8

Clearance Concepts

Pharmacokinetic theory of drug elimination has traditionally been based on rate concepts, and the apparent efficiency of elimination processes has usually been described in terms of first-order rate constants or half-lives. This approach has certainly been appropriate and useful for many applications but leads to rather serious problems when one wishes to apply pharmacokinetics in an anatomical/physiological context and to examine drug elimination in a mechanistic sense. An alternative approach that has been found to be much more valuable for such applications is the use of *clearance* parameters to characterize drug disposition.

ORGAN CLEARANCE

The best way to understand *clearance* is to consider the situation in a single, well-perfused organ that is capable of drug elimination (see Fig. 8.1). Blood flow through the organ is denoted as Q (ml/min). The drug concentration in the arterial blood entering the organ is C_A, whereas that in the venous blood leaving the organ is C_V. If the organ metabolizes or excretes some of the drug, $C_V < C_A$.

The rate at which drug enters the organ is given by the product of C_A and Q, whereas the rate at which drug leaves the organ is given by the product of C_V and Q. Mass-balance considerations dictate that the rate of drug elimination by the organ is equal to the difference between the rate in and the rate out:

$$\text{Rate of elimination} = C_A Q - C_V Q = Q(C_A - C_V) \qquad (8.1)$$

If one compares the rate of drug elimination with the rate at which drug enters the organ, one obtains a dimensionless quantity that is termed the extraction ratio, ER:

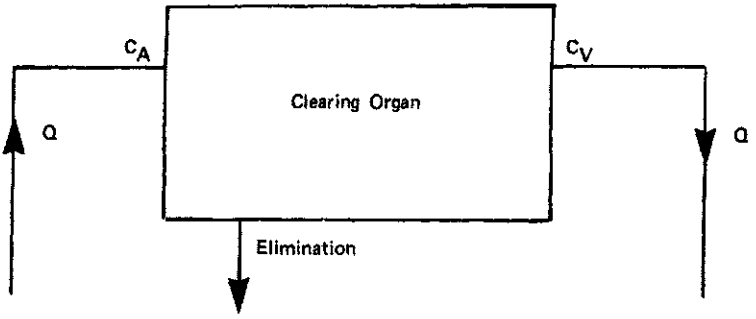

Fig. 8.1 Flow model for drug clearance by an organ. The term Q denotes blood flow rate through the organ and the terms C_A and C_V denote drug concentrations in arterial and venous blood, respectively. If the organ is a site of drug elimination, $C_V < C_A$.

$$ER = \frac{Q(C_A - C_V)}{QC_A} = \frac{C_A - C_V}{C_A} \tag{8.2}$$

The extraction ratio quantifies the efficiency of the organ with respect to drug elimination under fixed conditions of flow. If the organ is incapable of eliminating the drug, $C_A = C_V$ and the extraction ratio is zero. On the other hand, if the organ is so efficient in metabolizing or excreting the drug that $C_V \simeq 0$ the extraction ratio approaches unity.

We can also think of the extraction ratio as an index of how efficiently the organ clears the blood flowing through it of drug. For example, an extraction ratio of 0.8 tells us that 80% of the blood flowing through the organ will be completely cleared of drug. Following this line of reasoning, we can define the organ clearance of a drug as the product of extraction ratio and flow:

$$Cl = \frac{Q(C_A - C_V)}{C_A} = Q \cdot ER \tag{8.3}$$

It follows that the ratio of clearance to flow is equal to the extraction ratio.

We can also infer from Eq. (8.3) that clearance is the ratio of elimination rate to the drug concentration in blood entering the organ. This relationship makes it relatively easy to determine the renal clearance of any drug that is excreted, to some measurable extent, unmetabolized in the urine. The excretion rate of a drug can be estimated by determining the drug concentration in a volume of urine collected for relatively short, known periods of time after administration. By dividing the excretion rate by the drug concentra-

tion in plasma or blood at the midpoint of the urine collection period, one can estimate renal clearance. The same method can also be used under certain conditions to estimate biliary clearance.

TOTAL CLEARANCE

The total clearance of drug from the body almost always involves more than one organ. By definition, total or systemic clearance is the sum of all individual organ clearances that contribute to the overall elimination of a drug. However, the only organ clearance that can be routinely determined independently in humans is renal clearance because, for all practical purposes, this is the only organ for which we can easily determine an elimination rate. Therefore, a different approach is required to estimate the systemic or total clearance of most drugs.

We can state, by analogy to Eq. (8.3), that total or systemic clearance Cl_s is equal to the ratio of overall elimination rate dX/dt to drug concentration in blood or plasma C:

$$Cl_s = \frac{dX/dt}{C} \tag{8.4}$$

Integrating the right-hand side of Eq. (8.4) with respect to time from $t = 0$ to $t = \infty$, we obtain

$$Cl_s = \frac{\int_0^\infty (dX/dt)\, dt}{\int_0^\infty C\, dt} \tag{8.5}$$

The term $\int_0^\infty (dX/dt)\, dt$ is equal to the total amount of drug ultimately eliminated, or the administered dose D in the case of intravenous administration. The term $\int_0^\infty C\, dt$ is equivalent to the total area under the drug concentration in blood or plasma versus time curve, AUC. Therefore,

$$Cl_s = \frac{D}{AUC} \tag{8.6}$$

We can also show that the systemic clearance of a drug is equal to the infusion rate k_0 divided by the steady-state concentration C_{ss} of drug in blood or plasma after prolonged constant rate intravenous infusion:

$$Cl_s = \frac{k_0}{C_{ss}} \tag{8.7}$$

and that Cl_s is equal to the dosing rate divided by the average drug concentration in blood or plasma during a dosing interval at steady state after repetitive intravenous administration of fixed doses at fixed intervals, $\overline{C}_{ss}$:

$$Cl_s = \frac{\text{dosing rate}}{\overline{C}_{ss}} \tag{8.8}$$

Dosing rate is usually expressed in terms of mg/h (i.e., dose/τ), where τ is the fixed dosing interval. Equation (8.8) may be used for oral repetitive administration when complete systemic availability can be assumed. Hence for any drug we can determine renal clearance and systemic clearance.

HEPATIC CLEARANCE

The difference between systemic clearance and renal clearance is often termed nonrenal clearance. For certain drugs we can assume that nonrenal clearance is equal to hepatic clearance (i.e., the clearance of drug from the blood by the liver). For drugs that are virtually completely metabolized (i.e., renal clearance is negligible), we can sometimes assume that systemic clearance is equal to hepatic clearance. Under these conditions, it follows from Eq. (8.3) that hepatic clearance (Cl_H) is given by

$$Cl_H = Q_H \cdot ER \tag{8.9}$$

where Q_H is hepatic blood flow (about 1.5 liters/min in humans) and ER is the hepatic extraction ratio (which can range from 0 to 1).

The maximum value of Cl_H is hepatic blood flow. If the nonrenal clearance of a drug exceeds hepatic blood flow, it is evident that nonhepatic metabolism or other nonhepatic elimination processes (other than renal excretion) are taking place and that nonrenal clearance is not equal to hepatic clearance.

A cursory examination of Eq. (8.9) suggests that hepatic clearance is directly proportional to hepatic blood flow. This is not the case, however, because the extraction ratio is also dependent on hepatic blood flow. In principle, the larger the blood flow, the smaller is the extraction ratio [1]. The relationship between hepatic blood flow and extraction ratio has been derived using compartmental models [2] and using a perfusion model [3]. The latter approach is presented in this chapter.

Consider the model in Fig. 8.2 and assume that a bolus of drug is introduced into the reservoir, yielding an initial concentration C_i°. The principles of mass balance require the following relationships to exist:

$$-V_R \frac{dC_i}{dt} = Q(C_i - C_o) \tag{8.10}$$

and

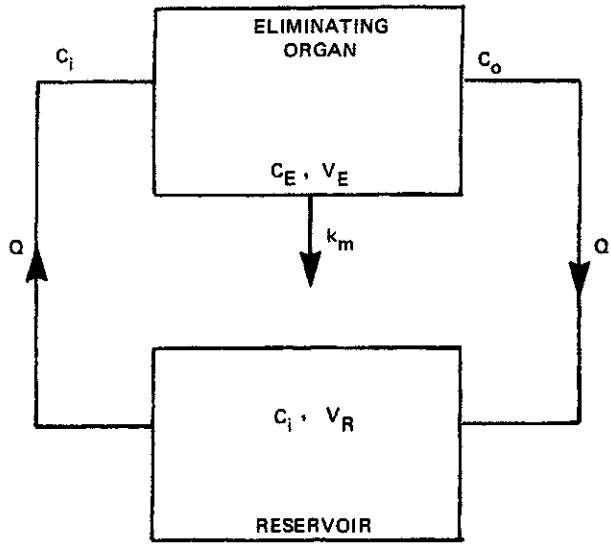

Fig. 8.2 Schematic representation of an isolated perfused organ system consisting of a reservoir and an eliminating organ. The terms are defined as follows: Q is perfusate (blood) flow rate, C_i is drug concentration in the reservoir and in the arterial blood entering the organ, C_o is drug concentration in emergent venous blood, V_E and V_R are the volumes of the eliminating organ and reservoir, respectively, and k_m is the first-order rate constant for drug elimination. C_E is the drug concentration in the eliminating organ and, in this case, is equivalent to $K_P C_o$, where K_P is a partition coefficient.

$$K_P V_E \frac{dC_o}{dt} = Q(C_i - C_o) - k_m K_P V_E C_o \qquad (8.11)$$

where C_i is the drug concentration in the reservoir and entering the eliminating organ; C_o is the drug concentration leaving the eliminating organ and entering the reservoir; V_E and V_R are the volumes of the eliminating organ and reservoir, respectively; Q is blood flow; k_m is the intrinsic first-order rate constant for drug elimination; and K_P is the apparent partition coefficient of drug between the eliminating organ and the emergent blood (i.e., $K_P = C_E/C_o$, where C_E is the drug concentration in the eliminating organ). Equation (8.10) tells us that the net rate of loss of drug from the reservoir is equal to the difference between the rate into and the rate out of the organ and Eq. (8.11) tells us that the rate of change of the amount ($V_E C_E$ or $K_P V_E C_o$) of drug in the eliminating organ is equal to the difference between the rate in QC_i and the sum of the rate out and the rate of elimination (i.e., the sum of QC_o and $k_m V_E C_E$ or $k_m K_P V_E C_o$).

Solving Eqs. (8.10) and (8.11) for C_i and C_o in the usual manner, we obtain [3]

$$C_i = C_i^\circ \frac{(Q/K_P V_E) + k_m - \alpha}{\beta - \alpha} e^{-\alpha t} + C_i^\circ \frac{(Q/K_P V_E) + k_m - \beta}{\alpha - \beta} e^{-\beta t} \tag{8.12}$$

and

$$C_o = \frac{C_i^\circ Q(e^{-\alpha t} - e^{-\beta t})}{K_P V_E(\beta - \alpha)} \tag{8.13}$$

where

$$\alpha + \beta = \frac{Q}{V_R} + \frac{Q}{K_P V_E} + k_m \tag{8.14}$$

and

$$\alpha\beta = \frac{Q k_m}{V_R} \tag{8.15}$$

Since clearance is equal to the ratio of dose to area [see Eq. (8.6)], it follows that

$$Cl = \frac{V_R C_i^\circ}{\int_0^\infty C_i \, dt} \tag{8.16}$$

Integrating Eq. (8.12) from $t = 0$ to $t = \infty$, and substituting this expression into Eq. (8.16), we obtain [3]

$$Cl = Q \frac{k_m K_P V_E}{Q + k_m K_P V_E} \tag{8.17}$$

It follows from Eq. (8.9) that

$$ER = \frac{k_m K_P V_E}{Q + k_m K_P V_E} \tag{8.18}$$

Equation (8.18) shows that the extraction ratio of a drug is a function of both the intrinsic ability of the organ to eliminate the drug, $k_m K_P V_E$, and the blood flow to the organ.

Equation (8.17) may also be derived by assuming that drug is infused into the reservoir at a constant rate k_0 until steady state is achieved, rather than administered as a single bolus. The net rate of loss of drug from the reservoir is now given by

$$-V_R \frac{dC_i}{dt} = Q(C_i - C_o) - k_0 \tag{8.19}$$

Equation (8.11) still describes the rate of change of the amount of drug in the eliminating organ. At steady state C_i and C_o are constant (i.e., $C_{i,ss}$ and $C_{o,ss}$, respectively). Therefore, $dC_{i,ss}/dt$ and $dC_{o,ss}/dt$ are equal to zero. It follows from Eqs. (8.19) and (8.11) that

$$k_o = Q(C_{i,ss} - C_{o,ss}) = k_m K_P V_E C_{o,ss} \tag{8.20}$$

and that

$$C_{i,ss} = \frac{k_m K_P V_E C_{o,ss} + QC_{o,ss}}{Q} \tag{8.21}$$

According to Eq. (8.3), clearance may be obtained by measurements across the eliminating organ:

$$Cl = \frac{Q(C_{i,ss} - C_{o,ss})}{C_{i,ss}} \tag{8.22}$$

Substituting for the numerator according to Eq. (8.20) and for $C_{i,ss}$ according to Eq. (8.21), and rearranging terms, we obtain

$$Cl = \frac{Qk_m K_P V_E C_{o,ss}}{k_m K_P V_E C_{o,ss} + QC_{o,ss}} \tag{8.23}$$

which simplifies to Eq. (8.17).

The term $k_m K_P V_E$ in Eq. (8.17) or (8.18) is equivalent to the clearance capacity or intrinsic clearance Cl_I of the organ for the specific drug. Thus we may write that

$$Cl = Q \frac{Cl_I}{Q + Cl_I} = Q \cdot ER \tag{8.24}$$

If Cl_I reflects solely hepatic metabolism of the drug by a single enzyme system, consideration of classical enzyme kinetics indicates that Cl is equivalent to the ratio of V_m (the maximum rate of metabolism) to K_m (the Michaelis constant) [4]. Experimental verification of this hypothesis has been provided for several drugs [4,5]. Examples are shown in Fig. 8.3.

Equation (8.24) tells us that the systemic clearance of a drug that is eliminated solely by metabolism in the liver is a function of both hepatic blood flow Q and the intrinsic ability of the liver to metabolize the drug, Cl_I. For many drugs, including antipyrine, most barbiturates, anticonvulsants, hypoglycemic agents, and

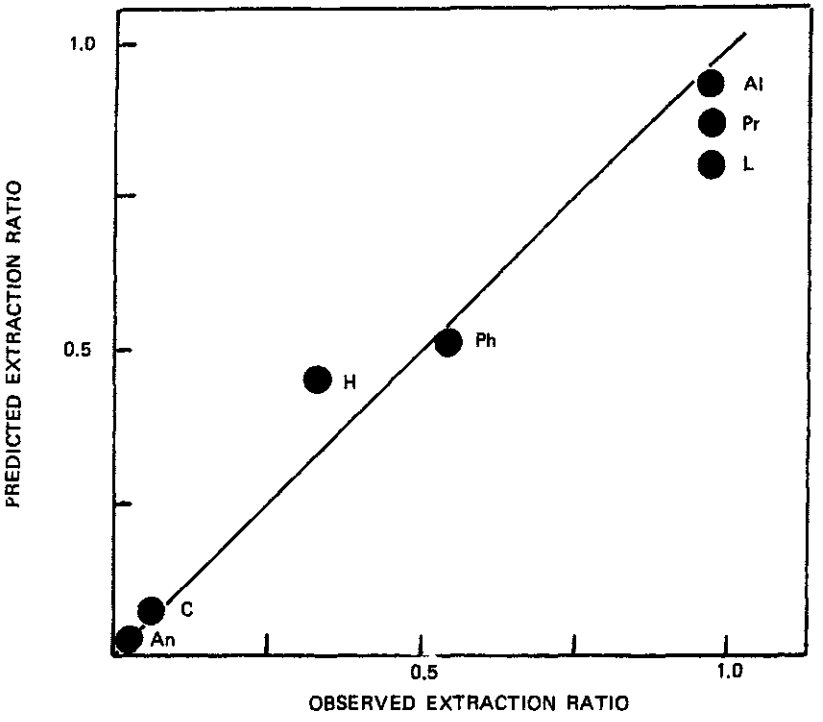

Fig. 8.3 Correlation between extraction ratios observed in an isolated perfused rat liver and those predicted from liver homogenate estimates of V_m and K_m. The drugs studied were alprenolol (Al), antipyrine (An), carbamazepine (C), hexobarbital (H), lidocaine (L), phenytoin (Ph), and propranolol (Pr). [From Ref. 4, © 1971 American Society for Pharmacology and Experimental Therapeutics. The Williams and Wilkins Company (agent).]

coumarin anticoagulants, we find that the intrinsic clearance in humans is considerably smaller than hepatic blood flow. If $Q >> Cl_I$, it follows that Eq. (8.24) reduces to

$$Cl \simeq Cl_I \tag{8.25}$$

Equation (8.25) was developed without taking plasma protein binding into consideration and is, therefore, an oversimplification for most drugs. It does, however, apply directly to antipyrine, because this drug is virtually unbound in body water and is essentially completely metabolized by the liver. In humans, the systemic clearance of antipyrine appears to be a direct measure of the liver's ability to metabolize the drug. Certain diseases, administration of drugs or chemicals that inhibit or induce enzymes in the liver, or other per-

turbations that affect the quality or quantity of hepatic microsomal enzymes or cellular access to these enzymes will proportionately affect the systemic clearance of antipyrine or similar drugs. For this reason it has been proposed that antipyrine clearance be used as an index of liver function [6].

In recent years it has come to light that some drugs, including many analgesics, tricyclic antidepressants, and beta blockers, have intrinsic clearance values in humans that significantly exceed hepatic blood flow. The systemic clearance of such drugs shows a strong dependence on hepatic blood flow. The reason for this is easily demonstrated by considering a second limiting case for Eq. (8.24). If $Cl_I >> Q$, then

$$Cl \simeq Q \tag{8.26}$$

Although this exact case is rare, Eq. (8.26) does approximate the situation for drugs such as propranolol or lidocaine. The systemic clearance of drugs that show hepatic blood flow-dependent elimination is affected by various factors that affect blood flow to the liver, including heart disease and liver disease or the administration of certain drugs that affect the cardiovascular system. On the other hand, the systemic clearance of such drugs is rather independent of factors that affect the drug-metabolizing enzymes in the liver, such as the administration of enzyme-inducing drugs or chemicals.

HEPATIC CLEARANCE AND DRUG BINDING IN BLOOD

As we have noted, the preceding discussion applies strictly to drugs that are unbound in the vascular space. However, it is well recognized that most drugs are bound to blood constituents, particularly to plasma proteins. Moreover, it has been generally believed that this binding retards hepatic metabolism or renal excretion since the availability of drug to the metabolic or excretory sites is limited to the fraction of drug in the circulating blood which is free or unbound. Although this restriction is true for many drugs, there are exceptions. It is apparent that the elimination of certain drugs is not limited to the free drug delivered to the liver or kidneys because their extraction ratio is greater than their free fraction [1]. In fact, there are examples, such as the elimination of propranolol in humans (see Fig. 8.4), where clearance is essentially independent of binding in the blood [7].

It is evident that Eq. (8.24) must be modified to take blood binding into account. The following relationship has been proposed [1] and experimentally verified [8]:

$$Cl = Q \frac{f_B Cl'_I}{Q + f_B Cl'_I} \tag{8.27}$$

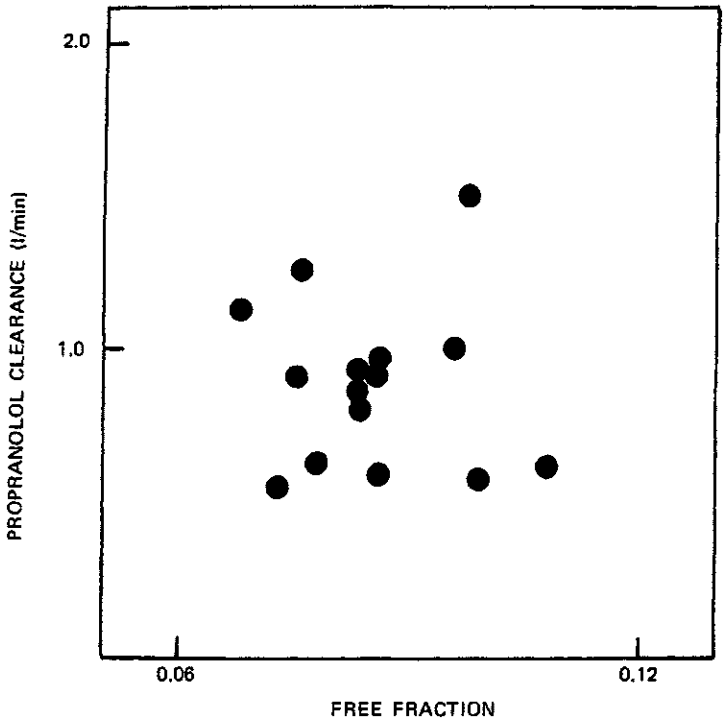

Fig. 8.4 Lack of correlation between the systemic clearance of propranolol and fraction of drug in the blood that is unbound. Because of propranolol's high hepatic extraction ratio, its clearance is largely dependent on hepatic blood flow and relatively independent of drug binding in blood or intrinsic hepatic clearance. (Data from Ref. 7.)

where f_B is the fraction free in blood [i.e., the ratio of free drug concentration in blood to total (bound and unbound) drug concentration in blood] and Cl_I' is the intrinsic clearance of free (unbound) drug. The relationship between clearance and drug binding for warfarin, phenytoin, and propranolol is shown in Fig. 8.5. Since most investigators measure the fraction free in plasma f_p rather than in blood, it is important to recognize that

$$f_B = \frac{f_P C_P}{C_B} \tag{8.28}$$

where C_P is the total drug concentration in plasma and C_B is the total drug concentration in blood. The drug concentration in blood may be calculated from the drug concentration in plasma by means of the following relationship:

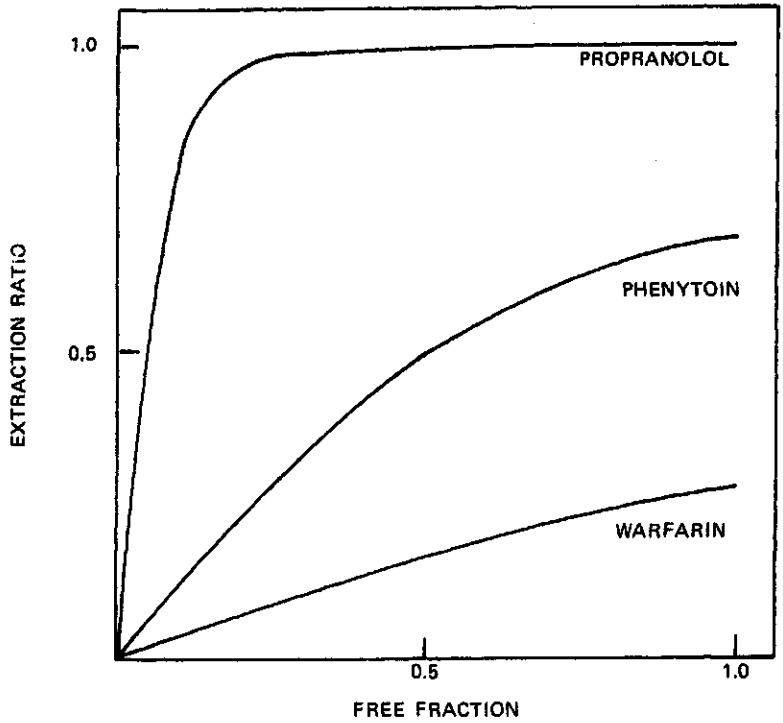

Fig. 8.5 Relationship between extraction ratio and fraction of drug in the blood that is unbound, for a drug (under physiological conditions) with a high extraction ratio (propranolol), one that has a low extraction ratio (warfarin), and a third that has an intermediate extraction ratio (phenytoin), in the isolated perfused rat liver. Throughout most of the range of free fraction values the extraction ratio of propranolol is virtually independent of drug binding, whereas that of warfarin shows an almost linear dependence on drug binding. (From Ref. 8.)

$$C_B = C_{RBC} \cdot HCT + C_P(1 - HCT) \tag{8.29}$$

where C_{RBC} is the drug concentration in the red blood cells and HCT is the hematocrit.

For drugs that show a low extraction ratio (i.e., $f_B Cl_I' << Q$), Eq. (8.27) reduces to

$$Cl = f_B Cl_I' \tag{8.30}$$

These drugs are said to be *restricted* in their hepatic metabolism. Systemic clearance is a function of both binding in the blood and the

intrinsic ability of the liver to eliminate the drug. Perturbations that affect plasma protein binding will have a direct effect on the clearance of such drugs (see warfarin and phenytoin in Fig. 8.5).

On the other hand, for drugs that show a high extraction ratio (i.e., $f_B Cl_I' >> Q$), Eq. (8.27) reduces to Eq. (8.26) (i.e., the systemic clearance approximates hepatic blood flow). The clearance of these so-called *nonrestricted* drugs is largely independent of changes in plasma protein binding (see propranolol in Fig. 8.5).

DRUG BINDING AND FREE DRUG CONCENTRATION

Since the steady-state concentration of a drug in plasma or blood is a function of clearance, it follows that a change in binding can markedly affect total drug levels at steady state of a restricted (low extraction ratio) drug, whereas the total levels at steady state of a nonrestricted (high extraction ratio) drug would be relatively unaffected. However, it is also important to consider the effect of binding on the steady-state concentration of free (unbound) drug since this is usually considered to be the pharmacologically active component. Total drug levels in blood after continuous constant rate intravenous infusion to steady state are given by

$$C_{ss} = \frac{k_0}{Cl} \tag{8.31}$$

and free drug levels are given by

$$C_{ss,free} = \frac{f_B k_0}{Cl} \tag{8.32}$$

For a restricted drug, $Cl \simeq f_B Cl_I'$. Therefore,

$$C_{ss} = \frac{k_0}{f_B Cl_I'} \tag{8.33}$$

and

$$C_{ss,free} = \frac{k_0}{Cl_I'} \tag{8.34}$$

On the other hand, for a totally nonrestricted drug, $Cl \simeq Q$. It follows that

$$C_{ss} = \frac{k_0}{Q} \tag{8.35}$$

and that

$$C_{ss,free} = \frac{f_B k_0}{Q} \tag{8.36}$$

Thus, for a poorly extracted drug, an increase in f_B can markedly affect systemic clearance and total drug levels but has little effect on free drug concentrations [see Eq. (8.34)]. Conversely, for a very well extracted drug, an increase in f_B will have little effect on systemic clearance and total drug levels but can substantially affect free drug concentrations [see Eq. (8.36)].

HALF-LIFE, INTRINSIC CLEARANCE, AND BINDING

The half-life of a drug is related to its apparent volume of distribution and its systemic clearance:

$$t_{1/2} = 0.693 \frac{V}{Cl_s} \tag{8.37}$$

In any case, we may substitute Eq. (5.48) for V, and in the case of a drug eliminated solely by hepatic metabolism, we may substitute Eq. (8.27) for Cl_s, to obtain

$$t_{1/2} = \frac{V_B + V_T(f_B/f_T)}{Q(f_B Cl_I')/(Q + f_B Cl_i')} (0.693) \tag{8.38}$$

where V_B and f_B are the volume and free fraction of drug in the vascular space, V_T and f_T are the volume and free fraction of drug in the extravascular space, and Q is the hepatic blood flow.

It follows that for a drug with a high extraction ratio

$$t_{1/2} = \frac{V_B + V_T(f_B/f_T)}{Q} (0.693) \tag{8.39}$$

whereas for a drug with a low extraction ratio

$$t_{1/2} = \frac{V_B + V_T(f_B/f_T)}{f_B Cl_I'} (0.693) \tag{8.40}$$

or

$$t_{1/2} = \left(\frac{V_B}{f_B Cl_I'} + \frac{V_T}{f_T Cl_I'} \right) 0.693 \tag{8.41}$$

Inspection of Eq. (8.39) indicates that the half-life of an unrestricted drug is a function of blood and tissue binding as well as hepatic blood flow. A change in intrinsic clearance is expected to have little effect on the half-life of a high-extraction-ratio drug. In

support of this hypothesis, the half-life of alprenolol in healthy volunteers was found to be 2.3 h before and 1.8 h during treatment with pentobarbital, an enzyme-inducing agent that increased the intrinsic clearance of the drug by more than fourfold [9]. On the other hand, a decrease in the plasma protein binding (i.e., an increase in f_B) of a drug with a high extraction ratio will increase the half-life of the drug, whereas an increase in binding results in a decrease in half-life [1]. Thus the response of such drugs to changes in binding appears to run counter to the conventional thinking that plasma protein binding protects a drug from elimination.

A similar evaluation of Eq. (8.41), which applies to a drug with a low extraction ratio, leads to more conventional conclusions. An increase in intrinsic clearance should produce a proportional decrease in half-life. An increase in plasma protein binding is predicted to produce a decrease in half-life, but the extent of the change in half-life depends on the relative magnitude of $V_B/f_B Cl_I'$ compared to $V_T/f_T Cl_I'$. If the first term predominates, an increase in binding should yield a proportional decrease in half-life. If the second term predominates, an increase in blood binding would have little effect on half-life. The latter situation appears to be the more common.

FIRST-PASS EFFECT

A particularly important characteristic of drugs that show a high hepatic extraction ratio, typified by propranolol or lidocaine, is that on oral administration *presystemic* or *first-pass* metabolism is significant and the amount of drug reaching the systemic circulation may be considerably less than the dose administered. Since the entire blood supply draining the upper gastrointestinal tract passes through the liver before reaching the general circulation, the fraction F of an oral dose that reaches the systemic circulation, assuming complete absorption, is given by

$$F = 1 - ER \tag{8.42}$$

where ER is the extraction ratio. Thus the area under the drug concentration in blood or plasma versus time curve after an oral dose of propranolol, which has a hepatic extraction ratio of 0.64 in humans [7], is only about one-third of that found on intravenous administration of the same dose.

The area under the drug concentration in blood or plasma versus time curve after oral administration of a drug that is completely absorbed and eliminated only by hepatic metabolism is, in fact, related to intrinsic hepatic clearance. Recognizing that F is simply the ratio of area under the curve after oral adminstration to that after intravenous administration and that ER is a function of intrinsic clearance and blood flow [see Eq. (8.24)], we may rewrite Eq. (8.24) as

$$\frac{AUC_{oral}}{AUC_{i.v.}} = 1 - \frac{Cl_I}{Q + Cl_I} \tag{8.43}$$

Rearranging terms and multiplying both sides of the equation by the administered dose D, we obtain

$$\frac{D(Q + Cl_I)}{(Q)AUC_{i.v.}} = \frac{D}{AUC_{oral}} = Cl_{oral} \tag{8.44}$$

The ratio of dose to AUC_{oral} has been termed the apparent oral clearance. Recognizing that $D/AUC_{i.v.}$ is the systemic clearance Cl and substituting for Cl according to Eq. (8.24), we obtain

$$Cl_{oral} = \frac{Q(Cl_I)(Q + Cl_I)}{Q(Q + Cl_I)} \tag{8.45}$$

On canceling terms we find that

$$Cl_{oral} = Cl_I = f_B Cl'_I \tag{8.46}$$

Thus, under the stated condition, we can obtain an estimate of the intrinsic hepatic clearance of total drug Cl_I by measuring the area under the curve after oral administration [2]. Furthermore, by determining the fraction free in blood, we can estimate the intrinsic clearance of free drug Cl'_I.

Equation (8.46) applies in principle to all drugs that are solely eliminated by the liver and that can be described by linear pharmacokinetics, irrespective of hepatic extraction ratio. Hence, for a drug with a low extraction ratio, the apparent clearance after oral administration (assuming complete absorption) is identical to its systemic clearance [see Eq. (8.30)]. This is not true for a drug with a high hepatic extraction ratio. The systemic clearance of such a drug is independent of Cl'_I [see Eq. (8.26)], whereas its oral clearance and the AUC resulting from oral administration are a direct function of Cl'_I. Thus various perturbations that affect liver enzyme activity may have little effect on the pharmacokinetics of a high clearance drug after intravenous administration but substantial effect after oral administration. For example, treatment with an enzyme inducer may have little effect on the systemic clearance of drugs such as propranolol, lidocaine, or imipramine but may substantially increase the first-pass effect to which the drug is subjected after oral administration, resulting in a far smaller systemic availability. In support of this hypothesis, Alvan et al. [9] report a ratio of AUC values on intravenous administration of alprenolol before and during treatment with an enzyme-inducing agent of 1.2, compared to a ratio of 4.6 on oral administration under the same conditions.

The equations presented above indicate that the area under the drug concentration in blood versus time curve after oral administration (AUC_{oral}) under conditions of constant hepatic blood flow is a function of administered dose (assuming complete absorption) and intrinsic clearance but is independent of blood flow. This is somewhat puzzling since we know that for a drug with a high extraction ratio, systemic clearance increases, extraction ratio decreases, and therefore $AUC_{i.v.}$ decreases and F increases with increasing blood flow [see Eqs. (8.18), (8.24), and (8.42)]. However, AUC_{oral} (assuming complete absorption) is given by

$$AUC_{oral} = \frac{FD}{Cl} \tag{8.47}$$

where F is the fraction of the dose escaping first-pass metabolism, and we find that an increase or decrease in hepatic blood flow from one administration to another produces exactly the same increase or decrease in both F and Cl so that there is no net effect on AUC_{oral}.

On the other hand, fluctuations in hepatic blood flow during a dosing interval may affect AUC_{oral}. For example, a higher than average hepatic blood flow during the gastrointestinal absorption of a drug with a high extraction ratio, followed by a return to normal when absorption is essentially complete but most of the drug is still in the body, will cause an increase in AUC_{oral} (see Fig. 8.6). The reason for this is that the transient increase in hepatic blood flow during absorption will have a much greater effect on the first-pass metabolism than on overall systemic clearance (i.e., F is increased more than is Cl). This phenomenon may explain why the administration of propranolol or metoprolol with a meal results in a larger AUC_{oral} than is found when the drug is given to fasted subjects [10].

Determination of the areas under the curves after intravenous and oral administration of a high extraction ratio drug permits one to estimate hepatic blood flow Q. The ratio of areas after administration of equal doses gives the systemic availability F. Assuming that absorption is complete and elimination occurs solely by hepatic metabolism, the extraction ratio is given by

$$ER = 1 - F \tag{8.48}$$

Rearranging Eq. (8.24), we obtain

$$Q = \frac{Cl}{ER} \tag{8.49}$$

where systemic clearance Cl is estimated from the ratio of intravenous dose to $AUC_{i.v.}$.

The extent to which a drug is subject to first-pass metabolism may be estimated from area-under-the-curve data obtained after oral or intravenous administration of a high extraction ratio drug [11]. Since the systemic availability of a drug is given by (8.42) and since systemic clearance is the product of Q and ER, we can show that

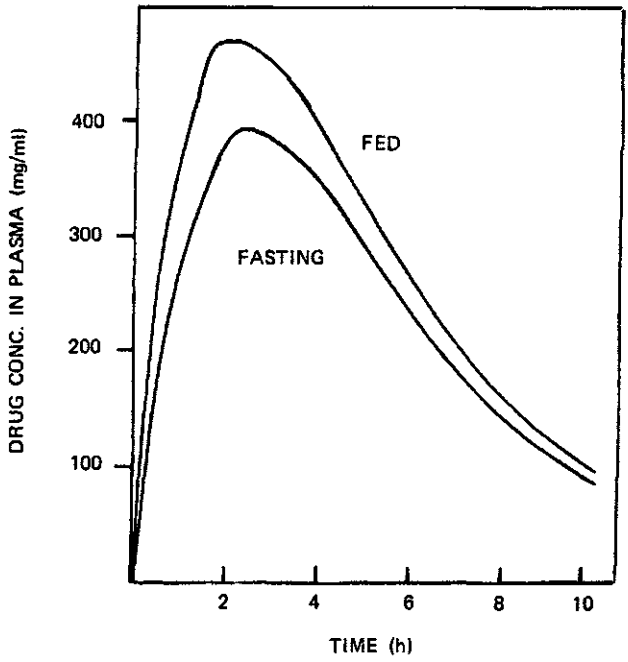

Fig. 8.6 Drug concentration in plasma after oral administration of a drug with a high hepatic extraction ratio under fasting and nonfasting conditions. The lower curve (labeled fasting) was simulated by maintaining hepatic blood flow constant at 1.5 liters/min throughout. The upper curve (labeled fed) was simulated assuming that, for the first 2 h after drug administration, hepatic blood flow was elevated to a value of 2.5 liters/min, then reduced to a value of 1.5 liters/min for the remainder of the observation period. (From Ref. 10.)

$$F = 1 - ER = 1 - \frac{Q \cdot ER}{Q} = 1 - \frac{Cl}{Q} = 1 - \frac{D}{Q \cdot AUC_{i.v.}} \qquad (8.50)$$

Thus the systemic availability of a drug subject to first-pass metabolism may be estimated from Eq. (8.50) by determining $AUC_{i.v.}$ and substituting an appropriate average value for Q (e.g., 1.5 liters/min in humans). Equation (8.50) tells us that drugs with low systemic clearances relative to hepatic blood flow will be subject to a negligible first-pass effect and will have a systemic availability after oral administration that approaches unity provided that gastrointestinal absorption is complete and chemical or enzymatic conversions in the gut are negligible. On the other hand, as systemic clearance approaches hepatic blood flow, systemic availability approaches zero.

If we multiply Eq. (8.50) by AUC_{oral}, we obtain

$$F \cdot AUC_{oral} = AUC_{oral} - \frac{D \cdot AUC_{oral}}{Q \cdot AUC_{i.v.}} \tag{8.51}$$

or

$$F \cdot AUC_{oral} = AUC_{oral} - \frac{FD}{Q} \tag{8.52}$$

Rearranging terms to solve for F, we obtain

$$F = \frac{Q}{Q + (D/AUC_{oral})} = \frac{Q}{Q + Cl_I} \tag{8.53}$$

Thus the systemic availability of a drug subject to first-pass metabolism may also be estimated from Eq. (8.53) by determining AUC_{oral} and substituting an appropriate average value for hepatic blood flow. Equation (8.53) tells that the higher the intrinsic hepatic clearance, the lower is the systemic availability of a drug.

Equations (8.50) and (8.53) apply exactly only to drugs with linear pharmacokinetic characteristics, which are absorbed completely after oral administration and are eliminated only by hepatic metabolism. Equation (8.50) may be applied to drugs that are partially excreted unchanged if Cl is replaced by hepatic clearance Cl_H. Hepatic clearance may be estimated from

$$Cl_H = Cl - Cl_r \tag{8.54}$$

where Cl is systemic or total clearance and Cl_r is renal clearance. Equation (8.54) assumes that all nonrenal clearance may be assigned to the liver.

The actual systemic availability of a drug may be less than or greater than the value predicted by Eq. (8.50). Less-than-predicted values will be observed if the drug is incompletely absorbed because of dosage form or permeability factors or if the drug is subject to chemical or metabolic breakdown in the gut. Greater-than-predicted values may be found if hepatic metabolism is capacity limited or if nonhepatic systemic metabolism is significant.

GUT WALL CLEARANCE

The systemic availability F of drugs subject to both first-pass hepatic and intestinal mucosa metabolism has also been considered [12,13]. Under certain conditions (see the model in Fig. 8.7), it can be shown that F is given by

$$F = \frac{Q_{HV}Q_{PV}}{(Q_{HV} + Cl_{HI})(Q_{PV} + Cl_{GI})} \tag{8.55}$$

where $F = (AUC)_{oral}/(AUC)_{i.v.}$, Q_{HV} is total hepatic blood flow, (i.e., the sum of hepatic arterial flow Q_{HA} and portal venous flow

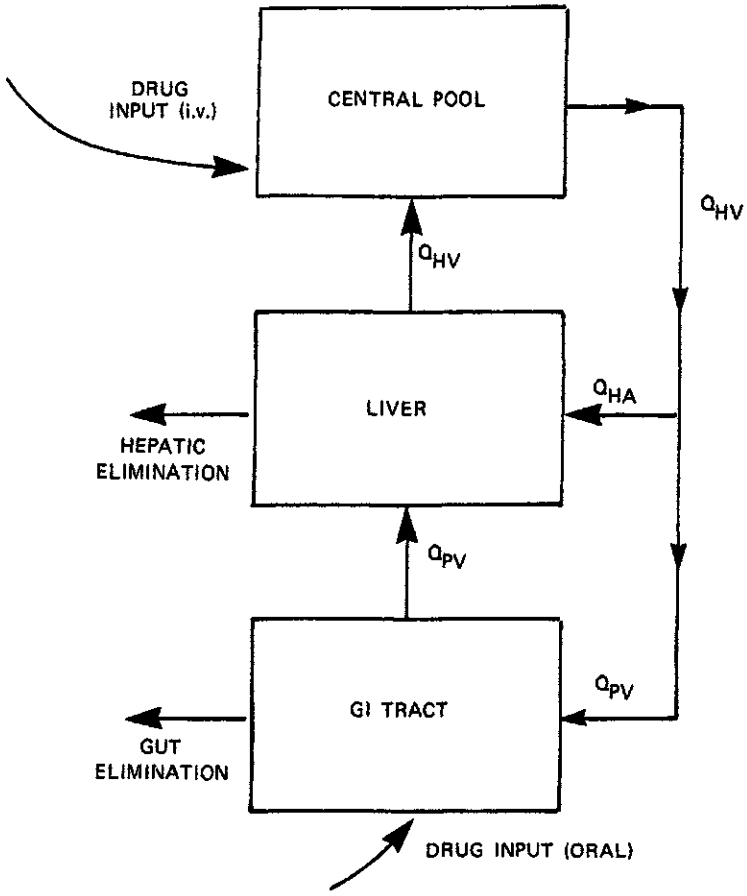

Fig. 8.7 Flow model describing the perfusion of the gastrointestinal tract and liver and showing the course of drug given orally and intravenously. After oral administration the drug is potentially subject to first-pass effects in the gut wall and in the liver. Blood flow terms are defined as follows: Q_{HV} is total hepatic blood flow, Q_{HA} is hepatic artery blood flow, and Q_{PV} is portal vein blood flow.

Q_{PV}, which is equal to the flow in the hepatic vein), Cl_{HI} is intrinsic hepatic clearance, and Cl_{GI} is intrinsic intestinal mucosal clearance. The ratio of Q_{PV} to Q_{HV} is about 0.8 in the rat, 0.75 in the dog, and 0.7 in humans.

In the absence of gut wall metabolism, Eq. (8.55) reduces to Eq. (8.53), whch can be rearranged to give Eq. (8.50), where $Q = Q_{HV}$. In the absence of significant first-pass hepatic metabolism (i.e., $Cl_{HI} << Q_{HV}$), Eq. (8.55) reduces to

$$F = \frac{Q_{PV}}{Q_{PV} + Cl_{GI}} \tag{8.56}$$

which can be rearranged to give

$$F = 1 - \frac{D}{AUC_{i.v.} \cdot Q_{PV}} \tag{8.57}$$

When a drug is subject to both first-pass hepatic metabolism and gut wall metabolism, it has been shown that the actual systemic availability is always intermediate between the value predicted by Eq. (8.57) (underestimate) and that predicted by Eq. (8.50) (overestimate) [12].

The Pang-Gillette model [13] for first-pass metabolism is more complex than that proposed by Colburn and Gibaldi [12] in that it incorporates biliary excretion of drug and metabolite as well as enterohepatic cycling of parent drug, and considers both oral and intraperitoneal administration of the drug.

LUNG CLEARANCE

It is well known that the liver is not the only site of drug metabolism. Several extrahepatic tissues, including the intestinal mucosa, kidney, and lung, contain drug-metabolizing enzymes. Because of the lung's unique anatomical position in the circulatory system (see Fig. 8.8), drug metabolism by this organ presents some interesting implications for the evaluation of first-pass effects and systemic availability.

In the absence of drug metabolism by the lung, the systemic availability of a drug is given by the well-known equation

$$F_{oral} = \frac{AUC_{oral}}{AUC_{i.v.}} \tag{8.58}$$

where F_{oral} is the fraction of the administered dose reaching the systemic circulation, and AUC_{oral} and $AUC_{i.v.}$ represent the total areas under the drug concentration in blood versus time curves after oral and intravenous administration, respectively, assuming venous blood sampling. A value of F_{oral} of less than 1 may be the result of one or more of the following factors: (1) physical-chemical properties of the drug and/or dosage form; (2) gut and/or gut wall metabolism of the drug, and (3) hepatic first-pass metabolism of the drug. Under these conditions Eq. (8.58) is assumed to provide an absolute estimate of the availability of the orally administered drug to the target organ(s) since a compound given intravenously may be regarded as 100% available.

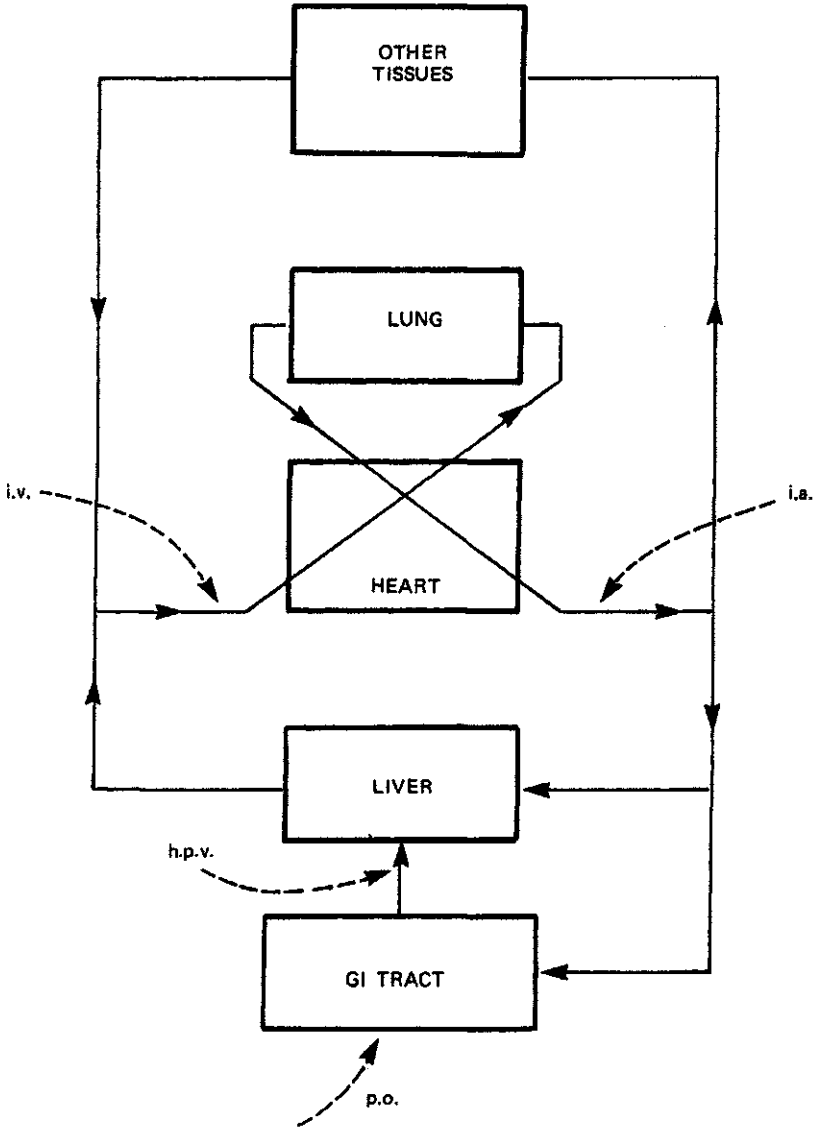

Fig. 8.8 Schematic representation of the anatomical positions of the potential sites of drug elimination (i.e., the gastrointestinal tract, the liver, and the lung) and of several routes of administration, including oral (p.o.), hepatic portal vein (h.p.v.), intravenous (i.v.), and intra-arterial (i.a.).

Strictly speaking, this is not correct when drug clearance by the lung is significant. Under these conditions a more appropriate expression for absolute availability is

$$F_{oral} = \frac{AUC_{oral}}{AUC_{i.a.}} \tag{8.59}$$

where $AUC_{i.a.}$ is the total area under the curve after intra-arterial administration, assuming arterial blood sampling. The AUC in arterial blood will be larger after intra-arterial administration of a drug than after intravenous administration of the same dose, if lung clearance is significant.

As shown in Fig. 8.8, there are three potential sites for metabolism across which an orally administered drug must pass before reaching the systemic circulation: the gastrointestinal mucosa, the liver, and the lung. Since these organs are arranged in series, it can be seen, if one assumes complete absorption, that F_{oral} is equal to the product of the fractions of dose escaping first-pass metabolism by the gastrointestinal mucosa f_G, liver f_H, and lung f_L:

$$F_{oral} = f_G f_H f_L \tag{8.60}$$

Similarly, the absolute systemic availability of a drug given by injection into the hepatic portal vein $F_{h.p.v.}$, or by intraperitoneal injection, may be represented as

$$F_{h.p.v.} = f_H f_L \tag{8.61}$$

whereas that of a drug given intravenously is simply

$$F_{i.v.} = f_L \tag{8.62}$$

It follows that

$$f_G = \frac{AUC_{oral}}{AUC_{h.p.v.}} \tag{8.63}$$

$$f_H = \frac{AUC_{hpv}}{AUC_{i.v.}} \tag{8.64}$$

and

$$f_L = \frac{AUC_{i.v.}}{AUC_{i.a.}} \tag{8.65}$$

where the subscripts on the right-hand side of each equation refer to route of administration and the AUC terms relate to drug concentrations in arterial blood.

Table 8.1 Effect of Route of Administration on the Area Under the Drug Concentration in Blood Versus Time Curve, AUC, After a Single 1.5 mg/kg Dose of Phenol.

Route	AUC	Relative Bioavailability (%)
Intra-arterial (i.a.)	6.13	100
Intravenous (i.v.)	2.53	41
Hepatic portal vein (h.p.v.)	2.22	36
Oral (p.o.)	0.18	3

Notes: The values represent the means of five to seven rats. The difference between p.o. and h.p.v. administration reflects a first-pass effect in the gut; the difference between i.v. and i.a. adminstration reflects a first-pass effect in the lung.
Source: From Ref. 14.

Cassidy and Houston [14] have used the equations outlined above to evaluate the relative contributions of intestinal mucosa, liver, and lung in the elimination of phenol in the rat. The AUC values (carotid artery blood) resulting from a single 1.5 mg/kg dose of phenol, using different routes of administration, are shown in Table 8.1. The results indicate that phenol undergoes a very large first-pass effect in the rat when given orally. Only 3% of the dose appears as parent drug in the systemic circulation. Application of Eqs. (8.63), to (8.65) to the data suggest that gut and/or gut wall metabolism is the major cause of the low systemic availability ($f_G = 0.08$), but pronounced lung metabolism is also evident ($f_L = 0.38$). The role of hepatic enzymes appears small ($f_H = 0.94$).

RENAL CLEARANCE

The theoretical concepts presented above concerning hepatic clearance and the relationship between drug binding in blood and hepatic clearance are well defined and largely experimentally verified. Corresponding theory and experimental data concerning renal clearance are much more limited. Because the net renal excretion of a drug is determined by filtration, active secretion, and reabsorption, the model for renal clearance is more complicated than that described for hepatic clearance. Renal clearance Cl_r can be described by the following equation [15]:

$$Cl_r = (Cl_{rf} + Cl_{rs})(1 - FR) \tag{8.66}$$

wher Cl_{rf} is renal filtration clearance, Cl_{rs} is renal secretion clearance, and FR is the fraction of drug filtered and secreted that is reabsorbed. The rate of filtration depends on the volume of fluid that is filtered in

the glomerulus and the unbound concentration of drug in the blood since plasma proteins and drug bound to these proteins are not filtered. The volume filtered is usually estimated from creatinine clearance Cl_{cr}. The renal filtration clearance may therefore be expressed as

$$Cl_{rf} = f_B Cl_{cr} \tag{8.67}$$

where f_B is the free fraction of drug in the blood.

Drug secretion in the kidney depends on the affinity of drug to active transport carrier proteins relative to plasma proteins, the rate of transfer of drug across the tubular membrane, and the rate of delivery of the drug to the secretory site. A relationship similar to Eq. (8.27) that incorporates these factors is the following.

$$Cl_{rs} = \frac{Q_K f_B Cl'_{I(K)}}{Q_K + f_B Cl'_{I(K)}} \tag{8.68}$$

where Q_K is blood flow to the kidney and $Cl'_{I(K)}$ is the intrinsic renal tubular secretion clearance with respect to unbound drug. Combining Eqs. (8.67) and (8.68) and making the appropriate substitutions in Eq. (8.66), we find that renal clearance is given by

$$Cl_r = f_B \left(Cl_{cr} + \frac{Q_K Cl'_{I(K)}}{Q_K + f_B Cl'_{I(K)}} \right) (1 - FR) \tag{8.69}$$

If $Q_K >> f_B Cl'_{I(K)}$, Eq. (8.69) reduces to

$$Cl_r = f_B (Cl_{cr} + Cl'_{I(K)})(1 - FR) \tag{8.70}$$

Under these conditions a plot of renal clearance versus f_B should be linear and intersect the origin [16].

If tubular reabsorption is prevented (which may be possible with certain acids or bases by changing urine pH), FR = 0 and Eq. (8.70) may be rearranged to yield

$$Cl'_{I(K)} = \frac{Cl_r}{f_B} - Cl_{cr} \tag{8.71}$$

On the other hand, if tubular secretion is blocked (which may be possible for certain acid drugs by administering probenecid), $Cl'_{I(K)} = 0$ and Eq. (8.70) may be rearranged to yield [16]

$$FR = 1 - \frac{Cl_r}{f_B Cl_{cr}} \tag{8.72}$$

With FR determined by means of Eq. (8.72), $Cl'_{I(K)}$ can be calculated by rearranging Eq. (8.70) [16]:

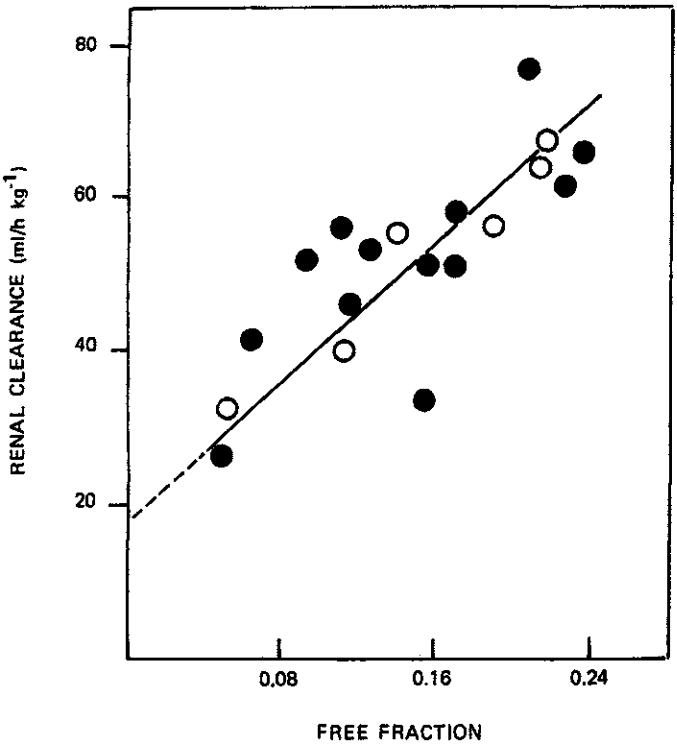

Fig. 8.9 Relationship between renal clearance and free fraction of sulfisoxazole in serum in 13 rats (●) and in six of these rats retested 1 week later (○). The regression line and correlation coefficient (r) are based on data from the first experiment; r = 0.79. According to Eq. (8.75), the slope of the regression line is related to the product of creatinine clearance and the fraction of drug evading tubular reabsorption and the intercept value is related to the product of renal blood flow and the fraction of drug evading reabsorption. (From Ref. 17, reprinted with permission.)

$$Cl'_{I(K)} = \frac{Cl_r}{f_B(1 - FR)} - Cl_{cr} \tag{8.73}$$

Thus under certain experimental conditions we may be able to estimate FR and intrinsic secretion clearance for some drugs.

Considering the other limiting case for Eq. (8.69) [i.e., $f_B Cl'_{I(K)} >> Q_K$], we find that this expression reduces to

$$Cl_r = f_B\left(Cl_{cr} + \frac{Q_K}{f_B}\right)(1 - FR) \tag{8.74}$$

or

$$Cl_r = f_B Cl_{cr}(1 - FR) + Q_K(1 - FR) \tag{8.75}$$

In this case a plot of renal clearance versus f_B should be linear and have a positive intercept. Such a relationship has been observed with respect to the renal clearance of sulfisoxazole in rats (see Fig. 8.9).

Dividing the slope of a plot of Cl_r versus f_B by its intercept yields

$$\frac{\text{Slope}}{\text{Intercept}} = \frac{Cl_{cr}}{Q_K} \tag{8.76}$$

By substituting experimental values for Cl_{cr} in this equation, we can calculate Q_K, the blood flow or effective blood flow to the kidney [16].

CLEARANCE CONCEPTS APPLIED TO METABOLITES

There is increasing interest in the contribution of drug metabolites to drug efficacy or adverse effects and we frequently wish to know the relative concentrations of metabolite and parent drug on chronic dosing. At steady state, the rate of formation of a metabolite must equal its rate of elimination. We may express this relationship for a one-compartment model as follows:

$$k_f V_p C_{p,ss} = k_m V_m C_{m,ss} \tag{8.77}$$

where k_f is the first-order formation rate constant, k_m is the metabolite elimination rate constant, and V_p and $C_{p,ss}$ and V_m and $C_{m,ss}$ denote the apparent volumes of distribution and steady-state concentrations of parent drug and metabolite, respectively. Recognizing that k_f is equal to $f_m K$, where f_m is the fraction of parent drug converted to this metabolite and K is the overall elimination rate constant of the drug, and that the product of a rate constant and a volume is clearance, we find that on rearranging Eq. (8.77),

$$\frac{C_{m,ss}}{C_{p,ss}} = \frac{f_m Cl_p}{Cl_m} \tag{8.78}$$

where Cl_p and Cl_m represent the total systemic clearances of parent drug and metabolite, respectively.

Equation (8.78) suggests that administration of the metabolite is required to calculate this ratio. However, Lane and Levy [18] have shown that this ratio, as well as the actual value of $C_{m,ss}$, can be estimated from data obtained after a single dose of the parent drug without the need for metabolite administration.

The clearance of parent drug after intravenous administration is given by

$$Cl_p = \frac{D_p}{(AUC_p)_p} \tag{8.79}$$

Kaplan et al. [19] have shown that f_m is equal to the ratio of AUC for the metabolite after administration of a dose D_p of the parent drug to that after administration of an equimolar dose D_m of the metabolite. That is,

$$f_m = \frac{(AUC_m)_p}{D_p} \frac{D_m}{(AUC_m)_m} = \frac{(AUC_m)_p}{D_p} Cl_m \tag{8.80}$$

where $(AUC_a)_b$ refers to the total area under the concentration of a in blood versus time curve after a single intravenous dose of b; the subscripts m and p refer to metabolite and parent drug, respectively. The ratio of dose of metabolite to $(AUC_m)_m$ is metabolite clearance Cl_m.

Substituting for Cl_p and f_m in Eq. (8.78) according to Eqs. (8.79) and (8.80), respectively, and canceling common terms yields

$$\frac{C_{m,ss}}{C_{p,ss}} = \frac{(AUC_m)_p}{(AUC_p)_p} \tag{8.81}$$

Equation (8.81) shows that the ratio of steady-state concentrations of metabolite and parent drug can be estimated by determining drug and metabolite concentrations in blood after a single intravenous dose of parent drug. Equation (8.81) also applies to the oral administration of any drug, irrespective of extraction ratio, if absorption is complete. It does not apply to intravenous administration of drugs with medium to high hepatic extraction ratios [20].

Clearance concepts have also been useful in understanding the effects of changes in plasma protein binding on the metabolic fate of a drug [21]. Consider a drug that is excreted in the urine and metabolized in the liver to a single product, which is excreted in the urine as such. The fraction metabolized f_m after intravenous administration is given by

$$f_m = \frac{Cl_H}{Cl_s} = \frac{Cl_H}{Cl_H + Cl_r} \tag{8.82}$$

where Cl_H is hepatic clearance, Cl_s is total or systemic clearance, and Cl_r is renal clearance. If the drug has a low hepatic extraction ratio and is excreted solely by glomerular filtration, then according to Eqs. (8.30), (8.66), and (8.67), we may rewrite Eq. (8.82) as follows:

$$f_m = \frac{f_B Cl'_{I(H)}}{f_B Cl'_{I(H)} + f_B Cl_{cr}(1 - FR)} \tag{8.83}$$

or

$$f_m = \frac{Cl'_{I(H)}}{Cl'_{I(H)} + Cl_{cr}(1 - FR)} \tag{8.84}$$

where f_B is the fraction unbound in blood, $Cl'_{I(H)}$ the intrinsic hepatic clearance of unbound drug, FR the fraction of drug filtered that is reabsorbed, and Cl_{cr} is creatinine clearance. Under these conditions the fraction metabolized is independent of plasma protein binding.

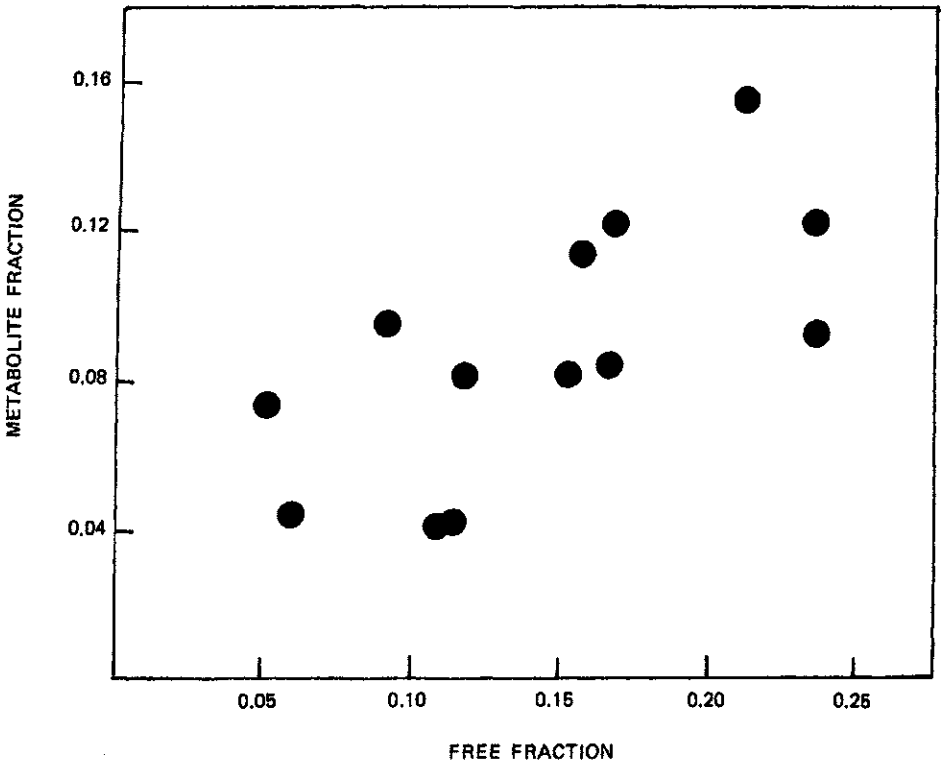

Fig. 8.10 Relationship between the fraction of a 20 mg/kg intravenous dose of sulfisoxazole excreted in the urine as metabolites and the free fraction of sulfisoxazole in serum in 13 rats. There is a distinct trend toward an increasing metabolite fraction with increases in free fraction as predicted by Eq. (8.86); the correlation coefficient is 0.68. (From Ref. 21, reprinted with permission.)

On the other hand, if the drug has a low extraction ratio but is excreted by filtration as well as tubular secretion, then according to Eqs. (8.30) and (8.69), we must express Eq. (8.82) as follows:

$$f_m = \frac{f_B Cl'_{I(H)}}{f_B Cl'_{I(H)} + f_B Cl_{cr}(1 - FR) + \dfrac{Q_K f_B Cl'_{I(K)}}{Q_K + f_B Cl'_{I(K)}}(1 - FR)} \tag{8.85}$$

or

$$f_m = \frac{Cl'_{I(H)}}{Cl'_{I(H)} + Cl_{cr}(1 - FR) + \dfrac{Q_K Cl'_{I(K)}}{Q_K + f_B Cl'_{I(K)}}(1 - FR)} \tag{8.86}$$

where Q_K denotes renal blood flow and $Cl'_{I(K)}$ denotes intrinsic secretory clearance with respect to unbound drug. In the case where $f_B Cl'_{I(K)} >> Q_K$, Eq. (8.86) reduces to [21]

$$f_m = \frac{Cl'_{I(H)}}{Cl'_{I(H)} + Cl_{cr}(1 - FR) + (Q_K/f_B)(1 - FR)} \tag{8.87}$$

Equations (8.86) and (8.87) indicate that under these conditions, the fraction metabolized increases as the binding of drug in blood decreases. This relationship has been observed with sulfisoxazole in the rat (see Fig. 8.10).

PHYSICAL MODELS OF ORGAN CLEARANCE

All of the equations and relationship developed thus far in this chapter are based on the assumption that the eliminating organ is a single (homogeneous) well-stirred compartment and that distribution occurs so rapidly that drug in the emergent venous blood is in equilibrium with that throughout the liver, so that, assuming passive diffusion, the concentrations of unbound drug in venous blood and in the clearing organ are equal. An alternative to the "well-stirred" model [3] is the "parallel tube" model [22–24], which envisions that the eliminating organ is composed of a number of identical and parallel tubes with enzymes distributed uniformly along the tubes. The parallel tube model probably provides a realistic description of the liver, at least from an anatomic point of view. Contrary to the assumptions of the well-stirred model, the parallel tube model suggests that the concentration of unbound drug in emergent venous blood will be less than the average

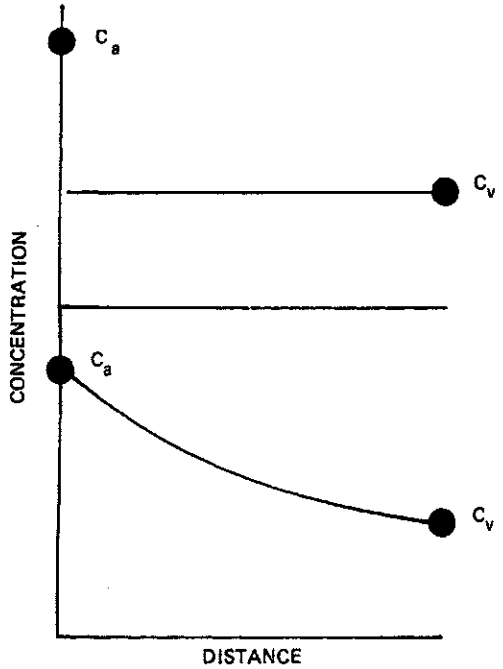

Fig. 8.11 Concentration gradient of a drug across an eliminating organ as envisioned by the well-stirred model (above) and the parallel tube model (below). C_a and C_v denote drug concentrations in arterial and emergent venous blood.

free drug concentration in the liver, which is given by $(C'_a - C'_v)/\ln (C'_a/C'_v)$, where C' denotes unbound drug concentration, and the subscripts a and v denote arterial and venous blood, respectively. The difference between the two models in terms of concentration gradient across the clearing organ can be seen in Fig. 8.11.

Each model gives rise to a unique set of equations to describe particular pharmacokinetic parameters [24]. For example, in the well-stirred model we have defined clearance by Eq. (8.27). The corresponding equation for clearance according to the parallel tube model is

$$Cl = Q(1 - e^{-f_B Cl'_I/Q}) \tag{8.88}$$

where the term in parentheses is equal to the extraction ratio ER.

It is difficult to prove the validity of either one of these models or even to differentiate experimentally between them because although the relationships among parameters such as blood flow, intrinsic clearance, clearance, and unbound fraction of drug are mathematically

distinct, they are quantitatively similar in most instances. In fact, for drugs with very high or very low extraction ratios, both models predict the same limiting equations for clearance [i.e., Eqs. (8.26) and (8.30)]. This is readily seen by considering Eq. (8.88) when $f_B Cl_I' >> Q$ or when $Q >> f_B Cl_I'$. In the former situation, $\exp(-f_B Cl_I'/Q) \to 0$ and $Cl \to Q$ [Eq. (8.26)], whereas in the latter situation, $\exp(-f_B Cl_I'/Q) \to 1 - (f_B Cl_I'/Q)$ and $Cl \to f_B Cl_I'$ [Eq. (8.30)] [24].

Theoretical analysis [24] of the two models of organ clearance has revealed that the most powerful discriminator between them is the effect of blood flow on either the emergent drug concentration in venous blood (C_{out} or C_v) of a drug with a very high extraction ratio [which is given by $C_{in}(1 - ER)$ or $C_a(1 - ER)$] or, in the case of hepatic clearance, the systemic availability F after oral administration of a drug with a very high extraction ratio (which is given by $1 - ER$). The reason for this discrimination is that the systemic availability of a drug with a high hepatic extraction ratio changes linearly with blood flow for the well-stirred model ($F = Q/f_B Cl_I'$) but changes exponentially with blood flow for the parallel tube model [$F = \exp(-f_B Cl_I'/Q)$] [24]. For a drug with an extraction ratio of 0.95, systemic availability would be expected to increase from 5% to 9.5% upon doubling of hepatic blood flow from 1 to 2 ml/min per gram of liver for the well-stirred model. An increase from 5% to 22.4% would be expected under the same circumstances for the parallel tube model [24].

The effect of changes in blood flow rate on the hepatic clearance of lidocaine (extraction ratio > 0.99) has been examined in the perfused rat liver [25,26]. Concentrations of lidocaine and its metabolite monoethyl glycine xylidide (MEGX) in the emergent venous blood were better predicted by the well-stirred model than by the parallel tube model. Despite these interesting findings, it is probably premature at this time to conclude which of the physical models for organ clearance is the more generally appropriate.

BLOOD CLEARANCE VERSUS PLASMA CLEARANCE

The various equations and relationships discussed throughout most of this chapter have not only been based on the well-stirred model, they have also assumed that blood rather than plasma is the perfusion medium which flows through and bathes the clearing organs. This conceptual approach is, at first glance, at variance with common experimental procedures which call for determining drug binding and drug concentrations in plasma rather than blood. However, this difficulty is easily overcome since relatively little more laboratory work need be done to express drug binding and drug concentration in terms of blood rather than plasma [see Eqs. (8.28) and (8.29)].

Unfortunately, most pharmacokinetic studies that have been published to date do not provide enough data to express drug binding and drug concentration in terms of blood. Moreover, most of the values of systemic clearance for individual drugs that have been reported are in fact plasma clearance rather than blood clearance values. It is appropriate, therefore, to consider under what circumstances plasma clearance is a reasonable approximation of blood clearance and under what circumstances it is not.

It is evident from Eq. (8.29) that when a drug is uniformly distributed throughout the blood (i.e., when drug binding is similar in plasma and red blood cells), $C_B \simeq C_p$ since $f_B \simeq f_p$. When this condition prevails, plasma clearance Cl_p will approximate blood clearance Cl_B.

In the more usual case, we find that drug binding in plasma exceeds that in red blood cells, so that $C_B < C_p$, AUC(blood) < AUC(plasma) and [according to Eq. (8.6)], $Cl_B > Cl_p$. Hence under these conditions plasma clearance will underestimate blood clearance. According to Eq. (8.29), the maximum error will occur when C_{RBC} is negligible, so that $C_B/C_p = 1 - HCT$ and $Cl_B/Cl_p = 1/(1 - HCT)$, or about 1.67 in humans.

Much larger errors may be encountered when drug binding to red blood cells exceeds binding in plasma. In this case $C_B > C_p$, AUC(blood) > AUC(plasma), and $Cl_p > Cl_B$. The ratio of C_B to C_p will depend on the relative binding to RBC and plasma; Cl_p can substantially overestimate Cl_B and, in fact, exceed hepatic blood flow.

It is also of interest to consider whether or not plasma parameters (i.e., C_p, f_p, and plasma flow rate Q_p) can be used to approximate intrinsic clearance (i.e., Cl_I'). We may rewrite Eq. (8.27) in terms of plasma parameters as follows:

$$Cl_p = Q_p \frac{f_p (Cl_I')_{pl}}{Q_p + f_p (Cl_I')_{pl}} \tag{8.89}$$

where $(Cl_I')_{pl}$ is the intrinsic clearance of unbound drug referenced to plasma. We can now solve Eq. (8.89) for $(Cl_I')_{pl}$ and compare this value with Cl_I' obtained from Eq. (8.27), which assumes blood parameters. Rearrangement of Eq. (8.89) yields

$$(Cl_I')_{pl} = \frac{Q_p Cl_p}{f_p (Q_p - Cl_p)} \tag{8.90}$$

Therefore, the ratio of intrinsic clearance using plasma data to that from blood data is

$$\frac{(Cl_I')_{pl}}{Cl_I'} = \frac{f_B}{f_p} \frac{Q_p Cl_p}{Q_B Cl_B} \frac{Q_B - Cl_B}{Q_p - Cl_p} \tag{8.91}$$

which may be simplified to

$$\frac{(Cl_I')_{pl}}{Cl_I'} = \frac{Q_p(Q_B - Cl_B)}{Q_B(Q_p - Cl_p)} \tag{8.92}$$

since $f_B/f_p = C_p/C_B$ and $Cl_p/Cl_B = C_B/C_p$.

For drugs that bind preferentially in plasma (i.e., $Cl_B > Cl_p$) and have a low extraction ratio (i.e., $Q_B >> Cl_B$ and $Q_p >> Cl_p$), we find that the ratio of intrinsic clearance values [Eq. (8.92)] approximates unity and conclude that $(Cl_I')_{pl} \simeq Cl_I'$. This case holds for any drug, irrespective of extraction ratio, that is negligibly bound to red blood cells and is essentially restricted to the plasma, since under these conditions $(Q_B - Cl_B)/(Q_p - Cl_p) \simeq Q_B/Q_p$. However, as the extraction ratio of a drug increases, any binding to red blood cells will cause $(Cl_I')_{pl}$ to increasingly overestimate Cl_I'. Very large errors are encountered with drugs that have high extraction ratios and are uniformly distributed in blood (i.e., when $C_p \to C_B$ and $Cl_p \to Q_p$).

The situation is still more complicated when blood binding is greater than plasma binding (i.e., when $f_B < f_p$ and $Cl_B < Cl_p$). Even under these conditions, drugs with very low extraction ratios present few problems since $Q_B >> Cl_B$ and $Q_p >> Cl_p$, and $(Cl_I')_{pl} \simeq Cl_I'$. However, the ratio of $(Cl_I')_{pl}$ to Cl_I' increases substantially in response to small changes in extraction ratio, so that even for drugs with medium extraction ratio values, $(Cl_I')_{pl}$ may seriously overestimate Cl_I'.

In summary, plasma clearance will reasonably approximate blood clearance when plasma binding equals or exceeds blood binding. Maximum errors are on the order of 40%. On the other hand, when blood binding exceeds plasma binding, very large errors may be introduced. The incorrect use of plasma parameters to calculate the intrinsic clearance of a drug [see Eq. (8.90)] yields reasonably accurate answers for drugs with low extraction ratios. Although this information is useful for evaluating literature data, it should be evident that all pharmacokinetic studies should be designed to yield information regarding blood-related parameters.

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