General Treatment of the Enterohepatic Recirculation of Drugs and Its Influence on the Area Under the Plasma Level Curves, Bioavailability, and Clearance

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A general treatment of enterohepatic recirculation of drugs has been developed based on the fraction of drug in systemic circulation that is excreted in the bile and the fraction of drug reabsorbed from the gut that reaches systemic circulation in each enterohepatic cycle. The deduced equations make it possible to establish mathematical relationships between the areas under the blood level curves (AUC) of a drug when administered to normal and bile duct-cannulated animals and to predict the effect of enterohepatic recycling on bioavailability and clearance. The results were compared with those obtained by other authors using different approaches to enterohepatic recirculation, and some discrepancies were found in the equations describing the effect of enterohepatic recycling on AUC and bioavailability of drugs. The cause of such discrepancies and the problems associated with the prediction of hepatic extraction ratio from *in vitro* studies are discussed.

KEY WORDS: enterohepatic recirculation; pharmacokinetics; bioavailability; clearance; biliary excretion; first-pass effect.

INTRODUCTION

The effects of enterohepatic circulation on pharmacokinetic parameters such as terminal half-life, clearance, apparent volume of distribution, area under the blood drug concentration versus time curve, and bioavailability have been examined by means of simulation studies and analytical evaluations of enterohepatic circulation (1–10). The purpose of the present study was to develop a mathematical treatment of enterohepatic circulation of drugs, which, although it assumes linear pharmacokinetics, is based on amounts of drug that reach systemic circulation rather than on rates of transfer between body compartments.

METHODS

In the framework of this paper, absorption is defined as the process by which a drug is transferred into the intestinal wall from the intestinal lumen, and the expression "complete absorption" means that the entire amount of drug disappears from the intestinal lumen by passing across the intestinal wall, although it may be subject to intestinal mucosa metabolism.

In the following analysis, drug disposition was assumed to be linear. Complete intestinal absorption of unchanged and conjugated drug excreted in the bile (after hydrolysis of conjugates in the intestinal lumen) was also assumed in order to simplify initial descriptions, but corrections for incomplete absorption and other features can easily be introduced. Another assumption was that conjugated drug in systemic circulation cannot be hydrolyzed to yield the parent drug, although it may be excreted in the bile and in the urine and metabolized to other compounds. Descriptions are given in terms of normal and bile duct-cannulated animals (with reabsorption and nonreabsorption of drug excreted in the bile, respectively).

As far as possible, we have used terms (effective dose, effective clearance, net clearance) described in previously published works which considered the influence of enterohepatic circulation on drug pharmacokinetics (6,9).

Intravenous Administration

Intravenous administration to bile duct-cannulated and normal animals (the latter with enterohepatic cycling of the drug) is represented schematically in Fig. 1. After intravenous administration to bile duct-cannulated animals, the amount of drug reaching systemic circulation is the administered dose (D), and the amount of drug excreted in the bile (A_{biv-c}) is given by the product Df_b, where f_b represents the fraction of the drug in the systemic circulation that is excreted in the bile as unchanged and/or conjugated drug.

In normal animals, the drug excreted in the bile (Df_b) enters the intestine and, after hydrolysis of conjugates, is subject to absorption across the intestinal wall and metabolic first-pass effect by the intestine and the liver. Therefore, the new amount of drug reaching the systemic circulation is Df_bF_t, where F_t is the fraction of the drug in the gut that reaches the systemic circulation unchanged. As a result, $E_t = 1 - F_t$ represents the fraction that does not reach systemic circulation as a consequence of the first pass-effect and may be divided into the fraction of absorbed drug that is excreted (unchanged and/or conjugated) in the bile (E_b) and the fraction that is irreversibly eliminated (E_m). It is clear, then, that

$$F_t = 1 - E_t = 1 - (E_m + E_b) \quad (1)$$

As a consequence of the first-pass effect by the intestinal mucosa and the liver, a fraction of absorbed drug may be excreted unchanged in the bile (E_{bu}), another fraction may be metabolized to noncycling species (E_{nc}), and still another (E_c) may be metabolized to drug conjugates. A fraction of these conjugates (G_s) can leave the liver in the hepatic venous blood and enter systemic circulation, whereas the remaining fraction ($1 - G_s$) is immediately excreted in the bile. Conjugated drug in systemic circulation can undergo, in the next circulatory cycles, biliary excretion and irreversible elimination (by renal excretion and metabolism to other compounds). The fraction of conjugated drug in the systemic

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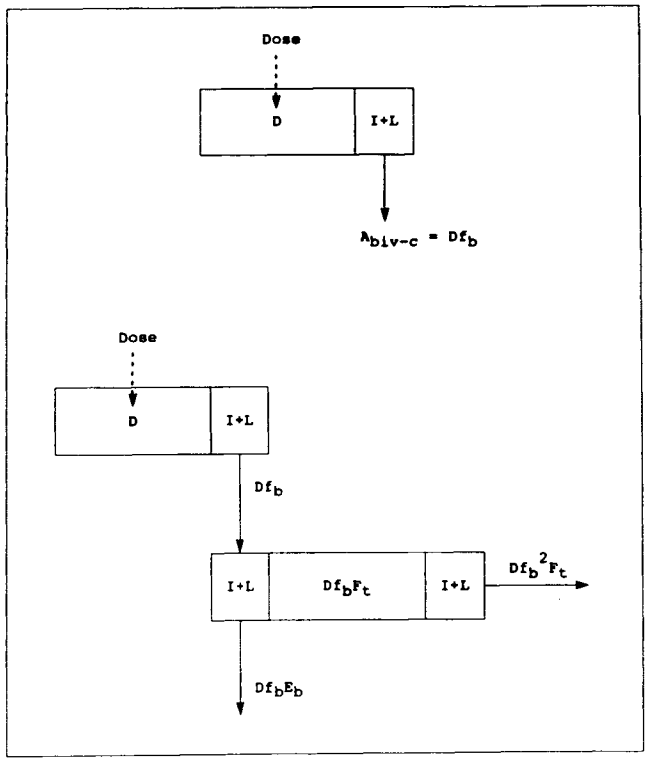
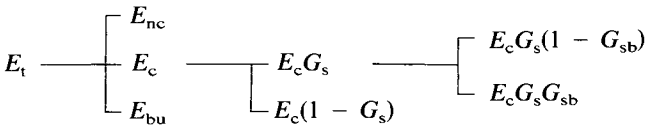


Fig. 1. Schematic representation of bile duct-cannulated animals (upper part) and normal animals (lower part) receiving an intravenous dose of a drug which can undergo enterohepatic recycling. The I + L box represents the liver and intestine as a whole, and the large box represents the systemic circulation. In normal animals, biliary excreted species are subject (after hydrolysis of conjugates) to first-pass elimination during absorption.

circulation which is excreted in the bile and the fraction undergoing irreversible elimination are represented by G_{sb} and $1 - G_{sb}$, respectively. In the following scheme, the relationship between the different fractions is given:



Then E_b (apparent biliary extraction ratio) represents the sum of the following fractions of absorbed drug:

$$\begin{aligned} E_b &= E_{bu} + E_c(1 - G_s) + E_cG_sG_{sb} \\ &= E_{bu} + E_c(1 - G_s + G_sG_{sb}) \\ &= E_{bu} + E_cG_b \end{aligned} \quad (2)$$

where G_b ($=1 - G_s + G_sG_{sb}$) is the fraction of conjugated drug formed by first-pass effect which is excreted in the bile. On the other hand, E_m is the irreversible presystemic metabolic extraction ratio and represents the fraction of absorbed drug that neither reaches systemic circulation as unchanged drug nor is excreted in the bile. Therefore, it includes drug metabolism to noncycling species and irreversible elimination of conjugated drug, and it represents the sum of the following fractions of absorbed drug:

$$E_m = E_{nc} + E_cG_s(1 - G_{sb}) = E_{nc} + E_c(1 - G_b) \quad (3)$$

The amount of drug excreted in the bile as a consequence of the first-pass effect (Df_bE_b) and the amount excreted from unchanged drug in the systemic circulation ($Df_b^2F_t$) are again subjected to the same process, as shown in Fig. 2. The sum of all the quantities which appear in the boxes (those shown and those which would appear if Fig. 2 were extended to infinite cycles) represents the total amount of unchanged drug that reaches the systemic circulation in normal animals (D^*_{iv-n}), using as a reference the amount that reaches it in bile duct-cannulated animals (D). In order to obtain a mathematical expression for D^*_{iv-n}, the sum of all terms of the indicated series must be calculated (see Appendix). The resulting equation is as follows:

$$D^*_{iv-n} = D\left[1 + \frac{f_bF_t}{1 - (f_bF_t + E_b)}\right] \quad (4)$$

D^*_{iv-n} is the "effective dose" for intravenous administration, as proposed by Tse *et al.* (9), which represents the amount of drug that reaches the systemic circulation in normal animals in comparison with bile duct-cannulated animals intravenously dosed (which is the administered dose, D). Assuming that the total clearance (Cl_t) remains constant for both series of animals, the ratio between "doses" equals the ratio between areas under the blood level/time curves after

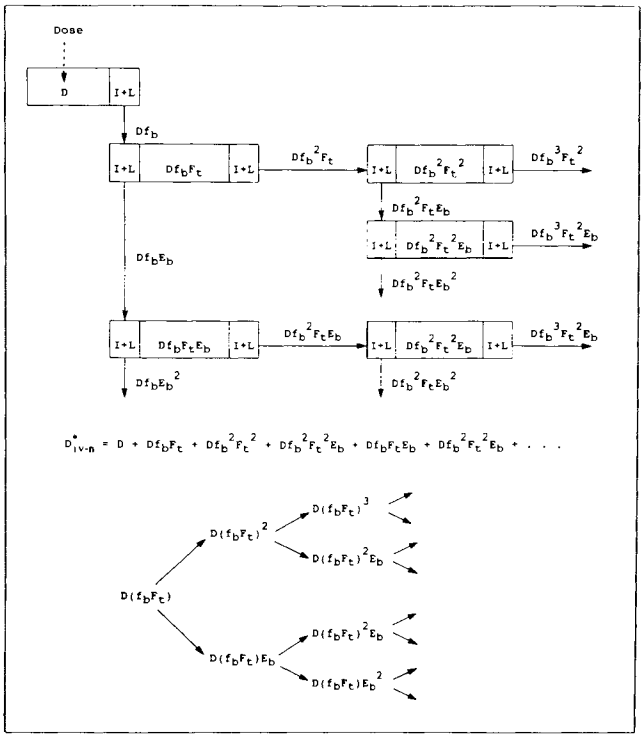


Fig. 2. Partial view of the enterohepatic recycling process after intravenous administration to normal animals. The effective dose (D^*) is the sum of all the quantities in the boxes. Starting from the amount of drug reaching the systemic circulation in the first cycle (Df_bF_t), the next amounts reaching the systemic circulation are equivalent to Df_bF_t multiplied by f_bF_t ($Df_b^2F_t^2$, from the biliary excretion of drug in the systemic circulation) and by E_b ($Df_bF_tE_b$, from the biliary excretion of drug as a consequence of the first-pass effect). This sequence continues in the other cycles, as can be seen in the lower part. The sum of all these values is given in the Appendix.

administration of the same dose to the animals (i.e., the magnitude of D^*_{iv-n} and D is reflected, respectively, by the area under the blood level curves). Therefore, in the case of intravenous administration,

$$Cl_t = \frac{D}{AUC_{iv-c}} = \frac{D^*_{iv-n}}{AUC_{iv-n}} \quad (5)$$

$$\frac{D^*_{iv-n}}{D} = \frac{AUC_{iv-n}}{AUC_{iv-c}} \quad (6)$$

Here AUC_{iv-c} and AUC_{iv-n} are the areas under the blood level curves in bile duct-cannulated and normal animals, respectively.

Substituting the "doses" for the respective areas in Eq. (4),

$$AUC_{iv-n} = AUC_{iv-c}\left[1 + \frac{f_b F_t}{1 - (f_b F_t + E_b)}\right] \quad (7)$$

Oral Administration

Bile Duct-Cannulated Animals

Figure 3 shows the schemes corresponding to oral and intravenous administration to bile duct-cannulated animals. The amount of drug reaching systemic circulation after oral administration is DF_t, and F_t can be calculated as follows:

$$F_t = \frac{AUC_{or-c}}{AUC_{iv-c}} \quad (8)$$

where or−c indicates oral administration to bile duct-cannulated animals.

It is important to note the difference between f_b and E_b in Fig. 3. f_b is the fraction of intravenously administered dose that is excreted in the bile as unchanged and/or conjugated drug, whereas E_b is the fraction of orally administered dose excreted in the bile as a consequence of the first-pass effect (assuming complete intestinal absorption). E_b may be estimated by rearranging the lower equation shown in the figure:

$$E_b = \frac{A_{bor-c} - DF_t f_b}{D} \quad (9)$$

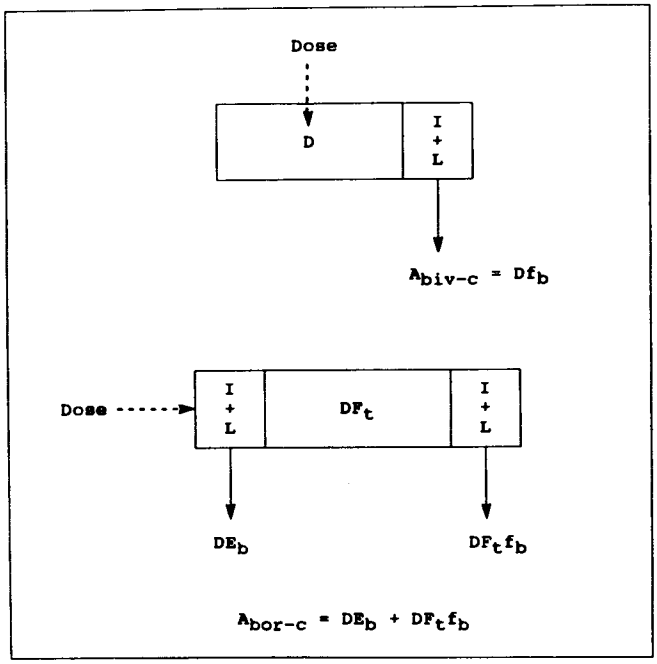


Fig. 3. Schemes for intravenous (upper part) and oral (lower part) administration in bile duct-cannulated animals. A_{biv-c} and A_{bor-c} are the amounts of drug excreted in the bile after intravenous and oral administration, respectively.

Normal Animals

In Fig. 4, a schematic representation of oral administration to normal animals is shown. The effective dose, in this case, is the sum of DF_t, D^*_1, and D^*_2. The mathematical expressions corresponding to D^*_1 and D^*_2 can be obtained by the rule described in the Appendix, making $C = DF_t^2 f_b$ for the calculation of D^*_1 and $C = DF_t E_b$ for the calculation of D^*_2. In both cases, $A = f_b F_t$ and $B = E_b$. The resulting equations are as follows:

$$D^*_1 = \frac{D f_b F_t^2}{1 - (f_b F_t + E_b)} \quad (10)$$

$$D^*_2 = \frac{DF_t E_b}{1 - (f_b F_t + E_b)} \quad (11)$$

Hence,

$$D^*_{or-n} = DF_t + D^*_1 + D^*_2 = DF_t\left[1 + \frac{f_b F_t + E_b}{1 - (f_b F_t + E_b)}\right] \quad (12)$$

and assuming that total clearance is the same for these animals and for bile duct-cannulated animals intravenously dosed,

$$AUC_{or-n} = AUC_{iv-c} F_t\left[1 + \frac{f_b F_t + E_b}{1 - (f_b F_t + E_b)}\right] \quad (13)$$

Bioavailability

The most commonly used method for estimating the extent of oral bioavailability is to compare the total areas under the drug concentration in plasma versus time curve after oral and intravenous administration. In this way, a mathematical expression relating bioavailability in normal animals (F_{t-n}) to bioavailability in bile duct-cannulated animals (F_t) can be obtained from the quotient of Eqs. (13) and (7):

$$F_{t-n} = \frac{AUC_{or-n}}{AUC_{iv-n}} = \frac{F_t}{1 - E_b} \quad (14)$$

Since $F_t = 1 - E_t$ and $E_t = E_b + E_m$, Eq. (14) can be rewritten as follows:

$$F_{t-n} = 1 - \frac{E_m}{1 - E_b} = 1 - E_{t-n} \quad (15)$$

where $E_{t-n} = E_m/(1 - E_b)$ is the dose fraction which is apparently lost by first-pass effect in normal animals.

The above equations have been developed by assuming complete gastrointestinal absorption of the administered

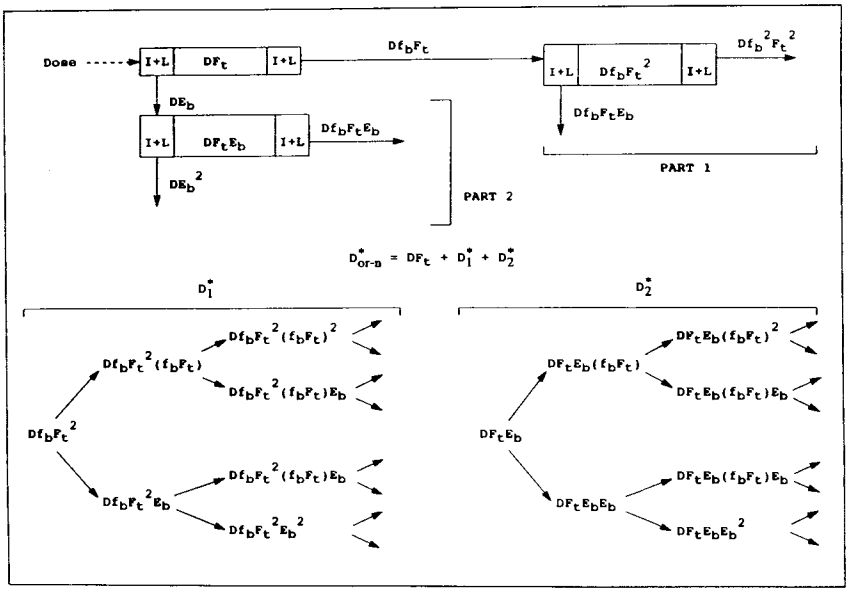


Fig. 4. Partial view of the enterohepatic recycling process after oral administration to normal animals. The effective dose (D^*_{or-n}) is the sum of DF_t and the amounts of drug in the systemic circulation of Part 1 (D^*_1) and Part 2 (D^*_2) in the scheme.

dose. If this does not occur, bioavailability in bile duct-cannulated animals is expressed by the product F_aF_t, where F_a is the dose fraction that disappears from gastrointestinal lumen by absorption, and bioavailability in normal animals is given by the expression

$$F_{t-n} = \frac{F_aF_t}{1 - E_b} \tag{16}$$

which, by replacing F_t and by operating, yields

$$F_{t-n} = F_a(1 - E_{t-n}) \tag{17}$$

Clearance

It is assumed here that the liver is the only metabolizing organ for the drug, that the drug can be excreted unchanged in the bile and urine, and that conjugated drug is subjected to biliary excretion and irreversible elimination (renal excretion and/or metabolism to other compounds).

In bile duct-cannulated animals, total clearance of the drug (Cl_t) can be calculated as the ratio between the administered dose and the AUC and expressed as the sum of the hepatic (Cl_h) and renal (Cl_r) clearances, as follows:

$$Cl_t = \frac{D}{AUC_{iv-c}} = Cl_h + Cl_r = Cl_{bu} + Cl_{nc} + Cl_c + Cl_r \tag{18}$$

Here, Cl_{bu} represents the clearance of the drug by biliary excretion as unchanged drug, Cl_{nc} represents the clearance of the drug by metabolism to noncycling species, and Cl_c represents the clearance of the drug by conjugation.

Equation (18) can also be expressed as

$$Cl_t = Q_hE_h + Cl_r = Q_h(E_{bu} + E_{nc} + E_c) + Cl_r \tag{19}$$

where Q_h is the total hepatic blood flow and E_h ($=E_{bu} + E_{nc} + E_c$) is the hepatic extraction ratio of the drug. E_{bu}, E_{nc}, and E_c were previously defined for the intestinal and hepatic first-pass effect. However, when there is no intestinal mucosa metabolism (as assumed here), they also represent the fraction of drug entering the liver which is excreted in the bile unchanged (E_{bu}), the fraction which is metabolized to noncycling species (E_{nc}), and the fraction metabolized to drug conjugates (E_c).

The total amount of drug eliminated by a given pathway is the product of AUC and clearance. Therefore, the total amount of drug excreted in the bile (unchanged and/or conjugated) is

$$\begin{aligned} A_{biv-c} &= AUC_{iv-c}Cl_{bu} + AUC_{iv-c}Cl_cG_b \\ &= AUC_{iv-c}\,Q_h(E_{bu} + E_cG_b) \end{aligned} \tag{20}$$

where G_b represents the fraction of conjugated drug which is excreted in the bile. Then the fraction of dose excreted in the bile after intravenous administration to bile duct-cannulated animals is

$$f_b = \frac{A_{biv-c}}{D} = \frac{AUC_{iv-c}Q_h(E_{bu} + E_cG_b)}{D} = \frac{Q_h(E_{bu} + E_cG_b)}{Cl_t} \tag{21}$$

Clearance estimated from the ratio between dose and AUC after intravenous dosing to normal animals,

$$Cl_{t-n} = \frac{D}{AUC_{iv-n}} \tag{22}$$

is an apparent clearance (net total clearance), which may be related to Cl_t and the hepatic extraction ratio in bile duct-cannulated animals as follows. By replacing AUC_{iv-n} in Eq.

(22) with the expression in Eq. (7) and rearranging, one obtains

$$Cl_{t-n} = \frac{Cl_t(1 - f_b F_t - E_b)}{(1 - E_b)} \quad (23)$$

Since it has been assumed that there is no intestinal mucosa metabolism, the fraction of drug absorbed from the intestine that reaches systemic circulation unchanged (F_t) is

$$F_t = 1 - E_t = 1 - E_h \quad (24)$$

and the fraction of absorbed drug that is excreted in the bile (unchanged and/or conjugated) as a consequence of the first-pass effect is

$$E_b = E_{bu} + E_c G_b \quad (25)$$

By using Eqs. (18), (21), (23), (24), and (25), one obtains

$$Cl_{t-n} = Q_h \frac{E_h - E_b}{1 - E_b} + Cl_r \quad (26)$$

or

$$Cl_{t-n} = Cl_{h-n} + Cl_r \quad (27)$$

where Cl_{h-n} represents the net hepatic clearance in normal animals. From Eq. (26), one realizes that the net hepatic extraction ratio in normal animals is

$$E_{h-n} = \frac{E_h - E_b}{1 - E_b} = \frac{E_{nc} + E_c(1 - G_b)}{1 - E_{bu} - E_c G_b} \quad (28)$$

when the liver is assumed to be the only metabolizing organ for the drug.

DISCUSSION

Area Under the Blood Level Curves

Mathematical expressions for AUC in normal and bile duct-cannulated animals (the latter orally dosed) are summarized in Table I. The increase in the area under blood level curves when drug excreted in the bile is allowed to recycle [Eqs. (7) and (13)] depends on f_b, F_t, and E_b values. Therefore, an increase in these parameters leads to larger AUC values in normal animals than in bile duct-cannulated animals.

Tse *et al.* (9) deduced an equation for the effective dose in normal animals intravenously dosed that was different from the one shown here [Eq. (4)]. Consequently, the mathematical expression for AUC in normal animals was also different from Eq. (7) here. The reason for such a discrepancy is that Tse *et al.* used only the fraction of the drug in the body that is excreted in the bile and the fraction of the excreted drug in bile subsequently reabsorbed from the gut (F_b and F_a in the original work, respectively) to evaluate the influence of the enterohepatic recycling of the drug on the effective dose, and they did not take into account biliary excretion of the drug as a consequence of the first-pass effect (E_b). This becomes evident when their Eq. 1 is compared with the amounts of drug represented in the boxes in Fig. 2.

Yamaoka *et al.* (10), using the concept of recirculatory process, obtained a relationship between AUC for normal animals and AUC for animals with inhibited enterohepatic recirculation (deduced from Eqs. 11, 13, and 15 in their paper) that also differs from the relationship expressed in Eq. (7) and is identical to that found by Tse *et al.* (9). This occurred because their model of enterohepatic recirculation included weight functions corresponding to the processes outside the body through the intestinal tract and inside the body through the blood circulation system. However, it did not take into account any function for the process of biliary excretion of the drug as a consequence of the first-pass effect (E_b), which was also ignored by Tse *et al.*

Bioavailability

Equation (14) shows that enterohepatic recycling leads to larger estimated bioavailability in normal animals (F_{t-n}) than in bile duct-cannulated animals (F_t), since $(1 - E_b)$ is less than 1. Equation (16) must be used if the administered dose is not completely absorbed, and bioavailability in normal animals is also larger in this case than in bile duct-cannulated animals ($F_a F_t$). It can be demonstrated that Eq. (16) is equivalent to the equation found by Shepard and Reuning using a very different mathematical process (8). However, it is different from the equation reported by Yamaoka *et al.* (10), for the above-mentioned reasons.

Mathematical expressions relating bioavailability with the irreversible presystemic metabolic extraction ratio (E_m) and the extent of enterohepatic recycling (evaluated by E_b) are given as Eq. (15) (for complete absorption) and Eq. (17) (for incomplete absorption). For a drug undergoing biliary recycling, an increase in E_b (when E_m is maintained constant) will lead to a decrease in bioavailability, i.e., the enterohepatic recycling will decrease bioavailability.

Table I. Mathematical Expressions for the Area Under the Blood Drug Concentration Versus Time Curves (AUC) in Normal and Bile Duct-Cannulated Animals as a Function of AUC_{iv-c}, f_b, F_t, and E_b[a]

Drug administration	AUCs relationship	
i.v. (normal)	$AUC_{iv-n} = AUC_{iv-c}\left[1 + \frac{f_b F_t}{1 - (f_b F_t + E_b)}\right]$	(7)
Oral (normal)	$AUC_{or-n} = AUC_{iv-c} F_t\left[1 + \frac{f_b F_t + E_b}{1 - (f_b F_t + E_b)}\right]$	(13)
Oral (b.d. cannul.)	$AUC_{or-c} = F_t AUC_{iv-c}$	

[a] Numbers in parentheses on the right indicate the equation number in the text. The last equation is Eq. (8) in the text, rearranged.

It should be pointed out that this statement does not contradict the conclusions drawn from Eq. (14). In a strict sense, bioavailability is decreased by enterohepatic recycling because E_{t-n} is larger than the irreversible presystemic metabolic extraction ratio (E_m), and an increase in E_b leads to an increase in E_{t-n}. However, when bioavailability in normal animals is compared with that found in bile duct-cannulated ones (which do not experience recycling), larger bioavailability should be obtained for the former because of enterohepatic recycling. For example,

- If two drugs, A and B, have complete gastrointestinal absorption and the same irreversible presystemic metabolic extraction ratio, with drug B undergoing biliary excretion and intestinal reabsorption (enterohepatic recycling), drug B [$E_{t-n} = E_m/(1 - E_b)$] will have a lower bioavailability than drug A ($E_{t-n} = E_m$).
- If two drugs, C and D, have complete gastrointestinal absorption, the same irreversible presystemic metabolic extraction ratio and biliary extraction ratio as conjugates, but the conjugates of C are very stable and those of D are not, biliary excretion represents a loss of drug for C, whereas labile conjugates of D can be hydrolysed and subjected to enterohepatic recycling. [This example is equivalent to administering the same drug to bile duct-cannulated (C) and normal (D) animals.] In this case, drug D [$E_{t-n} = E_m/(1 - E_b)$] will have a larger bioavailability than drug C ($E_{t-n} = E_m + E_b$).

When there is no irreversible presystemic metabolism, $E_m = 0$ and $E_{t-n} = 0$, and consequently, bioavailability in normal animals is unity or F_a [from Eqs. (15) and (17)], depending on whether the administered dose is completely absorbed or not.

It has been suggested that absorption can appear to be greater than 100% of the dose for drugs that undergo enterohepatic recycling (11). Equation (17) clearly shows that it is not possible when linear pharmacokinetics is assumed, because the highest possible value of F_{t-n} (when $F_a = 1$, due to complete absorption of the dose, and $E_{t-n} = 0$, due to absence of irreversible metabolic first-pass effect) is unity.

Clearance

For drugs that undergo enterohepatic circulation, Colburn (6) used the expression "effective clearance" to describe the intrinsic ability of the eliminating organs to remove drug from the blood and the expression "net clearance" to describe the irreversible elimination of the drug from the body. In that analysis of the enterohepatic recirculation phenomenon (6), the liver was considered the only eliminating organ of the body.

In this paper, the analysis of the effect of enterohepatic recycling of drugs on clearance focuses on drugs with hepatic and renal elimination, and no restrictions have been put on the species responsible for enterohepatic cycling (unchanged and/or conjugated drug). Individual organ clearances in bile duct-cannulated animals are effective clearances (Cl_h, Cl_r), and the total clearance calculated by applying Eq. (18) (Cl_t) reflects the intrinsic ability of the body, as a whole, to remove drug from the blood. However, when total clearance is calculated in normal animals by applying Eq. (22), Cl_{t-n} represents the net total clearance and reflects the irreversible elimination of the drug from the body.

By comparing Eqs. (19) and (26), one can assess the differences between total clearance and net total clearance. It then becomes clear that these differences are due to hepatic elimination of the drug. Therefore, irreversible hepatic elimination of the drug from the body in normal animals (net hepatic clearance, Cl_{h-n}) does not reflect the intrinsic ability of the liver to remove drug from the blood (effective hepatic clearance, Cl_h) because a fraction of drug removed from the blood by the liver and excreted in the bile (E_b) is not irreversibly eliminated since it will return, in part, to the blood after absorption in the intestine. On the other hand, by comparing Eqs. (18), (22), and (27), one realizes that $Cl_{h-n} < Cl_h$ and that $E_{h-n} < E_h$.

The different meanings of net and effective hepatic clearance could be relevant in studies relating metabolic parameters determined *in vitro* to those determined *in vivo*. The hepatic extraction ratio determined *in vitro* from the rate of disappearance of unchanged drug (12) is actually an estimation of the sum $E_{nc} + E_c$. Therefore, if the drug under study is excreted in the bile of the whole animal as a conjugated ($E_{bu} = 0$ and $E_h = E_{nc} + E_c$), the hepatic extraction ratio determined *in vitro* is an estimate of E_h rather than of E_{h-n}. On the other hand, if enterohepatic recycling in the whole animal is due to unchanged drug ($G_b = 0$), *in vitro* assays will actually estimate an hepatic extraction ratio ($E_{nc} + E_c$) lower than E_{h-n} [as easily deduced from Eq. (28) by making $G_b = 0$]. It is clear from this that *in vitro* estimations of *in vivo* hepatic first-pass effect could lead to erroneous results, by either overestimation (when $E_{bu} = 0$) or underestimation (when $G_b = 0$) of E_{h-n}, when enterohepatic recycling exists and is not considered.

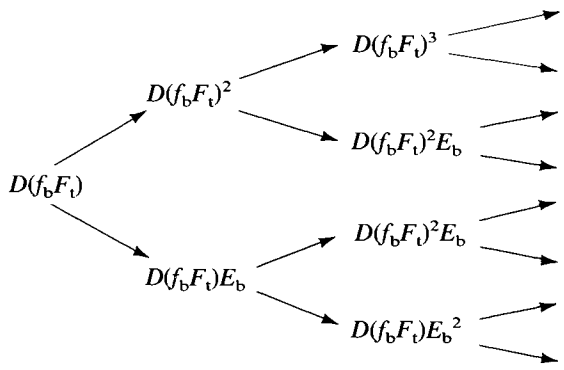
The treatment of enterohepatic recycling of drugs described in this paper can easily be adapted to different conditions, such as intraperitoneal administration, incomplete reabsorption of drug excreted in the bile, etc., in order to evaluate the influence of enterohepatic recycling on AUC and bioavailability estimations in these particular cases.

APPENDIX

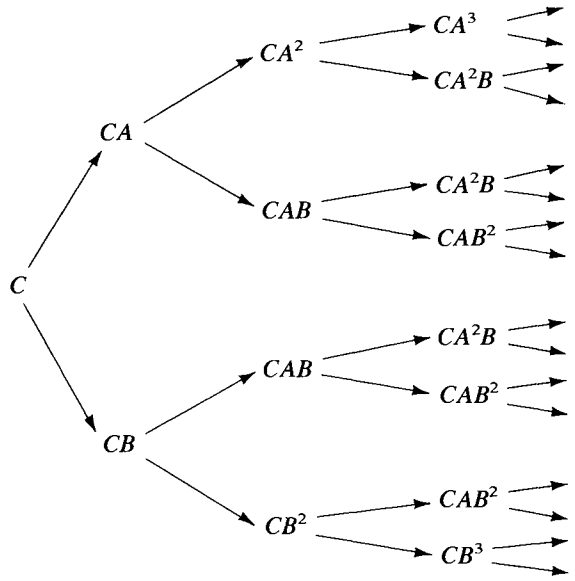
As pointed out in Fig. 2, the effective dose after intravenous administration to normal animals is

$$D^*_{iv-n} = D + Df_bF_t + Df_b^2F_t^2 + Df_b^2F_t^2E_b + Df_bF_tE_b + Df_b^2F_t^2E_b + \ldots \quad \text{(A1)}$$

where the terms after Df_bF_t show the following relationship:



By making $C = D(f_b F_t)$, $A = (f_b F_t)$, and $B = E_b$, this diagram can be written as follows:



Hence, Eq. (A1) can be written as

$$D^*_{iv-n} = D + C + \begin{bmatrix} CA \\ + \\ CB \end{bmatrix} + \begin{bmatrix} CA^2 \\ + \\ 2CAB \\ + \\ CB^2 \end{bmatrix} + \begin{bmatrix} CA^3 \\ + \\ 3CA^2B \\ + \\ 3CAB^2 \\ + \\ CB^3 \end{bmatrix} + \ldots \quad \text{(A2)}$$

which, on rearrangement, yields

$$D^*_{iv-n} = D + C \left[1 + \begin{bmatrix} A \\ + \\ B \end{bmatrix} + \begin{bmatrix} A^2 \\ + \\ 2AB \\ + \\ B^2 \end{bmatrix} + \begin{bmatrix} A^3 \\ + \\ 3A^2B \\ + \\ 3AB^2 \\ + \\ B^3 \end{bmatrix} + \ldots\right] \quad \text{(A3)}$$

As can be seen, the terms in brackets are analogous to those of the binomial expansion of $(A + B)^n$ for $n = 1, 2, 3, \ldots$ Thus,

$$D^*_{iv-n} = D + C\,[1 + (A + B) + (A + B)^2 + (A + B)^3 + \ldots] \quad \text{(A4)}$$

where the terms in brackets correspond to a geometric progression with a ratio $(A + B)$. Hence, the last equation can be rewritten as

$$D^*_{iv-n} = D + C\,[S] \quad \text{(A5)}$$

where S means the sum of n terms when n approaches infinity. Since the ratio of the geometric progression is less than 1 (see lower), this series is convergent and its sum is

$$S = \frac{1}{1 - (A + B)} \quad \text{(A6)}$$

By substituting this expression for S in Eq. (A5), we obtain

$$D^*_{iv-n} = D + C\frac{1}{1 - (A + B)} = D + \frac{Df_bF_t}{1 - (f_bF_t + E_b)} \quad \text{(A7)}$$

and, on rearranging,

$$D^*_{iv-n} = D\left[1 + \frac{f_bF_t}{1 - (f_bF_t + E_b)}\right] \quad \text{(A8)}$$

It can be demonstrated that the ratio of the geometric progression $(A + B)$ is less than 1:

$$F_t + E_b = 1 - (E_m + E_b) + E_b = 1 - E_m - E_b + E_b = 1 - E_m$$

Thus, $F_t + E_b$ is less than 1. On the other hand, since f_b is less than 1, the product f_bF_t will be less than F_t, and consequently,

$$A + B = f_bF_t + E_b < F_t + E_b < 1$$

Hence, $A + B < 1$.

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NOMENCLATURE

A_{biv-c}	Amount of drug (unchanged and/or conjugated) excreted in the bile after intravenous administration of the drug to bile duct-cannulated animals
A_{bor-c}	Amount of drug (unchanged and/or conjugated) excreted in the bile after oral administration of the drug to bile duct-cannulated animals
AUC_{iv-c}	Area under the blood level versus time curve after intravenous administration of the drug to bile duct-cannulated animals
AUC_{iv-n}	Area under the blood level versus time curve after intravenous administration of the drug to normal animals (bile duct noncannulated)
AUC_{or-c}	Area under the blood level versus time curve after oral administration of the drug to bile duct-cannulated animals
AUC_{or-n}	Area under the blood level versus time curve after oral administration of the drug to normal animals (bile duct noncannulated)
Cl_{bu}	Clearance of the drug by biliary excretion as unchanged drug
Cl_c	Clearance of the drug by metabolism to drug conjugates
Cl_{nc}	Clearance of the drug by metabolism to noncycling species
Cl_r	Renal clearance of unchanged drug
Cl_h	Effective hepatic clearance: $Cl_h = Cl_{bu} + Cl_{nc} + Cl_c$

when the liver is the only metabolizing organ for the drug

Cl_{h-n} Net hepatic clearance

Cl_t Total clearance

Cl_{t-n} Net total clearance

D Administered dose

D^*_{iv-n} Effective dose for intravenous administration to normal animals

D^*_{or-n} Effective dose for oral administration to normal animals

E_b Apparent biliary extraction ratio; fraction of absorbed drug that is excreted unchanged and/or conjugated in the bile as a consequence of the first-pass effect

E_{bu} Fraction of absorbed drug which is excreted unchanged in the bile as a consequence of the first-pass effect

E_c Fraction of absorbed drug which is metabolized to drug conjugates as a consequence of the first-pass effect

E_h Effective hepatic extraction ratio: $E_h = E_{bu} + E_{nc} + E_c$ when there is no intestinal metabolism

E_{h-n} Net hepatic extraction ratio

E_m Irreversible presystemic metabolic extraction ratio; fraction of absorbed drug that is irreversibly eliminated as a consequence of the first-pass effect. It includes the fraction of drug which is metabolized to noncycling species and the fraction that is conjugated and not excreted in the bile

E_{nc} Fraction of absorbed drug which is metabolized to noncycling species as a consequence of the first-pass effect

E_t Fraction of drug absorbed from the gut that does not reach systemic circulation unchanged in each enterohepatic cycle: $E_t = E_m + E_b$

E_{t-n} Fraction of the orally administered dose which is apparently lost by first-pass effect in normal animals

F_a Fraction of the orally administered dose that disappears from the gastrointestinal lumen by absorption

f_b Fraction of unchanged drug in systemic circulation that is excreted in the bile as unchanged and/or conjugated drug: $f_b = A_{biv-c}/D$

F_t Fraction of drug absorbed from the gut that reaches systemic circulation unchanged in each enterohepatic cycle ($F_t = 1 - E_t$). It represents oral bioavailability in bile duct-cannulated animals when complete intestinal absorption of the dose is assumed. If this is not the case, bioavailability is given by the product F_aF_t.

F_{t-n} Bioavailability in normal animals: $F_{t-n} = 1 - E_{t-n}$ when absorption is complete. If this is not the case, $F_{t-n} = F_a(1 - E_{t-n})$.

G_b Fraction of conjugated drug formed by first-pass effect which is excreted in the bile, immediately after formation or after entering systemic circulation: $G_b = 1 - G_s + G_sG_{sb}$

G_s Fraction of conjugated drug formed by first-pass effect which leaves the liver in the hepatic venous blood

G_{sb} Fraction of conjugated drug in systemic circulation that is excreted in the bile

Q_h Total hepatic blood flow

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