Volume of Distribution is Unaffected by Metabolic Drug–Drug Interactions

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Abstract
Introduction It has been recognized that significant transporter interactions result in volume of distribution changes in addition to potential changes in clearance. For drugs that are not clinically significant transporter substrates, it is expected that drug–drug interactions would not result in any changes in volume of distribution.

Methods An evaluation of this hypothesis proceeded via an extensive analysis of published intravenous metabolic drug–drug interactions, based on clinically recommended index substrates and inhibitors of major cytochrome P450 (CYP) isoforms.

Results 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 (area under the curve) up to 5.1-fold were observed; however, ratios of $V_{ss}$ changes have a range of 0.70–1.26, with one outlier displaying a $V_{ss}$ ratio of 0.57.

Discussion These results support the widely held founding tenant of pharmacokinetics that clearance and $V_{ss}$ are independent parameters. Knowledge that $V_{ss}$ is unchanged in metabolic drug–drug interactions can be helpful in discriminating changes in clearance from changes in bioavailability ($F$) when only oral dosing data are available, as we have recently demonstrated. As $V_{ss}$ remains unchanged for intravenous metabolic drug–drug interactions, 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 clearance alone from calculations of apparent clearance. Utilization of this simple methodology for orally dosed drugs will have a significant impact on how drug–drug interactions are interpreted from drug development and regulatory perspectives.

1 Introduction

Volume of distribution in pharmacokinetics 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 a drug. It has been recognized that xenobiotic transporters can influence 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 (CL) [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 the 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 CL from changes in bioavailability ($F$) 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...
Key Points

While it is expected that significant xenobiotic transporter interactions will result in volume of distribution changes of a victim drug, metabolic drug interactions 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 the extent of change in the apparent volume of distribution will reflect changes in bioavailability alone due to the unchanged volume of distribution.

Estimates of changes in bioavailability can subsequently be utilized to differentiate changes in clearance alone from measures of apparent clearance following oral dosing, as we have recently demonstrated [3].

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 vs disease-state subjects. Thus, we also analyze changes in $V_{ss}$ of the 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 is listed. This simple system classifies drugs based on solubility and permeability and can anticipate when metabolism vs 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), CL, $V_{ss}$, mean residence time (MRT), and terminal half-life ($t_{1/2,c}$) 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 the tables with a footnote). Although the initial volume of distribution in the central compartment and the terminal volume of distribution ($V_z$) are commonly reported in clinical PK 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 volume of distribution in the central compartment 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 area under the moment curve (AUMC).

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 a 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]:

$$V_{ss} = CL \cdot MRT.$$  

(1)

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

$$MRT = \frac{\text{AUMC}}{\text{AUC}} - \text{MIT},$$  

(2)

where MIT is the 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 ($\tau$), i.e., $\text{MIT} = \tau/2$. For investigations that did not report $V_{ss}$ (or any of the other PK parameters of interest), plasma concentration–time profiles were digitized using WebPlotDigitizer Version 4.2 (Ankit Rohatgi, San Francisco, CA, USA) and analyzed by a non-compartmental analysis with WinNonlin Professional Edition Version 2.1 (Pharsight, Mountain View, CA, USA). 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 PK ratios calculated from digitization of published concentration–time profiles are specifically indicated in the data tables with a footnote. Published values of PK 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 vs digitized, individual vs average PK data used for ratios, equations used, or assumptions made).

The average absolute differences in AUC and $V_{ss}$ were compared to one another for all 72 DDIs, as well as the subset of DDIs with a 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 the degree of change in these two parameters, which indicate the median and 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 PK 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, the AUC ratio range was 0.44–5.1 while the $V_{ss}$ range was 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 a greater than 30% change in $V_{ss}$ (i.e., ratios outside of the range of 0.77–1.30) with ratios of 0.70 [15], 1.40 [18], and 0.57 [24].

An additional ten DDI studies were identified from five studies for which only $V_z$ was reported and $V_{ss}$ could not be determined (due to a lack of published PK profiles) (Table 5). Changes in AUC had a range of 1.10–1.70, but $V_z$ had only a range of 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 the 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 pharmacokinetics of the index substrate alone between groups, $V_{ss}$ for the 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 patients vs patients with liver cirrhosis), 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 and control phases, with a ratio range of 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 had a range of 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 AUCs (or PK parameters derived from AUCs) are unreliable if the slope of the elimination phase is adequately captured. Additionally, the PK 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 because of 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 because of the lack of published IV PK 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 vs 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 enzymes [15, 21]. To examine the potential impact of inter-individual differences in $V_{ss}$, the PK 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

| Substrate | BDDCS class | Enzyme | Other relevant enzymes/transporters | Refs. |
|-----------|-------------|--------|-------------------------------------|-------|
| Antipyrine | 1           | CYP1A2 | Multiple CYPs (2A6, 2B6, 2C, 2E1)   | [7]   |
|           |             | CYP2C9 |                                     |       |
|           |             | CYP3A  |                                     |       |
| Alfentanil| 1           | CYP3A  | –                                   | [5]   |
| Caffeine  | 1           | CYP1A2 | Xanthine oxidase                   | [4]   |
|           |             |        | N-Acetyl transferase               |       |
| 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                             | [4]   |
|           |             |        | CYP3A                              |       |
| Tolbutamide| 2          | CYP2C9 | OAT2                               | [4, 10]|

**BDDCS** Biopharmaceutics Drug Disposition Classification System, **CYP** cytochrome P450, **OAT** organic anion transporter, **Refs** references.
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 and extensive metabolizers 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 extensive metabolizers than poor metabolizers, with CV values of 44% and 22%, respectively. The issue of variability between individuals is further

**Table 2** Inhibitory specificities of clinical index inhibitors and additional perpetrator drugs

| Index inhibitor       | BDDCS class | Enzyme          | Other relevant enzymes/transporters | Refs |
|-----------------------|-------------|-----------------|-------------------------------------|------|
| Cimetidine            | 3           | OCT2 CYP2C19 CYP3A | MATE1 CYP1A2 CYP2C9 CYP2D6         | [5]  |
| Ciprofloxacin         | 4           | CYP1A2          | CYP3A4                              | [4]  |
| Clarithromycin        | 3           | CYP3A4          | CYP2C19                             | [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         |                                    | [4]  |
| 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         |                                     | [4]  |
| Nelfinavir            | 2           | CYP3A4          | CYP2D6                              | [8]  |
| Norfloxacin           | 4           | CYP1A2          |                                     | [9]  |
| Ofloxacin             | 3           | Unknown         |                                     | [4]  |
| Olanzapine            | 2           | Unknown         |                                     | [4]  |
| Ondansetron           | 1           | Unknown         |                                     | [4]  |
| Primaquine            | 1           | Unknown         |                                     | [4]  |
| 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)       | (Inducer)                           | [6]  |
| Ritonavir (single dose)| 2          | CYP3A4          | P-gp                                | [4]  |
| Ritonavir (multiple dose)| 2         | CYP2C9          |                                     | [4]  |
| Sulfaphenazole        | 1           | CYP induction   |                                     | [4]  |
| Terbinafine           | 2           | CYP2D6          | CYP1A2                              | [4]  |
| Verapamil             | 1           | CYP3A4          | P-gp                                | [4]  |

* BDDCS: Biopharmaceutics Drug Disposition Classification System, *CYP* cytochrome P450, *MATE* Multidrug and Toxic Excretion, *OCT* organic cation transporter, *P-gp* P-glycoprotein, *Refs* references
| Victim | Perpetrator | Victim enzymes or transporters | Perpetrator enzymes or transporters | Population | N | AUC<sub>DDI</sub> / AUC<sub>Con</sub> | \( \Delta \text{CL} \) DDI / \( \Delta \text{CL} \) Con | \( \Delta \text{V} \) DDI / \( \Delta \text{V} \) Con | MRT<sub>DDI</sub> / MRT<sub>Con</sub> | Percent AUC extrapolation | Refs. |
|--------|-------------|--------------------------------|-----------------------------------|------------|---|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-------|
| Caffeine | Ketoconazole (400 mg; single dose) | CYPA2 NAT XO | CYP2A4 CYP2C19 | Healthy subjects | 8 | 1.17<sup>b</sup> 0.88<sup>b</sup> 0.97<sup>a</sup> 1.14<sup>a</sup> 1.18<sup>b</sup> 36%/30%<sup>a</sup> | [14] |
| Caffeine | Terbinafine (500 mg; single dose) | CYPA2 NAT XO | CYP2D6 CYP1A2 | Healthy subjects | 8 | 1.31<sup>b</sup> 0.81<sup>b</sup> 1.05<sup>a</sup> 1.48<sup>a</sup> 1.35<sup>b</sup> 45%/30%<sup>a</sup> | [14] |
| Metoprolol | Quinidine (50 mg; single dose) | CYP2D6 CYP3A4 | CYP2D6 P-gp | Healthy subjects; male, white, CYP2D6 extensive metabolizers | 3 | 2.43<sup>d</sup> 0.44<sup>b</sup> 0.87<sup>b</sup> 2.06<sup>f</sup> 1.56<sup>a</sup> 29%/15%<sup>a</sup> | [15] |
| Metoprolol | Quinidine (250 mg BID; 3 days) | CYP2D6 CYP3A4 | CYP2D6 P-gp | Healthy subjects; male, white, CYP2D6 extensive metabolizers | 4 | 3.08<sup>d</sup> 0.36<sup>b</sup> 0.70<sup>b</sup> 1.99<sup>f</sup> 2.36<sup>a</sup> 44%/15%<sup>a</sup> | [15] |
| Metoprolol | Quinidine (50 mg; single dose) | CYP2D6 CYP3A4 | CYP2D6 P-gp | Healthy subjects; male, white, CYP2D6 extensive metabolizers | 3 | 1.12<sup>d</sup> 0.98<sup>b</sup> 1.18<sup>f</sup> 1.30<sup>f</sup> 1.09<sup>a</sup> 35%/34%<sup>a</sup> | [15] |
| Metoprolol | Quinidine (250 mg BID; 3 days) | CYP2D6 CYP3A4 | CYP2D6 P-gp | Healthy subjects; male, white, CYP2D6 poor metabolizers | 3 | 1.26<sup>d</sup> 0.88<sup>b</sup> 1.26<sup>f</sup> 1.39<sup>f</sup> 1.32<sup>a</sup> 43%/34%<sup>a</sup> | [15] |
| Midazolam | Clarithromycin (500 mg BID; 7 days) | CYP3A4 | CYP3A4 CYP2C19 P-gp | Healthy subjects | 16 | 2.66 0.37 1.05<sup>a</sup> 2.79<sup>g</sup> 2.66 38%/12%<sup>a</sup> | [16] |
| Midazolam | Clarithromycin (500 mg BID; 7 days) | CYP3A4 | CYP3A4 CYP2C19 P-gp | Healthy subjects; elderly | 16 | 3.2 0.35 1.16<sup>a</sup> 2.24<sup>a</sup> 4.06 44%/20%<sup>a</sup> | [17] |
| Midazolam | Erythromycin (500 mg TID; 7 days) | CYP3A4 | CYP3A4 P-gp | Healthy subjects | 6 | 2.17<sup>c</sup> 0.46 1.40 3.03<sup>c</sup> 1.77 NR | [18] |
| Midazolam | Erythromycin (500 mg QID; 5 days) + Lidocaine (1 mg/kg; 2 days) | CYP3A4 | CYP3A4 P-gp | Healthy subjects | 8 | 1.60<sup>d</sup> 0.71<sup>b</sup> 0.93<sup>a</sup> 1.31<sup>a</sup> 1.50<sup>b</sup> 19%/13%<sup>a</sup> | [19] |
| Midazolam | Fluconazole (100 mg; single dose) | CYP3A4 | CYP3A4 CYP2C9 CYP2C19 | Healthy subjects | 12 | 1.3 0.78 1.01<sup>a</sup> 1.28<sup>a</sup> 1.16 10%/7%<sup>a</sup> | [20] |
| Midazolam | Fluconazole (200 mg; single dose) | CYP3A4 | CYP3A4 CYP2C9 CYP2C19 | Healthy subjects | 12 | 1.4 0.68 1.10<sup>a</sup> 1.68<sup>a</sup> 1.20 11%/7%<sup>a</sup> | [20] |
| Midazolam | Fluconazole (400 mg; single dose) | CYP3A4 | CYP3A4 CYP2C9 CYP2C19 | Healthy subjects | 12 | 2.0 0.54 0.93<sup>a</sup> 1.73<sup>a</sup> 1.56 17%/7%<sup>a</sup> | [20] |
| Midazolam | Fluconazole (400 mg; single dose) | CYP3A4 | CYP3A4 CYP2C9 CYP2C19 | Healthy subjects; African American CYP3A5*1/*1 | 6 | 1.62<sup>b</sup> 0.64<sup>b</sup> 0.81<sup>a</sup> 1.15<sup>a</sup> 1.35<sup>b</sup> 17%/14%<sup>a</sup> | [21] |
## Table 3 (continued)

| Victim | Perpetrator | Victim enzymes or transporters | Perpetrator enzymes or transporters | Population | N  |\( \text{AUC}_{\text{DDI}} \) |\( \text{CL}_{\text{DDI}} \) |\( \text{V}_{\text{ss,DDI}} \) |\( \text{MRT}_{\text{DDI}} \) |\( \text{AUC}_{\text{Con}} \) extrapolation | Refs. |
|--------|-------------|-------------------------------|-------------------------------------|------------|----|----------------|----------------|----------------|----------------|-----------------|-------|
| Midazolam | Fluconazole (400 mg; single dose) | CYP3A4 | CYP3A4, CYP2C9, CYP2C19 | Healthy subjects; African American CYP3A5*1/*X | 7 | 1.67<sup>b</sup> | 0.60<sup>b</sup> | 0.99<sup>a</sup> | 1.70<sup>a</sup> | 1.43<sup>b</sup> | 17%/8%<sup>a</sup> | [21] |
| Midazolam | Fluconazole (400 mg; single dose) | CYP3A4 | CYP3A4, CYP2C9, CYP2C19 | Healthy subjects; African American CYP3A5*1/*X | 6 | 1.97<sup>b</sup> | 0.51<sup>b</sup> | 0.79<sup>a</sup> | 1.61<sup>a</sup> | 1.44<sup>b</sup> | 16%/8%<sup>a</sup> | [21] |
| Midazolam | Fluconazole (400 mg, 1 day; 200 mg QD, 5 days) | CYP3A4 | CYP3A4, CYP2C9, CYP2C19 | Healthy subjects | 12 | 2.02<sup>c</sup> | 0.49 | 0.92 | 1.85<sup>c</sup> | 1.52 | 1%/1%<sup>a</sup> | [22] |
| Midazolam | Itraconazole (200 mg QD; 6 days) | CYP3A4 | CYP3A4, CYP2C9, CYP2C19 | Healthy subjects | 12 | 3.22<sup>c</sup> | 0.31 | 1.08 | 3.49<sup>c</sup> | 2.41 | 16%/1%<sup>a</sup> | [22] |
| Midazolam | Ketoconazole (200 mg BID; 2 days) | CYP3A4 | CYP3A4, CYP2C9, P-gp | Healthy subjects; white | 9 | 5.1 | 0.21 | 1.20<sup>a</sup> | 5.97<sup>a</sup> | 4.12 | 22%/6%<sup>a</sup> | [23] |
| Midazolam | Ketoconazole (400 mg QD; 4 days) | CYP3A4 | CYP3A4, CYP2C9, P-gp | Healthy subjects; female, Korean | 12 | 4.61<sup>c</sup> | 0.22 | 0.57<sup>b</sup> | 4.61<sup>b</sup> | 1.98 | 2%/2%<sup>b</sup> | [24] |
| Midazolam<sup>i</sup> | Nelfinavir (1250 mg BID; 14 days) | CYP3A4 | CYP3A4, CYP2C19, P-gp | Healthy subjects | 16 | 1.83 | 0.57 | 0.79<sup>a</sup> | 1.22<sup>a</sup> | 1.41 | 2%/3%<sup>a</sup> | [25] |
| Midazolam<sup>i</sup> | Rifampin [induction] (600 mg QD; 10 days) | CYP3A4 | CYP3A4, CYP2C19, P-gp | Healthy subjects; female, Korean | 12 | 0.48<sup>c</sup> | 2.07 | 1.01<sup>b</sup> | 0.50<sup>b</sup> | 0.74 | 2%/2%<sup>b</sup> | [24] |
| Midazolam<sup>i</sup> | Rifampin [induction] (600 mg QD; 14 days) | CYP3A4 | CYP3A4, CYP2C19, P-gp | Healthy subjects | 16 | 0.44 | 2.16 | 1.19<sup>a</sup> | 0.54<sup>a</sup> | 0.61 | 4%/3%<sup>a</sup> | [25] |
| Midazolam<sup>i</sup> | Ritonavir (600 mg TID; 1 day; 300 mg BID; 6 days; 400 mg BID; 7 days) | CYP3A4 | CYP3A4, CYP2C19, P-gp | Healthy subjects | 16 | 3.31 | 0.29 | 1.04<sup>a</sup> | 3.22<sup>a</sup> | 2.85 | 21%/3%<sup>a</sup> | [25] |
| Theophylline | Cimetidine (400 mg BID; 7 days) | CYP1A2, CYP3A4, CYP2E1 | CYP enzymes, OCT2, MATE1 | Healthy subjects; male, young | 8 | 1.31<sup>c</sup> | 0.77 | 1.10 | 1.44<sup>c</sup> | 1.41 | NR | [26] |
| Theophylline | Cimetidine (400 mg BID; 7 days) | CYP1A2, CYP3A4, CYP2E1 | CYP enzymes, OCT2, MATE1 | Healthy subjects; female, young | 8 | 1.42<sup>c</sup> | 0.71 | 1.05 | 1.48<sup>c</sup> | 1.43 | NR | [26] |
| Theophylline | Cimetidine (400 mg BID; 7 days) | CYP1A2, CYP3A4, CYP2E1 | CYP enzymes, OCT2, MATE1 | Healthy; male, elderly | 8 | 1.36<sup>c</sup> | 0.73 | 0.98 | 1.34<sup>c</sup> | 1.31 | NR | [26] |
| Theophylline | Cimetidine (400 mg BID; 7 days) | CYP1A2, CYP3A4, CYP2E1 | CYP enzymes, OCT2, MATE1 | Healthy; female, elderly | 8 | 1.33<sup>c</sup> | 0.75 | 1.08 | 1.43<sup>c</sup> | 1.36 | NR | [26] |
| Victim | Perpetrator | Victim enzymes or transporters | Perpetrator enzymes or transporters | Population | N  | AUC<sub>DDI</sub> | CL/CL<sub>Con</sub> | V<sub>ss</sub><sup>Con</sup> | MRT<sub>DDI</sub> | MRT<sub>Con</sub> | Percent AUC extrapolation | Refs. |
|--------|-------------|-------------------------------|------------------------------------|------------|----|-----------------|-----------------|----------------|----------------|----------------|--------------------------|------|
| Theophylline Cimetidine (1000 mg QD; 7 days) | CYP1A2 | CYP enzymes | OCT2 | Healthy subjects | 7 | 1.56<sup>d</sup> | 0.66<sup>b</sup> | 1.02<sup>b</sup> | 1.58<sup>f</sup> | 1.84<sup>b</sup> | NR | [27] |
| Theophylline Cimetidine (1000 mg QD; 8 days) | CYP1A2 | CYP enzymes | OCT2 | Healthy subjects | 9 | 1.33<sup>e</sup> | 0.75 | 1.13<sup>g</sup> | 1.83<sup>e</sup> | 1.24 | 19%/5%<sup>e</sup> | [28] |
| Theophylline Cimetidine (1000 mg QD; 8 days) | CYP1A2 | CYP enzymes | OCT2 | Patients with liver cirrhosis | 9 | 1.22<sup>c</sup> | 0.82 | 0.97<sup>g</sup> | 1.36<sup>d</sup> | 1.66 | 15%/9%<sup>g</sup> | [28] |
| Theophylline Cimetidine (300 mg QID; 2.75 days) | CYP1A2 | CYP enzymes | OCT2 | Healthy subjects; male | 5 | 1.69<sup>d</sup> | 0.61 | 1.11<sup>h</sup> | 1.90<sup>h</sup> | 1.73 | 32%/13%<sup>h</sup> | [29] |
| Theophylline Cimetidine (300 mg QID; 6 days) | CYP1A2 | CYP enzymes | OCT2 | Healthy subjects | 10 | 1.46<sup>d</sup> | 0.74<sup>b</sup> | 1.12<sup>a</sup> | 1.53<sup>a</sup> | 1.38<sup>b</sup> | 30%/17%<sup>a</sup> | [30] |
| Theophylline Cimetidine (400 mg TID; 9 days) | CYP1A2 | CYP enzymes | OCT2 | Healthy subjects; male | 7<sup>j</sup> | 1.42 | 0.73 | 1.02<sup>a</sup> | 1.30<sup>a</sup> | 1.38 | 13%/8%<sup>a</sup> | [31] |
| Theophylline Cimetidine<sup>e</sup> (800 mg BID; 9.5 days) | CYP1A2 | CYP enzymes | OCT2 | Patients with chronic obstructive pulmonary disease | 15 | 1.35<sup>d</sup> | 0.77<sup>b</sup> | 1.10<sup>b</sup> | 1.47<sup>b</sup> | 1.45<sup>b</sup> | 13%/6%<sup>a</sup> | [32] |
| Theophylline Cimetidine (600 mg QID; 6 days) | CYP1A2 | CYP enzymes | OCT2 | Healthy subjects | 8 | 1.63 | 0.60 | 1.07 | 2.01 | 1.80 | NR | [33] |
| Theophylline Ciprofloxacin (500 mg BID; 6 days) | CYP1A2 | CYP enzyme | MATE1 | Healthy subjects | 8 | 1.43 | 0.69 | 1.04 | 1.70 | 1.51 | NR | [33] |
| Theophylline Ciprofloxacin (500 mg BID; 7 days) | CYP1A2 | CYP enzyme | MATE1 | Healthy subjects; male | 8 | 1.34<sup>d</sup> | 0.76<sup>b</sup> | 1.02<sup>a</sup> | 1.36<sup>e</sup> | 1.43<sup>b</sup> | 21%/12%<sup>a</sup> | [34] |
| Theophylline Ciprofloxacin (500 mg BID; 8 days) | CYP1A2 | CYP enzyme | MATE1 | Healthy subjects; male, young | 8 | 1.49<sup>f</sup> | 0.67 | 1.02 | 1.52<sup>e</sup> | 1.51 | NR | [26] |
| Theophylline Ciprofloxacin (500 mg BID; 8 days) | CYP1A2 | CYP enzyme | MATE1 | Healthy subjects; female, young | 8 | 1.50<sup>f</sup> | 0.67 | 1.02 | 1.53<sup>e</sup> | 1.48 | NR | [26] |
| Theophylline Ciprofloxacin (500 mg BID; 8 days) | CYP1A2 | CYP enzyme | MATE1 | Healthy subjects; male, elderly | 8 | 1.42<sup>e</sup> | 0.71 | 1.04 | 1.47<sup>e</sup> | 1.40 | NR | [26] |
| Victim                  | Perpetrator                          | Victim enzymes or transporters | Perpetrator enzymes or transporters | Population               | N  | AUC<sub>DDI</sub> / AUC<sub>Con</sub> | CL<sub>DDI</sub> / CL<sub>Con</sub> | V<sub>ss</sub><sup>DDI</sup> / V<sub>ss</sub><sup>Con</sup> | MRT<sub>DDI</sub> / MRT<sub>Con</sub> | Percent AUC extrapolation | Refs. |
|------------------------|--------------------------------------|-------------------------------|----------------------------------|--------------------------|----|----------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|------|
| Theophylline           | Ciprofloxacin (500 mg BID; 8 days)   | CYP1A2                        | CYP1A2                           | Healthy subjects; female, elderly | 8  | 1.40<sup>a</sup>                  | 0.71                            | 1.08                            | 1.51<sup>b</sup>                | 1.45                             | NR   | [26]  |
| Theophylline           | Ciprofloxacin (500 mg BID; 6 days)   | CYP1A2                        | CYP1A2                           | Healthy subjects         | 8  | 1.80                            | 0.55                            | 1.11                            | 2.26                            | 2.03                             | NR   | [33]  |
| Theophylline           | Ciprofloxacin (500 mg BID; 15 days)  | CYP1A2                        | CYP1A2                           | Healthy subjects; male, young | 8  | 1.64<sup>c</sup>                  | 0.61                            | 1.08                            | 1.78<sup>c</sup>                | 1.73                             | NR   | [26]  |
| Theophylline           | Ciprofloxacin (500 mg BID; 15 days)  | CYP1A2                        | CYP1A2                           | Healthy subjects; female, young | 8  | 1.79<sup>c</sup>                  | 0.56                            | 1.02                            | 1.84<sup>c</sup>                | 1.75                             | NR   | [26]  |
| Theophylline           | Ciprofloxacin (500 mg BID; 15 days)  | CYP1A2                        | CYP1A2                           | Healthy subjects; female, elderly | 8  | 1.64<sup>c</sup>                  | 0.61                            | 1.00                            | 1.64<sup>c</sup>                | 1.64                             | NR   | [26]  |
| Theophylline           | Ciprofloxacin (500 mg BID; 15 days)  | CYP1A2                        | CYP1A2                           | Healthy subjects; female, elderly | 8  | 1.60<sup>c</sup>                  | 0.63                            | 1.08                            | 1.72<sup>c</sup>                | 1.68                             | NR   | [26]  |
| Theophylline           | Diltiazem (120 mg TID; 6 days)       | CYP1A2                        | CYP3A4                           | Healthy subjects         | 10 | 1.02<sup>c</sup>                  | 0.98                            | 1.11<sup>a</sup>               | 1.01<sup>c</sup>                | 1.06                             | 9%/9%<sup>a</sup>               | [35] |
| Theophylline           | Enoxacin (200 mg TID; 3 days)        | CYP1A2                        | CYP1A2                           | Healthy subjects         | 5  | 2.00<sup>c</sup>                  | 0.50                            | 1.09<sup>a</sup>               | 2.35<sup>a</sup>                | 2.12                             | 33%/7%<sup>a</sup>              | [36] |
| Theophylline           | Famotidine (40 mg BID; 6 days)       | CYP1A2                        | CYP3A4                           | Healthy subjects         | 10 | 0.95<sup>c</sup>                  | 1.07<sup>b</sup>                | 1.12<sup>a</sup>               | 1.06<sup>a</sup>                | 1.08<sup>b</sup>                | 17%/16%<sup>a</sup>             | [30] |
| Victim               | Perpetrator                          | Victim enzymes or transporters | Perpetrator enzymes or transporters | Population                                                                 | N | $\text{AUC}_{\text{DDI}}$ | $\text{AUC}_{\text{Con}}$ | $\text{CL}_{\text{DDI}}$ | $\text{CL}_{\text{Con}}$ | MRT$\text{DDI}$ | MRT$\text{Con}$ | $\%\text{AUC}$ extrapolation | Refs. |
|---------------------|--------------------------------------|---------------------------------|-------------------------------------|-----------------------------------------------------------------------------|---|---------------------|---------------------|---------------------|---------------------|----------------|-----------------|----------------------|-------|
| Theophylline        | Famotidine (40 mg BID; 9.5 days)     | CYP1A2, CYP3A4, CYP2E1          | Unknown                             | Patients with chronic obstructive pulmonary disease                        | 15 | 0.99$^d$           | 1.02$^b$           | 1.03$^b$           | 1.02$^b$           | 1.02$^b$       | 6%/6%$^a$           | [32]  |
| Theophylline        | Nalidixic acid (500 mg QID; 7 days)  | CYP1A2, CYP3A4, CYP2E1          | Unknown                             | Healthy subjects; male                                                      | 8  | 0.99$^d$           | 1.04$^b$           | 1.04$^e$           | 1.02$^g$           | 1.12$^h$       | NR               | [34]  |
| Theophylline        | Norfloxacin (200 mg TID; 3 days)     | CYP1A2                          | CYP1A2                              | Healthy subjects                                                            | 5  | 1.08$^e$           | 0.93               | 1.11$^a$           | 1.29$^a$           | 1.17            | 13%/7%$^a$         | [36]  |
| Theophylline        | Norfloxacin (400 mg BID; 7 days)     | CYP1A2, CYP3A4, CYP2E1          | CYP1A2                              | Healthy subjects; male                                                      | 8  | 1.17$^d$           | 0.86$^b$           | 1.02$^e$           | 1.19$^f$           | 1.24$^b$       | 18%/12%$^a$       | [34]  |
| Theophylline        | Ofloxacin (200 mg TID; 3 days)       | CYP1A2, CYP3A4, CYP2E1          | Unknown                             | Healthy subjects                                                            | 5  | 1.00$^d$           | 1.00               | 1.08$^a$           | 1.11$^a$           | 1.11$^a$       | 10%/7%$^a$         | [36]  |
| Theophylline        | Olanzapine (5 mg; 1 day; 7.5 mg; 1 day; 10 mg QD; 7 days) | CYP1A2, CYP3A4, CYP2E1          | Unknown                             | Healthy subjects; male                                                      | 12 | 0.94               | 1.04               | 1.08$^a$           | 1.11$^a$           | 1.02            | 7%/7%$^a$          | [31]  |
| 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               | [27]  |
| 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$^b$           | 1.11$^a$       | 15%/11%$^a$      | [37]  |
| 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$^c$           | 1.11$^a$       | 16%/11%$^a$      | [37]  |
| 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%$^a$      | [37]  |
| Theophylline        | Verapamil (120 mg TID; 8 days)       | CYP1A2, CYP3A4, CYP2E1          | CYP3A4, P-gp                        | Healthy subjects                                                            | 7  | 1.25$^e$           | 0.81$^b$           | 0.97$^b$           | 1.21$^f$           | 1.22$^b$       | 45%/37%$^a$      | [38]  |
| Theophylline        | Verapamil (120 mg QID; 6 days)       | CYP1A2, CYP3A4, CYP2E1          | CYP3A4, P-gp                        | Healthy subjects                                                            | 10 | 1.29$^e$           | 0.77               | 0.98$^g$           | 1.31$^e$           | 1.33            | 6%/3%$^a$         | [35]  |
| Tolbutamide         | Cimetidine (1000 mg QD; 4 days; 600 mg, 1 day) | CYP2C9                           | CYP enzymes OCT2, MATE1             | Healthy subjects                                                            | 6  | 1.15$^e$           | 0.87               | 1.01$^a$           | 1.19$^a$           | 1.13           | 4%/2%$^a$         | [39]  |
## Table 3 (continued)

| Victim                  | Perpetrator          | Victim enzymes or transporters | Perpetrator enzymes or transporters | Population          | N | $\text{AUC}_{\text{DDI}}/\text{AUC}_{\text{Con}}$ | $\text{CL}_{\text{DDI}}/\text{CL}_{\text{Con}}$ | $\text{V}_{\text{ss,DDI}}/\text{V}_{\text{ss,Con}}$ | $\text{MRT}_{\text{DDI}}/\text{MRT}_{\text{Con}}$ | Percent AUC extrapolation | Refs. |
|-------------------------|----------------------|--------------------------------|-------------------------------------|---------------------|---|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-------|
| Tolbutamide             | Cimetidine (400 mg QID; 4.5 days) | CYP2C9                          | CYP enzymes OCT2 MATE1              | Healthy subjects    | 6 | 1.53$^f$                                      | 0.65                                         | 0.96$^a$                                      | 1.46                                         | 1.46                                          | 5%/2%$^a$ | [39]  |
| Tolbutamide             | Primaquine (45 mg single dose)     | CYP2C9                          | Unknown                              | Healthy subjects    | 6 | 1.04$^f$                                      | 0.96                                         | 0.82$^a$                                      | 0.89$^a$                                      | 0.90                                          | 2%/4%$^a$ | [39]  |
| Tolbutamide             | Sulfaphenazole (500 mg BID; 3.5 days) | CYP2C9                          | CYP2C9                               | Healthy subjects    | 7 | 3.10$^f$                                      | 0.32                                         | 0.86$^a$                                      | 3.21$^a$                                      | 3.07                                          | 26%/4%$^a$ | [39]  |

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

- $\text{AUC}$ area under the curve, $\text{BID}$ twice daily, $\text{CL}$ clearance, $\text{Con}$ control, $\text{MATE1}$ Multidrug and Toxic Extrusion 1, $\text{MRT}$ mean residence time, $\text{NAT}$ N-acetyl transferase, $\text{NR}$ not reported, $\text{OCT}$ organic cation transporter, $\text{P-gp}$ P-glycoprotein, $\text{QD}$ once daily, $\text{QID}$ four times a day, $t_{1/2,z}$ terminal half-life, $\text{Refs}$ reference, $\text{TID}$ three times a day, $V_{ss}$ volume of distribution at steady state, $\text{XO}$ xanthine oxidase
- $^a$Ratios are calculated by digitization of published average plasma concentration–time profiles and performing a non-compartmental analysis
- $^b$Ratios are calculated for each individual using published individual pharmacokinetic data; the reported value reflects the average of each individual ratio
- $^c$AUC was calculated with the equation $\text{AUC} = \text{dose}/\text{CL}$ using known dose and reported average values of CL
- $^d$AUC was calculated for each individual with the equation $\text{AUC} = \text{dose}/\text{CL}$ 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 $V_{ss} = \text{CL} \cdot \text{MRT}$ using reported average values of CL and $V_{ss}$
- $^f$MRT was calculated for each individual with the equation $V_{ss} = \text{CL} \cdot \text{MRT}$ 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 a non-compartmental analysis; the reported value reflects the average of each individual ratio
- $^i$Midazolam was dosed intravenously at the same time as an oral probe cocktail of tolbutamide, dextromethorphan, and caffeine
- $^j$Interaction arm included $n=7$ subjects; however, the control arm is only $n=6$ as one subject dropped out of the study
- $^k$A list of additional drugs being taken by these subjects with chronic obstructive pulmonary disease can be found in the original article by Bachmann et al. [32]
Table 4 Intravenous drug–drug interaction (DDI) studies with additional substrates (not cytochrome P450 [CYP] index substrates)

| Victim | Perpetrator | Victim enzymes or transporters | Perpetrator enzymes or transporters | Population | N | AUC<sub>con</sub>/AUC<sup>ext</sup> | CL<sub>con</sub>/CL<sup>ext</sup> | V<sub>ss</sub><sup>con</sup>/V<sub>ss</sub><sup>ext</sup> | MRT<sub>con</sub>/MRT<sup>ext</sup> | Percent AUC extrapolation | Refs. |
|--------|-------------|--------------------------------|-------------------------------------|------------|---|-------------------------------|----------------|----------------|----------------|-----------------------------|-------|
| Alfentanil | Fluconazole (100 mg; single dose) | CYP3A4 | CYP3A4 CYP2C9 CYP2C19 | Healthy subjects | 12 | 1.2 | 0.84 | 0.93<sup>a</sup> | 1.18<sup>a</sup> | 1.18 | 2%/1% | [20] |
| | + Ondansetron (4 mg; single dose) | Unknown | Unknown | | | | | | | | | |
| | + Midazolam (1 mg; single dose) | Unknown | Unknown | | | | | | | | | |
| Alfentanil | Fluconazole (200 mg; single dose) | CYP3A4 | CYP3A4 CYP2C9 CYP2C19 | Healthy subjects | 12 | 1.6 | 0.62 | 0.89<sup>a</sup> | 1.45<sup>a</sup> | 1.36 | 3%/1% | [20] |
| | + Ondansetron (4 mg; single dose) | Unknown | Unknown | | | | | | | | | |
| | + Midazolam (1 mg; single dose) | Unknown | Unknown | | | | | | | | | |
| Alfentanil | Fluconazole (400 mg; single dose) | CYP3A4 | CYP3A4 CYP2C9 CYP2C19 | Healthy subjects | 12 | 2.2 | 0.46 | 0.90<sup>a</sup> | 1.92<sup>a</sup> | 1.73 | 5%/1% | [20] |
| | + Ondansetron (4 mg; single dose) | Unknown | Unknown | | | | | | | | | |
| | + Midazolam (1 mg; single dose) | Unknown | Unknown | | | | | | | | | |
| Antipyrine | Cimetidine (1000 mg BID; 7 days) | CYP enzymes | CYP enzymes OCT2 MATE1 | Healthy subjects | 7 | 1.33<sup>d</sup> | 0.76<sup>b</sup> | 1.05<sup>b</sup> | 1.40<sup>f</sup> | 1.30<sup>b</sup> | NR | [27] |
| Antipyrine | Ranitidine (150 mg BID; 7 days) | CYP enzymes | CYP3A CYP2C9 CYP2D6 OCT2 | Healthy subjects | 7 | 1.08<sup>d</sup> | 0.93<sup>b</sup> | 1.02<sup>b</sup> | 1.09<sup>f</sup> | 1.06<sup>b</sup> | NR | [27] |
| Lidocaine | Erythromycin (500 mg QID; 5 days) | CYP3A4 CYP1A2 | CYP3A4 P-gp | Healthy subjects | 8 | 1.19<sup>d</sup> | 0.96<sup>b</sup> | 1.14<sup>a</sup> | 1.19<sup>a</sup> | 1.37<sup>b</sup> | 28%/23%<sup>a</sup> | [19] |
| | + Midazolam (0.075 mg/kg; single dose) | Unknown | Unknown | | | | | | | | | |

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

- **AUC** area under the curve, **BID** twice daily, **CL** clearance, **Con** control, **MATE1** Multidrug and Toxic Extrusion 1, **MRT** mean residence time, **NR** not reported, **OCT** organic cation transporter, **P-gp** P-glycoprotein, **QID** four times a day, **Refs** reference, **t<sub>1/2,z</sub>** terminal half-life, **V<sub>ss</sub>** volume of distribution at steady state

- **<sup>a</sup>Ratios are calculated by digitization of published average plasma concentration–time profiles and performing a non-compartmental analysis**
- **<sup>b</sup>Ratios are calculated for each individual using published individual pharmacokinetic data; the reported value reflects the average of each individual ratio**
- **<sup>c</sup>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**
- **<sup>d</sup>MRT was calculated for each individual with the equation V<sub>ss</sub> = CL·MRT using reported individual values of CL and V<sub>ss</sub>; the reported value reflects the average of each individual ratio**
Table 5  Drug–drug interaction (DDI) studies that only report terminal volume of distribution ($V_z$)

| Victim | Perpetrator | Victim enzymes or transporters | Perpetrator enzymes or transporters | Population | $N$ | $\text{AUC}^{\text{DDI}}$ | $\text{AUC}^{\text{Con}}$ | $\text{CL}^{\text{DDI}}$ | $\text{CL}^{\text{Con}}$ | $\text{MRT}^{\text{DDI}}$ | $\text{MRT}^{\text{Con}}$ | Percent AUC extrapolation | Refs. |
|--------|-------------|-------------------------------|-------------------------------------|------------|----|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|-----------------------------|-------|
| Antipyrine | Cimetidine (1000 QD; 10 days) | CYP1A2 | CYP enzymes | Healthy subjects  | 7  | 1.41 | 0.79 | 1.24 | NR | 1.59 | NR | [40] |
| Desipramine | Disulfiram (500 mg QD; 31 days) | CYP2C9 | CYP enzymes | Healthy subject; male | 1 | 1.32 | 0.76 | 0.93 | NR | 1.20 | NR | [41] |
| Imipramine | Disulfiram (500 mg QD; 14 days) | CYP3A4 | CYP enzymes | Healthy subjects; male | 2 | 1.30 | 0.77 | 0.89 | NR | 1.16 | NR | [41] |
| Theophylline | Cimetidine (300 mg PO QID; 1.5 days) | CYP1A2 | CYP enzymes | Healthy subjects; male | 10 | 1.27 | 0.79 | 1.00 | NR | 1.24 | NR | [42] |
| Theophylline | Cimetidine (300 mg IV infusion QID; 1.5 days) | CYP3A4 | CYP enzymes | Healthy subjects; male | 10 | 1.21 | 0.83 | 1.02 | NR | 1.20 | NR | [42] |
| Theophylline | Cimetidine (400 mg BID; 7 days) | CYP2E1 | CYP enzymes | Healthy subjects; male | 6 | 1.34 | 0.74 | 1.04 | NR | 1.42 | NR | [43] |
| Theophylline | Cimetidine (1000 QD; 10 days) | CYP2C19 | CYP enzymes | Healthy subjects | 7 | 1.10 | 0.90 | 1.04 | NR | 1.15 | NR | [40] |
| Theophylline | Ciprofloxacin (500 mg BID; 7 days) | CYP2E6 | CYP enzymes | Healthy subjects; male | 6 | 1.48 | 0.68 | 1.00 | NR | 1.47 | NR | [43] |
| Theophylline | Ciprofloxacin (400 mg BID; 7 days) + Cimetidine (500 mg BID; 7 days) | CYP3A4 | CYP enzymes | Healthy subjects; male | 6 | 1.70 | 0.59 | 1.00 | NR | 1.78 | NR | [43] |
| Theophylline | Erythromycin (250 mg QID; 7 days) | CYP3A4 | CYP enzymes | Healthy subjects; male | 8 | 1.38 | 0.74 | 0.92 | NR | 1.27 | NR | [44] |

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

$AUC$ area under the curve, $BID$ twice daily, $CL$ clearance, $Con$ control, $CYP$ cytochrome P450, $IV$ intravenous, $MATE1$ Multidrug and Toxic Extrusion 1, $MRT$ mean residence time, $NR$ not reported, $OCT$ organic cation transporter, $PO$ oral, $QD$ once daily, $QID$ four times a day, $Refs$ reference, $t_{1/2,z}$ terminal half-life

$^b$Ratios are calculated for each individual using published individual pharmacokinetic data; the reported value reflects the average of each individual ratio

$^c$AUC was calculated with the equation $AUC = \text{dose}/\text{CL}$ using known dose and reported average values of CL
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 PK parameters are expected to be similar in homogenous populations, such as in healthy subjects, as 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 vs crossover). Further, based on this observation, we emphasize that the 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 as $V_{ss}$ 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 the 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 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 PK trend of changes in CL resulting in an equal but opposite change in MRT, owing to the fact that $V_{ss}$ remains unchanged for metabolic interactions (Eq. 1) [45]. These relationships are depicted in Fig. 2, 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 CL 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 a larger magnitude. In general, Fig. 2 highlights that changes in CL are opposite in direction but similar in magnitude to $t_{1/2,z}$ 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, owing to changes in $V_{ss}$ [2].

As our laboratory has recently presented, knowledge that $V_{ss}$ remains unchanged in metabolic DDI studies can facilitate the estimation of changes in CL from changes in $F$ 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 orally and intravenously dosed midazolam. Thus, estimates of changes in CL vs $F$ 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 with only a 3.2-fold increase in midazolam AUC in the IV drug interaction study) when clarithromycin was dosed 500 mg twice daily for 7 days (Table 7). Knowing that $V_{ss}$ largely remains unchanged for IV metabolic DDIs (based on the analysis presented here)
Table 6  Intravenous pharmacogenomic interaction studies and disease state drug–drug interaction studies

| Drug     | Enzyme | Population                                                                 | N  | AUC<sub>ext</sub> | CL<sub>ext</sub> | V<sub>ss</sub> | MRT<sub>ext</sub> | t<sub>1/2,z</sub> | Percent AUC extrapolation | Refs. |
|----------|--------|------------------------------------------------------------------------------|----|-------------------|-----------------|--------------|------------------|-----------------|----------------------------|-------|
| Metoprolol | CYP2D6 | Control: healthy subjects, white, male, CYP2D6 extensive metabolizers; 58–80 kg | 3  | 2.56<sup>a</sup>  | 0.40            | 0.51         | 1.29<sup>a</sup> | 1.81<sup>a</sup> | 34%/15<sup>a</sup>         | [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<sup>a</sup> | 0.70<sup>a</sup> | 0.93            | 8%/14<sup>a</sup>          | [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<sup>a</sup> | 0.70<sup>a</sup> | 0.96            | 8%/14<sup>a</sup>          | [21]  |
|          |        | Phenotype: healthy subjects, African American, CYP3A5*1/*X; 57–97 kg for all subjects | 6  |                   |                 |              |                  |                 |                            |       |
| Theophylline | CYP1A2 | Control: healthy subjects; average weight 80.7 kg                           | 9  | 1.54<sup>a</sup>  | 0.65            | 0.70<sup>a</sup> | 1.25<sup>c</sup> | 1.76            | 8%/14<sup>a</sup>          | [28]  |
|          | CYP3A4 |                                                                   |     |                   |                 |              |                  |                 |                            |       |
|          | CYP2E1 | Disease state: patients with liver cirrhosis; average weight 68.6 kg        | 9  |                   |                 |              |                  |                 |                            |       |

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

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, Refs reference, t<sub>1/2,z</sub> terminal half-life, V<sub>ss</sub>, volume of distribution at steady state.

<sup>a</sup>Ratios are calculated by digitization of published average plasma concentration–time profiles and performing a non-compartmental analysis.

<sup>c</sup>AUC was calculated with the equation AUC = dose/CL using known dose and reported average values of CL.

<sup>e</sup>MRT was calculated with the equation V<sub>ss</sub> = CL·MRT using reported average values of CL and V<sub>ss</sub>.

<sup>g</sup>Ratios are calculated by digitization of a published plasma concentration–time profile of a single representative subject (one healthy subject and one patient with liver cirrhosis), which may not be reflective of all subjects in the study.
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 apparent CL [3]. Utilizing this methodology, the predicted increase in $F$ was 2.84-fold and CL was predicted to decrease by 60% (ratio of 0.40), compared with the observed 2.12-fold increase in $F$ and 65% reduction in CL (ratio of 0.35) (Table 7). Thus, recognition that $V_{ss}$ remains unchanged in metabolic interactions allows the 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 three) 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 PK 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.

![Fig. 2](image.png) Ratios of change in a mean residence time (MRT) and b terminal half-life ($t_{1/2}$) compared with the inverse of change in clearance (CL). The red line indicates the line of unity

| Victim               | Perpetrator       | $\frac{AUC_{DDI}}{AUC_{control}}$ | Percent AUC extrapolation (DDI/control) | $\frac{V_{ss}/F_{DDI}}{V_{ss}/F_{control}}$ | $\frac{V_{ss}}{F_{DDI}}\frac{V_{ss}}{F_{control}}$ | $\frac{CL/F_{DDI}}{CL/F_{control}}$ | $\frac{CL}{F_{DDI}}\frac{CL}{F_{control}}$ | Refs. |
|----------------------|-------------------|----------------------------------|----------------------------------------|---------------------------------------------|-------------------------------------------------|-------------------------------------|-------------------------------------|-------|
| Midazolam (IV)       | Clarithromycin    | Observed: 3.2                    | Observed: 44%/19%$^a$                  | Observed: 1.16$^a$                         | --                                              | 2.12                                | --                                  | Observed: 0.35                      |
| $^{15}$N$_3$-Midazolam (oral) | Clarithromycin    | Observed: 8.2                    | Observed: 33%/12%$^a$                  | Observed: 0.35$^a$                        | Assumed: 1                                       | Estimated: 2.84$^b$                  | Estimated: 0.14                     | Observed: 0.40$^b$                  |

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]

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

$AUC$ area under the curve, $BID$ twice daily, $DDI$ drug–drug interaction, $IV$ intravenous, $Refs$ reference, $V_{ss}$ volume of distribution at steady state

$^a$Ratios are calculated by digitization of published average plasma concentration–time profiles and performing a non-compartmental analysis

$^b$Ratios are calculated for each individual using published individual pharmacokinetic data; the reported value reflects the average of each individual ratio
alone from calculations of apparent CL/F, two parameters that are considered indistinguishable from one another following oral dosing [3].

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Declarations

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Conflict of interest Jasleen K. Sodhi, Caroline H. Huang, and Leslie Z. Benet have no conflicts of interest that are directly relevant to the content of this study.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

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