Clearance Concepts: Fundamentals and Application to Pharmacokinetic Behavior of Drugs

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ABSTRACT: Clearance concepts were introduced into the pharmacokinetics discipline in the 1970s and since then have played a major role in characterization of the pharmacokinetic behavior of drugs. These concepts are based on the relationship between organ extraction ratio or clearance and physiologic parameters such as the organ blood flow and the intrinsic capability of the eliminating organ to remove the free (unbound) drug from the body. Several theoretical models have been developed, which define these relationships and may be used to predict the effects of changes in the physiological parameters on various pharmacokinetic parameters of drugs, such as drug clearance. In this communication, the fundamentals of the two most widely used models of hepatic metabolism, namely the well-stirred (venous equilibrium) and parallel-tube (sinusoidal perfusion) models, are reviewed. Additionally, the assumptions inherent to these models and the differences between them in terms of their predictive behavior are discussed. The effects of changes in the physiologic determinants of clearance on the blood concentration-time profiles of drugs with low and high extraction ratio are also presented using numerical examples. Lastly, interesting and unusual examples from the literature are provided where these concepts have been applied beyond their widely known applications. These examples include estimation of the oral bioavailability of drugs in the absence of otherwise needed intravenous data, differentiation between the role of liver and gut in the first-pass loss of drugs, and distinction between the incomplete absorption and first-pass metabolism in the gastrointestinal tract after the oral administration of drugs. It is concluded that the clearance concepts are a powerful tool in explaining the pharmacokinetics of drugs and predicting the changes in their blood concentration-time courses when the underlying physiologic parameters are altered due to age, disease states, or drug interactions.

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INTRODUCTION

Clearance concepts were introduced into the pharmacokinetics discipline in the 1970s by Gillette (1), Rowland et al. (2), and Wilkinson and Shand (3). As elegantly described by Benet (4) in a tribute to Dr. Rowland for his contributions in this area, many experimental observations could not be explained by the prevalent pharmacokinetic theories in the late 1960s and early 1970s before the introduction of clearance concepts. In contrast to the heavy reliance on mathematical relationships for description of the pharmacokinetic behavior of drugs in pre-clearance era, the clearance concepts were based on the relationship between organ clearance and physiologic parameters, such as drug free (unbound) fraction in blood (f_{ub}), intrinsic capability of the eliminating organ to remove the free drug from the body (Cl'_{int}), and the organ blood flow (Q). Since the 1970s, the clearance concepts have been widely used in the literature to explain the pharmacokinetic behavior of many drugs and the effects of changes in the physiological parameters, as a result of disease states, drug-drug interactions, or age, on the blood concentration-time courses of drugs after different routes of administration. The purpose of this communication is to 1) briefly review the fundamental principles of clearance concepts and 2)

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to present examples of the application of clearance concepts in interpretation of pharmacokinetic behavior of drugs.

FUNDAMENTAL CONCEPTS

Organ Clearance

The concept of organ clearance and loss of drugs across an organ of elimination have been described in detail previously (5-7). Briefly, the clearance of an eliminating organ (Cl_i) is the volume of blood cleared of drug by that organ per unit of time, which is defined by the following equation:

$$Cl_i = Q_i \cdot E_i \qquad (1)$$

where E_i is the organ extraction ratio or the fraction of the drug, which is eliminated by the organ during one passage, and Q_i represents the blood flow to the organ. The E_i value may be estimated from the steady state concentration of drug entering (C_{in}) and exiting (C_{out}) the eliminating organ, as shown in Equation 2:

$$E_i = \frac{C_{in} - C_{out}}{C_{in}} \qquad (2)$$

For hepatic clearance (Cl_h), Equation 1 may be rewritten in terms of hepatic extraction ratio (E_h) and blood flow (Q_h):

$$Cl_h = Q_h \cdot E_h \qquad (3)$$

Because the lower and upper limits of E_h are zero and 1, the Cl_h of drugs could potentially range from zero to Q_h.

Physiologic Determinants of E_h and Cl_h

In the liver, drugs travel through the sinusoids and come in contact with the hepatocytes, which contain enzymes for drug metabolism. The drug in the sinusoids may be in two forms of protein bound and free. The extent of extraction (and clearance) of drugs depends on at least 3 factors described below.

1.   Free fraction of the drug in blood (f_{ub}): It is generally assumed that only the free drug may enter the hepatocytes, where it is subject to metabolism or biliary excretion. As a general rule, the higher f_{ub}, the larger are E_h and Cl_h.

2.   Intrinsic clearance of the free drug (Cl'_{int}): This parameter is the intrinsic capability of the liver to remove the drug from the blood in the absence of any flow limitations. In other words, this is the hypothetical volume of blood the liver could clear per unit of time if Q_h were unlimited. As a general rule, when Cl'_{int} increases, both E_h and Cl_h will increase.

3.   The blood flow (Q_h): Q_h affects E_h and Cl_h differently. As the flow increases, the extraction of the drug into the hepatocytes decreases (less time for extraction). However, because Cl_h is a function of both E_h and Q_h (Equation 3), overall, an increase in Q_h results in an increase (less than proportional) in Cl_h.

Effects of Physiologic Determinants of E_h and Cl_h for High and Low E_h Drugs

The statements above are generally true for any drug with any E_h. However, the extent by which each of these three parameters (f_{ub}, Qh, and Cl'_{int}) affects E_h and Cl_h is dependent on the initial E_h of the drug. For drugs with high metabolic capacity (such as propranolol), Cl'_{int} may potentially be several-fold higher than the liver blood flow. Therefore, for these drugs, Cl_h is limited by perfusion (Q_h). Because of high intrinsic metabolic capacity, these drugs have high (close to 1) extraction ratios. At the other extreme, there are drugs for which Cl'_{int} is much less than Q_h. Therefore, Cl_h of these drugs is limited by their Cl'_{int}. These drugs have low E_h (close to zero).

Models of Hepatic Clearance

There are different models that may be used to define the relationship among physiologic parameters and hepatic extraction ratio or clearance (8-15). Two of the major models introduced in the 1970s, which are still widely used, are the well-stirred (or venous equilibrium) and parallel tube (or sinusoidal perfusion) models (8-10). These two models are graphically shown in Fig. 1. As shown in the figure, the well-stirred model assumes that the eliminating organ (liver) is a single well-stirred compartment, with the free concentration of the drug in the blood leaving the liver being in equilibrium with and equal to the free drug concentration in the liver water. The parallel-tube model assumes that the liver is composed of identical parallel tubes with even distribution of the enzymes along the length of the tube, and that the blood concentration of free drug decreases exponentially along the length of the tube (Fig. 1). For the parallel-tube model, the average concentration of the drug in the liver is estimated as the logarithmic averages of the inlet (C_{in}) and outlet (C_{out}) concentrations.

In both models, the hepatic clearance (Cl_h) is related to the hepatic blood flow (Q_h) and the extraction ratio (E_h) by Equation 3. Additionally, in both models, hepatic availability (F_h), which is defined by the $\frac{C_{out}}{C_{in}}$ ratio, is related to E_h using the following equation:

$$F_h = 1 - E_h \qquad (4)$$

As demonstrated in Equation 4, F_h is the fraction of the drug escaping extraction by the liver. In other words, it is the fraction of the concentration entering the liver, which exits the liver intact.

Well-Stirred Model

For the well-stirred model, the relationships between E_h or F_h and f_{ub}, Cl'_{int}, and Q_h are defined by the following equations:

$$E_h = \frac{f_{ub} \cdot Cl'_{int}}{Q_h + f_{ub} \cdot Cl'_{int}} \qquad (5)$$

$$F_h = 1 - E_h = 1 - \frac{f_{ub} \cdot Cl'_{int}}{Q_h + f_{ub} \cdot Cl'_{int}} = \frac{Q_h}{Q_h + f_{ub} \cdot Cl'_{int}} \qquad (6)$$

Therefore, based on the well-stirred model, Cl_h may be defined in terms of its individual components using the following equation:

$$Cl_h = Q_h \times \frac{f_{ub} \cdot Cl'_{int}}{Q_h + f_{ub} \cdot Cl'_{int}} \qquad (7)$$

The Cl'_{int} parameter, which is an indication of the intrinsic capability of the liver to remove the drug from the body in the absence of any flow limitation, is related to the sum of activities of the enzymes that metabolize the drug:

$$Cl'_{int} = \sum_{i=1}^{n} \frac{V_{max,i}}{K_{m,i} + C_{L,u}} \qquad (8)$$
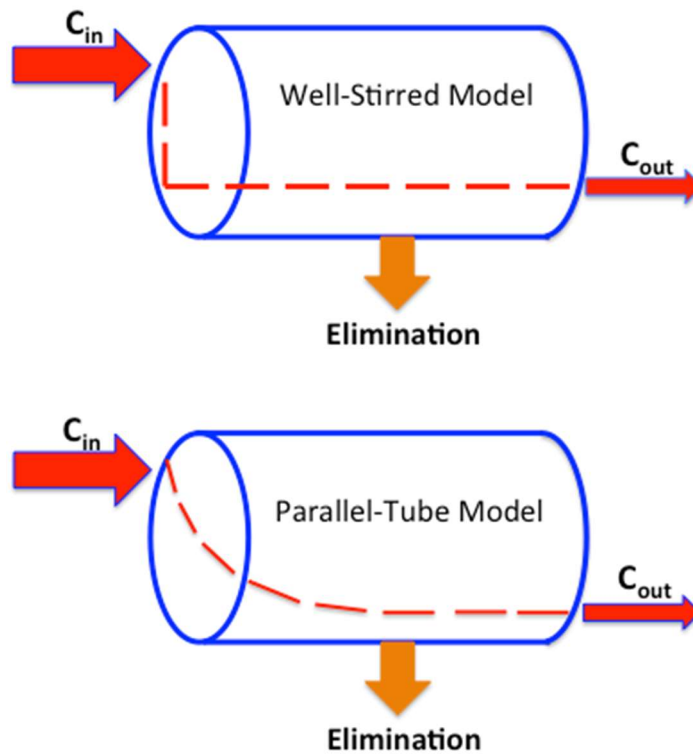
Figure 1. Graphical representations of the well-stirred (top) and parallel-tube (bottom) models of organ clearance. C_{in} and C_{out} represent concentration of the drug entering and leaving the liver, respectively, and the dashed lines indicate the unbound concentration of the drug in the liver along the direction of flow. Adapted from reference (8).

In the above equation, $V_{max,i}$, $K_{m,i}$, and $C_{L,u}$ refer to the maximum velocity and Michaelis-Menten constant of the individual enzymes involved in the metabolism of the drug and the unbound concentration of the drug in the liver, respectively. If the drug is also subject to biliary excretion, Cl'_{int} is the summation of both metabolic and excretory intrinsic clearances.

For simplicity, some investigators use Cl_{int}, instead of the term $f_{ub} \cdot Cl'_{int}$, in Equations 5, 6 and 7:

$$E_h = \frac{Cl_{int}}{Q_h + Cl_{int}} \qquad (9)$$

$$F_h = \frac{Q_h}{Q_h + Cl_{int}} \qquad (10)$$

$$Cl_h = Q_h \times \frac{Cl_{int}}{Q_h + Cl_{int}} \qquad (11)$$

The term Cl_{int} is defined as the intrinsic clearance of the total (free plus unbound) drug. Equation 9 may be rearranged to estimate Cl_{int} when the E_h and Q_h values are known:

$$Cl_{int} = \frac{E_h \times Q_h}{1 - E_h} = \frac{E_h \times Q_h}{F_h} \qquad (12)$$

For drugs with high E_h (i.e., high values of Cl_{int} relative to Q_h), Equations 9, 10, and 11 would simplify to the following equations:

$$E_h = \frac{Cl_{int}}{Q_h (\ll Cl_{int}) + Cl_{int}} \approx \frac{Cl_{int}}{Cl_{int}} \approx 1 \qquad (13)$$

$$F_h = \frac{Q_h}{Q_h (\ll Cl_{int}) + Cl_{int}} \approx \frac{Q_h}{Cl_{int}} \qquad (14)$$

$$Cl_h = Q_h \times \frac{Cl_{int}}{Q_h (\ll Cl_{int}) + Cl_{int}} \approx Q_h \times \frac{Cl_{int}}{Cl_{int}} \approx Q_h \qquad (15)$$

These approximate equations indicate that for drugs with very high E_h (close to 1), F_h is proportionally related to Q_h and inversely related to Cl_{int}. Additionally, the Cl_h of these drugs is perfusion-limited. Examples of drugs with high E_h include propranolol, verapamil, morphine, meperidine, nitroglycerine, and lidocaine.

On the other hand, for drugs with low E_h (i.e., low values of Cl_{int} relative to Q_h), E_h is directly related to Cl_{int} and inversely related Q_h, F_h is almost close to 1, and Cl_h of the drug becomes almost equal to Cl_{int} or $f_{ub} \cdot Cl'_{int}$:

$$E_h = \frac{Cl_{int}}{Q_h + Cl_{int} (\ll Q_h)} \approx \frac{Cl_{int}}{Q_h} \qquad (16)$$

$$F_h = \frac{Q_h}{Q_h + Cl_{int} (\ll Q_h)} \approx \frac{Q_h}{Q_h} \approx 1 \qquad (17)$$

$$Cl_h = Q_h \times \frac{Cl_{int}}{Q_h + C_{int} (\ll Q_h)} \approx Q_h \times \frac{Cl_{int}}{Q_h} \approx Cl_{int} \approx f_{ub} \cdot Cl'_{int} \qquad (18)$$

Examples of drugs with low E_h include warfarin, tolbutamide, diazepam, erythromycin, and theophylline.

Parallel-Tube Model

For the parallel-tube model, the relationships between E_h, F_h, or Cl_h and f_{ub}, Cl'_{int}, and Q_h are given below:

$$E_h = 1 - e^{\frac{-f_{ub} \cdot Cl'_{int}}{Q_h}} = 1 - e^{\frac{-Cl_{int}}{Q_h}} \qquad (19)$$

$$F_h = 1 - E_h = e^{\frac{-f_{ub} \cdot Cl'_{int}}{Q_h}} = e^{\frac{-Cl_{int}}{Q_h}} \qquad (20)$$

$$Cl_h = Q_h \cdot E_h = Q_h \left(1 - e^{\frac{-f_{ub} \cdot Cl'_{int}}{Q_h}} \right) = Q_h \left(1 - e^{\frac{-Cl_{int}}{Q_h}} \right) \qquad (21)$$

If Equation 19 or Equation 20 for the parallel tube model is to be used for the estimation of Cl_{int} when E_h and Q_h are known, this may be done by taking the natural logarithm of the exponential term:

$$\ln(1 - E_h) = \frac{-Cl_{int}}{Q_h} \qquad (22)$$

$$Cl_{int} = -Q_h \times \ln(1 - E_h) = -Q_h \times \ln F_h \qquad (23)$$

Similar to the well-stirred model, for drugs with the very high or very low E_h, Equation 21 predicts that the Cl_h is limited by Q_h or Cl_{int} ($f_{ub} \cdot Cl'_{int}$), respectively.

For both models, the above equations assume that the permeability of the drug across the interstitial space and hepatocyte membranes is much higher than the Cl'_{int} of the drug. Therefore, permeability is not the rate-limiting step in the elimination of the drug. However, if permeability becomes an issue, these equations need to be modified to account for the permeability parameters. Pravastatin is an

example of drugs with uptake permeability-limited elimination (16).

Differences between the Models in Predictions of Pharmacokinetics of Drugs

Simulations have shown (8) that the two models behave relatively close to each other with regard to the effects of changes in f_{ub} and/or Cl'_{int} (i.e., Cl_{int}). However, the major difference between the two models is with regard to their prediction of hepatic availability (F_h) based on changes in Q_h for the high E_h dugs. Although the differences between the two models for the prediction of E_h even at high E_h is relatively small (30%), this translates to very large differences between the two models in prediction of F_h and oral AUC of drugs with high hepatic E_h (8). This is because at high E_h, F_h changes linearly relative to Q_h for the well-stirred model as demonstrated in Equation 14 ($F_h \approx Q_h/Cl_{int}$). However, for the parallel-tube model, F_h changes exponentially relative to Q_h, as demonstrated in Equation 20 ($F_h = e^{-Cl_{int}/Q_h}$). Therefore, at the extreme E_h value of 0.99, the difference in prediction of F_h for the two models may be over a thousand-fold (8). Further experimental studies (9, 10) have suggested that for most drugs, such as lidocaine, the well-stirred model predicts the clearance of the drug better. Therefore, most investigators use the well-stirred model in their analysis of hepatic clearance of drugs, unless it is proven to be not applicable. However, it has recently been argued that the studies designed to distinguish between the two models are inherently biased towards the well-stirred model (17), a notion that is subject to debate (18) and outside the scope of this review. Because of the prevalence of the use of the well-stirred model in the literature, we will use this model for the remainder of our discussion and case studies presented here.

The Relationship between Hepatic Availability (F_h) and Oral Bioavailability (F)

Figure 2 depicts the potential barriers for an oral dose to reach systemic circulation, which may result in the loss of drugs after their oral administration (19). After the intravenous dosing, however, the drug is introduced directly into the systemic circulation. Therefore, the oral bioavailability of drugs (F), or the extent by which an oral dose enters the systemic circulation, is defined by the ratio of the blood AUCs after the oral and intravenous administration. As demonstrated in Fig. 2, after oral administration, the drug is absorbed from the gastrointestinal tract and passes through the liver before reaching the systemic circulation. This means the orally-administered drug entering the systemic circulation has to pass through the liver first ("first-pass effect"). This is different from the intravenous administration, where the drug is directly introduced into the systemic circulation without passing through the liver first (Fig. 2). Obviously, in both cases (intravenous and oral), after reaching the systemic circulation, a fraction of the drug will be passing through different organs, including the liver, with each circulation. However, the oral drug has one extra "pass" through the liver during the absorption process. Therefore, the oral bioavailability of drugs (F) is influenced by their hepatic availability (F_h). In addition to F_h, F is also affected by the loss of drug during the absorption process such as incomplete absorption and/or metabolism/degradation in the gastrointestinal tract (Fig. 2). To clarify this, consider an example where 200 mg of a drug is administered orally to a patient. Assume only 40% of the dose is absorbed orally (fraction of the dose absorbed or F_{ab} of 0.4), which means only 80 mg reaches the enterocytes. If the drug is subject to metabolism in the gut, resulting in 50% of the drug escaping metabolism in the enterocytes (F_g of 0.5), only 40 mg of the drug reaches the liver. Assuming a hepatic E_h of 0.7 (F_h or hepatic availability of 0.3), 30% of the drug reaching the liver will pass intact into the systemic circulation (0.3 x 40 mg or 12 mg). This means that out of the 200-mg oral dose, only 12 mg reaches the systemic circulation. Therefore, the oral bioavailability of this drug (relative to intravenous administration), which may be estimated experimentally by the oral AUC: intravenous AUC ratio, is only 0.06 or 6% (12/200). The following equation describes the relationship among F, F_{ab}, F_g, and F_h:

$$F = F_{ab} \times F_g \times F_h \quad (24)$$

$$F = 0.4 \times 0.5 \times 0.3 = 0.06$$

It should be noted that if the absorption of the drug is complete and there is no gastrointestinal metabolism (i.e., $F_{ab} \times F_g = 1$), the hepatic availability and oral bioavailability would be the same. In other words, the oral bioavailability of drugs cannot be more than their hepatic availability.
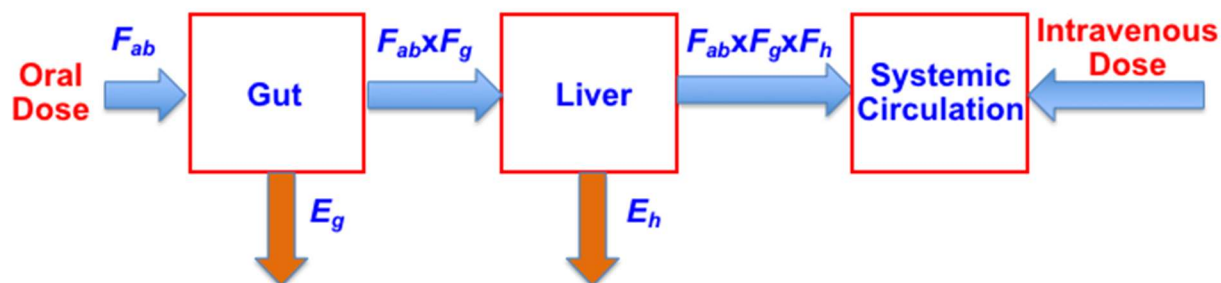
Figure 2. Barriers to drug entry into the systemic circulation after oral administration of drugs. For comparison, direct introduction of the drug into the systemic circulation after intravenous administration is also shown. Abbreviations: F_{ab}, fraction of the dose absorbed; F_g, fraction of the dose escaping gut metabolism; F_h, fraction of the dose escaping liver metabolism; E_g, gut extraction ratio; E_h, liver extraction ratio. Adapted from reference (19).

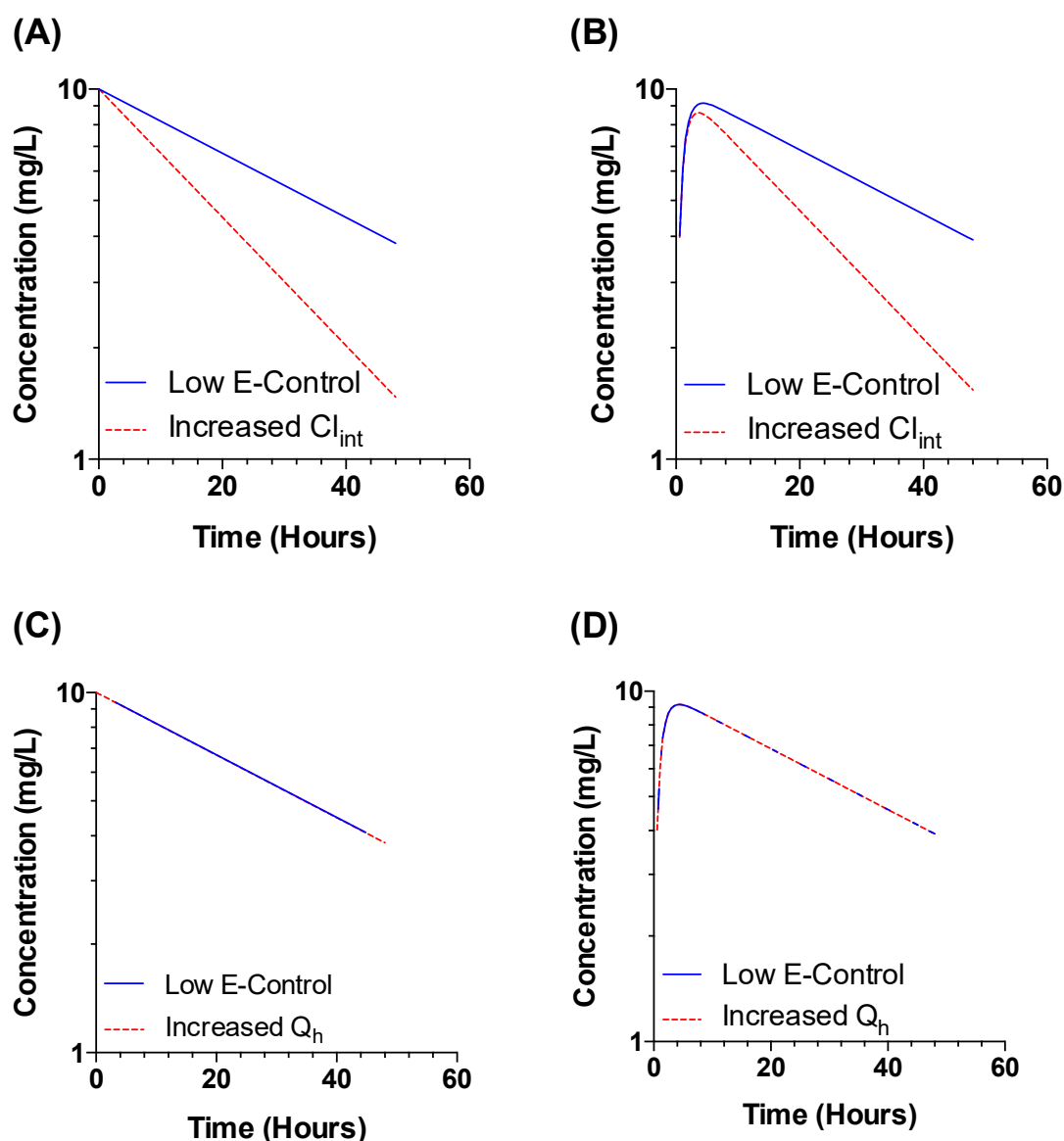## Effects of Q_h, f_{ub}, and Cl'_{int} on the Blood Concentration-Time Courses of Low and High E_h Drugs

After intravenous dosing, the only pharmacokinetic parameter that affects the AUC of a drug is its systemic Cl. However, after oral dosing, the AUC is dependent on both the systemic Cl and oral availability (F), both of which are subject to change if f_{ub}, Cl'_{int}, and/or Q_h is changed. Here, we examine the effects of a change in the determinants of Cl_h of drugs on their blood concentration-time profiles for the low and high E_h drugs. For simplicity, we assume that the drug is eliminated by hepatic metabolism only, which means the systemic Cl is equal to Cl_h. Additionally, we assume that the oral absorption of the drug is complete with no metabolism in the gut, which means the oral availability of the drug (F) is equal to its hepatic availability (F_h).

Low Extraction Ratio Drugs

The characteristics of a hypothetical drug with a very low E_h value of 0.0011 under normal conditions and when the Cl_{int} (Cl'_{int} or fub) or Q_h values are increased by a factor of 2 are listed in Table 1. Additionally, the corresponding blood concentration-time courses of the drug are presented in Fig. 3. After selection of Cl'_{int} and f_{ub} values for this drug to generate a low Cl_{int} value (0.1 L/h) relative to the hepatic blood flow (90 L/h), the E_h, F_h, and Cl_h are calculated using Equations 9, 4, and 3, respectively. As stated above, for a low E_h drug, Cl_h is expected to be close to Cl_{int} or $f_{ub} \cdot Cl'_{int}$. This is also shown in Table 1 for Control subjects, where the Cl_{int} and Cl_h values are almost identical for this

hypothetical drug. Additionally, F_h for this drug is very high (almost 1) (Table 1). Assuming a volume of distribution of 5 L, the half-life of the drug is 35 h in Control subjects (Table 1). As demonstrated in Table 1, the changes in either Cl'_{int} or f_{ub} would produce the same net effect on the other kinetic parameters of the drug because they are both reflected in the Cl_{int} value. A two-fold increase in Cl'_{int} or f_{ub} results in a two-fold increase in Cl_{int}, E_h, and Cl_h for this low E_h drug (Table 1). Additionally, a two-fold increase in Cl_h also results in a two-fold decrease in the half-life of the drug (Table 1). However, the F_h value of the drug remains close to 1, regardless of the changes in f_{ub} or Cl'_{int} (Table 1). As demonstrated in Figs. 3A and 3B, a two-fold increase in Cl_{int} for a low E_h drug results in an almost two-fold increase in its Cl, which is demonstrated by a corresponding two-fold decrease in the AUC and half-life after both intravenous and oral dosing. An example of such change is the effects of co-administration of warfarin, a low E_h drug, with rifampin, which induces the metabolism of warfarin (higher Cl'_{int}), resulting in a higher clearance, lower AUC, and a shorter half-life (20).

As for Q_h, neither intravenous nor oral profile of a low E_h drug is affected by a change in Q_h (Figs. 3C and 3D). Although a two-fold increase in Q_h results in a two-fold decrease in E_h, the Cl_h value remains unchanged because the decrease in E_h is compensated by a corresponding increase in Q_h (Table 1). This is consistent with the notion that the Cl of a low E_h drugs is mostly dependent on f_{ub} and Cl'_{int} (Equation 18). Additionally, F_h of the drug is very high regardless of the change in Q_h (Table 1).

Figure 3. Effects of a two-fold increase in Cl_{int} (f_{ub} or Cl'_{int}) (top panels) or Q_h (bottom panels) on the blood concentration-time courses of a hypothetical low E_h drug after intravenous (left) or oral (right) administration of a 50-mg dose of the drug. The kinetic parameters are listed in Table 1.

Table 1. The pharmacokinetic parameters of a hypothetical drug [a] with low hepatic extraction ratio (E_h) in the absence (Control) and presence of changes in the intrinsic capability of the liver to remove the free drug (Cl'_{int}), free drug fraction in blood (f_{ub}), or hepatic blood flow (Q_h).

Condition	Cl'_{int} (L/h)	f_{ub}	Cl_{int} (L/h)	Q_h (L/h)	E_h[b]	F_h[b]	Cl_h[b] (L/h)	V (L)	$t_{1/2}$[c] (h)
Control	10	0.01	0.10	90	0.00111	0.999	0.0999	5	34.7
↑ Cl'_{int} x 2	20	0.01	0.20	90	0.00222	0.998	0.200	5	17.4
↑ f_{ub} x 2	10	0.02	0.20	90	0.00222	0.998	0.200	5	17.4
↑ Q_h x 2	10	0.01	0.10	180	0.000555	0.999	0.0999	5	34.7

[a] The hypothetical drug has a Cl'_{int} of 10 L/h, a f_{ub} of 0.01, and a volume of distribution (V) of 5 L under baseline conditions, with elimination through the liver only.

[b] E_h, F_h, and Cl_h were estimated from the values of Cl'_{int}, f_{ub}, and Q_h using Equations 9, 4, and 3, respectively.

[c] Half-life ($t_{1/2}$) is estimated from $t_{1/2} = \frac{0.693 \times V}{Cl}$, where Cl is assumed to be equal to Cl_h.

High Extraction Ratio Drugs

The pharmacokinetic characteristics of a high E_h drug in the absence (Control) or presence of changes in Cl'_{int}, f_{ub}, or Q_h are listed in Table 2. Additionally, the corresponding blood concentration-time courses are shown in Fig. 4. The Cl_{int} of the drug in Control subjects (1500 L/h) is much more than the Q_h of 90 L/h, hence a high E_h of 0.943 (Table 2). As expected, the drug has a very low F_h value of 0.0566. Additionally, assuming a V of 400 L, the drug has a half-life of 3.26 h (Table 2). In contrast to the low E_h drug (Table 1), doubling the Cl_{int} by doubling either f_{ub} or Cl'_{int} does not substantially affect the E_h, Cl_h, or half-life of this high E_h drug (Table 2). The lack of changes in the Cl_h of this high E_h drug after doubling Cl_{int} is predictable because the Cl_h of these drugs are mostly perfusion limited. However, the hepatic availability (and oral bioavailability) of the drug is reduced by almost 50% when Cl_{int} is increased by a factor of 2 (Table 2). This is because after oral dosing, the F_h of the high E_h drugs is almost linearly (inversely) related to their Cl_{int} (Equation 14). Consequently, whereas the blood concentration-time courses of the high E_h drug after the intravenous administration are insensitive to changes in Cl_{int} (no change in Cl) (Fig. 4A), the F_h, blood concentrations, and AUC of the drug after the oral administration are reduced by an almost 50% in the presence of a two-fold increase in Cl_{int} (Fig. 4B).

The above discussion clearly shows that the disease states and/or drug interactions that affect Cl'_{int} and/or f_{ub} would be reflected in the blood concentration-time courses of high E_h drugs only after the oral dosing, but not after the intravenous administration (Figs. 4A and 4B).

An example of such effect is the interaction between the enzyme inducer pentobarbital and the high E_h drug alprenolol reported by Alvan et al. (21).

In that study, a single dose of alprenolol was administered intravenously or orally before and after 10-14 daily doses of pentobarbital. Whereas pentobarbital reduced the AUC of the orally-administered alprenolol by more than 75% without affecting the alprenolol's half-life, it did not significantly affect the AUC or half-life of the drug after its intravenous administration.

As for Q_h, in contrast to the low E_h drugs, the pharmacokinetics of high E_h drugs are affected by changes in this parameter after both intravenous and oral administration. As shown in Table 2, doubling Q_h hardly affects the E_h value but almost doubles the F_h and Cl_h of the drug. Therefore, the blood concentration-time course of the drug after the intravenous administration shows a 50% reduction in the AUC and half-life (Fig. 4C). The oral profile would be affected by changes in both Cl and F_h (Fig. 4D). After oral dosing, an increase in Cl due to an increase in Q_h causes a proportional reduction in AUC and shortening of half-life. However, an increase in Q_h also proportionally increases F_h ($F_h \approx \frac{Q_h}{Cl_{int}}$) and AUC. Therefore, as demonstrated in Fig. 4D, the AUC after oral dosing remains the same. Please note that the above discussions are based on the well-stirred model, which predicts that oral AUC is not dependent on Q_h for drugs that are eliminated by hepatic metabolism:

$$AUC_{PO} = \frac{F \cdot Dose}{Cl} \qquad (25)$$

In the above equation, an increase in Q_h causes proportional increases in both Cl and F, without any significant changes in the AUC for a drug with high E_h.

Table 2. The pharmacokinetic parameters of a hypothetical drug[a] with high hepatic extraction ratio (E_h) in the absence (Control) and presence of changes in the intrinsic capability of the liver to remove the free drug (Cl'_{int}), free drug fraction in blood (f_{ub}), or hepatic blood flow (Q_h)

Condition	Cl'_{int} (L/h)	f_{ub}	Cl_{int} (L/h)	Q_h (L/h)	E_h[b]	F_h[b]	Cl_h[b] (L/h)	V (L)	$t_{1/2}$[c] (h)
Control	15000	0.1	1500	90	0.943	0.0566	84.9	400	3.26
↑ Cl'_{int} x 2	30000	0.1	3000	90	0.971	0.0291	87.4	400	3.17
↑ f_{ub} x 2	15000	0.2	3000	90	0.971	0.0291	87.4	400	3.17
↑ Q_h x 2	15000	0.1	1500	180	0.893	0.107	161	400	1.72

[a] The hypothetical drug has a Cl'_{int} of 15000 L/h, a f_{ub} of 0.1, and a volume of distribution (V) of 400 L under baseline conditions, with elimination through the liver only.

[b] E_h, F_h, and Cl_h were estimated from the values of Cl'_{int}, f_{ub}, and Q_h using Equations 9, 4, and 3, respectively.

[c] Half-life ($t_{1/2}$) is estimated from $t_{1/2} = \frac{0.693 \times V}{Cl}$, where Cl is assumed to be equal to Cl_h.
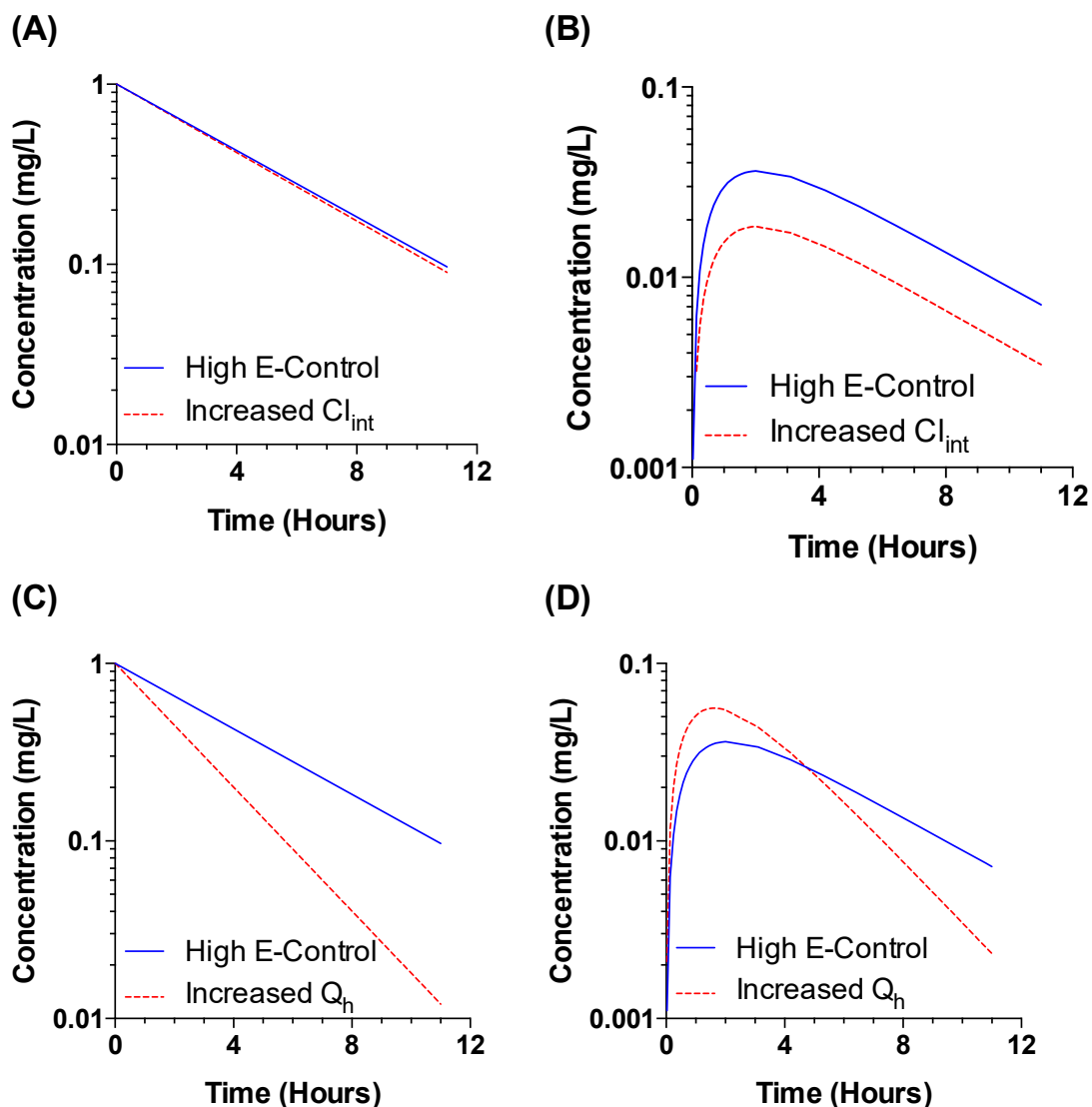
Figure 4. Effects of a two-fold increase in Cl_{int} (f_{ub} or Cl'_{int}) (top panels) or Q_h (bottom panels) on the blood concentration-time courses of a hypothetical high E_h drug after intravenous (left) or oral (right) administration of a 400-mg dose of the drug. The kinetic parameters are listed in Table 2.

An example of the effects of changes in the blood flow on the pharmacokinetics in the literature is related to the interaction of lidocaine, a high E_h drug, with metoprolol and propranolol, which reduce the cardiac output and hepatic blood flow (22). Lidocaine was administered by a short intravenous infusion alone or 1 day after pretreatment with metoprolol (50 mg orally every 6 h) or propranolol (40 mg orally every 6 h). Metoprolol and propranolol reduced the clearance of intravenous lidocaine by 30% and 50% respectively, presumably due to their effects on the hepatic blood flow.

It should be noted that the changes in the clearance, in addition to affecting the half-life of the drug, also affects the maximum plasma concentration (C_{max}) and the time to reach C_{max} for orally-administered drug.

Oral Clearance and Intrinsic Clearance
The well-stirred model predicts that the oral clearance (Cl_o or Cl/F) of a drug with hepatic elimination alone and no loss in the gastrointestinal tract ($F = F_h$) is in fact equal to its Cl_{int} ($f_{ub} \cdot Cl'_{int}$), therefore, being independent of Q_h regardless of drug's E_h:

$$Cl_O = \frac{Dose_{po}}{AUC_{po}} = \frac{Cl}{F} = \frac{Q_h \times E_h}{F_h} = \frac{Q_h \times \frac{Cl_{int}}{Q_h + Cl_{int}}}{\frac{Q_h}{Q_h + Cl_{int}}} =$$

$$Cl_{int} = f_{ub} \cdot Cl'_{int} \qquad (26)$$

Consequently, it is not surprising that the oral AUC is not affected by Q_h, as shown in Figs. 3D and 4D for the low and high E_h drugs, respectively. Even if the F_{ab} and/or F_g values are significantly lower than 1, Cl_o is still a function of Cl_{int} (and not Q_h) as shown below:

$$Cl_O = \frac{Dose_{po}}{AUC_{po}} = \frac{Cl}{F} = \frac{Q_h \times E_h}{F_{ab} \times F_g \times F_h} = \frac{Q_h \times \frac{Cl_{int}}{Q_h + Cl_{int}}}{F_{ab} \times F_g \times \frac{Q_h}{Q_h + Cl_{int}}} =$$

$$\frac{Cl_{int}}{F_{ab} \times F_g} \qquad (27)$$

EXAMPLES OF APPLICATION OF CLEARNCE CONCEPTS IN INTERPRETATION OF PHARMACOKINETIC BEHAVIOR OF DRUGS

Estimation of Hepatic Extraction Ratio of Drugs from In Vivo Pharmacokinetic Data

Equation 3 may be rearranged to estimate E_h of a drug after its intravenous administration:

$$E_h = \frac{Cl_h}{Q_h} \qquad (28)$$

After intravenous administration of the drug, the systemic Cl is estimated from the blood concentration-time data, and an estimate of Cl_h is obtained by either assuming Cl_h is equal to systemic clearance (i.e., for drugs with hepatic elimination only) or by subtracting renal Cl from the systemic clearance (i.e., for drugs with both renal and hepatic elimination), as discussed in detail recently (23). An estimate of E_h is then obtained using the calculated Cl_h and an average Q_h. The estimates of E_h value can then be used to predict the pharmacokinetics and blood concentration-time profiles of the drug in the presence of changes in the physiologic determinants of clearance such as organ blood flow, intrinsic clearance, or f_{ub}. The assumptions inherent to this type of calculation and the ramifications of using plasma or serum concentrations, instead of blood concentrations, and/or liver plasma flow, instead of liver blood flow, were recently discussed in detail (23). Briefly, it was shown that if plasma clearance and hepatic blood flow are used, the estimated E_h

would be accurate only if the blood: plasma concentration (B:P) ratio of the drug is equal to 1. However, the use of the plasma concentrations and plasma liver flow will always result in an overestimation of the true E_h unless the drug does not penetrate the red blood cells (23).

Prediction of Oral Bioavailability from Oral Data Only

In some cases, administration of a drug by intravenous method is not feasible or an injectable dosage form is not available. Using the clearance concepts, and some assumptions, it is possible to obtain a rough estimate of the extent of oral bioavailability of drugs using oral data only. We reported (24) the oral clearance (Cl_o) of tetrabenazine, a drug used for the control of movement disorders, in four patients with tardive dyskinesia. The Cl_o values were estimated by dividing the oral dose by the AUC. We then used the following equation, which is based on Equations 10 and 26 to estimate F_h in these patients, assuming a hepatic blood flow of 1.28 (L/h)/kg and complete oral absorption and intestinal availability (i.e., $F = F_h$):

$$F = F_h = \frac{Q_h}{Q_h + Cl_{int}} = \frac{Q_h}{Q_h + Cl_o} \qquad (29)$$

The estimated F values were 0.05, 0.08, 0.07, and 0.02 for patients with Cl_o values of 431, 252, 299, and 1090 (ml/min)/kg, respectively (24). Based on these values, we suggested that the oral bioavailability (F) of tetrabenazine in humans is very low. Indeed, the F value obtained in another study (25) after the intravenous and oral administration of the drug to humans (0.05) was very close to the values obtained from the oral data alone.

It should be noted that these calculations assume elimination by the liver alone (i.e., no renal or gastrointestinal clearance). However, a modified version of Equation 29 may be provided for drugs with both renal and hepatic clearance pathways, as shown below:

$$Cl_O = \frac{Cl}{F} = \frac{Cl_r + Cl_h}{F_h} = \frac{Cl_r + Q_h \times E_h}{F_h} =$$

$$\frac{Cl_r + Q_h \times (1 - F_h)}{F_h} = \frac{Cl_r + Q_h - Q_h F_h}{F_h} \qquad (30)$$

$$Cl_O \times F_h = Cl_r + Q_h - Q_h F_h \qquad (31)$$

$$F_h(Cl_O + Q_h) = Cl_r + Q_h \qquad (32)$$

$$F_h = \frac{Cl_r + Q_h}{Q_h + Cl_o} \qquad (33)$$

After determination of Cl_r and Cl_o, Equation 33 may be used to estimate F_h (or F) for drugs with both hepatic and renal elimination.

Differentiation of Gut and Hepatic First-Pass Metabolism of Drugs

An application of clearance concept in the literature is for differentiation of first-pass metabolism in the gut from that in the liver. After oral administration, the oral bioavailability of a drug (F) is a function of the fraction of the drug absorbed (F_{ab}), fraction of the drug escaping metabolism in the gastrointestinal tract (F_g), and fraction of the drug escaping the hepatic metabolism or hepatic availability (F_h), as demonstrated in Fig. 2 and Equation 24. Once a drug is administered by both oral and intravenous routes, F may be estimated from the oral and intravenous AUC values (correcting for the dose). Additionally, the hepatic E_h and F_h may be estimated from the intravenous data using Equations 28 and 4, respectively, assuming an average Q_h of 1500 mL/min in a 70-kg subject. Consequently, the value of $F_{ab} \times F_g$ may be estimated from the F and F_h values by rearranging Equation 24:

$$F_{ab} \times F_g = \frac{F}{F_h} \qquad (34)$$

This method allows one to separate the contribution of the liver (F_h) from that of the gut ($F_{ab} \times F_g$) to the overall loss of the drug after the oral administration. However, in the absence of any additional information about the extent of absorption of the drug, F_{ab} and F_g cannot be separated from each other.

An application of this method was demonstrated by Hebert et al. (26), who administered a single oral (10 mg/kg) or intravenous (3 mg/kg) dose of cyclosporine to six healthy subjects and found average blood AUC values of 8986 and 10092 ng.h/mL, respectively. Based on the oral and intravenous data, the oral bioavailability (F) of cyclosporine in these patients was 0.27:

$$F = \frac{AUC_{PO}}{AUC_{iv}} \times \frac{Dose_{iv}}{Dose_{po}} \qquad (35)$$
$$F = \frac{8986}{10092} \times \frac{3}{10} = 0.27$$

The systemic clearance of cyclosporine based on the intravenous dose of 3 mg/kg and AUC_{iv} of 10092 was 0.3 L/kg:

$$Cl = \frac{Dose_{iv}}{AUC_{iv}} = \frac{3000}{10092} = 0.3 \text{ L/kg}$$

Assuming the systemic clearance of cyclosporine is equal to its hepatic clearance (i.e., gut clearance doses not significantly contribute to the systemic clearance) and a Q_h of 1.286 L/h/kg (90 L/h in a 70-kg subject), the E_h and F_h values were then estimated:

$$E_h = \frac{0.3}{1.286} = 0.23$$
$$F_h = 1 - 0.23 = 0.77$$

Using the predicted F_h and measured F, the $F_{ab} \times F_g$ value of cyclosporine was then determined:

$$F_{ab} \times F_g = \frac{F}{F_h} = \frac{0.27}{0.77} = 0.35$$

A comparison of F (0.27), F_h (0.77), and $F_{ab} \times F_g$ (0.35) values of cyclosporine in these patients, clearly suggests that the low oral bioavailability of the drug is mostly due to the loss of drug in the gastrointestinal tract than its loss during the first-pass metabolism in the liver. Later, Galetin et al. (27) used this method to estimate the F_g of a number of drugs, with an assumption that the absorption of the drugs, if experimentally unknown, was complete ($F_{ab} = 1$).

Differentiation of Incomplete Absorption from the First-Pass Metabolism in the Gut and Liver

Wu et al. (19) proposed a method to determine F_{ab}, F_g, and F_h separately, based on the intravenous and oral administration of a drug in the absence and presence of interacting drugs known to inhibit its metabolism. If the interacting and victim drugs are administered several hours apart from each other, one may assume that the interacting drug would only affect the metabolism and not the extent of absorption of the victim drug. In that case, the following equations may be defined:

$$F = F_{ab} \times F_g \times F_h$$
In the Absence of Interaction

$$F_{itx} = F_{ab} \times F_{g,itx} \times F_{h,itx}$$
In the Presence of Interaction

where the subscript itx indicates the parameter in the presence of the interacting drug. The values of $F_{ab} \times F_g$ or $F_{ab} \times F_{g,itx}$ may be easily estimated from F and F_h or F_{itx} and $F_{h,itx}$, respectively, using Equation 34.

In the case of an enzyme inhibitor interaction, the value of F_{ab} may be estimated between its two minimum and maximum boundaries. The maximum boundary of F_{ab} is 1. The minimum boundary of F_{ab} is assuming $F_{g,itx}$ is equal to 1 (i.e., complete inhibition of gut metabolism). Setting F_{ab} to its maximum (i.e., 1) or minimum (calculated from the enzyme inhibition data) boundaries, the values of F_g in control subjects (i.e., the absence of drug interaction) may be estimated between a minimum and a maximum.

The method was used to determine the contribution of hepatic and gastrointestinal first-pass metabolism to the overall F of cyclosporine in the presence and absence of two enzyme inhibitors (erythromycin and ketoconazole) and an enzyme inducer (rifampin) (19). Here, we present the data (28) and calculations (19) for the ketoconazole inhibition study, which was conducted in five healthy subjects. The doses and average blood AUC values after the oral and intravenous administration of cyclosporine in the absence (Control) and presence of ketoconazole are listed in Table 3 (28).

Using the average values presented in Table 3, The F, F_h, and $F_{ab} \times F_g$ values in Control subjects may be estimated as shown below:

$$F = \frac{AUC_{PO}}{AUC_{iv}} \times \frac{Dose_{iv}}{Dose_{po}} = \frac{5938}{6683} \times \frac{0.5}{2} = 0.222$$

$$Cl = \frac{Dose_{iv}}{AUC_{iv}} = \frac{2000}{6683} = 0.299 \; L/h/kg$$

$$F_h = 1 - E_h = 1 - \frac{Cl_h}{Q_h} = 1 - \frac{0.299}{1.28} = 1 - 0.234$$
$$= 0.766$$

$$F_{ab} \times F_g = \frac{F}{F_h} = \frac{0.222}{0.766} = 0.290$$

Similarly, F_{itx}, $F_{h,itx}$, and $F_{ab} \times F_{g,itx}$ in the presence of ketoconazole may be calculated using the respective data in Table 3. The summary of the above calculations, based on the average AUC value reported before (28), are presented in Table 4.

The data in the presence of ketoconazole, presented in Table 4, suggest that two boundaries of F_{ab} are 1 and 0.722. Consequently, F_g may be estimated at these two boundaries:

$$F_{ab} \times F_g = 0.290$$

$$F_g = \frac{0.290}{F_{ab}}$$

$$F_{g-low} = \frac{0.290}{1} = 0.290$$

$$F_{g-upp} = \frac{0.290}{0.722} = 0.402$$

Therefore, the lower (F_{g-low}) and upper (F_{g-upp}) limits of F_g for cyclosporine in healthy volunteers are 0.290 and 0.402, whereas the lower and upper limits of F_{ab} are 0.722 and 1, respectively. Considering an F_h of 0.766 (Table 4), the data suggest that the low oral bioavailability of cyclosporine in Control subjects (0.222) is indeed mostly due to its first-pass metabolism in the gut (F_g of 0.290-0.402), whereas the oral absorption of the formulation is relatively high (F_{ab} of 0.722-1.0). Again, these calculations assume that gut clearance, although reducing the presystemic availability of the drug, does not significantly contribute to the systemic clearance of the drug, meaning that Cl is equal to Cl_h.

More recently, Hisaka et al. (29) developed a new method based on the concept of drug-drug interactions to estimate F_g values from the changes in the AUC and half-life values of the victim drug in the presence of the perpetrating drug. The method is based on the idea that the inhibition of intestinal metabolism causes a change in the AUC without any changes in the plasma half-life. However, inhibition of hepatic metabolism results in changes in both half-life and AUC, unless the clearance of the drug is flow-limited (i.e., drugs with high extraction ratio). Nevertheless, the method still requires an approximation of F_{ab} value. Using this method, the authors estimated F_g values of 0.56 ± 0.29 (mean $\pm$ SD) for 20 drugs that were CYP3A substrates and 0.86 ± 0.11 for 8 drugs that were not CYP3A substrates. The interested readers are referred to the original article (29) for details about the method and derivation of equations.

Table 3. The dose and average AUC values of cyclosporine after intravenous and oral administration of the drug to healthy subjects in the absence (Control) and presence of ketoconazole[a]

	Dose, mg/kg		AUC, ng.h/mL	
	Intravenous	Oral	Intravenous	Oral
Control	2	8	6683	5938
Plus Ketoconazole	0.5	2	3120	7883
[a] Data from reference (28).				

Table 4. The calculated oral bioavailability (F) and estimated hepatic availability (F_h) and products of fraction absorbed (F_{ab}) and gut availability (F_g) of cyclosporine in the absence (Control) and presence of ketoconazole[a]

	F	F_h	$F_{ab} . F_g$
Control	0.222	0.766	0.290
Plus Ketoconazole	0.632	0.875	0.722
[a] Calculations are based on the average AUC values and doses presented in Table 3.			

Estimation of Gastrointestinal Availability from Grapefruit Juice-Drug Interaction Studies

Grapefruit juice (GFJ) components are believed to irreversibly inhibit intestinal CYP3A4, without any major effect on the liver CYP3A4 (30). Therefore, co-administration of grapefruit juice with an orally-administered drug that is subject to intestinal CYP3A4 metabolism inhibits the drug's CYP3A4-mediated, presystemic intestinal metabolism. Gertz et al. (31) used available data in the literature related to the interaction of drugs with grapefruit juice to estimate their F_g, using the following equation:

$$F_g = \frac{AUC_{Control}}{AUC_{GFJ}} \qquad (36)$$

where $AUC_{Control}$ and AUC_{GFJ} are the AUC of the drug in the absence and presence of GFJ administration, respectively. This method assumes complete intestinal metabolism of the drug through CYP3A4, complete inhibition of intestinal metabolism with GFJ, and no effect of GFJ on the systemic (liver) metabolism or clearance or the extent of absorption (F_{ab}) of the drug. Additionally, the authors (31) suggested that the method's applicability to drugs that are subject to transport or efflux in the gastrointestinal tract is limited.

LIMITATIONS

It should be noted that while clearance concepts are very useful in predicting the pharmacokinetic behavior of drugs, their applications to estimation of F and its components (F_{ab}, F_g, and F_h) in different situations presented here are associated with a number of assumptions, hence subject to some degree of error. First, the AUC and clearance terms in the above equations are based on the blood concentrations of the drug. Therefore, the use of plasma values, which are commonly measured, may introduce substantial errors in the estimation of the kinetic parameters (23). Second, a number of calculations listed above use an average liver blood flow (e.g., 1500 mL/min), which might be different than the actual Q_h in the studied subjects. This is because although intra- and inter-individual variabilities in the hepatic blood flow in healthy subjects under controlled conditions appears to be relatively low (32-34), physiological factors (e.g., posture and exercise), pharmacological interventions (e.g., beta-blockers), disease states (e.g., heart failure), or food ingestion may significantly affect hepatic blood flow (35, 36). Other assumptions include linear pharmacokinetics and a constant systemic clearance after different routes of administration. With specific reference to methods estimating F_g, additional assumptions are that the intestinal clearance, although reducing the presystemic availability of the drug, does not significantly contribute to the systemic clearance of the drug. Lastly, estimation of F_g is also based on the assumption that the drug is not subject to influx or efflux transporters. Nevertheless, despite these assumptions and/or limitations, application of clearance concepts has resulted in substantial improvement in our understanding of the pharmacokinetics of many drugs.

CONCLUSIONS

In conclusion, development of clearance concepts has significantly moved the discipline of pharmacokinetics forward. Although clearance concepts are more discussed in terms of hepatic clearance, they are equally applicable to clearance by other eliminating organs, such as the kidneys. The concepts allow definition of organ and total clearance values in terms of physiologic parameters such as organ blood flow and intrinsic capability of the eliminating organ to remove the drug from the body. Furthermore, the clearance concepts allow prediction of the pharmacokinetics of drugs after intra- and extravascular routes in the presence of disease states, drug interactions, or as a result of patients' age. Researchers have applied these concepts to predict the oral bioavailability of drugs in the absence of otherwise needed intravenous data, to distinguish between the role of liver and gut in the first pass metabolism of drugs, and to differentiate between the incomplete oral absorption and metabolism in the gut after oral administration of drugs. More than 45 years after their introduction, clearance concepts remain a powerful tool in explaining the pharmacokinetics of drugs and predicting the changes in the blood concentration-time course of drugs when the underlying physiologic parameters are altered.

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