5 Oct 2004 :1308 AR AR232-PA45-28.tex XMLPublish^{SM}(2004/02/24) P1: JRX
AR REVIEWS IN ADVANCE10.1146/annurev.pharmtox.44.101802.121444

where I_{sys} and I_{pv} are the inhibitor concentration in the circulating blood and portal vein, respectively; f_u is the blood protein unbound fraction; v_{abs} is the absorption rate from the intestine to the portal vein; and Q_H is the hepatic blood flow. When the intestinal absorption is described by a first-order rate constant, this equation becomes (123, 124)

$$I_u = f_u \cdot \left(I_{sys} + \frac{F \cdot D \cdot k_a \cdot e^{-ka \cdot t}}{Q_H}\right) \leq f_u \cdot \left(I_{sys} + \frac{F \cdot D \cdot k_a}{Q_H}\right), \qquad (13)$$

where F is the fraction absorbed from the gastrointestinal tract, D is the dose, and k_a is the absorption rate constant. To avoid a false negative prediction, the unbound inhibitor concentration should be estimated by $f_u \cdot (I_{sys} + \frac{F \cdot D \cdot k_a}{Q_H})$ for a drug-drug interaction based on a hepatic transporter-mediated process.

To date, there are many published inhibition studies of renal and hepatic uptake transporters: OATs and OATPs. In this section, the inhibitory effects of therapeutic drugs on these transporters are evaluated using K_i values, comparing them with the therapeutic concentrations.

OAT-Mediated Drug-Drug Interactions

In the kidney, the OAT family transporters are involved in the uptake of organic anions with relatively low molecular weights into the renal tubules, although OAT2 and 5 are localized in the liver and OAT4 is expressed in the brush border membrane of the kidney and may be involved in efflux from the renal tubules into the urine (21–24). These OAT family transporters are inhibited by several compounds, including therapeutic drugs (Supplemental Table 1, Follow the Supplemental Material link from the Annual Reviews home page at http://www.annualreviews.org). Supplemental Table 1 gives a partial list of therapeutic drugs that interact with OAT family transporters, together with their maximum plasma concentration and maximum plasma unbound concentration in a clinical situation and R value.

The calculated R values suggest that many inhibitor drugs of OAT family transporters do not cause a serious drug-drug interaction because of the relatively low plasma concentrations compared with their K_i values (Supplemental Table 1). However, some cephalosporin antibiotics and probenecid exhibited low R values and, therefore, may lead to clinically relevant drug-drug interactions (Supplemental Table 1). These results suggest that the concomitant use of these drugs with OAT substrate drugs, which are mainly excreted in the urine, should be very carefully monitored. Such use may cause at least a partial reduction in the intrinsic clearance for renal secretion, possibly leading to an increase in plasma concentration.

OATP-Mediated Drug-Drug Interactions

Among OATP family transporters, OATP-B [OATP2B1], OATP-C/OATP2 [OATP1B1], and OATP8 [OATP1B3] are expressed in the human liver and are involved in the hepatic uptake of several compounds, including therapeutic drugs (54–58). Although, in rats, some Oatp family transporters, such as Oatp1 [Oatp1a1],

Oat-k1 [Oatp1a3], and k2, are reported to be expressed in the kidney (126–130), their human counterparts have not been characterized. As shown in Supplemental Table 2 (Follow the Supplemental Material link from the Annual Reviews home page at http://www.annualreviews.org), several therapeutic drugs are reported to inhibit OATP family transporters. Because they are hepatic uptake transporters, R values were calculated based on not only the maximum inhibitor unbound therapeutic concentration in the circulating blood but also that in the inlet to the liver, calculated by Equation 13 (123, 124). Values calculated based on the unbound concentration in the inlet to the liver are given as R'. Inhibitors of OATP family transporters consist of bulky compounds, including anions, neutral compounds, and even cations (Supplemental Table 2). In Supplemental Table 2, only cyclosporin A and rifampicin exhibited relatively low R and R' values and may lead to clinically relevant drug-drug interactions. On the other hand, pravastatin, an HMG-CoA reductase inhibitor, is not a cause of a severe drug-drug interaction based on OATP-mediated hepatic uptake because of its low plasma unbound concentration. As pravastatin is a potent HMG-CoA reductase inhibitor and is highly distributed to the liver, its target organ, a low plasma concentration is sufficient for its pharmacological effect, leading to a low risk of inhibition of transporter function (132). A small number of inhibitors with relatively low R values may be due to a lack of inhibition studies involving human OATP family transporters, and further studies may provide other inhibitors that cause clinically relevant drug-drug interactions. More inhibition studies on human OATP transporters are needed to allow the quantitative prediction of transporter-mediated drug-drug interactions.

MDR-Mediated Drug-Drug Interactions

MDR1 is expressed in the liver and kidney (7, 8, 15). Therefore, MDR1-mediated drug-drug interactions result in a reduction in renal and hepatobiliary excretion. It is also expressed in the intestine and the blood-brain barrier and, therefore, MDR1-mediated transport affects intestinal absorption and even distribution to the brain (7). MDR1-mediated drug-drug interactions cause complex effects. MDR1 has a broad substrate specificity and is inhibited by a large number of compounds. Quinidine is one MDR1 inhibitor (35). As the K_m value of quinidine for ATP-dependent efflux via MDR1 is approximately 5 μM (32), its K_i value for MDR1 can be assumed to be 5 μM. The therapeutic steady-state concentration of quinidine is approximately 4.5 μM and its unbound concentration is 0.59 μM. As MDR1 is an efflux transporter, the R value should be calculated using the unbound concentration of inhibitor in the cell. However, it is practically impossible to measure the intracellular unbound concentration of inhibitors in humans. Assuming the cell-to-medium concentration ratio to be 10 as a safety margin, the R value can be calculated to be $\frac{1}{1+10\times 0.59/5} = 0.46$, suggesting that renal efflux will be reduced to at most 46% of the control. For hepatobiliary efflux, the blood concentration at the inlet to the liver should be used. The plasma concentration of quinidine at the inlet to the liver is calculated to be 4.6 μM using $Q_H = 1.6$ liters min^{-1}, $F_a{*}F_g =$

0.8, $k_a = 0.1\ min^{-1}$, and $f_u = 0.13$. Using this and assuming a cell-to-medium concentration ratio of 10, the calculated R value is $\frac{1}{1+10\times4.6/5} = 0.098$, suggesting that hepatobiliary excretion will be reduced to at most 9.8% of the control. Actually, both the hepatobiliary and renal clearances of digoxin have been reported to be reduced when concomitantly administered with quinidine (133).

MRP2-Mediated Drug-Drug Interactions

MRP2 also has a broad substrate specificity and is inhibited by a large number of therapeutic drugs, including cyclosporin A, daunomycin, etoposide, probenecid, and pravastatin (33, 134, 135). MRP2 functions as an efflux transporter for CPT-11 and its metabolites, SN-38 and SN-38 glucuronide (SN38-glu) (136). CPT-11 is excreted into the bile mainly via MDR1 and, to a minor extent, via MRP2, whereas SN-38 and SN38-glu are excreted via MRP2 (136). The biliary excretion of its metabolites causes severe diarrhea as a side effect (137, 138). To prevent this side effect, inhibition of MRP2-mediated transport by coadministration of its inhibitor may be effective. Horikawa et al. have investigated the inhibitory effects of several compounds on rat Mrp2 function (139). Among them, probenecid, sulfobromophthalein, and the glutathione-conjugate of sulfobromophthalein had potent inhibitory effects (139). The inhibitory effects of probenecid were also confirmed for the in vitro human biliary excretion of SN-38 with a K_i value of 42 μM (139). The same authors also confirmed these inhibitors of rat Mrp2 significantly reduced the biliary excretion of CPT-11, SN-38, and SN38-glu (140). They suggested the possibility of using MRP2 inhibitors such as probenecid to prevent the clinically observed toxicity of diarrhea by CPT-11.

EXAMPLES OF CLINICALLY RELEVANT DRUG-DRUG INTERACTIONS BASED ON RENAL AND HEPATOBILIARY TRANSPORT

In this section, examples of clinically relevant drug-drug interactions based on membrane transport in the kidney and the liver are described.

HMG-CoA Reductase Inhibitors Versus Cyclosporin A

As cerivastatin, a potent HMG-CoA reductase inhibitor (statin), is metabolized by two different enzymes, cycochrome P450 2C8 (CYP2C8) and 3A4, the likelihood of a severe drug-drug interaction was believed to be low (141). However, the plasma concentration of cerivastatin was reported to be increased when coadministered with cyclosporin A (142).

The plasma AUC and maximum plasma concentration of cerivastatin increased by four- and fivefold, respectively, when concomitantly administered with cyclosporin A (142). Our group investigated the mechanism underlying this drug-drug interaction (62). We have shown that the transporter-mediated uptake of

cerivastatin is inhibited by cyclosporin A at a low concentration (K_i was 0.3 ~ 0.7 μM), whereas the in vitro metabolism of cerivastatin is inhibited with an IC_{50} value of more than 30 μM, suggesting that this clinically relevant drug-drug interaction was caused by a transporter-mediated process rather than a metabolic one (62). The unbound concentration of cyclosporin A in the circulating blood and at the inlet to the liver, calculated by Equation 13, are, at most, 0.1 μM and 0.6 μM, respectively, which may explain the clinically relevant drug-drug interaction, although there may be other mechanisms involved (62). We also showed that the OATP-C/OATP2 [OATP1B1]-mediated transport of cerivastatin was inhibited by cyclosporin A with a K_i value of less than 0.2 μM (Figure 7) (62).

In addition to cerivastatin, the plasma concentrations of pravastatin, pitavastatin, and HMG-CoA reductase inhibitory activity of atorvastatin are reported to be affected by concomitantly administered cyclosporin A (143–145). Among them, pravastatin and pitavastatin undergo only minimal metabolism, and the likelihood of a drug-drug interaction owing to this is quite low. As these statins are substrates of OATP-C/OATP2 [OATP1B1], interactions with cyclosporin A may also be caused by a transporter-based mechanism (55, 56, 121). Interaction between atorvastatin and cyclosporin A may be occurred by a transporter-mediated

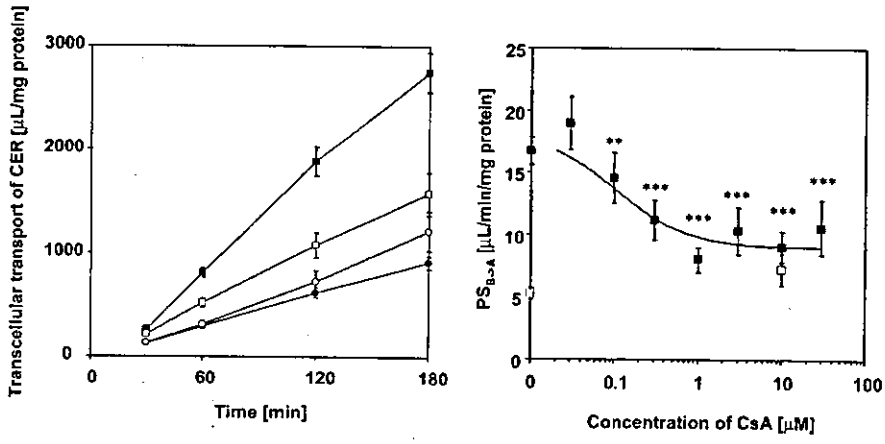

Figure 7 Transcellular transport of cerivastatin (CER) mediated by OATP-C/OATP2 [OATP1B1] and MRP2 and the inhibitory effect of cyclosporin A. (*a*) Transcellular transport of [^{14}C]CER in OATP-C/OATP2 [OATP1B1] and MRP2 double-transfected MDCK cells (*closed squares*) and in vector-transfected cells (*closed circles*) was examined. Addition of cyclosporin A (10 μM) inhibited OATP-C/OATP2 [OATP1B1]- and MRP2-mediated transport of CER (*open squares*), whereas it did not change the transcellular transport in vector transfected cells (*open circles*). (*b*) Cyclosporin A inhibited the transcellular transport ($PS_{B->A}$) in a concentration-dependent manner. The IC_{50} value obtained in this experimental system was 0.084 ± 0.015 μM. $^{**}p < 0.01$, $^{***}p < 0.001$.

TABLE 1 Kinetic parameters of HMG-CoA reductase inhibitors coadministered with cyclosporin A

HMG-CoAreductase inhibitors	Cyclosporin A (+/−) Cmax [ng/mL]	Ratio	AUC [ng·hr/mL]	Ratio	Major clearance mechanism	Reference
Simvastatin	18.9/2.5**	7.56	78.1/9.8**	7.97	CYP3A4	193
	20.6/9.9*	2.08	101/39.6*	2.55		194
Pravastatin	223/28.0	7.95	1300/57.1***		OATP-C	143
Fluvastatin	155/119	1.30	373/192	1.94	CYP2C9	195
Cerivastatin	7.82/1.56	5.01	36.2/9.53	3.80	CYP2C8/3A4OATP-C	142
Atorvastatin	58.0/8.8#*	6.59	595/79.9#*	7.45	CYP3A4-OATP-C	145
Pitavastatin	179/27.6***	6.49	347/76.9***	4.51	OATP-C	144

#ng eq./mL or ng eq. · hr/mL
*$p<0.05$, **$p<0.01$, ***$p<0.001$

and metabolism-based mechanism as atorvastatin is metabolized by CYP3A4 and cyclosporin A inhibits CYP3A4-mediated metabolism (146). In Table 1, we summarize pharmacokinetic interactions between HMG-CoA reductase inhibitors and cyclosporin A.

HMG-CoA Reductase Inhibitors Versus Gemfibrozil

Gemfibrozil also interacts with a wide range of statins (Table 2). In particular, interactions with cerivastatin have been reported to cause the severe side effect of myotoxicity, including lethal rhabdomyolysis (147). In addition, pharmacokinetic interaction between cerivastatin and gemfibrozil was reported (148, 149). Although our group examined the inhibitory effects of gemfibrozil and its major metabolites on the OATP-C/OATP2 [OATP1B1]-mediated uptake of cerivastatin, we found gemfibrozil and its glucuronide inhibited it with IC_{50} values of 72 and 24 μM, respectively, which were higher than their therapeutic unbound concentrations, suggesting a low possibility of a transporter-mediated drug-drug interaction (150). On the other hand, an interaction with rosuvastatin was reported to be caused by the inhibition of OATP-C/OATP2 [OATP1B1]-mediated uptake by Schneck et al. (151). In their report, gemfibrozil inhibited the OATP-C/OATP2 [OATP1B1]-mediated transport of cerivastatin with a low IC_{50} value of 4 μM (151). Although it is still higher than the therapeutic unbound concentration of cerivastatin, this value is lower than that we have obtained (150). This gap may be partly due to the difference in the experimental system, i.e., we used transporter-expressing MDCK cells, whereas Schneck et al. used cRNA-injected

TABLE 2 Kinetic parameters of HMG-CoA reductase inhibitors coadministered with gemfibrozil

HMG-CoA reductase inhibitors	Gemfibrozil (+/−)				Major clearance mechanism	Reference
	Cmax [ng/mL]	Ratio	AUC [ng · hr/mL]	Ratio		
Lovastatin	2.38/2.69	0.885	33.1/34.4	0.962	CYP3A4	196
Simvastatin	6.15/6.87	0.895	36.2/25.2**	1.44	CYP3A4	197
Pravastatin	120/66.3*	1.81	281/139*	2.02	OATP-C	198
Fluvastatin	54.3/48.4	1.12	213/227	0.938	CYP2C9	199
Cerivastatin	8.0/3.2**	2.5	91.1/20.9***	4.36	CYP2C8/3A4 OATP-C	148
	2.93/1.61	1.82	41.9/9.92	4.22		149
Pitavastatin	no data	1.30	no data	1.45	OATP-C	200
Rosuvastatin	109/49.5	2.20	771/410	1.88	CYP2C9 OATP-C	151

*p<0.05, **p<0.01, ***p<0.001

Xenopus laevis oocytes (150, 151). We also analyzed the inhibitory effects of gemfibrfozil and its metabolites on the P450-mediated metabolism of cerivastatin and found that gemfibrozil and its glucuronide inhibited the CYP2C8-mediated metabolism with IC_{50} values of 28 and 4 μM, respectively (150). They are still higher than the therapeutic unbound concentrations in the circulating blood. However, there are reports that, in rat perfusion studies, gemfibrozil-1-O-glucuronide is actively taken up into the liver and accumulates there (152–154). If this also took place in human liver, the concentrated gemfibrozil-1-O-glucuronide might act as an inhibitor of CYP2C8-mediated metabolism, leading to a drug-drug interaction. In this case, a transporter plays an important role, i.e., an inhibitor of the metabolism leading to accumulation in the liver via transporter-mediated uptake. Our hypothesis that interaction with gemfibrozil is not a transporter-mediated one, but a metabolism-mediated one is supported by the fact that gemfibrozil does not cause a severe interaction with pravastatin and pitavastatin, which are mainly cleared by the OATP-C/OATP2 [OATP1B1]-mediated hepatic uptake (Table 2). Therefore, we should also be more cautious about drug-drug interactions when inhibitors of the metabolism are substrates of hepatic uptake transporters (Figure 8).

Digoxin Versus Quinidine and Quinine

Digoxin undergoes biliary and renal excretion. Drug-drug interactions between digoxin and quinidine and between digoxin and quinine (a stereoisomer of quinidine) have been reported by Hedmann et al. (133). Quinidine reduced the renal and biliary excretion of digoxin, whereas quinine reduced only the biliary excretion of digoxin (133).

Because quinidine is a well-known P-gp inhibitor, its effect on biliary and urinary excretion may be related to P-gp (MDR1)- mediated transport (35). As de-

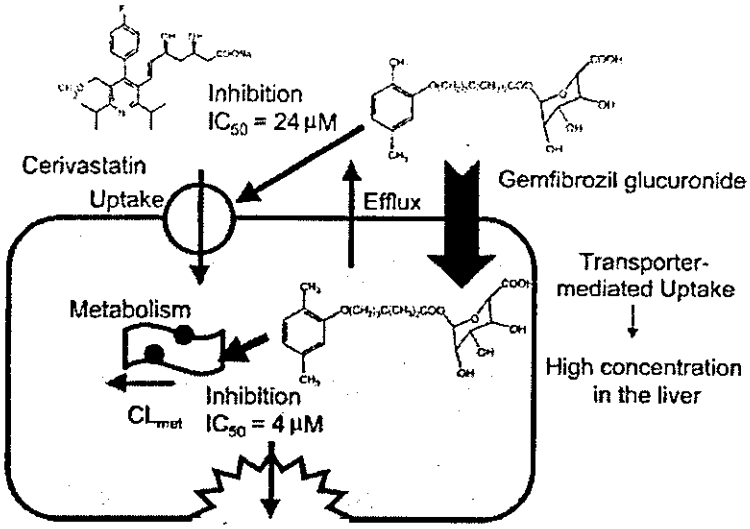

Figure 8 Possible mechanism of drug-drug interaction between cerivastatin and gemfibrozil. Gemfibrozil-1-O-glucuronide is actively taken up via transporter(s) and accumulates in the liver. In the liver, its concentration is hypothesized to be high enough to inhibit the P450-mediated metabolism of cerivastatin.

scribed in MDR-Mediated Drug-Drug Interactions (above), the K_i value of quinidine for the MDR1-mediated efflux can be assumed to be 5 μM. On the other hand, the steady-state plasma concentration of quinidine in this study was 4.5 μM, with a protein unbound fraction of 0.13. Therefore, the protein unbound concentration in the circulating blood is estimated to be 0.59 μM. The unbound concentration of quinidine at the inlet to the liver estimated by Equation 13 is 4.6 μM using $Q_H = 1.6$ liters min^{-1}, $F_a{}^*F_g = 0.8$, and $k_a = 0.1$ min^{-1}. With a safety margin of $1 \sim 10$ as a cell-to-medium concentration ratio, the estimated reduction in the renal excretion of digoxin is 46% to 89% of the control, and the estimated reduction in the hepatobiliary excretion of digoxin is 9.8% to 52% of the control. In clinical situations, the hepatobiliary excretion was reduced to 42% of the control, whereas the renal excretion was reduced to 60% of the control, which was within the predicted range (133).

In rat hepatocytes, the inhibitory effect on the uptake of digoxin was more potent for quinine than for quinidine, and the same tendency was observed using the rat Oatp2 [Oatp1a4] expression system (122, 155). Therefore, the mechanism of the drug-drug interaction between digoxin and quinine may be caused by the inhibition of the transporter-mediated uptake. However, there is a study that shows that both quinine and quinine had no inhibitory effects on the uptake of digoxin into isolated human hepatocytes, although both of them inhibited the uptake of digoxin into rat hepatocytes (156).

Drug-Drug Interactions Between Cephalosporin Antibiotics and Probenecid

There are many reports on the drug-drug interactions between cephalosporin antibiotics and probenecid (157). As both cephalosporins and probenecid interact with OAT family transporters, some of these drug-drug interactions may be due to an OAT-mediated uptake process. Most cephalosporins are excreted in the urine, which may be partly mediated by OAT family transporters. The elimination rates of cephazedone, cefazolin, cefalexin, cefradine, cefaclor, cefmetazole, cefoxitin, cefuroxime, cefmenoxime, ceftizoxime, and cedftriaxone were significantly reduced by coadministration of probenecid, which may be partly caused by the inhibition of their renal excretions (157).

Marino & Dominguez-Gil have shown that the pharmacokinetics of cefadroxil is altered by coadministration of probenecid (158). In their report, the peak concentration and half-life of cefadroxil was increased 1.4- and 1.3-fold, respectively, following coadministration of probenecid. Its urinary excretion rate constant falls by 58%, supporting the possibility of drug-drug interaction at the renal excretion. Supplemental Table 1 suggests that OAT1- and OAT3-mediated transport should be decreased to at most 25%–47% and 25%–69% of the control, and, therefore, it may be partly explained by the OAT-mediated drug-drug interaction.

Probenecid has also been shown to alter the plasma concentrations of cefamandole and ceftriaxone (159). The maximum plasma concentration and half-life of cefamandole were increased 6- and 1.8-fold by coadministration of probenecid (159). Also, 71% of cefamandole is excreted in the urine, and this was reduced to 66% of the control (159). The elimination of ceftriaxone was slightly affected by coadministration of probenecid (160). Probenecid reduced the serum clearance of ceftriaxone to 73% of the control (160). It reduced the renal and nonrenal clearance to 80% and 68% of the control, respectively, suggesting that this drug-drug interaction is, to a minor extent, due to renal excretion (160).

Drug-Drug Interaction Between Methotrexate and NSAIDs

To date, there are reports that coadministration of MTX with penicillin, probenecid, and NSAIDs cause drug-drug interactions and several potential sites for these DDI have been reported: an increase in the protein unbound fraction of MTX, a decrease in the urine flow rate resulting from the inhibition of prostaglandin synthesis, and inhibition of the renal tubular secretion of MTX (161–164). Nozaki et al. analyzed the uptake mechanism of MTX in rat kidney slices and examined the effects of NSAIDs on its uptake (165). They showed that rat Oat3 and reduced folate carrier 1 (RFC-1) equally contribute to the renal uptake (30% each), with the remaining fraction being accounted for by passive diffusion and/or adsorption, whereas rOat1 makes only a limited contribution (165). Many NSAIDs inhibited both rOat3- and RFC-1-mediated uptake of MTX, but the K_i value for Oat3 was lower than that for RFC-1 (165). At their therapeutic concentrations, they inhibited only Oat3-mediated uptake of MTX. Therefore, the affect of NSAIDs on the renal uptake of

5 Oct 2004 :1308 AR AR232-PA45-28.tex XMLPublish^{SM}(2004/02/24) PI: JRX
AR REVIEWS IN ADVANCE10.1146/annurev.pharmtox.44.101802.121444

MTX is expected to be nonextensive and partial. Many NSAIDs also inhibit human OAT3-mediated uptake of MTX with therapeutic relevant plasma concentrations of unbound drugs (26). However, also in humans, the contribution of OAT3 to the total renal uptake of MTX needs to be clarified for the identification of the mechanism of the clinically relevant DDI.

CONCLUSION

In addition to phase I and phase II enzymes, transporters also play an important role in drug elimination and distribution. Therefore, it is possible that transporter-mediated drug-drug interactions alter pharmacokinetics, and could result in severe side effects.

A large number of transporters have been characterized in rodents and humans, and the mechanism of the membrane transport of several compounds including endogenous compounds and therapeutic drugs has been clarified. However, the transport mechanism of most therapeutic drugs remains unknown. To predict a transporter-mediated drug-drug interaction, the transporters involved in the membrane transport of the drug need to be characterized. As multiple transporters have been characterized in the kidney and liver and their expression systems are available, it should be possible to predict a transporter-mediated drug-drug interaction by using these systems with the information of the contribution made by each transporter to the net transport in the kidney and liver.

We have estimated the possibility of a transporter-mediated drug-drug interaction from the R value calculated using the maximum unbound concentration of inhibitors. This method may avoid false negative predictions of drug-drug interactions. In conclusion, greater awareness of the possibility of transporter-mediated drug-drug interactions is necessary.

The *Annual Review of Pharmacology and Toxicology* is online at http://pharmatox.annualreviews.org

LITERATURE CITED

1. Petzinger E. 1994. Transport of organic anions in the liver. An update on bile acid, fatty acid, monocarboxylate, anionic amino acid, cholephilic organic anion, and anionic drug transport. *Rev. Physiol. Biochem. Pharmacol.* 123:47–211
2. Oude Elferink RPJ, Meijer DKF, Kuipers F, Jansen PLM, Groen AK, Groothis GMM. 1995. Hepatobiliary secretion of organic compounds; molecular mechanism of membrane transport. *Biochem. Biophys. Acta* 1241:215–68
3. Yamazaki M, Suzuki H, Sugiyama Y. 1996. Recent advances in carrier-mediated hepatic uptake and biliary excretion of xenobiotics. *Pharm. Res.* 13:497–513
4. Okudaira N, Sugiyama Y. 1996. Use of an isolated perfused kidney to assess renal clearance of drugs: information obtained in steady-state and non-steady-state experimental systems. In *Models for Assessing Drug Absorption and Metabolism*, ed RT Borchard, PL Smith, G Wilson, pp. 211–38. New York: Plenum Press

5. Giacomini KM, Hsyu PH, Gisclon JG. 1988. Renal transport of drugs: an overview of methodology with application to cimetidine. *Pharm. Res.* 5:465–71
6. van Aubel RAMH, Masereeuw R, Russel FGM. 2000. Molecular pharmacology of renal organic anion transporters. *Am. J. Physiol. Renal Physiol.* 279:F216–32
7. Kusuhara H, Sugiyama Y. 2002. Role of transporters in the tissue-selective distribution and elimination of drugs: transporters in the liver, small intestine, brain and kidney. *J. Control. Release* 78:43–54
8. Kusuhara H, Suzuki H, Sugiyama Y. 1998. The role of P-glycoprotein and canalicular multispecific organic anion transporter in the hepatobiliary excretion of drugs. *J. Pharm. Sci.* 87:1025–40
9. Suzuki H, Sugiyama Y. 2000. Transport of drugs across the hepatic sinusoidal membrane: sinusoidal drug influx and efflux in the liver. *Semin. Liver Dis.* 20:251–63
10. Inui K, Masuda S, Saito H. 2000. Cellular and molecular aspects of drug transport in the kidney. *Kidney Int.* 58:944–58
11. Dresser MJ, Leabman MK, Giacomini KM. 2001. Transporters involved in the elimination of drugs in the kidney: organic anion transporters and organic cation transporters. *J. Pharm. Sci.* 90:397–421
12. Sweet DH, Bush KT, Nigam SK. 2001. The organic anion transporter family: from physiology to ontogeny and the clinic. *Am. J. Physiol. Renal Physiol.* 281: F197–205
13. Sekine T, Cha SH, Endou H. 2000. The multispecific organic anion transporter (OAT) family. *Pflugers Arch.* 440:337–50
14. Koepsell H, Gorboulev V, Arndt P. 1999. Molecular pharmacology of organic cation transporters in the kidney. *J. Membr. Biol.* 167:103–17
15. Mizuno N, Sugiyama Y. 2002. Drug transporters: their roles and importance in the selection and development of new drugs. *Drug Metab. Pharmacokin.* 17:93–108
16. Meier PJ, Eckhardt U, Schroeder A, Hagenbuch B, Stieger B. 1997. Substrate specificity of sinusoidal bile acid and organic anion uptake systems in rat and human liver. *Hepatology* 26:1667–77
17. Pang KS, Rowland M. 1977. Hepatic clearance of drugs I: theoretical considerations of a "well-stirred" model and a "parallel-tube" model. Influence of hepatic blood flow, plasma and blood cell binding, and the hepatocellular enzymatic activity on hepatic drug clearance. *J. Pharmacokin. Biopharm.* 5:625–53
18. Pang KS, Gillette R. 1978. Kinetics of metabolite formation and elimination in the perfused rat liver preparation: difference between the elimination of preformed acetaminophen and acetaminophen formed from phenacetin. *J. Pharmacol. Exp. Ther.* 207:178–94
19. Miyauchi S, Sugiyama Y, Sawada Y, Morita K, Iga T, et al. 1987. Kinetics of hepatic transport of 4-methylumbelliferone in rats: analysis by multiple indicator dilution method. *J. Pharmacokin. Biopharm.* 15:25–38
20. Sekine T, Watanabe N, Hosoyamada M, Kanai Y, Endou H. 1997. Expression cloning and characterization of a novel multispecific organic anion transporter. *J. Biol. Chem.* 272:18526–29
21. Hosoyamada M, Sekine T, Kanai Y, Endou H. 1999. Molecular cloning and functional expression of a multispecific organic anion transporter from human kidney. *Am. J. Physiol. Renal Physiol.* 276:F122–28
22. Sun W, Wu RR, van Poelje PD, Erion MD. 2001. Isolation of a family of organic anion transporters from human liver and kidney. *Biochem. Biophys. Res. Comm.* 283:417–22
23. Race JE, Grassl SM, Williams WJ, Holtzman EJ. 1999. Molecular cloning and characterization of two novel human renal organic anion transporters (hOAT1 and hOAT3). *Biochem. Biophys. Res. Commun.* 255:508–14
24. Cha SH, Sekine T, Kusuhara H, Yu E,

Kim JY, et al. 2000. Molecular cloning and characterization of multispecific organic anion transporter 4 expressed in the placenta. *J. Biol. Chem.* 275:4507–12
25. Cha SH, Sekine T, Fukushima JI, Kanai Y, Kobayashi Y, et al. 2001. Identification and characterization of human organic anion transporter 3 expressing predominantly in the kidney. *Mol. Pharmacol.* 59:1277–86
26. Takeda M, Khamdang S, Narikawa S, Kimura H, Hosoyamada M, et al. 2002. Characterization of methotrexate transport and its drug interactions with human organic anion transporters. *J. Pharmacol. Exp. Ther.* 302:666–71
27. Takeda M, Khamdang S, Narikawa S, Kimura H, Kobayashi Y, et al. 2002. Human organic anion transporters and human organic cation transporters mediate renal antiviral transport. *J. Pharmacol. Exp. Ther.* 300:918–24
28. Jung KY, Takeda M, Kim DK, Tojo A, Narikawa S, et al. 2001. Characterization of ochratoxin A transport by human organic anion transporters. *Life Sci.* 69:2123–35
29. Lecureur V, Sun D, Hargrove P, Schuetz EG, Kim RB, et al. 2000. Cloning and expression of murine sister of P-glycoprotein reveals a more discriminating transporter than MDR1/P-glycoprotein. *Mol. Pharmacol.* 57:24–35
30. Yamazaki M, Neway WE, Ohe T, Chen I, Rowe JF, et al. 2001. In vitro substrate identification studies for p-glycoprotein-mediated transport: species difference and predictability of in vivo results. *J. Pharmacol. Exp. Ther.* 296:723–35
31. Ambudkar SV, Lelong IH, Zhang J, Cardarelli CO, Gottesman MM, et al. 1992. Partial purification and reconstitution of the human multidrug-resistance pump: characterization of the drug-stimulatable ATP hydrolysis. *Proc. Natl. Acad. Sci. USA* 89:8472–76
32. Adachi Y, Suzuki H, Sugiyama Y. 2001. Comparative studies on in vitro methods for evaluating in vivo function of MDR1 P-glycoprotein. *Pharm. Res.* 18:1660–68
33. Guo A, Marinaro W, Hu P, Sinko PJ. 2002. Delineating the contribution of secretory transporters in the efflux of etoposide using Madin-Darby canine kidney (MDCK) cells overexpressing P-glycoprotein (Pgp), multidrug resistance-associated protein (MRP1), and canalicular multispecific organic anion transporter (cMOAT). *Drug Metab. Dispos.* 30:457–63
34. Walle UK, Walle T. 1998. Taxol transport by human intestinal epithelial Caco-2 cells. *Drug Metab. Dispos.* 26:343–46
35. Tanigawara Y, Okamura N, Hirai M, Yasuhara M, Ueda K, et al. 1992. Transport of digoxin by human P-glycoprotein expressed in a porcine kidney epithelial cell line (LLC-PK1). *J. Pharmacol. Exp. Ther.* 263:840–45
36. Ueda K, Okamura N, Hirai M, Tanigawara Y, Saeki T, et al. 1992. Human P-glycoprotein transports cortisol, aldosterone, and dexamethasone, but not progesterone. *J. Biol. Chem.* 267:24248–52
37. Ganapathy ME, Brandsch M, Prasad PD, Ganapathy V, Leibach FH. 1995. Differential recognition of beta-lactam antibiotics by intestinal and renal peptide transporters, PEPT 1 and PEPT 2. *J. Biol. Chem.* 270:25672–77
38. Smith DE, Pavlova A, Berger UV, Hediger MA, Yang T, et al. 1998. Tubular localization and tissue distribution of peptide transporters in rat kidney. *Pharm. Res.* 15:1244–49
39. Shen H, Smith DE, Yang T, Huang YG, Schnermann JB, et al. 1999. Localization of PEPT1 and PEPT2 proton-coupled oligopeptide transporter mRNA and protein in rat kidney. *Am. J. Physiol. Renal Physiol.* 276:F658–65
40. Tsuji A. 2002. Transporter-mediated drug interactions. *Drug. Metabol. Pharmacokin.* 17:253–74
41. Han HK, Rhie JK, Oh DM, Saito G, Hsu

CP, et al. 1999. CHO/hPEPT1 cells overexpressing the human peptide transporter (hPEPT1) as an alternative in vitro model for peptidomimetic drugs. *J. Pharm. Sci.* 88:347–50

42. Gorboulev V, Ulzheimer JC, Akhoundova A, Ulzheimer-Teuber I, Karbach U, et al. 1997. Cloning and characterization of two human polyspecific organic cation transporters. *DNA Cell. Biol.* 16:871–81
43. Zhang L, Schaner ME, Giacomini KM. 1998. Functional characterization of an organic cation transporter (hOCT1) in a transiently transfected human cell line (HeLa). *J. Pharmacol. Exp. Ther.* 286:354–61
44. Dudley AJ, Bleasby K, Brown CD. 2000. The organic cation transporter OCT2 mediates the uptake of beta-adrenoceptor antagonists across the apical membrane of renal LLC-PK1 cell monolayers. *Br. J. Pharmacol.* 131:71–79
45. Busch AE, Karbach U, Miska D, Gorboulev V, Akhoundova A, et al. 1998. Human neurons express the polyspecific cation transporter hOCT2, which translocates monoamine neurotransmitters, amantadine, and memantine. *Mol. Pharmacol.* 54:342–52
46. Urakami Y, Akazawa M, Saito H, Okuda M, Inui K. 2002. cDNA cloning, functional characterization, and tissue distribution of an alternatively spliced variant of organic cation transporter hOCT2 predominantly expressed in the human kidney. *J. Am. Soc. Nephrol.* 13:1703–10
47. Tamai I, Yabuuchi H, Nezu J, Sai Y, Oku A, et al. 1997. Cloning and characterization of a novel human pH-dependent organic cation transporter, OCTN1. *FEBS Lett.* 419:107–11
48. Yabuuchi H, Tamai I, Nezu J, Sakamoto K, Oku A, et al. 1999. Novel membrane transporter OCTN1 mediates multispecific, bidirectional, and pH-dependent transport of organic cations. *J. Pharmacol. Exp. Ther.* 289:768–73
49. Tamai I, Ohashi R, Nezu J, Yabuuchi H, Oku A, et al. 1998. Molecular and functional identification of sodium ion-dependent, high affinity human carnitine transporter OCTN2. *J. Biol. Chem.* 273:20378–82
50. Wu X, Huang W, Prasad PD, Seth P, Rajan DP, et al. 1999. Functional characteristics and tissue distribution pattern of organic cation transporter 2 (OCTN2), an organic cation/carnitine transporter. *J. Pharmacol. Exp. Ther.* 290:1482–92
51. Nezu J, Tamai I, Oku A, Ohashi R, Yabuuchi H, et al. 1999. Primary systemic carnitine deficiency is caused by mutations in a gene encoding sodium ion-dependent carnitine transporter. *Nat. Genet.* 21:91–94
52. Ohashi R, Tamai I, Yabuuchi H, Nezu JI, Oku A, et al. 1999. Na^+-dependent carnitine transport by organic cation transporter (OCTN2): its pharmacological and toxicological relevance. *J. Pharmacol. Exp. Ther.* 291:778–84
53. Ganapathy ME, Huang W, Rajan DP, Carter AL, Sugawara M, et al. 2000. β-lactam antibiotics as substrates for OCTN2, an organic cation/carnitine transporter. *J. Biol. Chem.* 275:1699–707
54. Tamai I, Nezu J, Uchino H, Sai Y, Oku A, et al. 2000. Molecular identification and characterization of novel members of the human organic anion transporter (OATP) family. *Biochem. Biophys. Res. Commun.* 273:251–60
55. Hsiang B, Zhu Y, Wang Z, Wu Y, Sasseville V, et al. 1999. A novel human hepatic organic anion transporting polypeptide (OATP2). Identification of a liver-specific human organic anion transporting polypeptide and identification of rat and human hydroxymethylglutaryl-CoA reductase inhibitor transporters. *J. Biol. Chem.* 274:37161–68
56. Nakai D, Nakagomi R, Furuta Y, Tokui T, Abe T, et al. 2001. Human liver-specific organic anion transporter, LST-1, mediates uptake of pravastatin by human

hepatocytes. *J. Pharmacol. Exp. Ther.* 297:861–67

57. König J, Cui Y, Nies AT, Keppler D. 2000. A novel human organic anion transporting polypeptide localized to the basolateral hepatocyte membrane. *Am. J. Physiol. Gastrointest. Liver Physiol.* 278:G156–64
58. König J, Cui Y, Nies AT, Keppler D. 2000. Localization and genomic organization of a new hepatocellular organic anion transporting polypeptide. *J. Biol. Chem.* 275:23161–68
59. Jacquemin E, Hagenbuch B, Stieger B, Wolkoff AW, Meier PJ. 1994. Expression cloning of a rat liver Na^+-independent organic anion transporter. *Proc. Natl. Acad. Sci. USA.* 91:133–37
60. Noé B, Hagenbuch B, Stieger B, Meier PJ. 1997. Isolation of a multispecific organic anion and cardiac glycoside transporter from rat brain. *Proc. Natl. Acad. Sci. USA* 94:10346–50
61. Cattori V, Hagenbuch B, Hagenbuch N, Stieger B, Ha R, et al. 2000. Identification of organic anion transporting polypeptide 4 (Oatp4) as a major full-length isoform of the liver-specific transporter-1 (rlst-1) in rat liver. *FEBS Lett.* 474:242–45
62. Shitara Y, Itoh T, Sato H, Li AP, Sugiyama Y. 2003. Inhibition of transporter-mediated hepatic uptake as a mechanism for drug-drug interaction between cerivastatin and cyclosporin A. *J. Pharmacol. Exp. Ther.* 304:610–16
63. Pang KS, Wang PJ, Chung AYK, Wolkoff AW. 1998. The modified dipeptide enalapril, an angiotensin-converting enzyme inhibitor, is transported by the rat liver organic anion transport protein. *Hepatology* 28:1341–46
64. Ishizuka H, Konno K, Naganuma H, Nishimura K, Kouzuki H, et al. 1998. Transport of temocaprilat into rat hepatocytes: role of organic anion transporting polypeptide. *J. Pharmacol. Exp. Ther.* 287:37–42
65. Kullak-Ublick GA, Ismair MG, Stieger B, Landmann L, Huber R, et al. 2001. Organic anion-transporting polypeptide B (OATP-B) and its functional comparison with three other OATPs of human liver. *Gastroenterology* 120:525–33
66. Jansen PL, Peters WH, Lamers WH. 1985. Hereditary chronic conjugated hyperbilirunemia in mutant rats caused by defective hepatic anion transport. *Hepatology* 5:573–79
67. Hosokawa S, Tagaya O, Mikami T, Nozaki Y, Kawaguchi Y, et al. 1992. A new rat mutant with chronic conjugated hyperbilirunemia and renal glomerular lesions. *Lab. Animal Sci.* 42:27–34
68. Muller M, Jansen PL. 1997. Molecular aspects of hepatobiliary transport. *Am. J. Physiol. Gastrointest. Liver Physiol.* 272:G1285–303
69. Oude Elferink RP, Meijer DK, Kuipers F, Jansen PL, Groen AK, et al. 1995. Hepatobiliary secretion of organic compounds; molecular mechanisms of membrane transport. *Biochim. Biophys. Acta* 1241:215–68
70. Stieger B, Meier PJ. 1998. Bile acid and xenobiotic transporters in liver. *Curr. Opin. Cell. Biol.* 10:462–67
71. Suzuki H, Sugiyama Y. 1998. Excretion of GSSG and glutathione conjugates mediated by MRP1 and cMOAT/MRP2. *Semin. Liver Dis.* 18:359–76
72. König J, Nies AT, Cui Y, Leier I, Keppler D. 1999. Conjugate export pumps of the multidrug resistance protein (MRP) family: localization, substrate specificity, and MRP2-mediated drug resistance. *Biochim. Biophys. Acta* 1461:377–94
73. Paulusma CC, Bosma PJ, Zaman GJ, Bakker CT, Otter M, et al. 1996. Congenital jaundice in rats with a mutation in a multidrug resistance-associated protein gene. *Science* 271:1126–28
74. Ito K, Suzuki H, Hirohashi T, Kume K, Shimizu T, et al. 1997. Molecular cloning of canalicular multispecific organic anion transporter defective in EHBR. *Am. J. Physiol. Gastrointest. Liver Physiol.* 272:G16–22

75. Buchler M, König J, Brom M, Kartenbeck J, Spring H, et al. 1996. cDNA cloning of the hepatocyte canalicular isoform of the multidrug resistance protein, cMrp, reveals a novel conjugate export pump deficient in hyperbilirubinemic mutant rats. *J. Biol. Chem.* 271:15091–98
76. Taniguchi K, Wada M, Kohno K, Nakamura T, Kawabe T, et al. A human canalicular multispecific organic anion transporter (cMOAT) gene is overexpressed in cisplatin-resistant human cancer cell lines with decreased drug accumulation. *Cancer Res.* 56:4124–29
77. Borst .P, Evers R, Kool M, Wijnholds J. 1999. The multidrug resistance protein family. *Biochim. Biophys. Acta* 1461:347–57
78. Kuwano M, Toh S, Uchiumi T, Takano H, Kohno K, Wada M. 1999. Multidrug resistance-associated protein subfamily transporters and drug resistance. *Anticancer Drug Des.* 14:123–31
79. Jedlitschky G, Leier I, Buchholz U, Hummel-Eisenbeiss J, Burchell B, et al. 1997. ATP-dependent transport of bilirubin glucuronides by the multidrug resistance protein MRP1 and its hepatocyte canalicular isoform MRP2. *Biochem. J.* 327:305–10
80. Niinuma K, Kato Y, Suzuki H, Tyson CA, Weizer V, et al. 1999. Primary active transport of organic anions on bile canalicular membrane in humans. *Am. J. Physiol. Gastrointest. Liver Physiol.* 276:G1153–64
81. Cui Y, Konig J, Buchholz JK, Spring H, Leier I, et al. 1999. Drug resistance and ATP-dependent conjugate transport mediated by the apical multidrug resistance protein, MRP2, permanently expressed in human and canine cells. *Mol. Pharmacol.* 55:929–37
82. Niinuma K, Kato Y, Suzuki H, Tyson CA, Weizer V, et al. 1999. Primary active transport of organic anions on bile canalicular membrane in humans. *Am. J. Physiol. Gastrointest. Liver Physiol.* 276:G1153–64
83. Paulusma CC, van Geer MA, Evers R, Heijn M, Ottenhoff R, et al. 1999. Canalicular multispecific organic anion transporter/multidrug resistance protein 2 mediates low-affinity transport of reduced glutathione. *Biochem. J.* 338:393–401
84. Ryu S, Kawabe T, Nada S, Yamaguchi A. 2000. Identification of basic residues involved in drug export function of human multidrug resistance-associated protein 2. *J. Biol. Chem.* 275:39617–24
85. Sasaki M, Suzuki H, Ito K, Abe T, Sugiyama Y. 2002. Transcellular transport of organic anions across a double-transfected Madin-Darby canine kidney II cell monolayer expressing both human organic anion-transporting polypeptide (OATP2/SLC21A6) and multidrug resistance-associated protein 2 (MRP2/ABCC2). *J. Biol. Chem.* 277:6497–503
86. Hooijberg JH, Broxterman HJ, Kool M, Assaraf YG, Peters GJ, et al. 1999. Antifolate resistance mediated by the multidrug resistance proteins MRP1 and MRP2. *Cancer Res.* 59:2532–35
87. Tang F, Horie K, Borchardt RT. 2002. Are MDCK cells transfected with the human MRP2 gene a good model of the human intestinal mucosa? *Pharm. Res.* 19:773–79
88. Chen ZS, Kawabe T, Ono M, Aoki S, Sumizawa T, et al. 1999. Effect of multidrug resistance-reversing agents on transporting activity of human canalicular multispecific organic anion transporter. *Mol. Pharmacol.* 56:1219–28
89. Akita H, Suzuki H, Hirohashi T, Takikawa H, Sugiyama Y. 2002. Transport activity of human MRP3 expressed in Sf9 cells: comparative studies with rat MRP3. *Pharm. Res.* 19:34–41
90. Zeng H, Liu G, Rea PA, Kruh GD. 2000. Transport of amphipathic anions by human multidrug resistance protein 3. *Cancer Res.* 60:4779–84

91. Doyle LA, Yang W, Abruzzo LV, Krogmann T, Gao Y, et al. 1998. A multidrug resistance transporter from human MCF-7 breast cancer cells. *Proc. Natl. Acad. Sci. USA* 95:15665–70
92. Allikmets R, Schriml LM, Hutchinson A, Romano-Spica V, Dean M. 1998. A human placenta-specific ATP-binding cassette gene (ABCP) on chromosome 4q22 that is involved in multidrug resistance. *Cancer Res.* 58:5337–39
93. Miyake K, Mickley L, Litman T, Zhan Z, Robey R, et al. 1999. Molecular cloning of cDNAs which are highly overexpressed in mitoxantrone-resistant cells. *Cancer Res.* 59:8–13
94. Maliepaard M, Scheffer GL, Faneyte IF, van Gastelen MA, Pijnenborg ACLM, et al. 2001. Subcellular localization and distribution of the breast cancer resistance protein transporter in normal human tissues. *Cancer Res.* 61:3458–64
95. Suzuki M, Suzuki H, Sugimoto Y, Sugiyama Y. 2003. ABCG2 transports sulfated conjugates of steroids and xenobiotics. *J. Biol. Chem.* 278:22644–49
96. Urakami Y, Nakamura N, Takahashi K, Okuda M, Saito H, et al. 1999. Gender differences in expression of organic cation transporter OCT2 in rat kidney. *FEBS Lett.* 461:339–42
97. Hasegawa M, Kusuhara H, Sugiyama D, Ito K, Ueda S, et al. 2002. Functional involvement of rat organic anion transporter 3 (rOat3; Slc22a8) in the renal uptake of organic anions. *J. Pharmacol. Exp. Ther.* 300:746–53
98. Hori R, Ishikawa Y, Takano M, Okano T, Kitazawa S, et al. 1982. The interaction of cephalosporin antibiotics with renal cortex of rats: accumulation to cortical slices and binding to purified plasma membranes. *Biochem. Pharmacol.* 31:2267–72
99. Terada T, Sawada K, Ito T, Saito H, Hashimoto Y, et al. 2000. Functional expression of novel peptide transporter in renal basolateral membranes. *Am. J. Physiol. Renal Physiol.* 279:F851–57
100. Akhteruzzaman S, Kato Y, Kouzuki H, Suzuki H, Hisaka A, et al. 1999. Carrier-mediated hepatic uptake of peptidic endothelin antagonists in rats. *J. Pharmacol. Exp. Ther.* 290:1107–15
101. Ishigami M, Tokui T, Komai T, Tsukahara K, Yamazaki M, et al. 1995. Evaluation of the uptake of pravastatin by perfused rat liver and primary cultured rat hepatocytes. *Pharm. Res.* 12:1741–45
102. Madan A, DeHaan R, Mudra D, Carroll K, LeCluyse E, Parkinson A. 1999. Effect of cryopreservation on cytochrome P-450 enzyme induction in cultured rat hepatocytes. *Drug Metab. Dispos.* 27:327–35
103. Li AP, Maurel P, Gomez-Lechon MJ, Cheng LC, Jurima-Romet M. 1997. Preclinical evaluation of drug-drug interaction potential: present status of the application of primary human hepatocytes in the evaluation of cytochrome P450 induction. *Chem. Biol. Interact.* 107:5–16
104. Li AP, Lu C, Brent JA, Pham C, Fackett A, et al. 1999. Cryopreserved human hepatocytes: characterization of drug-metabolizing enzyme activities and applications in higher throughput screening assays for hepatotoxicity, metabolic stability, and drug-drug interaction potential. *Chem. Biol. Interact.* 121:17–35
105. Li AP, Gorycki PD, Hengstler JG, Kedderis GL, Koebe HG, et al. 1999. Present status of the application of cryopreserved hepatocytes in the evaluation of xenobiotics: consensus of an international expert panel. *Chem. Biol. Interact.* 121:117–23
106. Shitara Y, Li AP, Kato Y, Lu C, Ito K, et al. 2003. Function of uptake transporters for taurocholate and estradiol 17β-D-glucuronide in cryopreserved human hepatocytes. *Drug Metab. Pharmacokin.* 18:33–41
107. Olinga P, Hof IH, Merema MT, Smit M, de Jager MH, et al. 2001. The applicability of rat and human liver slices to the study of mechanisms of hepatic drug uptake.

5 Oct 2004 :1308 AR AR232-PA45-28.tex XMLPublish^{SM}(2004/02/24) P1: JRX
AR REVIEWS IN ADVANCE10.1146/annurev.pharmtox.44.101802.121444

J. Pharmacol. Toxicol. Methods 45:55–63

108. Shigematsu A, Motoji N, Momose Y, Iida A, Higashi N. 2000. Viability of liver slices exhibiting absorption, metabolism, and elimination of substrates in culture medium. *Exp. Mol. Pathol.* 69:119–43
109. Pritchard JB, Miller DS. 1993. Mechanisms mediating renal secretion of organic anions and cations. *Physiol. Rev.* 73:765–96
110. Murer H, Gmaj P, Steiger B, Hagenbuch B. 1989. Transport studies with renal proximal tubular and small intestinal brush border and basolateral membrane vesicles: vesicle heterogeneity, coexistence of transport system. *Methods Enzymol.* 172:346–64
111. Boyer JL, Meier PJ. 1990. Characterizing mechanisms of hepatic bile acid transport utilizing isolated membrane vesicles. *Methods Enzymol.* 192:517–33
112. Kinne-Saffran E, Kinne RK. Isolation of luminal and cotralumenal plasma membrane vesicles from kidney. *Methods Enzymol.* 191:450–69
113. Meier PJ, Boyer JL. 1990. Preparation of basolateral (sinusoidal) and canalicular plasma membrane vesicles for the study of hepatic transport processes. *Methods Enzymol.* 192:534–45
114. Meier PJ, St Meier-Abt A, Barrett C, Boyer JL. 1984. Mechanisms of taurocholate transport in canalicular and basolateral rat liver plasma membrane vesicles. Evidence for an electrogenic canalicular organic anion carrier. *J. Biol. Chem.* 259:10614–22
115. Cui Y, Konig J, Keppler D. 2001. Vectorial transport by double-transfected cells expressing the human uptake transporter SLC21A8 and the apical export pump ABCC2. *Mol. Pharmacol.* 60:934–43
116. Schinkel AH, Mayer U, Wagenaar E, Mol CA, van Deemter L, et al. 1997. Normal viability and altered pharmacokinetics in mice lacking mdr1-type (drug-transporting) P-glycoproteins. *Proc. Natl. Acad. Sci. USA* 94:4028–33
117. Hagenbuch B, Scharschmidt BF, Meier PJ. 1996. Effect of antisense oligonucleotides on the expression of hepatocellular bile acid and organic anion uptake systems in *Xenopus laevis* oocytes. *Biochem. J.* 316:901–4
118. Tamai I, Nakanishi T, Hayashi K, Terao T, Sai Y, et al. 1997. The predominant contribution of oligopeptide transporter PepT1 to intestinal absorption of beta-lactam antibiotics in the rat small intestine. *J. Pharm. Pharmacol.* 49:796–801
119. Kouzuki H, Suzuki H, Ito K, Ohashi R, Sugiyama Y. 1998. Contribution of sodium taurocholate co-transporting polypeptide to the uptake of its possible substrates into rat hepatocytes. *J. Pharmacol. Exp. Ther.* 286:1043–50
120. Kouzuki H, Suzuki H, Ito K, Ohashi R, Sugiyama Y. 1999. Contribution of organic anion transporting polypeptide to uptake of its possible substrates into rat hepatocytes. *J. Pharmacol. Exp. Ther.* 288:627–34
121. Hirano M, Maeda K, Shitara Y, Sugiyama Y. 2004. Contribution of OATP2 (OATP1B1) and OATP8 (OATP1B3) to the hepatic uptake of pitavastatin in humans. *J. Pharmacol. Exp. Ther.* 311:139–46
122. Shitara Y, Sugiyama D, Kusuhara H, Kato Y, Abe T. 2002. Comparative inhibitory effects of different compounds on rat oatp1 (*Slc21a1*)- and Oatp2 (*Slc21a5*)-mediated transport. *Pharm. Res.* 19:147–53
123. Ito K, Iwatsubo T, Kanamitsu S, Ueda K, Suzuki H, et al. 1998. Prediction of pharmacokinetic alterations caused by drug-drug interactions: metabolic interaction in the liver. *Pharmacol. Rev.* 50:387–412
124. Ito K, Iwatsubo T, Kanamitsu S, Nakajima Y, Sugiyama Y. 1998. Quantitative prediction of in vivo drug clearance and drug interactions from in vitro data on metabolism, together with binding and

transport. *Annu. Rev. Pharmacol. Toxicol.* 38:461–99

125. Ueda K, Kato Y, Komatsu K, Sugiyama Y. 2001. Inhibition of biliary excretion of methotrexate by probenecid in rats: quantitative prediction of interaction from in vitro data. *J. Pharmacol. Exp. Ther.* 297:1036–43
126. Saito H, Masuda S, Inui K. 1996. Cloning and functional characterization of a novel rat organic anion transporter mediating basolateral uptake of methotrexate in the kidney. *J. Biol. Chem.* 271:20719–25
127. Masuda S, Saito H, Inui K. 1997. Interactions of nonsteroidal anti-inflammatory drugs with rat renal organic anion transporter, OAT-K1. *J. Pharmacol. Exp. Ther.* 283:1039–42
128. Masuda S, Takeuchi A, Saito H, Hashimoto Y, Inui K. 1999. Functional analysis of rat renal organic anion transporter OAT-K1: bidirectional methotrexate transport in apical membrane. *FEBS Lett.* 459:128–32
129. Masuda S, Ibaramoto K, Takeuchi A, Saito H, Hashimoto Y, et al. 1999. Cloning and functional characterization of a new multispecific organic anion transporter, OAT-K2, in rat kidney. *Mol. Pharmacol.* 55:743–52
130. Takeuchi A, Masuda S, Saito H, Abe T, Inui K. 2001. Multispecific substrate recognition of kidney-specific organic anion transporters OAT-K1 and OAT-K2. *J. Pharmacol. Exp. Ther.* 299:261–67
131. Lu R, Kanai N, Bao Y, Wolkoff AW, Schuster VL. 1996. Regulation of renal oatp mRNA expression by testosterone. *Am. J. Physiol. Renal Physiol.* 270:F332–37
132. Yamazaki M, Tokui T, Ishigami M, Sugiyama Y.1996. Tissue-selective uptake of pravastatin in rats: contribution of a specific carrier-mediated uptake system. *Biopharm. Drug Dispos.* 17:775–89
133. Hedman A, Angelin B, Arvidsson A, Dahlqvist R, Nilsson B. 1990. Interactions in the renal and biliary elimination of digoxin: stereoselective difference between quinine and quinidine. *Clin. Pharmacol. Ther.* 47:20–26
134. Bohme M, Jedlitschky G, Leier I, Buchler M, Keppler D. 1994. ATP-dependent export pumps and their inhibition by cyclosporins. *Adv. Enzyme Regul.* 34:371–80
135. Versantvoort CH, Broxterman HJ, Lankelma J, Feller N, Pinedo HM. 1994. Competitive inhibition by genistein and ATP dependence of daunorubicin transport in intact MRP overexpressing human small cell lung cancer cells. *Biochem. Pharmacol.* 48:1129–36
136. Chu XY, Kato Y, Niinuma K, Sudo KI, Hakusui H, et al. 1997. Multispecific organic anion transporter is responsible for the biliary excretion of the camptothecin derivative irinotecan and its metabolites in rats. *J. Pharmacol. Exp. Ther.* 281:304–14
137. Araki E, Ishikawa M, Iigo M, Koide T, Itabashi M, et al. 1993. Relationship between development of diarrhea and the concentration of SN-38, an active metabolite of CPT-11, in the intestine and the blood plasma of athymic mice following intraperitoneal administration of CPT-11. *Jpn. J. Cancer Res.* 84:697–702
138. Gupta E, Lestingi TM, Mick R, Ramirez J, Vokes EE, et al. 1994. Metabolic fate of irinotecan in humans: correlation of glucuronidation with diarrhea. *Cancer Res.* 54:3723–25
139. Horikawa M, Kato Y, Tyson CA, Sugiyama Y. 2002. The potential for an interaction between MRP2 (ABCC2) and various therapeutic agents: probenecid as a candidate inhibitor of the bibiary excretion of irinotecan metabolites. *Drug Metab. Pharmacokin.* 17:23–33
140. Horikawa M, Kato Y, Sugiyama Y. 2002. Reduced gastrointestinal toxicity following inhibition of the biliary excretion of irinotecan and its metabolites by probenecid in rats. *Pharm. Res.* 19:1345–53

141. Mück W. 2000. Clinical pharmacokinetics of cerivastatin. *Clin. Pharmacokinet.* 39:99–116
142. Mück W, Mai I, Fritsche L, Ochmann K, Rohde G, et al. 1999. Increase in cerivastatin systemic exposure after single and multiple dosing in cyclosporin-treated kidney transplant recipients. *Clin. Pharmacol. Ther.* 65:251–61
143. Regazzi MB, Campana IC, Raddato V, Lesi C, Perani G, et al. 1993. Altered disposition of pravastatin following concomitant drug therapy with cyclosporin A in transplant recipients. *Transplant. Proc.* 25:2732–34
144. Hasunuma T, Nakamura M, Yachi T, Arisawa N, Fukushima K, et al. 2003. The drug-drug interactions of pitavstatin (NK-104), a novel HMG-CoA reductase inhibitor and cyclosporine. *J. Clin. Ther. Med.* 19:381–89
145. Asberg A, Hartmann A, Fjeldsa E, Bergan S, Holdaas H. 2001. Bilateral pharmacokinetic interaction between cyclosporine A and atorvastatin in renal transplant recipients. *Am. J. Transplant.* 1: 382–86
146. Lennernas H. 2003. Clinical pharmacokinetics of atorvastatin. *Clin. Pharmacokinet.* 42:1141–60
147. Bruce-Joyce J, Dugas JM, MacCausland OE. 2001. Cerivastatin and gemfibrozil-associated rhabdomyolysis. *Ann. Pharmacother.* 35:1016–19
148. Mueck W, Frey R, Boix O, Voith B. 2001. Gemfibrozil/cerivastatin interaction. *AAPS PharmSci.* 3(Suppl.):3566 (Abstr.)
149. Backman JT, Kyrklund C, Neuvonen M, Neuvonen PJ. 2002. Gemfibrozil greatly increases plasma concentrations of cerivastatin. *Clin. Pharmacol. Ther.* 72:685–91
150. Shitara Y, Hirano M, Sato H, Sugiyama Y. 2004. Gemfibrozil and its glucuronide inhibit the OATP2(OATP1B1:*SLC21A6*)-mediated hepatic uptake and CYP2C8-mediated metabolism of cerivastatin—analysis of the mechanism of the clinically relevant drug-drug interaction between cerivastatin and gemfibrozil. *J. Pharmacol. Exp. Ther.* 311:228–36
151. Schneck DW, Birmingham BK, Zalikowski JA, Mitchell PD, Wang Y, et al. 2004. The effect of gemfibrozil on the pharmacokinetics of rosuvastatin. *Clin. Pharmacol. Ther.* 75:455–63
152. Sallustio BC, Fairchild BA, Shanahan K, Evans AM, Nation RL. 1996. Disposition of gemfibrozil and gemfibrozil acyl glucuronide in the rat isolated perfused liver. *Drug Metab. Dispos.* 24:984–89
153. Sabordo L, Sallutio BC, Evans AM, Nation RL. 1998. Hepatic disposition of the acyl glucuronide 1-O-gemfibrozil β-D-glucuronide: effects of dibromosulfophthalein on membrane transport and aglycone formation. *J. Pharmacol. Exp. Ther.* 288:414–20
154. Sabordo L, Sallustio BC, Evans AM, Nation RL. 2000. Hepatic disposition of the acyl glucuronide 1-O-gemfibrozil-β-D-glucuronide: effects of clofibric acid, acetaminophen, and acetaminophen glucuronide. *J. Pharmacol. Exp. Ther.* 295: 44–50
155. Hedman A, Meijer DK. 1998. Stereoselective inhibition by the diastereomers quinidine and quinine of uptake of cardiac glycosides into isolated rat hepatocytes. *J. Pharm. Sci.* 87:457–61
156. Olinga P, Merema M, Hof IH, Slooff MJ, Proost JH, et al. 1998. Characterization of the uptake of rocuronium and digoxin in human hepatocytes: carrier specificity and comparison with in vivo data. *J. Pharmacol. Exp. Ther.* 285:506–10
157. Brown GR. 1993. Cephalosporin-probenecid drug interactions. *Clin. Pharmacokinet.* 24:289–300
158. Marino EL, Dominguez-Gil A. 1981. The pharmacokinetics of cefadroxil associated with probenecid. *Int. J. Clin. Pharmacol. Ther. Toxicol.* 19:506–8
159. Griffith RS, Black HR, Brier GL, Wolny JD. 1977. Effect of probenecid on

the blood levels and urinary excretion of cefamandole. *Antimicrob. Agents Chemother.* 11:809–12

160. Stoeckel K, Trueb V, Dubach UC, McNamara PJ. 1988. Effect of probenecid on the elimination and protein binding of ceftriaxone. *Eur. J. Clin. Pharmacol.* 34:151–56
161. Furst DE. 1995. Practical clinical pharmacology and drug interactions of low-dose methotrexate therapy in rheumatoid arthritis. *Br. J. Rheumatol.* 34(Suppl. 2):20–25
162. Tracy TS, Krohn K, Jones DR, Bradley JD, Hall SD, et al. 1992. The effects of a salicylate, ibuprofen, and naproxen on the disposition of methotrexate in patients with rheumatoid arthritis. *Eur. J. Clin. Pharmacol.* 42:121–25
163. Kremer JM, Hamilton RA. 1995. The effects of nonsteroidal antiinflammatory drugs on methotrexate (MTX) pharmacokinetics: impairment of renal clearance of MTX at weekly maintenance doses but not at 7.5 mg. *J. Rheumatol.* 22:2072–77
164. Frenia ML, Long KS. 1992. Methotrexate and nonsteroidal antiinflammatory drug interactions. *Ann. Pharmacother.* 26:234–37
165. Nozaki Y, Kusuhara H, Endou H, Sugiyama Y. 2004. Quantitative evaluation of the drug-drug interactions between methotrexate and nonsteroidal anti-inflammatory drugs in the renal uptake process based on the contribution of organic anion transporters and reduced folate carrier. *J. Pharmacol. Exp. Ther.* 309: 226–34
166. Apiwattanakul N, Sekine T, Chairoungdua A, Kanai Y, Nakajima N, et al. 1999. Transport properties of nonsteroidal anti-inflammatory drugs by organic anion transporter 1 expressed in *Xenopus laevis* oocytes. *Mol. Pharmacol.* 55:847–54
167. Uwai Y, Saito H, Inui K. 2000. Interaction between methotrexate and nonsteroidal anti-inflammatory drugs in organic anion transporter. *Eur. J. Pharmacol.* 409:31–36
168. Lu R, Chan BS, Schuster VL. 1999. Cloning of the human kidney PAH transporter: narrow substrate specificity and regulation by protein kinase C. *Am. J. Physiol. Renal Physiol.* 276:F295–303
169. Ohtsuki S, Asaba H, Takanaga H, Deguchi T, Hosoya K, et al. 2002. Role of blood-brain barrier organic anion transporter 3 (OAT3) in the efflux of indoxyl sulfate, a uremic toxin: its involvement in neurotransmitter metabolite clearance from the brain. *J. Neurochem.* 83:57–66
170. Sekine T, Cha SH, Tsuda M, Apiwattanakul N, Nakajima N, et al. 1998. Identification of multispecific organic anion transporter 2 expressed predominantly in the liver. *FEBS Lett.* 429:179–82
171. Morita N, Kusuhara H, Sekine T, Endou H, Sugiyama Y. 2001. Functional characterization of rat organic anion transporter 2 in LLC-PK1 cells. *J. Pharmacol. Exp. Ther.* 298:1179–84
172. Kusuhara H, Sekine T, Utsunomiya-Tate N, Tsuda M, Kojima R, et al. 1999. Molecular cloning and characterization of a new multispecific organic anion transporter from rat brain. *J. Biol. Chem.* 274:13675–80
173. Jariyawat S, Sekine T, Takeda M, Apiwattanakul N, Kanai Y, et al. 1999. The interaction and transport of beta-lactam antibiotics with the cloned rat renal organic anion transporter 1. *J. Pharmacol. Exp. Ther.* 290:672–77
174. Takeda M, Babu E, Narikawa S, Endou H. 2002. Interaction of human organic anion transporters with various cephalosporin antibiotics. *Eur. J. Pharmacol.* 438:137–42
175. Jung KY, Takeda M, Shimoda M, Narikawa S, Tojo A, et al. 2002. Involvement of rat organic anion transporter 3 (rOAT3) in cephaloridine-induced nephrotoxicity: in comparison with rOAT1. *Life Sci.* 70:1861–74
176. Uwai Y, Saito H, Inui K. 2002. Rat renal organic anion transporter rOAT1 mediated transport of urinary-excreted

5 Oct 2004 :1308 AR AR232-PA45-28.tex XMLPublish^{SM}(2004/02/24) P1: JRX
AR REVIEWS IN ADVANCE10.1146/annurev.pharmtox.44.101802.121444

cephalosporins, but not of biliary excreted cefoperazone. *Drug Metab. Pharmacokin.* 17:125–29

177. Babu E, Takeda M, Narikawa S, Kobayashi Y, Enomoto A, et al. 2002. Role of human organic anion transporter 4 in the transport of ochratoxin A. *Biochim. Biophys. Acta* 1590:64–75
178. Babu E, Takeda M, Narikawa S, Kobayashi Y, Yamamoto T, et al. 2002. Human organic anion transporters mediate the transport of tetracycline. *Jpn. J. Pharmacol.* 88:69–76
179. Uwai Y, Saito H, Hashimoto Y, Inui K. 2000. Interaction and transport of thiazide diuretics, loop diuretics, and acetazolamide via rat renal organic anion transporter rOAT1. *J. Pharmacol. Exp. Ther.* 295:261–65
180. Uwai Y, Saito H, Hashimoto Y, Inui K. 2000. Inhibitory effect of anti-diabetic agents on rat organic anion transporter rOAT1. *Eur. J. Pharmacol.* 398:193–97
181. Nagata Y, Kusuhara H, Endou H, Sugiyama Y. 2002. Expression and functional characterization of rat organic anion transporter 3 (rOat3) in the choroid plexus. *Mol. Pharmacol.* 61:982–88
182. Takeda M, Narikawa S, Hosoyamada M, Cha SH, Sekine T, et al. 2001. Characterization of organic anion transport inhibitors using cells stably expressing human organic anion transporters. *Eur. J. Pharmacol.* 419:113–20
183. Enomoto A, Takeda M, Shimoda M, Narikawa S, Kobayashi Y, et al. 2002. Interaction of human organic anion transporters 2 and 4 with organic anion transport inhibitors. *J. Pharmacol. Exp. Ther.* 301:797–802
184. Cvetkovic M, Leake B, Fromm MF, Wilkinson GR, Kim RB. 1999. OATP and P-glycoprotein transporters mediate the cellular uptake and excretion of fexofenadine. *Drug Metab. Dispos.* 27:866–71
185. Tokui T, Nakai D, Nakagomi R, Yawo H, Abe T, et al. 1999. Pravastatin, an HMG-CoA reductase inhibitor, is transported by rat organic anion transporting polypeptide, oatp2. *Pharm. Res.* 16:904–8
186. Kullak-Ublick GA, Fisch T, Oswald M, Hagenbuch B, Meier PJ, et al. 1998. Dehydroepiandrosterone sulfate (DHEAS): identification of a carrier protein in human liver and brain. *FEBS Lett.* 424:173–76
187. Bossuyt X, Muller M, Hagenbuch B, Meier PJ. 1996. Polyspecific drug and steroid clearance by an organic anion transporter of mammalian liver. *J. Pharmacol. Exp. Ther.* 276:891–96
188. Sugiyama D, Kusuhara H, Shitara Y, Abe T, Meier PJ, et al. 2001. Characterization of the efflux transport of 17β-estradiol-D-glucuronide from the brain across the blood-brain barrier. *J. Pharmacol. Exp. Ther.* 298:316–22
189. Sugiyama D, Kusuhara H, Shitara Y, Abe T, Sugiyama Y. 2002. Effect of 17β-estradiol-D-17β-glucuronide on the rat organic anion transporting polypeptide 2-mediated transport differs depending on substrates. *Drug Metab. Dispos.* 30:220–23
190. Abe T, Unno M, Onogawa T, Tokui T, Kondo TN, et al. 2001. LST-2, a human liver-specific organic anion transporter, determines methotrexate sensitivity in gastrointestinal cancers. *Gastroenterology* 120:1689–99
191. Vavricka SR, van Montfoort J, Ha HR, Meier PJ, Fattinger K. 2002. Interactions of rifamycin SV and rifampicin with organic anion uptake systems of human liver. *Hepatology* 36:164–72
192. Fattinger K, Cattori V, Hagenbuch B, Meier PJ, Stieger B. 2000. Rifamycin SV and rifampicin exhibit differential inhibition of the hepatic rat organic anion transporting polypeptides, Oatp1 and Oatp2. *Hepatology* 32:82–86
193. Ichimaru N, Takahara S, Kokado Y, Wang J-D, Hatori M, et al. 2001. Changes in lipid metabolism and effect of simvastatin in renal transplant recipients induced by cyclosporine or tacrolimus. *Atherosclerosis* 158:417–23