Determination of Bioavailability and Systemically Available Fractions of Drugs Undergoing Reversible Metabolism: Application to 4-Amino-5-chloro-2-[2-(methylsulfinyl)ethoxy]-*N*-[2-(diethylamino)ethyl]benzamide and Its Sulfide and Sulfone Metabolites in Rats

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Abstract □ Methods are discussed which permit the calculation of the bioavailability (*F*) and fraction of an oral dose entering the central circulation (*f*) of a drug and its interconversion metabolite. The interrelationships between the *F* and *f* and between the *F* and systemically available fractions afforded by reversible metabolism are also derived and described. The application of these principles is illustrated by the pharmacokinetic analysis of 4-amino-5-chloro-2-[2-(methylsulfinyl)ethoxy]-*N*-[2-(diethylamino)ethyl]benzamide (ML-1035, **1**) and its sulfide (**2**) and sulfone (**3**) metabolites in rats. Like intravenous ML-1035, ML-1035 administered orally underwent metabolic interconversion with **2** but not with **3** in this species. Both ML-1035 and **2** were absorbed rapidly and are pharmacologically active. On average, 8.3 and 13% of an oral dose (152.4 μmol/kg) of ML-1035 were bioavailable as ML-1035 and its sulfide metabolite, respectively, while 23 and 65% of a molar equivalent dose of the sulfide metabolite were bioavailable as either compound, respectively. Thus, the sulfide metabolite is better absorbed than ML-1035 in rats. Following oral administration of either ML-1035 or **2**, the systemically available fractions of both compounds were weakly to moderately influenced by the reversible metabolism process in rats. Moreover, the bioavailability of the sulfone metabolite was very poor (2.5–4%) following separate oral administration of ML-1035, **2**, and **3**.

Introduction

ML-1035, 4-amino-5-chloro-2-[2-(methylsulfinyl)ethoxy]-*N*-[2-(diethylamino)ethyl]benzamide (**1**; Figure 1), is a new 5-HT_3 receptor antagonist currently under evaluation as a gastroprokinetic agent. It has been reported previously that ML-1035, which is a sulfoxide compound, underwent interconversion with its sulfide metabolite (**2**; Figure 1) but not with its sulfone metabolite (**3**; Figure 1) in rats.[1]

For drugs undergoing reversible metabolism, the usual concept of bioavailability and existing experimental designs for its determination may not be adequate. In 1981 Hwang et al. presented a useful theoretical basis for the estimation of bioavailability for such drugs.[2] Later, a method for calculating the fractions of an oral dose entering the central circulation intact as the parent compound and as metabolite was also reported.[3] Although many drugs undergo reversible metabolism[4–17] and these approaches appear to be useful for quantitatively assessing the absorption of such drugs, no examples as yet exist in the literature where these approaches have been applied to actual oral data.

This report describes additional pharmacokinetic parameters unique to the first-pass metabolism and interconversion system after separate oral administration of the drug and the interconversion metabolite. The interrelationships between the bioavailability and the fractions of an oral dose entering the central circulation and between the bioavailability and systemically available fractions afforded by reversible metabolism are also derived and described. The application of these principles is illustrated by the pharmacokinetic analysis of ML-1035 and its sulfide and sulfone metabolites in rats.

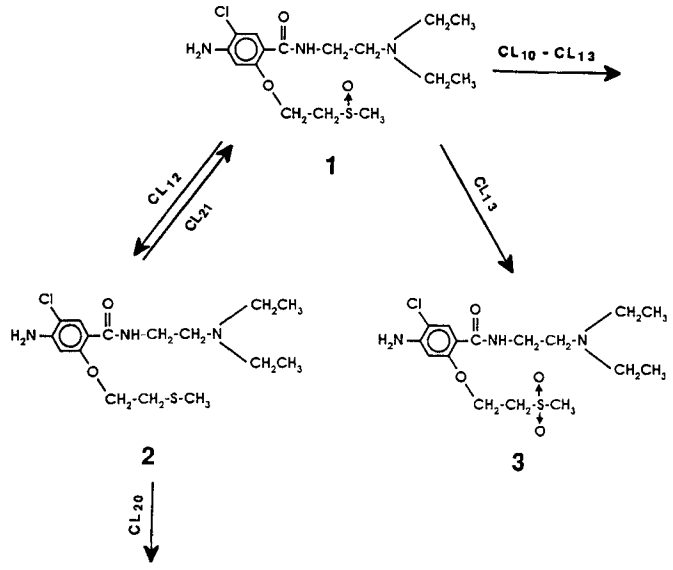

Figure 1—Chemical structures and reaction schedule of ML-1035 (**1**) and its sulfide (**2**) and sulfone (**3**) metabolites. CL_{12} is the conversion clearance of ML-1035 to **2**; CL_{21} is the conversion clearance of **2** to ML-1035; CL_{10} is the sum of all elimination processes operating on ML-1035 except CL_{12}; CL_{20} is the sum of all elimination processes operating on **2** except CL_{21}; and CL_{13} is the formation clearance of **3**.

Theoretical Section

By definition, the bioavailability of a drug (F_p^p) and of its metabolite (F_m^p) after oral administration of the drug can be calculated as follows:

$$F_p^p = \frac{AUC_p^{p,po} D^{p,iv}}{AUC_p^{p,iv} D^{p,po}} \quad (1)$$

and

$$F_m^p = \frac{AUC_m^{p,po} D^{m,iv}}{AUC_m^{m,iv} D^{p,po}} \quad (2)$$

where the superscripts p and m denote the dosed compound, superscripts po and iv denote oral and intravenous bolus administration, the subscripts denote the measured compound, AUC is the total area under the plasma concentration–time curve,

• Abstract published in *Advance ACS Abstracts*, December 15, 1993.

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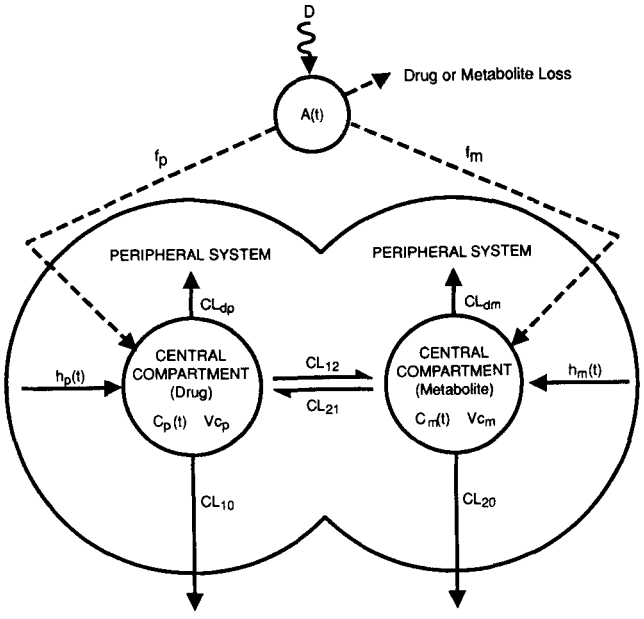

Figure 2—A general model for reversible drug metabolism. $C_p(t)$ and $C_m(t)$ are plasma concentrations of parent drug and of metabolite at time t; Vc_p and Vc_m are central volume of distribution of parent drug and of metabolite; CL_{dp} and CL_{dm} are the distribution clearances of parent drug and of metabolite; $h_p(t)$ and $h_m(t)$ are distribution functions of parent drug and of metabolite; and $A(t)$ is the amount of drug or of metabolite in absorption site at time t. The other symbols are defined in the text.

and D is the dose. Similarly, the bioavailability of the metabolite (F_m^m) and drug (F_p^m) after oral administration of the metabolite can be calculated as follows:

$$F_m^m = \frac{AUC_m^{m,po} D^{m,iv}}{AUC_m^{m,iv} D^{m,po}} \tag{3}$$

and

$$F_p^m = \frac{AUC_p^{m,po} D^{p,iv}}{AUC_p^{p,iv} D^{m,po}} \tag{4}$$

The following equations have previously[3] been derived for a drug undergoing reversible metabolism (Figure 2):

$$f_p^p = \frac{(AUC_p^{p,po} AUC_m^{m,iv} - AUC_m^{p,po} AUC_p^{m,iv}) D^{p,iv}}{(AUC_p^{p,iv} AUC_m^{m,iv} - AUC_m^{p,iv} AUC_p^{m,iv}) D^{p,po}} \tag{5}$$

$$f_m^p = \frac{(AUC_m^{p,po} AUC_p^{p,iv} - AUC_p^{p,po} AUC_m^{p,iv}) D^{m,iv}}{(AUC_p^{p,iv} AUC_m^{m,iv} - AUC_m^{p,iv} AUC_p^{m,iv}) D^{p,po}} \tag{6}$$

$$f_p^m = \frac{(AUC_p^{m,po} AUC_m^{m,iv} - AUC_m^{m,po} AUC_p^{m,iv}) D^{p,iv}}{(AUC_p^{p,iv} AUC_m^{m,iv} - AUC_m^{p,iv} AUC_p^{m,iv}) D^{m,po}} \tag{7}$$

$$f_m^m = \frac{(AUC_m^{m,po} AUC_p^{p,iv} - AUC_p^{m,po} AUC_m^{p,iv}) D^{m,iv}}{(AUC_p^{p,iv} AUC_m^{m,iv} - AUC_m^{p,iv} AUC_p^{m,iv}) D^{m,po}} \tag{8}$$

where f_p^p and f_m^p are the fractions of an oral dose of a drug entering the central circulation as intact drug and as the interconversion metabolite, respectively, f_m^m and f_p^m are the fractions of an oral dose of the metabolite entering the central circulation as intact metabolite and as the drug, respectively. Thus, f_m^p quantitates the magnitude of presystemic conversion of the drug to its reversible metabolite after first pass of the drug. Similarly, f_p^m quantitates the magnitude of presystemic conversion of the reversible metabolite to the drug after first pass of the metabolite. Also, the AUC can be calculated as follows:[18]

$$AUC_p^{p,iv} = \frac{D^{p,iv} CL_{22}}{CL_{11}CL_{22} - CL_{12}CL_{21}} \tag{9}$$

$$AUC_m^{p,iv} = \frac{D^{p,iv} CL_{12}}{CL_{11}CL_{22} - CL_{12}CL_{21}} \tag{10}$$

$$AUC_p^{m,iv} = \frac{D^{m,iv} CL_{21}}{CL_{11}CL_{22} - CL_{12}CL_{21}} \tag{11}$$

$$AUC_m^{m,iv} = \frac{D^{m,iv} CL_{11}}{CL_{11}CL_{22} - CL_{12}CL_{21}} \tag{12}$$

where CL_{12} is the conversion clearance of drug to metabolite, CL_{21} is the conversion clearance of metabolite to drug, CL_{10} is the sum of all irreversible elimination clearance processes operating on drug, and CL_{20} is the sum of all irreversible elimination clearance processes operating on metabolite. CL_{11} equals the sum of CL_{12} and CL_{10}, and CL_{22} equals the sum of CL_{21} and CL_{20}. From eqs 1, 5, 6, 9, and 11, it follows that

$$F_p^p = f_p^p + (f_m^p CL_{21}/CL_{22}) \tag{13}$$

Similarly, from eqs 2, 7, 8, 10, and 12, it follows that

$$F_m^p = (f_p^p CL_{12}/CL_{11}) + f_m^p \tag{14}$$

Rearranging eqs 13 and 14 yields

$$F_p^p - f_p^p = f_m^p CL_{21}/CL_{22} \tag{15}$$

and

$$F_m^p - f_m^p = f_p^p CL_{12}/CL_{11} \tag{16}$$

Thus, $(F_p^p - f_p^p)$ is the systemically available fraction of the oral drug afforded by systemic conversion of the generated reversible metabolite back to drug. $(F_m^p - f_m^p)$ is the systemically available fractions of the reversible metabolite generated systemically. Similarly, $(F_m^m - f_m^m)$ is the systemically available fraction of the oral metabolite afforded by systemic conversion of the generated drug back to metabolite and $(F_p^m - f_p^m)$ is the systemically available fractions of the drug generated systemically from the reversible metabolite. Obviously, CL_{21}/CL_{22} and CL_{12}/CL_{11} represent the fractions of first-time systemic conversion of reversible metabolite to drug, and vice versa.

Let F_{p+m}^p and F_{p+m}^m be defined as

$$F_{p+m}^p = f_p^p + f_m^p \tag{17}$$

and

$$F_{p+m}^m = f_m^m + f_p^m \tag{18}$$

From eqs 1, 2, 9, 10, 13, and 17, as well as eqs 3, 4, 11, 12, and 14, it follows that

$$F_{p+m}^p = \frac{(CL_{10} AUC_p^{p,po} + CL_{20} AUC_m^{p,po}) D^{p,iv}}{(CL_{10} AUC_p^{p,iv} + CL_{20} AUC_m^{p,iv}) D^{p,po}} \tag{19}$$

and

$$F^{m}_{p+m} = \frac{(CL_{10}AUC^{m,po}_{p} + CL_{20}AUC^{m,po}_{m})D^{m,iv}}{(CL_{10}AUC^{m,iv}_{p} + CL_{20}AUC^{m,iv}_{m})D^{m,po}} \quad (20)$$

Eqs 19 and 20 can also be obtained from a theoretical approach proposed by Hwang et al.[2]

Experimental Section

Materials—ML-1035, **2**, and **3** were obtained from Marion Merrell Dow, Inc. (Kansas City, MO). Metoclopramide, used as an internal standard, was purchased from Sigma Co. (St. Louis, MO).

Animals—Male Sprague–Dawley rats (Sasco Co., Omaha, NE) weighing 280–380 g were kept in a controlled environment (24 °C, and 12 h of light from 6 a.m. until 6 p.m.). All animals were fasted overnight before dosing and for 4 h after dosing.

Pharmacokinetic Studies—Three groups of four rats were used in the studies. The oral dosing solutions of ML-1035 and **3** were prepared in normal saline, while **2** was dissolved in 50 mM phophate buffer (pH = 4.0) due to its poor water solubility. The compounds (152.4 μmol/kg each) were administered separately to rats by gavage. The rats were anesthetized with ether prior to each blood sampling. Blood samples (250 μL) were collected into heparinized tubes from the orbital sinus at 0.25, 0.5, 1, 2, 4, 6, 8, 10, and 24 h postdose. The plasma was isolated and stored at −20 °C until analysis.

Analysis of Plasma Samples—Plasma concentrations of ML-1035, **2**, and **3** were determined by a column-switching HPLC method.[19] Briefly, a 100-μL plasma sample diluted with phosphate buffer (1:1, v/v) was injected directly onto a cyano extraction column (4.6 × 4 mm, 5 μm; Waters Associates, Milford, MA) for micellar clean up with 0.5% sodium dodecyl sulfate in 50 mM phosphate solution. The proteinaceous components were solubilized and flushed to the waste. The extracted compounds were then eluted onto an analytical C_8 column (4.6 × 150 mm; Alltech Associates, Deerfield, IL) for further separation. The column eluants were monitored with a fluorometric detector (LS-240, Perkin-Elmer, Norwark, CT). The fluorescence excitation and emission wavelengths were set at 308 and 350 nm. After the subsequent washing and re-equilibration with the mobile phases, the system was ready for the next injection. The lower limit of quantitation for ML-1035, **2**, and **3** was 0.026–0.042 nmol/mL. The intra- and interday precision values are within 10% of the relative standard deviation and the accuracy values are 95–105%.

Pharmacokinetic Analysis—Individual and mean (±SD) values of the AUC and terminal half-life ($t_{1/2}$) of ML-1035, **2**, and **3** were obtained using the LAGRAN program.[20] Together with the mean values of AUC, CL_{10}, and CL_{20} obtained previously[1] from separate intravenous administration of these compounds to rats, this allowed the calculation of the values of F, f, $(F-f)$, and F_{p+m} for ML-1035 and **2** and F for **3** according to eqs 1–8 and 15–18. The following equation and the mean AUC values have also been used to calculate the bioavailability (F^{x}_{m3}) of **3** following separate oral administration of ML-1035 (x = p), **2** (x = m2), and **3** (x = m3):

$$F^{x}_{m3} = \frac{AUC^{x,po}_{m3}D^{m3,iv}}{AUC^{m3,iv}_{m3}D^{x,po}} \quad (21)$$

The individual maximum plasma concentration (C_{max}) and time to reach the peak concentration (T_{max}) were observed values following separate oral administration of ML-1035, **2**, and **3**. The mean (±SD) values of C_{max} and T_{max} were also calculated from the individual data.

Results

ML-1035 and **2** were rapidly absorbed after oral dosing, as the mean T_{max} values of both compounds were less than 1 h (Table 1). Interestingly, ML-1035 was rapidly generated after oral administration of **2**, as indicated by a T_{max} value of 0.31 h, while the formation of **2** after ML-1035 was dramatically delayed, as indicated by a T_{max} value of 7.5 h (Figure 3 and Table 1).

The mean plasma concentrations of both ML-1035 and **2** were much higher after oral administration of **2** than after oral administration of ML-1035 (Figure 3). For example, the mean C_{max} of both compounds in rats receiving **2** averaged 7–8 nmol/mL. However, mean C_{max} values of ML-1035 and **2** were only 1.6 and 0.2 nmol/mL, respectively, in rats receiving ML-1035 (Figure 3 and Table 1). The mean AUC of both compounds in rats receiving **2** were approximately 3–5 times greater than those in rats receiving ML-1035. Mean $t_{1/2}$ values of both compounds in rats receiving **2** were approximately $^1/_3$–$^1/_5$ of those of both compounds in rats receiving ML-1035. Because of inadequate sampling times, the $t_{1/2}$ of **2** in rats receiving ML-1035 might not be accurately determined. This uncertainty in the estimation of the $t_{1/2}$ might add some error to the determination of the AUC of **2**.

Table 1—Pharmacokinetic Parameters for ML-1035 and 2 in Rats

Parameter	Dose	Parameter Value (Mean ± SD)[a] ML-1035	2
AUC (nmol h/mL)	ML-1035	4.87 ± 2.08	2.53 ± 1.48
	2	13.4 ± 9.0	12.3 ± 7.5
C_{max} (nmol/mL)	ML-1035	1.62 ± 1.38	0.22 ± 0.18
	2	7.76 ± 6.16	7.03 ± 3.42
T_{max} (h)	ML-1035	0.75 ± 0.84	7.5 ± 1.0
	2	0.31 ± 0.12	0.31 ± 0.12
$t_{1/2}$ (h)	ML-1035	6.2 ± 2.6	9.5 ± 7.4
	2	2.4 ± 1.3	2.1 ± 1.7

[a] $n = 4$.

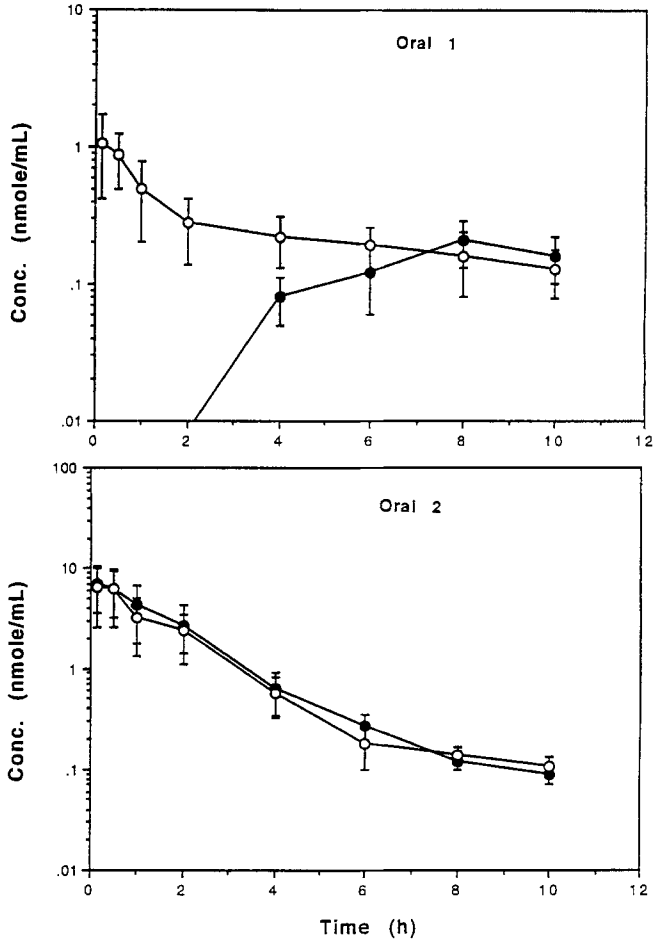

Figure 3—Mean (±SD; $n = 4$) plasma profiles of **1** (○) and **2** (●) after separate oral administration of 152.4 μmol/kg of **1** and **2** to rats.

Table 2—Bioavailability and Available Fractions of ML-1035 and 2 in Rats

Parameter	Eq no.	Dose	Parameter Value ML-1035	Parameter Value 2
F	1, 2	ML-1035	0.083	0.13
	3, 4	2	0.23	0.65
f	5, 6	ML-1035	0.08	0.12
	7, 8	2	0.19	0.62
$F - f$	—	ML-1035	0.003	0.01
	—	2	0.04	0.03
F_{p+m}	17	ML-1035	0.20[a]	
	18	2	0.81[a]	

[a] Parameter value is for both ML-1035 and 2.

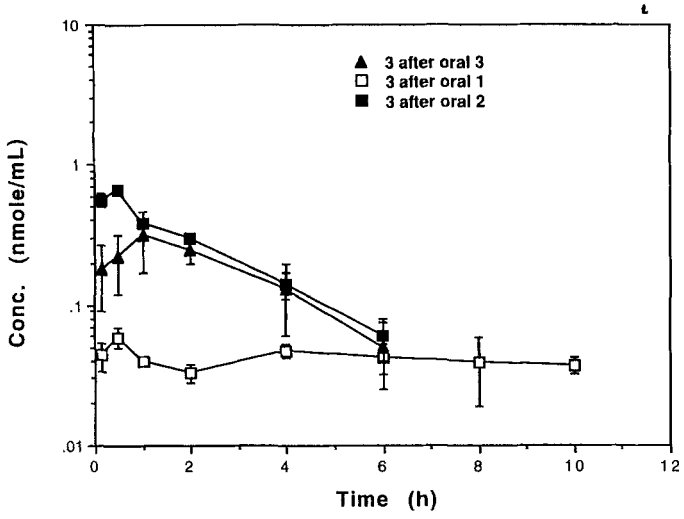

Figure 4—Mean (±SD; n = 4) plasma profiles of 3 after separate oral administration of 152.4 μmol/kg of 3, 1, and 2 to rats.

The bioavailability (F), f, (F-f) and F_{p+m} of ML-1035 and its interconversion metabolite 2 in rats are presented in Table 2. The F values of ML-1035 and 2 were 0.083 and 0.13, respectively, after dosing with ML-1035 and were 0.23 and 0.65, respectively, after dosing with 2. Of the former F values, 0.08 and 0.12 (or 96.4 and 92.3% of these values) were afforded by oral absorption (as ML-1035 and 2, respectively), while 0.003 and 0.01 (or 3.6 and 7.7% of these values) were afforded by systemically metabolic interconversion of these compounds, after oral administration of ML-1035. Similarly, when 2 was administered, 0.04 and 0.03 (or 17 and 4.6%) of the latter F values were the result of the systemic interconversion. The F_{p+m} value is 0.20 following an oral dose of ML-1035 and 0.81 following an oral dose of 2. On the basis of eqs 17 and 18, each F_{p+m} value equals the sum of the f values of ML-1035 and 2. For example, 62% of the oral dose of 2 entered the systemic circulation as intact 2 (f_m^m) and 19% as ML-1035 (f_p^m), which constitutes a total of 81% for 2 (F_{p+m}^m).

The mean AUC and C_{max} of 3 in rats receiving oral 2 were 1.98 nmol h/mL and 0.74 nmol/mL, respectively, and were larger than those in rats receiving oral ML-1035 or 3, while the corresponding T_{max} was smaller (Figure 4 and Table 3). The mean $t_{1/2}$ of 3 averaged 11.1 h following oral administration of ML-1035, 4 h following oral administration of 2, and 2.2 h following oral administration of 3. 3 was found to be poorly bioavailable (2.5–4.0%), regardless of whether ML-1035, 2, or 3 was administered. No measurable amount of ML-1035 was found after oral administration of 3, indicating that the biotransformation of ML-1035 to 3 is not reversible.

Table 3—Pharmacokinetic Parameters for 3 in Rats

Parameter	Parameter Value (Mean ± SD)[a] Oral ML-1035	Oral 2	Oral 3
AUC (nmol h/mL)	1.32 ± 0.39	1.98 ± 1.03	1.24 ± 0.29
C_{max} (nmol/mL)	0.077 ± 0.019	0.74 ± 0.37	0.51 ± 0.14
T_{max} (h)	3.2 ± 3.6	0.44 ± 0.12	1.12 ± 0.63
$t_{1/2}$ (h)	11.1 ± 3.3	4.0 ± 2.1	2.2 ± 0.9
F	0.027	0.040	0.025

[a] n = 4.

Discussion

ML-1035 was rapidly generated after oral administration of 2 (Figure 3). In contrast, the formation of 2 after ML-1035 was dramatically delayed. This delayed formation and the associated interconversion may explain why the mean terminal $t_{1/2}$ values of ML-1035 and 2 in rats receiving oral ML-1035 were much longer than those in rats receiving 2 (Table 1). It is possible that this longer $t_{1/2}$ of ML-1035 and 2 and delayed formation of 2 are due to bacterial reduction of ML-1035 in the lower intestines of the rat. The mean terminal $t_{1/2}$ values of 3 generated from either ML-1035 or 2 were approximately 2–5 times larger than that of the preformed 3 (Table 3), indicating that the formation of 3 might be the rate-limiting step after oral dosing of ML-1035 or 2.

Exploratory pharmacological studies (data not published) have demonstrated that, like ML-1035, both 2 and 3 possess a positive effect on gastric emptying in rats. Since rats have been used as the animal model for such studies,[1] the previous[1] and present investigations were conducted in this species. Again, like iv ML-1035, oral ML-1035 interconverted with 2 (Figure 3) but not with 3.

The fact that the mean, AUC values of ML-1035 and 2 were about 3–5 times higher after 2 was administered than after ML-1035 was given indicates that the bioavailability and f of both compounds are higher when 2 is administered. Indeed, the values of F and f for ML-1035 and 2 are about 2–5 times higher after dosing with 2 than after dosing with ML-1035 (Table 2), which is also reflected by a 4-fold higher F_{p+m} value.

According to eqs 13 and 14, F_p^p and F_m^p are functions of f_p^p, f_m^p, and metabolic conversion clearances. Although useful for describing absorption of drug, F_p^p and F_m^p are not functions of absorption kinetics alone but are also influenced by the reversible metabolic process. This fact implies the desirability of parameters for drug and its interconversion metabolite that are both descriptive of absorption kinetics and independent of reversible metabolic process. As shown previously,[3] f_p^p and f_m^p are functions of doses and input rates. Thus, they are intrinsic to absorption kinetics and may potentially satisfy this need. Obviously, being the sum of f_p^p and f_m^p, F_{p+m}^p is also an intrinsic absorption parameter for drugs undergoing reversible metabolism. It should be noted that all the equations mentioned or derived in the Theoretical section are valid only for linear reversible metabolic systems.

As shown in Table 2, following oral administration of ML-1035, the bioavailability of this compound or 2 is weakly influenced by the metabolic interconversion process, as only 3.6–7.7% of this value is produced by this process. Similarly, following oral administration of 2, the bioavailability of this compound or ML-1035 is weakly to moderately influenced by the metabolic interconversion process, as 4.6–17% of this fraction results from this process. Thus, perturbation of the degree of

metabolic interconversion between ML-1035 and 2 by disease states or drug interactions may not have substantial effect on the systemic availability of both compounds in rats.

Metabolite 3 was very poorly absorbed, as, on average, only 2.5% of the oral dose was bioavailable. The bioavailability of 3 following oral administration of 3 or ML-1035 was lower than that following oral administration of 2 (Table 3). Similarly, the plasma concentrations of 3 in rats receiving either ML-1035 or 3 were lower than those in rats receiving 2 (Figure 4).

According to eq 17, F^p_{p+m} is the sum of f^p_p and f^p_m. Also, F^p_p is the sum of f^p_p and $f^p_m CL_{21}/CL_{22}$ (eq 13). If there is no reversible metabolism (i.e., $CL_{21} = 0$), then $F^p_p = f^p_p$. If there is no input of metabolite into the systemic circulation (i.e., $f^p_m = 0$), then $F^p_{p+m} = F^p_p = f^p_p$. Thus, $F^p_{p+m} \geq F^p_p \geq f^p_p$. In the case of ML-1035, because $CL_{21} \neq 0$ and $f^p_m \neq 0$, $F^p_{p+m} > F^p_p > f^p_p$.

For compounds not undergoing reversible metabolism (e.g., 3), bioavailability assessment using only F is adequate. However, for compounds undergoing reversible metabolism, especially when both the parent compound and the interconversion metabolite are pharmacologically active (e.g., ML-1035 and 2), it is also important to quantify the f and $(F - f)$. As shown above, the F parameters for drugs undergoing reversible metabolism are not intrinsic absorption parameters and are influenced by the extent of metabolic interconversion, which may have large intersubject variation and may be perturbed by disease states or drug interactions. Thus, caution should be exercised when these parameters are used alone to evaluate absorption of a drug undergoing reversible metabolism.

In conclusion, the present investigation has shown that ML-1035 underwent reversible metabolism with its sulfide metabolite but not with sulfone metabolite in rats receiving these compounds separately and orally. The facts that 2 is better absorbed than ML-1035 in rats and both compounds are pharmacologically active suggest that 2 may be a better drug candidate than ML-1035 in humans. However, further investigations of the absorption and disposition kinetics of these compounds in humans are essential before this contention can be established.

GLOSSARY

AUC	total area under the plasma concentration–time curve
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 the 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_{12}) and all irreversible elimination (CL_{10}) processes operating on metabolite
D	administered dose
f^p_p	fraction of an oral dose of parent drug entering the central compartment intact as parent drug
f^p_m	fraction of an oral dose of parent drug entering the central compartment as metabolite
f^m_p	fraction of an oral dose of metabolite entering the central compartment as parent drug
f^m_m	fraction of an oral dose of metabolite entering the central compartment intact as metabolite
F^p_p	bioavailability of parent drug after oral administration of parent drug ($f^p_p + f^p_m CL_{21}/CL_{22}$)
F^p_m	bioavailability of metabolite after oral administration of parent drug ($f^p_p CL_{12}/CL_{11} + f^p_m$)
F^m_p	bioavailability of parent drug after oral administration of metabolite
F^m_m	bioavailability of metabolite after oral administration of metabolite
F^p_{p+m}	$f^p_p + f^p_m$
F^m_{p+m}	$f^m_p + f^m_m$

References and Notes

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