**Prediction of Inter-individual Variability in the Pharmacokinetics of CYP2C19 Substrates in Humans**

Koji Chiba, Keiko Shimizu, Motohiro Kato, Takaaki Nishibayashi, Kazuki Terada, Nobuo Izumo and Yuichi Sugiyama

1Laboratory of Clinical Pharmacology, Yokohama College of Pharmacy, Yokohama, Japan
2Department of Drug Development Science & Clinical Evaluation, Faculty of Pharmacy, Keio University, Tokyo, Japan
3Sugiyama Laboratory, RIKEN Innovation Center, Research Cluster for Innovation, RIKEN, Yokohama, Japan
4Kyorin Pharmaceutical Co., Ltd., Tochigi, Japan
5Chugai Pharmaceutical Co., Ltd., Shizuoka, Japan

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**Summary:** Significant inter-individual variability of exposure for CYP2C19 substrates may be only partly due to genetic polymorphism. Therefore, the in vivo inter-individual variability in hepatic intrinsic clearance (CL_{int,h}) of CYP2C19 substrates was estimated from reported AUC values using Monte Carlo simulations. The coefficient of variation (CV) for CL_{int,h} in poor metabolizers (PM) expected from genotypes CYP2C19*2/*2, CYP2C19*3/*3 or CYP2C19*2/*3 was estimated as 25.8% from the CV for AUC of omeprazole in PMs. With this, CVs of CL_{int,h} in extensive metabolizers (EM: CYP2C19*1/*1), intermediate metabolizers (IM: CYP2C19*1/*2 or *3) and ultra-rapid metabolizers (UM), CYP2C19*17/*17 and *1/*17, were estimated as 66.0%, 55.8%, 6.8% and 48.0%, respectively. To validate these CVs, variability in the AUC of CYP2C19 substrates lansoprazole and rabeprazole, partially metabolized by CYP3A4 in EMs and IMs, were simulated using the CV in CL_{int,h} for CYP2C19 EMs and IMs and 33% of the CV previously reported for CYP3A4. Published values were within 2.5–97.5 percentile range of simulated CVs for the AUC. Furthermore, simulated CVs for the AUC of omeprazole and lansoprazole in ungenotyped populations were comparable with published values. Thus, estimated CL_{int,h} variability can predict variability in the AUC of drugs metabolized not only by CYP2C19 but also by multiple enzymes.

**Keywords:** CYP2C19; inter-individual variability; human pharmacokinetics; Monte Carlo simulation; pharmacogenetics; drug development

**Introduction**

The cytochrome P450 2C19 (CYP2C19) is important for the metabolism of several therapeutic agents, such as proton pump inhibitors (PPIs), antiepileptics and antidepressant drugs. It is well known that genetic polymorphism exists for this enzyme and affects its activity. In addition to the wild-type CYP2C19*1 allele, 33 variant CYP2C19 alleles with mutations have been identified (CYP2C19*2 to *34) ([http://www.cypalleles.ki.se/cyp2c19.htm](http://www.cypalleles.ki.se/cyp2c19.htm)). Of these mutated alleles, CYP2C19*2 and CYP2C19*3 are the most common variants to contain a splice-defective mutation and premature stop codon, respectively, which lead to the creation of truncated nonfunctional proteins. By contrast, the CYP2C19*17 allelic variant with an 806C > T mutation is associated with an increased, ultra-rapid enzyme activity for CYP2C19. The frequency of the alleles varies across ethnic populations. The CYP2C19*2 and CYP2C19*3 alleles are found in 28.6% and 8.8% of individuals in Eastern Asia but only 12.8–16.1% and ~0.1% in Europe, respectively. The frequency of CYP2C19*17 alleles is 19.0–27.2% in Europe but 1.1% in Eastern Asia. Due to this ethnic difference in the frequency of the alleles, the exposure of CYP2C19 substrates varies among ethnic groups and shows a large inter-individual variability.

The inter-individual variability is an important factor in determining the dosing regimen, because the variability of exposure may be associated with differences in pharmacological effects. Therefore, individual therapy based on testing for the CYP2C19 genotype is recommended in gastroesophageal reflux disease and in Helico-
bacter pylori infection) to reduce the variability of exposure of PPIs and for antiplatelet therapy to adjust for clopidogrel exposure.

Recently, we used the metabolic ratio of dextromethorphan to demonstrate that different genotypes showed variability in their intrinsic hepatic clearance (CLint,h) of CYP2D6, such that the homozygotes CYP2D6*1, CYP2D6*2 and CYP2D6*10 demonstrated coefficients of variation (CV) values of 43%, 63% and 66%, respectively. Moreover, the variability of exposure of CYP2D6 substrates was successfully predicted using the estimated CV values for CLint,h and the frequency of the genotypes.7)

Abundant data for exposure of CYP2C19 substrates for each of the CYP2C19 genotypes have been accumulated, especially for PPIs. The exposure and its variability for a substrate can be converted to those of CLint,h for the substrate based on a mathematical model such as a dispersion model. It is then possible to simulate the variability of exposure with the variability of CLint,h and other physiological parameters, such as blood flow rate, protein content bound to the drug, liver volume and body weight, using Monte Carlo simulations. Conversely, the appropriate CLint,h (mean and CV) can be estimated to determine the mean and CV for the area under the plasma concentration-time curves (AUCs). In our previous paper, a method to estimate the CLint,h and its variability for CYP3A4 substrates was proposed.8) Various CV values for the CYP3A4 content in human liver microsomes (33–99%) were collected from the published literature. Then, the variability in the CLint,h of CYP3A4 substrates was determined to be 33% using a dispersion model based on the variability in the AUCs for the CYP3A4 substrates in vivo; thus the theory could be applied to obtain the variability in CLint,h of CYP2C19 (CLint,h,2C19) substrates separately from the variability of other parameters.

In this study, a similar process was applied to transfer the variability in the values for the AUC of CYP2C19 substrates to that for the CLint,h,2C19 of CYP2C19 substrates and produce an estimated variability for each CYP2C19 genotype. These values were then used to estimate the mean population exposure and variability in various ethnic groups.

Methods

Data collection: The mean and variability values (standard deviation, SD; standard error, SE; confidence interval, CI) for the AUCs following oral administration of the CYP2C19 substrates lansoprazole, omeprazole, and rabeprazole to healthy volunteers were collected from published data (Supplemental Table S1). The published literature was searched via PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and the selected references were cited. The AUC values were used from studies that included population data with CYP2C19 genotypes or ethnicity, or from those studies that included the clinical studies where the clinical studies were conducted.

Estimation of the mean and CV for CLint,h,2C19 and CLint,h of enzymes other than CYP2C19 for omeprazole: The mean and CV values for the AUC of omeprazole in human subjects with CYP2C19 genotypes that are active [denoted extensive metabolizers (EM: CYP2C19*1/*1)] are inactive [denoted poor metabolizers (PM: CYP2C19*2/*2, CYP2C19*3/*3, CYP2C19*2/*3)], have intermediate activity [denoted intermediate metabolizers (IM: CYP2C19*1/*2 and CYP2C19*1/*3)], and have CYP2C19*17 allele which indicates ultra-rapid activity (CYP2C19*17/*17, CYP2C19*17/*1, CYP2C19*1/*17 and *2/*17) were collected separately. If there were multiple sources for AUCs in each group, their respective values were pooled (see Statistical methods). Since the mean and CV values for the omeprazole AUC among CYP2C19*2/*2, CYP2C19*3/*3 and CYP2C19*2/*3 in the PM group, were theoretically indistinguishable, those were pooled. Similarly those in the IM group, CYP2C19*1/*2 and CYP2C19*1/*3, were also pooled. The AUCs for omeprazole with CYP2C19*17/*17 and CYP2C19*1/*17 [ultra-rapid metabolizer (UM) group] were designated separately, but those for CYP2C19*2/*2 and *3/*17 in that same group were pooled.

The CV values for the AUC of omeprazole were also estimated using Monte Carlo simulations from the mean and CV of the CLint,h (Fig. 1). First, numerous values of intrinsic clearance mediated by metabolism other than CYP2C19 (CLint,h,other) were generated using Monte Carlo simulations with one log-normal distribution of mean (μ) and variance (σ²). From each CLint,h,other, the AUC was calculated (see Simulation of AUC). Then, numerous combinations of AUC, expressed as an arithmetic mean and CV, and of CLint,h,other with a log-normal distribution [μ, σ²] or (mean, CV), see Statistical methods) were made. These AUC values were assumed equivalent to those for the PM group. To find the simulated AUC (mean, CV) with the combinations (simulated AUC – CLint,h,other) corresponding to published AUC values, the mean and CV values of the CLint,h,other were changed manually to obtain the same values for the mean and CV as those obtained for the pooled literature AUC values. Similarly, numerous values of CLint,h,2C19 (mean, CV) for the PM group (CLint,h,2C19EM) and CLint,h,other obtained from the PM group were generated and each CLint,h,2C19EM and CLint,h,other were summed randomly. The AUC for the sum of CLint,h,2C19EM and CLint,h,other were calculated, and this corresponded to the AUC of the EM group (combination of simulated AUC – CLint,h,2C19EM). The CLint,h,2C19EM (mean, CV) values corresponding to the published values for the AUC of the EM group were found from the combinations. For the UM and IM groups, the CLint,h,2C19 (mean, CV) was estimated from the pooled literature values of the AUCs for these respective groups.

To confirm whether the CV values of CLint,h,2C19EM and CLint,h,2C19EM could be used to predict the variability in the AUCs for other CYP2C19 substrates, those CLint,h,2C19 CV values were applied to Monte Carlo simulations for CV values for the AUC of lansoprazole and rabeprazole. The mean values for CLint,h,2C19EM and CLint,h,2C19EM were estimated according to a dispersion model, if necessary, following transfer of the AUC values to the geometric mean.

Simulation of AUC: The fraction of drug excreted unchanged in urine for omeprazole, lansoprazole and rabeprazole was reported as < 1%8,9–11 and could be disregarded for the calculation of AUC divided by dose (AUC/D) in the following equation:

\[
\text{AUC/D} = \frac{F_a \cdot F_g (1 - \text{CL}_h/\text{Qh})}{\text{CL}_h} \tag{1}
\]

where \(F_a\) and \(F_g\) are assumed to be 1.0. \(\text{CL}_h\) was determined with Eq. (2) using a dispersion model as the mathematical model for the liver:

\[
\text{CL}_h = \text{Qh} \left[ 1 - \frac{4a}{(1 + a^2) \cdot \text{exp}(a - 1)/D_N} - (1 - a^2) \cdot \text{exp}(-(a + 1)/2/D_N) \right]
\]

\[a = (1 + 4R_N \cdot D_N)^{1/2}, \quad R_N = F_b \cdot \left(\frac{\text{CL}_{\text{int},h}}{\text{Qh}} \right) \tag{2}\]

where \(F_a\) and \(D_N\) are the unbound fraction in the blood and the dispersion number, respectively, and \(Qh\) is the liver blood flow. \(D_N\)
is assumed to be 0.17.\textsuperscript{12–14} CL\textsubscript{int,h} is the summation of CL\textsubscript{int,h,2C19} and CL\textsubscript{int,h,other}.

The dispersion model was chosen rather than well-stirred or parallel-tube models, which are widely used as liver mathematical models, because the dispersion model reportedly fitted best to the observed data in a correlation between in vitro microsomal data and the corresponding data from isolated perfused liver in rats.\textsuperscript{12)} Moreover, in our previous study,\textsuperscript{8)} the simulated curves for the relationships between the CV for the AUC and the AUC/D after oral administration of CYP3A4 substrates using the dispersion and parallel-tube models were consistent with observed data, whereas those derived using a well-stirred model deviated from observed data.

The plasma unbound fraction (fp) was calculated from the equation

$$fp = \frac{1}{1 + n \cdot Pt/Kd}$$

where n, Pt, and Kd are the number of binding sites, concentration of plasma protein binding to drug, and dissociation constant, respectively. No inter-individual variability of Kd was assumed. Values for n were set at unity.

The blood-plasma concentration ratio (Rb) of each compound was obtained from the published literature or calculated using fp, according to a method described previously.\textsuperscript{15)} The fps for omeprazole, lansoprazole and rabeprazole were reported as 0.04,\textsuperscript{15)} 0.031,\textsuperscript{10} and 0.037,\textsuperscript{16} respectively. The Rb for omeprazole was 0.59\textsuperscript{15} and those for lansoprazole (0.74) and rabeprazole (0.75) were calculated by a method described previously.\textsuperscript{15)} The contribution of CYP2C19 to the metabolism (fm\textsubscript{2C19}) was determined using the following Eq. (3).

$$fm_{2C19} = \frac{CL_{int,h,2C19}}{CL_{int,h,2C19} + CL_{int,h,other}}$$

In the simulation, one set of AUC values for the same number of subjects as those in the previous study used for the pooled AUC was generated from the CL\textsubscript{int,h,2C19} values according to Eqs. (1) and (2) with Monte Carlo simulations using SAS (Version 9.2, SAS Institute, Cary, NC), and 1,000 sets were repeatedly generated. The distribution of CL\textsubscript{int,h,2C19} was assumed to be log-normal.

The reported values of Qh (1.22 mL/min/mL liver, CV: 12.9%),\textsuperscript{17)} liver volume (19.5 mL/kg, 11.4%)\textsuperscript{–21} and body weight (66.2 kg/Asian subject, 12.4%; 78.8 kg/Caucasian subject, 11.7%;\textsuperscript{22} and 64.3 kg/Mexican subject, 13.8%\textsuperscript{23}) were used for the simulation. The liver density was assumed to be at unity.

Lansoprazole and rabeprazole are metabolized primarily by CYP2C19 and secondarily by CYP3A4. It is well known that CYP3A4 is localized in the intestine. However, the value for the fraction of absorption (Fa) multiplied by intestinal availability (Fg) was approximately 0.9 for both drugs (data not shown). Therefore, the contribution of intestinal CYP3A4 to the variability of the AUC was disregarded for the simulation.

Statistical methods: The mean, SD, CV and 2.5 and 97.5 percentiles were estimated using SAS PROC UNIVARIATE. The CV value was calculated using SD/mean as the normal scale. The exchange between the log-transformed mean (μ) and SD and the arithmetic mean (m) and CV was calculated according to Eqs. (4) and (5):

$$\mu = \ln(m) - \frac{\sigma^2}{2}$$

$$\sigma = \sqrt{\ln(CV^2 + 1)}$$

When multiple sources of AUC (mean ± SD) values for the same genotype were available, the overall mean and SD values...
were estimated by integration of each mean and SD value using the following calculations.

Weighted mean (WM) was calculated as:

\[
WM = \frac{\sum_{i=1}^{n} (N_i \cdot m_i)}{\sum_{i=1}^{n} N_i}
\]  

(6)

Overall SD was calculated as:

\[
SD = \sqrt{\frac{\sum_{i=1}^{n} [SD_i^2 \cdot (N_i - 1) + N_i \cdot m_i^2] - WM^2 \cdot \sum_{i=1}^{n} N_i}{\sum_{i=1}^{n} N_i - 1}}
\]  

(7)

where \(N_i\) is the number of observations, \(m_i\) is the mean value from the \(i\)th study, and \(SD_i\) is the SD from the \(i\)th study. The inter-study variability was assumed to be included in the inter-individual variability.

An outlier was defined as any case with a published mean value greater than twice the overall SD. Once an outlier was observed, all data included in that report were excluded from analysis.

Results

Extracted data: From 13 studies with EMs, the mean and SD were collected or calculated from the reported variability (Supplemental Table S1). For IM and PM, 10 studies each were extracted. The mean and SD of AUC values were pooled and summarized as mean and CV, as shown in Table 1. The majority of the AUC values in EMs, IMs and PMs were from the Asian participants, whereas the AUC values in UMs were obtained from two studies with Caucasian subjects. The AUCs from an ungenotyped population (other than Asian) were also collected (Supplemental Table S1).

**Clint,h,2C19 variability from omeprazole AUC:** The mean and CV of the Clint,h,2C19 for omeprazole in PMs (25.8%) were estimated from the AUC/D and its CV in PMs to be 29.1 mL/min/kg and 25.8%, respectively (Table 1). These values theoretically corresponded to those of the Clint,h,other and were used for the estimation of Clint,h,2C19EM and Clint,h,2C19IM. The CV value of Clint,h,2C19EM was estimated as 66.0%.

By using the mean values of Clint,h,2C19EM, the relationships between sample size and CV of the AUCs were drawn as shown in Figure 2a. The curves for the relationships between the CVs of the Clint,h and AUC were overlaid for sample sizes of 89 and 1,000. However, when the sample size was six, which was the number of subjects frequently used in published studies (Supplemental Table S1), the curve was lower than that for the larger sample population. Therefore, the values for the AUC of omeprazole were pooled to avoid the influence of different sample sizes and to decrease the intervals of 2.5 and 97.5 percentiles.

The curves simulated using the estimated mean Clint,h,2C19 of omeprazole in UMs with genotype CYPC219*17/*17 and in EMs and IMs (listed in Table 1) are shown in Figure 2b. The CV values for the AUCs reported in the literature were also plotted on the curves and the corresponding CV values for Clint,h,2C19 were obtained (summarized in Table 1). The CV value of Clint,h,2C19EM (66.0%) was larger than that of Clint,h,2C19IM (55.8%). The lowest variability was observed for subjects with the genotype CYPC219*17/*17 in the UM group (6.8%, Table 1), which was accounted for by the variability in the liver volume (11.4% CV). The 2.5 and 97.5 percentiles for the CV values of the AUC simulated from the estimated CV values of the Clint,h,2C19 were approximately +/-10% CV, although the estimated CV values for the AUC in EMs, IMs and UMs with the genotype CYPC219*17/*17 were different (60%, 43% and 19%, respectively). Therefore, the estimated CV value for Clint,h,2C19 in UM CYPC219*17/*17 subjects (6.8%) was less accurate due to the small sample size (n = 10).

One thousand omeprazole AUC/D values with CV values in the virtual omeprazole study in EM subjects (n = 6) were simulated using the CV values from the estimated Clint,h,2C19EM (66.0%) (Fig. 3a) and compared with literature values (n = 5–11, Supplemental Table S1). Almost all values obtained from the literature were within the simulated values. In addition, 9 out of 13 plots were observed inside and 3 were near the 2.5 percentile.

**Application of Clint,h,2C19 to lansoprazole and rabeprazole:** To determine whether the estimated variability of Clint,h,2C19EM (66.0%) and Clint,h,2C19IM (55.8%) of omeprazole was appropriate, the CV values were applied for estimation of variability in the AUC/D for two additional PPIs: lansoprazole and rabeprazole. The mean values of Clint,h,2C19EM and Clint,h,2C19IM (Table 2) were used for the Monte Carlo simulation of the AUC/D of lansoprazole and rabeprazole, with the variability of Clint,h,2C19EM.

**Table 1.** Estimated mean and CV values for the intrinsic hepatic clearance of omeprazole mediated by CYPC219 (Clint,h,2C19) or by other intrinsic hepatic clearance (Clint,h,other) from subjects with varying CYPC219 enzyme activities

<table>
<thead>
<tr>
<th>Genotyped group</th>
<th>Number of groups</th>
<th>Number of subjects</th>
<th>AUC/D&lt;sup&gt;a&lt;/sup&gt;</th>
<th>References</th>
<th>Estimated data</th>
<th>Genotyped group</th>
<th>Number of groups</th>
<th>Number of subjects</th>
<th>AUC/D&lt;sup&gt;a&lt;/sup&gt;</th>
<th>References</th>
<th>Estimated data</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean (min/L)</td>
<td>CV (%)</td>
<td>Mean (mL/min/kg)</td>
<td>CV (%)</td>
<td></td>
<td></td>
<td>Mean (mL/min/kg)</td>
<td>CV (%)</td>
<td>Mean (mL/min/kg)</td>
</tr>
<tr>
<td>*17/*17</td>
<td>2</td>
<td>10</td>
<td>0.60</td>
<td>19.0</td>
<td>25, 26</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>*17/17</td>
<td>2</td>
<td>7</td>
<td>0.81</td>
<td>46.9</td>
<td>27</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>*17/*23</td>
<td>2</td>
<td>2</td>
<td>1.66</td>
<td>NA</td>
<td>27</td>
<td></td>
<td></td>
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<tr>
<td>EM</td>
<td>13</td>
<td>89</td>
<td>1.16</td>
<td>59.8</td>
<td>25–36</td>
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<tr>
<td>IM</td>
<td>10</td>
<td>62</td>
<td>2.24</td>
<td>43.4</td>
<td>27–35</td>
<td></td>
<td></td>
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<tr>
<td>PM</td>
<td>10</td>
<td>55</td>
<td>8.02</td>
<td>31.3</td>
<td>27–36</td>
<td></td>
<td></td>
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</table>

*Clint,h,2C19* was estimated by Eq. (3) using Clint,h,other.

<sup>a</sup>AUC/D represents area under the curve of blood concentration divided by dose.

Genotypes of CYPC219 EM, IM and PM contain CYPC219*1/*1, CYPC219*1/*2 and CYPC219*1/*3, CYPC219*2/*2 and CYPC219*3/*3, respectively.

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and CLint,h,2C19IM estimated using that of omeprazole for EM (66.0%) and IM (55.8%). The results indicated that the estimated CV values of the AUC/D for lansoprazole and rabeprazole in EMs and IMs were consistent with the published values, which were within 2.5–97.5 percentile range of the estimated CV values (Fig. 3b). For the variability estimation of the AUC/D, the variability of the CLint,h,other for lansoprazole and rabeprazole was set at 33%, which was the variability in the CLint,h of CYP3A4 substrates in a previous study,8) because CYP3A4 also contributes to the metabolic clearance of lansoprazole and rabeprazole. For rabeprazole, the contribution of a nonenzymatic pathway following metabolism by CYP2C19 has also been reported.24) To confirm the variability of the CLint,h,other for lansoprazole and rabeprazole, the variability for the CLint,h in PM subjects was estimated for lansoprazole (23.9%) and rabeprazole (35.2%), as well as for omeprazole (25.8%) and was found to be comparable with the variability reported for the CLint,h of CYP3A4 substrates (33%).8)

The CV values for the AUC decreased with increasing AUC/D mean values (Fig. 3b). The CV was also influenced by fm2C19. The CV value for lansoprazole in EMs with a higher fm2C19 (0.8) was larger than that for IMs with a lower fm2C19 (0.65). Similarly, the CV value for rabeprazole in EMs with a higher fm2C19 (0.54) was greater than that for IMs with a lower fm2C19 (0.40). Moreover, CV values for all plots, including those for omeprazole in EM (0.85) and IM (0.71) subjects, were less than those for the simulation curves with fm2C19 at unity. The CV values for the AUC/D of omeprazole in IMs, lansoprazole in IMs, and rabeprazole in EMs and IMs were plotted with the CV value (33%) from the simulation curves with fm2C19 of 0.5. The simulation curves with fm2C19 at unity. The CV values for the AUC/D of lansoprazole and rabeprazole (mean and CV) in EMs and IMs were simulated using mean values of CLint,h,other and subject numbers (listed in Table 2), and the estimated variability for omeprazole (see Table 1). The curve and dotted line curve express the variability in the AUC of 66% and in the CLint,h of 33% with fm at unity.

Fig. 2. Relationship between the coefficient of variation (CV) for CLint,h,2C19 and for the AUC with regard to (a) impact of sample size and (b) 2.5–97.5 percentile range of CV for AUC and CV for CLint,h,2C19 in each genotype

(a) Relationship between the CVs for AUC and CLint,h,2C19 were simulated with various subject numbers in a virtual study. The simulation was carried out with CLint,h,other (29.1 mL/min/kg, 25.8% CV in Table 1) for sample sizes of 6, 89 and 1,000, which represent subject numbers frequently referred to in the literature (Supplemental Table S1), pooled numbers for omeprazole in EMs (Table 1), and a typical large number. (b) The range of 2.5 and 97.5 percentiles of CV for AUC, corresponding to CV for CLint,h,2C19 in EM and IMs and CYP2C19*17/*17 in the UM group, are expressed as error bars obtained as the 25th and 975th estimates from 1,000 (EM and IM) or as the 50th and 1,950th estimates from 2,000 (UM) Monte Carlo simulations, with the mean values for CLint,h,2C19, CLint,h,other and subject numbers listed in Table 1.

Fig. 3. Simulation of the variability in the AUC obtained in a virtual study with (a) a typical Phase 1 sample size (n = 6) for omeprazole in EMs and (b) for lansoprazole and rabeprazole in EMs and IMs using the variability in CLint,h,2C19 obtained from that for the AUC of omeprazole

The relationships between the mean values for the AUC/D and the CV for AUC were simulated with the most frequent number of subjects (n = 6) in the omeprazole studies (listed in Supplemental Table S1). The mean values of AUC/D and the CV of AUC for 1,000 virtual studies (Q) were simulated with CLint,h,other (167 mL/min/kg, 66.0% CV in Table 1) and CLint,h,other (29.1 mL/min/kg, 25.8% CV in Table 1) and other parameters described in Simulation of AUC in the Methods. The open (△), closed (●) triangles and error bars express published and the pooled values, and 2.5–97.5 percentile range, respectively. (b) Simulation and published values for the AUC of omeprazole in EMs (●) and IMs (□) and of rabeprazole in EMs (●) and IMs (□) are expressed with and without 2.5–97.5 percentile range as error bars, respectively. Published values for the AUC of omeprazole in EMs (●) and IMs (□) are also plotted. The AUC/D values for lansoprazole and rabeprazole (mean and CV) in EMs and IMs were simulated using mean values of CLint,h,2C19, CLint,h,other and subject numbers (listed in Table 2), and the estimated variability for omeprazole (see Table 1). The curve and dotted line curve express the variability in the AUC of 66% and in the CLint,h of 33% with fm at unity.
CLint,h,2C19. This is likely because even if two different enzymes have the same CV for activity, the CV for the total activity will be less than the CV of any single enzyme, according to the rule for propagation errors.

Application of the variability of CLint,h,2C19 to various ethnic groups: The mean values of CLint,h,2C19EM and CLint,h,2C19IM for omeprazole and lansoprazole and CV values of CLint,h,2C19EM and CLint,h,2C19IM were used for the Monte Carlo simulation of AUC values (mean and CV) from ungenotyped subjects along with the frequency of genotype (Supplemental Table S2). The results showed that all reported values for the mean and CV of the AUCs were within 2.5–97.5 percentile range of the estimated values (Fig. 4). No published data were available for rabeprazole.

Discussion

In the present study, the variability of CLint,h,2C19EM (66.0%) and CLint,h,2C19IM (55.8%) was estimated from the variability for the AUC of omeprazole and used for predicting the variability of two additional CYP2C19 substrates, lansoprazole and rabeprazole. The variability of CLint,h,2C19EM (66.0%) was significantly larger than that for CYP3A4 CLint,h (33%) and similar to that of CYP2D6 extensive metabolizer (CYP2D6 EM: approximately 60%) , resulting in the order of variability as CYP2C19 EM > CYP2D6 EM > CYP3A4.

The variability of CLint,h can be explained by the variability in the amount of the enzyme and in the mutation of the polymorphism. The variability of CLint,h,2C19EM (66.0%) was larger than that of CLint,h,2C19IM (55.8%), although the active allele in EM (CYP2C19*1/*1) and IM (CYP2C19*1/*2 and CYP2C19*1/*3) subjects was the same, that is, CYP2C19*1. A difference in variability was also observed between enzymes homozygous for the active allele and those heterozygous with an active and null allele for CYP2D6 (i.e., CYP2D6*1, CYP2D6*2, and CYP2D6*10).

Table 2. Estimated CLint,h,2C19 in CYP2C19 EMs and IMs and CLint,h,other in PMs obtained from literature AUC values for CYP2C19 substrates lansoprazole and rabeprazole

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Number of group</th>
<th>Number of subjects</th>
<th>Literature value</th>
<th>Estimated value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td></td>
<td>AUCb/D (mean)</td>
<td>fm2C19</td>
</tr>
<tr>
<td></td>
<td>of group</td>
<td>Number of subjects</td>
<td>(min/L)</td>
<td>References</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>EM</td>
<td>10</td>
<td>122</td>
<td>3.50</td>
</tr>
<tr>
<td></td>
<td>IM</td>
<td>7</td>
<td>40</td>
<td>6.01</td>
</tr>
<tr>
<td></td>
<td>PM</td>
<td>6</td>
<td>38</td>
<td>17.17</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>EM</td>
<td>6</td>
<td>37</td>
<td>2.42</td>
</tr>
<tr>
<td></td>
<td>IM</td>
<td>6</td>
<td>40</td>
<td>3.19</td>
</tr>
<tr>
<td></td>
<td>PM</td>
<td>6</td>
<td>34</td>
<td>5.50</td>
</tr>
</tbody>
</table>

fm2C19 was estimated by Eq. (3) using CLint,h,other.

AUCb/D represents area under the curve of blood concentration divided by dose.

*To estimate CLint,h,2C19 of CYP2C19 substrates in EMs and IMs, CLint,h in PMs (CLint,h,other) was subtracted from CLint,h values calculated from literature AUC values.

Genotypes of CYP2C19 EM, IM and PM contain CYP2C19*1/*1, CYP2C19*1/*2 and CYP2C19*1/*3, and CYP2C19*2/*2 and CYP2C19*3/*3, respectively.

Fig. 4. Simulations for the variability in the AUCs of CYP2C19 substrates in nonAsian populations

Simulation and literature values for the AUC [mean and CV (%)] of omeprazole in Portuguese (n = 20, ▲) and Mexicans (34, ▼) and of lansoprazole in Americans (242, □) and Romanians (30, □) are plotted with and without 2.5–97.5 percentile range as error bars, respectively, to show the relationship between AUC/D and the CV of AUC. The plot with vertical and horizontal bars indicates 2.5–97.5 percentile range for the mean and CV based on 1,000 simulations. The simulations carried out for 1,000 subjects were created using the values of CLint,h in UMs, EMs, IMs and PMs in Table 1 for omeprazole and Table 2 for lansoprazole with the genotype frequency in each location (Supplemental Table S2). Values for the AUC using the same subject number as that in the pooled literature were extracted from the virtual ethnic population using 1,000 repeats.
DNA strands of one gene in one transcription, the variability of transcription is likely to be independent between two alleles in the same gene. Regulation of alleles after transcription may also have an impact on the variability in the production of the CYP2C19 enzyme. However, no reports have examined the relationship between the variability of CYP enzymes and allele synthesis, necessitating further study to better understand the mechanism for this variability.

There is an ethnic difference in the frequency of CYP2C19 genotypes, and the majority of clinical pharmacokinetic studies for the CYP2C19 genotype have been conducted in Asian populations with EM and IM but without UM subjects. In our study, the variability of \( {\text{CL}_{\text{int,2C19}}} \) of substrates for the UM subjects was estimated from that for the AUC using a small number of Caucasian subjects \( (n = 10) \). The estimated variability for the \( {\text{CL}_{\text{int,2C19}}} \) of CYP2C19*17/*17 in the UM group was essentially negligible because the variability in the physiological parameters could account for all the variability in the AUC for substrates of CYP2C19*17/*17 \(<19\%\)\. Hence, the variability would be influenced by the variability determined for the physiological parameters. For the heterozygotes CYP2C19*1 (CYP2C19*1/*17), the CV was estimated as 47.5\%, based on seven subjects (Table 2). To confirm that this variability could be used for estimating the variability of exposure in a CYP2C19*17-rich population in non-Asians, the AUC data from an ungenotyped population with a high frequency of CYP2C19*17 were collected from the published literature and compared with the variability in the AUC from simulated data. The results demonstrated that all simulated values were within 2.5–97.5 percentile range and that the plots generated from these data were similar to those reported values, suggesting that using the variability in \( {\text{CL}_{\text{int,2C19}}} \) for CYP2C19*17/*17 \( (6.8\%) \) and CYP2C19*1/*17 \( (47.5\%) \) was appropriate for estimating the variability of exposure in the population.

In the present study, the mean values of \( {\text{CL}_{\text{int,2C19}}} \) for CYP2C19 substrates were also estimated. The ratios of the \( {\text{CL}_{\text{int,2C19}}}/\text{VM} \) to \( {\text{CL}_{\text{int,2C19}}}/\text{VM} \) for omeprazole, lansoprazole and rabeprazole were similar at 0.43, 0.48, and 0.59, respectively, suggesting that estimating the values in IM from those in EM was also possible. Because no information was available on CYP2C19 activity for non-Asians, the AUC data from an ungenotyped population with a high frequency of CYP2C19*17 were collected from the published literature and compared with the variability in the AUC from simulated data. The results demonstrated that all simulated values were within 2.5–97.5 percentile range and that the plots generated from these data were similar to those reported values, suggesting that using the variability in \( {\text{CL}_{\text{int,2C19}}} \) for CYP2C19*17/*17 \( (6.8\%) \) and CYP2C19*1/*17 \( (47.5\%) \) was appropriate for estimating the variability of exposure in the population.

This report is the first to describe a method for estimating the variability in \( {\text{CL}_{\text{int,2C19}}} \) for an enzyme that has no probe substrate metabolized by a single enzyme (fm; 1.0) but the enzyme in PM subjects consists of nonfunctional proteins. Using this method, the variability in hepatic clearance of CYP2C19 substrates was provided for EMs \( (66.0\%) \) and IMs \( (55.8\%) \), as well as a possible value for UM \( (6.8\%) \). Using the variability with those \( {\text{CL}_{\text{int,2C19}}} \) values, PM activity (mean and CV) for each PPI along with the variability of \( {\text{CL}_{\text{int,2C19}}} \) \( (33\% \) could be set for 3A4) and the frequency of the genotypes (UM, EM, IM and PMs), it was feasible to estimate the variability in the AUC of PPIs for ungenotyped populations. Additionally, the variability in the AUC of drugs metabolized by multiple enzymes, i.e., CYP2C19 and CYP3A4, could be estimated. Furuta et al. demonstrated that lower exposure might be predictable in an Asian population for EM subjects using a genotyping test necessary for gastroesophageal reflux disease and Helicobacter pylori infection to facilitate adjustment to the PPI exposure. It is expected that the estimated variability in \( {\text{CL}_{\text{int,2C19}}} \) could be applied to estimate the variability in efficacy and safety using PK/PD models for various CYP2C19 substrates.

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