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Report

Effects of First-Pass Metabolism on Metabolite Mean Residence Time Determination After Oral Administration of Parent Drug

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Metabolite kinetics after oral drug administration can be determined, without separate metabolite administration, using the concepts of mean residence time (MRT). The MRT of parent drug and metabolite after oral administration of the parent drug, MRTp,p(oral) and MRTm,p(oral), can be calculated directly from the drug and metabolite profiles. The difference between MRTm,p(oral) and MRTp,p(oral), termed Delta MRT, yields an estimate of MRT of metabolite when the metabolite is given as an iv bolus, MRTm,m(iv). The calculation is simple for drugs that are known to undergo negligible first-pass metabolism. Correction can also be made when extent of first-pass metabolism is known. Ambiguity is encountered, however, when the degree of first-pass metabolism is unknown. When the delta MRT is negative, then first-pass metabolism must be considered. A positive value of delta MRT, on the other hand, is not a definitive indication of the absence of first-pass metabolism. It may occur in the presence or absence of first-pass metabolism. Ignoring the possibility of first-pass metabolism when a positive value of delta MRT occurs may lead to an incorrect estimate of MRTm, m(iv). The estimation error is relatively small, however, when MRTm,m(iv) $\gg$ MRTp,p(iv), even when first-pass metabolism is extensive. This situation may apply to the administration of a prodrug.

KEY WORDS: metabolite; mean residence time; first-pass metabolism.

INTRODUCTION

Evaluation of metabolite kinetics is of interest especially in the case where a metabolite is responsible for, or contributes significantly to, the pharmacological and/or toxicological response. Unfortunately, use of classical compartmental methods to assess metabolite kinetics after administration of the parent drug usually leads to complex kinetic relationships involving both the parent drug and its metabolite. Metabolite kinetics cannot be determined unequivocally unless intravenous data on the metabolite are available.

The determination of mean residence time, based on the statistical moments theory, has largely been applied to evaluate the kinetics of the parent drug (1–9). Recently, Veng-Pedersen and Gillespie (10,11) proposed a method for evaluating the mean residence time of metabolite in the body, systemic circulation, and peripheral tissue after a single intravenous or oral administration of parent drug. Metabolite kinetics can be readily calculated without the need to administer the metabolite separately. However, the method is applicable only to drugs with little or no first-pass metabolism after oral administration. Midha *et al.* (12) and Brockmeier and Ostrowski (13) investigated the mean residence times of parent drug and metabolite and suggested that when the mean residence time of the metabolite was shorter than the mean residence time of the parent drug, relevant first-pass metabolism had to be considered. However, a situation was not considered where the mean residence time of the metabolite is longer than the mean residence time of the parent drug, which does not necessarily indicate a lack of first-pass metabolism. Erroneous results will be obtained if first-pass metabolism is not accounted for. In the present report, we examine the effects of first-pass metabolism on the relationship between the mean residence time of the parent drug and that of the metabolite after a single oral dose of parent drug. The same concept can also be applied to prodrugs where the pharmacologically active component (metabolite) is formed following oral administration of the precursor.

THEORY

Case 1: No First-Pass Metabolism

A model describing the oral administration of drug and the formation of metabolite is depicted in Fig. 1. The following sequence applies: parent drug is administered orally, some drug may be lost in the GI lumen and some drug is absorbed through the gut wall, and passes the portal vein and liver. Finally, the drug is converted to metabolite in the systemic circulation. After the first pass, the gut wall, portal

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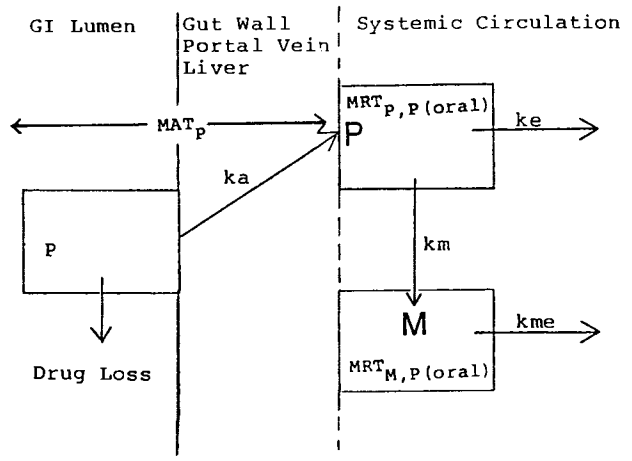

Fig. 1. Model describing the oral administration of parent drug (P) and the formation of metabolite (M) without first-pass metabolism (Case 1).

vein, and liver are considered part of the systemic circulation. Under these conditions, the mean residence time of the parent drug after oral administration of parent drug, MRTp, p(oral), is given by

$$\text{MRTp,p(oral)} = \text{MATp} + \text{MRTp,p(iv)} \quad (1)$$

where MATp is the mean absorption time of the parent drug and MRTp,p(iv) is the mean disposition residence time of the parent drug or mean residence time of the parent drug when the parent drug is given as an iv bolus.

The mean residence time of the metabolite after oral administration of the parent drug, MRTm,p(oral), is given by

$$\begin{aligned}\text{MRTm,p(oral)} &= \text{MRTp,p(oral)} + \text{MRTm,m(iv)} \\ &= \text{MATp} + \text{MRTp,p(iv)} + \text{MRTm,m(iv)}\end{aligned} \quad (2)$$

where MRTm,m(iv) is the mean disposition residence time of the metabolite or mean residence time of the metabolite when the metabolite is given as an iv bolus.

MRTp,p(oral) and MRTm,p(oral) can be calculated directly from the parent drug and metabolite profiles after oral administration of parent drug using the following equations:

$$\text{MRTp,p(oral)} = \frac{\text{AUMCp,p(oral)}}{\text{AUCp,p(oral)}} \quad (3)$$

$$\text{MRTm,p(oral)} = \frac{\text{AUMCm,p(oral)}}{\text{AUCm,p(oral)}} \quad (4)$$

where AUMC and AUC are the areas under the first and zero moments of the plasma concentration–time curve.

It is clear, from Eqs. (1) and (2), that the difference between MRTm,p(oral) and MRTp,p(oral) provides an estimate of MRTm,m(iv):

$$\begin{aligned}\text{delta MRT} &= \text{MRTm,p(oral)} - \text{MRTp,p(oral)} \\ &= \text{MRTm,m(iv)}\end{aligned} \quad (5)$$

In this case, MRTm,p(oral) is always larger than MRTp,p(oral) so that delta MRT or MRTm,m(iv) is positive.

Case 2: First-Pass Metabolism

Another model describing the oral administration of drug and the formation of metabolite is depicted in Fig. 2. Parent drug is administered orally; some drug may be lost in the GI lumen and some drug is absorbed through the gut wall and passes the portal vein and liver. A fraction of the absorbed dose (F) escapes the first-pass metabolism, reaches the systemic circulation, and is subsequently converted to metabolite in the systemic circulation. A complementary fraction of the absorbed dose ($1 - F$) is converted to metabolite during the first pass through the liver. Under these conditions, the mean residence time of the parent drug after oral administration of the parent drug, MRTp,p(oral), is also given by Eq. (1). However, the MRTm,p(oral) is contributed by two routes of input: (1) metabolite formed duing first-pass metabolism ($1 - F$) and (2) metabolite in the systemic circulation from parent drug that has escaped first-pass metabolism (F). The overall MRTm,p(oral) is given by the sum of these two routes of input with respect to their relative weight of contribution.

$$\begin{aligned}\text{MRTm,p(oral)} &= F\,[\text{MRTp,p(oral)} + \text{MRTm,m(iv)}] \\ &\quad + (1 - F)\,[\text{MATp} + \text{MRTm,m(iv)}]\end{aligned} \quad (7)$$

$$\begin{aligned}&= F\,[\text{MATp} + \text{MRTp,p(iv)} + \\ &\quad \text{MRTm,m(iv)}] \\ &\quad + (1 - F)\,[\text{MATp} + \text{MRTm,m(iv)}]\end{aligned} \quad (7a)$$

Solving Eq. (7) gives

$$\begin{aligned}\text{MRTm,p(oral)} &= F{*}\text{MRTp,p(oral)} + (1 - F){*}\text{MATp} \\ &\quad + \text{MRTm,m(iv)}\end{aligned} \quad (8)$$

Again, the MRTp,p(oral) and MRTm,p(oral) can be calculated directly from the parent drug and metabolite profiles after oral administration of parent drug, using Eqs. (3) and (4). The difference between MRTm,p(oral) and MRTp, p(oral) is

$$\text{delta MRT} = \text{MRTm,p(oral)} - \text{MRTp,p(oral)} \quad (9)$$

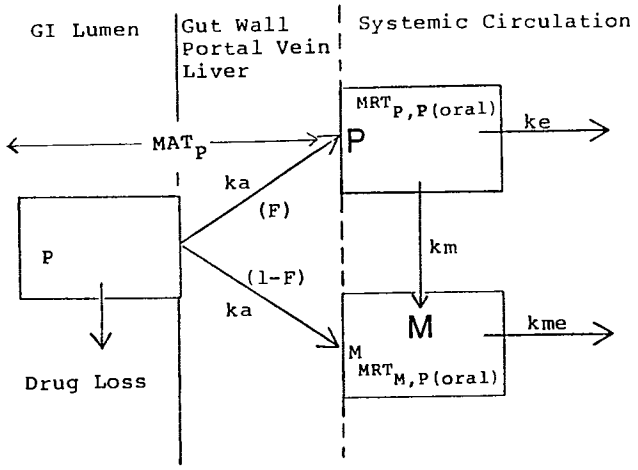

Fig. 2. Model describing the oral administration of parent drug (P) and the formation of metabolite (M) with first-pass metabolism (Case 2).

Table I. Calculated Pharmacokinetic Parameters as Determined by Eqs. (7) and (7a): MRTm,m(iv) Was Held Constant at 10

		Calculated			Calculated		
MRTp,p(iv)	MRTm,m(iv)	F	$1 - F$	MATp	MRTm,p(oral)	MRTp,p(oral)	Delta MRT
2.5	10	1	0	0	12.5	2.5	10
2.5	10	1	0	10	22.5	12.5	10
2.5	10	1	0	20	32.5	22.5	10
2.5	10	0.75	0.25	0	11.875	2.5	9.375
2.5	10	0.75	0.25	10	21.875	12.5	9.375
2.5	10	0.75	0.25	20	31.875	22.5	9.375
2.5	10	0.5	0.5	0	11.25	2.5	8.75
2.5	10	0.5	0.5	10	21.25	12.5	8.75
2.5	10	0.5	0.5	20	31.25	22.5	8.75
2.5	10	0.25	0.75	0	10.625	2.5	8.125
2.5	10	0.25	0.75	10	20.625	12.5	8.125
2.5	10	0.25	0.75	20	30.625	22.5	8.125
2.5	10	0	1	0	10	2.5	7.5
2.5	10	0	1	10	20	12.5	7.5
2.5	10	0	1	20	30	22.5	7.5
5	10	1	0	0	15	5	10
5	10	1	0	10	25	15	10
5	10	1	0	20	35	25	10
5	10	0.5	0.5	0	12.5	5	7.5
5	10	0.5	0.5	10	22.5	15	7.5
5	10	0.5	0.5	20	32.5	25	7.5
5	10	0	1	0	10	5	5
5	10	0	1	10	20	15	5
5	10	0	1	20	30	25	5
10	10	1	0	0	20	10	10
10	10	1	0	10	30	20	10
10	10	1	0	20	40	30	10
10	10	0.5	0.5	0	15	10	5
10	10	0.5	0.5	10	25	20	5
10	10	0.5	0.5	20	35	30	5
10	10	0	1	0	10	10	0
10	10	0	1	10	20	20	0
10	10	0	1	20	30	30	0
20	10	1	0	0	30	20	10
20	10	1	0	10	40	30	10
20	10	1	0	20	50	40	10
20	10	0.5	0.5	0	20	20	0
20	10	0.5	0.5	10	30	30	0
20	10	0.5	0.5	20	40	40	0
20	10	0	1	0	10	20	−10
20	10	0	1	10	20	30	−10
20	10	0	1	20	30	40	−10
50	10	1	0	0	60	50	10
50	10	1	0	10	70	60	10
50	10	1	0	20	80	70	10
50	10	0.75	0.25	0	47.5	50	−2.5
50	10	0.75	0.25	10	57.5	60	−2.5
50	10	0.75	0.25	20	67.5	70	−2.5
50	10	0.5	0.5	0	35	50	−15
50	10	0.5	0.5	10	45	60	−15
50	10	0.5	0.5	20	55	70	−15
50	10	0.25	0.75	0	22.5	50	−27.5
50	10	0.25	0.75	10	32.5	60	−27.5
50	10	0.25	0.75	20	42.5	70	−27.5
50	10	0	1	0	10	50	−40
50	10	0	1	10	20	60	−40
50	10	0	1	20	30	70	−40

$$= F*\text{MRTp,p(iv)} - \text{MRTp,p(iv)} + \text{MRTm,m(iv)} \quad (9a)$$

$$= (F - 1)\,\text{MRTp,p(iv)} + \text{MRTm,m(iv)} \quad (9b)$$

It is clear that the difference between MRTm,p(oral) and MRTp,p(oral) will not provide an estimate of MRTm, m(iv), as is the case where there is no first-pass metabolism. In fact, Eq. (9b) can yield either positive or negative values depending on the F value and the relative magnitude of MRTp,p(iv) and MRTm,m(iv). If F is equal to 1 (case 1: no first-pass metabolism), then Eq. (9) simplifies to Eq. (5) where delta MRT provides an estimate of MRTm,m(iv). If F is equal to zero (all parent drug converted to metabolite after first pass), then

$$\text{delta MRT} = \text{MRTm,m(iv)} - \text{MRTp,p(iv)} \quad (10)$$

Equation (10) represents the limiting value for delta MRT. It is clear, under these conditions, that if MRTm,m(iv) is smaller than MRTp,p(iv), delta MRT will be negative. This serves as an indication of first-pass metabolism. However, if MRTm,m(iv) is greater than MRTp,p(iv), delta MRT will be positive even though there is extensive first-pass metabolism. Whether delta MRT is positive or negative depends on the relative magnitude of the parent drug and metabolite mean residence times as well as the degree of first-pass metabolism.

METHODS

We examined the relationships between MRTp,p(iv), MRTm,m(iv), and delta MRT using Eq. (7). Various values of F and MATp were used to calculate $1 - F$, MRTp,p(oral), and MRTm,m(oral). The following values were used for the evaluation: MRTp,p(iv) ranged from 2.5 to 50; MRTm,m(iv) was held constant at 5, 10, and 20; F ranged from 0 to 1; and MATp ranged from 0 to 20.

RESULTS

The results for the case where MRTm,m(iv) = 10 are tabulated in Table I and depicted in Fig. 3. Similar results were obtained for MRTm,m(iv) = 5 and 20 and are not presented. Two extreme and two general situations were examined and the following conclusions can be drawn.

(1) As the difference between MRTp,p(iv) and MRTm, m(iv) becomes smaller [i.e., as MRTm,m(iv) becomes larger than MRTp,p(iv); MRTp,p(iv)/MRTm,m(iv) ratio $\ll 1$], the effects of first-pass metabolism on delta MRT are smaller. In other words, the error in determining MRTm,m(iv) using delta MRT is smaller. However, under these conditions, the value of delta MRT is positive and first-pass metabolism may not be signaled by the data.

(2) As the difference between MRTp,p(iv) and MRTm, m(iv) becomes larger [i.e., as MRTm,m(iv) becomes smaller than MRTp,p(iv), MRTp,p(iv)/MRTm,m(iv) $\gg 1$], the effects of first-pass metabolism on delta MRT are greater. In other words, the error in determining MRTm,m(iv) using delta MRT and ignoring first-pass metabolism is greater. Under these conditions, delta MRT is negative at relatively low values of F. For example, delta MRT reaches negative when $F < 0.5$ with a MRTp,p(iv)/MRTm,m(iv) ratio = 2 (see Table I and Fig. 3).

(3) When MRTp,p(iv), MRTm,m(iv), and F are held constant, a change in MATp may affect the value of MRTp, p(oral) and MRTm,p(oral) but has no effect on the resultant delta MRT.

(4) When MRTp,p(iv)/MRTm,m(iv) ratio is equal to or less than 1, delta MRT values are always positive and approach zero as the MRTp,p(iv)/MRTm,m(iv) ratio approaches 1 and F approaches zero.

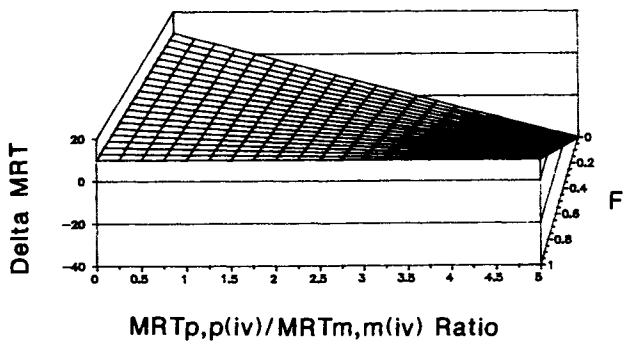

Fig. 3. Three-dimensional plot of delta MRT versus MRT ratio and F. MRTm,m(iv) was held constant at 10.

DISCUSSION

The results of this investigation indicate that if first-pass metabolism is ignored in estimating MRTm,m(iv), the error may or may not be substantial, depending upon the relative values of MRTp,p(iv) and MRTm,m(iv). Furthermore, a negative delta MRT value may not be observed if MRTm, m(iv) is larger than MRTp,p(iv) as in the prodrug situation where the metabolite usually has a greater mean residence time than the precursor. On the other hand, if first-pass metabolism is not substantial, the error in determining MRTm, m(iv) may be acceptable. For example, the error in estimating MRTm,m(iv) is only 12.5% with 50% first-pass metabolism when MRTp,p(iv) = 2.5 and MRTm,m(iv) = 10 (Table I and Fig. 3). On the other hand, when MRTm,m(iv) < MRTp,p(iv), a common situation where a more polar metabolite is eliminated faster than parent drug, ignoring first-pass metabolism leads to a highly unacceptable error. However, the likelihood of detecting negative delta MRT values is higher, and adjustments can be made to account for first-pass metabolism.

The results from the above analysis clearly indicate that detection of the fraction of first-pass metabolism is of utmost importance. It is safe to assume that any drug which can be metabolized by the body will undergo some first-pass metabolism. Notice that MRTm,p(oral) and MRTp,p(oral) are the only experimental calculable parameters [Eqs. (3) and (4)] and we have no way of knowing the relative magnitude of MRTm,m(iv) and MRTp,p(iv). Equation (8), with first-pass metabolism, is more general than Eq. (5) and, therefore, should always be considered. According to Eq. (8), and as suggested by Brockmeier and Ostrowski (14), when several subjects are involved in the study, plotting MRTm,p(oral) values aganst MRTp,p(oral) values from each individual, the slope of such plot yield the overall F and the intercept yields $[(1 - F)*\text{MATp} + \text{MRTm,m(iv)}]$. Unfortunately, this method assumes that MATp is constant for all subjects involved in the study and may not be valid in most cases. The plot should be evaluated with caution.

In closing, metabolite kinetics are easily evaluated for a

drug known to undergo negligible first-pass metabolism [Eq. (5)]. Ambiguity is encountered, however, when the degree of first-pass metabolism, if any, is unknown. A negative value of delta MRT, in this case, signals first-pass metabolism, which must be taken into account when estimating MRTm, m(iv). A positive value of delta MRT, on the other hand, is not definite; it may occur in the presence or absence of first-pass metabolism. Ignoring the possibility of first-pass metabolism when a positive value of delta MRT occurs may lead to an incorrect estimate of MRTm,m(iv). The estimation error is relatively small, however, when MRTm,m(iv) $\gg$ MRTp,p(iv), even when first-pass metabolism is extensive. This situation may apply to the administration of a prodrug.

REFERENCES

1. K. Yamaoka, T. Nakagawa, and T. Uno. *J. Pharmacokin. Biopharm.* 6:547–558 (1978).
2. S. Riegelman and P. Collier. *J. Pharmacokin. Biopharm.* 8:509–534 (1980).
3. D. J. Culter. *J. Pharm. Pharmacol.* 30:476–478 (1978).
4. L. A. Bauer and M. Gibaldi. *J. Pharm Sci.* 72:978–979 (1983).
5. M. Chung. *J. Pharm. Sci.* 73:570–571 (1984).
6. D. Perrier and M. Mayersohn. *J. Pharm. Sci.* 71:372–373, 1427–1428 (1982).
7. P. Veng-Pedersen and W. R. Gillespie. *J. Pharmacokin. Biopharm.* 12:535–543 (1984).
8. P. Veng-Pedersen and W. R. Gillespie. *J. Pharm. Sci.* 74:791–792 (1985).
9. M. Gibaldi and D. Perrier. *Pharmacokinetics,* Marcel Dekker, New York, 1982.
10. P. Veng-Pedersen. *J. Pharm. Sci.* 75:818–819 (1986).
11. P. Veng-Pedersen and W. R. Gillespie. *Biopharm. Drug Dispos.* 8:395–401 (1987).
12. K. K. Midha, R. M. H. Roscoe, T. W. Wilson, J. K. Cooper, J. C. K. Loo, A. Ho-Ngoc, and I. J. McGilveray. *Biopharm. Drug Dispos.* 4:331–338 (1983).
13. D. Brockmeier and J. Ostrowski. *Eur. J. Clin. Pharmacol.* 29:45–48 (1985).