Pharmaceutical Research, Vol. 10, No. 1, 1993

Research Article

Mean Residence Time of Oral Drugs Undergoing First-Pass and Linear Reversible Metabolism

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Received September 10, 1991; accepted March 20, 1992

Equations for the mean residence times in the body (MRT) and AUMC/AUC of a drug and its metabolite have been derived for an oral drug undergoing first-pass and linear reversible metabolism. The mean residence times of the drug or interconversion metabolite in the body after oral drug are described by equations which include the mean absorption time (MAT), the mean residence times of the drug or metabolite in the body after intravenous administration of the drug, the fractions of the dose entering the systemic circulation as the parent drug and metabolite, and the systemically available fractions of the drug (F_p^p) or metabolite (F_m^p). Similarly, the AUMC/AUC of the drug and metabolite after oral drug can be related to the MAT, ratios of the fraction of the dose entering the systemic circulation to the systemically available fraction, the first-time fractional conversion of each compound, and AUMC/AUC ratios after separate intravenous administration of each compound. The F_p^p and F_m^p values, in turn, are related to the first-pass availabilities of both drug and metabolite and the first-time fractional conversion fractions. The application of these equations to a dual reversible two-compartment model is illustrated by computer simulations.

KEY WORDS: oral administration; mean residence time; reversible metabolism; first-pass metabolism; pharmacokinetics.

INTRODUCTION

Reversible metabolism complicates pharmacokinetic analysis and caution must be exercised in estimating pharmacokinetic parameters such as clearances (1–4), bioavailability (5,6), steady-state volumes of distribution (7), and mean residence times (8,9). Although many methods for obtaining pharmacokinetic parameters for drugs undergoing reversible metabolism have been presented (1–12), except for the approaches of Hwang *et al.* (5,6) and Nagamine *et al.* (10), they have been limited to the consideration of intravenous drugs. This report presents methods for calculating the mean residence time (MRT) and the ratio of the first to the zeroth moments of the plasma concentration–time curve (AUMC/AUC) parameters for an oral drug undergoing linear reversible metabolism.

THEORETICAL

For a drug (p) and its interconversion metabolite (m), both following a two-compartment model with central (V_c) and peripheral (V_T) compartment volumes (Fig. 1), the rate of change of the amount at the absorption site [$A(t)$] and the rates of change of drug and metabolite plasma concentrations [$C_p^{p,po}(t)$ and $C_m^{p,po}(t)$] and tissue concentrations [$C_{Tp}^{p,po}(t)$ and $C_{Tm}^{p,po}(t)$] following an oral dose ($D^{p,po}$) of the drug can be described by the following equations:

$$dA(t)/dt = -k_a \cdot A(t) \quad (1)$$

$$V_{Tp} \cdot dC_{Tp}^{p,po}(t)/dt = -k_{31} \cdot V_{Tp} \cdot C_{Tp}^{p,po}(t) + k_{13} \cdot Vc_p \cdot C_p^{p,po}(t) \quad (2)$$

$$Vc_p \cdot dC_p^{p,po}(t)/dt = k_a \cdot f_p^p \cdot A(t) + k_{31} \cdot V_{Tp} \cdot C_{Tp}^{p,po}(t) - k_1 \cdot Vc_p \cdot C_p^{p,po}(t) + k_{21} \cdot Vc_m \cdot C_m^{p,po}(t) \quad (3)$$

$$Vc_m \cdot dC_m^{p,po}(t)/dt = k_a \cdot f_m^p \cdot A(t) + k_{12} \cdot Vc_p \cdot C_p^{p,po}(t) - k_2 \cdot Vc_m \cdot C_m^{p,po}(t) + k_{42} \cdot V_{Tm} \cdot C_{Tm}^{p,po}(t) \quad (4)$$

$$V_{Tm} \cdot dC_{Tm}^{p,po}(t)/dt = k_{24} \cdot Vc_m \cdot C_m^{p,po}(t) - k_{42} \cdot V_{Tm} \cdot C_{Tm}^{p,po}(t) \quad (5)$$

with initial conditions of $A(0) = D^{p,po}$ and $C^{p,po}(0) = C_T^{p,po}(0) = 0$, and where the superscripts denote the dosed compound and the route of administration, po refers to oral administration, the subscripts represent the measured compound, k_a is the first-order rate constant for loss of drug from the absorption site, f_p^p and f_m^p are the fractions of the dose entering the central compartment intact as the parent drug and metabolite following oral administration of the drug, and the summary rate constants are $k_1 = k_{10} + k_{12} + k_{13}$ and $k_2 = k_{20} + k_{21} + k_{24}$. The other symbols are depicted and defined in Fig. 1. This model and equations assume entirely linear conditions and that first-pass effects on drug or metabolite are instantaneous and do not entail an intermediary

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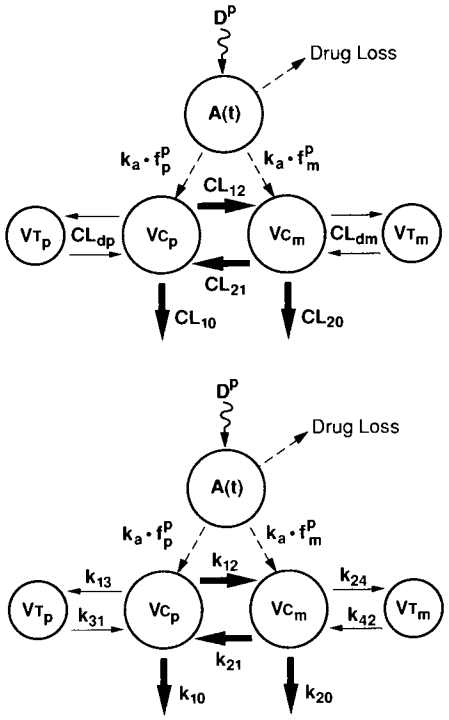

Fig. 1. Two-compartment models of reversible drug metabolism based on metabolic (thick arrows; CL_{ij}) and distribution (thin arrows; CL_d) clearances (top) or rate constants for metabolism and distribution (bottom), where k_{ij} (i = 1, 2, 3, or 4; j = 0, 1, 2, 3, or 4) are the first-order rate constants. Vc_p, Vc_m, V_{T_p}, and V_{T_m} are the apparent volumes of distribution of the central (c) and tissue (T) compartments of the drug (p) and its metabolite (m).

hepatic compartment between the absorption site and the systemic circulation. From Eqs. (1)–(5) the following equations for the parameters of the area under the plasma concentration–time curve (AUC) can be derived:

$$AUC_p^{p,po} = \frac{D^{p,po} \cdot (f_p^p \cdot CL_{22} + f_m^p \cdot CL_{21})}{CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}} \quad (6)$$

$$AUC_m^{p,po} = \frac{D^{p,po} \cdot (f_p^p \cdot CL_{12} + f_m^p \cdot CL_{11})}{CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}} \quad (7)$$

with clearances as depicted in Fig. 1 and summary clearances of

$$CL_{11} = CL_{10} + CL_{12} \quad \text{and} \quad CL_{22} = CL_{20} + CL_{21} \quad (8)$$

The following equations have previously (9) been derived following an intravenous (iv) bolus dose of the parent drug ($D^{p,iv}$):

$$AUC_p^{p,iv} = \frac{D^{p,iv} \cdot CL_{22}}{CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}} \quad (9)$$

$$AUC_m^{p,iv} = \frac{D^{p,iv} \cdot CL_{12}}{CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}} \quad (10)$$

$$AUC_p^{m,iv} = \frac{D^{m,iv} \cdot CL_{21}}{CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}} \quad (11)$$

$$AUC_m^{m,iv} = \frac{D^{m,iv} \cdot CL_{11}}{CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}} \quad (12)$$

Combining Eqs. (6) and (9) as well as Eqs. (7) and (12) separately yields

$$\frac{AUC_p^{p,po} \cdot D^{p,iv}}{AUC_p^{p,iv} \cdot D^{p,po}} = f_p^p + f_m^p \cdot CL_{21}/CL_{22} = f_p^p + f_m^p \cdot f_{1m} \quad (13a, b)$$

$$\frac{AUC_m^{p,po} \cdot D^{m,iv}}{AUC_m^{m,iv} \cdot D^{p,po}} = f_m^p + f_p^p \cdot CL_{12}/CL_{11} = f_m^p + f_p^p \cdot f_{1p} \quad (14a, b)$$

where $f_{1m} = CL_{21}/CL_{22}$ and $f_{1p} = CL_{12}/CL_{11}$, which represent the fractions of first-time conversion of metabolite to drug, and vice versa, following intravenous dosages of each (7). By definition, the systemically available fractions of the drug (F_p^p) and the metabolite (F_m^p) can be calculated as follows:

$$F_p^p = \frac{AUC_p^{p,po} \cdot D^{p,iv}}{AUC_p^{p,iv} \cdot D^{p,po}} \quad (15)$$

$$F_m^p = \frac{AUC_m^{p,po} \cdot D^{m,iv}}{AUC_m^{m,iv} \cdot D^{p,po}} \quad (16)$$

Combining Eqs. (13) and (15) as well as Eqs. (14) and (16) separately yields:

$$F_p^p = \frac{AUC_p^{p,po} \cdot D^{p,iv}}{AUC_p^{p,iv} \cdot D^{p,po}} = f_p^p + f_m^p \cdot f_{1m} \quad (17a, b)$$

$$F_m^p = \frac{AUC_m^{p,po} \cdot D^{m,iv}}{AUC_m^{m,iv} \cdot D^{p,po}} = f_m^p + f_p^p \cdot f_{1p} \quad (18a, b)$$

In addition, the following equations can be derived from Eqs. (1)–(5) (see Appendix):

$$MRT_p^{p,po} = 1/k_a + F_p^p \cdot MRT_p^{p,iv}/(f_p^p + f_m^p) \quad (19)$$

$$MRT_m^{p,po} = 1/k_a + F_m^p \cdot MRT_m^{m,iv}/(f_p^p + f_m^p) \quad (20)$$

$$AUMC_p^{p,po}/AUC_p^{p,po} = 1/k_a + (f_p^p/F_p^p) \cdot AUMC_p^{p,iv}/AUC_p^{p,iv} + f_{1m} \cdot (f_m^p/F_p^p) \cdot AUMC_p^{m,iv}/AUC_p^{m,iv} \quad (21)$$

$$AUMC_m^{p,po}/AUC_m^{p,po} = 1/k_a + (f_m^p/F_m^p) \cdot AUMC_m^{m,iv}/AUC_m^{m,iv} + f_{1p} \cdot (f_p^p/F_m^p) \cdot AUMC_m^{p,iv}/AUC_m^{p,iv} \quad (22)$$

where $MRT_p^{p,po}$ and $MRT_m^{p,po}$ are the mean residence times (MRT) of the drug and metabolite in the body after oral administration of the drug, $MRT_p^{p,iv}$ and $MRT_m^{m,iv}$ are the MRT of the drug and metabolite after their intravenous administration, and AUMC is the area under the first moment curve. From Eqs. (19)–(22), we derive the following.

(i) When $f_p^p \leq 1$ and $f_m^p = 0$ (no first-pass metabolism),

$$MRT_p^{p,po} = 1/k_a + MRT_p^{p,iv} \quad (23)$$

$$MRT_m^{p,po} = 1/k_a + MRT_m^{p,iv} \quad (24)$$

$$\frac{AUMC_p^{p,po}}{AUC_p^{p,po}} = \frac{1}{k_a} + \frac{AUMC_p^{p,iv}}{AUC_p^{p,iv}} \quad (25)$$

$$\frac{AUMC_m^{p,po}}{AUC_m^{p,po}} = \frac{1}{k_a} + \frac{AUMC_m^{p,iv}}{AUC_m^{p,iv}} \quad (26)$$

Subtracting Eq. (25) from Eq. (26) yields

$$(AUMC_m^{p,po}/AUC_m^{p,po}) - (AUMC_p^{p,po}/AUC_p^{p,po}) = (AUMC_m^{p,iv}/AUC_m^{p,iv}) - (AUMC_p^{p,iv}/AUC_p^{p,iv}) \quad (27)$$

Here we define this relationship as $\Delta(AUMC/AUC)^{po}$

$$\Delta(AUMC/AUC)^{po} = (AUMC_m^{p,po}/AUC_m^{p,po}) - (AUMC_p^{p,po}/AUC_p^{p,po}) \quad (28)$$

Combining Eq. (27) with Eqs. (9), (10), (A19), (A20), and (28) yields

$$\Delta(AUMC/AUC)^{po} = V_{ss}^m/CL_{22} \quad (29)$$

From Eq. (29) it can readily be shown that

$$\Delta(AUMC/AUC)^{po} = MRT_m^{m,iv}/EE \quad (30)$$

where EE is the exposure enhancement parameter, which is defined as (7)

$$EE = 1 + \frac{CL_{12} \cdot CL_{21}}{CL_{10} \cdot CL_{21} + CL_{20} \cdot CL_{12} + CL_{10} \cdot CL_{20}} \quad (31)$$

(ii) When $f_p^p = 0$ and $f_m^p \leq 1$,

$$MRT_p^{p,po} = 1/k_a + MRT_p^{m,iv} \quad (32)$$

$$MRT_m^{p,po} = 1/k_a + MRT_m^{m,iv} \quad (33)$$

$$\frac{AUMC_p^{p,po}}{AUC_p^{p,po}} = \frac{1}{k_a} + \frac{AUMC_p^{m,iv}}{AUC_p^{m,iv}} \quad (34)$$

$$\frac{AUMC_m^{p,po}}{AUC_m^{p,po}} = \frac{1}{k_a} + \frac{AUMC_m^{m,iv}}{AUC_m^{m,iv}} \quad (35)$$

Combining Eqs. (28), (34), and (35) yields

$$\Delta(AUMC/AUC)^{po} = (AUMC_m^{m,iv}/AUC_m^{m,iv}) - (AUMC_p^{m,iv}/AUC_p^{m,iv}) \quad (36)$$

EXPERIMENTAL

The evaluation of the proposed relationships was illustrated with simulated plasma data of a hypothetical drug and its interconversion metabolite resulting from separate iv doses of the drug and its metabolite and oral administration of the drug. The iv data have previously (9) been generated from a dual two-compartment model with the following parameters: $D^{p,iv} = 5$ mg, $D^{m,iv} = 5$ mg, $Vc_p = 73.4$ liters, $Vc_m = 39.0$ liters, $k_{10} = 0.817\ hr^{-1}$, $k_{20} = 0.246\ hr^{-1}$, $k_{12} = 0.188\ hr^{-1}$, $k_{21} = 0.385\ hr^{-1}$, $k_{13} = 0.123\ hr^{-1}$, $k_{31} = 0.300\ hr^{-1}$, $k_{24} = 0.103\ hr^{-1}$, and $k_{42} = 0.400\ hr^{-1}$. The oral data were generated with the above disposition parameters and the following parameters: $D^{p,po} = 5$ mg, $k_a = 1.0\ hr^{-1}$, $f_p^p = 0.6$, and $f_m^p = 0.4$.

The values of AUC, AUMC, $AUMC_p^{p,po}/AUC_p^{p,po}$, and $AUMC_m^{p,po}/AUC_m^{p,po}$ were calculated using the LAGRAN program (15). Values of $MRT_p^{p,po}$, $MRT_m^{p,po}$, $AUMC_p^{p,po}/AUC_p^{p,po}$, and $AUMC_m^{p,po}/AUC_m^{p,po}$ were also calculated using Eqs. (19)–(22)]

RESULTS

The simulated plasma concentration versus time profiles from the oral dose of parent drug and the calculated pharmacokinetic parameters are presented in Fig. 2 and Table I. As shown in Fig. 2, the drug given by oral administration shows an absorption/distribution profile, while its interconversion metabolite shows an absorption/formation/distribution phases. Both curves attain a maximum concentration followed by a multiexponential decline. As expected for a linear, equilibrium system, the two curves eventually attain a terminal phase with parallel slopes. These slopes ($\lambda = 0.10\ hr^{-1}$) are identical to those found previously when simulating iv dose disposition.

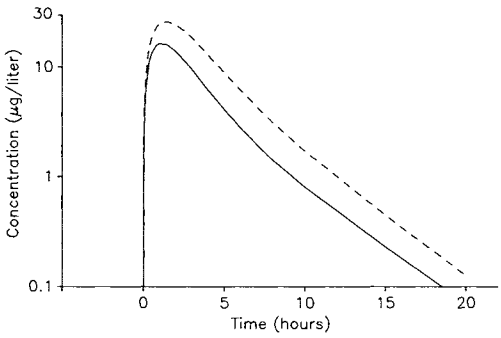

Fig. 2. Simulated concentration–time profiles for the two-compartment model of reversible drug metabolism following an oral dose of parent drug. Parameter values are listed under Experimental. Profiles of parent drug (——) and metabolite (---).

Table I lists values of the AUMC/AUC and mean residence times. Values of $MRT_p^{p,po}$ and $MRT_m^{p,po}$ are 2.33 and 2.15 hr. Corresponding values of $AUMC_p^{p,po}/AUC_p^{p,po}$ and $AUMC_m^{p,po}/AUC_m^{p,po}$ calculated from Eqs. (21) and (22) are longer, 3.41 and 3.74 hr. These calculated values are identical to those obtained by numerical integration using the LAGRAN program. In comparing the oral and iv dose AUC ratios [Eqs. (15) and (16)], the calculated value of $F_p^p = 0.84$, while $F_m^p = 0.51$. These results agree well with values obtained from the composite functions [Eqs. (17b) and (18b)].

DISCUSSION

Equations for the MRT and AUMC/AUC parameters of an oral drug obeying a two-compartment model and subject to linear reversible metabolism have been derived. According to Eq. (19), the $MRT_p^{p,po}$ is a function of the mean absorption time ($1/k_a$), $MRT_p^{p,iv}$, f_p^p, f_m^p, and systemically available fraction of the drug. Similarly, as shown in Eq. (20), the $MRT_m^{p,po}$ is determined by analogous factors for the metabolite. When there is no first-pass metabolism (i.e., $f_p^p \leq 1$ and $f_m^p = 0$), Eqs. (19) and (20) degenerate to Eqs. (23) and (24). Conversely, when all the drug is converted to its metabolite after first pass (i.e., $f_p^p = 0$ and $f_m^p \leq 1$), Eqs. (19) and (20) simplify to Eqs. (32) and (33). In all of these instances, it is

Table I. Estimates of Mean Residence Times and AUMC/AUC for a Two-Compartment System

Parameter (units)	Eq. no.	Value
$MRT_p^{p,po}$ (hr)	19	2.33
$MRT_m^{p,po}$ (hr)	20	2.15
$AUMC_p^{p,po}/AUC_p^{p,po}$ (hr)	21	3.41
$AUMC_m^{p,po}/AUC_m^{p,po}$ (hr)	22	3.74

noteworthy that the MRT for the measured compound can be generalized as

$$MRT_x^{po} = MAT + (\text{"fraction available"}) \cdot MRT_x^{iv}/(f_p^p + f_m^p) \quad (37)$$

where MAT is the mean absorption time. This requires that drug and metabolite be administered iv for calculation of MRT_x^{iv}.

According to Eqs. (21) and (22), the $AUMC_p^{p,po}/AUC_p^{p,po}$ and $AUMC_m^{p,po}/AUC_m^{p,po}$ are functions of the mean absorption time, several fraction values, and first moment/area ratios. They are contributed by two routes of input: (i) absorbed drug or metabolite that enters the systemic circulation and (ii) drug or metabolite formed by reversible biotransformation. The overall oral dose AUMC/AUC ratios are the sums of these two routes of input with respect to their weights of contribution, as reflected in the fractions of f_p^p/F_p^p or $f_{1m} \cdot (f_m^p/F_p^p)$ proceeding the AUMC/AUC values in Eq. (21). Obviously, these moment area ratios are not equal to the true MRT values. Thus, the common approach for calculating MRT of oral drugs using moment analysis is not valid when first-pass reversible metabolism occurs. However, the AUMC/AUC parameter remains of analytical value owing to its ease of computation and the ability to relate it to the MAT. According to Eq. (21), MAT can be calculated from the AUMC/AUC ratios, f_{1m}, and three available fractions. f_{1m} and one of these fractions, F_p^p, can be obtained from dose-normalized AUC ratios. The other two fractions, f_p^p and f_m^p, can be calculated from the following equations (6):

$$f_p^p = \frac{(AUC_p^{p,po} \cdot AUC_m^{m,iv} - AUC_m^{p,po} \cdot AUC_p^{m,iv}) \cdot D^{p,iv}}{(AUC_p^{p,iv} \cdot AUC_m^{m,iv} - AUC_m^{p,iv} \cdot AUC_p^{m,iv}) \cdot D^{p,po}} \quad (38)$$

$$f_m^p = \frac{(AUC_m^{p,po} \cdot AUC_p^{p,iv} - AUC_p^{p,po} \cdot AUC_m^{p,iv}) \cdot D^{m,iv}}{(AUC_p^{p,iv} \cdot AUC_m^{m,iv} - AUC_m^{p,iv} \cdot AUC_p^{m,iv}) \cdot D^{p,po}} \quad (39)$$

Similarly, MAT can also be obtained from Eq. (22). Thus, it is feasible to employ Eq. (21) or (22) to generate the value of MAT.

When there is no first-pass metabolism, Eqs. (21) and (22) degenerate to Eqs. (25) and (26). Conversely, when all the drug is converted to its metabolite after first pass, Eqs. (21) and (22) simplify to Eqs. (34) and (35). When the biotransformation of the drug is irreversible (i.e., $CL_{21} = 0$, $f_{1m} = 0$), Eq. (21) degenerates to Eq. (25) and the oral dose AUMC/AUC is simply a function of MAT and the iv dose AUMC/AUC ratio. However, under this condition, Eq. (22) remains the same. Thus, Eq. (22) is also meaningful for oral drugs not undergoing reversible metabolism. Similarly, according to moment theory, Eq. (25) is also valid for oral drugs not undergoing reversible metabolism (16–18). Moreover, for such drugs, the validity of Eq. (25) is not limited to the case of no first-pass metabolism. In essence, the AUMC/AUC ratio for the metabolite reflects a catenary sum of the MAT and fraction ratio-weighted AUMC/AUC values for metabolite following iv administration of drug and metabolite. However, first-pass metabolism complicates the additive properties of moment theory described in Eq. (25).

Recently, the effects of first-pass metabolism on the determination of metabolite mean residence time after oral administration of parent drug not undergoing reversible metabolism were examined by Chan and Gibaldi (19). As pointed out by them, for drugs not undergoing reversible metabolism and significant first-pass metabolism, $\Delta(AUMC/AUC)^{po}$ (or delta MRT in Ref. 19) equals $MRT_m^{m,iv}$. However, as shown in Eq. (30), for drugs undergoing reversible metabolism, $\Delta(AUMC/AUC)^{po}$ does not equal $MRT_m^{m,iv}$; instead, it equals $MRT_m^{m,iv}/EE$. Thus, in addition to complicating the meaning of the $MRT_p^{p,iv}$ calculated from the moment theory (8,9), reversible metabolism also confounds the meaning of the $MRT_m^{m,iv}$ calculated from $\Delta(AUMC/AUC)^{po}$.

According to Eq. (36), if $AUMC_m^{m,iv}/AUC_m^{m,iv}$ is smaller than $AUMC_p^{m,iv}/AUC_p^{m,iv}$, $\Delta(AUMC/AUC)^{po}$ will be negative. This negative value of $\Delta(AUMC/AUC)^{po}$ indicates the occurrence of first-pass metabolism. However, a positive value of $\Delta(AUMC/AUC)^{po}$ does not reflect the absence of first-pass metabolism. Similar indications have also been reported recently by Chan and Gibaldi (19) for drugs not undergoing reversible metabolism.

Finally, although the equations derived in this work have been based only on the two-compartment model, the above discussion and these equations are valid for an oral drug and its interconversion metabolite obeying any multiperipheral compartment model with elimination from the central compartment. Also, the term MAT can be used in place of $1/k_a$, providing that the absorption kinetics of the drug do not affect the first-pass availabilities of drug and metabolite.

APPENDIX

The coefficients of Eqs. (1)–(5) may be written as one matrix **B**:

$$\mathbf{B} = \begin{vmatrix} -k_a & 0 & 0 & 0 & 0 \\ 0 & -k_{31} & k_{13} & 0 & 0 \\ f_p^p \cdot k_a & k_{31} & -k_1 & k_{21} & 0 \\ f_m^p \cdot k_a & 0 & k_{12} & -k_2 & k_{42} \\ 0 & 0 & 0 & k_{24} & -k_{42} \end{vmatrix} \quad (A1)$$

The determinant of **B**, B, can be obtained from **B** as

$$B = k_a \cdot k_{31} \cdot k_{42} \cdot (k_{11} \cdot k_{22} - k_{12} \cdot k_{21}) = k_a \cdot k_{31} \cdot k_{42} \cdot k_b \quad (A2a, b)$$

where $k_b = k_{11} \cdot k_{22} - k_{12} \cdot k_{21}$. The negative of the inverted matrix, $-\mathbf{B}^{-1}$, is

$$-\mathbf{B}^{-1} = \begin{vmatrix} -B_{11}/B & -B_{21}/B & -B_{31}/B & -B_{41}/B & -B_{51}/B \\ -B_{12}/B & -B_{22}/B & -B_{32}/B & -B_{42}/B & -B_{52}/B \\ -B_{13}/B & -B_{23}/B & -B_{33}/B & -B_{43}/B & -B_{53}/B \\ -B_{14}/B & -B_{24}/B & -B_{34}/B & -B_{44}/B & -B_{54}/B \\ -B_{15}/B & -B_{25}/B & -B_{35}/B & -B_{45}/B & -B_{55}/B \end{vmatrix} \quad (A3)$$

where B_{ij} (i,j = 1–5) are the adjoints of the minor matrix for row i and column j of **B**. It can readily be shown that

$$B_{11} = -k_a \cdot k_{31} \cdot k_{42} \cdot k_b \quad \text{(A4)}$$

$$B_{12} = -k_{13} \cdot k_a \cdot k_{42} \cdot (f_p^p \cdot k_{22} + f_m^p \cdot k_{21}) \quad \text{(A5)}$$

$$B_{13} = -k_{31} \cdot k_a \cdot k_{42} \cdot (f_p^p \cdot k_{22} + f_m^p \cdot k_{21}) \quad \text{(A6)}$$

$$B_{14} = -k_{31} \cdot k_a \cdot k_{42} \cdot (f_p^p \cdot k_{12} + f_m^p \cdot k_{11}) \quad \text{(A7)}$$

$$B_{15} = -k_{31} \cdot k_a \cdot k_{24} \cdot (f_p^p \cdot k_{12} + f_m^p \cdot k_{11}) \quad \text{(A8)}$$

According to the stochastic approach (13,14), the $MRT_p^{p,po}$ and $MRT_m^{p,po}$ can be calculated as follows:

$$MRT_p^{p,po} = -(B_{11}/B) - (B_{12} + B_{13})/[(f_p^p + f_m^p) \cdot B] \quad \text{(A9)}$$

$$MRT_m^{p,po} = -(B_{11}/B) - (B_{14} + B_{15})/[(f_p^p + f_m^p) \cdot B] \quad \text{(A10)}$$

Substituting Eqs. (A2b) and (A4)–(A8) into Eqs. (A9) and (A10) yields

$$MRT_p^{p,po} = 1/k_a + (f_p^p \cdot k_{22} + f_m^p \cdot k_{21}) \cdot [1 + (k_{13}/k_{31})]/[(f_p^p + f_m^p) \cdot k_b] \quad \text{(A11)}$$

$$MRT_m^{p,po} = 1/k_a + (f_p^p \cdot k_{12} + f_m^p \cdot k_{11}) \cdot [1 + (k_{24}/k_{42})]/[(f_p^p + f_m^p) \cdot k_b] \quad \text{(A12)}$$

The traditional equations for V_{ss}^p and V_{ss}^m are

$$V_{ss}^p = [1 + (k_{13}/k_{31})] \cdot Vc_p \quad \text{(A13)}$$

$$V_{ss}^m = [1 + (k_{24}/k_{42})] \cdot Vc_m \quad \text{(A14)}$$

Also, the mean residence times of the drug ($MRT_p^{p,iv}$) and of its interconversion metabolite ($MRT_m^{m,iv}$) after their separate iv administration can be calculated as follows (9):

$$MRT_p^{p,iv} = V_{ss}^p \cdot CL_{22}/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad \text{(A15)}$$

$$MRT_m^{m,iv} = V_{ss}^m \cdot CL_{11}/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad \text{(A16)}$$

Combining Eqs. (A11), (A13), (A15), and (17) as well as Eqs. (A12), (A14), (A16), and (18) separately yields Eqs. (19) and (20).

The following equations can also be derived from Eqs. (1)–(5):

$$\frac{AUMC_p^{p,po}}{AUC_p^{p,po}} = \frac{1}{k_a} + \frac{f_p^p \cdot (V_{ss}^p \cdot CL_{22}^2 + V_{ss}^m \cdot CL_{12} \cdot CL_{21})}{(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \cdot (f_p^p \cdot CL_{22} + f_m^p \cdot CL_{21})} + \frac{f_m^p \cdot (V_{ss}^p \cdot CL_{21} \cdot CL_{22} + V_{ss}^m \cdot CL_{21} \cdot CL_{11})}{(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \cdot (f_p^p \cdot CL_{22} + f_m^p \cdot CL_{21})} \quad \text{(A17)}$$

$$\frac{AUMC_m^{p,po}}{AUC_m^{p,po}} = \frac{1}{k_a} + \frac{f_p^p \cdot CL_{12} \cdot (V_{ss}^p \cdot CL_{22} + V_{ss}^m \cdot CL_{11})}{(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \cdot (f_p^p \cdot CL_{12} + f_m^p \cdot CL_{11})} + \frac{f_m^p \cdot (V_{ss}^p \cdot CL_{12} \cdot CL_{21} + V_{ss}^m \cdot CL_{11}^2)}{(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \cdot (f_p^p \cdot CL_{12} + f_m^p \cdot CL_{11})} \quad \text{(A18)}$$

The following equations have been derived previously (9):

$$AUMC_p^{p,iv} = \frac{D^{p,iv} \cdot (V_{ss}^p \cdot CL_{22}^2 + V_{ss}^m \cdot CL_{12} \cdot CL_{21})}{(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21})^2} \quad \text{(A19)}$$

$$AUMC_m^{p,iv} = \frac{D^{p,iv} \cdot CL_{12} \cdot (V_{ss}^p CL_{22} + V_{ss}^m \cdot CL_{11})}{(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21})^2} \quad \text{(A20)}$$

$$AUMC_p^{m,iv} = \frac{D^{m,iv} \cdot CL_{21} \cdot (V_{ss}^p \cdot CL_{22} + V_{ss}^m \cdot CL_{11})}{(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21})^2} \quad \text{(A21)}$$

$$AUMC_m^{m,iv} = \frac{D^{m,iv} \cdot (V_{ss}^p \cdot CL_{12} \cdot CL_{21} + V_{ss}^m \cdot CL_{11}^2)}{(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21})^2} \quad \text{(A22)}$$

Thus, combining Eqs. (9), (11), (17), (18), (A17), (A19), and (A21) as well as Eqs. (10), (12), (17), (18), (A18), (A20), and (A22) separately yields Eqs. (21) and (22) for the AUMC/AUC ratios.

NOMENCLATURE

$A(t)$	Amount of compound in absorption site at time t
AUC	Area under the concentration–time curve
AUMC	Area under the first moment curve (integral of $tC(t)$ versus t)
CL_{12}	Conversion clearance of parent drug to metabolite
CL_{21}	Conversion clearance of metabolite to parent drug
CL_{10}	Sum of all irreversible elimination clearance processes operating on parent drug
CL_{20}	Sum of all irreversible elimination clearance processes operating on metabolite
CL_{11}	Sum of conversion (CL_{12}) and all irreversible elimination (CL_{10}) processes operating on parent drug
CL_{22}	Sum of conversion (CL_{21}) and all irreversible elimination (CL_{20}) processes operating on metabolite
CL_{dp}	Distribution clearance of parent drug
CL_{dm}	Distribution clearance of metabolite
C_p	Plasma concentration of parent drug at time t
C_m	Plasma concentration of metabolite at time t
C_{Tp}	Tissue concentration of parent drug at time t
C_{Tm}	Tissue concentration of metabolite at time t
D	Administered dose
EE	Exposure enhancement parameter
f_p^p	Fraction of the oral dose entering the central compartment intact as parent drug
f_m^p	Fraction of the oral dose entering the central compartment as metabolite
F_p^p	Systemically available fraction of drug
F_m^p	Systemically available fraction of metabolite
f_{1p}	Fractional first-time conversion of drug to metabolite (iv dose)
f_{1m}	Fractional first-time conversion of metabolite to drug (iv dose)
k_a	First-order rate constant for parent drug and metabolite loss from the absorption site

k_{10}	First-order elimination rate constant of parent drug
k_{20}	First-order elimination rate constant of metabolite
k_{12}	First-order conversion rate constant of parent drug to metabolite
k_{21}	First-order conversion rate constant of metabolite to parent drug
k_{13}	First-order rate constant for drug distribution from central to tissue compartment
k_{31}	First-order rate constant for drug distribution from tissue to central compartment
k_{24}	First-order rate constant for metabolite distribution from central to tissue compartment
k_{42}	First-order rate constant for metabolite distribution from tissue to central compartment
MAT	Mean absorption time of compound
MRT	Mean residence time of compound in body
Vc_p	Central volume of parent drug
Vc_m	Central volume of metabolite
V_{Tp}	Apparent tissue volume of parent drug
V_{Tm}	Apparent tissue volume of metabolite
V_{ss}^{p}	Steady-state volume of distribution, parent drug
V_{ss}^{m}	Steady-state volume of distribution, metabolite

Superscripts

p or m	Administered parent drug (p) or metabolite (m)
po	Oral administration of indicated compound
iv	Intravenous administration of indicated compound

Subscripts

p or m	Measured parent drug or metabolite

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