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# Basic Principles of Pharmacokinetics*

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ABSTRACT

Pharmacokinetics may be defined as what the body does to a drug. It deals with the absorption, distribution, and elimination of drugs but also has utility in evaluating the time course of environmental (exogenous) toxicologic agents as well as endogenous compounds. An understanding of 4 fundamental pharmacokinetic parameters will give the toxicologic pathologist a strong basis from which to appreciate how pharmacokinetics may be useful. These parameters are clearance, volume of distribution, half-life, and bioavailability.

*Keywords.* Clearance; volume of distribution; half-life; bioavailability; extraction ratio

## INTRODUCTION

An understanding of the basic principles of pharmacokinetics is necessary to appreciate how this discipline may serve as a tool for the toxicologic pathologist in understanding models that can be used for predicting and assessing drug-related toxic responses. Pharmacokinetics may be defined as what the body does to a drug. It deals with the absorption, distribution, and elimination of drugs but also has utility in evaluating the time course of environmental (exogenous) toxicologic agents as well as endogenous compounds. A fundamental hypothesis of pharmacokinetics is that a relationship exists between a pharmacologic or toxic effect of a drug and the concentration of that drug in a readily accessible site of the body (e.g., blood). This hypothesis has been documented for many drugs (5, 6), although for some drugs no clear relationship has, as yet, been found between pharmacologic effect and plasma or blood concentrations. An understanding of 4 fundamental pharmacokinetic parameters will give the toxicologic pathologist a firm basis from which to appreciate how pharmacokinetics may be useful. These parameters are clearance, a measure of the body's ability to eliminate drug; volume of distribution, a measure of the apparent space in the body available to contain the drug; half-life, a measure of the time required for a substance to change from one concentration to another; and bioavailability, the fraction of drug absorbed as such as the systemic circulation. These 4 parameters will be discussed here in detail. A number of classic pharmacokinetic texts may be consulted for further elucidation of these and other more detailed principles (4, 5, 8, 12, 15).

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## CLEARANCE

Clearance is the measure of the ability of the body to eliminate a drug. Clearance is expressed as a volume per unit of time. Clearance is usually further defined as blood clearance ($CL_b$), plasma clearance ($CL_p$), or clearance based on the concentration of unbound or free drug ($CL_u$), depending on the concentration measured ($C_b$, $C_p$, or $C_u$).

Clearance by means of various organs of elimination is additive. Elimination of drug may occur as a result of processes that occur in the liver, kidney, and other organs. Division of the rate of elimination for each organ by a concentration of drug (e.g., systemic concentration) will yield the respective clearance by that organ. Added together, these separate clearances will equal total systemic clearance:

$$CL_{hepatic} + CL_{renal} + CL_{other} = CL_{systemic}. \quad (1)$$

Other routes of elimination could include that in saliva or sweat, partition into the gut, and metabolism at sites other than the liver (e.g., nitroglycerin, which is metabolized in all tissues of the body).

Figure 1 depicts how a drug is removed from the systemic circulation when it passes through an eliminating organ. The rate of presentation of a drug to a drug-eliminating organ is the product of organ blood flow (Q) and the concentration of drug in the arterial blood entering the organ ($C_A$). The rate of exit of a drug from the drug eliminating organ is the product of the organ blood flow (Q) and the concentration of the drug in the venous blood leaving the organ ($C_V$). By mass balance, the rate of elimi-

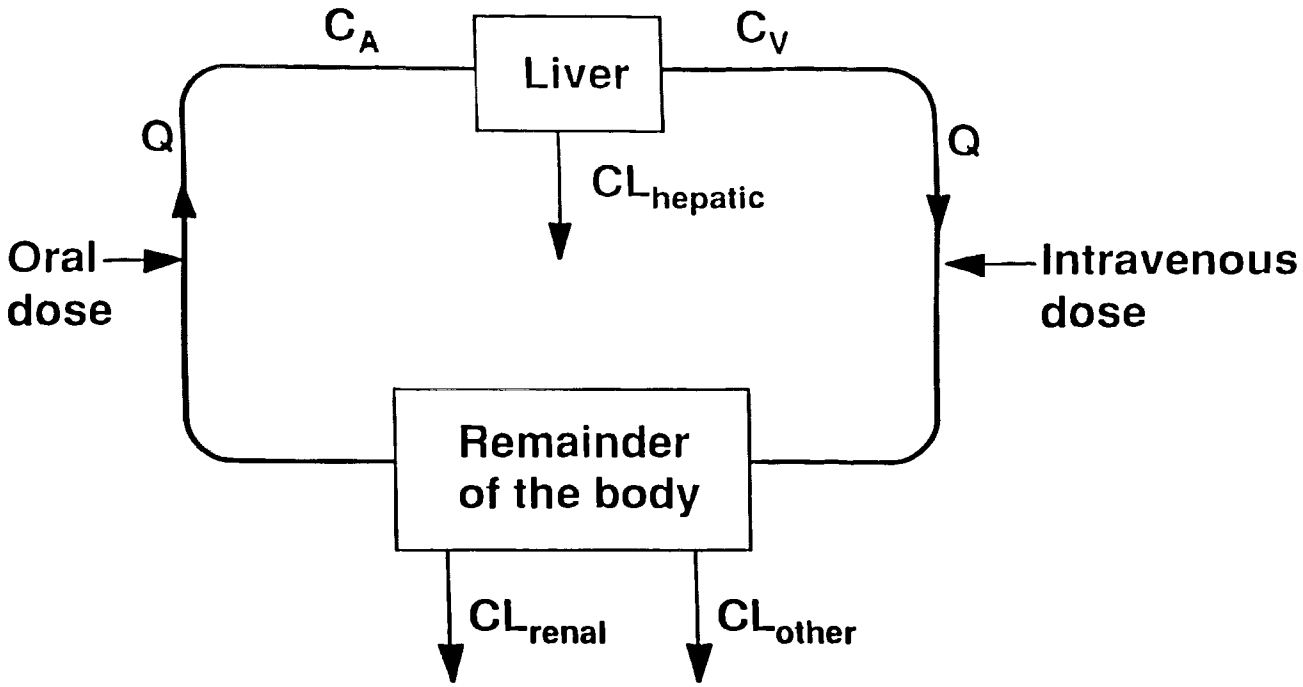


FIG. 1.—A schematic representation of the concentration–clearance relationship.

nation (or extraction) of a drug by a drug-eliminating organ is the difference between the rate of presentation and the rate of exit:

$$\text{rate of presentation} = Q \cdot C_A, \quad (2)$$

$$\text{rate of exit} = Q \cdot C_V, \quad (3)$$

$$\text{rate of elimination} = Q \cdot C_A - Q \cdot C_V = (C_A - C_V) \quad (4)$$

Extraction ratio (ER) of an organ can be defined as the ratio of the rate of elimination to the rate of presentation:

$$ER = \frac{Q \cdot (C_A - C_V)}{Q \cdot C_A} = \frac{(C_A - C_V)}{C_A} \quad (5)$$

The maximum possible extraction ratio is 1.0 when no drug emerges into the venous blood upon presentation to the eliminating organ (i.e., $C_V = 0$). The lowest possible extraction ratio is zero when all the drug passing through the potential drug-eliminating organ appears in the venous blood (i.e., $C_V = C_A$). Drugs with an extraction ratio more than 0.7 are by convention considered as high extraction ratio drugs, whereas those with an extraction ratio less than 0.3 are considered as low extraction ratio drugs.

The product of organ blood flow and extraction ratio of an organ represents a rate at which a certain volume of blood is completely cleared of a drug. This expression defines the organ clearance ($CL_{organ}$) of a drug.

$$CL = Q \cdot ER = Q \cdot \frac{(C_A - C_V)}{C_A} \quad (6)$$

It is obvious from Equation 6 that an organ's clearance is limited by the blood flow to that organ (i.e., when ER = 1). Among the many organs that are capable of eliminating drugs, the liver has the highest metabolic capability. The liver may also clear drug by excretion in the bile. Kidney eliminates drugs primarily by excretion into the urine, but kidney metabolism may occur for some drugs.

Drug in blood is bound to blood cells and plasma proteins such as albumin and $\alpha_1$-acid glycoprotein. Only unbound drug molecules can pass through hepatic membranes into the hepatocytes where they are metabolized by hepatic enzymes or transported into the bile. Thus, to be eliminated, the drug molecules must partition out of the red blood cells and dissociate from plasma proteins to become unbound or free drug molecules. The ratio of the unbound drug concentration ($C_u$) to total drug concentration (C) is defined as the fraction unbound ($f_u$):

$$f_u = \frac{C_u}{C} \quad (7)$$

Because an equilibrium exists between the unbound drug molecules in the blood cells and the plasma, the rate of elimination of unbound drugs is the same in the whole blood as in the plasma at steady state. Thus,

$$CL_p \cdot C_p = CL_b \cdot C_b = CL_u \cdot C_u, \quad (8)$$

where the subscripts p, b, and u refer to plasma,

Since the pioneering discussions of clearance in the early 1970s (11, 13), much has been made of the differences between high and low clearance (extraction ratio) drugs and the interpretation of the effects of pathological and physiologic changes on the kinetics of drug elimination processes. Utilizing the simplest model of organ elimination, designated the venous equilibration or well-stirred model, the blood clearance of an organ can be expressed according to the following relationship:

$$CL_{organ} = Q_{organ} \cdot \frac{(f_u)_b \cdot CL_{int}}{Q_{organ} + (f_u)_b \cdot CL_{int}} \quad (9)$$

Here, $(fu)_b$ represents fraction unbound in the blood and $CL_{int}$ represents intrinsic clearance of the organ, that is, the ability of the organ to clear unbound drug when there are no limitations due to flow or binding considerations. Knowing that organ clearance is equal to the product of organ blood flow and extraction ratio of the organ (Equation 6), according to the well-stirred model, then

$$ER_{organ} = \frac{(f_u)_b \cdot CL_{int}}{Q_{organ} + (f_u)_b \cdot CL_{int}} \quad (10)$$

Examining Equations 9 and 10, one finds that for drugs with a low extraction ratio $Q_{organ}$ is much greater than $(f_u)_b \cdot CL_{int}$; thus, clearance is approximated by $(f_u)_b \cdot CL_{int}$. However, in the case of a high extraction ratio drug (i.e., ER approaching 1.0), $(f_u)_b \cdot CL_{int}$ is much greater than $Q_{organ}$, and clearance approaches $Q_{organ}$. Therefore, the clearance of a high extraction ratio drug is perfusion rate–limited. Equations 11 and 12 describe these two cases:

If $Q_{organ} \gg (f_u)_b \cdot CL_{int}$, then

$$CL_{organ} \approx (f_u)_b \cdot CL_{int} \quad (ER < 0.3, \text{low ER}) \quad (11)$$

If $Q_{organ} \ll (f_u)_b \cdot CL_{int}$, then

$$CL_{organ} \approx Q_{organ} \quad (ER > 0.7, \text{high ER}) \quad (12)$$

Examples of low and high extraction ratio drugs are chlordiazepoxide and imipramine, respectively. The pharmacokinetic parameters for both drugs in humans are shown in Table I (6). Due to the low recovery in the urine (% excreted unchanged), one may assume that these drugs are mainly eliminated by the liver. Thus, hepatic extraction ratios for chlordiazepoxide and imipramine are 0.02 and 0.7, respectively. Note that the value of $(f_u)_b \cdot CL_{int}$ (35.8) for chlordiazepoxide is much lower than liver blood flow (1,500 ml/min) and conversely the value of $(f_u)_b \cdot CL_{int}$ for imipramine is more than twice the value of liver blood flow. Thus, elimination (clearance) of chlordiazepoxide is limited by fraction unbound and the intrinsic clearance of the liver, where-

TABLE I.—Pharmacokinetic parameters of chlordiazepoxide and imipramine in 70-kg humans.

| Pharmacokinetic parameter | Chlordiazepoxide | Imipramine |
|---|---|---|
| CL (ml/min) | 35 | 1,050 |
| % Excreted unchanged | <1 | <2 |
| $ER_{hepatic}$ | 0.02 | 0.7 |
| % Protein bound | 96.5 | 94.8 |
| F (%) | 100 | 27 |
| $t_{1/2}$ (hr) | 10 | 18 |
| $V_d$ (L) | 21 | 1,600 |
| $CL_{int}$ (ml/min) | 1,025 | 67,310 |
| $(f_u)_b \cdot CL_{int}$ | 35.8 | 3,500 |

Elimination of both chlordiazepoxide and imipramine were studied in an *in vitro* rat microsomal system prepared from livers of rats that were injected with phenobarbital (an inducer of the P-450 enzyme family). In this *in vitro* system, the elimination of both drugs was higher in the phenobarbital-induced microsomes than in control microsomes. *In vivo* measured clearance of chlordiazepoxide in rats who had received phenobarbital was higher than the control rats (no phenobarbital administration). This is due to the fact that induction of enzymes by phenobarbital increases the hepatic $CL_{int}$ and, because for this low extraction ratio drug $CL_{hepatic} \approx (f_u)_b \cdot CL_{int}$, a higher CL is measured in the presence of phenobarbital. In contrast, the *in vivo* measured clearance of imipramine in rats that received phenobarbital could not be differentiated from that measured in control rats. This is due to the fact that the value of $(f_u)_b \cdot CL_{int}$ for imipramine is already greater than liver blood flow. Thus, *in vivo*, liver blood flow is the limiting factor for the elimination of this drug and, because of this, enzyme induction will not substantially affect clearance of imipramine.

The ability of an organ to clear a drug is directly proportional to the activity of the metabolic enzymes in the organ. In fact, it is now well recognized that the product $(f_u)_b \cdot CL_{int}$ is the parameter best related to the Michaelis-Menten enzymatic saturability parameters of maximum velocity ($V_{max}$) and the Michaelis constant ($K_m$) as given in Equation 13, where $C_{organ}$ is the total (bound + unbound) concentration of drug in the organ of elimination:

$$(f_u)_b \cdot (CL_{int}) = \frac{V_{max}}{K_m + C_{organ}} \quad (13)$$

Thus, only low extraction ratio drugs will exhibit saturable elimination kinetics following intravenous dosing. However, as shown subsequently in Equation 29, AUCs (area under the curves) following oral doses will be inversely related to $CL_{int}$ for both high and low extraction ratio drugs.

regimen, whereby after some time drug concentrations reach a steady-state level. At steady state, the rate of drug input to the body is equal to the rate of drug elimination from the body. The input rate is given by the dosing rate (dose/$\tau$, where $\tau$ is the dosing interval) multiplied by the drug availability (F), whereas the rate of elimination is given by clearance multiplied by the systemic concentration (C). That is, at steady state,

$$\text{input rate} = \text{elimination rate}, \tag{14}$$

$$\frac{F \cdot (\text{dose})}{\tau} = (CL) \cdot (C) \tag{15}$$

When Equation 15 is integrated over all time from 0 to infinity, Equation 16 results:

$$F \cdot (\text{dose}) = (CL) \cdot (AUC), \tag{16}$$

where AUC is the area under the concentration–time curve and F is the fraction of dose available to the systemic circulation.

Thus, clearance may be calculated as the available dose divided by the AUC:

$$CL = \frac{F \cdot (\text{dose})}{AUC} \tag{17}$$

As described in the text following Equation 12, the maximum value for organ clearance is limited by the blood flow to the organ. The average blood flows to the kidneys and the liver are, respectively, approximately 72 and 90 L/hr.

## Volume of Distribution

Volume of distribution (V) relates the amount of drug in the body to the concentration of drug in the blood or plasma, depending on the fluid in which concentration is measured. This relationship is defined by Equation 18:

$$V = \frac{\text{amount of drug in the body}}{C} \tag{18}$$

For an average 70-kg human, the plasma volume is 3 L, the blood volume is 5.5 L, the extracellular fluid outside the plasma is 12 L, and the total body water is approximately 42 L. However, many classical drugs exhibit volumes of distribution far in excess of these known fluid volumes. The volume of distribution for digoxin in a healthy volunteer is about 700 L, which is approximately 10 times greater than the total body volume of a 70-kg human. This serves to emphasize that the volume of distribution does not represent a real volume. Rather, it is an apparent volume that should be considered as the size of the pool of body fluids that would be required if the drug were equally distributed throughout all portions of the body. In fact, the relatively hydrophobic digoxin has a high apparent volume of distribution because it distributes predominantly into muscle and adipose tissue, leaving only a very small amount of drug in the plasma in which the concentration of drug is measured.

At equilibrium, the distribution of a drug within the body depends on binding to blood cells, plasma proteins, and tissue components. Only the unbound drug is capable of entering and leaving the plasma and tissue compartments. Thus, the apparent volume can be expressed as follows:

$$V = V_p + V_{TW}\frac{f_u}{f_{u,T}}, \tag{19}$$

where $V_p$ is the volume of plasma, $V_{TW}$ is the aqueous volume outside the plasma, $f_u$ is the fraction unbound in plasma, and $f_{u,T}$ is the fraction unbound in tissue. Thus, a drug that has a high degree of binding to plasma proteins (i.e., low $f_u$) will generally exhibit a small volume of distribution. Unlike plasma protein binding, tissue binding of a drug cannot be measured directly. Generally, this parameter is assumed to be constant unless indicated otherwise.

Several volume terms are commonly used to describe drug distribution, and they have been derived in a number of ways. The volume of distribution defined in Equation 19, considers the body as a single homogeneous pool (or compartment) of body fluids. In this 1-compartment model, all drug administration occurs directly into the central compartment (the site of measurement of drug concentration, usually plasma), and distribution of drug is considered to be instantaneous throughout the volume. Clearance of drug from this compartment occurs in a first-order fashion, as defined in Equation 20; that is, the amount of drug eliminated per unit time depends on the amount (concentration) of drug in the body compartment. Figure 2A and Equation 20 describe the decline of plasma concentration with time for a drug introduced into this compartment:

$$C = \frac{\text{dose}}{V}\exp^{(-kt)}, \tag{20}$$

where k is the rate constant for elimination of the drug from the compartment. This rate constant is inversely related to the half-life of the drug ($k = 0.693/t_{1/2}$).

In this case (Fig. 2A), drug concentrations were measured in plasma 2 hr after the dose was administered. The semi-logarithmic plot of plasma concentration versus time appears to indicate that the drug is eliminated from a single compartment by a first-order process (Equation 20) with a half-life of 4 hr ($k = 0.693/t_{1/2} = 0.173\ hr^{-1}$). The volume of distribution may be determined from the value of

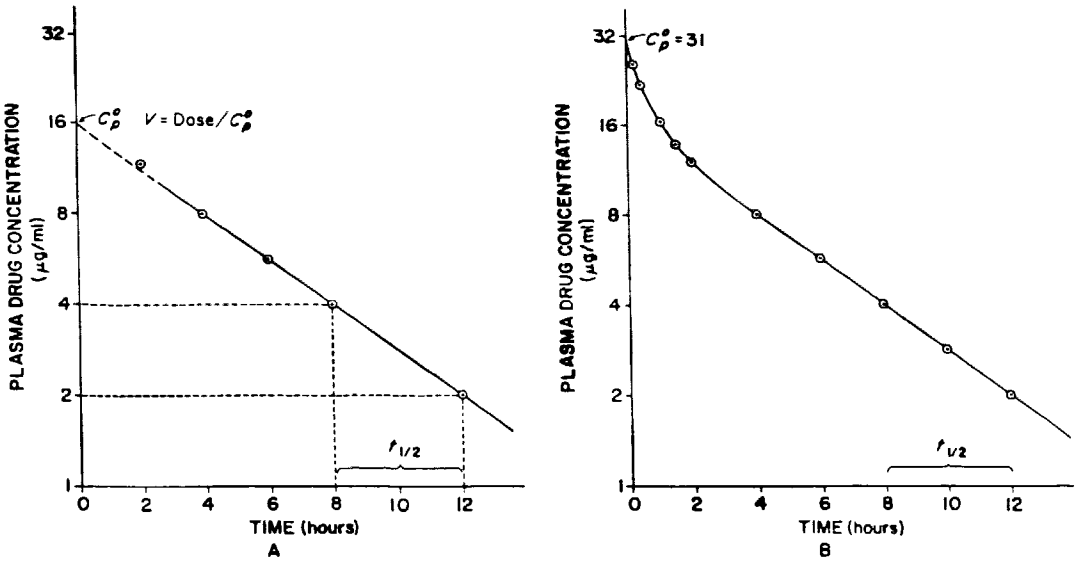


FIG. 2.—Plasma concentration–time curves following intravenous administration of a drug (500 mg) to a 70-kg human.

$C_p$ obtained by extrapolation to t = 0 ($C_p^0$ = 16 μg/ml). In this example, the volume of distribution for the 1-compartment model is 31.3 L or 0.45 L/kg (V = dose/$C_p^0$). The clearance for this drug is 92 ml/min; for a 1-compartment model, CL = k·V.

For most drugs, however, the idealized 1-compartment model discussed earlier does not describe the entire time course of the systemic concentrations. That is, certain tissue reservoirs can be distinguished from the central compartment, and the drug concentration appears to decay in a manner that can be described by multiple exponential terms (Fig. 2B). Two different terms have been used to describe the volume of distribution for drugs that follow multiple exponential decay. The first, designated $V_{area}$, is calculated as the ratio of clearance to the rate constant describing the terminal decline of concentration during the elimination (final) phase of the logarithmic concentration versus time curve:

$$V_{area} = \frac{CL}{k} = \frac{(dose)}{k \cdot (AUC)} \qquad (21)$$

The calculation of this parameter is straightforward, and the volume term may be determined after administration of drug by intravenous or enteral routes (where the dose used must be corrected for bioavailability). However, another multicompartment volume of distribution may be more useful, especially when the effect of disease states on pharmacokinetics is to be determined. The volume of distribution at steady state ($V_{ss}$) represents the volume in which a drug would appear to be distributed during steady state if the drug existed throughout that volume at the same concentration as that in the measured fluid (plasma or blood). This volume can be determined by the use of areas, as described by Benet and Galeazzi (3):

$$V_{ss} = \frac{(dose)_{iv} \cdot (AUMC)}{(AUC)^2}, \qquad (22)$$

where AUMC is the area under the first moment of the curve that describes the time course of the plasma or blood concentration, that is, the area under the curve of the product of time t and plasma or blood concentration C over the time span 0 to infinity.

Although $V_{area}$ is a convenient and easily calculated parameter, it varies when the rate constant for drug elimination changes, even when there has been no change in the distribution space. This is because the terminal rate of decline of the concentration of drug in blood or plasma depends not only on clearance but also on the rates of distribution of drug between the central and final volumes. $V_{ss}$ does not suffer from this disadvantage (4).

In the case of the example given in Fig. 2, sampling before 2 hr indicated that the drug follows multiexponential kinetics. The terminal disposition half-life is 4 hr, clearance is 103 ml/min (calculated from a measurement of AUC and Equation 17), $V_{area}$ is 28 L (Equation 21), and $V_{ss}$ is 25.4 L (Equation 22). The initial, or "central," distribution volume for the drug (V = dose/$C_p^0$) is 16.1 L. This example indicates that multicompartment kinetics may be overlooked when sampling at early times is neglected. In this particular case, there is only a 10% error

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