Mean Residence Times and Distribution Volumes for Drugs Undergoing Linear Reversible Metabolism and Tissue Distribution and Linear or Nonlinear Elimination from the Central Compartments

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Equations for the mean residence times in the body (MRT) and in the central compartment (MRTc) are derived for bolus central dosing of a drug and its metabolite which undergo linear tissue distribution and linear reversible metabolism but are eliminated either linearly or nonlinearly (Michaelis–Menten kinetics) from the central compartments. In addition, a new approach to calculate the steady-state volumes of distribution for nonlinear systems (reversible or nonreversible) is proposed based on disposition decomposition analysis. The application of these equations to a dual reversible two-compartment model is illustrated by computer simulations.

KEY WORDS: mean residence time; pharmacokinetics; steady-state volume of distribution; Michaelis–Menten elimination; reversible metabolism; disposition decomposition analysis; compartmental models.

INTRODUCTION

Recent literature has abounded with reports dealing with residence time analysis as applied to both linear and nonlinear drug disposition systems. Using a stochastic approach, Aarons (1) derived the mean residence time in the body (MRT) for one-compartmental drugs undergoing reversible metabolism. Recently, this approach was extended to multicompartmental drugs (2) and the following equations for the mean residence times in the body and in the central compartment (MRTc) have been derived:

$$MRT_p^p = V_{ss}^p \cdot AUC_p^p/Dose^p \quad (1)$$

$$MRT_m^p = V_{ss}^m \cdot AUC_m^p/Dose^p \quad (2)$$

$$MRT_p^m = V_{ss}^p \cdot AUC_p^m/Dose^m \quad (3)$$

$$MRT_m^m = V_{ss}^m \cdot AUC_m^m/Dose^m \quad (4)$$

$$MRTc_p^p = Vc_p \cdot AUC_p^p/Dose^p \quad (5)$$

$$MRTc_m^p = Vc_m \cdot AUC_m^p/Dose^p \quad (6)$$

$$MRTc_p^m = Vc_p \cdot AUC_p^m/Dose^m \quad (7)$$

$$MRTc_m^m = Vc_m \cdot AUC_m^m/Dose^m \quad (8)$$

where V_{ss} and Vc are the steady-state and central volumes of distribution of the parent drug (p) and of the metabolite (m), and AUC is the area under the plasma concentration–time curve following a bolus dose of the drug ($Dose^p$) or of the metabolite ($Dose^m$). The superscripts denote the dosed compound and the subscripts represent the measured compound. These equations, however, were shown to be meaningful only for drugs behaving linearly. The validity of these equations for drugs undergoing linear reversible metabolism and tissue distribution and with nonlinear elimination from the central compartment remains uncertain. Numerous drugs undergo interconversion with their metabolites and the possibility of capacity-limited elimination of either drug or metabolite exists at higher doses.

The purposes of this report are (a) to show that Eqs. (1)–(8) are meaningful for drugs undergoing linear reversible metabolism and tissue distribution regardless of the linearity of their elimination kinetics and (b) to derive new equations to calculate steady-state volumes of distribution for drugs which obey these kinetics.

THEORETICAL

Consider the bolus administration of a drug with linear distribution and linear or nonlinear elimination only from the central compartment and subject to linear reversible metabolism directly from the central compartment (Fig. 1). Note that drug is administered only into the central compartment and the only possible nonlinearity pertains to irreversible elimination from this site. The rate of change of amount of drug in the central compartment [$Ac_p^{p\prime}(t)$] and in the peripheral tissues [$A_{T_p}^{p\prime}(t)$] under these conditions can be described according to disposition decomposition analysis (DDA) (3) as follows:

$$Ac_p^{p\prime}(t) = -[CL_p(t) + CL_{Dp} + CL_{12}] \cdot C_p^p(t) + CL_{21} \cdot C_m^p(t) + Vc_p \cdot C_p^p(t) * h_p(t) \quad (9)$$

and

$$A_{T_p}^{p\prime}(t) = CL_{Dp} \cdot C_p^p(t) - Vc_p \cdot C_p^p(t) * h_p(t) \quad (10)$$

where $Ac_p^{p\prime}(t)$ and $A_{T_p}^{p\prime}(t)$ are the first derivatives of the amount of drug in the central compartment [$Ac_p^p(t)$] and in the peripheral tissues [$A_{T_p}^p(t)$], the asterisk denotes convolution, and the symbols are defined and depicted in Fig. 1 and under Nomenclature. Integrating Eq. (10) from time 0 to ∞ and substituting $A_{T_p}^p(0) = A_{T_p}^p(\infty) = 0$ yields

$$0 = CL_{Dp} \cdot AUC_p^p - Vc_p \cdot \int_0^\infty h_p(t)dt \cdot AUC_p^p \quad (11)$$

or

$$\int_0^\infty h_p(t)dt = CL_{Dp}/Vc_p \quad (12)$$

An analogous expression of Eq. (12) has previously been derived for drugs which do not undergo reversible metabolism (4). Integrating Eq. (10) from time 0 to time t yields

$$A_{T_p}^p(t) = \left[CL_{Dp} - Vc_p \cdot \int_0^t h_p(u)du\right] * C_p^p(t) \quad (13)$$

From Eqs. (12) and (13) it follows that

$$A_{T_p}^p(t) = Vc_p \cdot \int_t^\infty h_p(u)du * C_p^p(t) \quad (14)$$

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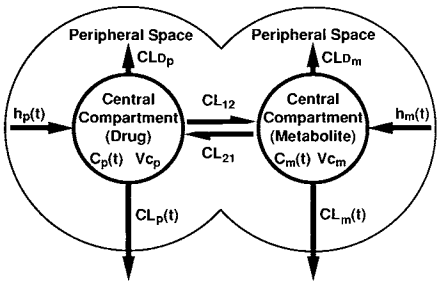

Fig. 1. Generalized reversible metabolic system. $C_p(t)$ and $C_m(t)$ are plasma concentrations of parent drug (p) and of metabolite (m) at time t; Vc_p and Vc_m are central volumes of distribution; CL_{12} and CL_{21} are the conversion clearances of parent drug to metabolite, and vice versa; CL_{Dp} and CL_{Dm} are the distribution clearances; $CL_p(t)$ and $CL_m(t)$ are the total exit clearances; and $h_p(t)$ and $h_m(t)$ are the distribution functions (3).

Integrating Eq. (14) from time 0 to ∞ yields

$$\int_0^\infty A_{Tp}^p(t)dt = \text{AUMDC}_p \cdot \text{AUC}_p^p \cdot Vc_p \tag{15}$$

where AUMDC_p is the area under the first moment curve of the distribution function of the drug and is given by

$$\text{AUMDC}_p = \int_0^\infty \int_t^\infty h_p(u)du\,dt = \int_0^\infty t \cdot h_p(t)dt \tag{16a, b}$$

and

$$\text{AUC}_p^p \cdot Vc_p = \int_0^\infty Ac_p(t)dt \tag{17}$$

From Eqs. (15) and (17) it follows that

$$\int_0^\infty A_{bp}^p(t)\,dt = \int_0^\infty A_{Tp}^p(t)dt + \int_0^\infty Ac_p^p(t)dt = (\text{AUMDC}_p + 1) \cdot Vc_p \cdot \text{AUC}_p^p \tag{18a, b}$$

where $A_{bp}^p(t)$ is the amount of drug in the body and equals the sum of $Ac_p^p(t)$ and $A_{Tp}^p(t)$. By definition (5),

$$\text{MRT}_p^p = \int_0^\infty A_{bp}^p(t)dt/\text{Dose}^p \tag{19}$$

and

$$\text{MRTc}_p^p = \int_0^\infty Ac_p^p(t)dt/\text{Dose}^p \tag{20}$$

Combining Eqs. (17) and (20) as well as Eqs. (18b) and (19) yields Eq. (5) and

$$\text{MRT}_p^p = (\text{AUMDC}_p + 1) \cdot Vc_p \cdot \text{AUC}_p^p/\text{Dose}^p = (\text{AUMDC}_p + 1) \cdot \text{MRTc}_p^p \tag{21a, b}$$

or

$$\text{AUMDC}_p = \text{MRT}_{Tp}^p/\text{MRTc}_p^p \tag{22}$$

where MRT_{Tp}^p is the mean residence time of drug in the peripheral tissues following a bolus dose of the parent drug and equals $\text{MRT}_p^p - \text{MRTc}_p^p$. It can be readily shown that Eq. (14) is valid if the drug is intravenously infused at a constant rate R_o^p to steady states of both drug and metabolite. By definition,

$$A_{bp}^p(t) = Ac_p^p(t) + A_{Tp}^p(t) \tag{23}$$

Combining Eqs. (14) and (23) yields

$$A_{bp}^p(t) = Ac_p^p(t) + Vc_p \cdot \int_t^\infty h_p(u)du * C_p^p(t) = Vc_p \cdot C_p^p(t) + Vc_p \cdot \int_t^\infty h_p(u)du * C_p^p(t) \tag{24a, b}$$

From Eq. (24b), it follows that

$$\begin{aligned} A_{bp,ss}^p &= \lim_{t\to\infty} A_{bp}^p(t) \\ &= Vc_p \cdot C_{p,ss}^p + Vc_p \cdot C_{p,ss}^p \cdot \int_0^\infty \int_t^\infty h_p(u)du\,dt \\ &= Vc_p \cdot C_{p,ss}^p \cdot \left[1 + \int_0^\infty t \cdot h_p(t)dt\right] \\ &= Vc_p \cdot C_{p,ss}^p \cdot (1 + \text{AUMDC}_p) \end{aligned} \tag{25a–d}$$

where $A_{bp,ss}^p$ and $C_{p,ss}^p$ are the amount of drug in the body and plasma concentration of the drug at steady state. When the parent drug is intravenously infused to the steady states of both the drug and the metabolite, $A_{bp,ss}^p$ is given by

$$A_{bp,ss}^p = V_{ss}^p \cdot C_{p,ss}^p \tag{26}$$

Combining Eqs. (25d) and (26) yields

$$V_{ss}^p = (\text{AUMDC}_p + 1)Vc_p \tag{27}$$

or

$$\text{AUMDC}_p = (V_{ss}^p - Vc_p)/Vc_p \tag{28}$$

Combining Eqs. (21a) and (27) yields Eq. (1). Similarly, Eqs. (2)–(4) and (6)–(8) and the following equations can also be derived:

$$\int_0^\infty h_m(t)dt = \text{CL}_{Dm}/Vc_m \tag{29}$$

$$\text{AUMDC}_m = \int_0^\infty t \cdot h_m(t)dt = (V_{ss}^m - Vc_m)/Vc_m = \text{MRT}_{Tm}^m/\text{MRTc}_m^m \tag{30a–c}$$

and

$$V_{ss}^m = (\text{AUMDC}_m + 1) \cdot Vc_m \tag{31}$$

where MRT_{Tm}^m is the mean residence time of metabolite in the peripheral tissues following intravenous administration of a bolus dose of metabolite. Thus, Eqs. (1)–(8) are meaningful for drugs undergoing linear reversible metabolism and tissue distribution and eliminated either linearly or nonlinearly from the central compartments.

METHODS

Separate intravenous administration of a bolus dose of a drug and its metabolite was considered where both follow a nonlinear two-compartment model (Fig. 2). Plasma concentrations of both compounds were generated by numerical integration of the following equations using PCNONLIN (6):

$$Ac_p'(t) = -\{[Vm_p/(Km_p + C_p(t))] + \text{CL}_{12} + \text{CL}_{Dp}\} \cdot C_p(t) + \text{CL}_{21} \cdot C_m(t) + \text{CL}_{Dp} \cdot C_{Tp}(t)/R_p \tag{32}$$

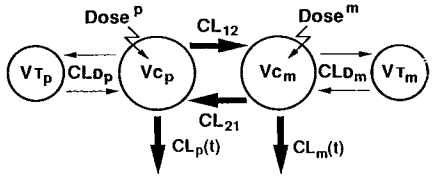

Fig. 2. Specific two-compartment model of reversible drug metabolism used for computer simulations. Symbols are identical to those in Fig. 1, with the addition of V_T as the peripheral compartment volume.

$$A_{Tp}'(t) = CL_{Dp} \cdot C_p(t) - CL_{Dp} \cdot C_{Tp}(t)/R_p \quad (33)$$

$$Ac_m'(t) = -\{[Vm_m/(Km_m + C_m(t))] + CL_{21} + CL_{Dm}\} \cdot C_m(t) + CL_{12} \cdot C_p(t) + CL_{Dm} \cdot C_{Tm}(t)/R_m \quad (34)$$

$$A_{Tm}'(t) = CL_{Dm} \cdot C_m(t) - CL_{Dm} \cdot C_{Tm}(t)/R_m \quad (35)$$

where R_p and R_m are the tissue:plasma distribution ratios and Vm and Km are the Michaelis–Menten capacity and affinity constants for drug and metabolite. Initial conditions accounted for administration of either Dose^P or Dose^m into Vc_p or Vc_m with the other compartment values set = 0 at t = 0. Simulated data were obtained by assigning numerical values of Dose^P (3.0 g), Dose^m (3.0 g), Vc_p (73.4 liters), Vc_m (39.0 liters), V_{Tp} (30.1 liters), V_{Tm} (10.0 liters), Vm_p (360 mg/hr), Vm_m (115.2 mg/hr), Km_p (6.0 mg/liter), Km_m (12.0 mg/liter), CL_{12} (13.8 liter/hr), CL_{21} (15.0 liter/hr), CL_{Dp} (9.0 liter/hr), CL_{Dm} (4.0 liter/hr), R_p = 1, and R_m = 1. The values of AUC were generated using the LAGRAN program (7). Values of MRT and MRTc for drug and interconversion metabolite were then calculated using Eqs. (1)–(8) and the theoretical values of V_{ss} and Vc.

RESULTS

Application of Eqs. (1)–(8) to calculate MRT and MRTc for drugs undergoing linear reversible metabolism and tissue distribution and eliminated nonlinearly from the central compartment was illustrated by computer simulations. As shown in Fig. 3, the plasma profiles of compounds given by bolus administration show an exponential decline, while the paired metabolites show a formation/distribution phase followed by the exponential decline. As expected for any linear or nonlinear system which eventually equilibrates, all curves attain a terminal phase with parallel slopes.

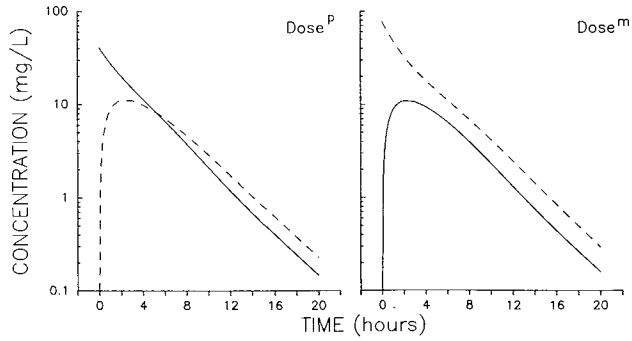

Fig. 3. Simulated concentration–time profiles for the two-compartment model of reversible drug metabolism following separate intravenous administration of parent drug and metabolite. Parameter values are listed under Methods. Lines depict profiles of parent drug (——) and metabolite (---).

Table I lists the mean time values calculated using Eqs. (1)–(8). Values of MRTc for the dosed compounds range from 1.09 to 3.15 hr, while the corresponding values of MRT are larger and vary from 1.37 to 4.44 hr.

DISCUSSION

Equations derived previously for the MRT and MRTc parameters [Eqs. (1)–(8)] have now been shown to be meaningful for drugs undergoing linear reversible metabolism and tissue distribution regardless of the linearity of the elimination kinetics of drugs or their metabolites. According to Eqs. (1)–(4), one must know or predetermine the V_{ss} parameters in order to calculate the values of the MRT parameters. For a drug and its metabolite both behaving linearly, V_{ss}^p and V_{ss}^m can be determined from AUC and AUMC values obtained by separately administering an intravenous bolus dose of drug and of metabolite (8). However, except at low doses, this approach is not meaningful for a drug or metabolite eliminated nonlinearly from the central compartment. For a drug or metabolite behaving nonlinearly, as shown in Eqs. (27) and (31), V_{ss}^p or V_{ss}^m can be obtained from Vc and AUMDC [or $h(t)$]. The values of Vc can easily be generated from the dose and zero-time plasma concentration of administered compound. Based on plasma drug profiles from two different intravenous bolus doses, determination of $h(t)$ for a drug which distributes linearly into peripheral tissues and is eliminated nonlinearly from the central compartment without undergoing reversible metabolism has been demonstrated previously by Veng-Pedersen (9). A similar approach can be used to determine $h(t)$ and AUMDC for a drug eliminated nonlinearly from the central compartment and undergoing linear tissue distribution and reversible metabolism. In principle, this is possible but it requires a computer program to obtain $h(t)$.

The concept of AUMDC is of value for several reasons. The AUMDC parameter allows two important parameters, MRT_T and MRTc, to be closely related regardless of the linearity of the elimination kinetics of a drug or its metabolite. As shown in Eqs. (28) and (30a), $V_{ss} - Vc$ and Vc for both compounds can also be related through AUMDC. This allows us to calculate values of V_{ss} from AUMDC and Vc for the administered bolus drug or metabolite. Moreover, of considerable general importance is that this approach to calculate V_{ss} can also be applied to drugs not undergoing reversible metabolism (10). Trying to fit or generate this pa-

Table I. The Mean Residence Time Values for a Two-Compartment System

Compound				
Administered, i	Measured, j	Eqs.	$MRTc_j^i$ (hr)	MRT_j^i (hr)
p	p	(5), (1)	3.15	4.44
p	m	(6), (2)	1.09	1.37
m	p	(7), (3)	1.87	2.64
m	m	(8), (4)	2.86	3.59

rameter for multicompartment nonlinear systems is otherwise difficult.

Since the AUC parameters for a drug or metabolite undergoing linear reversible metabolism and nonlinear elimination from the central compartment depend on the dose of the administered compound, as shown in Eqs. (1)–(8), both the MRT and the MRTc are functions of AUC and, thus, are dose-dependent parameters. On the contrary, according to Eqs. (27) and (31), V_{ss}^{p} and V_{ss}^{m} are dose-independent parameters, as AUMD*C* are not functions of the dose of the administered compound [Eqs. (16) and (30a)].

In conclusion, this report shows that equations derived previously for calculating the values of MRT and MRTc parameters for linear systems with linear reversible metabolism are also meaningful for systems with nonlinear central elimination and linear reversible metabolism. The application of these equations to such drugs has also been illustrated with computer simulations.

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NOMENCLATURE

$A_b(t)$	Amount of compound in body at time t
$A_{b,ss}$	Steady-state amount of compound in body
$Ac(t)$	Amount of compound in the central compartment at t
$A_T(t)$	Amount of compound in the peripheral tissues at t
AUC	Area under the concentration–time curve
AUMC	Area under the first moment curve [integral of $tC(t)$ versus t]
AUMDC	Area under the first moment curve of the distribution function of compound
CL_{12}	Conversion clearance of parent drug to metabolite
CL_{21}	Conversion clearance of metabolite to parent drug
$CL(t)$	Sum of all irreversible elimination clearance processes operating on compound
CL_D	Distribution clearance of compound
$C(t)$	Plasma concentration of compound at t
$C_T(t)$	Tissue concentration of compound at t
C_{ss}	Steady-state plasma concentration of compound
$h(t)$	Distribution function
Km	Michaelis–Menten affinity constant
MRT	Mean residence time of compound in body
MRTc	Mean residence time of compound in the central compartment
MRT_T	Mean residence time of compound in the peripheral tissues
^{p} or ^{m}	Administered parent drug (p) or metabolite (m)
$_{p}$ or $_{m}$	Measured parent drug or metabolite
R	Tissue:plasma distribution ratio of compound
R_o	Constant intravenous infusion rate of compound
t	Time
Vc	Central volume of distribution
Vm	Michaelis–Menten capacity constant
V_T	Apparent tissue volume of distribution
V_{ss}	Steady-state volume of distribution

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