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Research Article

Mean Interconversion Times and Distribution Rate Parameters for Drugs Undergoing Reversible Metabolism

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The mean interconversion time and recycling numbers are introduced as intrinsic metabolic interconversion and distribution parameters for drugs undergoing linear reversible metabolism. Equations for these parameters, the distribution clearance, and the mean transit time in the central and peripheral compartments are derived for a metabolic pair where interconversion and elimination occur in central compartments. These parameters can be calculated from plasma concentration versus time slopes and intercepts, AUC, and AUMC data of parent drug and its metabolite partner following iv administration of each compound. The mean time analysis is illustrated with disposition data obtained previously for methylprednisolone and methylprednisone in the rabbit. Examination of mean times and additional properties of the system reveals that total exposure time of methylprednisolone is weakly influenced by the metabolic interconversion process, whereas the total exposure time of methylprednisone is strongly influenced by the process. In addition, the tissue distribution processes moderately influence the total exposure times of both compounds. The derived mean time parameters, along with previously evolved equations for clearances, volumes of distribution, moments, and mean residence times allow comprehensive analysis of linear, multicompartmental reversible metabolic systems.

KEY WORDS: reversible metabolism; mean metabolic interconversion time; mean transit time; mean residence time; recycling numbers; moment analysis; methylprednisolone; methylprednisone.

INTRODUCTION

Tissue distribution, metabolic interconversion, and enterohepatic recycling are pharmacokinetic factors that may increase transit times and prolong the duration of exposure of drug to target tissues. The mean residence and transit times (MRT_T and MTT_T) in the peripheral tissues have been proposed as indicators of tissue persistency of gentamicin and other drugs (1,2). Similarly, the degree of conservation or exposure enhancement afforded by metabolic interconversion can be described in terms of the mean interconversion time (MIT), which is defined as the mean time for a parent drug molecule (or a metabolite molecule) to be converted to its metabolite molecule (or parent drug molecule) and back converted once.

The role of reversible metabolism has been gradually appreciated. Methods for obtaining various pharmacokinetic parameters, particularly clearances and volumes of distribution, for this class of compounds have been developed (3–10). Recently, more specific methods for calculating the mean residence time parameters for drugs undergoing reversible metabolism have been proposed for paired one (11)- or two (12)-compartment models. This report extends these principles and mean time concepts to evolve methods for calculating the distribution clearance, recycling numbers, and mean transit and interconversion times for drugs subject to linear reversible metabolism. Derivation methods based on system approaches (1,13) were utilized. Comprehensive equations are developed for parameters that may provide insight into the principles of conservation or exposure enhancement of drugs via tissue distribution and/or reversible metabolism. The application of these methods is illustrated by an extended pharmacokinetic analysis of the interconversion between methylprednisolone and methylprednisone in rabbits.

THEORETICAL

For a bolus drug with linear disposition and subject to reversible metabolism (Fig. 1), the rate of irreversible drug elimination from the central compartment is $CL_{10} \cdot C_p(t)$, the rates of drug distribution and biotransformation to metabolite are $CL_{Dp} \cdot C_p(t)$ and $CL_{12} \cdot C_p(t)$, and the rates of drug return from the peripheral space (1) and from back conversion of the metabolite are $Vc_p \cdot C_p(t) * h_p(t)$ and $CL_{21} \cdot C_m(t)$, where the asterisk denotes convolution and the symbols are defined and depicted in Fig. 1. By definition,

$$P = CL_{11}/(CL_{11} + CL_{Dp}) \quad (1)$$

where $CL_{11} = CL_{10} + CL_{12}$ and P equals the probability of a parent drug molecule leaving the central compartment via irreversible elimination and/or reversible metabolism. Consequently, $1 - P$ equals the probability of peripheral tissue

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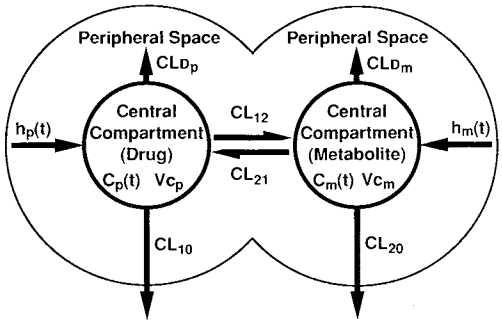

Fig. 1. Basic reversible metabolic system. $C_p(t)$ and $C_m(t)$ are plasma concentrations of parent drug and of metabolite at time t; Vc_p and Vc_m are central volumes of distribution of parent drug and of metabolite; CL_{12} is the conversion clearance of parent drug to metabolite; CL_{21} is the conversion clearance of metabolite to parent drug; CL_{Dp} and CL_{Dm} are the distribution clearances of parent drug and of metabolite; CL_{10} and CL_{20} are the total exit clearances of parent drug and of metabolite; and $h_p(t)$ and $h_m(t)$ are the distribution functions of parent drug and of metabolite similar to the definitions provided in Ref. 1.

distribution of the parent drug molecules. Similarly, the constant Q can also be defined as

$$Q = 1 - [CL_{12} \cdot CL_{21}/(CL_{11} \cdot CL_{22})] \quad (2)$$

where $CL_{22} = CL_{20} + CL_{21}$, and Q equals the probability of a parent drug molecule not being subject to reversible metabolism. Thus, $1 - Q$ equals the probability of a parent drug molecule being converted to metabolite and being back converted, and the constant M can be defined by

$$M = (1 - P) + (1 - P) \cdot (1 - Q) \quad (3)$$

which equals the probability of peripheral tissue distribution of a parent drug molecule being or not being subject to reversible metabolism. Let N_0 denote the number of the parent drug molecules initially injected intravenously into the central compartment, then $N_0 \cdot [(1 - P) + (1 - P) \cdot (1 - Q)]$ parent drug molecules will distribute at least once to the peripheral system, and of these, $N_0 \cdot [(1 - P) \cdot P + (1 - P) \cdot P \cdot (1 - Q) \cdot Q]$ molecules will be eliminated following the first return to the central compartment from the peripheral system. By induction, it follows that of the N_0 parent drug molecules initially injected, before being eliminated $N_0 \cdot [(1 - P)^r \cdot P + (1 - P)^r \cdot P \cdot (1 - Q)^s \cdot Q]$ distribute r times to the peripheral system after undergoing or not undergoing s times metabolic interconversion. Let M_r and N_s be the random variables representing the number of times (r) that a parent drug molecule distributes into the peripheral system and the number of times (s) that a parent drug molecule converts to metabolite and back converts. The frequency distributions of M_r and M_rN_s are

$$f(r) = P(M_r) = N_0 \cdot [(1 - P)^r \cdot P]/N_0 = (1 - P)^r \cdot P \quad (4a, b, c)$$

and

$$f(r,s) = P(M_rN_s) = N_0 \cdot [(1 - P)^r \cdot P \cdot (1 - Q)^s \cdot Q]/N_0 = (1 - P)^r \cdot P \cdot (1 - Q)^s \cdot Q \quad (5a, b, c)$$

$r = s = 0, 1, 2, \ldots$.

where $P(M_r)$ is the probability that the random variable M_r equals r, $P(M_rN_s)$ is the probability that the random variables M_r and N_s equal r and s. According to probability theory (14), the expected values of M_r and M_rN_s are

$$E(M_r) = \sum_{i=0}^{\infty} i \cdot (1 - P)^i \cdot P \quad (6)$$

and

$$E(M_rN_s) = \sum_{i=0}^{\infty} \sum_{j=0}^{\infty} i \cdot (1 - P)^i \cdot P \cdot j \cdot (1 - Q)^j \cdot Q \quad (7)$$

where $E(M_r)$ and $E(M_rN_s)$ are the expected values of M_r and M_rN_s. From Eq. (6) it has readily been shown that (1)

$$E(M_r) = (1 - P)/P \quad (8)$$

According to probability theory (14), since these two events, peripheral distribution (M_r) and metabolic interconversion (N_s), are stochastically independent, from Eq. (7) it follows that

$$E(M_rN_s) = E(M_r) \cdot E(N_s) = \sum_{i=0}^{\infty} i \cdot (1 - P)^i \cdot P \cdot \sum_{j=0}^{\infty} j \cdot (1 - Q)^j \cdot Q = (1 - P) \cdot (1 - Q)/PQ \quad (9a, b, c)$$

Therefore, the total number of times (R_{Tp}) that the N_0 parent drug molecules undergoing reversible metabolism distribute to the peripheral system can be described as follows:

$$R_{Tp} = E(M_r) + E(M_rN_s) = (1 - P)/P + (1 - P) \cdot (1 - Q)/PQ = (1 - P)/PQ \quad (10a, b, c)$$

Combining Eqs. (1), (2), and (10c) yields

$$R_{Tp} = CL_{Dp} \cdot CL_{22}/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad (11)$$

For reasons of symmetry in the system of reversible metabolism (Fig. 1), it follows that

$$R_{Tm} = CL_{Dm} \cdot CL_{11}/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad (12)$$

where R_{Tm} is the number of times that a metabolite molecule distributes to the peripheral system before being irreversibly eliminated. The following equations have been derived previously for drugs subject to reversible metabolism (6,12,15):

$$AUC_p^p = Dose^p \cdot CL_{22}/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad (13)$$

$$AUC_m^m = Dose^m \cdot CL_{11}/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad (14)$$

$$CL_{10} = \frac{Dose^p \cdot AUC_m^m - Dose^m \cdot AUC_m^p}{AUC_p^p \cdot AUC_m^m - AUC_m^p \cdot AUC_p^m} \quad (15)$$

$$CL_{12} = \frac{Dose^m \cdot AUC_m^p}{AUC_p^p \cdot AUC_m^m - AUC_m^p \cdot AUC_p^m} \quad (16)$$

$$CL_{20} = \frac{Dose^m \cdot AUC_p^p - Dose^p \cdot AUC_p^m}{AUC_p^p \cdot AUC_m^m - AUC_m^p \cdot AUC_p^m} \quad (17)$$

and

$$CL_{21} = \frac{Dose^p \cdot AUC_p^m}{AUC_p^p \cdot AUC_m^m - AUC_m^p \cdot AUC_p^m} \quad (18)$$

where AUC_p^p and AUC_m^p are the area under the plasma concentration–time curve (AUC) of parent drug and metabolite following administration of a bolus dose of parent drug ($Dose^p$), and AUC_p^m and AUC_m^m are the AUC of parent drug and metabolite after intravenous administration of a bolus dose ($Dose^m$) of metabolite. Combining Eqs. (11) and (13) yields

$$R_{Tp} = CL_{Dp} \cdot AUC_p^p/Dose^p \quad (19)$$

From Eqs. (12) and (14), it follows that

$$R_{Tm} = CL_{Dm} \cdot AUC_m^m/Dose^m \quad (20)$$

For a drug subject to reversible metabolism, the following equations have been derived previously for the mean residence times in the body (MRT) and in the central compartment (MRTc) for both parent drug and metabolite following separate administration of a bolus dose of each compound (12):

$$MRT_p^p = V_{ss}^p \cdot AUC_p^p/Dose^p \quad (21)$$

$$MRT_m^p = V_{ss}^m \cdot AUC_m^p/Dose^p \quad (22)$$

$$MRT_p^m = V_{ss}^p \cdot AUC_p^m/Dose^m \quad (23)$$

$$MRT_m^m = V_{ss}^m \cdot AUC_m^m/Dose^m \quad (24)$$

$$MRTc_p^p = Vc_p \cdot AUC_p^p/Dose^p \quad (25)$$

$$MRTc_m^p = Vc_m \cdot AUC_m^p/Dose^p \quad (26)$$

$$MRTc_p^m = Vc_p \cdot AUC_p^m/Dose^m \quad (27)$$

and

$$MRTc_m^m = Vc_m \cdot AUC_m^m/Dose^m \quad (28)$$

where V_{ss}^p and V_{ss}^m are the steady-state volumes of distribution of the parent drug and the metabolite, the MRT and MRTc superscripts refer to the dosed compound, and the subscripts refer to the measured compound. By definition,

$$MRT_{Tp}^p = MRT_p^p - MRTc_p^p \quad (29)$$

$$MRT_{Tm}^p = MRT_m^p - MRTc_m^p \quad (30)$$

$$MRT_{Tp}^m = MRT_p^m - MRTc_p^m \quad (31)$$

$$MRT_{Tm}^m = MRT_m^m - MRTc_m^m \quad (32)$$

and

$$MTT_{Tp} = (MRT_p^p - MRTc_p^p)/R_{Tp} \quad (33)$$

where the superscripts and subscripts of either MRT_T or MTT_T refer again to the dosed compound and the measured compound. Combining Eq. (19), (21), (25), and (33) yields

$$MTT_{Tp} = (V_{ss}^p - Vc_p)/CL_{Dp} \quad (34)$$

Here, V_{ss}^p and Vc_p can be calculated from the following equations (10):

$$V_{ss}^p = \frac{Dose^p[(AUC_m^m)^2 \cdot AUMC_p^p - (AUC_m^p \cdot AUC_p^m \cdot AUMC_m^m)]}{(AUC_p^p)^2 \cdot (AUC_m^m)^2 - (AUC_m^p \cdot AUC_p^m)^2} \quad (35)$$

and

$$Vc_p = Dose^p/C_p^p(0) \quad (36)$$

where $C_p^p(0)$ is $C_p^p(t)$ at time 0, $AUMC_p^p$ is the area under the first moment curve (AUMC) of parent drug following administration of parent drug, and $AUMC_m^m$ is the AUMC of metabolite following administration of metabolite. It can also be readily shown that

$$CL_{Dp} = -[Dose^p \cdot C_p^{p\prime}(0)/C_p^p(0)^2] - CL_{11} \quad (37)$$

and

$$CL_{Dm} = -[Dose^m \cdot C_m^{m\prime}(0)/C_m^m(0)^2] - CL_{22} \quad (38)$$

where $C_m^m(0)$ is $C_m^m(t)$ at time 0, and $C_p^{p\prime}(0)$ and $C_m^{m\prime}(0)$ are the first derivatives of $C_p^p(t)$ and of $C_m^m(t)$ at time 0. In addition, according to Eqs. (15)–(18), the parameters which reflect the total elimination rate of the parent drug (CL_{11}) and the metabolite (CL_{22}) can be calculated as follows:

$$CL_{11} = CL_{10} + CL_{12} = Dose^p \cdot AUC_m^m/(AUC_p^p \cdot AUC_m^m - AUC_m^p \cdot AUC_p^m) \quad (39a,b)$$

and

$$CL_{22} = CL_{20} + CL_{21} = Dose^m \cdot AUC_p^p/(AUC_p^p \cdot AUC_m^m - AUC_m^p \cdot AUC_p^m) \quad (40a,b)$$

Combining Eqs. (34)–(37) and (39b) gives

$$MTT_{Tp} = \frac{(AUC_m^m)^2 \cdot AUMC_p^p - (AUC_m^p \cdot AUC_p^m \cdot AUMC_m^m)}{(AUC_p^p \cdot AUM_m^m)^2 - (AUC_m^p \cdot AUC_p^m)^2} - \frac{1}{C_p^p(0)} - \frac{C_p^{p\prime}(0)}{C_p^p(0)^2} - \frac{AUC_m^m}{(AUC_p^p \cdot AUC_m^m) - (AUC_m^p \cdot AUC_p^m)} \quad (41)$$

Similarly, it can be readily shown that

$$MTT_{Tm} = (V_{ss}^m - Vc_m)/CL_{Dm} \quad (42)$$

and

$$MTT_{Tm} = \frac{(AUC_p^p)^2 \cdot AUMC_m^m - (AUC_p^m \cdot AUC_m^p \cdot AUMC_p^p)}{(AUC_m^m \cdot AUC_p^p)^2 - (AUC_p^m \cdot AUC_m^p)^2} - \frac{1}{C_m^m(0)} - \frac{C_m^{m\prime}(0)}{C_m^m(0)^2} - \frac{AUC_p^p}{(AUC_m^m \cdot AUC_p^p) - (AUC_p^m \cdot AUC_m^p)} \quad (43)$$

where MTT_{Tm} is the mean transit time of the metabolite in the peripheral system.

Similarly, from Eq. (2), it can be shown that the number of times that a parent drug molecule converts to metabolite and back converts (R_{Ip}) can be calculated as

$$R_{Ip} = (1 - Q)/Q = CL_{12} \cdot CL_{21}/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad (44a,b)$$

The following equation has been derived for the mean residence time of the interconversion metabolite in the central compartment following administration of a bolus dose of the parent drug (12):

$$MRTc_m^p = CL_{12} \cdot Vc_m/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad (45)$$

By definition, the mean time for a bolus dose of a parent drug to convert to metabolite and back convert once in the central compartment (MIT_p) can be described as

$$MIT_p = MRTc_m^p/R_{Ip} \quad (46)$$

Substituting Eqs. (44) and (45) into Eq. (46) and simplifying the result yield

$$MIT_p = Vc_m/CL_{21} \quad (47)$$

For reasons of symmetry in the system of reversible metabolism (Fig. 1), it follows that

$$R_{Im} = R_{Ip} = CL_{12} \cdot CL_{21}/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad (48a,b)$$

and

$$MIT_m = Vc_p/CL_{12} \quad (49)$$

where R_{Im} is the number of times that a metabolite molecule converts to the parent drug and back converts, and MIT_m is the mean interconversion time of the metabolite in the central compartment. It should be noted that $R_{Ip} + 1$ and $R_{Im} + 1$ are analogous to the exposure enhancement (EE) defined previously (10). The following equations have also been defined or derived previously (10):

$$Vc_m = Dose^m/C_m^m(0) \quad (50)$$

and

$$V_{ss}^m = \frac{Dose^m \cdot [(AUC_p^p)^2 \cdot AUMC_m^m - (AUC_p^m \cdot AUC_m^p \cdot AUMC_p^p)]}{(AUC_p^p)^2 \cdot (AUC_m^m)^2 - (AUC_m^p \cdot AUC_p^m)^2} \quad (51)$$

Substituting Eqs. (18) and (50) into Eq. (47) as well as Eqs. (36) and (16) into Eq. (49) gives

$$MIT_p = (AUC_p^p \cdot AUC_m^m - AUC_m^p \cdot AUC_p^m)/[AUC_p^m \cdot C_m^m(0)] \quad (52)$$

and

$$MIT_m = (AUC_p^p \cdot AUC_m^m - AUC_m^p \cdot AUC_p^m)/[AUC_m^p \cdot C_p^p(0)] \quad (53)$$

For drugs subject to reversible metabolism, the total number of times ($R_{\Sigma p}$) that a parent drug molecule recycles around the central compartment via tissue distribution and/or reversible metabolic biotransformation can be calculated as follows:

$$R_{\Sigma p} = 1 + R_{Tp} + R_{Ip} \quad (54)$$

Combining Eqs. (11), (44), and (54) yields

$$R_{\Sigma p} = CL_{22} \cdot (CL_{11} + CL_{DP})/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad (55)$$

By definition (2,15),

$$MTTc_p = MRTc_p^p/R_{\Sigma p} \quad (56)$$

where $MTTc_p$ is the mean transit time through the central compartment for the parent drug. Combining Eqs. (13), (25), (55), and (56) yields

$$MTTc_p = Vc_p/(CL_{11} + CL_{Dp}) \quad (57)$$

From similar considerations, it follows that

$$R_{\Sigma m} = 1 + R_{Tm} + R_{Im} = CL_{11} \cdot (CL_{22} + CL_{Dm})/(CL_{11} \cdot CL_{22} - CL_{12} \cdot CL_{21}) \quad (58a, b)$$

and

$$MTTc_m = MRTc_m^m/R_{\Sigma m} = Vc_m/(CL_{22} + CL_{Dm}) \quad (59a, b)$$

where $R_{\Sigma m}$ is the total number of times that the metabolite recycles around the central compartment, and $MTTc_m$ is the mean transit time through the central compartment for the metabolite. Equations (57) and (59b) can also be obtained from the following equation on which the MTTc definition is based (15,2):

$$MTTc = -C(0)/C'(0) \quad (60)$$

EXPERIMENTAL

To illustrate the application and physiological relevance of the newly derived equations and concepts to a drug subject to reversible metabolism, methylprednisolone and methylprednisone data obtained previously from a pharmacokinetic study in rabbits (10) were analyzed further. The pharmacokinetic parameters $C(0)$ and $C'(0)$ for the administered compounds were estimated by fitting the plasma concentration–time curves (Fig. 2) to appropriate polyexponential equations using the nonlinear least-squares regression program NONLIN (16). The AUC and AUMC values were obtained using the LAGRAN program (17). This allowed the calculation of the clearances, volumes, distribution clearances, mean transit and residence times, mean interconversion times, and recycling numbers for the metabolic pair as cited in the subsequent text and tables and described under Theoretical.

RESULTS

Following iv administration of either the active drug, methylprednisolone, or the inactive metabolite, methylprednisone, the administered compound declines polyexponentially while the corresponding metabolite is rapidly formed and ultimately falls in parallel with its metabolic partner. All four curves in Fig. 2 exhibit essentially identical terminal slopes. These are typical characteristics of a linear reversible metabolic system. In a more extensive analysis of these data, Ebling and Jusko (10) found that both compounds ex-

hibited multicompartment properties in addition to undergoing interconversion. Primary evidence for this was the existence of $V_{ss} > V_c$ for both forms of the steroid. The occurrence of "hidden" exponential terms prevents the use of conventional model analysis techniques to identify the number of compartments associated with drug and metabolite. The interconversion process results in the active compound, methylprednisolone, always dominating in plasma regardless of which form is administered. The liver and kidneys are probably the main organs responsible for interconversion, thus justifying consideration of this process in the central compartment.

Clearances. The equations in this report, together with those in previous publications (4–10), allow for a more comprehensive analysis of linear reversible metabolic systems with an unspecified type of noneliminating peripheral space associated with a central, plasma compartment (Fig. 1). The essential features of such models are the clearances associated with formation (CL_{12}) and reconversion (CL_{21}) of metabolite and drug, the clearances of these compounds by all other pathways (CL_{10} and CL_{20}), and the total elimination clearance of drug [CL_{11}, Eq. (39)] and metabolite [CL_{22}, Eq. (40)]. These parameters can be easily calculated from the two dose and four AUC values obtained following iv administration of both drug and metabolite [Eqs. (15)–(18)]. In the case of methylprednisolone/methylprednisone in rabbits, the average clearance values were $CL_{10} = 6.26$, $CL_{12} = 4.98$, $CL_{21} = 28.9$, and $CL_{20} = 14.5$ ml/min/kg, indicating that the dominant rate processes were the conversion of metabolite to drug and secondary elimination of metabolite. This readily explains why methylprednisone disappears so rapidly from plasma and methylprednisolone exists as the primary form of the steroid (Fig. 2). The net clearance of methylprednisone ($CL_{22} = 43.4$ ml/min/kg) is four times that of methylprednisolone ($CL_{11} = 11.2$ ml/min/kg).

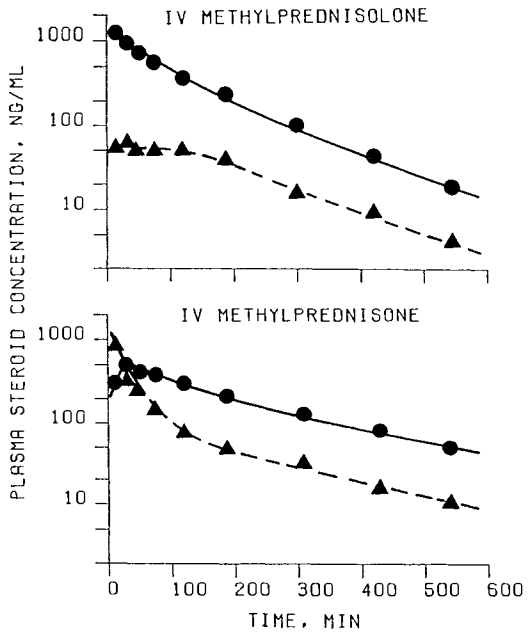

Fig. 2. Plasma concentration versus time profiles of methylprednisolone (●) and methylprednisone (▲) following iv doses of the former (top) and the latter (bottom) in a typical rabbit. Data from Ref. 10.

Distribution. The advent of moment analysis greatly facilitated identification of whether the drug/metabolite kinetics are multicompartmental and calculation of the central (V_c) and steady-state volumes of distribution (V_{ss}) in a straightforward manner (10). Again, both forms of the compound must be administered to yield two zero-time intercepts [Eqs. (36) and (40)] and four AUC and AUMC values [Eqs. (35) and (51)]. Methylprednisolone exhibits multicompartment distribution, with $V_c = 793$ and $V_{ss} = 1000$ ml/kg, as does methylprednisone, with $V_c = 1030$ and $V_{ss} = 1773$ ml/kg. Corticosteroids are moderately lipid soluble and generally exhibit V_{ss} values which are consistent with their ease of intracellular penetration and limited binding to tissue proteins and receptors (18).

Of related interest are the apparent distribution or intercompartmental clearances of the drug (CL_{DP}) and metabolite (CL_{Dm}). Equations (37) and (38) are new relationships which allow calculation of two CL_D values based on the zero-time intercepts and the first derivative of the iv disposition curve evaluated at time zero. For models with multiple extravascular compartments, the CL_D values represent the total flow/diffusion/transport clearance of compounds for plasma into all peripheral spaces. The CL_D values are 4.9 and 11.4 ml/min/kg for methylprednisolone and methylprednisone. These are a small fraction of the normal cardiac output of a rabbit (215 ml/min/kg) (19), suggesting that diffusion is the main process accounting for appearance of these compounds in the peripheral compartment.

Residence/Transit Times. Mean residence time parameters of multicompartmental drugs which undergo reversible metabolism were recently evolved (12) and can be readily generated from values of V_c (for MRTc) or V_{ss} (for MRT) and appropriate AUC/dose ratios [see Eqs. (21)–(28)]. These parameters provide useful means of quantitating the average age of drug molecules in various phases of their distributive and metabolic destiny. It is of interest to assess the contributions of reversible metabolism to the overall MRT of corticosteroids.

Mean residence time parameters of methylprednisolone and methylprednisone disposition in rabbits are presented in Table I and Fig. 3. The MRT values of methylprednisolone and methylprednisone are 127.9 and 25.9 min following a bolus dose of methylprednisolone and 85.7 and 58.6 min following a bolus dose of methylprednisone. Thus, the total exposure time of methylprednisolone in the body as drug and metabolite is 153.8 min, a time parameter that can be partitioned into four main components. Of the total, 25.9 min (or 16.8% of the time) is afforded by metabolic interconversion. Of the 25.9 min, 11.0 min (7.2% of the total exposure time) is the time spent by methylprednisolone as its metabolite partner in peripheral tissues. In addition, methylprednisolone itself stays in peripheral tissues for 28.2 min, which is 18.3% of its total exposure time. In contrast, of the total exposure time of methylprednisone in the body (144.3 min), 85.7 min (or 59.4% of the time) is the result of the reversible metabolic process. Of the 85.7 min, 18.0 min (12.5% of the total exposure time) can be ascribed to the presence of methylprednisone as its parent drug in the peripheral tissues. Besides, 17.0% (24.6 min) of the total exposure time is spent by methylprednisone in peripheral tissues. Thus, the metabolic interconversion and tissue distribution processes contribute

Table I. Mean Residence Time Parameters of Methylprednisolone/Methylprednisone Disposition in Rabbits[a]

Parameter	Eq. Nos.	Dose	Time parameter (min)	
			Methylprednisolone	Methylprednisone
MRT	(21), (22)	Methylprednisolone	127.9	25.9
			(24.2)	(8.1)
MRT	(23), (24)	Methylprednisone	85.7	58.6
			(20.2)	(17.0)
MRTc	(25), (26)	Methylprednisolone	99.7	14.9
			(15.3)	(3.0)
MRTc	(27), (28)	Methylprednisone	67.7	34.0
			(19.0)	(5.3)
MRT_T	(29), (30)	Methylprednisolone	28.2	11.0
			(23.7)	(6.1)
MRT_T	(31), (32)	Methylprednisone	18.0	24.6
			(15.5)	(15.1)

[a] Mean; $n = 10$. Values in parentheses are standard deviations.

over 35 and 76% of the total exposure times of methylprednisolone and methylprednisone.

Mean transit times (MTT) are more restrictive parameters that refer to the average interval of time spent by a drug particle from its entry to its next exit from a compartment. A specific array of MTT parameters is relevant to the present model (Fig. 1). According to Eqs. (34) and (41)–(43), MTT_{TP} and MTT_{Tm} can be obtained from AUC, AUMC, $C(0)$, and $C'(0)$ and are independent of the elimination kinetics of the metabolic partner. Consequently, they are intrinsic distribution parameters for drugs subject to reversible metabolism. Also, $MTTc_p$ and $MTTc_m$ can be calculated from V_c, CL_D, and CL_{11} or CL_{22} according to Eqs. (57) and (59). In the present model, these parameters retain their traditional meanings (15) as the volume of the specific compartment divided by all exit clearances. However, their calculation requires preliminary measurement of the appropriate volume and clearance terms as described above.

The transit time parameters for the two corticosteroids are listed in Table II. The rapid disappearance of methylprednisone from plasma (Fig. 2) is reflected in its brief MTTc of 19.3 min. In comparison, the prolonged C vs t profile of methylprednisolone yields a MTTc of 53.5 min. However, the MTT_T value of methylprednisone (88.2 min) is larger than that of methylprednisolone (62.4 min).

Mean Interconversion Time. An additional set of time parameters has been developed in this report, the MIT values.

It is of interest and seemingly contrary that, according to Eqs. (47) and (49), MITp depends on the V_c and CL_{21} of the metabolite, while MIT_m depends on the V_c and CL_{12} of the parent drug. However, both parameters are independent of the other elements of distribution and elimination of the

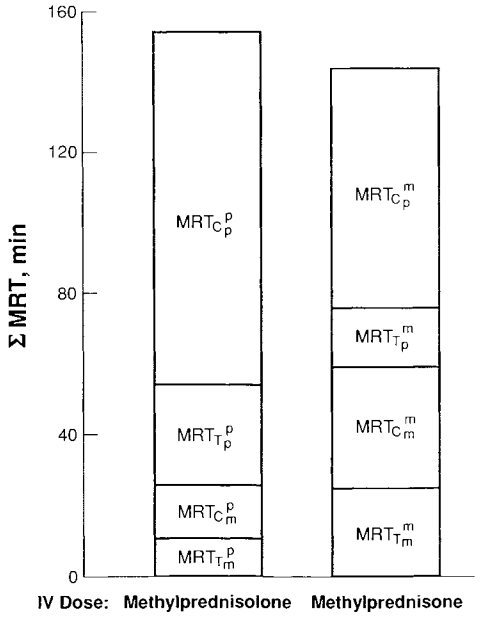

Fig. 3. Fraction of total MRT values divided into time spent as parent drug (p) and metabolite (m) in central (c) and tissue (T) compartments.

Table II. Interconversion, Mean Time, and Recycling Parameters of Methylprednisolone/Methylprednisone Disposition in Rabbits[a]

Parameter (units)	Eq. No.(s)	Methyl-prednisolone	Methyl-prednisone
CL_D (ml/min/kg)	(37), (38)	4.9	11.4
		(3.9)	(11.0)
R_Σ	(55), (58)	2.08	1.82
		(0.55)	(0.39)
MTTc (min)	(57), (59)	53.5	19.3
		(22.7)	(4.6)
R_T	(19), (20)	0.66	0.40
		(0.56)	(0.42)
MTT (min)	(41), (43)	62.4	88.2
		(68.2)	(63.6)
R_1	(48)	0.42	0.42
		(0.11)	(0.11)
MIT (min)	(52), (53)	36.3	171.4
		(6.5)	(63.7)

[a] Mean; $n = 10$. Values in parentheses are standard deviations.

metabolic partner. In other words, they are intrinsic to the reversible metabolism process. As such, MIT_p and MIT_m may be used to measure the time dependency of and effect of disease state on metabolic interconversion. As depicted in Eqs. (52) and (53), both parameters can also be readily calculated from AUC and $C(0)$ values. For methylprednisolone/methylprednisone, a considerable difference exists in their MIT values (Table II), with the former exhibiting a much smaller value (36.3 min) than the latter (171.4 min).

Recycling Numbers. Three pairs of recycling numbers can be calculated for multicompartment models with linear, reversible metabolism. The R_T value [Eqs. (19), (20)] provides the number of times the compound recycles in the peripheral compartment before elimination, the R_I value [Eq. (48)] reflects the number of times each compound converts and back converts, and the R_Σ [Eqs. (55), (58)] sums the central, peripheral, and interconversion cycling numbers. The R_T values arise from CL_D, AUC, and dose [Eqs. (19), (20)], while the R_I parameter relates to the interconversion and elimination clearances [Eq. (48)]. These parameters are thus ancillary to the basic characterization of this model.

The recycling numbers for methylprednisolone and methylprednisone are listed in Table II. The mean number of times that the compounds undergo interconversion is, of course, the same for both drug and metabolite (0.42). In fact, all three recycling numbers are similar for both forms of the drug.

Interconversion Interrelationships. The total exposure time of methylprednisolone in rabbits (153.8 min) is weakly influenced by the metabolic interconversion (Fig. 2 and Table I), as only 16.8% of this exposure time is produced by the interconversion process. In contrast, the total exposure time of methylprednisone (144.3 min) is strongly influenced by metabolic interconversion. Almost 60% of this exposure time results from interconversion. This behavior is also reflected by the MIT of methylprednisolone, which is about five times larger than that of methylprednisolone. In addition, the total exposure times of both compounds are moderately influenced by their tissue distribution processes (Table I), as MRT_T values contribute about one-third of the total.

The CL_D and MTT_T values of methylprednisolone are about four-tenths and three-quarters those of methylprednisone. This indicates more rapid penetration and longer persistency of methylprednisone relative to its parent compound in the peripheral tissues. However, based on MRT_T, both compounds remain in the peripheral system about the same length of time (28.5 vs 24.6 min). In other words, on each pass through the peripheral tissues, methylprednisone and methylprednisolone remain there for 88.2 and 62.4 min, but the former passes through the peripheral system an average of 0.4 time versus 0.66 time for the latter. It has been reported that prednisone instead of prednisolone accumulates in kidney and spleen tissues in rabbits (20). In the present study, as an analogue of prednisone, methylprednisone might also accumulate in these tissues. If this is true, then MTT_T might be a better indicator of tissue persistency of methylprednisolone/methylprednisone.

In summary, the results of this mean time analysis indicates that in rabbits (a) the total exposure times of methylprednisolone and methylprednisone are weakly and strongly influenced by the reversible metabolic process, and (b) the total exposure times of both compounds are moderately influenced by their tissue distribution processes.

DISCUSSION

Previous efforts in the area of reversible metabolism have generated methods to calculate the interconversion and elimination clearances (4–9), volumes of distribution (10), and mean residence times (11,12). To these, we have presently added equations for distribution clearance, mean transit times, metabolite interconversion times, and recycling numbers. These relationships are applicable to models such as in Fig. 1 with metabolic interconversion and other elimination occurring in a pair of central compartments with nonspecific peripheral spaces which do not allow for elimination. The data required are four sets of polyexponential plasma concentration versus time curves, i.e., drug and metabolite following separate iv administration of each. Curve analysis can yield appropriate zero-time intercepts, slopes, areas, and first-moment values which, in turn, can be converted into the array of clearance, volume, various mean time, and recycling number parameters. These methods are much easier to apply than a model-building approach where peripheral compartments are successively added until the best-fitting curves are obtained. Using data for methylprednisolone and methylprednisone, we have demonstrated the application and interpretation of these parameters as they allow a more complete understanding of all facets of the interrelated and separate behaviors of interconverting drug and metabolites.

The derivations performed are based on systems analysis (13) with use of probability theory (14) to capture the recycling numbers. A general model with paired central and tissue compartments were used. This model evolves from the classical compartmental models of reversible drug metabolism (6,10) and a model for drugs which do not undergo reversible metabolism (1). This approach, however, extends the classical compartmental approaches for drugs undergoing reversible metabolism to the treatment of peripheral tissue distribution and mean times. It also extends the probability approach described by Veng-Pedersen and Gillespie (1), which considered only tissue distribution, to drugs undergoing reversible metabolism. The latter is more complex because of the need to separate the contributions of the two processes.

It should be noted that our derivations of equations for MIT [Eqs. (47) and (49)] were based on the assumption that metabolic interconversion occurs only in the central compartment. If interconversion also occurs in the tissue compartment, MIP_p and MIT_m can be calculated as V_{ss}^m/CL_{21} and V_{ss}^p/CL_{12}, where CL_{21} and CL_{12} become the total metabolic clearances accounting for reversible metabolism enzyme activity in the body.

The MIT parameters are of value for several reasons. As stated above, they can be used to measure the time dependency and effect of disease state on metabolic interconversion. The MIT are also indicators of persistency of drug (or interconversion metabolite) as its metabolic partner in the central compartment or in the body. Moreover, as illustrated by the above pharmacokinetic analysis of methylpred-

nisolone/methylprednisone data, together with other mean time parameters, they allow the degree of conservation or exposure enhancement of drug afforded by either tissue distribution or reversible metabolism to be isolated and quantified separately.

The transit time and MRTc parameters either evolve from or resemble the calculations and definitions proved by Rescigno and Gurpide (15). As shown previously (12), however, the MRT parameters are different from what were originally defined (15). For drugs which do not undergo reversible metabolism and exhibit linear disposition kinetics, the following assumptions and limitations associated with MTT_T and requirements for its estimation have been addressed by Veng-Pedersen and Gillespie (1): (a) the drug must be administered to and eliminated from only the sampling compartments; and (b) sufficient data during the initial "distributive" phase following drug administration and in the terminal portion of the plasma concentration–time curve must be obtained to calculate accurately $C'(0)$, $C(0)$, AUC, and AUMC. Analogous properties pertain to MTT_T in the present report, but our equations are more complex and allow for separation of the metabolic interconversion from other features of the general model.

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NOMENCLATURE

$—^p$, $—^m$	Administered parent drug (p) or metabolite (m)
$—_p$, $—_m$	Measured parent drug (p) or metabolite (m)
AUC	Area under the plasma concentration versus time curve
AUMC	Area under the moment curve (integral of $t \cdot C$ vs t)
C	Plasma compartment concentration
C'	First derivative of C vs t function
CL_D	Distribution clearance
CL_{12}	Conversion clearance of parent drug to metabolite
CL_{21}	Conversion clearance of metabolite to parent drug
CL_{10}	Sum of all elimination clearance processes operating on parent drug except CL_{12}
CL_{20}	Sum of all elimination clearance processes operating on metabolite except CL_{21}
CL_{11}	Summary clearance: $CL_{10} + CL_{12}$
CL_{22}	Summary clearance: $CL_{20} + CL_{21}$
Dose	Dose of compound administered
E(—)	Expected value of parameter in parentheses
EE	Exposure enhancement
$h_p(t)$	Distribution function of parent drug
$h_m(t)$	Distribution function of metabolite
M	Probability of peripheral tissue distribution
MIT	Mean interconversion time
M_r	Random variable associated with r
MRT	Mean residence time of compound in body
MRTc	Mean residence time of compound in central compartment
MTT	Mean transit time
N_s	Random variable associated with s
N_0	Number of parent drug molecules given iv
P,Q	Probability
r	Number of times parent drug molecule distributes into peripheral system
s	Number of times parent drug molecule converts to metabolite and back converts
t	Time
R_I	Number of times a molecule converts to metabolic partner and back converts
R_T	Number of times a molecule distributes to the peripheral system before being irreversibly eliminated
R_Σ	Total recycling time by all processes
V_c	Volume of central compartment
V_{ss}	Steady-state volume of distribution

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