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Hepatic Clearance of Drugs. I. Theoretical Considerations of a "Well-Stirred" Model and a "Parallel Tube" Model. Influence of Hepatic Blood Flow, Plasma and Blood Cell Binding, and the Hepatocellular Enzymatic Activity on Hepatic Drug Clearance[1]

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Two commonly used models of hepatic drug clearance are examined. The "well-stirred" model (model I) views the liver as a well-stirred compartment with concentration of drug in the liver in equilibrium with that in the emergent blood. The "parallel tube" model (model II) regards the liver as a series of parallel tubes with enzymes distributed evenly around the tubes and the concentration of drug declines along the length of the tube. Both models are examined under steady-state considerations in the absence of diffusional limitations (cell membranes do not limit the movement of drug molecules). Equations involving the determinants of hepatic drug clearance (hepatic blood flow, fraction of drug in blood unbound, and the hepatocellular enzymatic activity) and various pharmacokinetic parameters are derived. Similarities and differences between the models are explored. Although both models predict similar hepatic drug clearances under a variety of conditions, marked differences between them become apparent in their predictions of the influence of changes in the determinants of drug clearance on various pharmacokinetic parameters.

KEY WORDS: hepatic drug clearance; models; blood flow; drug binding; hepatocellular enzymatic activity; intrinsic clearance.

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GLOSSARY

AUC total area under the blood drug concentration–time profile
C drug concentration
C_{In}, C_{Out} concentration of drug entering and leaving the liver, respectively
$\hat{C}$ logarithmic average concentration of drug in hepatocyte,

$$\hat{C} = \frac{C_{In} - C_{Out}}{\ln(C_{In}/C_{Out})}$$

CL steady-state hepatic drug clearance
CL_{int} intrinsic hepatic drug clearance
$CL_{int,l}$ intrinsic hepatic drug clearance when operating under linear conditions ($C_{L,u} \ll K_{m,i}$)
E steady-state hepatic extraction ratio
f_B ratio of the unbound drug concentration in plasma water to the whole blood drug concentration
f_P ratio of the unbound drug concentration in plasma water to the total plasma drug concentration
f_{BC} ratio of the unbound drug concentration in plasma water to the total drug concentration in blood cells
F systemic availability of a drug given orally
H hematocrit
$K_{m,i}$ Michaelis–Menten constant of the ith enzyme
R rate of drug administration
$t_{1/2}$ elimination half-life of the drug
v velocity of a reaction
V volume
Q hepatic blood flow
$V_{max,i}$ maximum velocity of the ith enzyme
τ interval between doses
subscripts L, B, BC, P, and R liver, whole blood, blood cells, plasma, and reservoir, respectively
subscripts x and tube point x and the tube, respectively
subscript u unbound drug
subscripts oral, i.v., inf oral and intravenous routes and constant intravenous infusion, respectively
subscripts l and ss linear and steady-state conditions

INTRODUCTION

The concept of clearance evolved with attempts to describe the renal excretion of urea (1). This concept has since been extended to describe both the renal and hepatic handling of drugs as well as their handling by less obvious eliminating organs, including the stomach (2), the lung (3), and plasma (4). Clearance concepts are now widely utilized in pharmacokinetics and in therapeutics to determine the half-life of a drug, to predict the steady-state blood (or plasma) drug concentration after constant drug administration (5), to assess or to predict the availability of a drug given by different routes of administration (6,7), and to measure organ function (8).

The clearance of an eliminating organ is defined as the volume of perfusing medium that is effectively cleared of drug by that organ per unit time; as such, clearance relates the rate of drug elimination by the organ to the incoming drug concentration. Since blood is the usual perfusing medium, as pointed out by Rowland (7) and further emphasized by Wilkinson (9), blood clearance, rather than plasma clearance, should be used as a measure of the eliminating efficiency of the organ. In many of the other applications in pharmacokinetics mentioned above, however, plasma clearance measurements suffice. Clearance is an additive property; total clearance denotes the sum of the clearances by all the eliminating organs. Total clearance is often determined by dividing the dose by the total area under the blood drug concentration–time curve following a single intravenous bolus dose; the value so derived is a time-averaged value which, when the system is linear, equals the steady-state value (10). The latter value is most commonly estimated by dividing the rate of drug administration by the plateau drug concentration following constant intravenous drug infusion.

Hepatic drug clearance is of considerable importance, partly because the liver is a major site of drug elimination and partly because of the unique anatomical position of the liver. By lying between the gastrointestinal tract and the general circulation, and by receiving the majority of the blood supply perfusing the gastrointestinal tract, the liver can reduce the oral availability of a drug, i.e., the fraction of an orally administered dose that reaches the systemic circulation intact. This presystemic hepatic drug elimination, which occurs on the first passage of drug through the liver, and hence is commonly referred to as "the first-pass effect" (6), is particularly significant for drugs that are highly extracted by the liver. Examples include propranolol (11), lidocaine (12), and propoxyphene (13).

When measured directly across an organ, drug clearance is given by the product of the organ blood flow and the extraction ratio of the drug. This relationship among organ clearance, blood flow, and extraction ratio is more complex than it may appear. Increasing hepatic blood flow has essentially no effect on the hepatic clearance of antipyrine (14), whereas the hepatic clearance of chromic phosphate colloid increases with increasing blood flow rate but not proportionately, the extraction ratio decreasing with blood flow (15). Even so, drugs can usefully be classified on the basis of their extraction ratio (16). An examination of hepatic elimination shows that extraction can be limited by liver blood flow, by the resistance to transport of drug from blood to the site of elimination, and by the intrinsic ability of the organ to eliminate drug; the last usually depends on the maximum velocity and the Michaelis–Menten constant of the appropriate eliminating enzyme system(s) involved. At the one extreme are drugs

whose extraction ratio approaches 1; examples are the previously mentioned drugs propranolol, lidocaine, and propoxyphene. Here, the liver has such a high intrinsic ability to metabolize these drugs that all the drug in blood, whether unbound or bound either to plasma proteins or to blood cells, is removed as it passes through the liver; hepatic clearance approaches and becomes sensitive to hepatic blood flow and insensitive to drug binding within blood. At the other extreme are drugs whose extraction ratio approaches 0; examples are antipyrine (14) and warfarin (17). Here, the limitation is not perfusion but the low intrinsic ability of the hepatic enzymes to metabolize these drugs. And, assuming that only the unbound drug can traverse membranes and that the rate of metabolism depends on the unbound drug surrounding the enzymatic site, clearance of a poorly extracted drug should be sensitive to changes in drug binding within blood. This sensitivity to protein binding is seen with warfarin; clearance is directly proportional to the fraction of unbound drug in plasma (17).

Two commonly used models have emerged to explain and to quantitatively predict the influence of these physiological factors, blood flow, drug binding, and hepatocellular enzymatic activity, on the extraction ratio and hence hepatic clearance of drugs. The "well-stirred" model (model I, Fig. 1) (10) assumes that the liver is a single well-stirred compartment and that the concentration of unbound drug in the emergent blood is in equilibrium with the unbound drug within the liver. The "parallel tube" model (model II, Fig. 2) (18,19) assumes that the liver is composed of a number of identical and parallel tubes with enzymes distributed evenly in each cross-

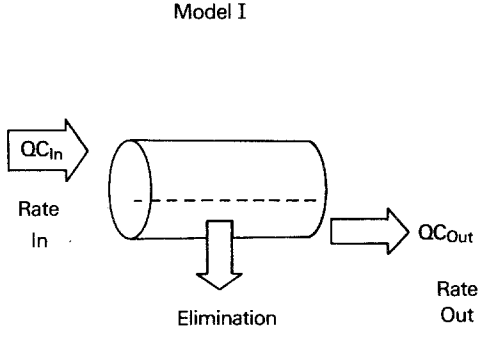

Fig. 1. Diagrammatic representation of hepatic elimination in the "well-stirred" model (model I). The liver is depicted as a single well-stirred compartment. The rate of drug elimination is given by the difference between the rate of presentation of drug to and its rate of exit from the liver at steady state. The dashed line represents the unbound hepatic drug concentration.

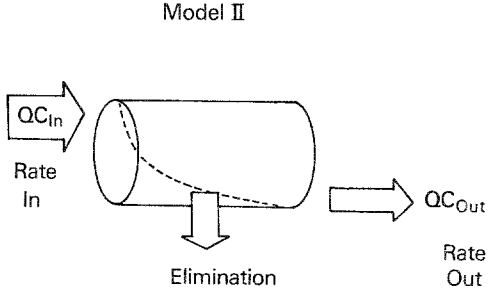

Fig. 2. Diagrammatic representation of hepatic elimination in the "parallel tube" model (model II). The liver is composed of k identical cylinders; each cylinder represents a sinusoid. Mass balance relationships across the liver are the same as those in model I. The dashed line represents the declining unbound hepatic drug concentration along the direction of blood flow.

section of the sinusoidal vascular and perisinusoidal space. The total liver enzymatic activity (with a maximum velocity V_{max}) is the sum of the individual enzymatic activity for each tube. At any point along the tube, the concentration of the equilibrating species at the hepatocyte is the same as that in the sinusoid. The behavior of both models has been explored under steady-state (or quasi-steady-state) conditions and usually but not necessarily (20) when a transport barrier across the hepatocyte is absent.

As yet, no critical comparison between these two models of hepatic drug clearance has been forthcoming. The purpose of the present article is to derive equations, for both models, that relate the determinants of hepatic drug clearance (hepatic blood flow, fraction of drug in blood unbound, and the hepatocellular enzymatic activity) with various pharmacokinetic parameters and to explore similarities and differences in the behavior of these models to changes in these determinants of drug clearance.

THEORETICAL

A number of elements and assumptions are common to both models. Blood entering and leaving the liver contains unbound drug and drug bound either to plasma constituents (usually proteins) or to blood cell constituents; f_B denotes the ratio of the concentration of drug in plasma water (C_u) to the whole blood drug concentration (C_B). Within the liver are a variety of eliminating enzymes (designated from i to n) each characterized by a maximum velocity ($V_{max,i}$) and Michaelis–Menten constant ($K_{m,i}$).

It is also assumed that

1. Intimate mixing takes place between the hepatic portal blood and the hepatic arterial blood before drug partitions into the sinusoids. Experimental evidence generally supports this hypothesis (21).
2. Only unbound drug can traverse membranes.
3. There is no diffusional barrier between the drug in blood and the enzyme within the hepatocyte; that is, the rate of distribution is perfusion limited. When examined, this assumption appears to hold (22,23).
4. The rate of drug elimination is a function of the concentration of unbound drug bathing the enzymes, $C_{L,u}$. (For acids and bases, one would need to take into account the degree of ionization of the drug if one assumes that only the un-ionized moiety traverses membranes. As the general behavior of the system is relatively unaffected by this further refinement, however, it has been ignored in the present analysis.)

The equations are derived from mass balance relationships. By Fick's principle, at any moment the velocity of removal of drug from blood into the liver (v) is given by the difference between the influent (C_{In}) and effluent (C_{Out}) concentration of drug in blood times the hepatic blood flow (Q). (Strictly speaking, the blood flow leaving the liver is less than that entering the liver, the difference being the bile flow; this difference of less than 0.2% is often ignored.) This loss of drug from blood is matched by uptake of drug into the liver, by metabolism, and by biliary excretion:

$$v = Q(C_{In} - C_{Out}) = \begin{matrix}\text{rate of}\\ \text{change}\\ \text{of drug}\\ \text{in the}\\ \text{liver}\end{matrix} + \begin{matrix}\text{rate of}\\ \text{metabolism}\end{matrix} + \begin{matrix}\text{rate of}\\ \text{biliary}\\ \text{excretion}\end{matrix} \quad (1)$$

At steady state, the net rate of change of drug in the liver is 0, and v equals the sum of the rates of metabolism and biliary excretion. Hence, by definition, at steady state

$$\text{hepatic clearance, } CL = v/C_{In} = Q(C_{In} - C_{Out})/C_{In} = QE \quad (2)$$

Before proceeding, there is an additional concept that needs to be defined, namely that of intrinsic (hepatic drug) clearance, CL_{int} (16). This concept was developed in an attempt to measure hepatocellular enzymatic activity, independent of hepatic blood flow and binding within the vascular system. Recall that both these factors, flow and binding, can influence drug clearance as defined by equation 2. The intrinsic clearance, which relates

the rate of hepatic elimination to the concentration of drug surrounding the hepatic enzymes, thus

$$CL_{int} = v/C_{L,u} \tag{3}$$

may be defined as the volume of liver water that is effectively cleared of drug per unit time. By definition, $CL_{int} > CL$.

Well-Stirred Model (Model I)

Additional assumptions of model I are

1. That the liver is a single well-stirred compartment.
2. That distribution equilibrium is achieved so rapidly that drug in the emergent venous blood is in equilibrium with that in the liver. Assuming passive diffusion, it then follows that the concentrations of unbound drug in venous blood ($C_{Out,u}$) and in liver ($C_{L,u}$) are equal. (If drug transport is an active process, then equilibrium is still achieved, but $C_{Out,u}/C_{L,u}$ is not equal to 1.)

Then the appropriate steady-state mass balance equation is

$$v = Q(C_{In} - C_{Out}) = \sum_{i=1}^{n} \frac{V_{max,i} C_{L,u}}{K_{m,i} + C_{L,u}} \tag{4}$$

so that

$$CL = QE = \frac{1}{C_{In}} \sum_{i=1}^{n} \frac{V_{max,i} C_{L,u}}{K_{m,i} + C_{L,u}} \tag{5}$$

Also

$$CL_{int} = \sum_{i=1}^{n} \frac{V_{max,i}}{K_{m,i} + C_{L,u}} \tag{6}$$

Substituting equation 6 into equation 5, and realizing that $C_{L,u} = C_{Out,u} = f_{B,Out} C_{Out}$, where $f_{B,Out} = C_{Out,u}/C_{Out}$, yields

$$E = f_{B,Out} C_{Out} CL_{int} / Q C_{In} \tag{7}$$

which upon substituting $1 - E$ for C_{Out}/C_{In} and appropriate rearrangement gives

$$E = f_{B,Out} CL_{int} / (f_{B,Out} CL_{int} + Q) \tag{8}$$

so that

$$CL = Q[f_{B,Out} CL_{int} / (f_{B,Out} CL_{int} + Q)] \tag{9}$$

Also, two conditions are worth noting:

a. $C_{L,u} \ll K_{m,i}$. At drug concentrations well below the K_m of the enzyme system, the kinetics becomes independent of drug concentration.

Under linear conditions, the intrinsic clearance reaches a constant maximum value, $CL_{int,l} = \sum_{i=1}^{n} V_{max,i}/K_{m,i}$.

b. Unienzyme system ($n = 1$). For a unienzyme system, equation 4 with appropriate substitution reduces to

$$v = Q(C_{In} - C_{Out}) = V_{max}C_{Out}/(K_m/f_{B,Out} + C_{Out}) \quad (10)$$

A linearized transformation of equation 10 is

$$C_{Out}/(C_{In} - C_{Out}) = K_m Q/f_{B,Out} V_{max} + QC_{Out}/V_{max} \quad (11)$$

Parallel Tube Model (Model II)

Additional assumptions of model II are

1. The liver is composed of a large number of identical cylindrical tubes, arranged in parallel, with enzymes uniformly distributed in parenchymal cells surrounding the cylinders. Blood flows unidirectionally along the cylinders.
2. At any point along the cylinder, distribution equilibrium exists between drug at the enzymatic site and that in the cylinder.

Consider one of the tubes of length D (Fig. 2), with blood flowing through it at a rate Q_{tube}, having the ith enzyme characterized by $V_{max,i,tube}$ and $K_{m,i}$, and a steady-state velocity of the reaction along the entire tube, v_{tube}. Then, if the liver is composed of k such tubes

$$\text{liver blood flow, } Q = kQ_{tube} \quad (12a)$$

$$\text{maximum velocity of the } i\text{th enzyme, } V_{max,i} = kV_{max,i,tube} \quad (12b)$$

$$\text{total rate of drug elimination, } v = kv_{tube} \quad (12c)$$

At steady state, the velocity of drug removal (v_x) over an increment dx from point x along the tube is given by

$$v_x = \frac{dx}{D} \sum_{i=1}^{n} \frac{V_{max,i,tube}C_{L,u,x}}{K_{m,i} + C_{L,u,x}} = -Q_{tube}\, dC_x \quad (13)$$

where $C_{L,u,x}$ is the unbound drug concentration in the hepatocyte at point x, and C_x is the concentration of drug in blood at point x. Recalling that $C_{L,u,x} = C_{u,x} = f_{B,x}C_x$, where $C_{u,x}$ is the unbound drug concentration in plasma at point x, and $f_{B,x}$ is the fractional term, $C_{u,x}/C_x$ at that point, it follows that

$$v_x = \frac{dx}{D} \sum_{i=1}^{n} \frac{V_{max,i,tube}f_{B,x}C_x}{K_{m,i} + f_{B,x}C_x} = -Q_{tube}\, dC_x \quad (14)$$

By definition, the value of the intrinsic clearance at point x, $CL_{int,x}$ is given by

$$CL_{int,x} = \frac{v_x}{C_{L,u,x}} = \frac{dx}{D} \sum_{i=1}^{n} \frac{V_{max,i,tube}}{K_{m,i} + f_{B,x}C_x} \tag{15}$$

Clearly, as C_x changes along the tube, so does the value of the intrinsic clearance. Substitution of equation 15 into equation 14 yields

$$v_x = f_{B,x} CL_{int,x} C_x = -Q_{tube}\, dC_x \tag{16}$$

The nonlinearity of the rate equations 14 and 16 precludes an explicit solution for the velocity, $v_{tube} (= -Q_{tube} \int_{C_{In}}^{C_{Out}} dC_x)$ and hence v, as a function of C_{In}. Explicit solutions for the overall velocity and hence extraction ratio and clearance do, however, exist for several limiting situations:

a. $C_{u,x} \ll K_{m,i}$; $f_{B,x} = f_{B,Out} =$ constant. The first condition, of an unbound drug concentration below the K_m of any enzyme system, is most likely to ensure the second condition, by preventing a sufficiently high drug concentration to saturate any binding sites either on the plasma proteins or in the blood cells. The ratio $f_{B,Out}$ is also constant when vascular binding does not exist ($f_{B,Out} = 1$). Under these conditions, equation 14 reduces to

$$v_x = \frac{dx}{D} f_{B,Out} \sum_{i=1}^{n} \frac{V_{max,i,tube} C_x}{K_{m,i}} = -Q_{tube}\, dC_x \tag{17}$$

The intrinsic clearance at point x reaches the corresponding maximal limiting value

$$CL_{int,l,x} = \frac{dx}{D} \sum_{i=1}^{n} \frac{V_{max,i,tube}}{K_{m,i}} \tag{18}$$

and the maximal intrinsic clearance for the entire liver, $CL_{int,l}$, is given by

$$CL_{int,l} = k \int_0^D CL_{int,l,x}\, dx = \sum_{i=1}^{n} \frac{V_{max,i}}{K_{m,i}} \tag{19}$$

Returning to equation 17, the changes in C_x along the tube are given by appropriate arrangement and substitution

$$\frac{dC_x}{C_x} = \frac{f_{B,Out} \sum_{i=1}^{n} \frac{V_{max,i}}{K_{m,i}} dx}{QD} = -\frac{f_{B,Out} CL_{int,l}\, dx}{QD} \tag{20}$$

which upon integration

$$\int_{C_{In}}^{C_{Out}} \frac{dC_x}{C_x} = -\frac{f_{B,Out} CL_{int,l}}{QD} \int_0^D dx \tag{21}$$

yields

$$C_{Out} = C_{In}\, e^{-f_{B,Out}CL_{int,l}/Q} \tag{22}$$

The corresponding steady-state extraction ratio and clearance are therefore

$$E = 1 - e^{-f_{B,Out}CL_{int,l}/Q} \tag{23}$$

$$CL = Q(1 - e^{-f_{B,Out}CL_{int,l}/Q}) \tag{24}$$

b. Unienzyme system ($n = 1$), $f_{B,x} = f_{B,Out}$ = constant. For a unienzyme system, rearrangement and integration of equation 14 yield for all values of C_{In}

$$v = Q(C_{In} - C_{Out}) = (QK_m/f_{B,Out}) \ln (C_{Out}/C_{In}) + V_{max} \tag{25}$$

which upon dividing by blood flow yields

$$C_{In} - C_{Out} = (K_m/f_{B,Out}) \ln (C_{Out}/C_{In}) + (V_{max}/Q) \tag{26}$$

Furthermore, defining the term $(C_{In} - C_{Out})/\ln (C_{In}/C_{Out})$ as the logarithmic average concentration, $\hat{C}$, appropriate substitution and rearrangement give (24)

$$v = V_{max}\hat{C}/(K_m + \hat{C}) \tag{27}$$

BEHAVIOR OF MODELS I AND II

The behavior of the two models of hepatic clearance was explored by examining the response of the extraction ratio and clearance to changes in the three determinants of clearance. The impact of these changes on a number of important pharmacokinetic and therapeutic parameters was also explored. These parameters include half-life ($t_{1/2}$), oral availability (F), total area under the blood drug concentration–time curve when the drug is given either intravenously ($AUC_{i.v.}$) or orally (AUC_{oral}), as well as the steady-state blood drug concentration following either chronic oral medication ($\bar{C}_{B,ss,oral}$) or constant intravenous infusion ($C_{B,ss,inf}$). Because, at least for model II, explicit solutions do not exist for the extraction ratio and clearance at drug concentrations exceeding either the K_m values of the enzyme systems (except for the relatively rare unienzyme system, *cf.* equation 25) or the affinity constants of the binding species within the blood, most of the comparisons between the models have been best made under linear conditions ($C_{L,u} \ll K_m$), when all parameters become concentration independent.

How changes in the extraction ratio and clearance affect various pharmacokinetic parameters is explored in a relatively simple system (Fig.

3). The liver is the sole eliminating compartment connected to a noneliminating compartment, the reservoir (which represents the rest of the body), via the bloodstream. The concentrations of drug in blood leaving the liver and entering the reservoir are assumed equal. Elimination can occur by metabolism or by biliary excretion. The introduction of drug into the reservoir (site 1, Fig. 3) is analogous to intravenous administration. Drug distributes throughout the reservoir (body) before reaching the eliminating organ. The introduction of drug at a site just prior to the liver (site 2, Fig. 3) is analogous to oral administration; some drug is eliminated by the liver before it reaches the reservoir. The fraction of the oral dose escaping into the reservoir, $1-E$, is the availability, F. The extraction ratio can be obtained directly by dividing the drop in drug concentration across the liver by the influent drug concentration. Clearance is calculated by multiplying the extraction ratio by the blood flow. Clearance is also estimated indirectly by dividing a single intravenous dose by the corresponding total area under the blood drug concentration–time curve in the reservoir. The availability, F, for an orally administered dose can be determined experimentally by comparing the area under the reservoir (blood) drug concentration–time curve following an orally administered dose (AUC_{oral}) to that following an intravenous dose ($AUC_{i.v.}$), appropriately correcting for dose. Chronic drug administration eventually results in a steady-state condition. The steady-state blood drug concentration ($\bar{C}_{B,ss}$) in the reservoir is achieved when the rate of drug entering the reservoir equals the rate of drug elimination. For a drug given orally every dosing interval τ, the average rate of drug input into the reservoir is $F \cdot \text{dose}/\tau$; given intravenously the rate is R_{inf}.

Table I summarizes the equations that express the interrelationships among blood flow, binding within blood, intrinsic clearance, and various

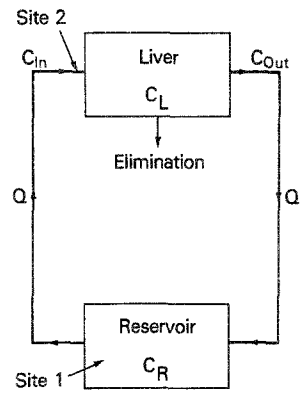

Fig. 3. Diagrammatic representation of the liver, an eliminating compartment, and the reservoir, a noneliminating compartment. The arrow indicates the direction of blood flow (Q). C_{In}, C_{Out}, C_L, and C_R are the concentrations of drug in the blood entering and leaving the liver, in the liver, and in the reservoir, respectively.

Table I. Interrelationships Among Hepatic Blood Flow (Q), Ratio of Drug Concentration Unbound in Plasma to That in Whole Blood (f_B), Maximum Intrinsic Clearance ($CL_{int,l}$), and Various Pharmacokinetic Parameters Under Linear Kinetic Conditions According to Models I and II

Parameter	Symbol	Basic equation	Interrelationships defined by	
			Model I	Model II
Extraction ratio	E		$\frac{f_B CL_{int,l}}{f_B CL_{int,l} + Q}$	$1 - e^{-(f_B CL_{int,l}/Q)}$
Hepatic clearance	CL	QE	$Q\frac{f_B CL_{int,l}}{f_B CL_{int,l} + Q}$	$Q[1 - e^{-(f_B CL_{int,l}/Q)}]$
Total area under blood drug concentration–time curve following a single intravenous dose	$AUC_{i.v.}$	$\frac{dose}{CL}$	$\frac{dose(f_B CL_{int,l} + Q)}{f_B CL_{int,l} Q}$	$\frac{dose}{Q[1 - e^{-(f_B CL_{int,l}/Q)}]}$
Steady-state blood drug concentration following constant intravenous infusion	$C_{B,ss,inf}$	$\frac{R_{inf}}{CL}$	$\frac{R_{inf}(f_B CL_{int,l} + Q)}{f_B CL_{int,l} Q}$	$\frac{R_{inf}}{Q[1 - e^{-(f_B CL_{int,l}/Q)}]}$
Availability	F	$1 - E$	$\frac{Q}{f_B CL_{int,l} + Q}$	$e^{-(f_B CL_{int,l}/Q)}$
Steady-state output drug concentration from liver (hepatic venous blood)	C_{Out}	$C_{In}(1 - E)$	$\frac{C_{In} Q}{f_B CL_{int,l} + Q}$	$C_{In}\, e^{-(f_B CL_{int,l}/Q)}$
Total area under blood drug concentration–time curve following a single oral dose	AUC_{oral}	$\frac{F \cdot dose}{CL}$	$\frac{dose}{f_B CL_{int,l}}$	$\frac{dose[e^{-(f_B CL_{int,l}/Q)}]}{Q(1 - e^{-(f_B CL_{int,l}/Q)})}$
Steady-state blood drug concentration following constant oral administration	$\bar{C}_{B,ss,oral}$	$\frac{F \cdot dose/\tau}{CL}$	$\frac{dose/\tau}{f_B CL_{int,l}}$	$\frac{[dose/\tau][e^{-(f_B CL_{int,l}/Q)}]}{Q[1 - e^{-(f_B CL_{int,l}/Q)}]}$

pharmacokinetic parameters for the two models operating under linear conditions.

Hepatic Blood Flow

Figure 4A–E illustrates the influence of hepatic blood flow on various parameters for the two models, using the equations in Table I, under the conditions $C_{L,u} \ll K_{m,i}$, $f_{B,\mathrm{Out}} = 1$, dose/$\tau = 1$, $R_{\mathrm{inf}} = 1$. The family of curves was calculated as follows:

A reference point (the extraction ratio at a hepatic perfusion rate of 1.0 ml/min/g liver) was established and used to calculate the values of $\mathrm{CL}_{\mathrm{int},l}$ for models I and II, according to equations 8 and 23. These calculated values of the intrinsic clearance were then used to predict the changes in the extraction ratio with perfusion flow rates at 0.5, 1.5, and 2.0 ml/min/g liver for the two models. As an example, the reference point

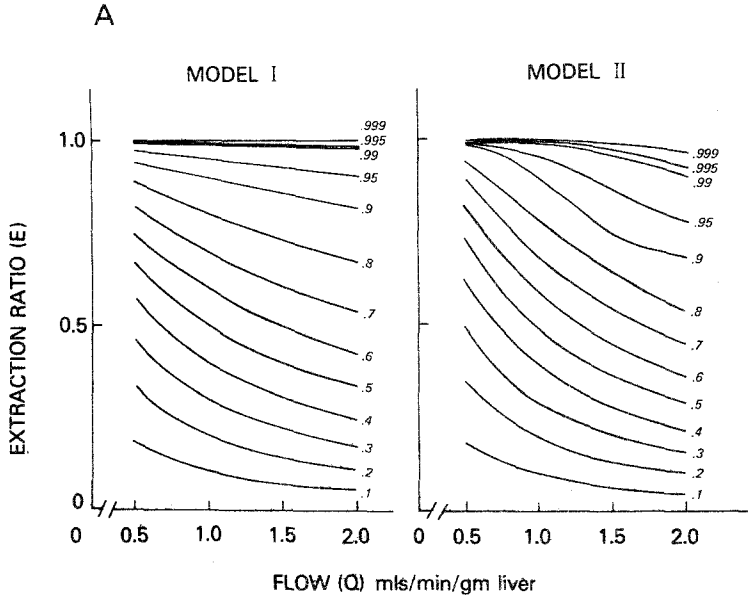

Fig. 4. Influence of changes in hepatic blood flow on (A) extraction ratio, (B) clearance, (C) the total area under the blood drug concentration–time curve following a single intravenous dose and the steady-state blood drug concentration following constant intravenous infusion, (D) availability, and (E) total area under the blood drug concentration–time curve following a single oral dose and the steady-state blood drug concentration following constant oral administration, as predicted by models I and II when operating under linear conditions and assuming $f_B = 1$. The number next to each curve is the extraction ratio at the normal flow rate of 1.0 ml/min/g liver. See text for details of computations.

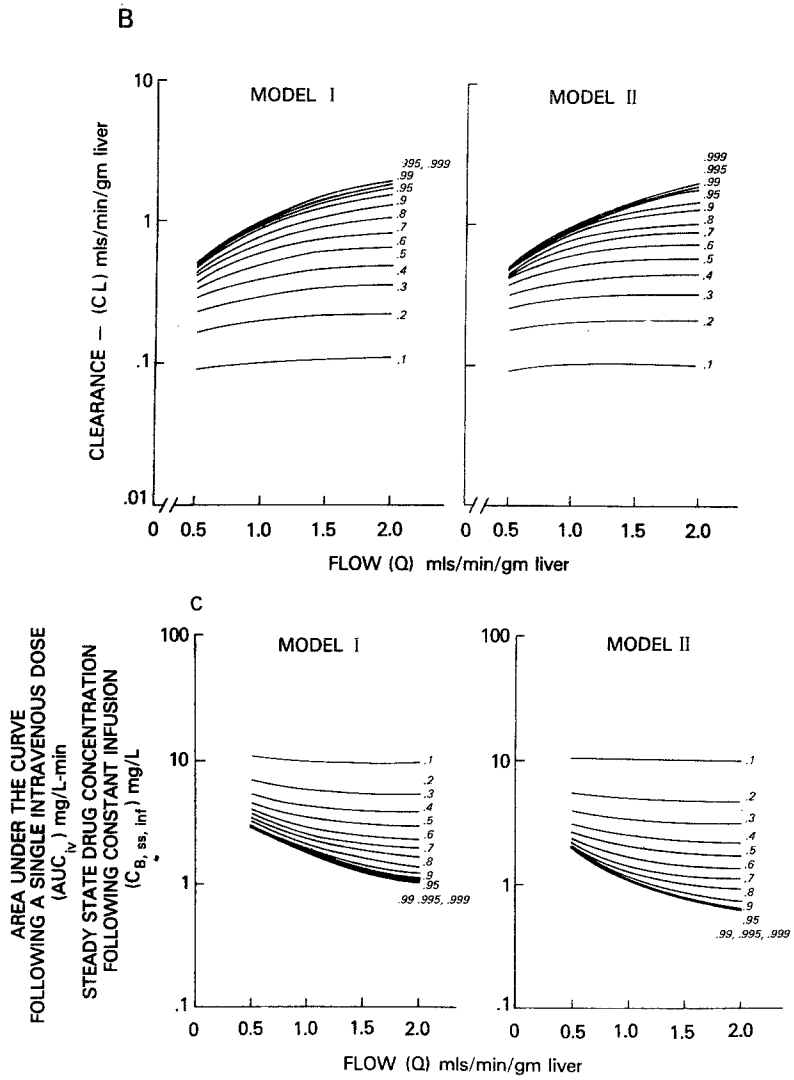

Fig. 4. Continued.

has an extraction ratio 0.9 at the perfusion rate of 1.0 ml/min g liver. The value of $CL_{int,l}$ for model I is obtained from equation 8:

$$0.9 = CL_{int,l}/(CL_{int,l} + 1.0) \qquad CL_{int,l} = 9.0 \text{ ml/min/g liver}$$

By appropriate substitution into equation 8, the extraction ratios at perfusion rates of 0.5, 1.5, and 2.0 ml/min/g liver are therefore 0.9414, 0.8571, and 0.8182, respectively. A curve is generated by connecting these

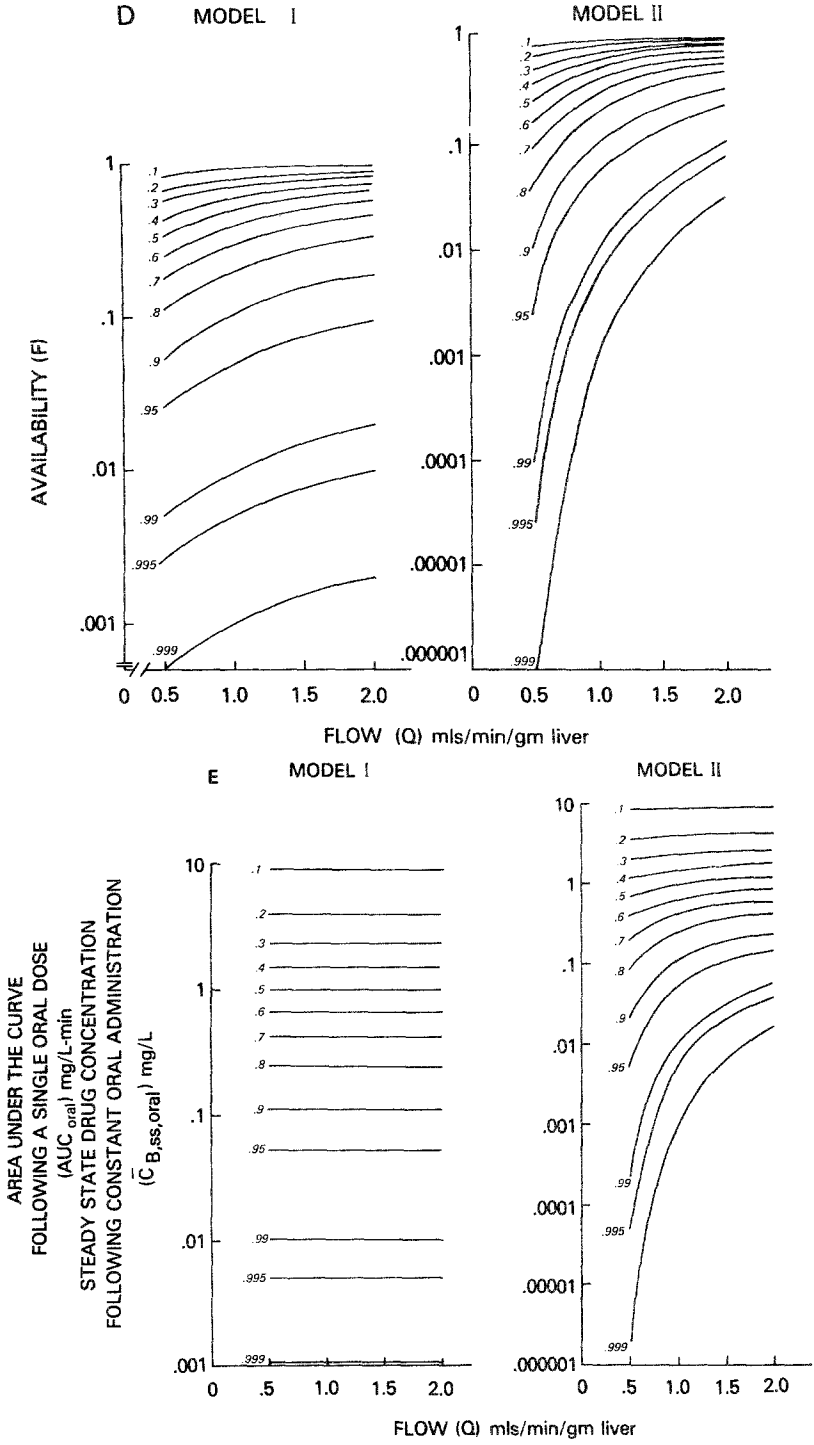

Fig. 4. Continued.

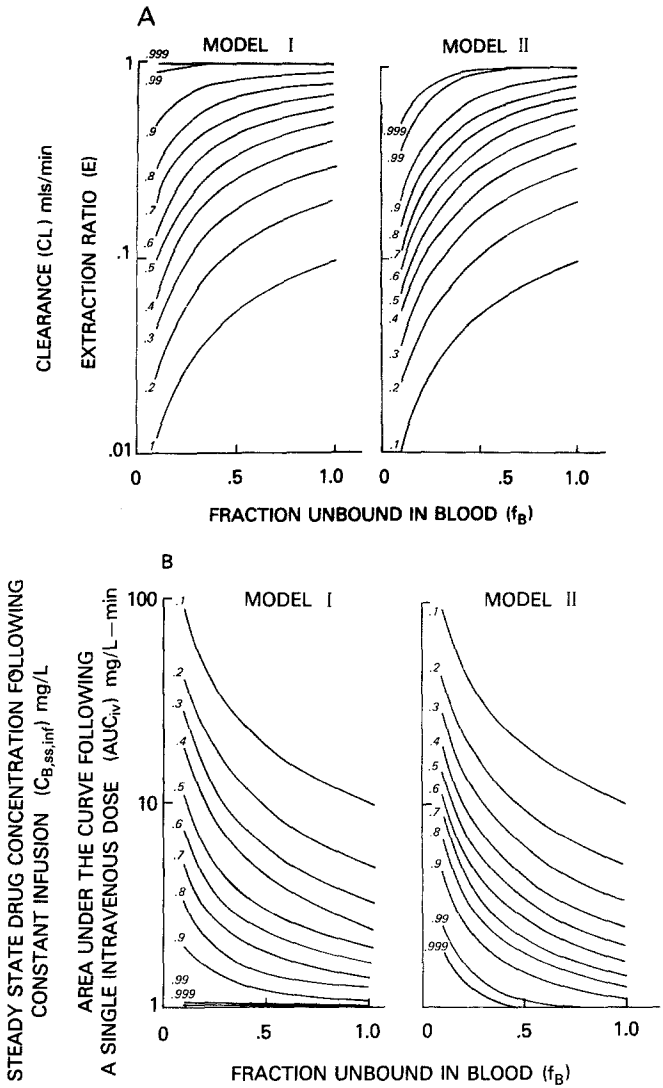

Fig. 5. Influence of drug binding within blood on (A) extraction ratio and clearance, (B) the total area under the blood drug concentration–time curve following a single intravenous dose and the steady-state blood drug concentration following a constant intravenous infusion, (C) availability, and (D) the total area under the blood drug concentration–time curve following a single oral dose and the steady-state blood drug concentration following constant oral medication as predicted by models I and II operating under linear conditions and assuming $Q = 1.0$ ml/min/g liver. The number next to each curve is the extraction ratio at the normal flow rate of 1.0 ml/min/g liver and at $f_B = 1$. See text for details of computations.

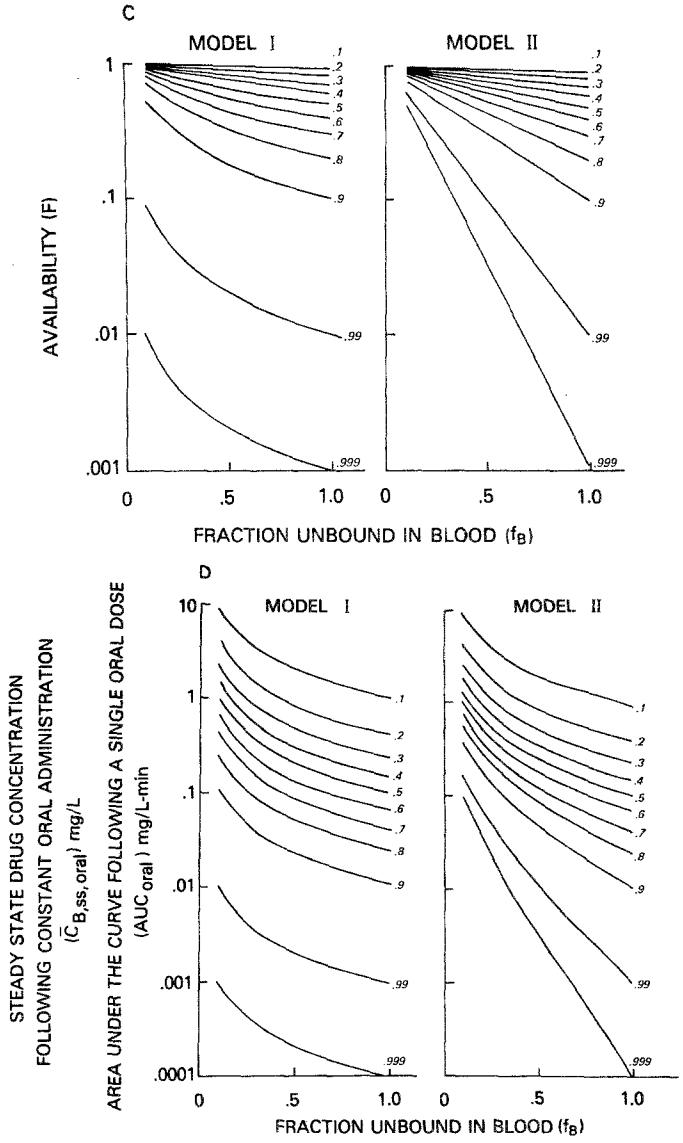

Fig. 5. Continued.

four points. A family of curves can be constructed utilizing different reference points with the extraction ratios ranging from 0.1 to 0.999 at the perfusion flow rate of 1.0 ml/min/g liver. Predicted values for other pharmacokinetic parameters are obtained in a similar manner using the appropriate equations in Table I.

Degree of Binding Within Blood

Figure 5A–D illustrates the influence of the changes of drug binding in blood on various parameters, for the two models, using the equations in Table I, under the conditions $C_{L,u} \ll K_{m,i}$, dose/$\tau = 1$, $R_{inf} = 1$, and $Q =$ 1.0 ml/min/g liver. The family of curves was calculated in an analogous manner to that for investigating the influence of hepatic blood flow. The same reference points (the extraction ratio at 1.0 ml/min/g liver; $f_{B,Out} = 1$) were used to calculate $CL_{int,I}$ for each model, and then $f_{B,Out}$ was varied from 0.1 to 1.0.

Intrinsic Clearance

Figure 6A,B illustrates the influence of changes in the intrinsic clearance, expressed as multiples of hepatic blood flow, on the extraction ratio and clearance for the two models under the conditions of constant-perfusion conditions (1.0 ml/min/g liver) and no drug binding in blood ($f_{B,Out} = 1$).

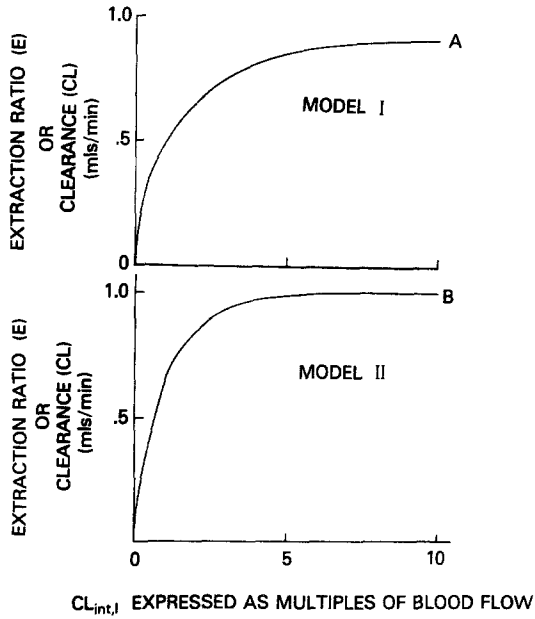

Fig. 6. Relationship between the extraction ratio and the clearance with the intrinsic clearance (expressed as multiples of hepatic blood flow) as predicted (A) by model I and (B) by model II, when operating under linear conditions and $f_B = 1$.

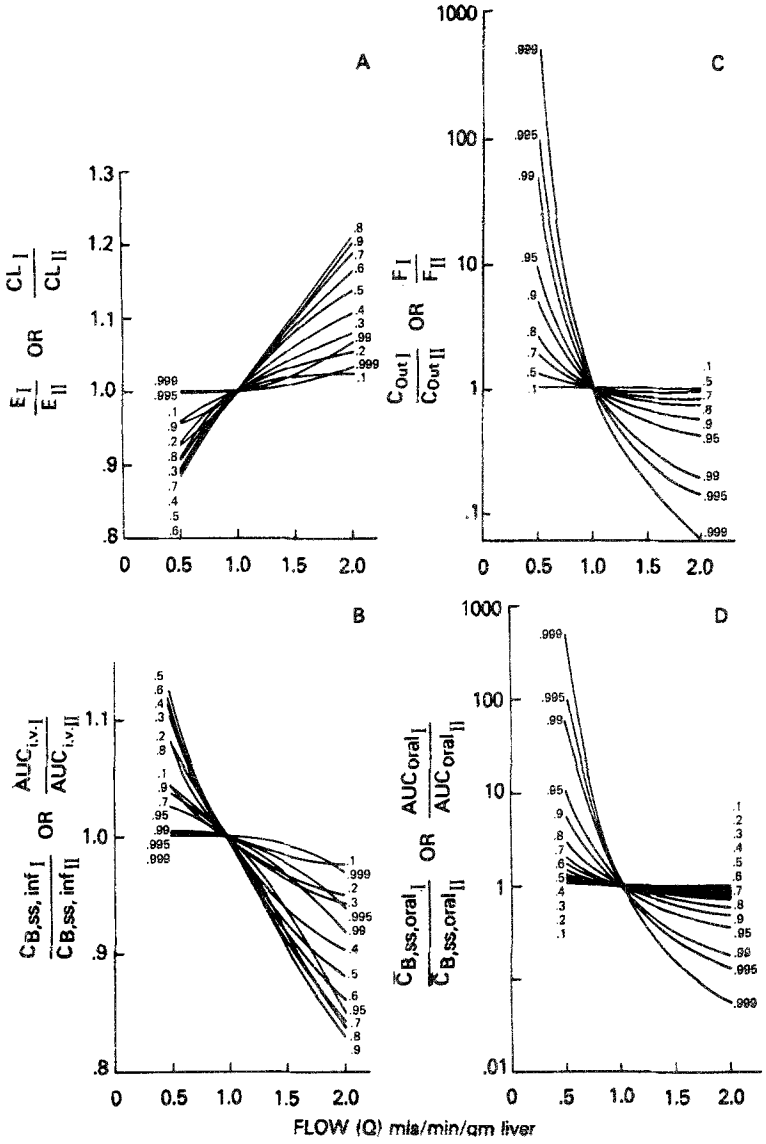

Fig. 7. Ratio of the predicted values of the pharmacokinetic parameters (A) extraction ratio and clearance, (B) the total area under the blood drug concentration–time curve following a single intravenous dose and the steady-state blood drug concentration following constant intravenous infusion, (C) the steady-state output blood drug concentration (hepatic venous) from the liver and the availability, and (D) the total area under the blood drug concentration–time curve following a single oral dose and the steady-state blood drug concentration following constant oral administration, as predicted by models I and II with perturbations of hepatic blood flow (0.5–2.0 ml/min/g liver) while operating under linear kinetic conditions and assuming $f_B = 1$. The number next to each curve is the extraction ratio at the normal flow rate of 1.0 ml/min/g liver. See text for details of computations.

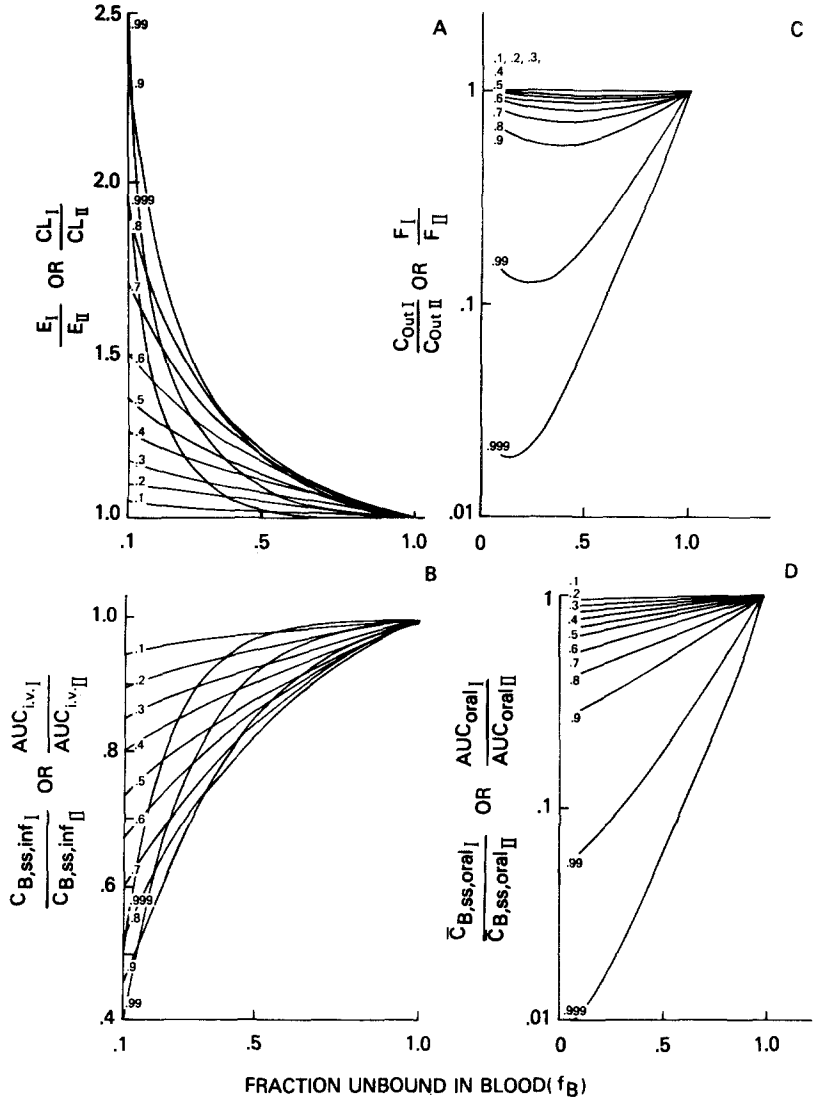

Fig. 8. Ratio of the predicted values of the pharmacokinetic parameters (A) extraction ratio and clearance, (B) the total area under the blood drug concentration–time curve following a single intravenous dose and the steady-state blood drug concentration following constant intravenous infusion, (C) the steady-state output blood drug concentration (hepatic venous) from the liver and the availability, and (D) the total area under the blood drug concentration–time following a single oral dose and the steady-state blood drug concentration following constant oral administration, as predicted by models I and II with perturbations of f_B (0.1–1.0) while operating under linear kinetic conditions and assuming $Q =$ 1.0 ml/min/g liver. The number next to each curve is the extraction ratio at the normal flow rate of 1.0 ml/min/g liver and $f_B = 1$. See text for details of computations.

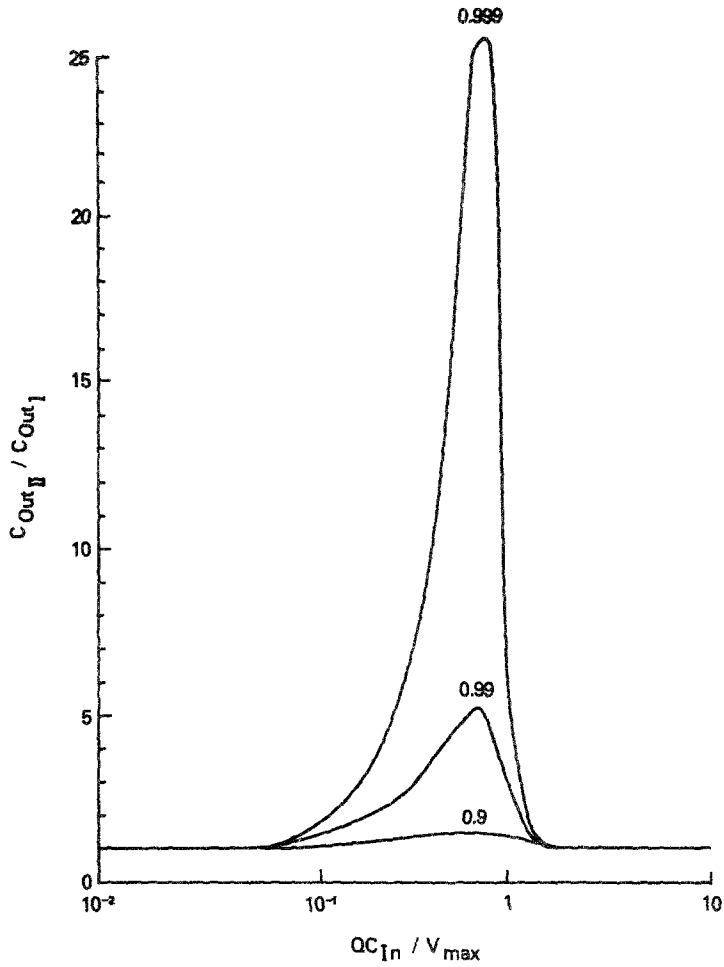

Fig. 9. Ratio of the values of the emergent drug blood concentration, as predicted by models I and II, for a unienzyme system operating under saturable conditions vs. changes in input drug concentration. $Q =$ 1 ml/min/g liver and $f_{B,Out} = 1$. The input data are normalized by dividing the rate of drug entering into the liver (QC_{In}) by the V_{max} of the enzyme. The number next to each curve is the extraction ratio at $Q = 1$ ml/min/g liver when operating under linear conditions.

COMPARISON BETWEEN TWO MODELS

A comparison among the extraction ratio, clearance, and other pharmacokinetic parameters as predicted by the two models operating under linear conditions is summarized in Table II. It can be seen that the

Table II. A Comparison of the Predicted Pharmacokinetic Parameters in Terms of Q, f_B, and $CL_{int,l}$ for Models I and II Under Linear Kinetic Conditions

Ratio	Interrelationships defined by models I and II
$\frac{ER_I}{ER_{II}}$ and $\frac{CL_I}{CL_{II}}$	$\frac{f_B CL_{int,l}}{f_B CL_{int,l}+Q} \Big/ (1-e^{-(f_B CL_{int,l}/Q)})$
$\frac{AUC_{i.v.I}}{AUC_{i.v.II}}$ and $\frac{C_{B,ss,inf_I}}{C_{B,ss,inf_{II}}}$	$\frac{f_B CL_{int,l}+Q}{f_B CL_{int,l}} \Big/ \frac{1}{1-e^{-(f_B CL_{int,l}/Q)}}$
$\frac{F_I}{F_{II}}$ and $\frac{C_{Out_I}}{C_{Out_{II}}}$	$\frac{Q}{f_B CL_{int,1}+Q} \Big/ e^{-(f_B CL_{int,l}/Q)}$
$\frac{AUC_{oral_I}}{AUC_{oral_{II}}}$ and $\frac{\bar{C}_{B,ss,oral_I}}{\bar{C}_{B,ss,oral_{II}}}$	$\frac{1}{f_B CL_{int,l}} \Big/ \frac{e^{-(f_B CL_{int,l}/Q)}}{Q[1-e^{-(f_B CL_{int,l}/Q)}]}$

extraction ratio (E_I/E_{II}) equals that for clearance (CL_I/CL_{II}); the ratio of the total area under the blood drug concentration–time curve following a single intravenous dose ($AUC_{i.v._I}/AUC_{i.v._{II}}$) equals that for the steady-state blood drug concentration following constant intravenous infusion ($C_{B,ss,inf_I}/C_{B,ss,inf_{II}}$) and are reciprocals of E_I/E_{II} and CL_I/CL_{II}; the ratio of the total area under the blood drug concentration–time curve following a single oral dose ($AUC_{oral_I}/AUC_{oral_{II}}$) equals that for the steady-state blood drug concentration following chronic oral medication ($\bar{C}_{B,ss,oral_I}/\bar{C}_{B,ss,oral_{II}}$); the ratio of the availability (F_I/F_{II}) equals that for the steady-state output drug concentration in the emergent blood (hepatic vein) from the liver ($C_{Out_I}/C_{Out_{II}}$). The predicted pharmacokinetic parameters (expressed as their ratios) with perturbations of hepatic blood flow (0.5–2.0 ml/min/g liver) when the drug is totally unbound ($f_{B,Out}=1$), and with perturbations of drug binding within blood (0.1–1.0) at constant hepatic blood flow (1.0 ml/min/g liver) operating under linear kinetic and steady-state conditions according to the models are graphically depicted in Figs. 7A–D and 8A–D, respectively.

Intrinsic clearance, and hence clearance, decreases as drug concentration at the enzymatic site approaches and exceeds the K_m of the enzyme system. Figure 9 depicts the ratio of the emergent steady-state drug concentration ($C_{Out_{II}}/C_{Out_I}$) with changes in the rate of drug entry, relative to $V_{max}(QC_{In}/V_{max})$ for a unienzyme system. Liver blood flow is held constant (1 ml/min/liver) and the drug is totally unbound ($f_{B,Out}=1$). The value of C_{Out}, for a given C_{In}, predicted for each model was calculated as follows: Under linear conditions, the value of $CL_{int,l}$ (V_{max}/K_m) for a given E and Q was calculated for models I and II according to equations 8 and 23, respectively. And fixing the value for V_{max}, which is independent of the model, the corresponding value for K_m for each model was calculated. Then, in the case of model I, for each value of C_{In}, C_{Out_I} was calculated as

the greater of the two roots of the quadratic equation for C_{Out}, obtained upon rearrangement of equation 10. For model II, although there is no explicit solution for $C_{Out_{II}}$ in equation 25, its value for each C_{In} value was calculated by the Newton–Rapson iterative procedure using the corresponding value of C_{Out_I} as the initial estimate for $C_{Out_{II}}$.

DISCUSSION

Many properties of the "well-stirred" and the "parallel tube" models have been explored independently (10,16,18–20,22–28) but rarely comparatively (29). A comparison is needed to determine where the similarities and differences lie, thereby so permitting one to evaluate the model that best describes any experimental data. It is immediately apparent that at the two extremes, namely for drugs with either very high or very low extraction ratios, no distinction between the models can be made based on the behavior of the extraction ratio and clearance (hence half-life, $AUC_{i.v.}$ and $C_{B,ss,inf}$) with respect to changes in either blood flow, binding within the blood, or intrinsic clearance. When the intrinsic clearance greatly exceeds hepatic blood flow (high values of the extraction ratio), for both models the extraction ratio approaches unity (equations 8 and 23); all drug in blood, whether bound or unbound, is completely extracted, and clearance approaches the limiting value of hepatic blood flow (equations 9 and 24). When the intrinsic clearance is small compared to hepatic blood flow (low values of the extraction ratio), for both models the extraction ratio of the drug approaches $f_{B,Out}CL_{int,l}/Q$ (equations 8 and 23), and changes proportionally with $f_{B,Out}$ and inversely with blood flow, while clearance approaches $f_{B,Out}CL_{int,l}$ and is insensitive to changes in blood flow. To distinguish between the models, one must explore how changes in the determinants of hepatic clearance, namely hepatic blood flow, drug binding within blood, and intrinsic clearance, affect the extraction ratio and clearance of drugs with intermediate extraction ratios, as well as examine the influence of these determinants on other parameters.

Hepatic Blood Flow

A reference value for hepatic perfusion of 1.0 ml/min/g liver was chosen, as this is the normal value in several animal species including man (21,30,31). The range explored, 0.5–2.0 ml/min/g liver, was chosen because this encompasses the majority of values seen under a variety of physiological and pathological conditions or following drug administration (14,32,33).

Even though hepatic blood flow and extraction ratio are inversely and exponentially related in models I and II, respectively, as can be seen in Fig.

4A,B, there is very little difference in the change in extraction ratio and clearance between both models for a change in hepatic blood flow. At maximum, this difference is only 30%, and occurs for drugs having extraction ratios between 0.7 and 0.8 (Fig. 7A). This point is well illustrated in our analysis (34) of the data from Brauer *et al.* (15), where these authors examined the hepatic extraction ratio of radiocolloid chromic phosphate over a wide hepatic perfused rate (0.5–6.0 ml/min/g liver) in the isolated perfused rat liver preparation. The data were predicted equally well by both models, and there is no statistical difference between the predictions. Similar findings were obtained in our analyses (34) of the data from Whitsett *et al.* (35) on the hepatic extraction ratio of oxyphenbutazone with organ blood flow (0.5–2.0 ml/min/g liver) in the dog *in vivo*, as well as the data from Branch *et al.* (25) on the hepatic extraction ratio of propranolol with hepatic perfusion rate in the isolated perfused rat liver. The comment that the predicted change in clearance with blood flow does not vary much between the models applies equally well to $AUC_{i.v.}$ and $C_{B,ss,inf}$ (Figs. 4C and 7B) since both parameters vary inversely with clearance (Tables I and II). In contrast, the predicted change in either availability (Figs. 4D and 7C), AUC_{oral}, or $\bar{C}_{B,ss,oral}$ (Figs. 4E and 7D) with blood flow differs greatly between the models, especially for a drug with a high extraction ratio.

For a drug with a low extraction ratio, availability $(1-E)$ is high, and a large difference between the predictions of the two models is not expected. However, on examining the appropriate equations for availability (Table I), one finds that for highly extracted compounds ($CL_{int,l} \gg Q$), the availability changes linearly with blood flow for model I ($F \simeq Q/f_{B,Out}CL_{int,1}$) and exponentially for model II ($F = e^{-f_{B,Out}CL_{int,l}/Q}$). As an illustration, for a drug with $E = 0.95$, the availability would be expected to increase from 5% to 9.5% upon doubling of hepatic blood flow from 1 to 2 ml/min/g liver for model I. An increase from 5% to 22.4% would be expected under the same circumstances in model II. Clearly, the higher the extraction ratio of the drug, the greater the difference in the predicted increase in availability with increasing hepatic blood flow between the models. A discrepancy of over a thousandfold exists between the predictions in the models for drugs with extraction ratios greater than 0.99 (Fig. 7C).

The predicted insensitivity of both AUC_{oral} and $\bar{C}_{B,ss,oral}$ to hepatic blood flow in model I for all values of extraction ratio contrasts with the expectations of model II (Fig. 4E). This contrast is particularly marked for drugs with high values of extraction ratio. While this independence of AUC_{oral} and $\bar{C}_{B,ss,oral}$ on hepatic blood flow in model I is seen by the absence of Q in the analytical solutions for these parameters in Table I, it is also apparent intuitively that the major determinant of both AUC_{oral} and

$\bar{C}_{B,ss,oral}$, irrespective of the particular model, is the ratio F/CL (Table I). In model I, a change in F caused by a change in flow is always matched by a corresponding change in CL, so that F/CL remains unaltered. This is true even at high values of the extraction ratio since as demonstrated previously both F and CL vary in direct proportion to flow. (Because of the dependence on clearance, although AUC_{oral} and $\bar{C}_{B,ss,oral}$ do not change, the half-life and hence the shape of the curve do vary with hepatic blood flow, especially for a drug with a high extraction ratio.) In contrast, in model II, particularly at high values of the extraction ratio, while F increases exponentially with flow, CL increases only linearly, and the ratio F/CL therefore increases. A discrepancy of over a thousandfold exists between the predictions in the models for drugs with extraction ratios greater than 0.99 (Fig. 7D).

Degree of Binding Within Blood

The value of f_B is a complex function, being dependent on drug concentration, on the affinity constants, on the concentrations of the binding constituents in plasma and in blood cells, as well as on the hematocrit (36,37). Consider for example, mass balance for drug within whole blood:

$$V_B C_B = V_B(1-H)C_P + V_B H C_{BC} \tag{28}$$

or

$$V_B C_B = V_B(1-H)(C_{P,u}/f_P) + (V_B H C_{BC,u}/f_{BC}) \tag{29}$$

where f denotes the ratio of unbound to total drug concentration, C denotes concentration, subscripts B, P, and BC denote whole blood, plasma, and blood cells respectively, and V and H denote volume and hematocrit, respectively. Rearrangement of equation 29 yields

$$f_B = \frac{C_{P,u}}{C_B} = \frac{1}{(1-H)/f_P + HC_{BC,u}/f_{BC}C_{P,u}} \tag{30}$$

In the case where the unbound drug concentration within the blood cells and that in plasma water are equal ($C_{BC,u} = C_{P,u}$; no active transport for drug into blood cells), then equation 30 reduces to

$$f_B = \frac{1}{(1-H)/f_P + H/f_{BC}} \tag{31}$$

Note that f_P and f_{BC} vary with the concentration of both the drug and binding species in blood. Since by definition $C_{P,u} = f_B C_B = f_P C_P$, the drug concentration in blood is related to that in plasma as follows:

$$C_B = f_P C_P / f_B = C_P[(1-H) + (Hf_P/f_{BC})] \tag{32}$$

As mentioned previously, differences between the predictions of the two models for the influence of f_B on the extraction ratio and clearance are small for drugs with the both very high and very low extraction ratios. But as seen in Figs. 5A and 8A, differences are also small (2.5-fold change over tenfold change in f_B) for drugs with intermediate extraction ratios. The above comments apply equally to the influence of f_B on $AUC_{i.v.}$ and $C_{B,ss,inf}$, although a difference between the predictions of the two models exists for a drug with a high extraction ratio (Figs. 5B and 8B). Examination of the appropriate equations in Table I shows that for high values of the extraction ratio ($f_B CL_{int,l} \gg Q$), $AUC_{i.v.}$ and $C_{B,ss,inf}$ are essentially independent of f_B in model I, whereas the parameters vary exponentially with f_B in model II. But the greatest difference between the models is demonstrated in the predicted changes with f_B of either the availability (Figs. 5C and 8C), AUC_{oral}, or $\bar{C}_{B,ss,oral}$ (Figs. 5D and 8D). This is especially so for drugs with high values of the extraction ratio, when F, AUC_{oral}, and $\bar{C}_{B,ss,oral}$ are all varying in inverse proportion to f_B in model I, while they vary exponentially with f_B in model II (Table I). A large discrepancy of over a thousandfold exists between the predictions on these parameters by both models for a drug with an extraction ratio greater than 0.99 (Fig. 8C–D).

Intrinsic Clearance

Enzyme stimulation or inhibition will affect the intrinsic clearance of drugs. Contrary to the statements by Keiding (38), intrinsic clearance is independent of both blood flow and binding within blood. The definition of intrinsic clearance in both models is the same; what differs is its predicted value based on a given extraction ratio. As seen from Fig. 6A,B, and from equations 8 and 23, the value of the intrinsic clearance predicted from model I is higher than that from model II, especially for a drug with a high extraction ratio. At sufficiently high drug concentrations the value of V_{max} can be accurately measured, independent of the model of hepatic drug clearance, and, for a given unienzyme system, differences in the estimates of the maximum intrinsic clearance (V_{max}/K_m) between the two models will be interpreted as differences in the K_m value of the enzyme system. If a reliable independent method exists for estimating the true K_m value, distinctions between the two models might be possible.

The common existence of the cross-product $f_B CL_{int,l}$ in all equations (Table I) indicates that conclusions drawn about changes in any parameter with f_B are equally applicable to changes with the intrinsic clearance when operating under linear conditions; that is, changes in F, AUC_{oral}, and

$\bar{C}_{B,ss,oral}$ of highly extracted drugs with a change in the intrinsic clearance appears to offer the best means of discrimination between models I and II.

As the intrinsic clearance of a drug is also decreased by saturating the drug-eliminating enzymes, discrimination between the models might be possible by increasing the influent drug concentration. As seen from Fig. 9, for a unienzyme system, operating under these nonlinear conditions, a difference in the steady-state emergent drug blood concentration (and hence steady-state availability) between the two models is predicted when the rate of entry of drug into the liver approximates the V_{max} of the system. The higher the value of the extraction ratio of the drug when operating under linear conditions, the greater is this difference. These comments apply equally well to the steady-state drug blood concentration in the reservoir ($C_{B,ss}$) following a constant infusion of drug directly into the liver; at steady state the rate of drug entering the reservoir ($QC_{Out,ss}$) is matched by that leaving the reservoir ($QC_{B,ss}$). As discussed previously, under the same conditions, extraction ratio and hence clearance are poor discriminators for the following reasons. First, if a twofold difference in the predictions between models I and II is the acceptable lower limit for discrimination, then the extraction ratio of the drug when operating under linear conditions must exceed 0.9. Moreover, the range of the input concentrations, by which such a difference between the model predictions is likely to be detected, is narrow (Fig. 9). To ensure that an input concentration lies within this narrow range, the value of V_{max} must be known reasonably accurately in advance; although the average value for V_{max} might be known, it is frequently not known for an individual enzyme system. Second, unienzyme systems are rare; most of the drugs are eliminated by several enzymes, each with a different K_m and V_{max}. The net result is that in such multienzyme systems the differences in C_{Out} values predicted between the models will be much less than those depicted in Fig. 9. Such possibilities as end-product inhibition and hepatic damage, induced by drug concentrations needed to saturate the enzymes, would further limit the suitability of operating under saturable conditions to discriminate between models of hepatic drug clearance.

One might be tempted to use the change in elimination half-life ($t_{1/2}$) with changes in the determinants of hepatic clearance as a discriminator between the models. But as even the simplest model ($t_{1/2} = 0.693 \times$ volume of distribution/clearance) proves, half-life is not better than clearance, itself a poor discriminator. Moreover, although changes in blood flow and the intrinsic clearance are unlikely to have any effect, changes in f_B may also affect the volume of distribution of a drug, raising further doubts about the use of half-life measurements (16).

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