

Introduction to Pharmacokinetics

Advancements in biopharmaceutics have come about largely through the development and application of pharmacokinetics. Pharmacokinetics is the study and characterization of the time course of drug absorption, distribution, metabolism, and excretion, and the relationship of these processes to the intensity and time course of therapeutic and toxicologic effects of drugs. Pharmacokinetics is used in the clinical setting to enhance the safe and effective therapeutic management of the individual patient. This application has been termed *clinical pharmacokinetics*.

DISTRIBUTION AND ELIMINATION

The transfer of a drug from its absorption site to the blood, and the various steps involved in the distribution and elimination of the drug in the body, are shown in schematic form in Figure 1-1. In the blood, the drug distributes rapidly between the plasma and erythrocytes (red blood cells). Rapid distribution of drug also occurs between the plasma proteins (usually albumin but sometimes α_1 -acid glycoproteins and occasionally globulin) and plasma water. Since most drugs are relatively small molecules they readily cross the blood capillaries and reach the extracellular fluids of almost every organ in the body. Most drugs are also sufficiently lipid soluble to cross cell membranes and distribute in the intracellular fluids of various tissues. Throughout the body there is a distribution of drug between body water and proteins or other macromolecules that are dispersed in the body fluids or are components of the cells.

The body can be envisioned as a collection of separate compartments, each containing some fraction of the administered dose. The transfer of drug from one compartment to another is associated with

a rate constant (k). The magnitude of the rate constant determines how fast the transfer occurs.

The transfer of drug from blood to extravascular fluids (i.e., extracellular and intracellular water) and tissues is called *distribution*. Drug distribution is usually a rapid and reversible process. Fairly quickly after intravenous (iv) injection, drug in the plasma exists in a distribution equilibrium with drug in the erythrocytes, in other body fluids, and in tissues. As a consequence of this dynamic equilibrium, changes in the concentration of drug in the plasma are indicative of changes in drug level in other tissues including sites of pharmacologic effect (bioreceptors).

The transfer of drug from the blood to the urine or other excretory compartments (i.e., bile, saliva, and milk), and the enzymatic or biochemical transformation (*metabolism*) of drug in the tissues or plasma to metabolic products, are usually irreversible processes. The net result of these irreversible steps, depicted in Figure 1-1, is called *drug elimination*. Elimination processes are responsible for the physical or biochemical removal of drug from the body.

The moment a drug reaches the bloodstream, it is subject to both distribution and elimination. The rate constants associated with distribution, however, are usually much larger than those related to drug elimination. Accordingly, drug distribution throughout the body is usually complete while most of the dose is still in the body. In fact, some drugs attain distribution equilibrium before virtually any of the dose is eliminated. In such cases, the body appears to have the characteristics of a single compartment.

This simplification, however, may not be applied to all drugs. For most drugs, concentrations in plasma measured shortly after iv injection reveal a

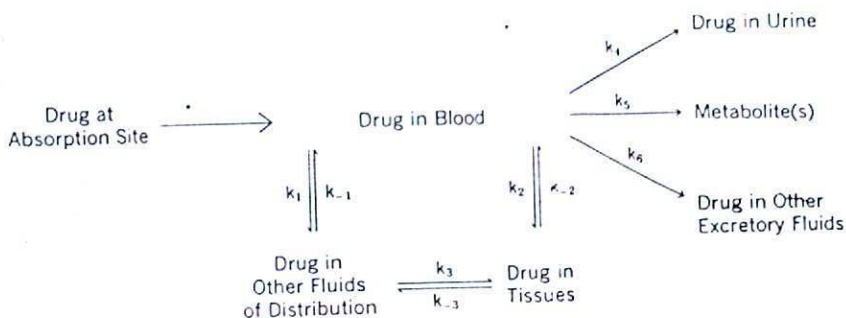


Fig. 1-1. Schematic representation of drug absorption, distribution, and elimination.

distinct distributive phase. This means that a measurable fraction of the dose is eliminated before attainment of distribution equilibrium. These drugs impart the characteristics of a multicompartiment system upon the body. No more than two compartments are usually needed to describe the time course of drug in the plasma. These are often called the rapidly equilibrating or central compartment and the slowly equilibrating or peripheral compartment.

PHYSICAL SIGNIFICANCE OF DRUG CONCENTRATION IN PLASMA

Blood samples taken shortly after intravenous administration of equal doses of two drugs may show large differences in drug concentration despite the fact that essentially the same amount of each drug is in the body. This occurs because the degree of distribution and binding is a function of the physical and chemical properties of a drug and may differ considerably from one compound to another.

At distribution equilibrium, drug concentrations in different parts of the body are rarely equal. There may be some sites such as the central nervous system or fat that are poorly accessible to the drug. There may be other tissues that have a great affinity for the drug and bind it avidly. Drug concentrations at these sites may be much less than or much greater than those in the plasma.

Despite these complexities, once a drug attains distribution equilibrium its concentration in the plasma reflects distribution factors and the simple relationship between amount of drug in the body (A) and drug concentration in the plasma (C) shown in Equation 1-1 applies:

$$A = VC \quad (1-1)$$

The proportionality constant relating amount and concentration is called the apparent volume of distribution (V). In most situations, V is independent of drug concentration. Doubling the amount of drug in the body (e.g., by doubling the iv dose) usually results in a doubling of drug concentration in plasma. This is called *dose proportionality*; it is often used as an indicator of *linear pharmacokinetics*.

The apparent volume of distribution is usually a characteristic of the drug rather than of the biologic system, although certain disease states and other factors may bring about changes in V. The magnitude of V rarely corresponds to plasma volume, extracellular volume, or the volume of total body water; it may vary from a few liters to several hundred liters in a 70-kg man. V is usually not an anatomic volume but is a reflection of drug distribution and a measure of the degree of drug binding.

Acid drugs, such as sulfisoxazole, tolbutamide, or warfarin, are often preferentially bound to plasma proteins rather than extravascular sites. Although these drugs distribute throughout body water, they have small volumes of distribution ranging from about 10 to 15 L in man. A given dose will result in relatively high initial drug concentrations in plasma.

On the other hand, many basic drugs including amphetamine, meperidine, and propranolol are more extensively bound to extravascular sites than to plasma proteins. The apparent volumes of distribution of these drugs are large, ranging from 4 to 8 times the volume of total body water (i.e., 180 to 320 L in a 70-kg man). The frequently small doses and large distribution volumes of these drugs often make their quantitative detection in plasma difficult.

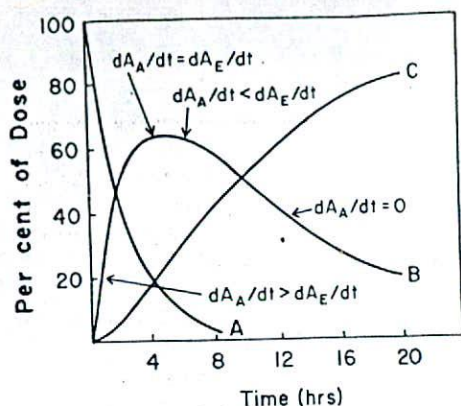


Fig. 1-2. Time course of drug disappearance from the absorption site (curve A) and appearance of eliminated drug in all forms (curve C). The net result is curve B; which depicts the time course of drug in the body.

PHARMACOKINETIC CONSIDERATIONS OF DRUG CONCENTRATIONS IN PLASMA

The plasma contains measurable quantities of many endogenous chemicals. In healthy individuals these biochemicals are present in concentrations that are reasonably constant, and it is appropriate to speak of creatinine or bilirubin levels in the plasma. Drug levels or concentrations in the plasma are rarely level. One usually finds different concentrations of drug in the plasma at different times after administration. These changes reflect the dynamics of drug absorption, distribution, and elimination (Fig. 1-2).

Intravenous Administration

Absorption need not be considered when a drug is given by rapid iv injection. As soon as the drug is administered it undergoes distribution and is subject to one or more elimination pathways. The amount of drug in the body and the drug concentration in plasma decrease continuously after injection. At the same time, there is continuous formation of metabolites and continuous excretion of drug and metabolites. Eliminated products accumulate while drug levels in the body decline.

Most drugs distribute rapidly so that shortly after iv injection, distribution equilibrium is reached. Drug elimination at distribution equilibrium is usually described by first-order kinetics. This means that the rate of the process is proportional to the amount or concentration of substrate (drug) in the system. As drug concentration falls, the elimina-

tion rate falls in parallel. The proportionality constant relating rate and amount or concentration is called a rate constant. Accordingly, the elimination rate is written as follows:

$$-\frac{dA}{dt} = \frac{dA_E}{dt} = kA \quad (1-2)$$

where A is the amount of drug in the body at time t, A_E is the amount of drug eliminated from the body (i.e., the sum of the amounts of metabolites that have been formed and the amount of drug excreted) at time t, and k is the first-order elimination rate constant.

The elimination rate constant is the sum of individual rate constants associated with the loss of parent drug. For example, the overall elimination rate constant (k) in the model depicted in Figure 1-1 is given by.

$$k = k_1 + k_3 + k_6 \quad (1-3)$$

Dimensional analysis of Equation 1-2 indicates that the units of k are reciprocal time (i.e., day^{-1} , hr^{-1} , or min^{-1}).

Since there is a relationship between the amount of drug in the body and the drug concentration in the plasma (Eq. 1-1), we may rewrite Equation 1-2 as

$$-\frac{d(VC)}{dt} = -V\frac{dC}{dt} = k(VC)$$

or

$$-\frac{dC}{dt} = kC \quad (1-4)$$

Integrating this expression between the limits $t = 0$ and $t = t$ yields

$$\log C = \log C_0 - \frac{kt}{2.303} \quad (1-5)$$

Equation 1-5 indicates that a plot of $\log C$ versus t will be linear once distribution equilibrium is reached. The term C_0 is the intercept on the log concentration axis, on extrapolation of the linear segment to $t = 0$.

Figure 1-3 shows the average concentration of a semisynthetic penicillin in the plasma as a function of time after an intravenous injection of a 2-g dose. The concentration values are plotted on a log scale; the corresponding times are plotted on a linear scale. The semilogarithmic coordinates make it convenient to plot first-order kinetic data for they

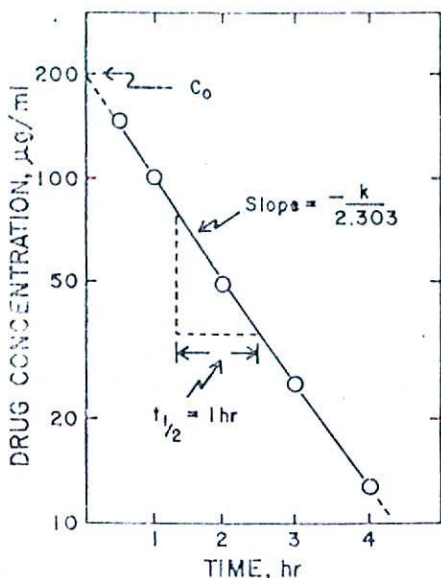


Fig. 1-3. Semilogarithmic plot of penicillin concentrations in plasma after a 2-g intravenous dose. Concentrations decline in a first-order manner with a half-life of 1 hr.

avoid the necessity of converting values of C to $\log C$.

According to Equation 1-5, the linear portion of the semilogarithmic plot of C versus t has a slope corresponding to $-k/2.303$ and an intercept, on the y -axis (i.e., at $t = 0$), corresponding to C_0 . If a drug were to distribute almost immediately after injection, C_0 would be a function of the dose and the apparent volume of distribution. Therefore, we would be able to calculate V as follows:

$$V = \frac{\text{iv dose}}{C_0} \quad (1-6)$$

For the data shown in Figure 1-3 we can determine that $C_0 = 200$ mg/ml and that $V = 10$ L.

This approach, however, is seldom useful; Equation 1-6 usually gives a poor estimate of V , always larger and sometimes substantially larger than the true volume of distribution. Equation 1-6 assumes that drug distribution is immediate, whereas most drugs require a finite time to distribute throughout the body space. Other methods to calculate V will be described subsequently.

Although it is possible to calculate the elimination rate constant from the slope of the line, it

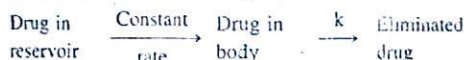
is much easier to determine k by making use of the following relationship:

$$k = 0.693/t_{1/2} \quad (1-7)$$

where $t_{1/2}$ is the half-life of the drug (i.e., the time required to reduce the concentration by 50%). This parameter is determined directly from the plot (see Fig. 1-3). In a first-order process, the half-life is independent of the dose or initial plasma concentration. One hour is required to observe a 50% decrease of any plasma concentration of the semi-synthetic penicillin, once distribution equilibrium is attained. It follows that the elimination rate constant of this drug is equal to $0.693/t_{1/2}$ or 0.693 hr^{-1} . Knowledge of the half-life or elimination rate constant of a drug is useful because it provides a quantitative index of the persistence of drug in the body. For a drug that distributes very rapidly after iv injection and is eliminated by first-order kinetics, one-half the dose will be eliminated in one half-life after administration; three-quarters of the dose will be eliminated after two half-lives. Only after four half-lives will the amount of drug in the body be reduced to less than one-tenth the dose. For this reason, the half-life of a drug can often be related to the duration of clinical effect and the frequency of dosing.

Short-Term Constant Rate Intravenous Infusion

Few drugs should be given as a rapid intravenous injection (bolus) because of the potential toxicity that may result. Many drugs that require intravenous administration, including theophylline, procainamide, gentamicin, and many other antibiotics, are given as short-term constant rate infusions over 5 to 60 min, or longer. The following scheme describes this situation:



The rate of change of the amount of drug in the body (A) during infusion is given by

$$dA/dt = k_0 - kA \quad (1-8)$$

where k_0 is the infusion rate expressed in amount per unit time (e.g., mg/min), kA is the elimination rate, and k is the first-order elimination rate constant. This relationship assumes that the drug reaches distribution equilibrium quickly. Integrating Equation 1-8 from $t = 0$ to $t = t$ yields

$$A = k_0[1 - \exp(-kt)]/k \quad (1-9)$$

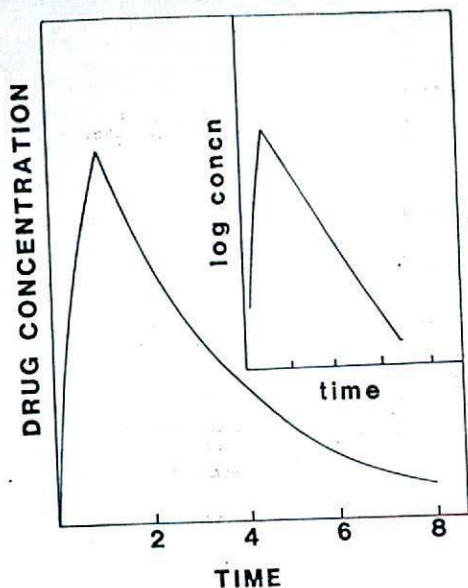


Fig. 1-4. Drug concentration in plasma during and after a 1-hr constant rate intravenous infusion. The inset shows the same data, plotted on semilogarithmic coordinates.

or

$$C = k_0[1 - \exp(-kt)]/kV \quad (1-10)$$

According to Equation 1-10, drug concentration in plasma increases during infusion. When the entire dose has been infused at time T , drug concentration reaches a maximum given by

$$C_{\max} = k_0[1 - \exp(-kT)]/kV \quad (1-11)$$

and thereafter declines. The declining drug concentration is described by

$$C = C_{\max} \exp(-kt') \quad (1-12)$$

or

$$\log C = \log C_{\max} - (kt' / 2.303) \quad (1-13)$$

where $t' = t - T$. Equations 1-12 and 1-13 apply when distribution equilibrium is essentially reached by the end of the infusion. A semilogarithmic plot of C (post-infusion drug concentration in plasma) versus t' yields a straight line, from which the half-life and elimination rate constant can be estimated. The entire drug concentration-time profile during and after a short-term infusion is shown in Figure 1-4.

Equation 1-11 may be arranged to calculate V ,

since all other terms are known. This estimate may be less than accurate but it is always better than that provided by Equation 1-6.

The maximum or peak drug concentration in plasma is always lower after intravenous infusion than after bolus injection of the same dose. The more slowly a fixed dose of a drug is infused, the lower the value of C_{\max} . Consider a rapidly distributed drug with a half-life of 3 hr. A given dose administered as an iv bolus results in an initial plasma level of 100 units. The same dose, infused over 3 hr ($T = t_{1/2}$) gives a C_{\max} value of 50 units ($C_{\max}/2$); infused over 6 hr ($T = 2t_{1/2}$), it gives a concentration of 25 units ($C_{\max}/4$). Also, since C_{\max} is a linear function of k_0 , doubling the infusion rate and infusing over the same period of time (i.e., doubling the dose) doubles the maximum concentration.

Extravascular Administration

A more complex drug concentration-time profile is observed after oral, intramuscular, or other extravascular routes of administration because absorption from these sites is not instantaneous, nor does it occur at a constant rate. As shown in Figure 1-2, the rate of change of the amount of drug in the body (dA/dt) is a function of both the absorption rate (dA_A/dt) and the elimination rate (dA_E/dt); that is,

$$\frac{dA}{dt} = \frac{dA_A}{dt} - \frac{dA_E}{dt} \quad (1-14)$$

or

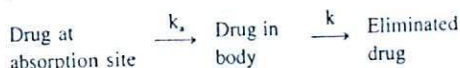
$$\frac{dC}{dt} = \frac{1}{V} \left[\frac{dA_A}{dt} - \frac{dA_E}{dt} \right] \quad (1-15)$$

where V is the apparent volume of distribution. When the absorption rate is greater than the elimination rate (i.e., $dA_A/dt > dA_E/dt$), the amount of drug in the body and the drug concentration in the plasma increase with time. Conversely, when the amount of drug remaining at the absorption site is sufficiently small so that the elimination rate exceeds the absorption rate (i.e., $dA_E/dt > dA_A/dt$), the amount of drug in the body and the drug concentration in the plasma decrease with time. The maximum or peak concentration after drug administration occurs at the moment the absorption rate equals the elimination rate (i.e., $dA_A/dt = dA_E/dt$). The faster a drug is absorbed, the higher is the maximum concentration in plasma after a given

dose, and the shorter is the time after administration when the peak is observed.

First Order In—First Order Out

Many drugs appear to be absorbed in a first-order fashion and the following scheme often applies:



Under these conditions

$$dA/dt = k_a A_s - kA \quad (1-16)$$

where k_a is the apparent first-order absorption rate constant, k is the first-order elimination rate constant, A is the amount of drug in the body, and A_s is the amount of drug at the absorption site. Integrating Equation 1-16 from $t = 0$ to $t = t$ and converting amounts to concentrations results in the complicated equation shown below:

$$C = k_a F D [\exp(-kt) - \exp(-k_a t)] / V(k_a - k) \quad (1-17)$$

where F is the fraction of the administered dose (D) that is absorbed and reaches the bloodstream. V is the apparent volume of distribution, and C is the drug concentration in plasma any time after administration. Equation 1-17 is often used to describe drug concentrations in plasma after extravascular administration.

The absorption rate constant of a drug is frequently larger than its elimination rate constant. In this case, at some time after administration, the absorption rate term in Equation 1-15 approaches zero, indicating that there is no more drug available for absorption, and Equation 1-17 simplifies to

$$C = k_a F D [\exp(-kt)] / V(k_a - k) \quad (1-18)$$

or

$$C = C_0^* \exp(-kt) \quad (1-19)$$

and

$$\log C = \log C_0^* - \frac{kt}{2.303} \quad (1-20)$$

Equation 1-18 assumes that distribution equilibrium is essentially reached by the end of the absorption phase.

When absorption is complete, the rate of change of the amount of drug in the body equals the elim-

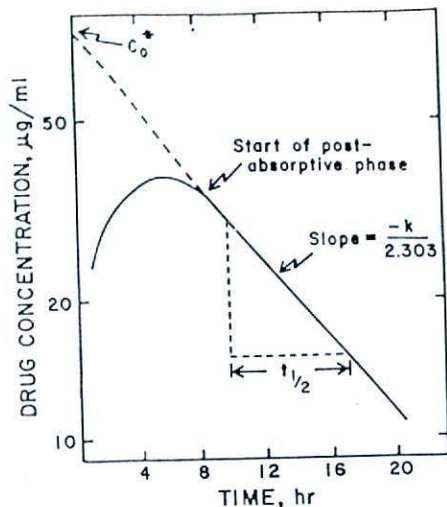


Fig. 1-5. Typical semilogarithmic plot of drug concentration in plasma following oral or intramuscular administration of a slowly absorbed form of the drug.

ination rate, and Equation 1-15 reduces to Equation 1-4. The portion of a drug concentration in the plasma versus time curve, commencing at the time absorption has ceased, is called the postabsorptive phase. During this phase, the decline in drug concentration with time follows first-order kinetics. A semilogarithmic plot of drug concentration in the plasma versus time after oral or other extravascular routes of administration usually shows a linear portion that corresponds to the postabsorptive phase. A typical plot is shown in Figure 1-5; the slope of the line is equal to $-k/2.303$.

The intercept of the extrapolated line (C_0^*) is a complex function of absorption and elimination rate constants, as well as the dose or amount absorbed and the apparent volume of distribution. It is incorrect to assume that the intercept approximates the ratio of dose to volume of distribution unless the drug is very rapidly and completely absorbed, and displays one-compartment characteristics (i.e., distributes immediately). This rarely occurs.

Occasionally, the absorption of a drug is slower than its elimination, a situation that may be found with drugs that are rapidly metabolized or excreted and with drugs that are slowly absorbed because of poor solubility or administration in a slowly releasing dosage form. When this occurs, a semilogarithmic plot of drug concentration versus time

(see Fig. 1-5) after oral administration cannot be used to estimate k or half-life because the slope is related to the absorption rate constant rather than the elimination rate constant. The drug must be administered in a more rapidly absorbed form or given intravenously.

Patient-To-Patient Variability

The time course of drug in the plasma after administration of a fixed dose may show considerable intersubject variability. The variability after intravenous administration is due to differences between patients in distribution and elimination of the drug. These differences may be related to disease or concomitant drug therapy or they may be genetic in origin. Variability is greater after intramuscular administration because, in addition to differences in distribution and elimination, absorption may be variable. Differences in absorption rate after intramuscular injection have been related to the site of injection and the drug formulation. Still greater variability may be found after oral administration. The absorption rate of a drug from the gastrointestinal tract varies with the rate of gastric emptying, the time of administration with respect to meals, the physical and chemical characteristics of the drug, and the dosage form, among other factors. Similarly, the amount of an oral dose of a drug that is absorbed depends on biologic, drug, and dosage form considerations. Many commonly used drugs are less than completely available to the bloodstream after oral administration because of incomplete absorption or presystemic metabolism.

Absorption Rate and Drug Effects

The influence of absorption on the drug concentration-time profile is shown in Figure 1-6. Administration of an equal dose in three different dosage forms results in different time courses of drug in the plasma. The faster the drug is absorbed, the greater is the peak concentration and the shorter is the time required after administration to achieve peak drug levels.

Many drugs have no demonstrable pharmacologic effect or do not elicit a desired degree of pharmacologic response unless a minimum concentration is reached at the site of action. Since a distribution equilibrium exists between blood and tissues, there must be a minimum therapeutic drug concentration in the plasma that corresponds to, though may not equal, the minimum effective con-

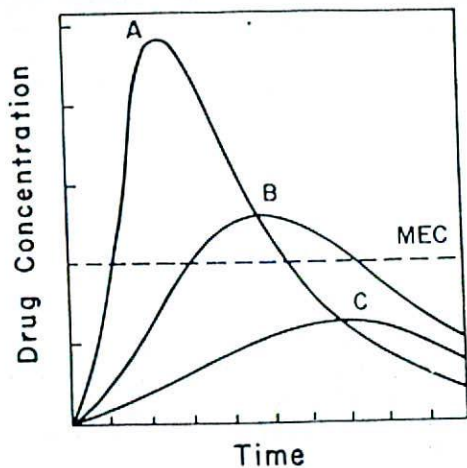


Fig. 1-6. The effects of absorption rate on drug concentration-time profile. The same amount of drug was given orally with each dosage form. The drug is absorbed most rapidly from dosage form A. Drug absorption after administration of dosage form C is slow and possibly incomplete. The dotted line represents the minimum effective concentration (MEC) required to elicit a pharmacologic effect.

centration (MEC) at the site of pharmacologic effect. Thus, the absorption rate of a drug after a single dose may affect the clinical response. For example, it is evident from Figure 1-6 that the more rapid the absorption rate, the faster is the onset of response. The drug is absorbed so slowly from dosage form C that the minimum effective level is never attained. No effect is observed after a single dose, but effects may be seen after multiple doses.

The intensity of many pharmacologic effects is a function of the drug concentration in the plasma. The data in Figure 1-6 suggest that administration of dosage form A may evoke a more intense pharmacologic response than that observed after administration of dosage form B since A produces a higher concentration of drug. When dosage form C is considered, it is clear that an active drug may be made to appear inactive by administering it in a form that results in slow or incomplete absorption.

BIOAVAILABILITY

The bioavailability of a drug is defined as its rate and extent of absorption. Rapid and complete absorption is usually desirable for drugs used on an acute or "as needed" basis for pain, allergic re-

sponse, insomnia, or other conditions. As suggested in Figure 1-6, the more rapid the absorption, the shorter is the onset and the greater is the intensity of pharmacologic response. The efficacy of a single dose of a drug is a function of both the rate and extent of absorption. In such cases, there is no assurance of the bioequivalence of two dosage forms of the same drug simply because the amount of drug absorbed from each is equivalent; the absorption rate of drug from each drug product must also be comparable. Rapid absorption may also reduce the frequency and severity of gastrointestinal distress observed after oral administration of certain drugs, including aspirin and tetracycline, by reducing the contact time in the gastrointestinal tract.

Usually, a useful estimate of the relative absorption rate of a drug from different drug products or under different conditions (e.g., with food or without food) can be made by comparing the magnitude and time of occurrence of peak drug concentrations in the plasma after a single dose.

Estimating the Extent of Absorption

The extent of absorption or relative extent of absorption of a drug from a product can be estimated by comparing the total area under the drug concentration in plasma versus time curve (AUC), or the total amount of unchanged drug excreted in the urine after administration of the product to that found after administration of a standard. The standard may be an intravenous injection, an orally administered aqueous or water-miscible solution of the drug, or even another drug product accepted as a standard. When an iv dose is used as the standard and the test product is given orally (or via some other extravascular route), we determine absolute bioavailability. If, following equal doses of the test product and the iv standard, the AUC values are the same, we conclude that the drug in the test product is completely absorbed and not subject to presystemic metabolism.

Frequently, however, the standard is an oral solution or an established product. If, following equal doses of the test product and standard, the AUC values are the same, we conclude that the test product is 100% bioavailable, *relative* to the standard; we need use the word *relative* because we do not know *a priori* that the standard is completely absorbed or completely available. When two products produce the same peak concentration of drug in

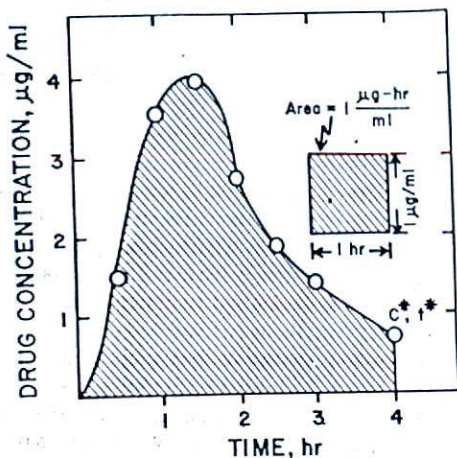


Fig. 1-7. Typical rectilinear plot of drug concentration in the plasma following an oral dose. The area under the concentration-time plot from $t = 0$ to $t = 4$ hrs is denoted by shading.

plasma and the same AUC, the products are *bioequivalent*.

The area under a drug concentration in the plasma versus time curve has the units of concentration-time (e.g., $\mu\text{g} - \text{hr}/\text{ml}$), and can be estimated by several methods. One method is to use a planimeter, an instrument for mechanically measuring the area of plane figures. Another procedure, known as the "cut and weigh method," is to cut out the area under the entire curve on rectilinear graph paper and to weigh it on an analytical balance. The weight thus obtained is converted to the proper units by dividing it by the weight of a unit area of the same paper (Fig. 1-7). The most common method of estimating area under curves is by means of the trapezoidal rule, which is described in Appendix I.

Sometimes, single dose bioavailability studies are not carried out long enough to allow drug concentrations to fall to negligible levels. We cannot determine directly the total AUC, only the partial AUC. In this case, a widely used method is to determine the AUC from $t = 0$ to the last sampling time (t^*), by means of the trapezoidal rule, and to estimate the missing area by means of the equation

$$\text{Area from } t^* \text{ to } \infty = C^*/k \quad (1-21)$$

where C^* is the drug concentration at $t = t^*$, and k is the apparent first-order elimination rate con-

stant. This area must be added to the area calculated from time zero to t^* to obtain the total area under the curve.

The total area under the drug level-time curve for drugs eliminated by first-order kinetics is given by

$$\text{AUC} = \frac{\text{Amount of drug reaching the bloodstream}}{k \cdot V} \quad (1-22)$$

It follows that the bioavailability (F) of a drug from a drug product may be determined from the expression

$$F = \frac{(\text{AUC})_{\text{Drug product}}}{(\text{AUC})_{\text{Standard}}} \quad (1-23)$$

when equal doses are administered. If different doses of the product and standard are given, the area estimates should be scaled appropriately to permit comparison under conditions of equivalent doses, assuming AUC is proportional to dose.

The amount of drug excreted unchanged in the urine (A_u) after administration is given by

$$A_u = F \cdot \text{Dose} \cdot (k_u/k) \quad (1-24)$$

where k_u is the urinary excretion rate constant and k is the overall elimination rate constant. It follows that the fraction of the dose absorbed from a drug product relative to that absorbed from a standard may be calculated from the expression

$$F = \frac{(A_u)_{\text{Drug product}}}{(A_u)_{\text{Standard}}} \quad (1-25)$$

The usefulness of Equation 1-25 depends on how much of the drug is eliminated by urinary excretion, the sensitivity of the assay for drug in urine, and the variability in urinary output of the drug. Many drugs are extensively metabolized and little, if any, appears unchanged in the urine. In such cases, bioavailability is estimated from plasma concentration data.

CONTINUOUS DRUG ADMINISTRATION

Most drugs are administered in a constant dose given at regular intervals for prolonged periods of time. For some of these drugs a therapeutic plasma concentration range has been identified. By prescribing a drug in an appropriate dosing regimen, the physician hopes to elicit a prompt and adequate clinical response. This is often predicated upon the prompt attainment of adequate drug concentration in the plasma.

Constant Rate Infusion

It is convenient to consider first the simpler case of continuous administration of a drug by intravenous infusion; this method of drug administration results in a plasma concentration-time profile that is similar in many ways to that found on intermittent repetitive dosing. Figure 1-8 illustrates the time course of drug concentration in plasma during and after infusion at a constant rate. At the outset, drug concentration increases gradually but at a diminishing rate. If infusion is continued, drug concentration eventually reaches a plateau or steady state. A steady state is reached because the amount of drug in the body reaches a level where the elimination rate, given by kA , is equal to the infusion rate (k_0). Whenever input rate equals output rate, $dA/dt = 0$, $dC/dt = 0$, and steady state exists.

By considering Equation 1-10, which describes drug concentration in plasma during constant rate infusion, at times that are sufficiently large so that $\exp(-kt)$ approaches zero, drug concentration at steady state (C_{ss}) is given by

$$C_{ss} = k_0/kV \quad (1-26)$$

Since attainment of steady state often represents the stabilization of a patient on a given course of therapy, it is of interest to know how long it takes to reach steady state. For drugs with pharmacokinetic characteristics that can be described by a one-compartment model (i.e., drugs that distribute rapidly) we have a relatively simple relationship between attainment of steady state and the half-life of the drug. One half the steady-state concentration is reached within a period of time equal to the half-life of the drug. Following a period of infusion equal to four times the half-life, the plasma concentration is within 10% of the eventual steady-state concentration.

If the time to reach steady-state represents an unacceptable delay, one may wish to use an iv bolus loading dose or a series of iv bolus minidoses before starting the infusion. The loading dose is estimated from the ratio of infusion rate (k_0) to elimination rate constant (k). This approach works well for most drugs given intravenously.

If one knows the drug level (C_{ss}) needed to produce a satisfactory response, Equation 1-26 can be used to calculate the infusion rate (k_0) needed to reach the desired level. Under these conditions, $k_0 = C_{ss} \cdot k \cdot V$ and loading dose = $C_{ss} \cdot V$.

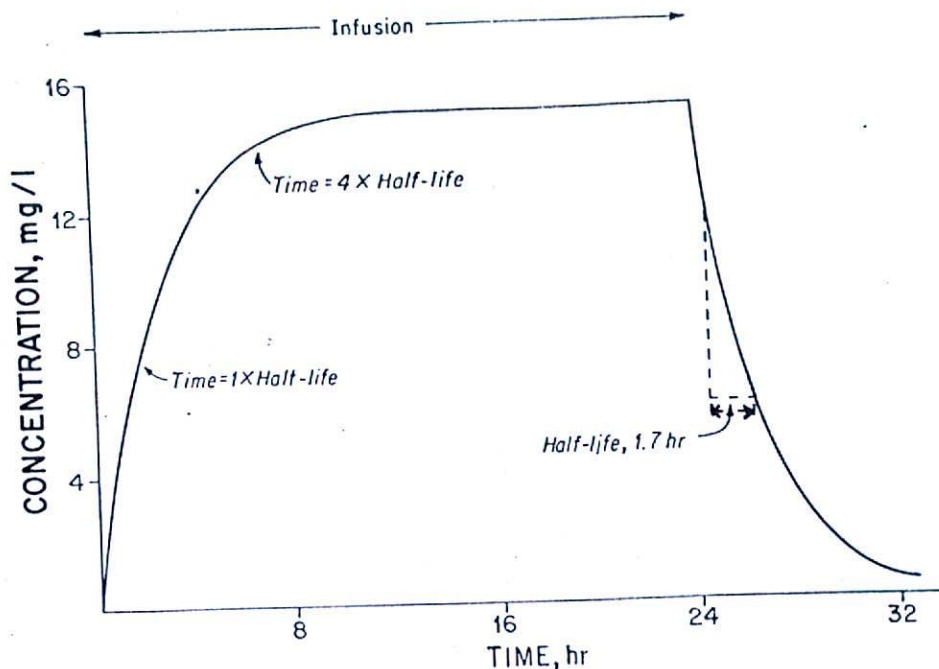


Fig. 1-8. Drug concentration in plasma during and after prolonged constant rate intravenous infusion. (From Gibaldi, M., and Levy, G.: *Pharmacokinetics in clinical practice. II. Applications.* JAMA, 235:1987, 1976. Copyright 1976. American Medical Association.)

Repetitive Dosing

Turning now to the more common case of repetitive oral administration of the same dose of a drug at regular intervals (Fig. 1-9), we find that although drug accumulates in much the same way as during constant infusion, drug concentrations in plasma during a dosing interval first increase and then decrease as a result of absorption, distribution, and elimination. The magnitude of the concentration difference in a dosing interval depends on the rates of absorption and distribution and on the half-life of the drug; this concentration difference increases with increasing absorption rate and decreasing half-life. Drugs with long half-lives or slow absorption show rather constant blood levels at steady state.

Drug concentration at any time during a dosing interval at steady state can usually be described by the following equation:

$$C_{ss} = \frac{k_a FD}{V(k_a - k)} \left[\frac{\exp(-kt)}{1 - \exp(-k\tau)} - \frac{\exp(-k_a t)}{1 - \exp(-k_a \tau)} \right] \quad (1-27)$$

where τ is the dosing interval. Equation 1-27 is too complicated to be of routine use; however, if we could estimate the maximum and minimum drug concentrations, we would be able to characterize steady state. Solving Equation 1-27 for the maximum drug concentration at steady state yields an equally complex equation. Better results are obtained when we solve for the minimum concentration at steady state, particularly if we assume that a dose is always given in the postabsorptive phase of the previous dose. Under these conditions,

$$(C_{min})_{ss} = \frac{k_a FD \exp(-k\tau)}{V(k_a - k)[1 - \exp(-k\tau)]} \quad (1-28)$$

Since the minimum drug concentration after the first dose of a repetitive dosing regimen is given by

$$C_{min} = k_a FD \exp(-k\tau)/V(k_a - k) \quad (1-29)$$

we can write a relatively simple expression for the degree of drug accumulation during multiple dosing by comparing the minimum drug concentration

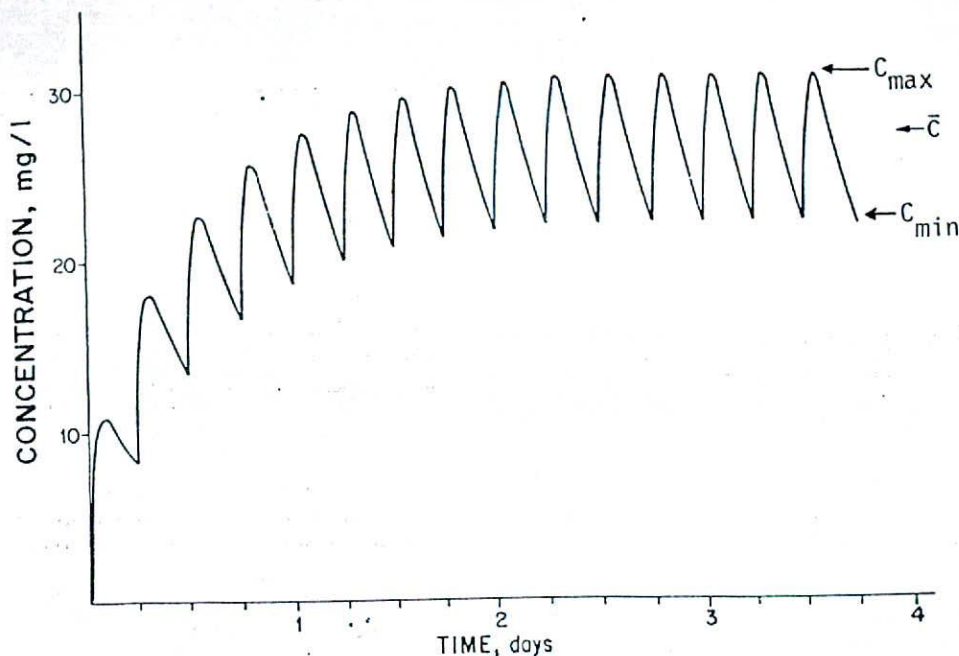


Fig. 1-9. Drug concentration in plasma during repetitive oral administration of 250 mg every 6 hr. The maximum (C_{max}), minimum (C_{min}), and average (\bar{C}) drug concentrations at steady state are noted. (From Gibaldi, M., and Levy, G.: Pharmacokinetics in clinical practice. II. Applications. JAMA, 235:1987, 1976. Copyright 1976, American Medical Association.)

at steady state to that after the first dose. Dividing Equation 1-28 by Equation 1-29 yields

$$\begin{aligned} \text{Accumulation} &= (C_{min})_{ss}/C_{min} \quad (1-30) \\ &= 1/[1 - \exp(-k\tau)] \end{aligned}$$

Therefore, by merely knowing the elimination rate constant (k) or half-life of a drug we can predict the degree of accumulation for a given dosing regimen. If a drug is given every half-life ($\tau = t_{1/2}$) the accumulation at steady state will be about 2-fold relative to the first dose.

Some drugs, including the penicillins and cephalosporins, are given less frequently than once every half-life. These drugs have half-lives in the order of 1 hr, but are usually given every 6 to 8 hr. Virtually no accumulation is observed on repeated administration. Many drugs, such as diazepam, amiodarone, phenobarbital, and digoxin, are given more frequently than once every half-life. For these drugs the half-life is greater than one day

but they are given either several times a day or once a day. Drug accumulation may be substantial.

When appropriate, it has become increasingly common to administer a drug once every half-life. The current use of theophylline, procainamide, phenytoin, and tricyclic antidepressants reflects this trend.

Average Drug Concentration at Steady State

An alternative and simpler way of describing steady state is to consider the average drug concentration (\bar{C}_{ss}), which is analogous to the steady-state concentration during continuous infusion. If drug concentration during each dosing interval is viewed in terms of an average concentration, we can express the intermittently administered dose in terms of an average dosing rate. For example, 100 mg given every 4 hr can be viewed as a 25 mg/hr average dosing rate. When based on these considerations, Equation 1-26 for a constant rate intravenous infusion can be applied to the intermittent oral administration of a drug with one additional

provision; allowance must be made for the possibility that absorption of the drug is less than complete. Then,

$$\bar{C}_{ss} = F(\text{average dosing rate})/V_k \quad (1-31)$$

where F is the fraction of the administered dose that actually reaches the bloodstream. The properties and usefulness of \bar{C}_{ss} are discussed in greater detail in Chapter 2.

Loading Dose

Whether a drug is given by continuous intravenous infusion or by repetitive oral administration, it usually requires about 4 times the half-life of the drug to reach an average concentration within 10% of the steady-state concentration. In some instances, this may represent too long a period to wait for optimum drug effects, and an initial loading dose is used.⁷

Assuming that it is clinically acceptable to do this in a single dose, one can estimate a loading dose based on the usual maintenance dose and elimination rate constant of the drug as follows:

$$\text{Loading dose} = \frac{\text{Maintenance dose}}{1 - \exp(-k\tau)} \quad (1-32)$$

This loading dose will provide a drug concentration τ hr after administration that is equal to the minimum drug concentration at steady state following repetitive administration of the maintenance dose. If a drug is administered every half-life, the appropriate loading dose is 2 times the maintenance dose. Therapy with tetracycline ($t_{1/2} = 8$ hr) is often initiated with a 500-mg loading dose followed by 250 mg every 8 hr.

The difference between loading dose and maintenance dose depends on the dosing interval and the half-life of the drug. Digoxin, which has a half-life of about 44 hr but is administered once a day, is typically given as a loading dose of 1.0 to 1.5 mg followed by daily doses of 0.125 to 0.5 mg; the ratio of loading dose to maintenance dose is about 3 or 4. The half-life of digitoxin is about 6 days; typically digitoxin therapy is initiated with a loading dose of up to 1.6 mg followed by daily doses of 0.1 to 0.2 mg; the ratio of loading dose to maintenance dose is usually about 10. The smaller the ratio of dosing interval to half-life, the larger is the ratio of loading dose to maintenance dose.

Loading of drugs may be hazardous, particularly

for those drugs which distribute slowly or to which patients become accustomed only gradually. Caution should be applied at all times. With digoxin or digitoxin therapy, loading (or digitalization) is almost always carried out with 3 or 4 divided doses over the first 1 or 2 days of therapy.

Treatment of epileptic patients with phenytoin is often initiated with a regular maintenance dose, divided or single, of 300 to 400 mg daily. When phenytoin therapy is begun in this manner, steady-state plasma phenytoin levels are achieved after 7 to 10 days. Some clinicians believe, however, that in the patient with frequent seizures a delay in reaching the therapeutic steady-state phenytoin plasma level may be detrimental because attacks may occur before the drug develops its full anticonvulsant effect. Several clinical investigators have suggested initial loading of selected patients with phenytoin.^{1,2} In one study,² 61 patients received a 1-g loading dose of phenytoin followed by a constant daily maintenance dose of 300 to 400 mg. Seizure control was obtained promptly in all patients who responded to the drug. Patients tolerated the loading doses well, and therapeutic phenytoin levels were achieved rapidly. Studies in children have confirmed the efficacy but have raised questions regarding the safety of this approach.³

It is well recognized that more than a week of treatment with a given maintenance dose of guanethidine may be required to produce the maximum antihypertensive effect of this dose. This results from the fact that elimination of the drug from the body is slow (average half-life about 5 days). A regimen has been devised for achieving the pharmacologic effects of guanethidine relatively rapidly, using the concept of loading and maintenance doses based on the kinetics of guanethidine elimination.⁴ This regimen was tested in 6 hypertensive patients. Reduction of blood pressure was achieved with individualized divided loading doses of 150 to 525 mg guanethidine administered over a period of 1 to 3 days. Maintenance doses ranging from 20 to 65 mg per day were calculated from the loading dose by assuming a daily loss of about one seventh of the body stores of drug. Satisfactory control of blood pressure was maintained following the guanethidine load, without side effects.

Dosing Interval

The frequency of dosing is often based on tradition and usage (e.g., the t.i.d. or q.i.d. regimen). From a pharmacokinetic point of view, however,

a rational dosing interval for most drugs approximates the biologic half-life. Thus, it has been found that the traditional 3-times-a-day dose of phenytoin, a drug with an average half-life of about one day, is unnecessary in many patients and that the total daily dose can often be administered once a day.⁵

Similar conclusions have been reached with respect to dosing of griseofulvin. Comparable steady-state plasma levels of griseofulvin are achieved whether the drug is given in doses of 125 mg 4 times a day or in a single daily dose of 500 mg.⁶ Apparently, treatment with griseofulvin can be simplified to once-a-day administration with no loss of efficacy or safety.

Many neuroleptics and tricyclic antidepressants have rather long biologic half-lives. Almost from the beginning of psychopharmacotherapy, certain clinicians have recognized that the traditional t.i.d. or q.i.d. division of drug administration is not as necessary as generally believed and that single daily doses are sufficient for many patients, particularly those on maintenance therapy.⁷

For the past 15 years, the most commonly used dosage of allopurinol has been 100 mg 3 times a day. Although the half-life of allopurinol is only about 1 hr, the half-life of its active metabolite, oxypurinol, is much longer, about 30 hr. In recognition of this, it has been suggested that allopurinol be administered as a single daily dose. When 300 mg of allopurinol given in a single daily dose was compared with 100 mg given 3 times a day, it was found to be equally effective in reducing and controlling uric acid levels and equally well tolerated.^{8,9} A more recent study confirmed these results and found that 27 of 33 patients preferred the once-a-day regimen to the divided-dose regi-

men because it was easier to remember or easier to take and more convenient.¹⁰

Less frequent dosing may not be feasible with some rapidly absorbed drugs that produce high peak concentrations in the plasma, resulting in adverse effects. This problem may be overcome by using slow-release dosage forms. Thus, slow-release forms may be rational even for some drugs with long biologic half-lives. Presumably, once-a-day dosing of griseofulvin and certain phenytoin products is well tolerated because these drugs are absorbed rather slowly. High doses of most neuroleptics and tricyclic antidepressants tend to sedate and, for most patients, late evening administration of the total dose is preferable. This may offer the additional advantage of avoiding the need for a hypnotic drug.

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