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Prediction of Interindividual Variability in Pharmacokinetics for CYP3A4 Substrates in Humans

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Summary: A method for predicting the interindividual variability of human exposure for CYP3A4 substrates using Monte Carlo simulation was developed based on relevant factors. The coefficient of variation (CV) values for CYP3A4 content in human liver microsomes, hepatic blood flow, liver volume and body weight, and the unbound blood fraction were collected from the published literature. The parallel tube and dispersion models were found to be appropriate mathematical models to describe the pharmacokinetics (PK). Simulation results using 33% as the CV for CYP3A4 content reflected reported CV values of the area under the curve (AUC) for 40 CYP3A4 substrates for both intravenous and oral administration. We also successfully predicted the clearance of midazolam in Japanese and in European American subjects. In all cases, the simulated mean and SD values reflected the reported values. Thus, the interindividual variability of the AUC of CYP3A4 substrates was predictable for both intravenous and oral administration.

Keywords: Interindividual variability; CYP3A4; prediction; Monte Carlo simulation; physiologically based pharmacokinetics; drug discovery

Introduction

A given drug can be effective for some patients and ineffective for others. This phenomenon is well known and might be caused by the large interindividual variability in pharmacokinetics (PK) for drugs. If a drug has a narrow therapeutic window due to large variability in PK, therapeutic drug monitoring will be necessary to maintain efficacy and to avoid side effects; however, these compounds require a large body of test subjects to obtain a significant difference from the reference group, which needs much time and money to organize. Clinical trials that consider interindividual variability will be needed for efficient drug development in the future. At present, frequent blood sampling from many volunteers has become necessary to evaluate the variability in PK for any drug in development. For this reason, population pharmacokinetics (PPK) was developed to evaluate the variability of PK for drugs using data from small, multiple blood samples from each patient, enabling the analysis of factors that influence interindividual variability.1) A Bayesian approach using PPK parameters makes it possible to predict the plasma concentration profile of each patient from repeated small sampling, and PPK analyses have now been performed on many drugs.2) Although useful for the prediction of PK in the later stages of drug development and in a clinical setting, PPK analyses need hard clinical data and cannot be used to predict interindividual variability at the early drug development stage. Moreover, to predict the plasma concentration profile for any drug, the concentration in each patient needs to be measured. PPK analysis is drug specific and cannot be used to predict the performance of other drugs. Thus, being able to predict pharmacokinetic variability during the discovery stage may improve the success rate and reduce the cost and time of drug development.

Both genetic and non-genetic factors may affect interindividual variability. Investigations of twins have shown that the metabolic rates of some drugs were similar in monozygotic twins but not in dizygotic twins,4,5) suggesting the importance of genetic factors. Hence, genetic polymorphisms of metabolic enzymes have been
researched as genetic factors of interindividual variability.6,7) For example, CYP2C9, 2C19 and 2D6 are known to be associated with genetic polymorphisms, and dosage adjustments for these cytochrome P450 (CYP) substrates have been proposed.8) Ideally, clarification of the genetic factors and genotyping for clinical trials will lead to efficient drug development and useful therapeutic agents. However, in enzymes and transporters, interindividual variability in PK is not simply caused by genetic polymorphisms. There are other influences such as transcription factors, mutation of nuclear receptors, and environmental factors. Furthermore, not all the factors that influence interindividual pharmacokinetic variability have been clarified. Other factors such as food effects and smoking may cause interindividual variability. For example, St John’s wort induces CYP3A4 expression,9) smoking induces CYP1A10) and grapefruit juice inhibits CYP3A.11) In addition, body weight, age, sex, liver volume and hepatic blood flow rate may all have an effect on variability. Many factors contribute to interindividual pharmacokinetic variability, and their influences have not been fully elucidated.

A Monte Carlo simulation was developed to predict interindividual variability of PK based on the available information on contributing factors. A block diagram of the general flow of the process is shown in Figure 1. There are two objectives for developing such a prediction system. One is to predict the variability of PK for drugs in populations and the other is to predict the individual PK based on individual information such as body weight, age and genetic data. The prediction of population variability will be useful to select drug candidates with potentially low interindividual variability based on in vitro data at the drug discovery stage. For this, prediction software Simcyp,12) which predicts the variability of PK from the results of recombinant CYP systems, is applicable and available.13) The system presented herein was constructed from both in vitro and in vivo information, and prediction of interindividual variability in exposure for CYP3A substrates was attempted.

Methods

Data collection: Information on the means and standard deviations (SD) of physiological parameters such as liver volume, hepatic blood flow rate, CYP3A4 content in human microsomes, and serum albumin concentration was collected from the literature and is shown in Table 1.14–26) The CV (%) values indicate the variation in the parameters. In addition, information on the pharmacokinetic parameters for drugs mainly metabolized by CYP3A4 after intravenous and oral administration in healthy humans was also collected.27–76) These CYP3A4 substrates were selected based on a urinary excretion rate of less than 20% and are listed in Table 2.

Determination of physiological parameters: No significant differences in the mean and SD values for hepatic blood flow rate and liver volume were found in the reported data,14–18) and values were adopted from Wynne et al.,14) thus determining the mean and CV values of liver volume and hepatic blood flow rate to be 19.5 mL/kg and 11.4%, and 1.22 mL/min/g liver and 12.9%, respectively. The CVs for albumin concentration ranged from 1.3% to 12.5%17,19–21) and the mean value was adopted, setting the CV value for albumin concentration at 5.8%. When the calculated CV of the parameters was less than 20%, the distribution of parameters was as-

![Fig. 1. Schematic for the prediction of interindividual variability in drug exposure by Monte Carlo simulation](image-url)
Table 1. Physiological and biochemical factors

<table>
<thead>
<tr>
<th></th>
<th>Unit</th>
<th>Mean</th>
<th>CV (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic blood flow rate</td>
<td>mL/min</td>
<td>1699</td>
<td>19.5</td>
<td>14</td>
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<tr>
<td></td>
<td></td>
<td>1445</td>
<td>15.2</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1503</td>
<td>28.8</td>
<td>16</td>
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<tr>
<td></td>
<td></td>
<td>1314</td>
<td>17.9</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>mL/min/kg</td>
<td>23.4</td>
<td>12.2</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>mL/min/mL liver</td>
<td>1.22</td>
<td>12.9</td>
<td>14</td>
</tr>
<tr>
<td>Liver volume</td>
<td>mL</td>
<td>1406</td>
<td>16.0</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1467</td>
<td>16.1</td>
<td>17</td>
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<td></td>
<td></td>
<td>1523–1659</td>
<td>18.1–21.2</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>mL/kg</td>
<td>19.5</td>
<td>11.4</td>
<td>14</td>
</tr>
<tr>
<td>Albumin conc.</td>
<td>g/L</td>
<td>47.4</td>
<td>3.9</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>39.4</td>
<td>5.6</td>
<td>20</td>
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<td></td>
<td></td>
<td>44.5</td>
<td>1.3</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>41.6</td>
<td>12.5</td>
<td>17</td>
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<tr>
<td>CYP3A4 contents in human liver microsomes</td>
<td>pmol/mg protein</td>
<td>104</td>
<td>90</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>96</td>
<td>53</td>
<td>23</td>
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<td>48.7</td>
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<td>66.2</td>
<td>99</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td>77.8</td>
<td>42</td>
<td>26</td>
</tr>
</tbody>
</table>

The mean and CV values for body weight were assumed to be 70 kg and 10%, respectively. The distribution of hepatic intrinsic clearance (CLint, h) was assumed to be log-normal and the mean values were set at 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 20, 40, 80, 160 and 320 mL/min/mL liver volume. Parameters were generated for 200 individuals in the simulation. The well-stirred, the parallel tube and the dispersion models were used as mathematical models for the liver.77)

Hepatic availability (Fh) values were calculated from the following equations for the well-stirred (Eq. 7), parallel tube (Eq. 8) and dispersion (Eq. 9) models:

\[
F_h = \frac{Q_h}{Q_h + f_B \cdot CL_{\text{int},h}} \tag{7}
\]

\[
F_h = \exp\left(-\frac{f_B \cdot CL_{\text{int},h}}{Q_h}\right) \tag{8}
\]

\[
F_h = \left(\frac{4a}{(1+a)^2} \exp\left\{(a-1)/2/D_n\right\} - (1-a)^2 \exp\left\{-(a+1)/2/D_n\right\}\right)
\]

where Qh is the hepatic blood flow rate, fB is the unbound fraction in the blood and Dn is the dispersion number (Dn = 0.17 was used).

The plasma unbound fraction (fp) was calculated from the equation fp = 1/(1 + nPt/Kd) where n, Pt and Kd are the number of binding sites, the albumin concentration and the dissociation constant, respectively. No interindividual variability of n or Kd was assumed. The ratio of the blood-to-plasma concentration (Rb), the fraction absorbed (Fa) and intestinal availability (Fg) were assumed to be 1.0. The hepatic clearance was calculated from the equation CLh = Qh(1 − Fh). The dose-normalized area under the curve (AUCdose) after intravenous and oral administration was calculated from the equations AUCdose = 1/CLh and FaFgFh/CLh, respectively. The mean and

\[
\mu = \ln(\text{arithmetic mean}) - \frac{\sigma^2}{2} \tag{3}
\]

\[
\sigma = \sqrt{\ln\left(\left(\frac{CV}{100}\right)^2 + 1\right)} \tag{4}
\]

Parameters were generated using the following equations for normal (Eq. 5) and log-normal (Eq. 6) distributions:

\[
\text{parameter} = \text{arithmetic mean} \cdot \left(1 + \frac{CV}{100} \cdot z\right) \tag{5}
\]

\[
\text{parameter} = e^{\mu + \sigma \cdot z} \tag{6}
\]
Table 2. List of CYP3A4 substrates selected to compare reported and simulated AUC and CV values

<table>
<thead>
<tr>
<th>Compound</th>
<th>Route</th>
<th>Ref.</th>
<th>Compound</th>
<th>Route</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)-α-Acetyl-methadol (LAAM)</td>
<td>iv, po</td>
<td>27</td>
<td>Nelfinavir</td>
<td>po</td>
<td>53</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>iv</td>
<td>28</td>
<td>Nevirapine</td>
<td>po</td>
<td>54</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>iv, po</td>
<td>29</td>
<td>Nifedipine</td>
<td>po</td>
<td>55, 56</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>po</td>
<td>30</td>
<td>Nisoldipine</td>
<td>po</td>
<td>57</td>
</tr>
<tr>
<td>Buspirone</td>
<td>iv, po</td>
<td>31, 32</td>
<td>Nitrendipine</td>
<td>po</td>
<td>58</td>
</tr>
<tr>
<td>Cisapride</td>
<td>po</td>
<td>33</td>
<td>Pimozide</td>
<td>po</td>
<td>59</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>iv, po</td>
<td>34</td>
<td>Prednisolone</td>
<td>iv, po</td>
<td>60</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>iv, po</td>
<td>35</td>
<td>Quinidine</td>
<td>iv, po</td>
<td>61, 62</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>iv, po</td>
<td>36</td>
<td>Quinine</td>
<td>iv, po</td>
<td>63</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>po</td>
<td>37</td>
<td>Repaglinide</td>
<td>iv, po</td>
<td>64, 65</td>
</tr>
<tr>
<td>Dapsone</td>
<td>iv, po</td>
<td>38, 39</td>
<td>Ritonavir</td>
<td>po</td>
<td>66</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>po</td>
<td>40</td>
<td>Saquinavir</td>
<td>po</td>
<td>53</td>
</tr>
<tr>
<td>Diazepam</td>
<td>iv</td>
<td>41</td>
<td>Sildenafil</td>
<td>po</td>
<td>67</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>po</td>
<td>42, 43</td>
<td>Simvastatin</td>
<td>po</td>
<td>68</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>iv, po</td>
<td>44</td>
<td>Sirolimus</td>
<td>po</td>
<td>69</td>
</tr>
<tr>
<td>Etoposide</td>
<td>po</td>
<td>45</td>
<td>Tacrolimus</td>
<td>po</td>
<td>70</td>
</tr>
<tr>
<td>Felodipine</td>
<td>iv, po</td>
<td>46</td>
<td>Toremifene</td>
<td>po</td>
<td>71</td>
</tr>
<tr>
<td>Finasteride</td>
<td>po</td>
<td>47</td>
<td>Trazodone</td>
<td>iv, po</td>
<td>72</td>
</tr>
<tr>
<td>Indinavir</td>
<td>po</td>
<td>48</td>
<td>Triazolam</td>
<td>iv, po</td>
<td>73</td>
</tr>
<tr>
<td>Loratadine</td>
<td>po</td>
<td>49</td>
<td>Verapamil</td>
<td>po</td>
<td>74, 75</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>iv, po</td>
<td>50, 51</td>
<td>Zolpidem</td>
<td>iv, po</td>
<td>76</td>
</tr>
<tr>
<td>Midazolam</td>
<td>iv, po</td>
<td>52</td>
<td></td>
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</table>

CV values of the simulated parameters were derived using arithmetic calculus. The reported AUCs for drugs were normalized by the dose and converted to the AUC in blood using the corresponding Rb values. If the Rb value was not known, it was assumed to be 1.0. These reported AUC values were compared with the simulated values.

**Prediction of intestinal availability and its variability:** Fg values were predicted from the equation:

\[
F_g = \frac{PS}{PS + CL_{int,g}} = \frac{1}{1 + \frac{PS}{CL_{int,g}}}
\]  

(10)

where \(CL_{int,g}\) and PS are intestinal intrinsic clearance and membrane permeability clearance, respectively. To predict the mean and CV values of \(F_g\), the mean and CV values of \(CL_{int,g}/PS\) were determined by the following analyses. A good relationship between hepatic clearance and FaFg was observed in our previous report.\(^{\text{39}}\) Fa was assumed to be 1. The data of \(CL_{int,h}\) and FaFg\(^{\text{39}}\) were fitted to Eq. 11 using WinNonlin (Pharsight, Mountain View, CA, USA).

\[
F_g = \frac{CL_{g,50}}{CL_{g,50} + CL_{int,h}}
\]  

(11)

where \(CL_{g,50}\) takes the same value as \(CL_{int,h}\) at \(F_g = 0.5\). The \(CL_{g,50}\) value was estimated to be 402 mL/min/kg body weight. The mean \(CL_{int,g}/PS\) was calculated from the mean \(CL_{int,h}\) set using the following equation for the simulation:

\[
\frac{CL_{int,g}}{PS} = \frac{CL_{int,h}}{402}
\]  

(12)

The following analyses were performed to determine the CV value of \(CL_{int,g}/PS\). Individual \(CL_{int,g}/PS\) values were estimated from the clearance data of midazolam after intravenous and oral administration\(^{\text{52}}\) using the following equations. Urinary excretion of midazolam was negligible. The Rb value of midazolam was 0.52.\(^{\text{52}}\) The total body clearance of midazolam was assumed to be \(CL_h\).
Prediction of variability for clearance of midazolam: To predict the variability of midazolam hepatic blood flow rate. In the case of oral administration, CYP3A4 content and CLint, g/PS were set at 33% and 81%, respectively. The CV of hepatic variability was set at 16.3 mL/min/mL liver volume. The mean value of intrinsic clearance for CYP3A4 sub-classes was set at 10, 30, 100, 300, 500, 1000, 2000, 3000 and 10000 mL/min/mL liver volume.

The mean and CV values for AUCdose were simulated with intestinal first-pass metabolism and various blood unbound fractions (0.1, 0.01 and 0.001) under the same conditions as those without intestinal metabolism described above, except for Fg and the use of various unbound fractions. The AUCdose was calculated from the equation AUCdose = FaFgFh/CLh, assuming Fa to be 1.

The nPt/Kd of midazolam was calculated from the following equation:

\[
\text{CL}_{\text{int}, h} = \frac{Q h}{f_b} \ln \left(1 - \frac{C_{Lh}}{Q h}\right) 
\]

The mean value of intrinsic clearance for CYP3A4 substrates was set at 16.3 mL/min/mL liver volume. The unbound fraction was set at 0.02. The CV of hepatic CYP3A4 content and CLint, g/PS were set at 33% and 81%, respectively. The CLh and Fh values were calculated using the parallel tube model. The means and 95% confidence limits were simulated for body weights from 50 to 120 kg.

**Prediction of interindividual variability in exposure**

**Variability in intestinal metabolism:** The variability of Fg values was simulated using the CV for the CLint, g/PS stated above and was compared with the reported variability of Fg for alfentanil, midazolam and triazolam (Fig. 3). The simulated values were similar to the CVs of Fg for triazolam and alfentanil.

The effect of the variability of Fg on the variability of AUCdose was determined from simulated data. The CLg, 50 (CLint, h at Fg = 0.5) was estimated to predict Fg from CLint, h. The value of CLg, 50 was estimated to be 402 mL/min/kg body weight (r = 0.877) (Fig. 4). AUCdose values were simulated using various blood unbound fractions because the blood unbound fraction affects Fh but not Fg (Fig. 5). For unbound fractions greater than 0.1, no differences were observed in the simulated CV values for a given AUCdose.

**Influence of each factor on interindividual variability:** The effects of factors such as liver volume, hepatic blood flow rate, plasma albumin concentration and intestinal variability were studied using a parallel tube model without consideration of the effect of intestinal metabolism. To clarify the effect of the parameters, each parameter in turn was given variability with the other parameters having no variability and the CVs of AUCdose were simulated (Fig. 6). The variability of CYP3A4 content contributes predominantly to the value of the CV of AUCdose. When the CYP3A4 content did not have variability and the other parameters did, the CV value of the simulated AUCdose value was determined to be 18% for low-clearance drugs (drugs with high AUCdose values) (Fig. 7).

**Prediction of variability for the PK of midazolam:** The total body clearance and oral clearance of midazolam in Japanese and European American subjects were simulated using the parameter data collected and compared with observed clearances. The reported mean and SD values for body weight and the other parameters for both Japanese and European Americans were used for the predictions. In all cases, the simulated mean and SD values reflected the observed values in humans (Table 3), suggesting that this method may be useful to
**Fig. 2.** Prediction of interindividual variability of dose-normalized AUC after intravenous and oral administration of CYP3A4 substrates using well-stirred, parallel tube and dispersion models

The CYP3A4 substrates plotted are listed in Table 2. The parameters for 200 people were generated from a random number set. CV values in the inset are the CVs of intrinsic clearance for CYP3A4 in the simulation. The mean values of intrinsic clearance for CYP3A4 used were 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 20, 40, 80, 160 and 320 mL/min/mL liver volume. The unbound fraction was assumed to be 0.1. The prediction model does not include intestinal metabolism.

**Fig. 3.** Comparison between predicted and observed variability of intestinal availability (Fg)

The open circle, closed circles and the open square represent the observed mean and CV values of Fg for alfentanil,80) midazolam80,81) and triazolam,81) respectively. The line represents predicted variability. The CV value of CL_{int, g/PS} was 81%. The mean values of intrinsic clearance for hepatic CYP3A4 used were 10, 30, 100, 300, 500, 1000, 2000, 3000 and 10000 mL/min/mL liver volume.

**Fig. 4.** Relationship between Fg and hepatic intrinsic clearance

Closed circles represent the observed Fg and hepatic intrinsic clearance values for CYP3A4 substrates. Data from our previous study78) were used. Solid line represents a fitted line.

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**Table 2**

<table>
<thead>
<tr>
<th>CYP3A4 Substrate</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfentanil</td>
<td>33</td>
</tr>
<tr>
<td>Midazolam</td>
<td>37</td>
</tr>
<tr>
<td>Triazolam</td>
<td>51</td>
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</table>

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Motohiro Kato, et al.
predict the variability of CYP3A4 substrates. For each subject, the 95% confidence intervals for clearance of midazolam after intravenous or oral administration depending on his or her body weight were predicted and are shown in Figure 8. Ninety-five percent \(^{38,40}\) of all reported clearances after intravenous or oral administration were found within the 95% confidence intervals of the predicted values.

**Discussion**

We report here the construction of a method to predict interindividual variability for PK (AUC\(_{\text{dose}}\)) in humans. First, a method for predicting the variability of a given compound eliminated by metabolism in healthy humans was developed based on factors that can affect PK interindividual variability. Sensitivity analysis was performed and the influence of each parameter on the prediction result was examined (Figs. 5 and 6). The CYP3A4 contents variability greatly affected the variability of the AUC (Fig. 6), whereas the influence of other parameters was slight. The CVs for liver weight, hepatic blood flow rate and serum albumin concentration were all less than 20% (Table 1).

The well-stirred, the parallel tube and the dispersion models are all widely used as prediction models, but the prediction of hepatic availability using the well-stirred model is known to be overestimated when the product of
the intrinsic clearance and blood unbound fraction of a compound is greater than the hepatic blood flow rate. The present study used comparison of simulated and reported CVs to confirm the suitability of each model, and results suggested that both the parallel tube and dispersion models are suitable (Fig. 2). For drugs in which the hepatic clearance is limited by hepatic blood flow, the CV values exhibited small or large variability after intravenous or oral administration, respectively, suggesting that there might be greater variability with low-bioavailability drugs. Hellriegel[82] also reported that low-bioavailability drugs exhibited larger variability, which supports our simulation results. However, variability in drug absorption also affects the variability of bioavailability and must be evaluated. The present simulation indicated that a drug with low bioavailability exhibits large variability in AUC. Large variability in PK might influence efficacy and safety of the drug and become a disadvantage in clinical use. This study makes it possible to predict not only the mean of exposure but also the variability.

The prediction of interindividual variability for the PK of CYP3A4 substrates was attempted. Simulation results using 33% as the CV of CYP3A4 contents—the smallest CV value used in the simulation—reflected the reported CV values for both intravenous and oral administration (Fig. 2). Interindividual variability of microsomal intrinsic clearances for benzodiazepines were also reported to be greater than for in vivo intrinsic clearances obtained from healthy human volunteers.83) The wide variability in the amount of microsomal CYP3A4 might be caused by recovery or degradation in the microsomal preparation. Simcyp software uses a similar approach and predicts the variability for PK using the variability obtained from human microsomes.13) Our results suggest that prediction using the variability of microsomes might overestimate the variability of PK for CYP3A4 substrates. Therefore, it is necessary to evaluate real variability from in vivo data.

Some CYP3A4 substrates are metabolized by intestinal first-pass metabolism. It is not clear whether intestinal first-pass metabolism affects interindividual PK variability after oral administration. Hence, in this study, the variability for AUCdose was simulated with intestinal first-pass metabolism. The relation between hepatic intrinsic clearance and Fgh in previous reports[78] was used to predict the variability for Fg (Fig. 4), even though a standard method for the prediction of Fg has not been established. Although the CV value of CLint,g/PS was estimated to be 81%, there is a bias in that value because the individual Fh was estimated using the mean value of the hepatic blood flow rate; nevertheless, the simulated variability of Fg for triazolam and alfentanil were similar to the reported variability (Fig. 3), so 81% might be an appropriate value. When the effect of Fg on the CVs of AUCdose was investigated using the simulation (Fig. 5), the blood unbound fraction affected the CV. The prediction of Fg does not require the unbound fraction but, for the prediction of Fh, unbound fraction information is essential. The effect of unbound fraction on AUCdose is due to the difference between the prediction settings for Fh and Fg. When CLint,h was 40.2 mL/min/kg body weight and fb was 0.1, Fg and Fh were predicted to be 0.91 and 0.84, respectively. When CLint,h was 4020 mL/min/kg body weight and fb was 0.001, Fg and Fh were predicted to be 0.09 and 0.84, respectively. Although Fh values were the same in both cases, the Fg values were different. When Fg was 0.09, the CV of Fg was approximately 80% (Fig. 3). A drug with a CLint,h higher than 402 mL/min/kg body weight and a low unbound fraction of less than 0.01 may thus exhibit a wide range of variability. These predictions are in perspective because these phenomena have not been observed. Additionally, the prediction method of Fg is the empirical rule from the relation between CLint,h and Fg. More studies are needed to establish a method for predicting interindividual variability with intestinal first-pass metabolism.
The total body clearance and oral clearance of midazolam in Japanese and European American subjects were simulated and compared with observed clearances (Table 3). In all cases, the simulated mean and SD values were comparable to the observed values in humans. This result suggests that it is possible to predict the variability of PK of a drug from the mean and SD values of body weight and from the intrinsic clearance for a drug. In the discovery stage, the mean intrinsic clearance of a candidate is predicted using human microsomes or hepatocytes, the predictability of which, according to in vitro data, was 50% within a threefold range and 70% within a fivefold range. After phase I studies, the mean and SD values of clearance for a drug will be known, and these parameters can be used to predict the interindividual variability of PK together with information of the relation between these parameters and pathophysiological conditions in further clinical studies.

While the present study’s attempt to use only body weight data to predict mean and 95% confidence intervals of the clearance for midazolam was successful, the predictive accuracy should be improved by adding further genetic information, such as that mentioned in the Introduction. Moreover, the 20% value for the CV of AUC for low-clearance drugs may have been caused in part by variability in liver volume, blood flow rate and plasma albumin concentration, so information on non-genetic factors is also important because these factors affect interindividual variability. More studies are needed to improve the prediction accuracy.

In this study, it was assumed that drugs bind to albumin. Some drugs bind to other proteins such as alpha 1-acid glycoprotein (AGP). Good correlation between the AUCs of imatinib and AGP concentrations has been observed, suggesting that AGP is one of the factors affecting interindividual variability. For prediction of the variability for basic drugs such as CYP2D6 substrates, the variability of AGP concentration may need to be considered.

Having developed a method for predicting the variability of exposure for CYP3A4 substrates in this study, we are planning future studies to predict the variability of PK for CYP2C9, 2C19 and 2D6 substrates which will include the effects of sex, age, ethnic origin and pathological conditions. This system will lead to more efficient drug development and should be useful in designing personalized therapies. Furthermore, in combination with a pharmacokinetic/pharmacodynamic model, this method would enable the simulation of clinical studies.

In conclusion, a method for predicting the variability in PK in healthy subjects was developed. The parallel tube and dispersion models were found to be suitable. Simulated AUC values using 33% as the CV of CYP3A4 content reflected the reported AUC variability for both intravenous and oral administration. Interindividual variability in the PK of CYP3A4 substrates is thus predictable.

References


