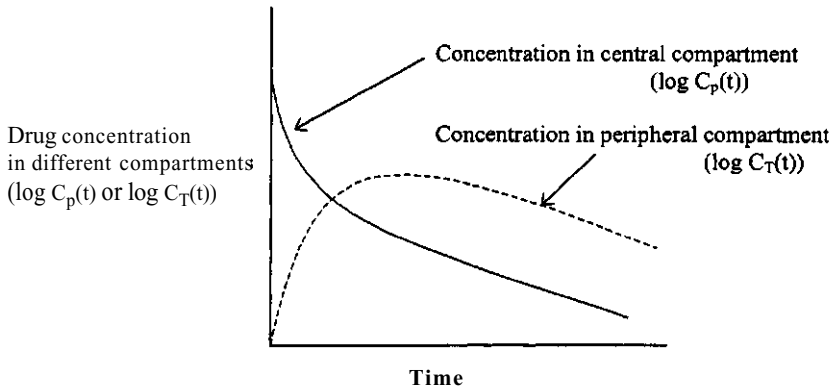


Figure 2.9. Semilogarithmic plots of drug concentrations in the central [——, measured concentrations in plasma, $C_p(t)$] and peripheral [……, projected concentrations in tissues, $C_T(t)$] compartments. The extent of drug concentrations in the peripheral compartment can vary, depending on the rate of drug distribution between the plasma and the tissues.

in a multicompartment fashion in relation to the drug. For instance, exposure profiles of drugs with one of the following disposition characteristics can also exhibit a biexponential decline, even if the body behaves as a single compartment for drug distribution.

• Nonlinear protein binding. At high drug concentrations during the early time points after intravenous injection, the fraction of the drug not bound to plasma protein can be higher owing to binding saturation than that during the later time points. Unless intrinsic clearance becomes saturated, drug clearance is generally faster when there is less protein binding than otherwise. This more rapid clearance can cause a steeper decline in drug concentrations during the initial phase as compared to the later phase. As concentrations decrease, protein binding of the drug becomes more extensive, causing slower clearance, which is reflected in a shallower slope of the concentration profile with time.

• Product inhibition. Metabolite(s) of a drug can inhibit clearance mechanisms of the parent drug. The effects of metabolite(s) on drug clearance shortly after drug administration may be negligible because there is not much metabolite formation. However, once a sufficient quantity of metabolite(s) is accumulated, drug clearance can be significantly impaired, resulting in a slower decline of plasma drug concentrations during the later phase.

• Cosubstrate depletion. Depletion of cosubstrate required for elimination (e.g., metabolism) of drug after a certain period of time can result in an apparent biphasic decline in the drug concentration profile.

• Pharmacokinetic differences of enantiomers. When a drug is administered as a racemic mixture and pharmacokinetic behaviors of the enantiomers of the drug are different, it is possible to have apparent biphasic profiles of drug concentrations in plasma when determined as a racemate.

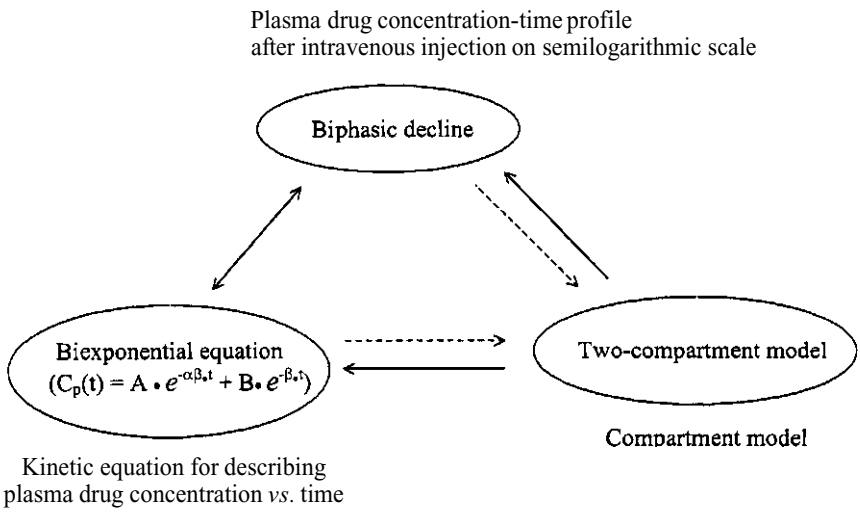


Figure 2.10. Relationships among a biphasic decline of a plasma drug concentration–time profile after intravenous injection on a semilogarithmic scale, a biexponential equation, and a two-compartment model. A solid arrow from the two-compartment model to the biphasically declining plasma concentration–time plot implies that if the body behaves as two compartments, a plasma drug concentration profile will be biphasic. However, a biphasic exposure profile does not necessarily mean that the body behaves as two compartments, as indicated with a dotted arrow.

2.3.1.4. Model Selection

The most important factor in selecting a pharmacokinetic model to fit the experimental data is its physiological relevance to kinetic behaviors of the drug. Especially when there is experimental evidence suggesting particular drug distribution patterns or elimination routes, pharmacokinetic models that can accommodate those findings should be considered. For instance, if the data suggest that the elimination of a drug occurs mainly via hepatic metabolism with a biphasically declining plasma concentration profile after intravenous injection, a two-compartment model with elimination of the drug from the central compartment rather than from the peripheral compartment would be more reasonable.

Many different compartmental models can be used for the same data. The most complicated model with numerous compartments and parameters for the data is not necessarily the best model for the characterization of drug pharmacokinetic profiles. A rule of thumb for model selection is "the principle of parsimony." That is, the simpler the model, the better it can be. There are several statistical approaches to identifying the most appropriate pharmacokinetic model among those available for the same data.

(a) Akaike Information Criterion (AIC). The most well known method for model selection is the so-called Akaike information criterion (AIC) value estimation (Akaike, 1974). An AIC value for a particular model can be obtained as follows:

$$\text{AIC value} = n \cdot \ln(\text{WSS}) + 2 \cdot m \tag{2.17}$$

where n and m are, respectively, the number of data points and parameters used in the model, and WSS is the weighted sum of squares estimated as

$$\text{WSS} = \sum_{i=1}^{i=n} (Y_{\text{obs},i} - Y_{\text{calc},i})^2 \cdot W_i \tag{2.18}$$

where W_i is a weighting factor for fitting the model to the experimental data (drug concentrations) and can be $1/Y$ or $1/Y^2$, $Y_{\text{obs},i}$ is the observed y-value (measured drug concentration), and $Y_{\text{calc},i}$ is the calculated y-values (estimated drug concentration according to the model). Among different models, the model yielding the lowest AIC value (highest negative in the case of negative values) is the most appropriate model for describing the data.

(b) Schwarz Criterion. The Schwarz criterion (SC) is similar to the ACI criterion (Schwarz, 1978), and its value is calculated as follows:

$$\text{SC value} = n \cdot \ln(\text{WSS}) + m \cdot \ln(n) \tag{2.19}$$

Similarly to the AIC criterion, the model yielding the lowest SC value is the most appropriate model.

2.3.2. Noncompartmental Approach

The noncompartmental approach for data analysis does not require any specific compartmental model for the system (body) and can be applied to virtually any pharmacokinetic data. There are various noncompartmental approaches, including statistical moment analysis, system analysis, or the noncompartmental recirculatory model. The main purpose of the noncompartmental approach is to estimate various pharmacokinetic parameters, such as systemic clearance, volume of distribution at steady state, mean residence time, and bioavailability without assuming or understanding any structural or mechanistic properties of the pharmacokinetic behavior of a drug in the body. In addition, many noncompartmental methods allow the estimation of those pharmacokinetic parameters from drug concentration profiles without the complicated, and often subjective, nonlinear regression processes required for the compartmental models. Owing to this versatility and ruggedness, the noncompartmental approach is a primary pharmacokinetic data analysis method for the pharmaceutical industry. Moment analysis, the most commonly used noncompartmental method, is discussed below.

2.3.2.1. Moment Analysis

Statistical moment analysis has been used extensively in chemical engineering to elucidate diffusion characteristics of chemicals in liquid within tubes. Similar concepts were applied to pharmacokinetics to analyze drug disposition and to estimate pharmacokinetic parameters (Yamaoka *et al.,* 1978). The plasma concentration–time profile of a drug can be thought of as a statistical distribution curve, for which the first two moments (zero and first) are defined as the area under the plasma

concentration–time curve (AUC) and as the mean residence time (MRT), a mean time interval during which a drug molecule resides in the body before being excreted. According to moment analysis, the AUC and MRT of a drug can be calculated from plasma drug concentration–time profiles, regardless of the route of administration, as follows:

$$AUC_{0-\infty} = \int_0^\infty C_p(t)\,dt \tag{2.20}$$

$$MRT = \frac{AUMC_{0-\infty}}{AUC_{0-\infty}} = \frac{\int_0^\infty t \cdot C_p(t)\,dt}{\int_0^\infty C_p(t)\,dt} \tag{2.21}$$

where AUMC is the area under the first-moment curve of the plasma drug concentration–time curve from time zero to infinity.

(a) Units of AUC, AUMC, and MRT.
AUC: concentration.time, e.g., $g \cdot hr/ml$ or $M \cdot hr$.
AUMC: (concentration. time). time, e.g., $g \cdot hr^2/ml$ or $M \cdot hr^2$.
MRT: time, e.g., hr

(b) Pharmacokinetic Implications of AUC and AUMC. AUC is an important pharmacokinetic parameter in quantifying the extent of exposure of a drug and of its clearance from the body. AUC is considered a more reliable parameter for assessing the extent of overall exposure of a drug than individual drug concentrations. AUMC is used for assessing the extent of distribution, i.e., the volume of distribution at steady state and the persistence of a drug in the body.

(c) Estimating AUC and AUMC.

(i) Linear trapezoidal method. The linear trapezoidal method is the one most well-known for estimating AUC and AUMC. For instance, AUC over two adjacent time points, t_1 and t_2, (AUC_{t1-t2}, Fig. 2.11) can be approximated as the area of a trapezoid formed by connecting the adjacent points with a straight line [Eq. (2.22)]. An estimate of AUC over an extended period of time can be obtained by adding the areas of a series of individual trapezoids. Estimating AUC by the linear trapezoidal method should be done on a linear scale.

$$AUC_{t1-t2} = \text{Area of a trapezoid between } t_1 \text{ and } t_2$$

$$= (t_2 - t_1) \cdot \frac{C_2 + C_1}{2} \tag{2.22}$$

↑ *Adjacent time points (time interval)*

↖ *Concentrations of drug corresponding to the time points (mean concentration)*

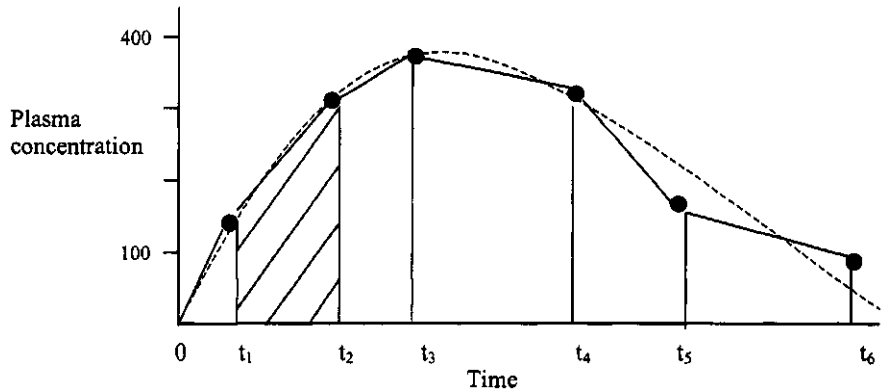


Figure 2.11. Estimate of AUC by the linear trapezoidal method on a linear scale. AUC between t_1 and t_2 is shown as a hatched area. A discrepancy can be seen between a plot from interpolation of data points (solid line) and a nonlinear regression plot (dotted line) fitted to the individual data.

The advantages and disadvantages of the linear trapezoidal method are as follows:

1. Advantages: (a) Easy to use. (b) Reliable for slow declining or ascending curves.
2. Disadvantages: (a) Owing to the linear interpolation between data points, it tends to over- or underestimate the true AUC, depending, respectively, on the concave or convex shape of the curve (Fig. 2.11). (b) Error-prone whenever there is a sharp bending in concentration values between time points. (c) Error-prone for data points with a wide interval.

AUMC can be also estimated with the linear trapezoidal approximation from the area under the curve of *the product of concentration and time* $[C_p(t)\cdot(t)]$ *vs.* time on a linear scale. An example for AUC and AUMC calculation with the linear trapezoidal method after oral administration of a hypothetical drug is shown in Table 2.1. When the concentration of a drug in plasma at the last sampling time point (t_{last}) is not zero, $AUC_{0-\infty}$ can be estimated by combining AUC from time zero to t_{last} ($AUC0-t_{last}$) using the trapezoidal method and AUC from t_{last} to infinity ($AUC_{last-\infty}$) estimated using the following equation:

$$AUCt_{last-\infty} = \frac{C^*}{\lambda_z} \tag{2.23}$$

where C* is the estimated drug concentration at $t_{last,}$ and λ_z is the slope of the terminal phase of the plasma drug concentration–time profile on a semilog scale. C* and λ_z can be obtained using an appropriate linear regression method with the last few (usually three) data points during the terminal phase. An estimate of $AUMCt_{last-\infty}$ can be obtained from

$$AUMCt_{last-\infty} = \frac{C^* t_l}{\lambda_0} + \frac{C^*}{\lambda_z^2} \tag{2.24}$$

Table 2.1. Estimates of AUC and AUMC from 0 to 7 hr Based on the Linear Trapezoidal Method with Plasma Drug Concentrations after Oral Administration of a Hypothetical Drug

Sampling time (hr)	Plasma drug concentration (ng/ml)	Plasma drug concentration x time (ng·hr/ml)	AUC^{α} (ng·hr/ml)	$AUMC^{\alpha}$ (ng·hr²/ml)
0	0	0	0	0
1	100	100	50	50
2	200	400	150	250
3	300	900	250	650
4	200	800	250	850
6	100	600	300	1400
7	0	0	50	300
			AUC_{0-7}: 1050	$AUMC_{0-7}$: 3500

[a]AUC or AUMC between adjacent time points.

Similarly, $AUMC_{0-\infty}$ can be obtained by adding $AUMC_{0-t_{last}}$ calculated using the linear trapezoidal method and $AUMC_{t_{last}-\infty}$ estimated.

(ii) Log trapezoidal method. The so-called log trapezoidal method assumes that the concentration values vary linearly within each sampling interval. $AUC_{t_1-t_2}$ can be estimated as follows:

$$AUC_{t_1-t_2} = (t_2 - t_1) \cdot \frac{C_2 - C_1}{\ln(C_2/C_1)} \tag{2.25}$$

Equation (2.25) is most appropriate for an exponentially declining concentration–time profile. The method is error-prone in an ascending curve, near a peak, or in a steeply descending multiexponential curve, and it cannot be used if the concentration is zero or if the two values are equal. There are several other methods for estimating AUC. For instance, the Lagrange method uses a cubic polynomial equation [$C_p(t) = a + b \cdot t + c \cdot t^2 + d \cdot t^3$] instead of the linear function, and the Spline method uses piecewise polynominals for curve-fitting (Yeh and Kwan, 1978).

NOTE: ESTIMATED CONCENTRATION AT THE LAST TIME POINT (C*). Drug concentration ($C_{t_{last}}$) measured at the last time point (t_{last}) is analytically most error-prone, because $C_{t_{last}}$ is generally closest to the limit of quantification of an assay. It is thus considered to be more reliable to use a concentration C* at t_{last} estimated using a proper linear regression method with the last few (usually three) data points for calculation of $AUC_{t_{last}-\infty}$ (Fig. 2.12).

2.3.2.2. Estimating Pharmacokinetic Parameters with Moment Analysis

(a) Clearance. The systemic clearance (Cl_s) of a drug (see Chapter 6) can be estimated as the reciprocal of the zero moment of a plasma concentration–time

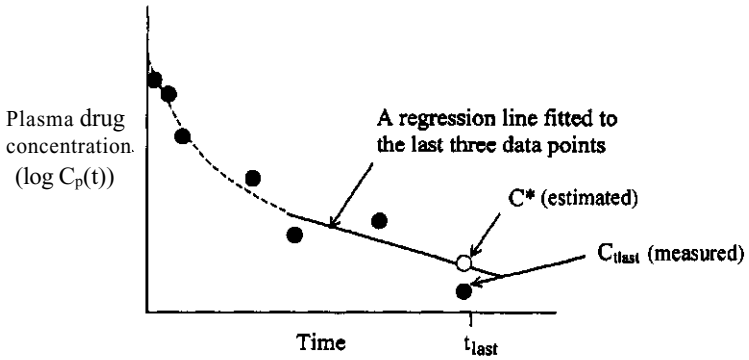


Figure 2.12. Estimated concentration (C*, O) at the last time point (t_{last}) according to linear regression with the last three data points measured. C_{last} is the actual concentration measured at t_{last}.

curve after intravenous administration (AUC_{iv}) normalized by an intravenous dose (D_{iv}) as shown below:

(2.26)
$$Cl_s = \frac{D_{iv}}{AUC_{iv}}$$

(b) Volume of Distribution at Steady State. The volume of drug distribution at steady state (Vd_{ss}) (see Chapter 5) can be estimated as the product of MRT after intravenous bolus injection (MRT_{iv}) and Cl_s:

(2.27)
$$Vd_{ss} = MRT_{iv} \cdot Cl_s = \frac{AUMC_{iv}}{AUC_{iv}} \cdot \frac{D_{iv}}{AUC_{iv}}$$

NOTE: RELATIONSHIP AMONG AUC, Cl_s AND V_{ss}. The $AUC_{0-\infty}$ of a drug inversely reflects the extent of Cl_s, but does not have a direct correlation with the size of V_{ss}. This is because Cl_s affects only the $AUC_{0-\infty}$ whereas V_{ss} is governed by both $AUC_{0-\infty}$ and $AUMC_{0-\infty}$ [Eq. (2.26) and (2.27)]. Therefore, it is true that a drug with a smaller $AUC_{0-\infty}$ after intravenous injection has a faster Cl_s than one with a larger $AUC_{0-\infty}$ at the same dose. However, the drug with the smaller $AUC_{0-\infty}$ does not necessarily have a greater V_{ss}. Let us assume that there are two drugs (A and B) and that both $AUC_{0-\infty}$ and $AUMC_{0-\infty}$ of drug A are smaller than those of drug B (Table 2.2) after intravenous injection at 3 mg/kg in rats (Fig. 2.13). Cl_s and V_{ss} estimated based on $AUC_{0-\infty}$ and $AUMC_{0-\infty}$ (Table 2.2) indicate that Cl_s of drug A is greater than that of drug B, reflected by its lower $AUC_{0-\infty}$ whereas V_{ss} of drug B is greater than that of drug A, despite the fact that $AUC_{0-\infty}$ of drug B is greater than that of drug A.

(c) Bioavailability. Bioavailability (F) of a drug generally refers to the fraction of a dose administered via a route other than intravenous injection that reaches the

Table 2.2. Summary of Pharmacokinetic Parameters for Drugs A and B

Parameters	A	B
D_{iv} (mg/kg)	3	3
$AUC_{0-\infty}$ (μg·hr/ml)	2	3
$AUMC_{0-\infty}$ (μg·hr²/ml)	1	4.5
Cl_s (ml/min/kg)	25	16.7
V_{ss} (liter/kg)	0.75	1.5

systemic circulation. For instance, F after oral administration can be estimated as the ratio of the dose-normalized zero moments ($AUC_{0-\infty}$) after oral and intravenous administration (see Chapter 4):

(2.28)
$$F = \frac{D_{iv} \cdot AUC_{po}}{D_{po} \cdot AUC_{iv}}$$

where D_{iv} and D_{po} are intravenous and oral doses, and AUC_{iv} and AUC_{po} are $AUC_{0-\infty}$ after intravenous and oral administration of the drug, respectively.

(d) Mean Residence Time. The mean residence time (MRT) is the average time spent by a single drug molecule in the body before being excreted via elimination processes, regardless of the route of administration. When a drug disappearance curve exhibits a monophasic decline after intravenous injection on a semilog scale, its MRT_{iv} is the time required for 63.2% of the dose to be eliminated from the body. The MRT values after administration by routes other than intravenous bolus injection are always greater than MRT_{iv}. Differences in MRT values following administration via these other routes and MRT_{iv} can be viewed as the average time required for drug molecules to reach the systemic circulation from the site of administration. For instance, a difference between MRT after oral administration (MRT_{po}) and MRT_{iv} is the mean absorption time (MAT; see Chapter 4), represen-

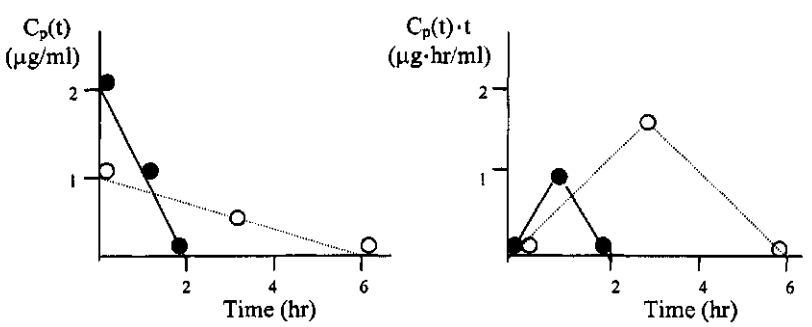


Figure 2.13. Plasma drug concentration–time profiles (left) and drug first-moment curves (right) for drugs A(•) and B (O)on a linear scale.

ting the average time required for the drug to reach the systemic circulation from the gastrointestinal tract after oral administration:

(2.29) $$\boxed{MAT = MRT_{po} - MRT_{iv}}$$

$$MRT_{po} = \frac{AUMC_{po}}{AUC_{po}}$$

If drug absorption can be assumed to be a single first-order kinetic process, the absorption rate constant (k_a) after oral dosing can be estimated as the reciprocal of MAT:

(2.30) $$\boxed{k_a = 1/MAT}$$

(e) Half-Life. The half-life ($t_{1/2}$) of a drug generally implies the *terminal* half-life during the terminal phase where a plot of log $C_p(t)$ *vs*. time exhibits a straight line (Gibaldi and Weintraub, 1971). The half-life of a drug is the period of time over which its concentration in plasma decreases by half from a reference concentration at any given time point. When drug disappearance shows a monophasic decline after intravenous injection, $t_{1/2}$ is proportional to MRT_{iv}:

(2.31) $$t_{1/2} = 0.693 \cdot MRT_{iv}$$

When a plasma drug concentration–time plot exhibits a bi- or a triphasic decline on a semilog scale, $t_{1/2}$ is longer than $0.693 \cdot MRT_{iv}$ (Kwon, 1996).

(i) Estimating half-life. There are several ways to estimate $t_{1/2}$ of a drug from its plasma concentration–time profile.

- Visual inspection of the plasma concentration–time profile. A rough estimate of $t_{1/2}$ can be obtained from a plasma concentration–time profile simply by eyeballing a time interval over which the concentration decreases by half from any reference time point.

- Curve fitting. In general, three data points during the terminal phase are used, over which the time interval is greater than at least twice the estimated t1/2 based on those points. The slope (λ_z) during the terminal phase of a plasma drug concentration–time plot on a semilog scale is inversely related to $t_{1/2}$:

(2.32) $$\boxed{t_{1/2} = 0.693/\lambda_z}$$

where λ_z is equal to k [Eq. (2.5)] or β [Eq. (2.9)] when a plasma drug concentration–time plot exhibits a monophasic or a biphasic decline, respectively.

• Estimation between two data points. The following equation can be used to estimate $t_{1/2}$ between two drug concentrations (C_1 and C_2) at two different time points (t_1 and t_2). In this case, the estimated $t_{1/2}$ indicates how much time it would take for a drug concentration to decrease by half, if C_1 decreases to C_2 from t_1 to t_2:

$$t_{1/2} = \frac{(0.693)\cdot(t_2 - t_1)}{\ln(C_1/C_2)} \tag{2.33}$$

(ii) Pharmacokinetic implications of half-life. The terminal half-life of a drug is probably the most important parameter in assessing the *duration* of drug exposure.

• Relationship between terminal half-life and efficacy of drug. If there is a direct correlation between plasma exposure levels of a drug and its pharmacological response, absolute exposure levels during the terminal phase and $t_{1/2}$ can be important in assessing the duration of its efficacy. Let us assume that drugs A and B have the same *in vitro* potency, but that $AUC_{0-\infty}$ of drug A is greater than that of drug B after intravenous injection, while the exposure levels of B during the terminal phase are higher with a longer $t_{1/2}$ than those of A (Fig. 2.14). If there are direct relationships among EC_{50}, *in vivo* efficacy, and plasma drug levels, drug B may be more desirable for a longer duration of efficacy than drug A, despite A's greater AUC.

• Significance of half-life after multiple dosing. Regardless of the route of administration, $t_{1/2}$ of a drug after multiple dosing becomes close to that during the true terminal phase after single dosing; i.e., $t_{1/2}$ after multiple dosing is dictated by the true terminal $t_{1/2}$ after single dosing. It is not uncommon to see the apparent $t_{1/2}$ of a drug after multiple doses being longer than that after a single dose. This can be simply because the true terminal $t_{1/2}$ after a single dose cannot be readily measured owing to assay limitations and/or inadequate sampling time points (Fig. 2.15).

• Time to reach steady state after multiple dosing. The time required to reach steady state exposure levels of a drug after multiple dosing is directly related to its

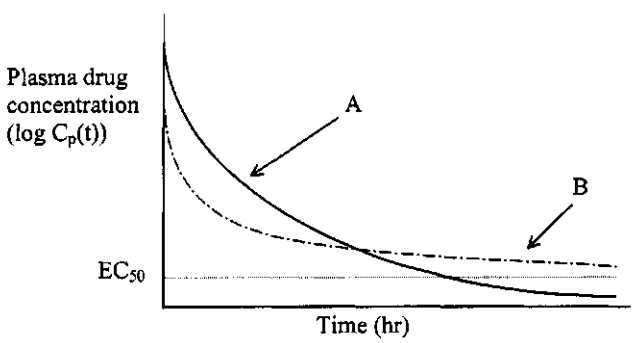


Figure 2.14. Plasma drug concentration profiles of drugs A and B with the same EC_{50}. $AUC_{0-\infty}$ of drug A is greater than that of drug B, whereas exposure levels of drug B during the terminal phase are higher with a longer terminal half-life as compared to those of drug A.

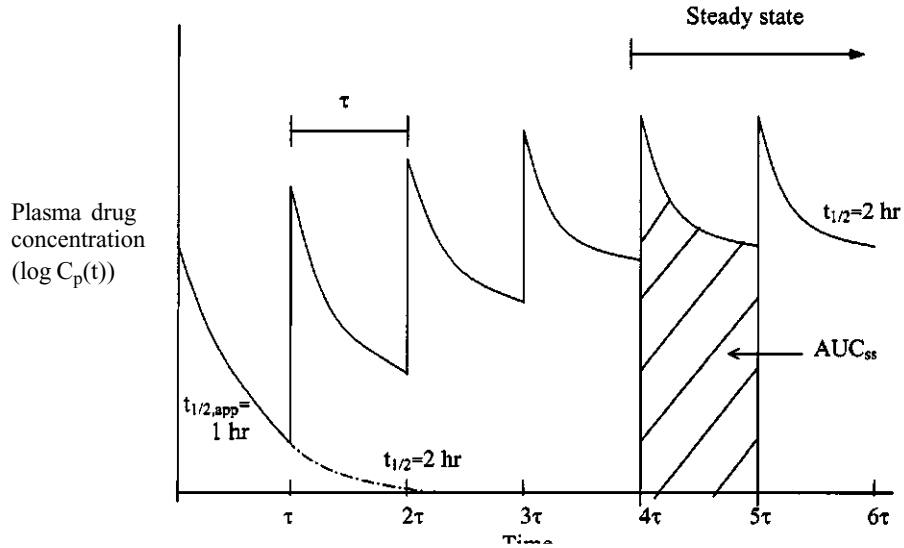


Figure 2.15. A schematic description of changes in plasma drug exposure profiles and apparent half-lives after multiple dosing. The plots show that owing to insufficient data collection and/or detection limitations of assay the apparent terminal half-life ($t_{1/2,app}$ = 1 hr) estimated after a single dose (up to time τ) can be shorter than that ($t_{1/2}$ = 2 hr) after multiple dosing. τ is the dosing interval, and AUC_{ss} is the AUC between dosing intervals after reaching steady state.

$t_{1/2}$ after a single dose. It usually takes about five half-lives to reach steady state drug concentrations after multiple dosing for a drug exhibiting one-compartment kinetic characteristics, regardless of the dose or the dosing interval, under linear conditions. For instance, if $t_{1/2}$ of a drug after a single dose is 10 hr, steady state concentrations upon multiple dosing will be achieved after approximately 50 hr, regardless of how much or how often the drug has been dosed during that period. The size of the dose and the dosing interval determine the extent of the steady state drug concentrations after multiple dosing, depending on clearance of the drug but not on the time to reach the steady state.

NOTE: ACCUMULATION FACTOR AFTER MULTIPLE DOSING. The accumulation factor (R) reflects how much drug is accumulated in the body at steady state after multiple dosing as compared to that after single dosing. The value of R can be estimated by dividing AUC over the dosing interval (τ) at steady state after multiple dosing (AUC_{ss}) divided by AUC from 0 to τ ($AUC_{0-\tau}$) after the first dose. Instead of AUC_{ss}, $AUC_{0-\infty}$ after a single dose can be used, since $AUC_{0-\infty}$ is equal to AUC_{ss}. (Fig. 2.15):

(2.34)
$$R = \frac{AUC_{ss}}{AUC_{0-\tau}} = \frac{AUC_{0-\infty}}{AUC_{0-\tau}}$$

The average plasma drug concentration at steady state ($C_{avg,ss}$) after multiple dosing, which is $AUCs_{ss}$ divided by τ, can be also estimated by dividing $AUC_{0-\infty}$ by τ:

$$C_{avg,ss} = \frac{AUC_{ss}}{\tau} = \frac{AUC_{0-\infty}}{\tau} \quad (2.35)$$

These equations enable the estimation of R and $C_{avg,ss}$ after multiple dosing, based on drug exposure levels after *a single dose.*

(iii) Assay limitation and half-life. An arbitrary study protocol for blood sampling over a fixed period without consideration of appropriate time points can lead to a significant underestimate of the true $t_{1/2}$ of a drug. Another factor that makes an accurate estimate of $t_{1/2}$ difficult is assay sensitivity for drug concentrations during the terminal phase. It is not uncommon to observe apparently longer terminal $t_{1/2}$ of a drug at a higher dose level, compared to that at a lower dose level. This may be due to nonlinear pharmacokinetics of a drug at a higher concentration; however, it can be due simply to an inability to accurately measure drug concentrations at a later time point because of limited assay sensitivity at a lower dose level (Fig. 2.16). It is, therefore, important to measure and compare $t_{1/2}$ of a drug over an extended period of time during the terminal phase at different dose levels, in order to obtain a reliable estimate of $t_{1/2}$. Another approach is to measure $t_{1/2}$ at elevated exposure levels after multiple dosing, which is the true $t_{1/2}$ of a drug, assuming that there are no dose- or time-dependent pharmacokinetic variations.

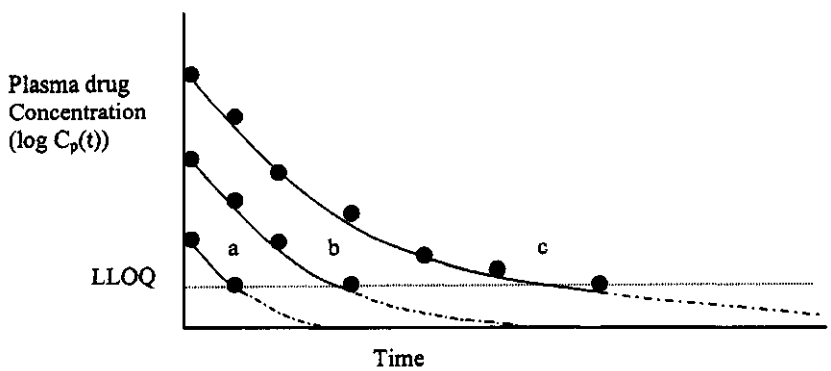


Figure 2.16. Plasma drug concentration–time profiles of a hypothetical drug at three different dose levels (dose levels: a < b < c) under linear conditions. Estimates of terminal half-lives based on plasma drug concentrations appear to be shorter at the low and medium dose levels (a and b) compared to the high dose level (c), albeit there are no dose-dependent changes in drug disposition. The apparently shorter half-life of a drug at lower dose levels is due to limited assay sensitivity. The dotted lines below LLOQ at a and b indicate actual drug concentrations, which decrease in parallel to those at c. LLOQ is the lower limit of quantitation of the assay.

REFERENCES

Akaike H., A new look at the statistical model identification, *IEEE Trans. Automat. Control* **19:** 716–723, 1974.

Balant L. P. and Gex-Fabry M., Physiological pharmacokinetic modelling, *Xenobiotica* **20:** 1241–1257, 1990.

Gerlowke L. E. and Jain R. K., Physiologically based pharmacokinetic modeling: principles and applications, *J. Pharm. Sci.* **72**: 1103–1127, 1983.

Gibaldi M. *et al.*, Relationship between drug concentration in plasma or serum and amount of drug in the body, *J. Pharm. Sci.* **58** 193–197, 1969.

Gibaldi M. and Weintraub H., Some considerations as to the determination and significance of biological half-life, *J. Pharm. Sci.* **60:** 624–626, 1971.

Gillespie W. R., Noncompartmental versus compartmental modelling in clinical pharmacokinetics, *Clin. Pharmacokinet.* **20:**253–262, 1991.

Jusko W. J. and Gibaldi M., Effects of change in elimination on various parameters of the two-compartment open model, *J. Pharm. Sci.* **61:** 1270–1273, 1972.

Kwon Y., Volume of distribution at pseudo-distribution equilibrium: relationship between physiologically based pharmacokinetic parameters and terminal half-life of drug, *Pharm. Sci.* **2:** 387–388, 1996.

Riegelman *S. et al.,* Shortcomings in pharmacokinetic analysis by conceiving the body to exhibit properties of a single compartment, *J. Pharm. Sci.* **57:** 117–123, 1968.

Schwarz G., Estimating the dimension of model, *Ann. Stat.* ***6*** 461–464, 1978.

Yamaoka K. ***et al.,*** Statistical moments in pharmacokinetics, *J. Pharmacokinet. Biopharm.* **6:** 547–557, 1978.

Yeh K. C. and Kwan K. C., A comparison of numerical integrating algorithms by trapezoidal, Lagrange, and Spline approximation, *J. Pharmacokinet. Biopharm* ***6*** 79–97, 1978.

Zierler L., A critique of compartmental analysis, *Ann. Rev. Biophys. Bioeng.* **10:**531–562, 1981.