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Volume of Distribution is Unaffected by Metabolic Drug-Drug Interactions

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Abbreviation List:

AUC, area under the curve; *AUMC,* area under the moment curve; BDDCS, Biopharmaceutics Drug Disposition Classification System; *CL,* clearance; *CL/F,* apparent clearance; CYP, cytochrome P450; DDI, drug-drug interaction; EM, extensive metabolizers; *F,* bioavailability; IV, intravenous; *MIT,* mean input time; *MRT,* mean residence time; PK, pharmacokinetics; PM, poor metabolizers; τ, dosing interval; $t_{1/2,z,}$, terminal half-life; $V_{ss,}$, volume of distribution at steady-state; $V_{z,}$, terminal volume of distribution; $V_{1,}$, initial volume of distribution in the central compartment; $V_{ss}/F,$ apparent volume of distribution at steady-state

ABSTRACT (248 of 250 words)

It has been recognized that significant transporter interactions result in volume of distribution changes in addition to potential changes in clearance (*CL*). For drugs that are not clinically significant transporter substrates, it is expected that drug-drug interactions (DDIs) would not result in any changes in volume of distribution. An evaluation of this hypothesis proceeded via an extensive analysis of published intravenous (IV) metabolic DDIs, based on clinically recommended index substrates and inhibitors of major cytochrome P450 (CYP) isoforms. Seventy-two metabolic drug interaction studies were identified where volume of distribution at steady-state (V_{ss}) values were available for the CYP index substrates caffeine (CYP1A2), metoprolol (CYP2D6), midazolam (CYP3A4), theophylline (CYP1A2), and tolbutamide (CYP2C9). Changes in exposure (*AUC*) up to 5.1-fold were observed, however ratios of V_{ss} changes only ranged from 0.70 – 1.26, with one outlier displaying a V_{ss} ratio of 0.57. These results support the widely-held founding tenant of pharmacokinetics that *CL* and V_{ss} are independent parameters. Knowledge that V_{ss} is unchanged in metabolic DDIs can be helpful in discriminating changes in *CL* from changes in bioavailability (*F*) when only oral dosing data are available, as we have recently demonstrated. Since V_{ss} remains unchanged for IV metabolic DDIs, following oral dosing changes in V_{ss}/F will reflect changes in *F* alone. This estimation of *F* change can subsequently be utilized to assess changes in *CL* alone from calculations of *CL*/*F*. Utilization of this simple methodology for orally dosed drugs will have a

significant impact on how DDIs are interpreted from drug development and regulatory perspectives.

KEY POINTS

- While it is expected that significant xenobiotic transporter interactions will result in volume of distribution changes of victim drug, metabolic drug interaction should not result in any volume of distribution changes
- Evaluation of exemplary metabolic drug-drug interactions with clinically recommended index substrates and inhibitors indicates that volume of distribution is largely unchanged in metabolic interactions, highlighting that volume and clearance are indeed independent parameters
- Understanding that metabolic interactions do not result in volume changes can allow for estimation of bioavailability changes in oral drug-drug interactions. Examination of extent of change in apparent volume of distribution (V_{ss}/F) will reflect changes in bioavailability (F) alone due to unchanged V_{ss}
- Estimates of changes in F can subsequently be utilized to differentiate changes in clearance alone from measures of apparent clearance (CL/F) following oral dosing, as we have recently demonstrated [3]

1. INTRODUCTION

Volume of distribution in pharmacokinetics (PK) is the theoretical volume in which a drug must distribute to relate the observed systemic drug concentrations to the amount of drug present in the body. It is a non-physiologic volume that reflects the degree of tissue distribution of drug. It has been recognized that xenobiotic transporters can influence the volume of distribution of drugs by allowing or restricting drug access to various tissues throughout the body [1], and therefore significant transporter drug interactions may result in changes in volume of distribution in addition to potential changes in clearance [2]. For drugs that are not clinically significant transporter substrates, it is expected that drug-drug interactions (DDIs) would not result in any changes in steady-state volume of distribution (V_{ss}). As our laboratory has recently demonstrated, knowledge that V_{ss} is unchanged in metabolic DDIs can be helpful in implicating transporter involvement in complex DDIs as well as in facilitating the discrimination of changes in clearance from changes in bioavailability when only oral dosing data are available [3]. Here we present a comprehensive evaluation of the hypothesis that V_{ss} remains unchanged in metabolic drug interaction studies.

2. METHODS

2.1 Literature Search Strategy and Inclusion/Exclusion Criteria

Based on a recent compilation of recommended clinical index substrates of major drug metabolizing enzymes and cytochrome P450 (CYP) isoforms [4], a

comprehensive literature search identified caffeine (CYP1A2), metoprolol (CYP2D6), midazolam (CYP3A4), theophylline (CYP1A2) and tolbutamide (CYP2C9) as index substrates for which intravenous (IV) dosing drug interaction data were available. Oral drug interaction studies of these index substrates were excluded from the analysis to avoid the confounding impact that changes in bioavailability (F) would have on apparent volume of distribution (V_{ss}/F). Due to the large number of IV interaction studies for the probe substrate midazolam, the scope of the analysis was further refined to primarily include DDIs involving index inhibitors with known clinical inhibitory specificities against the various CYP isoforms and xenobiotic transporters, again based on the recent recommendations of Tornio et al. [4]. If additional victim-perpetrator combinations were investigated in these studies, these interaction data were also included in the analysis and information regarding the *in vivo* substrate or inhibitory specificities of these drugs were referenced from the literature [5-11]. Since V_{ss} is not often reported by clinical investigators, estimation of this parameter often proceeded via digitization and non-compartmental analysis of published pharmacokinetic profiles. If V_{ss} was not reported, studies were excluded if (1) pharmacokinetic profiles were not reported and/or were difficult to reliably digitize, or if (2) resulting estimates of *AUC* were greater than 25% different from reported values. The latter aspect will be further discussed in the next section.

This analysis focuses on DDI studies conducted with the same subjects in the control and treatment arms, and as such, four midazolam studies with

a parallel study design were excluded. However, some studies included in this analysis conducted the DDI investigation (within the same person) in multiple populations, for example, with respect to pharmacogenomic variance of drug metabolizing enzymes or in healthy versus disease state subjects. Thus, we also analyze changes in V_{ss} of victim drug only between these populations to investigate the inherent potential of V_{ss} to change between different individuals.

The specificities of all substrates and inhibitors are summarized, and in addition, the Biopharmaceutics Drug Disposition Classification System (BDDCS) is listed. This simple system classifies drugs based on solubility and permeability and can anticipate when metabolism versus transporter-mediated processes (such as renal and biliary elimination) are the major route of drug elimination [12].

2.2 Data Analyses

Thirty published DDI studies were examined and changes in exposure (*AUC*), clearance (*CL*), V_{ss}, mean residence time (*MRT*) and terminal half-life ($t_{1/2,z}$) were calculated and reported as ratios of interaction/control. When individual PK data were reported, the ratios of the parameters-of-interest were calculated for each individual and the average of this ratio for all subjects was reported (and indicated in tables with a footnote). Although initial volume of distribution in the central compartment (V_1) and terminal volume of distribution (V_z) are commonly reported in clinical pharmacokinetic

studies, our primary analysis was based on changes in V_{ss} as it is a non-compartmental parameter that represents the whole-body volume of distribution, theoretically is independent of elimination measures [13], and is not associated with a particular compartment or phase of the PK curve (as is the case for V_1 and V_z for drugs that display multi-compartment kinetics). Methods of each paper were carefully reviewed to ensure reported V_{ss} was appropriately calculated. For investigations in which V_{ss} could not be determined, data for V_z were reported with the understanding that V_z changes will only reflect the same degree of change as V_{ss} if the victim drug follows a one compartment model or if the distribution phase minimally affects measures of both *AUC* and *AUMC* (area under the moment curve).

For investigations that did not explicitly report all parameters-of-interest, the parameter was either (1) back-calculated from reported data or (2) estimated by digitization of reported plasma-concentration time profiles. Clearance and *AUC* could be calculated from one another if only one of the two parameters were reported by using known dose and the equation: $CL = Dose / AUC$. Similarly, *CL* can be used to calculate either V_{ss} or *MRT* (if one of the two parameters were reported) using Eq. 1 [13]:

$$V_{ss} = CL \bullet MRT \qquad \text{(Eq. 1)}$$

If *MRT* values were not reported, *MRT* was calculated via non-compartmental methods by Eq. 2:

$$MRT = \frac{AUMC}{AUC} - MIT \qquad \text{(Eq. 2)}$$

where *MIT* is mean input time. For IV bolus doses, *MIT* is zero. For IV infusions, *MIT* is defined as half of the length of the dosing interval (τ), i.e. $MIT = \tau / 2$. For investigations that did not report V_{ss} (or any of the other pharmacokinetic parameters of interest), plasma concentration-time profiles were digitized using WebPlotDigitizer Version 4.2 (San Francisco, CA) and analyzed by non-compartmental analysis with WinNonlin Professional Edition Version 2.1 (Pharsight, Mountain View, CA). Digitized *AUC* values were compared to reported *AUC* values and studies were excluded if reported average *AUC* values were greater than 25% different from digitized values. All pharmacokinetic ratios calculated from digitization of published concentration-time profiles are specifically indicated in the data tables with a footnote. Published values of pharmacokinetic parameters were reported in priority, with digitization/reanalysis of reported average concentration-time profiles utilized only to supplement unreported data. Each value in the data tables is annotated based on calculation methods (published versus digitized, individual versus average PK data used for ratios, equations used or assumptions made).

The average absolute difference in *AUC* and V_{ss} were compared to one another for all 72 DDIs, as well as the subset of DDIs with greater than 30% *AUC* change (i.e. ratios outside of the range of 0.77 and 1.30, n=49), which

could be considered a potentially clinically significant interaction. To account for interactions resulting in a decrease in *AUC*, such as potential enzyme induction, the inverse for all ratios less than unity was utilized in calculation of average absolute *AUC* and V_{ss} changes. Box plot representations of the data were generated to allow visual depiction of any differences in degree of change in these two parameters, which indicate the median, 25th and 75th percentiles, range from minimum to maximum values, and depict each individual point. To investigate if the classic trend of *CL* changes being equal (but opposite in magnitude) to half-life and *MRT* changes in these metabolic DDIs, the relationship between changes in half-life and *MRT* were compared to the inverse of the change in *CL*.

3. RESULTS

Relevant information on the specificity of all substrates analyzed are outlined in Table 1 and the inhibitory specificities of the perpetrator drugs included in this analysis are listed in Table 2. The comprehensive literature search identified DDI studies for the following index substrates where V_{ss} measurements were available: caffeine [14], metoprolol [15], midazolam [16-25], theophylline [26-38], and tolbutamide [39] (Table 3). Any additional victim-perpetrator combinations (with non-index substrates) investigated in these studies where V_{ss} measurements were available were also analyzed, including alfentanil [20], antipyrine [27], and lidocaine [19] (Table 4). When only V_z values were available, these studies are summarized in Table 5 and

include the victim drugs antipyrine [40], desipramine [41], imipramine [41], and theophylline [40, 42-44].

The changes in pharmacokinetic parameters (*AUC*, *CL*, V_{ss}, *MRT* and $t_{1/2,z}$) of clinically recommended index substrates are listed in Table 3 and additional victim drugs in Table 4, totaling 72 DDI studies. For these primarily metabolized drugs, *AUC* ratios ranged from 0.44 - 5.1 while V_{ss} ranged from 0.57 - 1.40. The average absolute difference in *AUC* ratios for these 72 DDI studies averaged 1.69 ± 0.78, while the average absolute difference in V_{ss} averaged 1.10 ± 0.12. For the 49 interactions with at least a 30% change, i.e., those interactions that could potentially be clinically significant, the absolute *AUC* changes averaged 1.95 ± 0.83, while V_{ss} averaged 1.11 ± 0.13. Figure 1 depicts box plot representations of these values. Of the 72 DDI studies examined, only three (4.2%) resulted in greater than a 30% change in V_{ss} (i.e. ratios outside of the range of 0.77 to 1.30) with ratios of 0.70 [15], 1.40 [18] and 0.57 [24].

An additional 10 DDI studies were identified from 5 studies for which only V_z was reported and V_{ss} could not be determined (due to lack of published PK profiles) (Table 5). Changes in *AUC* ranged from 1.10 – 1.70, but V_z only ranged from 0.89 – 1.24.

While the inclusion criteria of this analysis focused on studies that include the same patients in the control and interaction phases, three DDI studies investigated here performed the same drug interaction study in multiple groups, either with respect to pharmacogenomic variance of

metabolizing enzyme [15, 21] or disease state [28]. To investigate the impact of inter-individual variability on V_{ss}, the control phase (victim drug only) between each group were compared to one another (Table 6). When comparing the PK of the index substrate alone between groups, V_{ss} for victim drug was observed to change with ratios of 0.51 (metoprolol with CYP2D6 pharmacogenomics), 0.72 and 0.79 (midazolam with CYP3A5 pharmacogenomics), and 0.70 (healthy versus liver cirrhosis patients), while *AUC* was observed to change 0.98- to 2.56-fold in these studies. In the same studies, however, minimal change in V_{ss} was observed in the same individual between the drug interaction versus control phases, with ratios ranging from 0.70 – 1.13 (Table 3).

4. DISCUSSION

For primarily metabolized drugs, IV drug interaction studies resulted in minimal changes to V_{ss}. Changes in drug exposure (*AUC*) up to 5.1-fold were observed, however ratios of V_{ss} changes only ranged from 0.70 – 1.40, with one outlier displaying a 43% decrease in V_{ss} (ratio of 0.57) (Table 3) for a midazolam-ketoconazole interaction in healthy female Koreans where the *AUC* ratio was 4.61 [24]. In contrast, a second midazolam-ketoconazole interaction study in healthy White subjects with a similar *AUC* ratio of 5.1 only exhibited a V_{ss} ratio of 1.20 [23]. The trend of unchanged V_{ss} was observed for all index substrates and CYP isoforms investigated (caffeine and

theophylline, CYP1A2; metoprolol, CYP2D6; tolbutamide, CYP2C9; midazolam, CYP3A4) (data not shown).

It should be noted that a listed high percent *AUC* extrapolation value does not necessarily indicate that *AUC* (or PK parameters derived from *AUC*) are unreliable if the slope of the elimination phase is adequately captured. Additionally, the pharmacokinetic parameters reported by the original authors were used in priority to calculate the ratios presented in this analysis, such as the frequently reported parameters *AUC*, *CL* and $t_{1/2,z}$. Estimation of less-frequently reported parameters, such as V_{ss} and *MRT*, proceeded via digitization of the average concentration-time profiles reported by the original authors, and it should be noted that these average profiles may not accurately represent changes within any one particular individual in the DDI study.

When V_{ss} was not reported (and could not be calculated due to the lack of published PK curves), changes in V_z were examined (Table 5). Changes in V_z were minimal (0.89 – 1.24). Examination of theophylline PK curves from the other studies in this analysis indicate that the distribution phase of theophylline is very short, and therefore V_z changes would likely be similar to V_{ss} changes. No such conclusions related to the potential similarity between V_z and V_{ss} could be made for the antipyrine, desipramine or imipramine data due to the lack of published IV pharmacokinetic curves in the other studies examined here.

Of note, the clinical studies included in this analysis were all conducted with the same individuals in the control versus interaction arms, to minimize the confounding effects of inter-individual variability. Three of the studies examined here also conducted DDIs in multiple subject groups with respect to disease state [28] or pharmacogenomic variance of drug metabolizing enzyme [15, 21]. To examine the potential impact of inter-individual differences in V_{ss}, the pharmacokinetic parameters associated with the control arms (victim drug only) of each group were compared to one another, resulting in V_{ss} ratios of 0.51 – 0.79 associated with *AUC* changes of 0.98 – 2.56 (Table 6). In comparison to the earlier part of this analysis where changes in V_{ss} within the same individual (with and without addition of a perpetrator drug) were examined, these same studies displayed V_{ss} ratios of 0.70 – 1.26 associated with *AUC* increases of 1.12 – 3.08. Reported data related to the body weights of individuals in each arm are also noted in Table 5. However accounting for average differences in body weight between the two groups does not necessarily result in V_{ss} ratios that are closer to unity. For instance, the reported differences in metoprolol V_{ss} between CYP2D6 poor metabolizers (PM) and extensive metabolizers (EM) resulted in a ratio of 0.51, and the reported values used to calculate this ratio were normalized by body weight of each individual by the original investigators. This indicates that volume of distribution differences in different individuals can be significant and do not only depend on total body weight differences. Further, the variability associated with V_{ss} values was much greater in EM than PM,

with CV values of 44% and 22%, respectively. The issue of variability between individuals is further compounded in pharmacogenomic studies where often only a very small number of individuals can be recruited for the less frequently occurring genotypes.

This highlights that for the same drug, V_{ss} may change significantly between subjects. These findings are in contradiction to the belief that all pharmacokinetic parameters are expected to be similar in homogenous populations, such as in healthy subjects, since the pharmacogenomic interactions studied here included healthy subjects in each arm. As a result, we suggest that it may not appropriate to assume that V_{ss} is unchanged across different subject populations and therefore, it is crucial to consider clinical study design (parallel versus crossover). Further, based on this observation we emphasize that examination of differences in pharmacokinetics in different pharmacogenomic variance or disease state populations should be considered as a qualitative outcome. Although changes in *AUC* and *CL* can reasonably be compared between groups, however, since V_{ss} may inherently be different between individuals in each group, changes in terminal half-life should not be considered significant nor be utilized to suggest changes in dosing regimen between the two populations studied. Further investigation into this finding is warranted, and is an area of high interest to our laboratory.

It should be noted that perpetrator drugs have the potential to displace victim drug from plasma or tissue binding sites, which may result in V_{ss}

changes. From Eq. 1, changes in protein binding should result in comparable changes for *CL* and V_{ss} with no change in *MRT* or half-life. However, we find no examples of such an interaction in the same subjects within our dataset. Thus, the data presented here presented here for IV metabolic drug interaction studies very strongly support our contention that V_{ss} does not change to any significant degree for metabolic DDIs.

The DDI studies evaluated here follow the classic pharmacokinetic trend of changes in *CL* resulting in an equal but opposite change in *MRT*, due to the fact that V_{ss} remains unchanged for metabolic interactions (Eq. 1) [45]. These relationships are depicted in Figure 3, where the inverse of ratios of *CL* changes are plotted against both *MRT* and $t_{1/2,z}$ ratios. The results for each comparison fall very close to the line of unity, highlighting the intuitive trend that decreases in clearance result in increases in *MRT* and $t_{1/2,z}$ of approximately equal magnitude. In comparing the *AUC*-*MRT* relationship to the *AUC*-$t_{1/2,z}$ relationship, as expected the *MRT* relationship falls closer to the line of unity than a few of the $t_{1/2,z}$ points associated with larger *1/CL* ratios, as $t_{1/2,z}$ may change differently than *MRT* for drugs that display multi-compartment kinetics, and this difference is likely amplified in DDI studies of larger magnitude. In general, Figure 3 highlights that changes in clearance are opposite in direction but similar in magnitude to *MRT* and $t_{1/2,z}$ and this is in sharp contrast to significant transporter-drug interactions, where decreases in *CL* can often be associated with decreases in half-life and *MRT*, due to changes in V_{ss} [2].

As our laboratory has recently presented, knowledge that V_{ss} remains unchanged in metabolic DDI studies can facilitate estimation of changes in clearance from changes in bioavailability following an oral dose [3]. In the Quinney et al. [17] study of the interaction of midazolam and clarithromycin in elderly subjects, the interaction was conducted following both oral and IV dosed midazolam. Thus, estimates of changes in *CL* versus *F* based on the oral interaction study can be confirmed by examining the observed changes resulting from the IV midazolam interaction study. Following oral dosing, an 8.2-fold increase in midazolam exposure was observed (compared to only a 3.2-fold increase in midazolam *AUC* in the IV drug interaction study) when clarithromycin was dosed 500 mg BID for 7 days (Table 7). Knowing that V_{ss} largely remains unchanged for IV metabolic DDIs (based on the analysis presented here) supports the assumption that changes in V_{ss}/F following an oral dose will reflect changes in *F* alone. This estimation of *F* change can subsequently be utilized to assess changes in *CL* alone from calculations of *CL*/*F* [3]. Utilizing this methodology, the predicted increase in bioavailability was 2.84-fold and *CL* was predicted to decrease by 60% (ratio of 0.40), compared to the observed 2.12-fold increase in bioavailability and 65% reduction of *CL* (ratio of 0.35) (Table 7). Thus, recognition that V_{ss} remains unchanged in metabolic interactions allows discrimination of two PK parameters thought to be indistinguishable from one another following oral dosing.

5. CONCLUSIONS

Based on an extensive evaluation of 72 clinical DDI studies, V_{ss} remains unchanged for IV metabolic drug interactions as expected, with a small minority of outliers (only 3) with ratios indicating a change, where for the largest V_{ss} change, a second study of the same interacting drugs in a different population did not show this marked V_{ss} change. These results uphold the widely-held founding tenant of pharmacokinetics that *CL* and V_{ss} are independent parameters. Differences in victim drug V_{ss} can significantly vary throughout the population due to inter-individual variability that may not necessarily be accounted for by body weight. This highlights that differences in pharmacokinetic parameters observed between groups in pharmacogenomic and disease state studies (or any clinical trial with a parallel study design) should be accompanied with the understanding that V_{ss} could differ significantly between groups. Therefore, although changes in *AUC* and *CL* between groups indicate meaningful differences, terminal half-life differences should be considered qualitative due to their dependence on the inherently variable V_{ss} value between individuals. Further, following oral dosing the changes in V_{ss}/F will reflect only changes in *F* for metabolic interactions. Therefore, this estimation of *F* change can subsequently be utilized to assess changes in *CL* alone from calculations of *CL*/*F*, two parameters that are considered indistinguishable from one another following oral dosing [3].

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Compliance with Ethical Standards:

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Figure Legends:

Figure 1: Box plot depictions of the absolute magnitude of change in victim drug exposure (*AUC*) and volume of distribution at steady state (V_{ss}) expressed as ratios of interaction to control for (A) all drug-drug interactions (n=72) and (B) the subset of these interactions that are potentially clinically significant (with absolute *AUC* ratios > 1.3; n=49). The box indicates the median, 25th and 75th percentiles, the whiskers range from minimum to maximum values, and each individual data point is also depicted.

Figure 2: Ratios of change in (A) mean residence time (*MRT*) and (B) terminal half-life ($t_{1/2,z}$) compared with the inverse of change in clearance (*CL*). Red line indicates the line of unity.

Figure 1.

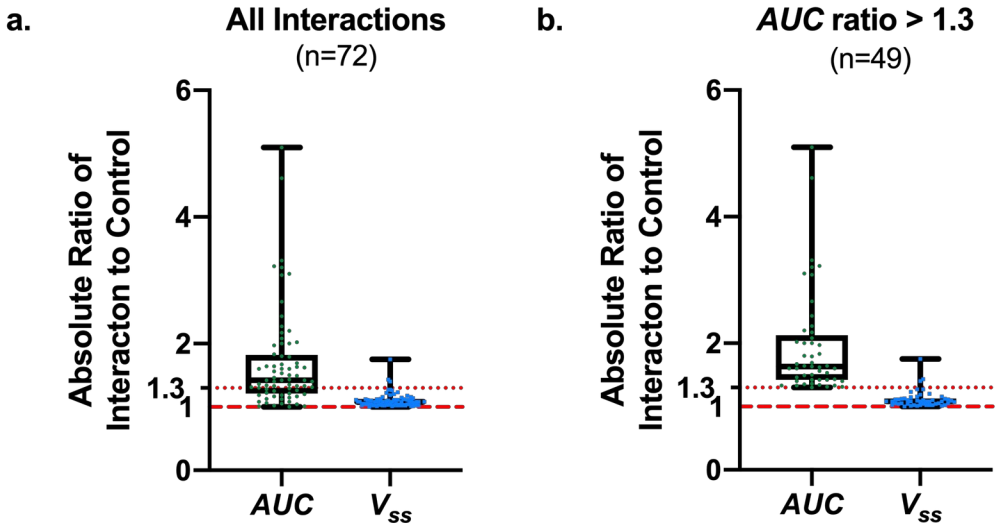
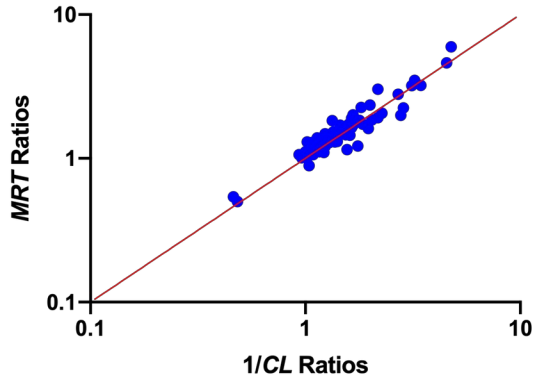

a.
All Interactions
(n=72)
Absolute Ratio of Interacton to Control
6
4
2
1.3
1
0
AUC
V_{ss}
b.
AUC ratio > 1.3
(n=49)
Absolute Ratio of Interacton to Control
6
4
2
1.3
1
0
AUC
V_{ss}

Figure 2.

a.


10
1
0.1
0.1
1
10
MRT Ratios
1/CL Ratios

b.

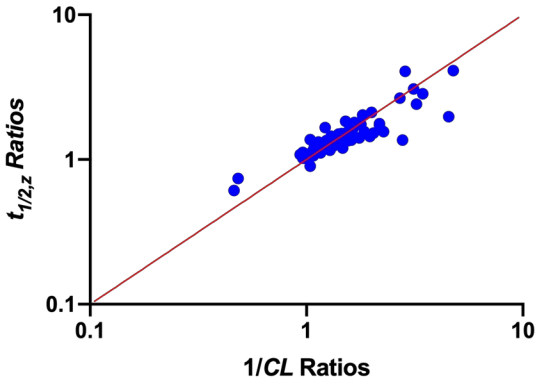

10
1
0.1
0.1
1
10
$t_{1/2,z}$ Ratios
1/CL Ratios

Table 1: Enzyme Specificities of Clinical Index Substrates and Additional Victim Drugs

Substrate	BDDCS Class	Enzyme	Other Relevant Enzymes / Transporters	Reference
Antipyrine	1	CYP1A2 CYP2C9 CYP3A	Multiple CYPs (2A6, 2B6, 2C, 2E1)	[7]
Alfentanil	1	CYP3A	-	[5]
Caffeine	1	CYP1A2	Xanthine Oxidase N-Acetyl Transferase	[4]
Desipramine	1	CYP2D6	CYP3A	[4]
Imipramine	1	CYP2C19	CYP2D6	[5]
Lidocaine	1	CYP3A	CYP1A2	[7]
Metoprolol	1	CYP2D6	CYP3A	[4]
Midazolam	1	CYP3A	-	[4]
Theophylline	1	CYP1A2	CYP2E1 CYP3A	[4]
Tolbutamide	2	CYP2C9	OAT2	[4, 10]

Abbreviations: BDDCS, Biopharmaceutics Drug Disposition Classification System; CYP, Cytochrome P450; OAT, Organic Anion Transporter

Table 2: Inhibitory Specificities of Clinical Index Inhibitors and Additional Perpetrator Drugs

Index Inhibitor	BDDCS Class	Enzyme	Other Relevant Enzymes / Transporters	Reference
Cimetidine	3	OCT2 CYP2C19 CYP3A	MATE1 CYP1A2 CYP2C9 CYP2D6	[5]
Ciprofloxacin	4	CYP1A2	CYP3A4	[4]
Clarithromycin	3	CYP3A4	CYP2C19 P-gp	[4]
Diltiazem	1	CYP3A4	CYP1A2 CYP2D6 P-gp	[5]
Disulfiram	2	CYP2E1	CYP1A2 CYP2C9 CYP2D6	[5]
Enoxacin	4	CYP1A2		[4]
Erythromycin	4	CYP3A4	P-gp	[4]
Famotidine	3	Unknown		
Fluconazole	3	CYP2C9 CYP2C19	CYP3A4	[4]
Itraconazole	2	CYP3A4	CYP2J2 P-gp	[4]
Ketoconazole	2	CYP3A4	CYP2C19 P-gp	[4]
Lidocaine	1	CYP3A4	CYP1A2	[7]
Nalidixic Acid	2	Unknown		
Nelfinavir	2	CYP3A4	CYP2D6	[8]
Norfloxacin	4	CYP1A2		[9]
Ofloxacin	3	Unknown		
Olanzapine	2	Unknown		
Ondansetron	1	Unknown		
Primaquine	1	Unknown		
Quinidine	1	CYP2D6	P-gp	[4]
Ranitidine	3	OCT2 CYP3A	CYP2C9 CYP2D6	[5]
Rifampin (Single Dose)	2	OATPs	CYP3A4	[6, 11]
Rifampin (Multiple Dose)	2	(Inducer) CYP3A CYP2C9 P-gp	(Inducer) CYP1A CYP2B6 CYP2C8 CYP2C19	[6]
Ritonavir (Single Dose)	2	CYP3A4	P-gp	[4]
Ritonavir (Multiple Dose)	2	CYP Induction		[4]
Sulfaphenazole	1	CYP2C9		[8]
Terbinafine	2	CYP2D6	CYP1A2	[4]
Verapamil	1	CYP3A4	P-gp	[4]

Abbreviations: BDDCS, Biopharmaceutics Drug Disposition Classification System; CYP, Cyotochrome P450; MATE, Multidrug and Toxic Extrusion; OCT, Organic Cation Transporter; P-gp, P-glycoprotein;

Table 3: Intravenous Drug-Drug Interaction Studies of Cytochrome P450 Index Substrates

Victim	Perpetrator	Victim Enzymes or Transporters	Perpetrator Enzymes or Transporters	Population	N	$\frac{AUC^{DDI}}{AUC^{Con}}$	$\frac{CL^{DDI}}{CL^{Con}}$	$\frac{V_{ss}^{DDI}}{V_{ss}^{Con}}$	$\frac{MRT^{DDI}}{MRT^{Con}}$	$\frac{t_{1/2,z}^{DDI}}{t_{1/2,z}^{Con}}$	Percent *AUC* Extrapolation
Caffeine	Ketoconazole (400 mg; Single Dose)	CYP1A2 NAT XO	CYP3A4 CYP2C19 P-gp	Healthy Subjects	8	1.17[b]	0.88[b]	0.97[a]	1.14[a]	1.18[b]	36%/30%[a]
Caffeine	Terbinafine (500 mg; Single Dose)	CYP1A2 NAT XO	CYP2D6 CYP1A2	Healthy Subjects	8	1.31[b]	0.81[b]	1.05[a]	1.48[a]	1.35[b]	45%/30%[a]
Metoprolol	Quinidine (50 mg; Single Dose)	CYP2D6 CYP3A4	CYP2D6 P-gp	Healthy Subjects, Male, White, CYP2D6 Extensive Metabolizers	3	2.43[d]	0.44[b]	0.87[b]	2.06[f]	1.56[a]	29%/15%[a]
Metoprolol	Quinidine (250 mg BID; 3 Days)	CYP2D6 CYP3A4	CYP2D6 P-gp	Healthy, Male, White, CYP2D6 Extensive Metabolizers	4	3.08[d]	0.36[b]	0.70[b]	1.99[f]	2.36[a]	44%/15%[a]
Metoprolol	Quinidine (50 mg; Single Dose)	CYP2D6 CYP3A4	CYP2D6 P-gp	Healthy, Male, White, CYP2D6 Poor Metabolizers	3	1.12[d]	0.98[b]	1.18[b]	1.30[f]	1.09[a]	35%/34%[a]
Metoprolol	Quinidine (250 mg BID; 3 Days)	CYP2D6 CYP3A4	CYP2D6 P-gp	Healthy, Male, White, CYP2D6 Poor Metabolizers	3	1.26[d]	0.88[b]	1.26[b]	1.39[f]	1.32[a]	43%/34%[a]
Midazolam	Clarithromycin (500 mg BID; 7 Days)	CYP3A4	CYP3A4 CYP2C19 P-gp	Healthy Subjects	16	2.66	0.37	1.05[a]	2.79[a]	2.66	38%/12%[a]
Midazolam	Clarithromycin (500 mg BID; 7 Days)	CYP3A4	CYP3A4 CYP2C19 P-gp	Healthy Subjects, Elderly	16	3.2	0.35	1.16[a]	2.24[a]	4.06	44%/20%[a]
Midazolam	Erythromycin (500 mg TID; 7 Days)	CYP3A4	CYP3A4 P-gp	Healthy Subjects	6	2.17[c]	0.46	1.40	3.03[e]	1.77	NR
Midazolam	Erythromycin (500 mg QID; 5 Days) + Lidocaine (1 mg/kg; 2 Days)	CYP3A4	CYP3A4 P-gp CYP3A4 CYP1A2	Healthy Subjects	8	1.60[d]	0.71[b]	0.93[a]	1.31[a]	1.50[b]	19%/13%[a]
Midazolam	Fluconazole (100 mg; Single Dose)	CYP3A4	CYP3A4 CYP2C9 CYP2C19	Healthy Subjects	12	1.3	0.78	1.01[a]	1.28[a]	1.16	10%/7%
Midazola	Fluconazole	CYP3A4	CYP3A4	Healthy Subjects	12	1.4	0.68	1.10[a]	1.68[a]	1.20	11%/7%

m	(200 mg; Single Dose)		CYP2C9 CYP2C19								
Midazolam	Fluconazole (400 mg; Single Dose)	CYP3A4	CYP3A4 CYP2C9 CYP2C19	Healthy Subjects	12	2.0	0.54	0.93[a]	1.73[a]	1.56	17%/7%
Midazolam	Fluconazole (400 mg; Single Dose)	CYP3A4	CYP3A4 CYP2C9 CYP2C19	Healthy Subjects; African American CYP3A5*1/*1	6	1.62[b]	0.64[b]	0.81[a]	1.15[a]	1.35[b]	17%/14%[a]
Midazolam	Fluconazole (400 mg; Single Dose)	CYP3A4	CYP3A4 CYP2C9 CYP2C19	Healthy Subjects; African American CYP3A5*1/*X	7	1.67[b]	0.60[b]	0.99[a]	1.70[a]	1.43[b]	17%/8%[a]
Midazolam	Fluconazole (400 mg; Single Dose)	CYP3A4	CYP3A4 CYP2C9 CYP2C19	Healthy Subjects; African American CYP3A5*X/*X	6	1.97[b]	0.51[b]	0.79[a]	1.61[a]	1.44[b]	16%/8%[a]
Midazolam	Fluconazole (400 mg, 1 Day; 200 mg QD, 5 Days)	CYP3A4	CYP3A4 CYP2C9 CYP2C19	Healthy Subjects	12	2.02[c]	0.49	0.92	1.85[e]	1.52	1%/1%[a]
Midazolam	Itraconazole (200 mg QD; 6 Days)	CYP3A4	CYP3A4 CYP2J2 P-gp	Healthy Subjects	12	3.22[c]	0.31	1.08	3.49[e]	2.41	16%/1%[a]
Midazolam	Ketoconazole (200 mg BID; 2 Days)	CYP3A4	CYP3A4 CYP2C19 P-gp	Healthy Subjects; White	9	5.1	0.21	1.20[a]	5.97[a]	4.12	22%/6%[a]
Midazolam	Ketoconazole (400 mg QD; 4 Days)	CYP3A4	CYP3A4 CYP2C19 P-gp	Healthy Subjects; Korean; Female	12	4.61[c]	0.22	0.57[b]	4.61[b]	1.98	2%/2%[b]
Midazolam*	Nelfinavir (1250 mg BID; 14 Days)	CYP3A4	CYP3A4 Inhibition and Induction	Healthy Subjects	16	1.83	0.57	0.79[a]	1.22[a]	1.41	2%/3%[a]
Midazolam	Rifampin (induction) (600 mg QD; 10 Days)	CYP3A4	CYP3A4 Inhibition and Induction	Healthy Subjects; Korean; Female	12	0.48[c]	2.07	1.01[b]	0.50[b]	0.74	2%/2%[b]
Midazolam*	Rifampin (induction) (600 mg QD; 14 Days)	CYP3A4	CYP3A4 Inhibition and Induction	Healthy Subjects	16	0.44	2.16	1.19[a]	0.54[a]	0.61	4%/3%[a]
Midazolam*	Ritonavir (600 mg TID, 1 Day; 300 mg BID, 6 Days; 400 mg BID, 7	CYP3A4	CYP3A4 Inhibition and Induction	Healthy Subjects	16	3.31	0.29	1.04[a]	3.22[a]	2.85	21%/3%[a]

	Days)										
Theophylline	Cimetidine (400 mg BID; 7 Days)	CYP1A2 CYP3A4 CYP2E1	CYP Enzymes OCT2 MATE1	Healthy; Young Men	8	1.31[c]	0.77	1.10	1.44[e]	1.41	NR
Theophylline	Cimetidine (400 mg BID; 7 Days)	CYP1A2 CYP3A4 CYP2E1	CYP Enzymes OCT2 MATE1	Healthy; Young Women	8	1.42[c]	0.71	1.05	1.48[e]	1.43	NR
Theophylline	Cimetidine (400 mg BID; 7 Days)	CYP1A2 CYP3A4 CYP2E1	CYP Enzymes OCT2 MATE1	Healthy; Elderly Men	8	1.36[c]	0.73	0.98	1.34[e]	1.31	NR
Theophylline	Cimetidine (400 mg BID; 7 Days)	CYP1A2 CYP3A4 CYP2E1	CYP Enzymes OCT2 MATE1	Healthy; Elderly Women	8	1.33[c]	0.75	1.08	1.43[e]	1.36	NR
Theophylline	Cimetidine (1000 mg BD; 7 Days)	CYP1A2 CYP3A4 CYP2E1	CYP Enzymes OCT2 MATE1	Healthy Subjects	7	1.56[d]	0.66[b]	1.02[b]	1.58[f]	1.84[b]	NR
Theophylline	Cimetidine (1000 mg QD; 8 Days)	CYP1A2 CYP3A4 CYP2E1	CYP Enzymes OCT2 MATE1	Healthy Subjects	9	1.33[c]	0.75	1.13[g]	1.83[g]	1.24	19%/5%[g]
Theophylline	Cimetidine (1000 mg QD; 8 Days)	CYP1A2 CYP3A4 CYP2E1	CYP Enzymes OCT2 MATE1	Liver Cirrhosis Patients	9	1.22[c]	0.82	0.97[g]	1.36[g]	1.66	15%/9%[g]
Theophylline	Cimetidine (300 mg QID; 2.75 Days)	CYP1A2 CYP3A4 CYP2E1	CYP Enzymes OCT2 MATE1	Healthy Subjects; Males	5	1.69[d]	0.61	1.11[h]	1.90[h]	1.73	32%/13%[h]
Theophylline	Cimetidine (300 mg QID; 6 Days)	CYP1A2 CYP3A4 CYP2E1	CYP Enzymes OCT2 MATE1	Healthy Subjects	10	1.46[d]	0.74[b]	1.12[a]	1.53[a]	1.38[b]	30%/17%[a]
Theophylline	Cimetidine (400 mg TID; 9 Days)	CYP1A2 CYP3A4 CYP2E1	CYP Enzymes OCT2 MATE1	Healthy; Males	7**	1.42	0.73	1.02[a]	1.30[a]	1.38	13%/8%[a]
Theophylline	Cimetidine*** (800 mg BID; 9.5	CYP1A2 CYP3A4	CYP Enzymes	Chronic Obstructive Pulmonary Disease	15	1.35[d]	0.77[b]	1.10[b]	1.47[b]	1.45[b]	13%/6%[a]

	Days)	CYP2E1	OCT2 MATE1	(COPD) Patients							
Theophylline	Cimetidine (600 mg QID; 6 Days)	CYP1A2 CYP3A4 CYP2E1	CYP Enzymes OCT2 MATE1	Healthy Subjects	8	1.63	0.60	1.07	2.01	1.80	NR
Theophylline	Ciprofloxacin (500 mg BID; 6 Days)	CYP1A2 CYP3A4 CYP2E1	CYP1A2 CYP3A4	Healthy Subjects	8	1.43	0.69	1.04	1.70	1.51	NR
Theophylline	Ciprofloxacin (500 mg BID; 7 Days)	CYP1A2 CYP3A4 CYP2E1	CYP1A2 CYP3A4	Healthy Subjects; Males	8	1.34[d]	0.76[b]	1.02	1.36[e]	1.43[b]	21%/12%[a]
Theophylline	Ciprofloxacin (500 mg BID; 8 Days)	CYP1A2 CYP3A4 CYP2E1	CYP1A2 CYP3A4	Healthy; Young Men	8	1.49[c]	0.67	1.02	1.52[e]	1.51	NR
Theophylline	Ciprofloxacin (500 mg BID; 8 Days)	CYP1A2 CYP3A4 CYP2E1	CYP1A2 CYP3A4	Healthy; Young Women	8	1.50[c]	0.67	1.02	1.53[e]	1.48	NR
Theophylline	Ciprofloxacin (500 mg BID; 8 Days)	CYP1A2 CYP3A4 CYP2E1	CYP1A2 CYP3A4	Healthy; Elderly Men	8	1.42[c]	0.71	1.04	1.47[e]	1.40	NR
Theophylline	Ciprofloxacin (500 mg BID; 8 Days)	CYP1A2 CYP3A4 CYP2E1	CYP1A2 CYP3A4	Healthy; Elderly Women	8	1.40[c]	0.71	1.08	1.51[e]	1.45	NR
Theophylline	Ciprofloxacin (500 mg BID; 6 Days) + Cimetidine (600 mg QID; 6 Days)	CYP1A2 CYP3A4 CYP2E1	CYP1A2 CYP3A4 CYP Enzymes OCT2 MATE1	Healthy Subjects	8	1.80	0.55	1.11	2.26	2.03	NR
Theophylline	Ciprofloxacin (500 mg BID; 15 Days) + Cimetidine (400 mg BID; 8 Days)	CYP1A2 CYP3A4 CYP2E1	CYP1A2 CYP3A4 CYP Enzymes OCT2 MATE1	Healthy; Young Men	8	1.64[c]	0.61	1.08	1.78[e]	1.73	NR
Theophylline	Ciprofloxacin (500 mg BID; 15 Days) + Cimetidine (400 mg BID; 8	CYP1A2 CYP3A4 CYP2E1	CYP1A2 CYP3A4 CYP Enzymes	Healthy; Young Women	8	1.79[c]	0.56	1.02	1.84[e]	1.75	NR

	Days)		OCT2 MATE1								
Theophylline	Ciprofloxacin (500 mg BID; 15 Days) + Cimetidine (400 mg BID; 8 Days)	CYP1A2 CYP3A4 CYP2E1	CYP1A2 CYP3A4 CYP Enzymes OCT2 MATE1	Healthy; Elderly Men	8	1.64[c]	0.61	1.00	1.64[e]	1.64	NR
Theophylline	Ciprofloxacin (500 mg BID; 15 Days) + Cimetidine (400 mg BID; 8 Days)	CYP1A2 CYP3A4 CYP2E1	CYP1A2 CYP3A4 CYP Enzymes OCT2 MATE1	Healthy; Elderly Women	8	1.60[c]	0.63	1.08	1.72[e]	1.68	NR
Theophylline	Diltiazem (120 mg TID; 6 Days)	CYP1A2 CYP3A4 CYP2E1	CYP3A4 CYP1A2 CYP2D6 P-gp	Healthy Subjects	10	1.02[c]	0.98	1.11[g]	1.01[g]	1.06	9%/9%[g]
Theophylline	Enoxacin (200 mg TID; 3 Days)	CYP1A2 CYP3A4 CYP2E1	CYP1A2	Healthy Subjects	5	2.00[c]	0.50	1.09[a]	2.35[a]	2.12	33%/7%[a]
Theophylline	Famotidine (40 mg BID; 6 Days)	CYP1A2 CYP3A4 CYP2E1	Unknown	Healthy Subjects	10	0.95[d]	1.07[b]	1.12[a]	1.06[a]	1.08[b]	17%/16%[a]
Theophylline	Famotidine*** (40 mg BID; 9.5 Days)	CYP1A2 CYP3A4 CYP2E1	Unknown	Chronic Obstructive Pulmonary Disease (COPD) Patients	15	0.99[d]	1.02[b]	1.03[b]	1.02[b]	1.02[b]	6%/6%[a]
Theophylline	Nalidixic Acid (500 mg QID; 7 Days)	CYP1A2 CYP3A4 CYP2E1	Unknown	Healthy Subjects; Males	8	0.99[d]	1.04[b]	1.04	1.02[e]	1.12[b]	NR
Theophylline	Norfloxacin (200 mg TID; 3 Days)	CYP1A2 CYP3A4 CYP2E1	CYP1A2	Healthy Subjects	5	1.08[c]	0.93	1.11[a]	1.29[a]	1.17	13%/7%[a]
Theophylline	Norfloxacin (400 mg BID; 7 Days)	CYP1A2 CYP3A4 CYP2E1	CYP1A2	Healthy Subjects; Males	8	1.17[d]	0.86[b]	1.02	1.19[e]	1.24[b]	18%/12%[a]
Theophylline	Ofloxacin (200 mg TID; 3 Days)	CYP1A2 CYP3A4 CYP2E1	Unknown	Healthy Subjects	5	1.00[c]	1.00	1.08[a]	1.11[a]	1.06	10%/7%[a]
Theophylline	Olanzapine (5 mg 1 Day;	CYP1A2 CYP3A4	Unknown	Healthy; Males	12	0.94	1.04	1.08[a]	1.01[a]	1.02	7%/7%[a]

	7.5 mg 1 Day; 10 mg QD 7 Days)	CYP2E1									
Theophylline	Ranitidine (150 mg BID; 7 Days)	CYP1A2 CYP3A4 CYP2E1	CYP3A CYP2C9 CYP2D6 OCT2	Healthy Subjects	7	1.21[d]	0.92[b]	0.97[b]	1.16[f]	1.28[b]	NR
Theophylline	Verapamil (40 mg TID; 4 Days)	CYP1A2 CYP3A4 CYP2E1	CYP3A4 P-gp	Healthy Subjects, Male, White	12	1.13	0.92	0.98	1.06[e]	1.11	15%/11%[a]
Theophylline	Verapamil (80 mg TID; 4 Days)	CYP1A2 CYP3A4 CYP2E1	CYP3A4 P-gp	Healthy Subjects, Male, White	12	1.19	0.86	0.95	1.11[e]	1.11	16%/11%[a]
Theophylline	Verapamil (120 mg TID; 4 Days)	CYP1A2 CYP3A4 CYP2E1	CYP3A4 P-gp	Healthy Subjects, Male, White	12	1.28	0.82	0.90	1.10[e]	1.25	18%/11%[a]
Theophylline	Verapamil (120 mg TID; 8 Days)	CYP1A2 CYP3A4 CYP2E1	CYP3A4 P-gp	Healthy Subjects	7	1.25[d]	0.81[b]	0.97[b]	1.21[f]	1.22[b]	45%/37%[g]
Theophylline	Verapamil (120 mg QID; 6 Days)	CYP1A2 CYP3A4 CYP2E1	CYP3A4 P-gp	Healthy Subjects	10	1.29[c]	0.77	0.98[g]	1.31[g]	1.33	6%/3%[g]
Tolbutamide	Cimetidine (1000 mg QD, 4 Days; 600 mg 1 Day)	CYP2C9	CYP Enzymes OCT2 MATE1	Healthy	6	1.15[c]	0.87	1.01[a]	1.19[a]	1.13	4%/2%[a]
Tolbutamide	Cimetidine (400 mg QID; 4.5 Days)	CYP2C9	CYP Enzymes OCT2 MATE1	Healthy	6	1.53[c]	0.65	0.96[a]	1.46[a]	1.46	5%/2%[a]
Tolbutamide	Primaquine (45 mg; Single Dose)	CYP2C9	Unknown	Healthy	6	1.04[c]	0.96	0.82[a]	0.89[a]	0.90	2%/4%[a]
Tolbutamide	Sulfaphenazole (500 mg BID; 3.5 Days)	CYP2C9	CYP2C9	Healthy	7	3.10[c]	0.32	0.86[a]	3.21[a]	3.07	26%/4%[a]

Pharmacokinetic values reported in the table are based on published average values, unless otherwise noted

Abbreviations: *AUC*, area under the curve; *CL*, clearance; Con, control; CYP, cytochrome P450; DDI, drug-drug interaction; MATE1, Multidrug and Toxic Extrusion 1; *MRT*, Mean Residence Time; NAT, N, number of

subjects; N-acetyl transferase; NR, not reported; OCT, organic cation transporter; P-gp, P-glycoprotein; *REF*, references; $t_{1/2,z}$,terminal half-life; V_{ss}, volume of distribution at steady state; XO, xanthine oxidase
*Midazolam was dosed IV at the same time as a PO probe cocktail of tolbutamide, dextromethorphan and caffeine
**Interaction arm included n=7 subjects, however the control arm is only n=6 due to one subject dropping out of the study
***A list of additional drugs being taken by these chronic obstructive pulmonary disease subjects can be found in the original article by Bachmann et al. [32]
[a]Ratios are calculated by digitization of published average plasma concentration-time profiles and performing non-compartmental analysis
[b]Ratios are calculated for each individual using published individual PK data; the reported value reflects the average of each individual ratio
[c]*AUC* was calculated with the equation $AUC = dose / CL$ using known dose and reported average values of *CL*
[d]*AUC* was calculated for each individual with the equation $AUC = dose / CL$ using known dose and reported individual values of *CL*; the reported value reflects the average of each individual ratio
[e]*MRT* was calculated with the equation $V_{ss} = CL \cdot MRT$ using reported average values of *CL* and V_{ss}
[f]*MRT* was calculated for each individual with the equation $V_{ss} = CL \cdot MRT$ using reported individual values of *CL* and V_{ss}; the reported value reflects the average of each individual ratio
[g]Ratios are calculated by digitization of a published plasma concentration-time profile of a single representative subject, which may not be reflective of all subjects in the study
[h]Ratios are calculated by digitization of individual published plasma concentration-time profiles and performing non-compartmental analysis; the reported value reflects the average of each individual ratio

Table 4: Intravenous Drug-Drug Interaction Studies with Additional Substrates (Not Cytochrome P450 Index Substrates)

Victim	Perpetrator	Victim Enzymes or Transporters	Perpetrator Enzymes or Transporters	Population	N	$\frac{AUC^{DDI}}{AUC^{Con}}$	$\frac{CL^{DDI}}{CL^{Con}}$	$\frac{V_{ss}^{DDI}}{V_{ss}^{Con}}$	$\frac{MRT^{DDI}}{MRT^{Con}}$	$\frac{t_{1/2,z}^{DDI}}{t_{1/2,z}^{Con}}$	Percent *AUC* Extrapolation
Alfentanil	Fluconazole	CYP3A4	CYP3A4	Healthy Subjects	12	1.2	0.84	0.93[a]	1.18[a]	1.18	2%/1%

	(100 mg; Single Dose)		CYP2C9 CYP2C19								
	+ Ondansetron (4 mg; Single Dose)		Unknown								
	+ Midazolam (1 mg; Single Dose)		Unknown								
Alfentanil	Fluconazole (200 mg; Single Dose)	CYP3A4	CYP3A4 CYP2C9 CYP2C19	Healthy Subjects	12	1.6	0.62	0.89[a]	1.45[a]	1.36	3%/1%
	+ Ondansetron (4 mg; Single Dose)		Unknown								
	+ Midazolam (1 mg; Single Dose)		Unknown								
Alfentanil	Fluconazole (400 mg; Single Dose)	CYP3A4	CYP3A4 CYP2C9 CYP2C19	Healthy Subjects	12	2.2	0.46	0.90[a]	1.92[a]	1.73	5%/1%
	+ Ondansetron (4 mg; Single Dose)		Unknown								
	+ Midazolam (1 mg; Single Dose)		Unknown								
Antipyrine	Cimetidine (1000 mg BD; 7 Days)	CYP Enzymes	CYP Enzymes OCT2 MATE1	Healthy Subjects	7	1.33[d]	0.76[b]	1.05[b]	1.40[f]	1.30[b]	NR
Antipyrine	Ranitidine (150 mg BID; 7 Days)	CYP Enzymes	CYP3A CYP2C9 CYP2D6 OCT2	Healthy Subjects	7	1.08[d]	0.93[b]	1.02[b]	1.09[f]	1.06[b]	NR
Lidocaine	Erythromycin (500 mg QID; 5 days)	CYP3A4 CYP1A2	CYP3A4 P-gp	Healthy Subjects	8	1.19[d]	0.96[b]	1.14[a]	1.19[a]	1.37[b]	28%/23%[a]
	+Midazolam (0.075 mg/kg; Single Dose)		Unknown								

Pharmacokinetic values reported in the table are based on published average values, unless otherwise noted

Abbreviations: *AUC*, area under the curve; *CL*, clearance; Con, control; CYP, cytochrome P450; DDI, drug-drug interaction; MATE1, Multidrug and Toxic Extrusion 1; *MRT*, Mean Residence Time; N, number of subjects; NR, not reported; OCT, organic cation transporter; P-gp, P-glycoprotein; *REF*, references; $t_{1/2,z}$,terminal half-life; V_{ss}, volume of distribution at steady state

[a]Ratios are calculated by digitization of published average plasma concentration-time profiles and performing non-compartmental analysis
[b]Ratios are calculated for each individual using published individual PK data; the reported value reflects the average of each individual ratio
[d]*AUC* was calculated for each individual with the equation $AUC = dose / CL$ using known dose and reported individual values of *CL*; the reported value reflects the average of each individual ratio
[f]*MRT* was calculated for each individual with the equation $V_{ss} = CL \cdot MRT$ using reported individual values of *CL* and V_{ss}; the reported value reflects the average of each individual ratio

Table 5: Drug-Drug Interaction Studies that only Report Terminal Volume of Distribution (V_z)

Victim	Perpetrator	Victim Enzymes or Transporters	Perpetrator Enzymes or Transporters	Population	N	$\frac{AUC^{DDI}}{AUC^{Con}}$	$\frac{CL^{DDI}}{CL^{Con}}$	$\frac{V_z^{DDI}}{V_z^{Con}}$	$\frac{MRT^{DDI}}{MRT^{Con}}$	$\frac{t_{1/2,z}^{DDI}}{t_{1/2,z}^{Con}}$	Percent *AUC* Extrapolation
Antipyrine	Cimetidine (1000 QD; 10 Days)	CYP1A2 CYP2C9 CYP3A4	CYP Enzymes OCT2 MATE1	Healthy Subjects	7	1.41	0.79	1.24	NR	1.59	NR
Desipramine	Disulfiram (500 mg QD; 31 Days)	CYP2D6 CYP3A4	CYP2E1 CYP1A2 CYP2C9 CYP2D6	Healthy Subject; Male	1	1.32	0.76	0.93	NR	1.20	NR
Imipramine	Disulfiram (500 mg QD; 14 Days)	CYP2C19 CYP2D6	CYP2E1 CYP1A2 CYP2C9 CYP2D6	Healthy Subjects; Male	2	1.30[b]	0.77[b]	0.89[b]	NR	1.16[b]	NR
Theophylline	Cimetidine (300 mg PO QID; 1.5 Days)	CYP1A2 CYP3A4 CYP2E1	CYP Enzymes OCT2 MATE1	Healthy Subjects; Male	10	1.27[c]	0.79	1.00	NR	1.24	NR
Theophylline	Cimetidine (300 mg IV Infusion QID; 1.5 Days)	CYP1A2 CYP3A4 CYP2E1	CYP Enzymes OCT MATE1	Healthy Subjects; Male	10	1.21[c]	0.83	1.02	NR	1.20	NR
Theophylline	Cimetidine (400 mg BID; 7 Days)	CYP1A2 CYP3A4 CYP2E1	CYP Enzymes OCT MATE1	Healthy Subjects; Male	6	1.34[c]	0.74	1.04	NR	1.42	NR
Theophylline	Cimetidine (1000 QD; 10 Days)	CYP1A2 CYP3A4 CYP2E1	CYP Enzymes OCT MATE1	Healthy Subjects	7	1.10	0.90	1.04	NR	1.15	NR
Theophylline	Ciprofloxacin (500 mg BID; 7 Days)	CYP1A2 CYP3A4 CYP2E1	CYP1A2 CYP3A4	Healthy Subjects; Male	6	1.48[c]	0.68	1.00	NR	1.47	NR
Theophylline	Ciprofloxacin (400 mg BID; 7 Days) + Cimetidine (500 mg BID; 7	CYP1A2 CYP3A4 CYP2E1	CYP1A2 CYP3A4 CYP Enzymes	Healthy Subjects; Male	6	1.70[c]	0.59	1.00	NR	1.78	NR

	Days)		OCT2 MATE1								
Theophylline	Erythromycin (250 mg QID; 7 Days)	CYP1A2 CYP3A4 CYP2E1	CYP3A4 P-gp	Healthy Subjects; Male	8	1.38[c]	0.74[b]	0.92[b]	NR	1.27[b]	NR

Pharmacokinetic values reported in the table are based on published average values, unless otherwise noted

Abbreviations: *AUC*, area under the curve; *CL*, clearance; Con, control; DDI, drug-drug interaction; MATE1, Multidrug and Toxic Extrusion 1; *MRT*, Mean Residence Time; N, number of subjects; NR, not reported, OCT, organic cation transporter; *REF*, references; $t_{1/2,z}$,terminal half-life; V_z, terminal volume of distribution

[b]Ratios are calculated for each individual using published individual PK data; the reported value reflects the average of each individual ratio

[c]*AUC* was calculated with the equation *AUC = dose / CL* using known dose and reported average values of *CL*

Table 6: Intravenous Pharmacogenomic Interaction Studies and Disease State Drug-Drug Interaction Studies

Drug	Enzyme	Population	N	$\frac{AUC^{\int i}}{AUC^{Con}}$ ¿	$\frac{CL^{\int i}}{CL^{Con}}$ ¿	$\frac{V_{ss}^{\int i}}{V_{ss}^{Con}}$ ¿	$\frac{MRT^{\int i}}{MRT^{Con}}$ ¿	$\frac{t_{1/2,z}^{\int i}}{t_{1/2,z}^{Con}}$ ¿	Percent *AUC* Extrapolation	REF
Metoprolol	**CYP2D6**	**Control**: Healthy Subjects, White, Male, CYP2D6 Extensive Metabolizers; 58-80 kg	3	2.56[c]	0.40	0.51	1.29[e]	1.81[a]	34%/15%[a]	[15]
		Phenotype: Healthy Subjects, White, Male, CYP2D6 Poor Metabolizers; 65-86 kg	4							
Midazolam	**CYP3A**	**Control:** Healthy Subjects, African American, CYP3A5*1/*1; 57-97 kg for all subjects	6	0.98	1.04	0.79[a]	0.70[a]	0.93	8%/14%[a]	[21]
		Phenotype: Healthy Subjects, African-American, CYP3A5*1/*X; 57-97 kg for all subjects	7							
Midazolam	**CYP3A**	**Control:** Healthy Subjects, African American, CYP3A5*1/*1; 57-97 kg for all subjects	6	1.05	0.99	0.72[a]	0.70[a]	0.96	8%/14%[a]	[21]
		Phenotype: Healthy Subjects, African-American, CYP3A5*1/*X; 57-97 kg for all subjects	6							
Theophylline	**CYP1A2 CYP3A4 CYP2E1**	**Control:** Healthy Subjects; average weight 80.7 kg	9	1.54[c]	0.65	0.70[g]	1.2[g]	1.76	8%/14%[a]	[28]
		Disease State: Liver Cirrhosis Patients; average weight 68.6 kg	9							

Pharmacokinetic values reported in the table are based on published average values, unless otherwise noted

Abbreviations: *AUC*, area under the curve; *CL*, clearance; Con, control (indicating the wild-type pharmacogenomic phenotype or healthy subject group); CYP, cytochrome P450; Int, interaction (indicating the reduced function pharmacogenomic phenotype or disease state group); *MRT*, Mean Residence Time; N, number; REF, references; $t_{1/2,z}$, terminal half-life; V_{ss}, volume of distribution at steady state

[a]Ratios are calculated by digitization of published average plasma concentration-time profiles and performing non-compartmental analysis
[c]*AUC* was calculated with the equation $AUC = dose / CL$ using known dose and reported average values of *CL*
[e]*MRT* was calculated with the equation $V_{ss} = CL \cdot MRT$ using reported average values of *CL* and V_{ss}
[g]Ratios are calculated by digitization of a published plasma concentration-time profile of a single representative subject (one healthy subject and one liver cirrhosis patient), which may not be reflective of all subjects in the study

Table 7: Utilization of the Sodhi and Benet Methodology [3] to Discriminate Clearance (CL) from Bioavailability (F) Changes for Orally Dosed Midazolam (Victim) and Clarithromycin (Perpetrator) from the Study of Quinney et al.[17]

Victim	Perpetrator	$\frac{AUC^{DDI}}{AUC^{Control}}$	Percent *AUC* Extrapolation (DDI/ Control)	$\frac{V_{ss}/F^{DDI}}{V_{ss}/F^{Control}}$	$\frac{V_{ss}{}^{DDI}}{V_{ss}{}^{Control}}$	$\frac{F^{DDI}}{F^{Control}}$	$\frac{CL/F^{DDI}}{CL/F^{Control}}$	$\frac{CL^{DDI}}{CL^{Control}}$	REF
Midazolam (IV)	Clarithromycin (500 mg BID; 7 Days)	Observed: 3.2	Observed: 44% / 19%[a]	–	Observed: 1.16[a]	Observed: 2.12	–	Observed: 0.35	[17]
$^{15}N_3$-Midazolam (Oral)	Clarithromycin (500 mg BID; 7 Days)	Observed: 8.2	Observed: 33% / 12%[a]	Observed: 0.35[a]	Assumed: 1	Estimated: 2.84[b]	Observed: 0.14	Estimated: 0.40[b]	[17]

Pharmacokinetic values reported in the table are based on published average values, unless otherwise noted

Abbreviations: *AUC*, area under the curve; *CL*, clearance; DDI, drug-drug interaction; *F*, bioavailability; *REF*, reference; V_{ss}, volume of distribution at steady state

[a]Ratios are calculated by digitization of published average plasma concentration-time profiles and performing non-compartmental analysis

[b]Ratios are calculated for each individual using published individual PK data; the reported value reflects the average of each individual ratio