The Intestinal First-pass Metabolism of Substrates of CYP3A4 and P-glycoprotein —Quantitative Analysis Based on Information from the Literature

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Summary: It is suggested that the bioavailability of CYP3A4 substrates might be low due to first-pass metabolism in the small intestine, and it is possible that P-glycoprotein (P-gp) may influence first-pass metabolism in a co-operative manner. We have collected information of the pharmacokinetics of CYP3A4 substrates to evaluate the fraction absorbed (Fa), intestinal availability (Fg) and hepatic availability (Fh) and have investigated the intestinal first-pass metabolism and the effect of P-gp on this. The pharmacokinetic data involved ten compounds metabolized by CYP3A4 in humans, with and without an inhibitor or inducer. FaFg, which is the product of Fa and Fg, and Fh were calculated using three liver blood flow rates (17.1, 21.4, 25.5 mL/min/kg) in consideration of variations in the liver flow rate. Co-administration with an inhibitor of CYP3A4 and treatment of an inducer of CYP3A4 caused an increase and decrease in the FaFg of CYP3A4 substrates, regardless of the liver blood flow, indicating that CYP3A4 substrates exhibit a first-pass effect in their metabolism. This holds true regardless of whether the compounds are P-gp substrates or not. No relationship was observed between FaFg and Fh, regardless of the hepatic blood flow rate and the P-gp substrates. The FaFg of both P-gp and non-P-gp substrates decreased as the hepatic intrinsic clearance increased. FaFg was markedly reduced when the hepatic intrinsic clearance was more than 100 mL/min/kg. This phenomenon was not observed in substrates of CYP isoforms other than CYP3A4.

In conclusion, it is suggested that CYP3A4 substrates which have a hepatic intrinsic clearance of 100 mL/min/kg exhibit a low bioavailability due to intestinal first-pass metabolism, regardless of whether they are substrates of P-gp or not.

Key words: intestinal first-pass metabolism; CYP3A4; P-glycoprotein; bioavailability
Introduction

When given orally, a drug is absorbed from the gut to enter the systemic circulation via the liver. The fraction of the administered drug reaching the blood circulation is its bioavailability (F), and this is expressed by the product of the fraction absorbed (Fa), intestinal availability (Fg), and hepatic availability (Fh). Although it was thought that Fa and Fh predominantly contributed to F, Fg has been observed to make a significant contribution in the case of some CYP3A4 substrates such as cyclosporine, midazolam, sirolimus and nifedipine and it has been pointed out that some CYP3A4 substrates exhibit intestinal first-pass metabolism. Not only CYP3A4 but also P-glycoprotein (P-gp) is present in the small intestine acting as an efflux pump for drugs, and presenting a barrier to drug absorption.

Methods

The collection of pharmacokinetic parameters: CYP3A4 substrates that are substrates or non-substrates of P-gp were selected. Cyclosporine, indinavir, nicardipine, quinidine, tacrolimus, and verapamil were selected as P-gp substrates. Felodipine, midazolam, nifedipine, and propafenone were selected as non-Pgp substrates. The total body clearance (CLtot), renal clearance (CLR), distribution volume (Vd), elimination rate constant and F of these CYP3A4 substrates were obtained from the published literature. The CLtot or ke values of CYP3A4 substrates following co-administration of an inhibitor or inducer were obtained. The pharmacokinetic data for propafenone in poor metabolizers of CYP2D6 were used because propafenone is mainly metabolized by CYP2D6 and CYP3A4. The Fg of triazolam and zolpidem was used to clarify the effect of enzyme induction. The pharmacokinetic parameters of CYP1A, 2C, 2D and 3A substrates were obtained from Good- man and Gilman’s textbook, The Pharmacological Basis of Therapeutics, 9th ed.

Analysis: Total body clearances were calculated from the AUC after intravenous administration using equation 1. The hepatic clearance (CLh) was estimated from the CLtot and CLR using equation 2. Fh was calculated from equation 3.

\[
\text{CLh} = \frac{\text{Dose}}{\text{AUC}} \quad (1)
\]

\[
\text{CLh} = \text{CLtot} - \text{CLR} \quad (2)
\]

\[
\text{Fh} = 1 - \frac{\text{CLh}}{\text{Qh}} \quad (3)
\]

\[
\text{FaFg} = \frac{\text{F}}{\text{Fh}} \quad (4)
\]

Three rates (17.1 (1200 mL/min/70 kg), 21.4 (1500 mL/min/70 kg), and 25.5 mL/min/kg) were used as Qh. Fa and Fg were evaluated as FaFg, which is the product of Fa and Fg, because Fa and Fg cannot be separated. FaFg was obtained by dividing F by Fh. CLtot was obtained from equation 5 when there were no pharmacokinetic data on CYP3A4 substrates after intravenous administration during treatment with an inhibitor or inducer.

\[
\text{CLtot} = \text{ke Vd} \quad (5)
\]

The hepatic intrinsic clearance (CLint) of CYP3A4 substrates was calculated from equation 6 using the well-stirred model.
The Intestinal First-pass Metabolism

Table 1. Fh and FaFg of P-gp substrates and non substrates in human

<table>
<thead>
<tr>
<th>P-gp substrate</th>
<th>inhibitor or inducer</th>
<th>CLh (mL/min/kg)</th>
<th>Qh = 17.1 mL/min/kg</th>
<th>Qh = 21.4 mL/min/kg</th>
<th>Qh = 25.5 mL/min/kg</th>
<th>ref.</th>
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<tr>
<td>Cyclosporine</td>
<td>—</td>
<td>5.14</td>
<td>0.700</td>
<td>0.386</td>
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<td>7.07</td>
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<td>—</td>
<td>5.36</td>
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<td>0.320</td>
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<td>0.651</td>
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<td>—</td>
<td>4.53</td>
<td>0.736</td>
<td>0.256</td>
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<td>grapefruit juice</td>
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<td>0.755</td>
<td>0.404</td>
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<td>—</td>
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<td>0.788</td>
<td>1.019</td>
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<td>—</td>
<td>10.9</td>
<td>0.362</td>
<td>1.382</td>
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<td>0.955</td>
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<td>0.142</td>
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<td>—</td>
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<td>0.965</td>
<td>0.131</td>
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<td>Tacrolimus</td>
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<td>0.955</td>
<td>0.142</td>
<td>0.957</td>
<td>0.142</td>
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<td>0.949</td>
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<td>13.3</td>
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<td>1.500</td>
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<td>24.2</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>non P-gp substrate</td>
<td>—</td>
<td>11.6</td>
<td>0.323</td>
<td>1.239</td>
<td>0.459</td>
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<td>—</td>
<td>—</td>
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<td>Felodipine</td>
<td>—</td>
<td>11</td>
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<td>0.412</td>
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<td>iraconazol</td>
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<td>0.870</td>
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<td>—</td>
<td>1.6</td>
<td>0.907</td>
<td>0.882</td>
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<tr>
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<td>6.6</td>
<td>0.615</td>
<td>0.518</td>
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<td>Midazolam</td>
<td>—</td>
<td>15.7</td>
<td>0.084</td>
<td>0.373</td>
<td>0.267</td>
<td>0.117</td>
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<tr>
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<td>rifampicin</td>
<td>6.1</td>
<td>0.644</td>
<td>1.277</td>
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<tr>
<td>Propafenone</td>
<td>—</td>
<td>12.1</td>
<td>0.292</td>
<td>1.338</td>
<td>0.433</td>
<td>0.901</td>
</tr>
</tbody>
</table>

\[
\text{CLint} = \frac{Qh \times CLh}{(Qh - CLh)} / fp / Rb
\]  
where fp and Rb are the plasma unbound fraction and blood-to-plasma concentration ratio, respectively.

Results

Hepatic and intestinal availability: The FaFg and Fh of CY3A4 substrates were estimated using three Qh values (Table 1). The relationship between FaFg and Fh is shown in Fig. 1. No matter which Qh was used, the FaFg of nicardipine, felodipine, midazolam, cyclosporine, and tacrolimus was 0.5 or less. There was no relationship between FaFg and Fh regardless of the hepatic blood flow rate and P-gp substrates. In the case of co-administration of an inhibitor of CYP3A4, the FaFg of cyclosporine, quinidine, tacrolimus, felodipine and midazolam increased regardless of the Qh. There was no marked difference in the increase in FaFg produced by an inhibitor of CYP3A4 between P-gp and non-P-gp substrates. The FaFg of cyclosporine, tacrolimus, midazolam and nifedipine decreased following treatment with an inducer regardless of the Qh.

The relationship between hepatic intrinsic clearance and FaFg: The relationship between the hepatic intrinsic clearance and FaFg calculated using three hepatic blood rates is shown in Fig. 2. The FaFg of both P-gp and non-P-gp substrates decreased as the hepatic intrinsic clearance increased regardless of the Qh. The FaFg of CYP3A4 substrates decreased when the hepatic intrinsic clearance exceeded 100 mL/min/kg (Fig. 2 and 3). The FaFg of CYP1A2, 2C and 2D substrates did not decrease as the hepatic intrinsic clearance increased (Fig. 3).

Effect of enzyme induction: The relation between FaFg before treatment with rifampicin 600 mg/day and the ratio of FaFg before treatment to that after treatment is shown in Fig. 4. The data for triazolam and zolpidem, which are CYP3A4 substrates, were added. The smaller the values of FaFg, the greater the effect of rifampicin. A negative correlation between FaFg and the ratio of FaFg before treatment with rifampicin to that after treatment was observed except for cyclosporine and tacrolimus.
A certain Qh value has to be assumed when FaFg is estimated from AUCs after intravenous and oral administration. Some values of Qh have been reported previously such as 1200–1600 mL/min,31) 1314 ± 403 mL/min32) and 25.5 mL/min/kg.33) The estimated FaFg depends on the Qh. Therefore, three Qh values were used in the present studies. The Fh of CYP3A4 substrates for which the hepatic clearance was more than 8 mL/min/kg was influenced by the Qh (Fig. 1 and Table 1) and, therefore, the FaFg of those substrates was also influenced by the Qh (Fig. 1 and Table 1). The FaFg of nicardipine, felodipine, midazolam, cyclosporine and tacrolimus was less than 0.5 at all the hepatic blood flow rates. If the Fa of these substrates of CYP3A4 can be obtained, it is possible to estimate their intestinal first-pass metabolism. Nicardipine, felodipine and nifedipine were completely absorbed in animal studies and human studies using labeled compounds.34–36) The FaFg of felodipine and midazolam, which are non-P-gp substrates, increased following co-administration of an inhibitor of CYP3A4 (Table 1). These results suggest that these substrates may be metabolized by CYP3A4 in the intestine. The FaFg of P-gp substrates such as cyclosporine, tacrolimus, quinidine and verapamil also increased following co-administration of an inhibitor. The change in FaFg of P-gp substrates is not necessarily greater than that of non-P-gp substrates (Table 1). Benet et al. have proposed the possibility of high first-pass metabolism due to the synergistic effects of CYP3A4 and P-gp.8,9) Their proposal was also supported theoretically in our previous study.37) However, in the present study, no supporting evidence was obtained. This may not necessarily exclude a synergistic effect between P-gp and CYP 3A4. It might be due to the good absorption of the substrates selected in the present study. This problem should be examined in future studies.

It is expected that the FaFg and Fh of non-P-gp substrates are correlated and those of P-gp substrates do not fit this relationship because both Fh and Fg are functions of the intrinsic clearance. However, no significant correlation between FaFg and Fh was observed.
Fig. 2. Relationship between CLint and the FaFg of substrates of CYP3A4.
CLint and FaFg were calculated using 17.1 (A), 21.4 (B) and 25.5 (C) mL/min/kg as the hepatic blood flow rate. Open circles represent P-gp substrates. Closed circles represent non P-gp substrates. 1, cyclosporine; 2, indinavir; 3, nicardipine; 4, quinidine; 5, tacrolimus; 6, verapamil; 7, felodipine; 8, midazolam; 9, nifedipine; 10, propafenone.

Fig. 3. Relationship between CLint and the FaFg of substrates of CYP1A, 2C and 2D.
Open squares, closed triangles and open triangles represent 2C, 2D and 1A substrates, respectively. FaFg was calculated using 25.5 mL/min/kg as the hepatic blood flow rate. 1, cyclosporine; 2, indinavir; 3, nicardipine; 4, quinidine; 5, tacrolimus; 6, verapamil; 7, felodipine; 8, midazolam; 9, nifedipine; 10, propafenone; 11, amlopidine; 12, clonazepam, 13, carbamazepine, 14, alprazolam, 15, diclofenac; 16, glyburide; 17, tolbutamide; 18, propranolol; 19, fluoxetine; 20, imipramine; 21, nortriptyline; 22, amitriptyline; 23, risperidone; 24, mexiletine; 25, clozapine.
metabolism because FaFg was markedly decreased when useful as an index of substantial intestinal first-pass metabolism. The human liver weight, microsome hepatic intrinsic clearance 100 mL/min/kg as the hepatic blood flow rate. 1, tacrolimus; 2, cyclosporine; 3, midazolam; 4, triazolam; 5, nifedipine; 6, verapamil; 7, zolpidem; 8, quinidine; 9, propafenone.

(Fig. 1). This might be due to the plasma protein binding. Protein binding does not affect FaFg although it does affect Fh. The intrinsic clearance is a value corrected by the plasma unbound fraction. The FaFg of CYP3A4 substrates decreased as the hepatic intrinsic clearance increased (Fig. 2). This result suggests that a drug which is metabolized well in the liver may also be extensively metabolized in the intestine. The cDNA sequence of CYP3A4 obtained from the intestine was the same as that from the liver89 and the CYP3A4 in the liver and intestine might be the same protein. In addition, the Km values of CYP3A4 for some substrates in liver and intestine were similar.2 However, the ratio of the CYP3A4 content in the liver to that in the intestine can be considered to be the ratio of the intrinsic clearance between liver and intestine for CYP3A4 substrates. This reasonably explains the relationship between the hepatic intrinsic clearance and FaFg. The hepatic intrinsic clearance 100 mL/min/kg can be useful as an index of substantial intestinal first-pass metabolism because FaFg was markedly decreased when the hepatic intrinsic clearance was more than 100 mL/min/kg (Fig. 2). We investigated the relationship between the intrinsic clearance and the FaFg of other CYPs substrates such as CYP 1A, 2C and 2D. The FaFg of these substrates did not decrease as the intrinsic clearance increased (Fig. 3). It has been reported that approximately 70% of the total CYP in the small intestine is CYP3A4.48 CYP3A substrates, in particular, might be metabolized in the small intestine. For this reason we proposed a hepatic intrinsic clearance of 100 mL/min/kg as an index of substantial intestinal first-pass metabolism. The human liver weight, microsome content and body weight were assumed to be 1700 g, 52.5 mg/g liver and 70 kg, respectively. The intrinsic clearance 100 mL/min/kg corresponds to 78 mL/min/mg microsomal protein (1275 mg microsomal protein/kg B.W.). When the elimination rate constant is measured using human microsomes, 1 mg/mL, in a metabolic stability test, the hepatic intrinsic clearance 100 mL/min/kg corresponds to 0.078 min-1. The half-life is 8.9 min (= 0.693/0.078). When the elimination half-life of the substrate exceeds 10 minutes in that metabolic stability test using human liver microsomes, the possibility of a substantial degree of intestinal first-pass metabolism may be excluded. When the elimination half-life of the substrate is less than 10 minutes, the compound might be metabolized by CYP3A4 and exhibit low bioavailability.

Although rifampicin induces CYP3A4, it also induces P-gp.40 The contents of P-gp and CYP3A4 in biopsy samples after treatment with rifampicin, 600 mg/day, measured by Western blotting increased 3.5- and 4.4-fold compared with the values before treatment.42 It cannot be denied that the decrease in the FaFg of P-gp substrates may be due to the induction of P-gp. However, a decrease in the FaFg of non-P-gp substrates such as midazolam and nifedipine was observed. This result suggests that the decrease in FaFg may be due to the induction of CYP3A4. As shown in Fig. 4, compounds with low FaFg values are affected by treatment with rifampicin 600 mg/day. The phenomenon that the P-gp substrate was affected to a greater extent by enzyme induction was not observed. The behavior of cyclosporine and tacrolimus differs from that of other CYP3A4 substrates. There could be a number of reasons for this. The FaFg of cyclosporine and tacrolimus was 0.635 and 0.312, respectively, even when ketoconazole was co-administered. The changes in FaFg for cyclosporine and tacrolimus were smaller than those for other substrates, suggesting that Fa might be low. On the other hand, the increase in the hepatic intrinsic clearance of cyclosporine and tacrolimus produced by rifampicin was about 1.5-fold while the increase in the hepatic intrinsic clearance of quinidine and triazolam was about 3- to 4-fold. The low induction effect of rifampicin may be one reason. The present study indicates that the intestinal first-pass metabolism of substrates which are metabolized by CYP3A4 in the intestine may be influenced by enzyme induction in the intestine. In the present study, three Qh values were used. A suitable Qh for pharmacokinetic analysis remains to be established. When the hepatic intrinsic clearance of CYP3A4 substrates was estimated using 25.5 mL/min/kg as the Qh, the increase in the hepatic intrinsic clearance of CYP3A4 substrates was approximately 3- to 4-fold. However, when using values of 21.4 or 17.1 mL/min/kg, the increase in hepatic intrinsic clearance...
clearance was different for each substrate. A suitable hepatic blood flow rate may be in the region of 25.5 mL/min/kg.

The present study indicates that the CYP3A4 substrates which are metabolized extensively in the liver might also undergo first-pass intestinal metabolism and that the effect of P-gp on intestinal first-pass metabolism may be low. On the other hand, Lorn et al. have reported that for peak blood concentrations of cyclosporine, intrinsic clearance 100 mL/Wmin for a CYP3A4 substrate in the metabolic stability test using 1 mg human Ms protein and the small intestine.


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