Review

Clinical Importance of OATP1B1 and OATP1B3 in Drug–Drug Interactions

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Summary: OATP1B1 and OATP1B3 are transporters that are expressed on the sinusoidal membrane of hepatocytes; they accept a number of therapeutic reagents as their substrates. In vitro and in vivo studies have shown that some drugs inhibit these transporters and cause clinically relevant drug–drug interactions (DDIs). Among these drugs, cyclosporin A markedly increases the plasma concentrations of OATP1B1 substrates. In such cases, the area under the plasma concentration–time curve and the maximum concentration of the affected drugs are increased to a similar degree. Even for OATP1B1 substrates that are metabolized in the liver, the hepatic uptake rate is a determinant of overall hepatic clearance, and the DDIs are partly caused by the inhibition of OATP1B1. Gemfibrozil displays DDIs with some OATP1B1 substrates, although their extent is small. Rifampicin and some HIV protease inhibitors are also OATP1B1 inhibitors. Rifampicin is also an inducer of metabolic enzymes, and although its single coadministration produces an increase in the plasma concentration of the affected drugs, multiple coadministrations may result in reductions in the plasma concentrations of OATP1B1 and CYP3A4 bisubstrates. As a large number of therapeutic reagents are substrates and/or inhibitors of OATP1B1 and OATP1B3, we should be aware of DDIs caused by the inhibition of these transporters.

Keywords: OATP; drug–drug interactions; hepatic transport; transporters; pharmacokinetics

Introduction

Pharmacotherapy using multiple drugs is often applied and sometimes causes drug–drug interactions (DDIs). Pharmacokinetic interactions caused by the inhibition or induction of drug-metabolizing enzymes have been intensively investigated.1–4) Recently, a number of DDIs caused by the inhibition or induction of drug transporters have also been reported.5) Among these transporters, multidrug resistance 1 (MDR1) is responsible for the efflux of many therapeutic reagents in intestine, liver, and kidney.5–8) There have been a large number of reports on DDIs caused by the inhibition or induction of this transporter.9–11)

Organic anion transporting polypeptides (OATPs/Oatps) accept many therapeutic reagents as their substrates.12–15) OATP1B1 and OATP1B3 are reported to be exclusively expressed in the liver and play important roles in the hepatic uptake of many therapeutic reagents, although OATP1B3 is also expressed in tumor tissues.16–22) Although intracellular glutathione was suggested to be the driving force behind rat Oatp1a1 and Oatp1a5 activity, it does not facilitate transport mediated by OATP1B1 or OATP1B3, and their driving forces are unknown.23,24) Pharmacokinetic parameters for some OATP substrates are shown in Table 1. Some substrates of OATP1B1 and OATP1B3 are taken up into the liver, where they are metabolized (Table 1). Thus, for these substrates, the rate of transporter-mediated uptake is one of the determinants of their overall metabolic rate.25,26) Therefore, the inhibition of transporter-mediated hepatic uptake may change the plasma concentrations of drugs that are eliminated by hepatic metabolism. The DDI between cerivastatin and cyclosporin A (CsA) was at first reported to be caused by the inhibition of hepatic uptake transporters including OATP1B1.27,28) Before the report of this DDI, cerivastatin was believed to have a safe profile with a low risk of DDI because it has dual metabolic pathways that are mediated by cytochrome P450 2C8 (CYP2C8) and 3A4 (CYP3A4).29) After our report, there were a number of reports of clinically relevant DDIs caused by the inhibition of OATP1B1, and an increasing focus has been put on...
transporter-related DDIs. To evaluate the risk of transporter-mediated DDIs, the International Transporter Consortium produced a list of important transporters that should be subject to pharmacokinetic studies and suggested methods for transporter assays and data interpretation. In this review, I aim to show clinically relevant DDIs caused by the inhibition of OATPs and to elucidate their properties.

**Clinical Importance of OATP1B1 and OATP1B3**

OATP1B1 and OATP1B3 are expressed in the liver and are localized on the sinusoidal membrane. These transporters accept as substrates a number of organic anions and mediate their hepatic uptake, e.g., 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, valsartan, olmesartan, and bile acids in addition to the glucuronide and sulfate conjugates of many drugs.

To show their clinical importance, the effects of genetic polymorphism in OATP1B1 and OATP1B3 on the pharmacokinetics of drugs should be examined. There have been many reports of alterations in the pharmacokinetics of HMG-CoA reductase inhibitors, statins, olmesartan, and bile acids in addition to the glucuronide and sulfate conjugates of many drugs.

Table 1. Pharmacokinetic parameters for OATP1B1 substrate drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Atorvastatin</th>
<th>Cerivastatin</th>
<th>Fluvastatin</th>
<th>Pravastatin</th>
<th>Rosuvastatin</th>
<th>Repaglinide</th>
<th>Bosentan</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL</td>
<td>3.75 L/h</td>
<td>0.21 L/h/kg</td>
<td>0.96 L/h/kg</td>
<td>0.810 L/h/kg</td>
<td>48.9 L/h</td>
<td>331 L/h</td>
<td>4.8–8.71 L/h</td>
</tr>
<tr>
<td>A&lt;sub&gt;v&lt;/sub&gt;</td>
<td>~0</td>
<td>~0</td>
<td>0.049</td>
<td>0.467</td>
<td>0.278</td>
<td>0.003–0.026</td>
<td>~0</td>
</tr>
<tr>
<td>F&lt;sub&gt;e&lt;/sub&gt;</td>
<td>0.14</td>
<td>0.60</td>
<td>0.29</td>
<td>0.18</td>
<td>0.20</td>
<td>0.63</td>
<td>0.42–0.47</td>
</tr>
<tr>
<td>F&lt;sub&gt;e&lt;/sub&gt;</td>
<td>0.24</td>
<td>0.71</td>
<td>1</td>
<td>0.27</td>
<td>0.33</td>
<td>0.97</td>
<td>0.44–0.50</td>
</tr>
<tr>
<td>F&lt;sub&gt;h&lt;/sub&gt;</td>
<td>0.42</td>
<td>0.84</td>
<td>0.29</td>
<td>0.66</td>
<td>0.61</td>
<td>0.64</td>
<td>0.93–0.95</td>
</tr>
<tr>
<td>V&lt;sub&gt;d,ss&lt;/sub&gt;</td>
<td>381 L</td>
<td>0.31 L/kg</td>
<td>0.42 L/kg</td>
<td>0.46 L/kg</td>
<td>134 L</td>
<td>24.4–28.9 L</td>
<td>4.5–13.2 L</td>
</tr>
<tr>
<td>F&lt;sub&gt;P&lt;/sub&gt;</td>
<td>&lt;0.02</td>
<td>0.005–0.009</td>
<td>&lt;0.01</td>
<td>0.46–0.57</td>
<td>0.12</td>
<td>0.015–0.036</td>
<td>0.02</td>
</tr>
<tr>
<td>Metabolic enzymes</td>
<td>CYP3A4</td>
<td>CYP2C8</td>
<td>CYP2C9</td>
<td>CYP2C8</td>
<td>CYP2C9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>67 68 69</td>
<td>70 71</td>
<td>72 73</td>
<td>74</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Pharmacokinetic alterations caused by genetic polymorphisms in OATP1B1

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>521CC/521TT (fold increase)</th>
<th>521TC/521TT (fold increase)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>t&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>AUC</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>1.52</td>
<td>1.41</td>
<td>0.92</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>0.745</td>
<td>0.511</td>
<td>0.938</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>2.10</td>
<td>3.31</td>
<td>1.00</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>1.40</td>
<td>—</td>
<td>1.22</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>1.58</td>
<td>1.52</td>
<td>0.832</td>
</tr>
<tr>
<td>388GG or 388GA/388AA (fold increase)</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>1.846</td>
<td>1.713</td>
<td>1.014</td>
</tr>
<tr>
<td>—11187GA/—11187GG (fold increase)</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>0.265</td>
<td>0.187</td>
<td>1.13</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>1.46</td>
<td>1.3</td>
<td>1.15</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data from pediatric subjects.

<sup>b</sup>Subject carrying OATP1B1*5, *15 or *17.

<sup>c</sup>Subject carrying OATP1B1*1B/*1B vs. OATP1B1*1B/*1B.

half-life (t<sub>1/2</sub>) of statins was minimally affected (Table 2). This can be explained by the total body clearance (CL<sub>tot</sub>) and distribution volume (V<sub>d</sub>) being reduced to a similar degree, which would result in an unaltered t<sub>1/2</sub> value, because t<sub>1/2</sub> is expressed as ln 2 × CL<sub>tot</sub>/V<sub>d</sub>. As statins are easily taken up by the liver and localized there and as they are mainly...
eliminated by hepatic metabolism or biliary excretion (Table 1), altered hepatic uptake results in reductions in CL_{rat} and V_{d}. Genetic polymorphisms in OATP1B1 also cause altered responses to statin therapy. T521 resulted in attenuated response to statins in some reports, although there is some controversy on this point. The SEARCH Collaborative Group reported that variants in SLCO1B1 are strongly associated with an increased risk of myopathy induced by simvastatin, although the plasma concentration of simvastatin (lactone) was not significantly changed by genetic polymorphism in SLCO1B1. For simvastatin, it should be noted that the plasma concentration of simvastatin acid after oral administration of simvastatin (lactone) was altered in subjects carrying SLCO1B1 polymorphism, and simvastatin lactone as well as simvastatin acid interact with OATP1B1.

Genetic polymorphisms in OATP1B1 also affect the plasma concentrations of some therapeutic reagents. The fraction absorbed of drugs in the portal vein in their pharmacokinetics of lopinavir and torasemide, altering the trough concentration of lopinavir and the dose-normalized AUC of torasemide. The dose-normalized AUC and C_{max} of mycophenolic acid are significantly affected by genetic polymorphisms in OATP1B3. In this case, although mycophenolic acid is not a substrate of OATP1B1 or OATP1B3, its glucuronide is the substrate of both transporters. OATP1B3 is believed to contribute to the hepatoacellular uptake of mycophenolic acid glucuronide and to the enterohepatic recycling of mycophenolic acid after its hydrolyzation in the intestine. Other reports have stated that genetic polymorphisms in OATP1B1 affect the disposition of fexofenadine, talinolol, and ezetimibe and the induction of CYP3A4 by rifampicin in clinical situations. OATP1B1 and OATP1B3 play important roles in the clinical pharmacokinetics of many drugs.

**DDIs with CsA**

CsA is a well-known inhibitor of OATP1B1; it also inhibits CYP3A4 and MDR1. Therefore, it causes a number of clinically relevant DDIs. CsA was shown to be a more potent inhibitor of OATP1B1 than of CYP3A4; the IC_{50} value of CsA for OATP1B1 is 0.2 µM and the drug almost completely diminished OATP1B1 activity at 1 µM, whereas its IC_{50} for CYP3A4 is higher than 0.3 µM and it inhibited CYP3A4 by 70% at 3 µM. Considering this report, the therapeutic concentration of CsA in the systemic circulation is not sufficiently high to cause marked inhibition of hepatic CYP3A4 function, although this reagent may inhibit CYP3A4 in intestine when it is orally administered. Thus, among the DDIs caused by CsA, many are caused by the inhibition of OATP1B1. Table 3 summarizes the clinically reported DDIs between OATP1B1 substrates and CsA. A common feature of these DDIs is that AUC and C_{max} are more markedly altered than t_{1/2}, which is similar to the pharmacokinetic alterations caused by genetic polymorphisms of OATP1B1. This can be explained by the same mechanism as suggested for the pharmacokinetic alterations caused by the hepatic uptake transporter variants mentioned above, i.e., similar reductions in CL_{rat} and V_{d}. Considering that the maximum unbound concentration of CsA in circulating blood is approximately 0.1 µM, the increase in the AUC shown in Table 3 cannot be fully explained by the inhibition of hepatic uptake via OATP1B1 alone, assuming the fold increase in the AUC to be 1 + (unbound concentration of inhibitor drugs)/IC_{50}. Using the maximum unbound concentration of CsA at the inlet to the liver, the maximum fold increase in the AUC is estimated to be 3.55, which is still less than the fold increases observed for some drugs. The inhibition of intestinal or hepatic metabolism or the inhibition of intestinal efflux mediated by transporter(s) such as MDR1 would cause an increase in a drug’s C_{max}; however, some of the selected OATP1B1 drugs are minimally metabolized, as shown in Table 1. In addition, the fraction absorbed of drugs in the portal vein in their intact form (F_{a} · F_{g}) and the hepatic availability (F_{h}) of some of the drugs (i.e. cerivastatin, fluvastatin, and repaglinide for F_{a} · F_{g} and cerivastatin, pravastatin, rosuvastatin, repaglinide, and bosentan for F_{h}; Table 1) are too high to explain a marked increase in C_{max} by the inhibition of intestinal efflux and/or first pass metabolism. For rat Oatp1a1, a long-lasting inhibition by CsA was reported. In addition, preincubation with CsA enhanced its inhibitory effect on OATP1B1, suggesting a complex mechanism. This mechanism may cause stronger DDI than expected by the conventional prediction methods.

**DDIs with Gemfibrozil**

Gemfibrozil is another inhibitor of OATP1B1 and also causes a number of clinically relevant DDIs. Gemfibrozil inhibits not only OATP1B1 but also many kinds of metabolic enzymes including CYP1A2, CYP2C8, CYP2C9, and CYP19. In addition, gemfibrozil glucuronide is a potent mechanism-
Data are shown as the fold increase with gemfibrozil because the reported IC50 values of gemfibrozil and its glucuronide form for CYP2C8 (28 and 4 µM, respectively) are lower than the corresponding values for OATP1B1 (72 and 24 µM, respectively) and, in addition, gemfibrozil glucuronide irreversibly inhibits CYP2C8.51,58 The coadministration of gemfibrozil increased the AUC and Cmax of pravastatin and rosuvastatin, with a minimal effect on t1/2, which is similar to the effects of the DDIs caused by CsA.53,59 As these statins are mainly excreted in unchanged forms from the liver, these interactions are possibly caused by the inhibition of OATP1B1. On the other hand, the AUC and t1/2 of atorvastatin were altered, but its Cmax was not.60 Although CYP3A4 is responsible for its metabolism, gemfibrozil does not affect CYP3A4-mediated metabolism, and so this interaction might be caused by the inhibition of OATP1B1.51,56 We initially reported that the IC50 values of gemfibrozil and its glucuronide were too high to cause marked interactions with OATP1B1 substrates.51 We estimated that the AUC of OATP1B1 substrates could be increased at most 1.1-fold considering the therapeutic unbound concentrations of gemfibrozil and its glucuronide. However, more recently, lower IC50 values of gemfibrozil have been reported, suggesting potential interactions with OATP1B1 substrates. The reported IC50 value of gemfibrozil for OATP1B1-mediated uptake ranges widely from 7.4 (for the uptake of estradiol 17β-d-glucuronide) to 72.4 µM (for cerivastatin).51–55 More recently, the inhibitory effects of gemfibrozil were reported to differ depending on the substrate.61 In addition, the OATP1B1-mediated uptake of estrone 3-sulfate exhibited biphasic kinetics, and gemfibrozil only affects the high-affinity component of its uptake mediated by OATP1B1.61 This fact may explain the different IC50 values of gemfibrozil for OATP1B1 for different substrates. Thus, the OATP1B1-related interactions caused by gemfibrozil may be governed by complex mechanisms, and their effects may depend on the affected drugs.

### DDIs with Other Drugs

Recently, there have been reports of DDIs that are caused by other OATP1B1 inhibitors. Rifampicin inhibits OATP1B1-mediated transport in clinical situations, although it also acts as an inducer of metabolic enzymes and transporters.47,62 Lau et al. showed that a single concomitant intravenous administration of rifampicin (600 mg) increased the plasma concentration of atorvastatin via the inhibition of OATP1B1, although its repeated administration induced CYP3A4 expression, resulting in a reduction of the plasma concentration of atorvastatin.62 The single coadministration of rifampicin resulted in increases in the AUC and Cmax of atorvastatin by 8.04- and 10.5-fold, respectively, while its t1/2 was reduced. Some HIV protease inhibitors inhibit OATP1B1 and OATP1B3 at therapeutic concentrations. Among them, the coadministration of the combination of lopinavir and ritonavir reportedly caused clinically relevant DDIs with rosuvastatin and bosentan, resulting in marked increases in AUC and Cmax (AUC × 5.2 and Cmax × 6.1 for bosentan; AUC × 2.1 and Cmax × 4.7 for rosuvastatin).63,64 Clarithromycin and erythromycin are OATP1B1 inhibitors as well as potent mechanism-based inhibitors of CYP3A4.47 In fact, clarithromycin demonstrates clinically relevant DDIs with multiple statins in clinical situations, partly caused by the inhibition of OATP1B1.63 Clarithromycin increases the AUC of pravastatin, simvastatin, and atorvastatin by 2.1-, 10- (12- for simvastatin acid), and 4.5-fold, respectively, and the corresponding Cmax by 2.3-, 7.1- (10- for simvastatin acid), and 5.4-fold, respectively. Although simvastatin and atorvastatin are metabolized by CYP3A4, pravastatin is not metabolized by cytochrome P450. Thus, these interactions are at least partly caused by the inhibition of OATP1B1.

### Pharmacokinetic Alteration Caused by Hepatic Uptake Transporter Inhibition: Model-based Analysis

Pharmacokinetic alterations caused by inhibition of hepatic uptake transporter(s) can be analyzed by using physiologically based pharmacokinetic (PBPK) models. By using a simple PBPK model, we showed that alterations in the activity of hepatic uptake transporter(s) could change the plasma concentration of substrate drugs, but not their concentrations in the liver, when they are exclusively eliminated from the liver.44 Watanabe et al. (2008) succeeded in the prediction of alterations in transporter-mediated clearance and distribution of pravastatin by using a PBPK model.66 They also showed that the plasma concentration of pravastatin was markedly changed, while its concentration in the liver, the target organ for statin therapy, was minimally changed. These model-based analy-
ses suggest that changes in the pharmacological effects of statins should be small in subjects with altered function of hepatic uptake transporters (by DDIs or genetic polymorphisms), at least in the steady state (in other words, after long-term treatment) despite marked changes in their plasma concentrations. However, the frequency of myotoxicity associated with statin therapy can be affected by altered activity in the hepatic uptake transporter(s) because the systemic exposure of statins is a determinant of this toxicity.

**Conclusion**

Recently, there have been a large number of reports on OATP1B1-related DDIs in clinical as well as in *in vitro* studies. Because DDIs increase the risk of drug-induced adverse reactions and even the withdrawal of drugs from the market, they are important issues that require consideration for the discovery and development of drugs with safer profiles. OATP1B1- or OATP1B3-mediated hepatic uptake is reportedly an important mechanism that induces clinically relevant DDIs because a number of therapeutic reagents are substrates and/or inhibitors of these transporters. Thus, the hepatic uptake mediated by these transporters should be vigorously investigated in order to avoid DDIs.

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**References**


