Table 8
Transport profile of statins in transporter expression systems

	Transporter name	K_m [a] [μM]	Expression systems
(a) Human transporters			
Atorvastatin	OATP1B1	12.4	HEK293 cells
Pravastatin	OATP1B1	33.7	293c18 cells
Pravastatin	OATP1B1	11.5	*Xenopus laevis* oocytes
Pravastatin	OATP1B1	85.7	HEK293 cells
Cerivastatin	OATP1B1	+	MDCK II cells
Pitavastatin	OATP1B1	3.0	HEK293 cells
Rosuvastatin	OATP1B1	8.5	*Xenopus laevis* oocytes
Pitavastatin	OATP1B3	3.25	HEK293 cells
Pravastatin	OATP2B1	2250	HEK293 cells
Pravastatin	OAT3	+	S_2 cells
Pravastatin	MDR1 (ABCB1)	+	MDCK II cells (Double transfected cells)
Cerivastatin	MDR1 (ABCB1)	+	MDCK II cells (Double transfected cells)
Cerivastatin	MDR1 (ABCB1)	+	LLC-PK1 cells
Pravastatin	MRP2 (ABCC2)	+	MDCK II cells (Double transfected cells)
Cerivastatin	MRP2 (ABCC2)	+	MDCK II cells (Double transfected cells)
Pravastatin	BCRP (ABCG2)	+	MDCK II cells (Double transfected cells)
Cerivastatin	BCRP (ABCG2)	+	MDCK II cells (Double transfected cells)
Pravastatin	BSEP	124	membrane vesicles from HEK293 cells
Cerivastatin	BSEP	–	membrane vesicles from HEK293 cells
Fluvastatin	BSEP	–	membrane vesicles from HEK293 cells
Pitavastatin	BSEP	–	membrane vesicles from HEK293 cells
(b) Rat transporters			
Pravastatin	Oatp1a1	30	293c18 cells
Pravastatin	Oatp1a4	–	293c18 cells
Pravastatin	Oatp1a4	37.5	*Xenopus laevis* oocytes
Pravastatin	Oatp4	+	MDCK II cells (Double transfected cells)
Cerivastatin	Oatp14	1.34	HEK293 cells
Pravastatin	Oatp14	+	HEK293 cells
Pravastatin	Oat3	13.4	LLC-PK1 cells
Pravastatin	Bsep	+	membrane vesicles from HEK293 cells
Cerivastatin	Bsep	–	membrane vesicles from HEK293 cells
Fluvastatin	Bsep	–	membrane vesicles from HEK293 cells
Pitavastatin	Bsep		membrane vesicles from HEK293 cells

Reference: TP-search (http://www.TP-search.jp/).
[a] +, transported but no report of K_m value; –, not transported.

can be metabolized by the multiple pathways shown in Fig. 7: lactonized statins may be converted to the open acid form again by carboxy esterase and, subsequently, metabolized or excreted into the bile or urine, or directly metabolized by P450 as the lactone forms. Table 9 shows the rate of UGT-mediated glucuronidation of different statins. The lactone forms of statins are more rapidly metabolized by P450 than the open acid forms (Table 9). It may suggest that there is a metabolic pathway of lactonized statins mediated by P450 after the UGT-mediated lactonization. Prueksarinont et al. have shown that gemfibrozil, a fibrate, inhibited the P450- and UGT-mediated metabolism of simvastatin, atorvastatin and cerivastatin (Prueksaritanont et al., 2002b). In addition, when coadministered with gemfibrozil, the plasma concentration of simvastatin acid increased while the area under the plasma concentration–time curve (AUC) of the lactone form of simvastatin was reduced in dogs, suggesting that gemfibrozil inhibits the lactonization of simvastatin in vivo (Prueksaritanont et al., 2002b). But the metabolic rates by UGT are 7.2- to 71-fold lower than those mediated by P450 except for pitavastatin (Table 9) and, thus, this metabolic pathway is not likely to cause a serious interaction. For pitavastatin, biliary excretion of the intact form is the main elimination pathway in some experimental animals including rats, rabbits and dogs (Kojima et al., 1999), suggesting that the UGT-mediated lactonization makes only a minor contribution to the total body clearance.

3.5. Urinary excretion

Generally, urinary excretion of statins is low (Table 5). However, it is not negligible for pravastatin, since 40–47% of intravenously administered drug is excreted in the urine in humans (Hatanaka, 2000). Yamazaki et al. have shown that pravastatin undergoes renal uptake in rats although urinary excretion is low (Yamazaki et al., 1996c). In addition, more recent studies have shown that pravastatin is a substrate of rat Oat3 and human OAT3 (*SLC22A8*), which are involved in the renal uptake of drugs (Hasegawa et al., 2002; Takeda et al., 2004). In rats, the K_m value for the uptake of pravastatin in rat kidney slices was similar with that in rat Oat3-expressing LLC-PK_1 cells (Hasegawa et al., 2002). In addition, the inhibition studies of the uptake of pravastatin by *p*-aminohippurate (a relatively selective inhibitor of rat Oat1), benzylpenicillin (a relatively selective inhibitor of rat Oat3) and dibromosulfophthalein (a nonspecific inhibitor of rat Oat1 and Oat3) revealed that their K_i were similar in rat kidney slices and Oat3-expressing cells (Hasegawa et al., 2002). These results strongly support that its renal uptake is mediated by Oat3 (Hasegawa et al., 2002). Also in humans, OAT3 may be involved in the urinary excretion of pravastatin. Although Nishizato et al. failed to find a relationship between SNPs in human OAT3 and the pharmacokinetics of pravastatin, this does not rule out the contribution of human OAT3 to the elimination of this statin (Nishizato et al., 2003). The plasma concentration of pravastatin is affected by coadministration of gemfibrozil (Kyrklund et al., 2003). In this study, gemfibrozil reduced the renal clearance of pravastatin although the contribution of this reduction in urinary excretion to that in the total body clearance is minor and, thus, reduced renal clearance cannot fully explain the total pharmacokinetic alteration (Kyrklund et al., 2003). But, this observation supports the involvement of a transport system in the urinary excretion of pravastatin, which is inhibited by gemfibrozil.

3.6. Intestinal absorption and excretion

All statins currently on the market are well absorbed from the intestine. The mechanism for the intestinal absorption of statins

Table 9
P450- and UGT-mediated metabolism of statins in human liver microsomes

	P450-mediated metabolism for open acid forms		P450-mediated metabolism for lactone forms		UGT-mediated metabolism		
	CL_{int} (μL/min/mg protein)	Isoforms	CL_{int} (μL/min/mg protein)	Isoforms	CL_{int} ($=V_{max}/K_m$) (μL/min/mg protein)	K_m (μM)	V_{max} (pmol/min/mg protein)
Simvastatin	28.4	CYP3A4	1960	CYP3A4	0.4	416	162
Fluvastatin	33.2	CYP2C9 CYP3A4[a]	226	CYP3A4			
Cerivastatin	20.8	CYP2C8 CYP3A4	622	CYP3A4	2.9	8	238
Atorvastatin	26.0	CYP3A4	1890	CYP3A4	3.3	16	52
Pitavastatin	2.50	CYP2C9[a] CYP2C8[a]	5.40	CYP3A4 CYP2D6[a]	3.1	78	237

Reference: Fujino et al. (2004c).
[a] Involved but to a small extent; –, no data.

varies from one drug to another. Simvastatin and lovastatin, which are lipophilic, can easily penetrate the plasma membrane in a nonspecific manner while others may be recognized by specific transport system(s). Tamai et al. reported that pravastatin is taken up into rabbit intestinal brush border membrane vesicles by coupled transport with protons (Tamai et al., 1995). They also reported that it takes place more via specific transport than by passive diffusion (Tamai et al., 1995). It is inhibited by monocarboxylic acids, acetic acid and nicotinic acid, suggesting that this statin is also transported by a transporting system for monocarboxylic acids (i.e. MCT (monocarboxylic acid transporter)). However, to date, there have been no reports that pravastatin is a substrate of MCT. Recently, pravastatin was reported to be a substrate of OATP2B1 (OATP-B, *SLCO2B1/SLC21A9*), which is expressed in the intestine (Kobayashi et al., 2003; Nozawa et al., 2004). OATP2B1-mediated transport is reported to depend on the pH of the incubation buffer, and this agrees with the results of in vivo studies in rats (Tsuji, 1999). Although OATP2B1 is a candidate for one of the transporters involved in the intestinal absorption of pravastatin, its function in vivo has not been determined yet. However, we examined the uptake of pravastatin into rat everted sacs and found that it was comparable with that of polyethylene glycol 4000 (PEG4000), suggesting the minimal contribution of transporter-mediated absorption for pravastatin in rats (unpublished data; Fig. 8). On the other hand, a higher transport of cerivastatin was observed than PEG4000 and it was saturable (Fig. 8). The intestinal absorption of cerivastatin may, thus, be mediated by some transporter(s). If transporter-mediated intestinal transport takes place, intestinal absorption can be affected by coadministered drugs and is also a target for drug–drug interactions. It has been

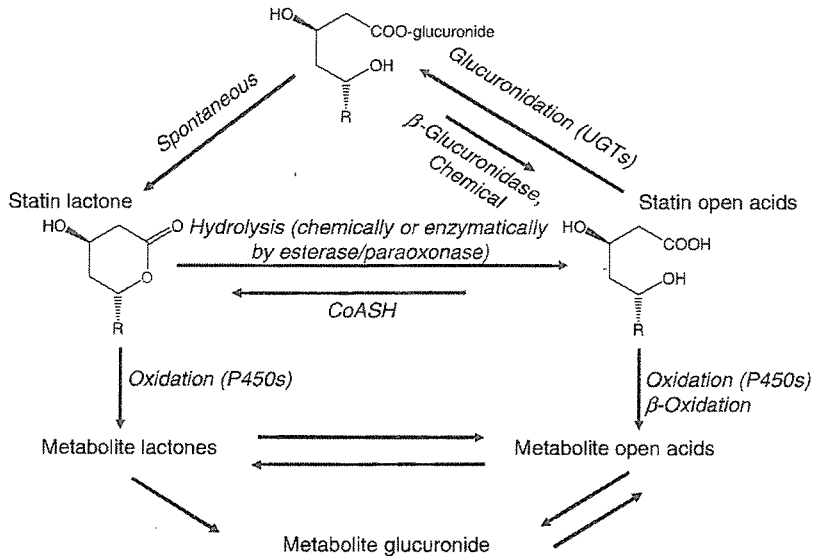

Fig. 7. Lactonization of statins mediated by UDP-glucuronosyl transferase. This scheme was originally proposed by Prueksaritanont et al. (2002a). The statins have an acid/lactone interconversion pathway and are metabolized by a complex mechanism. The statin lactones are hydrolyzed to their open acids chemically or enzymatically by esterases or paraoxonases. The statin acids are converted to the corresponding lactones by the acyl glucuronide intermediate and by the CoASH-dependent pathway. Both acyl glucuronide and acyl CoA derivatives may revert to the statin acids by hydrolysis. Reprint from "Glucuronidation of statins in animals and humans: a novel mechanism of statin lactonization" by Prueksaritanont et al., 2002a, with the permission from the American Society for Pharmacology and Experimental Therapeutics.

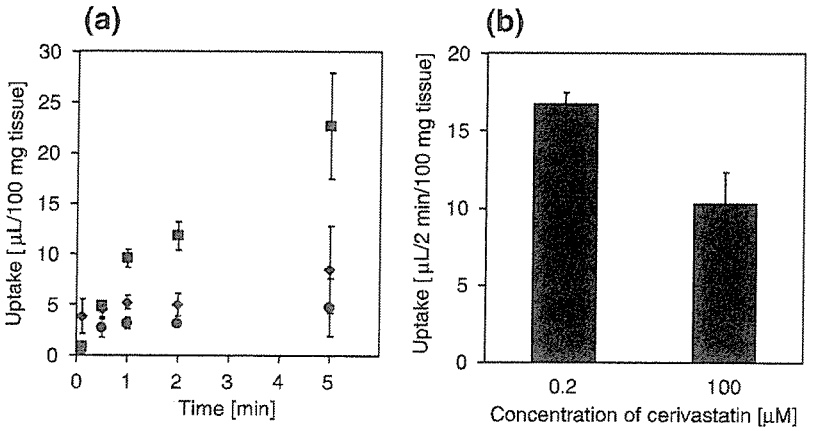

Fig. 8. Uptake of pravastatin and cerivastatin in rat jejunum everted sacs (a) and dose dependence of the cerivastatin uptake (b) (Kawakami-Takada, Hiroyuki Kusuhara & Yuichi Sugiyama, unpublished results). (a) The uptake of [^{14}C]cerivastatin (0.2 μM, ■) [^{3}H]pravastatin (1 μM, ◆) or [^{14}C]PEG4000 (●) in rat jejunum everted sacs is shown. Each point represents the mean±S.E. (n=3) using everted sacs from different rats. Time-dependent uptake of statins was observed but the uptake of pravastatin was not higher than that of PEG4000 while that of cerivastatin was higher. (b) The uptake of [^{14}C]cerivastatin in rat jejunum everted sacs at 2 min at 37 °C was examined at the concentrations of 0.2 and 100 μM. Specific uptake was observed by the subtraction of simultaneously determined [^{3}H]PEG4000 uptake from the total uptake of cerivastatin. Each data point represents the mean±S.E. (n=3).

shown that the intestinal absorption of fexofenadine is reduced by the concomitant intake of orange, grapefruit and apple juices (Dresser et al., 2002; Dresser et al., 2005). In addition, these fruit juices inhibit the OATP1A2 (OATP-A, *SLCO1A2/SLC21A3*) mediated uptake of fexofenadine although the expression and function of OATP1A2 in the intestine is unknown (Dresser et al., 2002, 2005). These observations may suggest a possibility of transporter-mediated drug–drug interactions (Dresser et al., 2002, 2005). More recently, Satoh et al. reported that citrus juice (i.e. grapefruit and orange juice) but not apple juice inhibited OATP2B1-mediated transport (Satoh et al., 2005). However, grapefruit juice does not affect the pharmacokinetics of pravastatin while it increases the plasma concentration of atorvastatin, which is possibly the result of a CYP3A4-mediated drug–drug interaction (Lilja et al., 1999; Fukazawa et al., 2004). The result obtained with the combination of grapefruit juice and pravastatin suggests that this interaction was not caused by a transporter-mediated process. To clarify the mechanism of drug–drug interactions involved in the intestinal absorption of statins, more details are required about the molecular mechanism of their intestinal absorption including the functions and contributions of transporters to the intestinal absorption of statins. Contributions of each transporter also need to be clarified.

Simvastatin, lovastatin, pravastatin, cerivastatin, atorvastatin and pitavastatin are substrates of P-glycoprotein (P-gp) (Sakaeda et al., 2002; Hochman et al., 2004; Kivisto et al., 2004a; Matsushima et al., 2005). Although pravastatin was reported not to be a substrate of MDR1 by Hirai et al. (2001), Wang et al. (2001) and Sakaeda et al. (2002), it was shown to be a moderate substrate of MDR1 by Matsushima et al. (2005). Although Matsushima et al. observed the MDR1-mediated transport of pravastatin, its transcellular transport mediated by OATP1B1 and MDR1 was lower than those of cerivastatin and pitavastatin (Matsushima et al., 2005). The pharmacokinetics of statins, which are substrates of P-gp, may be affected by P-gp inhibitors and their bioavailability may be increased. However, for statins with relatively high bioavailability, their plasma concentration is not that much affected by P-gp inhibitors. As the bioavailability of cerivastatin is about 60%, the increase in its plasma concentration by inhibition of P-gp-mediated intestinal efflux does not exceed 5/3-folds of that of the controls. Thus, cerivastatin is less likely to exhibit a serious interaction with P-gp inhibitors.

3.7. Distribution to the central nervous system

One of the side effects of statins is sleep disturbance (Schaefer, 1988; Barth et al., 1990). The distribution of statins to the central nervous system (CNS) may cause such a side effect. On the other hand, increasing data suggest that statins have properties that are potentially neuroprotective, that is, endothelial protection via actions on the nitric oxide synthase system, as well as antioxidant, anti-inflammatory and antiplatelet effects (Cucchiara & Kasner, 2001). Thus, statins can be used also for the treatment of CNS diseases. Increasing the access of statins to the brain may improve the therapeutic effects in the CNS although it may also increase their incidence of CNS side effects. Although simvastatin and lovastatin cause a sleep disturbance, pravastatin does not, indicating that simvastatin and lovastatin can easily penetrate the blood–brain barrier while pravastatin does not (Saheki et al., 1994). Comparison of pitavastatin and pravastatin suggests that the brain-to-plasma concentration ratio of pitavastatin is lower than that of pravastatin although pitavastatin is more lipophilic than pravastatin (Kikuchi et al., 2004; Table 3). The lower distribution of pitavastatin to the brain strongly supports the existence of efflux transporter(s). Kikuchi et al. analyzed the mechanism of efflux of statins from the CNS in rats and found a saturable and inhibitable efflux transport system for both of pitavastatin and pravastatin from the CNS, suggesting the existence of efflux transporting system(s) (Kikuchi et al., 2004). Their analyses also suggest that multiple transporters including rat

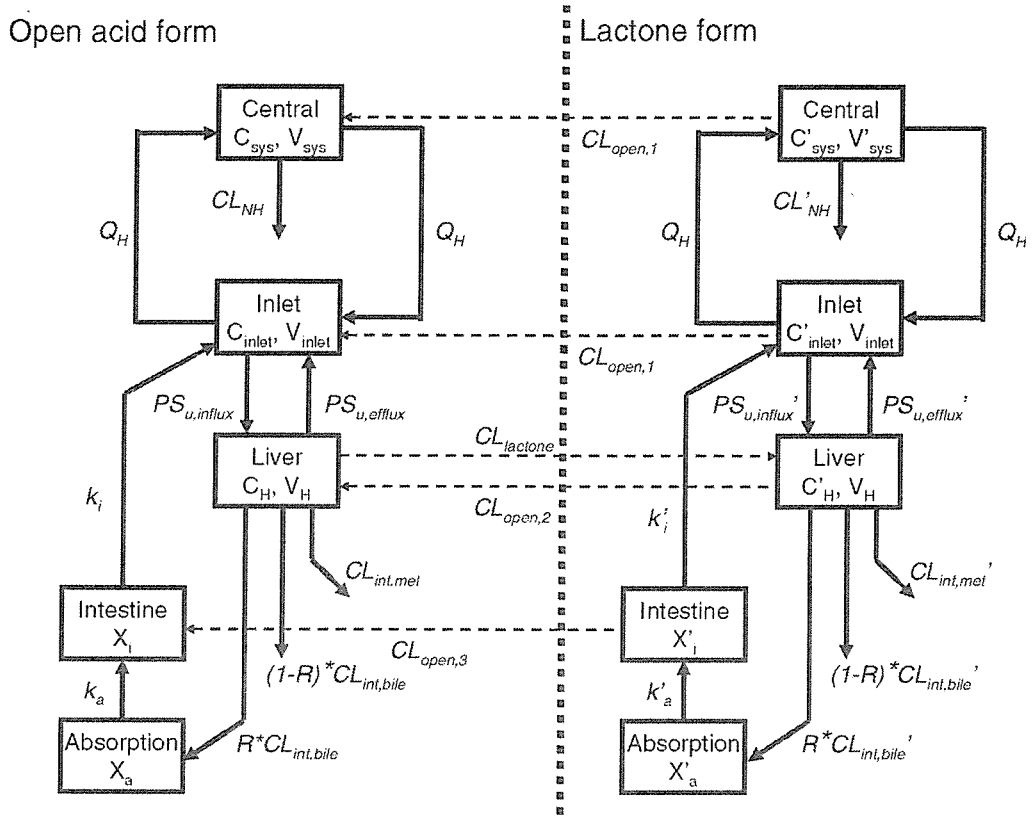

Fig. 9. A physiologically based pharmacokinetic model to describe the disposition of statins. Our analyses of statin disposition were performed using this physiologically based pharmacokinetic model. The meaning of all the parameters is given in Table 10. Because statins have an interconversion pathway between the lactones and open acids, the compartment for statins with open acids and lactones is separately described. In the present analysis, we have assumed that open acid statins are converted to lactones mainly via an acyl glucuronide intermediated pathway, mediated by UGT in the liver.

Oatp1a4 (Oatp2, *Slco1a4/Slc21a5*) and Oat3 are involved in the efflux of these statins from the CNS (Kikuchi et al., 2004). This process may also be inhibited by the coadministered drugs, resulting in the alteration of their therapeutic or side effects in the CNS.

3.8. Distribution to the skeletal muscle

One of the serious adverse effects of statins is myotoxicity including serious myopathy and rhabdomyolysis. Recently, there has been a report regarding the transporter which recognizes statins as its substrate localized in muscle (Takeda et al., 2004). Takeda et al. reported that OAT1 (*SLC22A6*) and OAT3 are expressed in muscle and OAT3 mediates the pravastatin transport (Takeda et al., 2004). They also observed that pravastatin, fluvastatin and simvastatin inhibit OAT1- and 3-mediated transport although the IC_{50} values are higher than their therapeutic concentrations in clinical situations (Takeda et al., 2004). OAT3 may be responsible for the myotoxicity of statins which are its substrates, especially in the case of statins of low lipophilicity. However, to date, there have not been any reports of the transporter-mediated saturable and inhibitable transport of statins to muscle. Thus, we cannot conclude that transporters mediate the uptake of statins by muscle and it is also unclear whether the transport of statins to muscle may be a target for drug–drug interactions or not.

3.9. Elimination mechasnisms

In this section, elimination mechanism for each statin is summarized. The target for drug–drug interactions is also provided here.

3.9.1. Simvastatin and lovastatin

Simvastatin and lovastatin are lipophilic statins with lactone forms, which easily cross the plasma membrane and, thus, they are easily absorbed from the intestine. However, they are substrates of CYP3A4 and P-gp with high affinities. CYP3A4 and P-gp are expressed in the liver and intestine and play an important role in the clearance in these tissues. Especially in intestine, these 2 systems coordinately work in drug detoxification and, thus, most of drugs, which are their bisubstrates, are well metabolized in intestine and their gut extraction is high (Benet et al., 1999). In part due to this mechanism, the bioavailabilities of these statins are low (<5 and 5% for simvastatin and lovastatin, respectively). Inhibition of CYP3A4 and/or P-gp may result in the increased absorption and cause a drug–drug interaction. In addition, mainly they are eliminated from the liver by the CYP3A4-mediated metabolism and, so, they are susceptible to CYP3A4-mediated drug–drug interactions also in the drug elimination process.

3.9.2. Pravastatin, rosuvastatin and pitavastatin

Pravastatin and rosuvastatin are not metabolized by P450. Although pitavastatin is metabolized by CYP2C9 in vitro, its metabolic rate is quite low. These statins are mainly eliminated from the body by a transporter-mediated excretion mechanism in the liver. Because they are substrates of OATP1B1, they are extensively taken up by the liver. In the particular case of pravastatin, a number of studies have investigated its transport mechanism. These suggest that enterohepatic recirculation contributes to its liver-specific distribution as shown in Fig. 5. For these statins, although P450-mediated drug–drug interactions are not possible, they are likely to be affected by transporter-mediated drug–drug interactions.

3.9.3. Fluvastatin

Fluvastatin is metabolized mainly by CYP2C9. It is unique among statins that are eliminated mainly by metabolism. This statin is not affected by CYP3A4 inhibitors although it is susceptible to CYP2C9-mediated drug–drug interactions. As fluvastatin is also a statin with a low lipophilicity, it is possible that some transport systems are involved in its hepatic uptake.

3.9.4. Cerivastatin

As this statin is no longer on the market, this information is of no clinical use. However, as this statin has some special characteristics, we will provide information about this statin. Cerivastatin is metabolized by 2 different enzymes, CYP2C8 and 3A4. This dual metabolic pathway is unique among statins. However, their estimated contributions are 61% and 37%, respectively (Shitara et al., 2004), and, due to the major contribution of CYP2C8, it is susceptible to CYP2C8-mediated drug–drug interactions. Generally, drugs, which have multiple metabolic pathways, are less susceptible to severe drug–drug interactions. However, if a contribution of 1 enzyme or transporter is relatively high, drug–drug interactions involving the process of metabolism or transport should be possible. As cerivastatin is a substrate of OATP1B1, transporter-mediated drug–drug interactions can also occur.

3.9.5. Atorvastatin

This statin also undergoes to CYP3A4-mediated metabolism. However, this hydrophilic statin is a substrate of OATP1B1 and actively taken up into the liver (Kameyama et al., 2005; Lau et al., 2006) prior to the metabolism. Lau et al. showed that saturable transport system involves in the hepatic uptake of atorvastatin in rats in vivo and it is inhibited by probenecid (Lau et al., 2006). As described in the Section 3.2, its clearance is affected not only by the metabolic rate but by the uptake rate (see Eq. (6)). This statin may be susceptible to the CYP3A4- and OATP1B1-mediated drug–drug interaction.

4. Model analysis of pharmacokinetic alterations of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors

In Section 3, some factors affecting the pharmacokinetics of statins were reviewed. In this section, we present some quantitative analyses of the effects of these factors (i.e. the increase or decrease in metabolic or transport rates) based on a physiological model. A physiological model based analysis is useful for the quantitative estimation of the impact of these factors on the plasma concentration or AUC. Here, we have carried out an analysis based on a physiological model as shown in Fig. 9 and Table 10. In this model, drug elimination from the liver is described by a hybrid process of uptake ($PS_{u,influx}$) and efflux

Table 10
Parameters used in the physiologically based pharmacokinetic model

Q_H	hepatic blood flow
C_H	concentration of statins in the liver
C_{inlet}	concentration of statins at the inlet to the liver
C_{sys}	concentration of statins in the circulating blood
X_a	total amount of statins pooled for the intestinal absorption
X_i	total amount of statins in the epithelial cells in the intestine
V_H	volume of liver
V_{inlet}	volume of inlet to the liver
V_{sys}	distribution volume of statins in the central compartment
$PS_{u,influx}$	permeability square product for the hepatic uptake of statins
$PS_{u,efflux}$	permeability square product for the efflux of statins across the sinusoidal membrane
CL_{int}	$CL_{int,met}+CL_{int,bile}$
$CL_{int,met}$	intrinsic clearance of statins for the hepatic metabolism
$CL_{int,bile}$	intrinsic clearance of statins for the biliary excretion
R	fraction of statins reabsorbed after biliary excretion
$CL_{open,1}$	clearance for conversation to the open acid form in the blood (including central compartment and inlet to the liver)
$CL_{open,2}$	clearance for conversion to the open acid form in the liver
$CL_{open,3}$	clearance for conversion to the open acid form in the intestine
$CL_{lactone}$	clearance for conversion to the lactone form in the liver
K_i	rate constant for the absorption from the intestinal epithelium to the hepatic portal vein
K_a	rate constant for the absorption from the intestinal lumen into the epithelium
f_u	protein unbound fraction in the circulating blood
f_i	protein unbound fraction in intestine
f_h	protein unbound fraction in liver

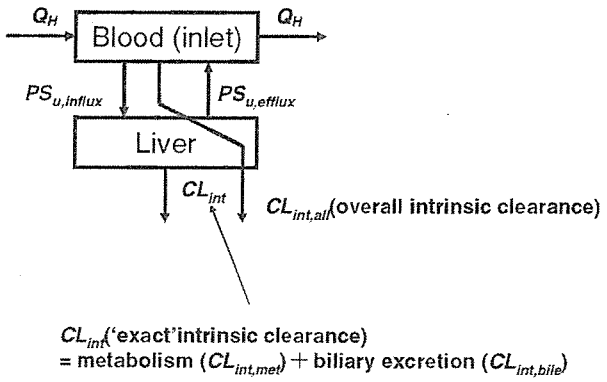

Fig. 10. Compartment model to describe elimination from the liver. The elimination from the liver can be described by the hybrid process of uptake ($PS_{u,influx}$) and efflux ($PS_{u,efflux}$) across the sinusoidal membrane and biliary excretion at the bile canalicular membrane ($CL_{int,bile}$) and/or metabolism ($CL_{int,met}$). CL_{int} represents the summation of $CL_{int,bile}$ and $CL_{int,\ met}$.

($PS_{u,efflux}$) across the sinusoidal membrane and subsequent biliary excretion ($CL_{int,bile}$) and/or metabolism ($CL_{int,met}$) ($CL_{int}=CL_{int,bile}+CL_{int,met}$) (Fig. 10). In this model, hepatic intrinsic clearance can be described by $PS\times(CL_{int}/PS_{u,efflux}+CL_{int})$. This is close to $PS_{u,influx}$ when $PS_{u,efflux}\ll CL_{int}$, or $PS_{u,influx}\times(CL_{int}/PS_{u,efflux})$ when $PS_{u,efflux}\gg CL_{int}$ (see Eq. (7) or Eq. (8)). Based on this model, the mass balance equations to express the drugs transported in and out of the each compartment can be described as follows:

$$V_{sys}\frac{dC_{sys}}{dt}=Q_H\cdot C_{inlet}-(CL_{NH}+Q_H)\cdot C_{sys}+f_u'\cdot CL_{open,1}\cdot C_{sys}' \tag{10}$$

$$V_{inlet}\frac{dC_{inlet}}{dt}=Q_H\cdot C_{sys}-(Q_H-f_u\cdot PS_{u,influx})\cdot C_{inlet}+f_u'\cdot CL_{open,1}\cdot C_{inlet}'+k_i\cdot X_i+f_H\cdot PS_{u,efflux}\cdot C_H \tag{11}$$

$$V_H\frac{dC_H}{dt}=f_u\cdot PS_{u,influx}\cdot C_{inlet}-f_H\cdot(PS_{u,efflux}+CL_{int,bile}+CL_{int,met}+CL_{lactone})\cdot C_H+f_H'\cdot CL_{open,2}\cdot C_H' \tag{12}$$

$$\frac{dX_a}{dt}=-k_a\cdot X_a+R\cdot CL_{int,bile}\cdot f_H\cdot C_H \tag{13}$$

$$\frac{dX_i}{dt}=k_a\cdot X_a-k_i\cdot X_i+f_i'\cdot CL_{open,3}\cdot\frac{X_i'}{V_i} \tag{14}$$

$$V_{sys}'\frac{dC_{sys}'}{dt}=Q_H\cdot C_{inlet}'-(CL_{NH}'+Q_H+f_u'\cdot CL_{open,1})\cdot C_{sys}' \tag{15}$$

$$V_{inlet}\frac{dC_{inlet}'}{dt}=Q_H\cdot C_{sys}'-(Q_H+f_u'\cdot PS_{u,influx}'+f_u'\cdot CL_{open,1})\cdot C_{inlet}'+k_i'\cdot X_i'+f_H'\cdot PS_{u,efflux}'\cdot C_H' \tag{16}$$

$$V_H\frac{dC_H'}{dt}=f_u'\cdot PS_{u,influx}'\cdot C_{inlet}'+f_H\cdot CL_{lactone}\cdot C_H-f_H'\cdot(CL_{open,2}+PS_{u,efflux}'+CL_{int,bile}+CL_{int,met}')\cdot C_H' \tag{17}$$

$$\frac{dX_a'}{dt}=-k_a'\cdot X_a'+R'\cdot CL_{int,bile}'\cdot f_H'\cdot C_H' \tag{18}$$

$$\frac{dX_i'}{dt}=k_a'\cdot X_a'-\left(k_i'+\frac{f_i'\cdot CL_{open,3}}{V_i}\right)\cdot X_i' \tag{19}$$

Table 10 shows the means of the parameters. Applying the Laplace transformation $(\tilde{f}(s)=\int_0^\infty e^{-st}\cdot F(t)dt)$ and $s\to 0$, the following equations are obtained.

$$Q_H\cdot AUC_{inlet}-(CL_{NH}+Q_H)\cdot AUC_{sys}+f_u'\cdot CL_{open,1}\cdot AUC_{sys}'=0 \tag{20}$$

$$Q_H\cdot AUC_{sys}-(Q_H+f_u\cdot PS_{u,influx})\cdot AUC_{inlet}+f_u'\cdot CL_{open,1}\cdot AUC_{inlet}'+k_i\cdot\int_0^\infty X_i dt+f_H\cdot PS_{u,efflux}\cdot AUC_H=0 \tag{21}$$

$$f_u \cdot PS_{u,influx} \cdot AUC_{inlet} - f_H \cdot (PS_{u,efflux} + CL_{int,bile} + CL_{int,met} + CL_{lactone}) \cdot AUC_H + f_H' \cdot CL_{open,2} \cdot AUC_H' = 0 \quad (22)$$

$$-k_a \cdot \int_0^\infty X_a dt + R \cdot CL_{int,bile} \cdot f_H \cdot AUC_H = -F_a \cdot D \quad (23)$$

$$k_a \cdot \int_0^\infty X_a dt - k_i \cdot \int_0^\infty X_i dt + \frac{f_i' \cdot CL_{open,3}}{V_i} \cdot \int_0^\infty X_i dt = 0 \quad (24)$$

$$Q_H \cdot AUC_{inlet}' - (CL_{NH}' + Q_H + f_u' \cdot CL_{open,1}) \cdot AUC_{sys}' = 0 \quad (25)$$

$$Q_H \cdot AUC_{sys}' - (Q_H + f_u' \cdot PS_{u,influx}' + f_u' \cdot CL_{open,1}) \cdot AUC_{inlet}' + k_i' \int_0^\infty X_i' dt + f_H' PS_{u,efflux}' \cdot AUC_H' = 0 \quad (26)$$

$$f_u' \cdot PS_{u,influx}' \cdot AUC_{inlet}' + f_H \cdot CL_{lactone} \cdot AUC_H - f_H' \cdot (CL_{open,2} + PS_{u,efflux}' + CL_{u,efflux}' + CL_{int,bile}' + CL_{int,met}') \cdot AUC_H' = 0 \quad (27)$$

$$-k_a' \cdot \int_0^\infty X_a' dt + R' \cdot CL_{int,bile}' \cdot f_H' \cdot AUC_H' = -F_a' \cdot D' \quad (28)$$

$$k_a' \cdot \int_0^\infty X_a' dt - \left(k_i' \cdot + \frac{f_i' \cdot CL_{open,3}}{V_i}\right) \cdot \int_0^\infty X_i' dt = 0 \quad (29)$$

where F_a is the fraction absorped in intestine, and D and D' are the dose of statins admininstered as open acid and lactone forms, respectively.

In the case of open acid statins, the ratio of the area under the time-unbound concentration of statins in the circulating blood curve (f_u*AUC_{sys}) to that under the time-unbound concentration of statins in the liver curve (f_H*AUC_H) can be described as follows:

$$\frac{f_u \cdot AUC_{sys}}{f_H \cdot AUC_H} = \frac{Q_H}{Q_H + CL_{NH}} \cdot \frac{PS_{u,efflux} + CL_{int,bile} + CL_{int,met} + CL_{lactone}}{PS_{u,influx}} - \frac{Q_H \cdot CL_{lactone}}{Q_H + CL_{NH}} \left[\left\{ \frac{f_u \cdot CL_{open,1} \left(\frac{CL_{open,2} + PS_{u,efflux}' + CL_{int,bile}' + CL_{int,met}'}{A} - 1 \right)}{CL_{NH}' + Q_H + f_u' \cdot CL_{open,1}} \right\} + \frac{1}{A} \cdot \frac{CL_{open,2}}{PS_{u,influx}} \right] \quad (30)$$

where,

$$A = CL_{open,2} + PS_{u,efflux}' + CL_{int,bile}' + CL_{int,met}' + \frac{f_u' \cdot PS_{u,efflux}' \cdot \left(\frac{R' \cdot CL_{int,bile}' \cdot K_i'}{k_i' + f_i' \cdot CL_{open,3}/V_i} + PS_{u,efflux}' \right)}{Q_H \cdot \left(\frac{Q_H}{Q_H + CL_{NH}' + f_u' \cdot CL_{open,1}} - \frac{Q_H + fu \cdot PS_{u,influx}' + fu' \cdot CL_{open,1}}{Q_H} \right)}$$

As this ratio of $f_u \cdot AUC_{sys}$ to $f_H \cdot AUC_H$ decreases, this means that the drug distributes to the liver specifically with low exposure to other tissues. Therefore, the drug with a lower ratio does not distribute to the target organ of the side effects but is highly exposed to the liver, suggesting a low likelihood of side effects with high pharmacological effects. In other words, this kind of statin has a wide therapeutic index with a wide safety margin. The reciprocal of the Eq. (30), that is, the ratio of $f_H \cdot AUC_H$ to $f_u \cdot AUC_{sys}$ reflects the width of the therapeutic index. When $CL_{lactone}$ is negligibly low, the reciprocal of the Eq. (30) gives the following equation:

$$\frac{f_H \cdot AUC_H}{f_u \cdot AUC_{sys}} = \frac{Q_H + CL_{NH}}{Q_H} \cdot \frac{PS_{u,influx}}{PS_{u,efflux} + CL_{int,bile} + CL_{int,met}} \quad (31)$$

As the extrahepatic clearance is negligible for all statins, this equation means that the safety margin of statins correlates with the ratio of the uptake of the statins by the liver ($PS_{u,influx}$) to the efflux, biliary excretion and metabolism ($PS_{u,efflux}$+$CL_{int,bile}$ +$CL_{int,met}$). For a statin with a high hepatic uptake and low efflux, biliary excretion and metabolism will result in a marked pharmacological effect. Because the lactonization rate is, in fact, low as shown in Table 9, the safety margin is determined only

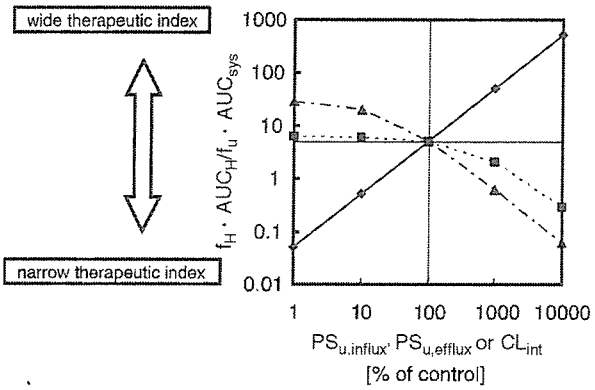

Fig. 11. Pharmacokinetic alterations associated with the change in $PS_{u,influx}$ (influx into hepatocytes), $PS_{u,efflux}$ (efflux from hepatocytes across the sinusoidal membrane) and CL_{int} (a hybrid parameter for biliary excretion and metabolism). The relationship between parameters ($PS_{u,influx}$, $PS_{u,efflux}$ and CL_{int}) and $f_H \cdot AUC_H/f_u \cdot AUC_{sys}$ ratio. Simulated pharmacokinetic alterations caused by a change in $PS_{u,influx}$, $PS_{u,efflux}$ and CL_{int} are shown. The $f_H \cdot AUC_H$ value represents the exposure of unbound statins to the liver, a target organ. A high $f_H \cdot AUC_H$ means a high pharmacological effect and a high $f_u \cdot AUC_{sys}$ may lead to exposure of unbound statins to other tissues and, therefore, a potential toxic side effect. Thus, a low $f_u \cdot AUC_{sys}$ with a high $f_H \cdot AUC_H$ means a selective distribution of statins to the liver, suggesting a high pharmacological effect with a low risk of side effects. Therefore, a statin with a high $f_H \cdot AUC_H/f_u \cdot AUC_{sys}$ ratio has a wide therapeutic index, with a high pharmacological effect and low likelihood of side effects.

by the balance of $PS_{u,influx}$, $PS_{u,efflux}$ and CL_{int} ($=CL_{int,bile}+CL_{int,met}$). Fig. 11 shows the correlation between $PS_{u,influx}$, $PS_{u,efflux}$ and CL_{int} and the ratio of $f_H \cdot AUC_H/f_u \cdot AUC_{sys}$. As shown in this figure, statins with a high $PS_{u,influx}$ and low $PS_{u,efflux}$ and CL_{int} are safe statins with a wide therapeutic index. A reduction in the $PS_{u,influx}$ caused by inter-individual differences in the transporter function or transporter-mediated drug–drug interactions will reduce the therapeutic index of statins.

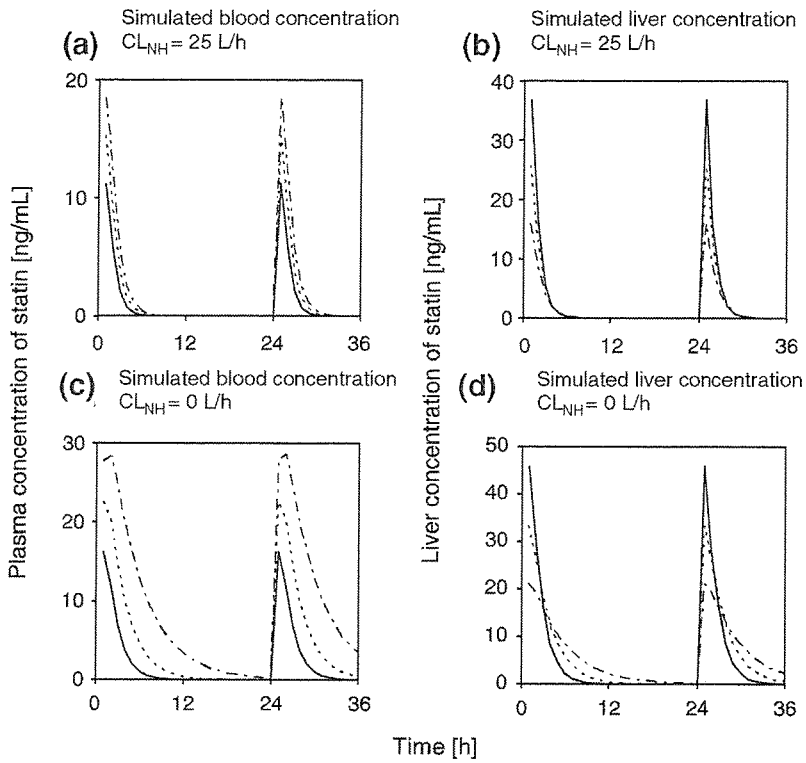

Fig. 12. Simulated blood and liver concentrations of statins for different $PS_{u,influx}$ values. The blood (**a**, **c**) and liver (**b**, **d**) concentrations of statin were simulated based on the physiologically based pharmacokinetic model shown in Fig. 9. (**a**, **b**) Simulation analysis shown by the solid line was performed using pravastatin parameters. Dotted and dashed lines show the simulated blood and liver concentrations of pravastatin when $PS_{u,influx}$ is reduced to 50% and 25% of the control, respectively (**c**, **d**). Similar simulation analyses were performed when the CL_{NH} was negligibly low. In this case, the area under the liver concentration–time curve is not altered by a change in $PS_{u,influx}$. However, the liver concentration–time profile is different when $PS_{u,influx}$ is reduced.

The AUC_H can be expressed by the following equation:

$$AUC_H = \frac{F_a \cdot D / \left\{ f_H \cdot \left(1 - \frac{f_u' \cdot CL_{repro,2}}{f_u \cdot V_1} \right) \right\}}{\left\{ 1 + \frac{Q_H \cdot CL_{int}}{f_u \cdot PS_{u,influx} \cdot (Q_H + CL_{int})} \right\} \cdot \left(PS_{u,efflux} + CL_{int,bile} + CL_{int,met} + CL_{lactone} - \frac{CL_{repro,2} \cdot CL_{lactone}}{A} \right) + \frac{CL_{repro,1} \cdot CL_{lactone}}{PS_{u,influx}} \left(1 - \frac{CL_{repro,2} + PS_{u,efflux} + CL_{int,bile} + CL_{int,met}}{A} \right) \cdot \left(1 - \frac{Q_H}{Q_H + CL_{int}} \cdot \frac{Q_H}{Q_H + CL_{NH} + f_u \cdot CL_{repro,1}} \right) - PS_{u,efflux} - \frac{R \cdot CL_{int,bile}}{1 - \frac{CL_{repro,2}}{f_u \cdot V_1}}}$$

(32)

This equation suggests that, for statins with an extrahepatic clearance (CL_{NH}) of 0 or close to zero, $f_H \cdot AUC_H$, that is, the exposure of statins to the liver, is not affected by $PS_{u,influx}$ hepatic uptake. This means that a reduction in $PS_{u,influx}$ does not affect the pharmacological effects of statins if there is a correlation between $f_H \cdot AUC_H$ and the pharmacological effect when CL_{NH} is negligibly low. Fig. 12 shows the plasma and liver concentrations of statins for different $PS_{u,influx}$ values. When $PS_{u,influx}$ decreases, that is, the hepatic uptake decreases, the plasma concentration increases. On the other hand, the liver concentration of statins falls for reduced $PS_{u,influx}$ values because of the reduced hepatic uptake. When $CL_{NH}=0$ or close to zero, the $f_H \cdot AUC_H$ is not altered for different $PS_{u,influx}$ values as described above (Fig. 12(**d**)). However, even in this case, the liver concentration–time profile appears to change with different $PS_{u,influx}$ values, leaving the $f_H \cdot AUC_H$ unchanged (Fig. 12(**d**)). If the pharmacological effect correlates with the $f_H \cdot AUC_H$, it would not change even if the $PS_{u,influx}$ was altered. However, if it was correlated with the liver concentration–time profile, then the pharmacological effect might be changed in the case of altered $PS_{u,influx}$ values because the maximum liver concentration and elimination rate from the liver is changed.

5. Clinically relevant drug–drug interactions with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors

5.1. OATP1B1 inhibitor

Among OATP1B1 inhibitors, there are only a few drugs which may cause a drug–drug interaction with coadministered drugs in clinical situations because of the lower therapeutic concentrations compared with K_i (Shitara et al., 2005). Among them, cyclosporin A (CsA) is one of the drugs which may affect the pharmacokinetics of other drugs by the inhibition of OATP1B1-mediated hepatic uptake. In addition, CsA also affects CYP3A4 and P-gp as well as OATP1B1. CsA affects the plasma concentrations of simvastatin, lovastatin, pravastatin, fluvastatin, cerivastatin, atorvastatin, pitavastatin and rosuvastatin (Arnadottir et al., 1993; Regazzi et al., 1993; Goldberg & Roth, 1996; Olbricht et al., 1997; Muck et al., 1999; Asberg et al., 2001; Ichimaru et al., 2001; Park et al., 2001; Hasunuma et al., 2003; Simonson et al., 2004). The pharmacokinetic changes in these statins are shown in Table 11. Among them, the interactions with pravastatin, pitavastatin and rosuvastatin are possibly due to OATP1B1 inhibition because they are not substrates of CYP3A4 and P-gp. As far as the interaction with cerivastatin is concerned, it has been reported that CsA inhibits OATP1B1-mediated hepatic uptake but not P450-mediated metabolism at therapeutic concentrations, suggesting this interaction is caused by transporter-inhibition (Shitara et al., 2003). In fact, the plasma concentration of cerivastatin was increased in patients concomitantly taking CsA (Muck et al., 1999). The plasma concentration of cerivastatin with or without coadministration of CsA is shown in Fig. 13(**a**). It is notable that coadministration of CsA increased the AUC, in other words, it decreased the oral clearance but it did not change the elimination half life ($t_{1/2}$). It is quite different from the interaction with gemfibrozil, which is shown in Fig. 13(**b**). $t_{1/2}$ life can be described by using CL_{tot} and distribution volime (V_d) as following:

$$t_{1/2} = \ln 2 \cdot \frac{V_d}{CL_{tot}} \tag{33}$$

In the case of the interaction between cerivastatin and CsA, CsA decreased the hepatic uptake and clearance of cerivastatin. As cerivastatin is highly and selectively distributed to the liver via transporter-mediated hepatic uptake, decreased hepatic uptake by the inhibition of hepatic uptake transporter leads to the reduction in not only CL_{tot} but also V_d. Thus, CsA decreased the V_d and CL_{tot} values of cerivastatin equally at the same time, resulting in little change of $t_{1/2}$ (see Eq. (33)).

Schneck et al. reported that gemfibrozil altered the plasma concentration of rosuvastatin by the inhibition of its OATP1B1-mediated hepatic uptake (Schneck et al., 2004). They showed that gemfibrozil inhibited the OATP1B1-mediated uptake at the relatively lower concentration (i.e. $IC_{50}=4.0$ μM) using OATP1B1-expressing *Xenopus laevis* oocytes. On the other hand, our group has shown that gemfibrozil and its glucuronide may not inhibit the OATP1B1-mediated hepatic clearance of cerivastatin at therapeutic unbound concentrations (i.e. 0.65–1.0 and 2 μM for gemfibrozil and its glucuronide, respectively) with the IC_{50} values of 72 and 24 μM, respectively, using OATP1B1-expressing mammalian cells (Shitara et al., 2003). This discrepancy may be due to the difference in the experimental system. However, gemfibrozil actually altered the pharmacokinetics of rosuvastatin and pravastatin to a small extent although it did not alter that of pitavastatin (Kyrklund et al., 2003; Mathew et al., 2004; Schneck et al., 2004; Table 11). Thus, gemfibrozil or its metabolite may reduce the OATP1B1-mediated hepatic uptake to a small extent. In the case of the interaction between cerivastatin and

Table 11
Pharmacokinetic alterations of statins following coadministration of CsA or gemfibrozil

	AUC fold increase	C_{max} fold increase
Coadministration of CsA		
Simvastatin	2.6	2.1
	8.0	7.6
Lovastatin	20	–
Pravastatin	7.9	22.8
	5–7	–
Fluvastatin	1.9	1.3
	3.1–3.5	4.1–6.0
Cerivastatin	3.8	5
Atorvastatin	7.4	6.7
Pitavastatin	4.5	6.5
Rosuvastatin	7.1	10.6
Coadministration of gemfibrozil		
Simvastatin	2.5	2.1
Lovastatin	2.8	2.8
Pravastatin	2	1.8
Fluvastatin	1.1	1.1
Cerivastatin	4.2	1.8
	4.4	2.5
Pitavastatin	1.3	1.1
Rosuvastatin	1.9	2.2

–, no report.
References: Arnadottir et al. (1993), Regazzi et al. (1993), Spence et al. (1995), Goldberg and Roth (1996), Olbricht et al. (1997), Muck et al. (1999), Backman et al. (2000), Asberg et al. (2001), Ichimaru et al. (2001), Kyrklund et al. (2001), Mueck et al. (2001), Park et al. (2001), Hasunuma et al. (2003), Kyrklund et al. (2003), Mathew et al. (2004) and Schneck et al. (2004).

gemfibrozil, as shown in Fig. 13(b), gemfibrozil altered $t_{1/2}$ of cerivastain and it is different from the interaction between cerivastatin and CsA. The increase in $t_{1/2}$ can be explained if the hepatic clearance is decreased to a higher extent than the distribution volume (V_d). It suggests that the pharmacokinetic alteration of cerivastatin caused by gemfibrozil is not mainly due to the reduction in the hepatic uptake although it may be involved to a limited extent.

5.2. CYP2C8 inhibitor

Cerivastatin is the only statin which is metabolized by CYP2C8. Our group has shown that the interaction between gemfibrozil and cerivastatin is due to CYP2C8 inhibition by gemfibrozil glucuronide (Shitara et al., 2004). Although gemfibrozil itself also inhibits CYP2C8-mediated metabolism, the IC_{50} values obtained were around 80 μM. This is much higher than its plasma unbound concentration in clinical situations, suggesting that clinically relevant drug–drug interactions are unlikely. On the other hand, gemfibrozil glucuronide is a more potent inhibitor of CYP2C8 whose IC_{50} value is 4 μM. However, this IC_{50} value is still higher than the plasma unbound concentration of gemfibrozil glucuronide in clinical situations (2 μM). We hypothesized that gemfibrozil glucuronide is actively taken up into the liver and concentrated there to high concentration enough to inhibit the CYP2C8-mediated metabolism. More recently, Ogilvie et al. reported that gemfibrozil glucuronide is a metabolism-dependent inhibitor of CYP2C8 (Ogilvie et al., 2006). Its inhibitory effect was enhanced by preincubation in the presence of NADPH with human liver microsomes in an incubation time dependent manner. Their data support it as an irreversible or quasi- irreversible inactivator of CYP2C8. The results by Ogilvie et al. have important implications for the mechanism of the clinically relevant interaction between gemfibrozil and CYP2C8 substrates such as cerivastatin, in addition to the higher concentration of gemfibrozil glucuronide in the liver compared to the plasma. The IC_{50} value for the inhibition of CYP2C8-mediated metabolism by gemfibrozil glucuronide

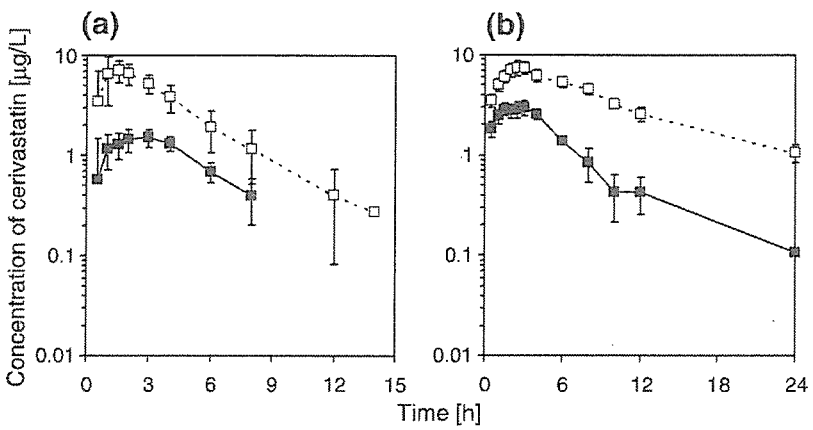

Fig. 13. Altered pharmacokinetics of cerivastatin by coadministrations of CsA (a) or gemfibrozil (b). (a) Plasma concentrations of cerivastatin in kidney transplant recipients receiving CsA treatment (□) or healthy subjects not receiving CsA(■) are shown. In kidney transplant recipients taking CsA, the AUC of cerivastatin was increased 3.8-fold: the C_{max} and $t_{1/2}$ were increased 5.0- and 1.2-fold, respectively. (b) Plasma concentrations of cerivastatin in healthy volunteers concomitantly taking gemfibrozil (□) or placebo (■) are shown. Concomitant administration of gemfibrozil increased the plasma concentration of cerivastatin. The AUC was increased 4.4-fold: the C_{max} and $t_{1/2}$ were increased 2.5- and 2.4-fold, respectively. Reprint from "Increase in cerivastatin systemic exposure after single and multiple dosing in cyclosporine-treated kidney transplant recipients" by Muck et al., 1999, and "Gemfibrozil greatly increases plasma concentrations of cerivastatin" by Backman et al., 2002, with permissions from the American Society for Clinical Pharmacology & Therapeutics.

decreased from 24 to 1.8 μM after 30 min preincubation with human liver microsomes and NADPH. In this case, the rate of inactivation (λ) of CYP2C8 can be described by the following Eq. (34):

$$\lambda = \frac{k_{inact} \cdot [I]}{K_{i,app} + [I]} \quad (34)$$

where k_{inact}, $[I]$ and $K_{i,app}$ are the maximal rate of inactivation, inhibitor concentration and the inhibitor concentration which produces half the maximal rate of inactivation, respectively. They estimated k_{inact} to be 0.21 min^{-1} and $K_{i,app}$ to be 20 and 52 μM with human liver microsomes at the concentration of 0.1 and 1.0 mg/mL, respectively. The fold increase in the oral AUC by coadministration of gemfibrozil was estimated by using the following Eq. (35), which was reported by Lu et al. (2003).

$$\frac{AUC_{po(i)}}{AUC_{po(c)}} = \frac{1}{\left(\frac{f_m \cdot f_{m,P450}}{1+[k_{inact}/K_{i,app}\ [I]/k_e]}\right) + \left[1-\left(f_m \cdot f_{m,P450}\right)\right]} \quad (35)$$

where $AUC_{po(i)}$ and $AUC_{po(c)}$ represent oral AUC with or without coadministration of metabolism-dependent inhibitors, and $f_m \cdot f_{m,P450}$ and k_e are fraction of the concomitantly administered drug metabolized by a P450 isoform in interest and the rate constant for enzyme degradation (0.0008 min^{-1}), respectively. For cerivastatin, the $f_m \cdot f_{m,P450}$ for CYP2C8 is 0.61 (Shitara et al., 2004). Thus, the fold increase in the oral AUC of cerivastatin by the metabolic alteration caused by gemfibrozil glucuronide is calculated to be 2.2–2.4 using the maximum plasma concentration (C_{max}) of gemfibrozil glucuronide not bound to plasma protein (2.3 M). It is less than the clinically observed increase in the oral AUC of cerivastatin, that is, 4.4-fold. Thus, this increase may not be explained only by the inhibition of CYP2C8. However, it should be kept in mind that the $f_m \cdot f_{m,P450}$ of CYP2C8 to the total clearance might exhibit interindividual differenceand for some individuals, the inhibition of CYP2C8 mediated metabolism may play more important role. In addition, the inhibition of transporter mediated transporter (hepatobiliary transport, renal uptake and secretion, and intestinal efflux) should be also taken into consideration in understanding the interactions between statins and gemfirozil. Table 11 shows the pharmacokinetic changes in statins produced by coadministration of gemfibrozil. Except for cerivastatin, the effect of gemfibrozil on other statins is small (Table 11). In the cases of simvastatin and lovastatin, the plasma concentration of the open acid form of the statin is affected while that of the lactone form is not. This may be explained by the inhibition of UGT-mediated lactonization (Prueksaritanont et al., 2002b). But, the reported IC_{50} values for the lactonization are also much higher than the therapeutic unbound concentration.

5.3. CYP3A4 inhibitor

As most statins are substrates of CYP3A4, many interactions involving CYP3A4-mediated metabolism have been reported. Table 12 shows the pharmacokinetic changes of statins following coadministration of CYP3A4 inhibitors.

The coadministration of itraconazole changed the plasma concentrations of statins (Fig. 14). It drastically increases the plasma concentration of simvastatin and lovastatin (Neuvonen & Jalava, 1996; Kivisto et al., 1998; Neuvonen et al., 1998). Itraconazole also increases the plasma concentration of atorvastatin (Kantola et al., 1998a; Mazzu et al., 2000). But the effect of itraconazole on the plasma concentration of atorvastatin is smaller than that of simvastatin and lovastatin although the dosing regimens and dosage periods were similar in these different studies and, thus, the different effects could not be attributed to the inhibitor concentrations. This difference will be explained below. On the other hand, itraconazole did not interact with statins, which are not substrates of CYP3A4 (i.e. pravastatin, fluvastatin and rosuvastatin) (Kivisto et al., 1998; Mazzu et al., 2000; Cooper et al., 2003a). In addition, there was no interaction with cerivastatin although it is metabolized by CYP3A4 (Kantola et al., 1999; Mazzu et al., 2000). This is due to the dual metabolic pathway involving CYP3A4 and 2C8 and the smaller contribution of CYP3A4 compared with 2C8 (Shitara et al., 2004). There have been some reports that coadministration of itraconazole causes a higher risk of myotoxicity as well as the pharmacokinetic changes (Vlahakos et al., 2002). This is due to the higher exposure of statins to muscle.

There are also many reports of interactions with macrolide antibiotics. Coadministration of erythromycin results in high plasma concentrations of simvastatin (Kantola et al., 1998b). Erythromycin and clarithromycin increase the plasma concentration of atorvastatin while azithromycin does not (Siedlik et al., 1999; Amsden et al., 2002). This observation is matched by the report that the inhibitory effect of azithromycin is less than erythromycin and clarithromycin (Ito et al., 2003). There are some reports that coadministration of macrolide antibiotics, including erythromycin and clarithromycin, and statins, including simvastatin and lovstatin, results in rhabdomyolysis and, thus, care should be taken when using these combinations (Spach et al., 1991; Grunden & Fisher, 1997; Lee & Maddix, 2001; Kahri et al., 2004; Trieu et al., 2004).

Human immunodeficiency virus (HIV) protease inhibitors also interact with statins. The plasma concentrations of simvastatin and atorvastatin are increased by coadministration of nelfinavir and combined therapy with ritonavir and saquinavir (Hsyu et al., 2001; Fichtenbaum et al., 2002). On the other hand, Fichtenbaum et al. reported that combination therapy involving ritonavir, saquinavir and pravastatin resulted in a reduction in the plasma concentration of pravastatin (58% of control in C_{max}; Fichtenbaum et al., 2002). These HIV protease inhibitors inhibit OATP1A2-mediated transport and this statin may be taken up into the intestine via OATP family transporter (s) (Cvetkovic et al., 1999; Kobayashi et al., 2003). Thus, the HIV protease inhibitors may inhibit the intestinal absorption of pravastatin although the mechanism of intestinal absorption of pravastatin in humans in vivo is unknown. There have been some reports of severe myotoxicity caused by the coadministrations of HIV protease inhibitors and statins, which are

Table 12
Clinically relevant pharmacokinetic alterations of statins following coadministration of CYP3A4 inhibitors

Inhibitor	Substrate	AUC fold increase	C_{max} fold increase	$t_{1/2}$ increase
Itraconazole	Simvastatin	10<	10<	
	Simvastatin acid	19	17	+25%
	Lovastatin	20<	20<	
	Lovastatin acid	20	13	
	Lovastatin	15<	15	
	Lovastatin acid	15	12	
	Pravastatin	<2	<2	–
	Pravastatin	1.51	1.24	+23%
	Fluvastatin	NS	NS	+17%
	Atorvastatin	2.5	1.38	+30%
	Atorvastatin	3	NS	× 3
	Cerivastatin	1.27	1.25	+19%
	Rosuvastatin (10 mg)	1.39	1.36	
	Rosuvastatin (80 mg)	1.28	1.15	
Ketoconazole	Rosuvastatin	1.02	0.954	
Fluconazole	Pravastatin	NS	NS	
	Fluvastatin	1.84	1.44	+80%
	Rosuvastatin	1.14	1.09	
Erythromycin	Simvastatin acid	3.9	5	
	Atorvastatin	1.33	1.38	
	Cerivastatin	NS	NS	
	Rosuvastatin	NS	NS	NS
Clarithromycin	Atorvastatin	1.82	1.56	
Azithromycin	Atorvastatin	NS	NS	
Nelfinavir	Simvastatin acid	6.05	6.17	
	Atorvastatin	1.74	2.22	
Ritonavir+ Saquinavir	Simvastatin acid	30.59	31	
	Atorvastatin	3.47	4.31	
	Pravastatin	0.5	0.58	
Verapamil	Simvastatin acid	2.8	3.4	
Grapefruit juice	Simvastatin	3.6	3.9	
	Simvastatin acid	3.3	4.3	
	Simvastatin	13.4	12	
	Simvastatin acid	4.51	5.03	
	Simvastatin	16	9	
	Simvastatin acid	7	7	
	Lovastatin	15	12	
	Lovastatin acid	5	4	
	Lovastatin	1.94	2.26	
	Lovastatin acid	1.57	1.65	
	Pravastatin	NS	NS	
	Pravastatin	0.92	0.94	
	Atorvastatin	1.4		
	Atorvastatin	2.46	1.06	

NS, not significantly increased.
References: Neuvonen and Jalava (1996), Kantola et al. (1998a, 1998b, 1998c), Kivisto et al. (1998), Lilja et al. (1998), Neuvonen et al. (1998), Kantola et al. (1999), Lilja et al. (1999), Rogers et al. (1999), Siedlik et al. (1999), Lilja et al. (2000), Mazzu et al. (2000), Hsyu et al. (2001), Amsden et al. (2002), Fichtenbaum et al. (2002), Cooper et al. (2003a), Fukazawa et al. (2004) and Lilja et al. (2004).

metabolized by CYP3A4 and, thus, concomitant use of these drugs should be carefully monitored (Cheng et al., 2002; Hare et al., 2002).

The concomitant intake of grapefruit juice also causes an interaction with statins. The plasma concentrations of simvastatin, lovastatin and atorvastatin have been reported to be increased by the intake of grapefruit juice although its effect differs from one statin to another (Kantola et al., 1998c; Lilja et al., 1998, 1999; Rogers et al., 1999; Lilja et al., 2000; Fukazawa et al., 2004; Lilja et al., 2004).

Table 12 shows many CYP3A4 inhibitors increased the AUC and C_{max} of atorvastatin to a lesser extent than those of simvastatin and lovastatin although they are all CYP3A4 substrates (also refer to Fig. 14). This gap may be explained taking the involvement of hepatic uptake transporter(s) into consideration. For atorvastatin, a hydrophilic statin with an open acid form, specific transporter(s) including OATP1B1 are involved in its hepatic uptake (Kameyama et al., 2005; Lau et al., 2006). In this case, the $CL_{int,all}$ can be described by the Eq. (6). Although the change of $PS_{u,influx}$ correlates with $CL_{int,all}$, the change of CL_{int} which includes metabolic clearance does not necessarily correlate with it. On the other hand, for simvastatin and lovastatin, liopophilic statins with lactone forms, their membrane permeabilities are mainly mediated by passive diffusion and not by the transporter-mediated mechanism. In this case, $CL_{int,all}$ can be described by the Eq. (9) and those of simvastatin and lovastatin are directly affected by CYP3A4 inhibitors. Thus, the change of the metabolic rate drastically alters the pharmacokinetics of simvastatin and lovastatin while it makes a smaller alteration in that of atorvastatin.

5.4. CYP2C9 inhibitor

As fluvastatin is mainly metabolized by CYP2C9 and eliminated by this pathway, the effect of CYP2C9 inhibitors could be important. However, there have been few reports of any clinically relevant drug–drug interactions involving fluvastatin and CYP2C9 inhibitors, including omeprazole and tolbutamide, and multiple P450 inhibitors, including cimetidine, fluvoxamine and azole antifungals. On the other hand, there are some reports that fluvastatin affects the pharmacokinetics of other drugs which are metabolized by CYP2C9. For example, fluvastatin produces a slight reduction in the clearance of glyburide, tolbutamide and diclofenac (Appel et al., 1995; Transon et al., 1995). However, it does not affect the plasma concentration of losartan (Meadowcroft et al., 1999). Although fluvastatin affects the plasma concentrations of glyburide and tolbutamide, it has no effects on their hypoglycemic action, which suggests that the pharmacokinetic changes are not great enough to influence their pharmacological effects (Appel et al., 1995).

5.5. Effect of enzyme induction

There are also some reports of drug–drug interactions associated with enzyme induction. When coadministererd with drugs that are enzyme inducers, the plasma concentrations of

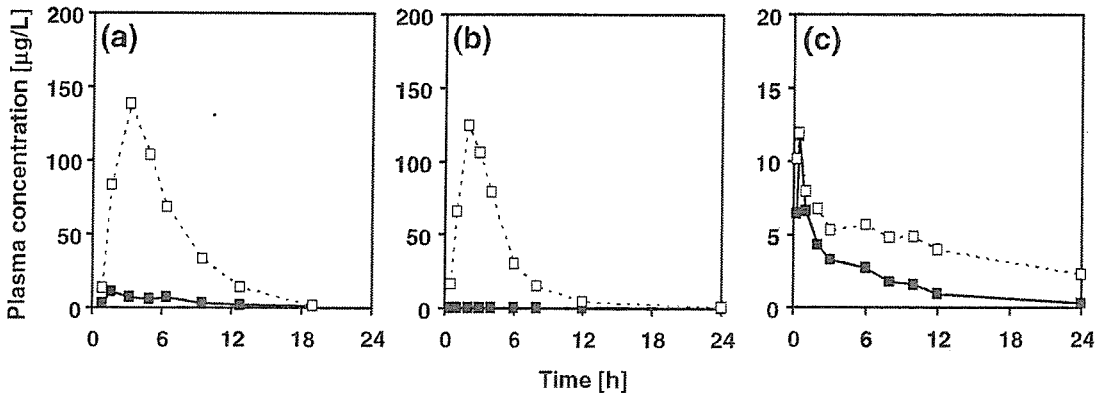

Fig. 14. Plasma concentrations of simvastatin (**a**), lovastatin (**b**), atorvastatin (**c**) with or without coadministration of itraconazole. The plasma concentrations of different statins in humans with (□) or without (■) itraconazole, a potent inhibitor of CYP3A4, are shown. While the plasma concentrations of simvastatin and lovastatin were drastically altered by itraconazole, that of atorvastatin was altered to a much smaller extent. It can be explained by the involvement of active transport system for atorvastatin though no involvement for simvastatin and lovastatin. Reprint from "Itraconazole drastically increases plasma concentrations of lovastatin and lovastatin acid" by Neuvonen and Jalava, 1996, and "Simvastatin but not pravastatin is very susceptible to interaction with the CYP3A4 inhibitor itraconazole" by Neuvonen et al., 1998, with permissions from the American Society for Clinical Pharmacology & Therapeutics.

statins may be reduced, leading to the decrease in their cholesterol-lowering effects.

The effects of rifampicin have been reported. When coadministered with rifampicin, the plasma AUC of simvastatin and simvastatin acid are reduced to 23% and 7% of the controls, respectively (Kyrklund et al., 2000; Niemi et al., 2003). This pharmacokinetic change may be caused by the induction of CYP3A4. In addition, rifampicin reduces the AUC of fluvastatin, a substrate of CYP2C9, to 50% of the control (Jokubaitis, 1994). Interestingly, it also reduces the AUC of pravastatin to 69% of the control although pravastatin is not metabolized by P450 (Kyrklund et al., 2004). It may suggest that rifampicin also induces drug transporters as well as metabolizing enzymes. As rifampicin induces MRP2, the plasma concentration of pravastatin may be affected by the induction of intestinal MRP2, leading to suppression of intestinal absorption (Fromm et al., 2000).

Carbamazepine reduces the plasma concentration of simvastatin by enzyme induction (Ucar et al., 2004). It reduces the AUC of simvastatin and simvastatin acid to 25% and 18% of the controls, respectively.

There was a case report showing that phenytoin reduce s the pharmacological effect of simvastatin (Murphy & Dominiczak, 1999). The serum cholesterol level in patients with hypercholesterolemia taking simvastatin is increased after taking phenytoin although there have been no reports about its plasma concentration (Murphy & Dominiczak, 1999). This can be explained by the induction of CYP3A4, leading to an increase in the clearance of simvastatin.

St. John's wort also reduces the plasma concentration of statins by the induction of CYP3A4. Sugimoto et al. reported that the administration of St. John's wort reduces the plasma AUC of simvastatin and simvastatin acid to 66% and 48% of control, respectively, although it has no effect on pravastatin concentrations (Sugimoto et al., 2001).

6. Interindividual variations in the pharmacokinetics of 3-hydroxy-3-methylglutaryl coenzyme A reducatase inhibitors and changes in their pharmacodynamics associated with pharmacokinetic alterations

6.1. OATP1B1

There have already been some reports of pharmacokinetic alterations of statins associated with the genetic polymorphism of OATP1B1 (Nishizato et al., 2003; Iwai et al., 2004; Morimoto et al., 2004; Mwinyi et al., 2004; Niemi et al., 2004; Tachibana-Iimori et al., 2004). Fig. 15 shows the reported genetic polymorphisms of this transporter and Table 13 shows the allelic frequencies of the variants found in the OATP1B1 gene (Tirona et al., 2001; Nozawa et al., 2002; Nishizato et al., 2003; Niemi et al., 2004). It should be noted that there exist great differences in the allelic frequencies of some SNPs, which may possibly lead to the ethnic differences observed in the pharmacokinetics of some statins. Nishizato et al. and Mwinyi et al. reported the pharmacokinetic alterations in pravastatin associated with the genetic polymorphism of OATP1B1 (Nishizato et al., 2003; Mwinyi et al., 2004; Niemi et al., 2004: Table 14). Nishizato et el. analyzed the relationship between the polymorphism in OATP1B1 and the pharmacokinetics of pravastatin in Japanese subjects (Nishizato et al., 2003; Fig. 16(**a**)). In the Japanese population, subjects with OATP1B1*1b/*1b are at the most common (Nishizato et al., 2003). Fig. 16(**a**) shows the plasma concentration of pravastatin in Japanese subjects with OATP1B1*1b/*1b, *1b/*15 and *15/*15. It was higher in subjects having the OATP1B1*15 allele (Fig. 16(**a**)). The clearance of pravastatin in subjects with *1b/*15 is significantly lower than that in subjects with *1b/*1b. Also, in subjects with *15/*15, the clearance is reduced and the plasma concentration of pravastatin is higher although the difference was not statistically significant due to the small

	217	245	388	411	455	463	467	521	571	578	597	721	1058	1294	1385	1463	1929	1964	2000	
	T	T	A	G	G	C	A	T	T	T	C	G	T	A	A	C	A	A	A	
*1a																				
*1b			G																	*1F, *1G, *1H
*1c					A							A								
*1J, *1K, *1L									C											
*2	C																			
*3		C					G													
*4						A														
*5								C												
*5B								C			T									
*6													C							
*7														G						
*8															G					
*9																C				
*10																		G		
*11																			G	
*12	C																	G		
*13		C					G												G	
*14			G			A														
*15			G					C												
*15B			G					C			T									
*16, *17			G					C			T									
*18			G	A		A			C		T									
*19									C								C			
*20, *21			G								T						C			

Fig. 15. Reported alignment of OATP1B1 haplotypes. The genetic polymorphism of OATP1B1 is summarized.

sample size. They also examined the correlation with the SNPs in OAT3, which is involved in the renal excretion of pravastatin, but they were unable to find any relationship. Mwinyi et al. examined the pharmacokinetics of pravastatin in comparison with the subjects with OATP1B1*1a/*1a (Mwinyi et al., 2004). They found that the plasma AUC of pravastatin in subjects with *1a/*5 was significantly higher than that in those with *1a/*1a. As *15 and *5 commonly have the same variation in T521C, this variation may be involved in the reduced clearance, that is, reduced hepatic uptake of pravastatin. Mwinyi et al. also

Table 13
Allelic frequencies of variations found in the OATP1B1 gene

	European American[1] (n=98)	African American[1] (n=44)	Japanese[2] (n=534)	Japanese[3] (n=240)	Finnish[4] (n=82)
T217C	0.02	0.00	–	–	–
T245C	0.02	0.00	–	–	–
A388G	0.30	0.74	0.534	0.458	0.447
(A388G/T521C)			0.103	0.150	
G411A	–	–	–	–	0.066
A452G	–	–	–	0.038	–
G455A	–	–	0.00	–	–
C463A	0.16	0.02	–	–	0.066
A467G	0.02	0.00			
T521C	0.14	0.02	0.007	0.000	0.183
(A388G/T521C)			0.103	0.150	
T571C					0.512
T578G					0.000
C597T				–	0.415
G721A		–			
T1058C	0.02	0.00	–	–	–
A1294G	0.01	0.00	–	–	–
A1385G	0.01	0.00	–	–	–
G1463C	0.00	0.09	–	–	–
A1929C	–	–	–	–	0.085
A1964G	0.02	0.00	–	–	–
A2000G	0.02	0.34	–	–	–

References: (1) Tirona et al. (2001), (2) Nozawa et al. (2002), (3) Nishizato et al. (2003), (4) Niemi et al. (2004).

Table 14
Pharmacokinetic alterations of pravastatin in subjects with a genetic polymorphism in OATP1B1

Variation	n	C_{max} [ng/mL]	AUC [ng h/mL]	$t_{1/2}$ [h]	k_{el} [h^{-1}]
11187GG	35	46±34	100±69.1	1.6±0.3	
11187GA	6	94±61	200±126.4	1.9±0.2	
521TT	28	40±29	90±64	1.7±0.1	
521TC	11	84±57	180±105	1.6±0.2	
521CC	2	52±19	140±39.3	1.8±0.4	
non-carriers of *15B	37	48±39	110±80	1.7±0.3	
heterozygous of *15B	4	92±57	210±120	1.7±0.3	
non-carriers of *17	38	47±37	110±80	1.6±0.3	
heterozygous of *17	3	120±50	250±70	2.0±0.2	
*1a/*1a	2		61		0.17
*1a/*1b	4		47±27		0.28±0.09
*1b/*1b	4		44±6		0.31±0.09
*1b/*1b	4		44±6		0.31±0.09
*1b/*15	9		62±22		0.26±0.09
*15/*15	1		110		0.21
*1b/*1b	4		44±6		0.31±0.09
*1b/*16	2		110		0.21
*1a/*1a	10	58±38	110±70		
*1a/*1b or *1b/*1b	10	37±21	75±36		
*1a/*1a	10	58±38	110±70		
*1a/*5	10	84±32	160±60		

References: Nishizato et al. (2003); Niemi et al. (2004); Mwinyi et al. (2004).

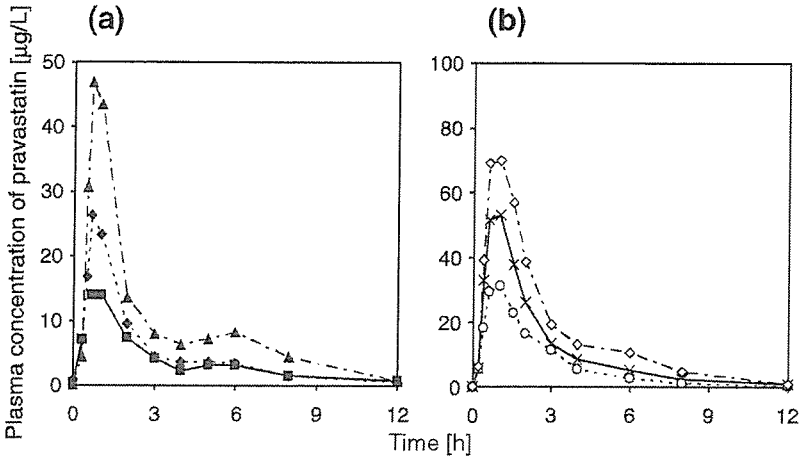

Fig. 16. Plasma concentration of pravastatin in subjects with genetic polymorphism in OATP1B1. (a) The plasma concentration of pravastatin in 23 Japanese male subjects with OATP1B1*1b/*1b (■, $n=4$), *1b/*15 (◆, $n=9$) and *15/*15 (▲, $n=1$) are shown. In subjects having *15 allele, the plasma concentration of pravastatin was increased. (b) The plasma concentration of pravastatin in 30 white male subjects in Germany with OATP1B1*1a/1a (X, $n=10$), *1a/*1b or *1b/*1b (○, $n=8$ for *1a/*1b, $n=2$ for *1b/*1b) and *1a/*5 (◊, $n=10$). In subjects having *5 allele, the plasma concentration was increased comparing to the subjects with *1a/*1a. On the other hand, in subjects having *1b, it was decreased. Reprint from "Polymorphisms of OATP-C (SLC21A6) and OAT3 (SLC22A8) genes: consequences for pravastatin pharmacokinetics" by Nishizato et al., 2003, and "Evidence for inverse effects of OATP-C (SLC21A6) 5 and 1b haplotypes on pravastatin kinetics" by Mwinyi et al., 2004, with permissions from the American Society for Clinical Pharmacology & Therapeutics.

compared the plasma concentration of pravastatin in patients with OATP1B1*1a/*1a and those with *1a/*1b or *1b/*1b. As shown in Fig. 16(b), in patients having *1b, the plasma concentration of pravastatin seems to be lower than that in patients with *1a/*1a. Thus *1b seems to increase the plasma clearance of pravastatin although a statistically significant difference was not observed. Tirona et al. reported that in HeLa cells transfected with cDNA encoding OATP1B1*5, the amount of OATP1B1 protein on the cell surface is reduced although total amount remains unchanged (Tirona et al., 2001). In addition, the transport activity in OATP1B1*5 is significantly reduced in the case of estradiol 17β-D-glucuronide and estrone 3-sulfate. In the case of estrone 3-sulfate, the maximum uptake rate, reflecting the transport capacity, is significantly reduced. On the other hand, Iwai et al. reported that the total protein expression and transport activity in *15 are markedly lower although the corresponding values in *5 are not altered in cDNA transfected HEK293 cells (Iwai et al., 2004). However, they did not determine the transporter expression level on the cell surface. These results suggest that allelic variations *5 and *15 are associated with reduced intrinsic transport acitivity and/or protein expression level on the cell surface, which would explain the in vivo phenomenon. Michalski et al. also showed that there is altered transporter expression on the plasma membrane associated with genetic polymorphism in human liver tissue samples (Michalski et al., 2002).

Tachibana-Iimori et al. carried out a retrospective cohort study of the pharmacological effect of statins in subjects with different OATP1B1 alleles (Tachibana-Iimori et al., 2004; Table 15). They found that the reduction in the total serum cholesterol was reduced in patients with the T521C variation. This variation was associated with higher plasma concentrations of pravastatin as reported by Nishizato et al. and Mwinyi et al., suggesting higher exposure (Nishizato et al., 2003; Mwinyi et al., 2004). Thus, in patients with higher plasma concentration of statins, the cholesterol lowering effect was decreased. It can be explained by our estimation that, as shown in the Section 4, the AUC of protein unbound statins in the liver is decreased by the reduction in the hepatic uptake rate when the renal excretion is not negligible (Fig. 12; also see Eq. (32)). Tachibana-Iimori et al. investigated patients taking statins including pravastatin, atorvastatin and simvastatin (Tachibana-Iimori et al., 2004). Among them, the renal excretion of pravastatin is not negligible, allowing them to observe different pharmacological effects of statins associated with SNPs in OATP1B1. In addition, even for statins with a very low renal clearance, the hepatic uptake rate affects the liver concentration–time profile of statins (Fig. 12). This change may affect the pharmacological effect.

Genetic polymorphism in the hepatic uptake transporter(s) may also lead to a change in the frequency of the side effects of

Table 15
Association of lipid-lowering effect by statins and OATP1B1 polymorphism

	T521C	n	Pre (mg/dL)	Post (mg/dL)	% Change	p
TC	TT	44	260±40	200±30	−22	<0.05
	TC	20	260±30	210±30	−17	0.094
LDL-C	TT	39	170±40	120±30	−29	0.745
	TC	20	160±50	120±20	−12	0.492
HDL-C	TT	38	56±15	57±14	1.2	
	TC	20	63±26	65±17	11	
TG	TT	40	170±90	130±70	−11	
	TC	19	150±100	130±60	3.4	

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; CI, confidence interval; UL, upper limit; LL, lower limit.
Reference: Tachibana-Iimori et al. (2004).

statins. Morimoto et al. found a novel polymorphism in OATP1B1 (T1628G; L543W) in patients with myopathy who were taking pravastatin (Morimoto et al., 2004). They also reported an association between OATP1B1*15 and pravastatin- or atorvastatin-induced myopathy (Morimoto et al., 2005a, 2005b). This may be explained by the different exposure to pravastatin due to the altered pharmacokinetics associated with the polymorphism in OATP1B1.

6.2. CYP2C8

CYP2C8 is involved in the pharmacokinetics of cerivastatin (Muck, 2000; Shitara et al., 2004). Ishikawa et al. analyzed genetic polymorphisms in OATP1B1, CYP2C8 and CYP3A4, which are determinants of cerivastatin pharmacokinetics, in patients with rhabdomyolysis taking cerivastatin and found variations in CYP2C8 (Ishikawa et al., 2004). They identified 475delA, G874C and T1551C and, among them, 475delA was found to be homozygous. As the 475delA alteration generally completely deletes the function of CYP2C8, this should result in a drastic reduction in the cerivastatin elimination rate although there have not been clinical data showing the change in pharmacokinetics and/or pharmacodynamics associated with such genetic polymorphisms. As the contribution of CYP2C8 to the metabolism of cerivastatin is relatively high, the altered function of CYP2C8 should lead to severe side effects. Hichiya et al. described other SNPs and, among them, R186X and R186G were associated with a change in the amino acid sequence, resulting in altered function (Hichiya et al., 2005).

6.3. CYP3A4/3A5

CYP3A4 is involved in the metabolism of many statins. Thus, a genetic polymorphism in CYP3A4 can be associated with the pharmacokinetic, pharmacodynamic and toxic effects of many statins. To date, there have been no reports of pharmacoikinetic changes in statins produced by SNPs in CYP3A4. However, there are some reports of a changed pharmacological effect associated with SNPs in CYP3A4 (Kajinami et al., 2004a; Wang et al., 2005). Table 16 shows these reports. Wang et al. reported stimulation of the pharmacological effect of simvastatin by the genetic variation of I118V in CYP3A4, which resulted in reduced metabolism (Wang et al., 2005). In Section 4, we showed that reduced metabolism (CL_{met}) results in an increase in the plasma concentration and the AUC of statins and enhancement of the pharmacological effect. Thus, the clinical report by Wang et al. agrees with our simulation analysis. Kajinami et al. examined the effects of a variation in the promoter region, A-290G, and amino acid substitution, M455T, on the pharmacological effect of atorvastatin (Kajinami et al., 2004a). They found a significant reduction in the pharmacological effect only in patients with A-290G (Table 16). The variation A-290G might alter the transcription of CYP3A4. However, they did not measure the enzyme activity. Their report was not confirmed by our simulation showing that a reduction in the metabolic rate should be associated with enhancement of

Table 16
Association of lipid-lowering effect by statins and CYP3A4/3A5 polymorphism

(a) Association of the effect of simvastatin and CYP3A4 Ile118Val

	Ile118Val	*n*	Pre (mmol/L)	Post (mmol/L)	% Change	*p*
TC	Ile/Ile		5.6±0.8	4.4±0.7	−22±20	0.034
	Ile/Val		5.1±0.8	3.1±0.7	−36±10	
LDL-C	Ile/Ile		3.5±0.7	2.5±±0.6	−29±7	0.072
	Ile/Val		3.2±0.9	2.0±.04	−37±9	
TG	Ile/Ile		2.3±1.0	1.9±0.6	−25±8	0.002
	Ile/Val		2.0±0.8	1.4±0.4	−38±8	

(b) Association of the effect of simvastatin and CYP3A4 A-290G

	A-290G	*n*	Pre (mg/dL)	Post (mg/dL)	% Change	*p* AA vs. AG	*p* (AA+AG) vs. GG
TC	AA	305	272±26	199±26	−27±8	0.604	0.385
	AG	27	262±22	190±24	−29±9		
	GG	8	269±19	203±29	−24±12		
LDL-C	AA	305	187±22	117±19	−37±10	0.372	0.113
	AG	27	190±23	116±18	−38±10		
	GG	8	193±15	131±21	−31±14		
HDL-C	AA	305	50±11	54±12	+8±12	0.182	0.672
	AG	27	47±10	49±10	+6±15		
	GG	8	47±6	51±7	+9±16		
TG	AA	305	175±72	139±59	16±31	0.096	0.34
	AG	27	159±63	125±53	19±19		
	GG	8	147±46	103±38	−27±24		

(c) Association of the effect of atorvastatin and CYP3A4 Met445Thr

	Met445Thr	*n*	Pre (mg/dL)	Post (mg/dL)	% Change	*p*
TC	Met/Met	335	270±30	200±30	−27±8	0.542
	Met/Thr	5	260±20	180±20	−29±6	
LDL-C	Met/Met	335	190±20	120±20	−37±10	0.469
	Met/Thr	5	170±30	100±20	−40±14	
HDL-C	Met/Met	335	50±11	53±12	+8±13	0.662
	Met/Thr	5	50±11	56±16	+10±22	
TG	Met/Met	335	170±70	140±60	−17±30	0.856
	Met/Thr	5	200±130	150±80	−15±43	

(d) Association of the effect of lovastatin, simvastatin or atorvastatin and CYP3A5 polymorphisms

	Variation	*n*	Pre (mmol/L)	Post (mmol/L)	% Change	*p*
TC	*1/*3	7	6.2±0.9	5.1±1.0	17±20	0.026
	*3/*3	39	6.0±0.8	4.1±0.6	−31±13	
LDL-C	*1/*3	7	3.9±0.6	2.5±0.8	−31±26	0.083
	*3/*3	39	3.9±0.6	2.1±0.5	−46±18	

(e) Association of the effect of fluvastatin or pravastatin and CYP3A5 polymorphisms

	Variation	*n*	Pre (mmol/L)	Post (mmol/L)	% Change	*p*
TC	*1/*3	6	5.5±0.2	4.3±0.5	−22±7	0.99
	*3/*3	17	5.8±1.0	4.5±0.5	−21±8	
LDL-C	*1/*3	6	3.2±0.4	2.1±0.4	−35±8	0.90
	*3/*3	17	3.6±0.8	2.4±0.5	−34±14	

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol.
References: Kajinami et al. (2004a), Kivisto et al. (2004b) and Wang et al. (2005).

the pharmacological effect. However, in patients with SNPs in CYP3A4, the serum cholesterol level may be different due to the altered metabolism of endogenous hormones metabolized by CYP3A4. This may account for the discrepancy between our simulation and the clinical data.

Interestingly, Kivisto et al. have described the effect of a polymorphism in CYP3A5 (Kivisto et al., 2004b). Due to a small sample size, they analyzed the effect of polymorphism in CYP3A5 on total cholesterol and LDL-cholesterol lowering effects of statins in patients dividing into 2 groups: lovastatin, simvastatin or atorvastatin taking group and fluvastatin or pravastatin taking group; although the effect may be different between lovastatin or simvastatin group and atorvastatin group due to the involvement of the hepatic uptake transporter(s) as described in the Section 5.3. In patients with reduced activity of CYP3A5 produced by the *3 variant, enhanced pharmacological effects of lovastatin, simvastatin and atorvastatin were reported. On the other hand, the effects of pravastatin and fluvastatin were unchanged because they are not metaobolized by CYP3A4. The enhancement of pharmacological effects associated with the reduced metabolism was matched by the report by Wang et al. (2005) and is fully explained by our analysis given in the Section 4.

6.4. CYP2C9

CYP2C9 is involved in the metabolism of fluvastatin and, thus, interindividual differences in this enzyme may result in changes in the pharmacokinetics of this statin. To date, there has been only one report by Kirchheiner et al. (2003) concerning the effect of a genetic polymorphism in CYP2C9 on the pharmacokinetics and pharmacodynamics of fluvastatin. Table 17 shows the results. In patients with CYP2C9*3/*3, the plasma concentration is increased whereas the pharmacological effect is reduced. The pharmacokinetic and pharmacodynamic changes conflicted and the mechanism is unknown.

7. Conclusion

In this review, we have described the pharmacokinetic properties and physicochemical features of the statins. In addition, we have performed a model-based analysis and shown how sensitively the pharmacokinetic alterations are caused by a change in the metabolizing enzymes and/or transporters. In the case of combination therapy with statins, their elimination pathways and mechanism, which includes the metabolizing enzyme(s) and transporter(s) involved in their

Table 17
Association of lipid-lowering effect and pharmacokinetics of fluvastatin, and CYP2C9 or CYP2D6 polymorphisms

(a) Association of the pharmacokinetics of fluvastatin and CYP2C9 or CYP2D6 polymorphisms

	n	(−)-3*S*,5*R*-fluvastatin				(+)-3*R*,5*S*-fluvastatin			
		AUC (μg h/L)	C_{max} (μg h/L)	$t_{1/2}$ (h)	t_{max} (h)	AUC (μg h/L)	C_{max} (μg/L)	$t_{1/2}$ (h)	t_{max} (h)
CYP2C9*1/*1	5	230±130	200±130	0.6±0.3	1.0±0.3	170±90	120±80	0.8±0.4	1.1±0.4
CYP2C9*1/*2	4	210±40	160±70	0.6±0.3	1.1±0.3	200±40	110±40	1.3±0.8	1.3±0.3
CYP2C9*2/*2	3	290±110	150±110	1.0±0.4	1.8±1.0	180±100	81±54	1.3±0.6	1.8±1.0
CYP2C9*1/*3	5	360±100	300±90	0.5±0.1	1.1±0.3	230±90	170±60	0.6±0.1	1.1±0.3
CYP2C9*2/*3	4	520±190	200±90	1.5±0.7	1.4±0.5	390±120	120±50	2.0±0.4	1.3±0.6
CYP2C9*3/*3	3	1100±300	490±110	1.4±0.6	1.0±0.1	530±120	250±40	0.9±0.3	1.0±0.1
CYP2C9*1/*1 and CYP2D6*4/*4	2	300±220	350±220	0.4±0.2	0.5±0.0	210±170	220±160	0.4±0.1	0.5±0.0

(b) Association of pharmacodynamic effect of fluvastatin and CYP2C9 or CYP2D6 polymorphisms

		n	Baseline (mg/dL)	Difference (mg/dL)	% Change
TC	CYP2C9*1/*1, *1/*2 and *2/*2	12	210±40	−35±25	16
	CYP2C9*1/*3 and *2/*3	9	200±40	−36±22	18
	CYP2C9*3/*3	3	180±20	2±19	+1.1
	CYP2D6*4/*4 (CYP2C9*1/*1)	2	200±20	3±16	+1.5
TG	CYP2C9*1/*1, *1/*2 and *2/*2	12	93±26	15±40	+16
	CYP2C9*1/*3 and *2/*3	9	110±70	18±41	+16
	CYP2C9*3/*3	3	57±13	20±19	+35
	CYP2D6*4/*4 (CYP2C9*1/*1)	2	110±70	3±41	+2.8
HDL−C	CYP2C9*1/*1, *1/*2 and *2/*2	12	63±21	0±7	0
	CYP2C9*1/*3 and *2/*3	9	64±14	1±6	+1.6
	CYP2C9*3/*3	3	68±12	4±2	+5.9
	CYP2D6*4/*4 (CYP2C9*1/*1)	2	55±6	7±4	+13
LDL-C	CYP2C9*1/*1, *1/*2 and *2/*2	12	130±30	−38±24	−29
	CYP2C9*1/*3 and *2/*3	9	110±30	−34±21	−30
	CYP2C9*3/*3	3	100±10	−6±18	−6.1
	CYP2D6*4/*4 (CYP2C9*1/*1)	2	120±0	−4±12	−3.3

Reference: Kirchheiner et al. (2003).

elimination, need to be known in order to predict and avoid any drug–drug interactions. The contribution of each enzyme or transporter in the liver, intestine and kidney to the total elimination and absorption also needs to be considered. Prior to the coadministration with other drugs, a consideration should be given to their effects on these enzymes or transporters. The inhibitory effects of other drugs must be predicted by comparison of K_i and therapeutic unbound concentrations. If the unbound concentration of the inhibitor drug(s) in clinical situations is much lower than K_i, a drug–drug interaction is unlikely to occur. The concentration of statins in the tissue is also important for the estimation of the extent of changes in pharmacological and toxicological effect caused by drug–drug interactions because the tissue concentration is their determinant. For the development of new statins, the balance of safety versus toxicity is also important. In other words, the pharmacokinetic properties, that is, selective distribution to the pharmacological target organs (liver for statins) but not to the toxic organs (muscle and brain), as well as the intrinsic potency of the pharmacological effect, that is, the affinity for the HMG-CoA reductase, need to be taken into consideration.

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References

Alberts, A. W., Chen, J., Kuron, G., Hunt, V., Huff, J., Hoffman, C., et al. (1980). Mevinolin: a highly potent competitive inhibitor of hydroxymethylglutaryl-coenzyme A reductase and a cholesterol-lowering agent. *Proc Natl Acad Sci U S A 77*, 3957–3961.

Amsden, G. W., Kuye, O., & Wei, G. C. (2002). A study of the interaction potential of azithromycin and clarithromycin with atorvastatin in healthy volunteers. *J Clin Pharmacol 42*, 444–449.

Appel, S., Rufenacht, T., Kalafsky, G., Tetzloff, W., Kallay, Z., Hitzenberger, G., et al. (1995). Lack of interaction between fluvastatin and oral hypoglycemic agents in healthy subjects and in patients with non-insulin-dependent diabetes mellitus. *Am J Cardiol 76*, 29A–32A.

Arnadottir, M., Eriksson, L. O., Thysell, H., & Karkas, J. D. (1993). Plasma concentration profiles of simvastatin 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitory activity in kidney transplant recipients with and without ciclosporin. *Nephron 65*, 410–413.

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*, 382–386.

Backman, J. T., Kyrklund, C., Kivisto, K. T., Wang, J. -S., & Neuvonen, P. J. (2000). Plasma concentrations of active simvastatin acid are increased by gemfibrozil. *Clin Pharmacol Ther 68*, 122–129.

Backman, J. T., Kyrklund, C., Neuvonen, M., & Neuvonen, P. J. (2002). Gemfibrozil greatly increases plasma concentrations of cerivastatin. *Clin Pharmacol Ther 72*, 685–691.

Barth, J. D., Kruisbrink, O. A., & Van Dijk, A. L. (1990). Inhibitors of hydroxymethylglutaryl coenzyme A reductase for treating hypercholesterolaemia. *Br Med J 301*, 669.

Benet, L. Z., Izumi, T., Zhang, Y., Silverman, J. A., & Wacher, V. J. (1999). Intestinal MDR transport proteins and P-450 enzymes as barriers to oral drug delivery. *J Control Release 62*, 25–31.

Bertolini, S., Bon, G. B., Campbell, L. M., Farnier, M., Langan, J., Mahla, G., et al. (1997). Efficacy and safety of atorvastatin compared to pravastatin in patients with hypercholesterolemia. *Atherosclerosis 130*, 191–197.

Brown, M. S., & Goldstein, J. L. (1986). A receptor-mediated pathway for cholesterol homeostasis. *Science 232*, 34–47.

Buckett, L., Davidson, R., Dunkley, C., Martin, L., Stafford, J., & McTaggart, F. (2000). Selectivity of ZD4522 for inhibition of cholesterol synthesis in hepatic versus non-hepatic cells. *Atherosclerosis 151*, 41.

Cheng, C. H., Miller, C., Lowe, C., & Pearson, V. E. (2002). Rhabdomyolysis due to probable interaction between simvastatin and ritonavir. *Am J Health Syst Pharm 59*, 728–730.

Chong, P. H., Seeger, J. D., & Franklin, C. (2001). Clinically relevant differences between the statins: implications for therapeutic selection. *Am J Med 111*, 390–400.

Cooper, K. J., Martin, P. D., Dane, A. L., Warwick, M. J., Schneck, D. W., & Cantarini, M. V. (2003a). Effect of itraconazole on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther 73*, 322–329.

Cooper, K. J., Martin, P. D., Dane, A. L., Warwick, M. J., Raza, A., & Schneck, D. W. (2003b). Lack of effect of ketoconazole on the pharmacokinetics of rosuvastatin in healthy subjects. *Br J Clin Pharmacol 55*, 94–99.

Corsini, A., Bellosta, S., Baetta, R., Fumagalli, R., Paoletti, R., & Bernini, F. (1999). New insights into the pharmacodynamic and pharmacokinetic properties of statins. *Pharmacol Ther 84*, 413–428.

Crespi, C. L., & Penman, B. W. (1997). Use of cDNA-expressed human cytochrome P450 enzymes to study potential drug–drug interactions. *Adv Pharmacol 43*, 171–188.

Cucchiara, B., & Kasner, S. E. (2001). Use of statins in CNS disorders. *J Neurol Sci 187*, 81–89.

Cvetkovic, M., Leake, B., Fromm, M. F., Wilkinson, G. R., & Kim, R. B. (1999). OATP and P-glycoprotein transporters mediate the cellular uptake and excretion of fexofenadine. *Drug Metab Dispos 27*, 866–871.

De Pinieux, G., Chariot, P., Ammi-Said, M., Louarn, F., Lejonc, J. L., et al. (1996). Lipid-lowering drugs and mitochondrial function: effects of HMG-CoA reductase inhibitors on serum ubiquinone and blood lactate/pyruvate ratio. *Br J Clin Pharmacol 42*, 333–337.

Dresser, G. K., Bailey, D. G., Leake, B. F., Schwarz, U. I., Dawson, P. A., Freeman, D. J., et al. (2002). Fruit juices inhibit organic anion transporting polypeptide-mediated drug uptake to decrease the oral availability of fexofenadine. *Clin Pharmacol Ther 71*, 11–20.

Dresser, G. K., Kim, R. B., & Bailey, D. G. (2005). Effect of grapefruit juice volume on the reduction of fexofenadine bioavailability: possible role of organic anion transporting polypeptides. *Clin Pharmacol Ther 77*, 170–177.

Endo, A., Kuroda, M., & Tsujita, Y. (1976). ML-236A, ML-236B, and ML-236C, new inhibitors of cholesterogenesis produced by *Penicillium citrinium*. *J Antibiot (Tokyo) 29*, 1346–1348.

Endo, A. (1992). The discovery and development of HMG-CoA reductase inhibitors. *J Lipid Res 33*, 1569–1582.

Fichtenbaum, C. J., Gerber, J. G., Rosenkranz, S. L., Segal, Y., Aberg, J. A., Blaschke, T., et al. (2002). Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. *AIDS 16*, 569–577.

Flint, O. P., Masters, B. A., Gregg, R. E., & Durham, S. K. (1997). Inhibition of cholesterol synthesis by squalene synthase inhibitors does not induce myotoxicity in vitro. *Toxicol Appl Pharmacol 145*, 91–98.

Folkers, K., Langsjoen, P., Willis, R., Richardson, P., Xia, L. J., Ye, C. Q., et al. (1990). Lovastatin decreases coenzyme Q levels in humans. *Proc Natl Acad Sci U S A 87*, 8931–8934.

Fromm, M. F., Kauffmann, H. M., Fritz, P., Burk, O., Kroemer, H. K., Warzok, R. W., et al. (2000). The effect of rifampin treatment on intestinal expression of human MRP transporters. *Am J Pathol 157*, 1575–1580.

Fujino, H., Yamada, I., Shimada, S., & Kojima, J. (2002). Metabolic fate of pitavastatin, a new inhibitor of HMG-CoA reductase–effect of cMOAT deficiency on hepatobiliary excretion in rats and of mdr1a/b gene disruption on tissue distribution in mice. *Drug Metab Pharmacokinet 17*, 449–456.

Fujino, H., Yamada, I., Shimada, S., Yoneda, M., & Kojima, J. (2003). Metabolic fate of pitavastatin, a new inhibitor of HMG-CoA reductase: human UDP-glucuronosyltransferase enzymes involved in lactonization. *Xenobiotica 33*, 27–41.

Fujino, H., Nakai, D., Nakagomi, R., Saito, M., Tokui, T., & Kojima, J. (2004a). Metabolic stability and uptake by human hepatocytes of pitavastatin, a new inhibitor of HMG-CoA reductase. *Arzneimittel-forschung 54*, 382–388.

Fujino, H., Saito, T., Tsunenari, Y., & Kojima, J. (2004b). Effect of gemfibrozil on the metabolism of pitavastatin—determining the best animal model for human CYP and UGT activities. *Drug Metabol Drug Interact 20*, 25–42.

Fujino, H., Saito, T., Tsunenari, Y., Kojima, J., & Sakaeda, T. (2004c). Metabolic properties of the acid and lactone forms of HMG-CoA reductase inhibitors. *Xenobiotica 34*, 961–971.

Fukazawa, I., Uchida, N., Uchida, E., & Yasuhara, H. (2004). Effects of grapefruit juice on pharmacokinetics of atorvastatin and pravastatin in Japanese. *Br J Clin Pharmacol 57*, 448–455.

Gadbut, A. P., Caruso, A. P., & Galper, J. B. (1995). Differential sensitivity of C2–C12 striated muscle cells to lovastatin and pravastatin. *J Mol Cell Cardiol 27*, 2397–2402.

Ghirlanda, G., Oradei, A., Manto, A., Lippa, S., Uccioli, L., Caputo, S., et al. (1993). Evidence of plasma CoQ10-lowering effect by HMG-CoA reductase inhibitors: a double-blind, placebo-controlled study. *J Clin Pharmacol 33*, 226–229.

Goldberg, R., & Roth, D. (1996). Evaluation of fluvastatin in the treatment of hypercholesterolemia in renal transplant recipients taking cyclosporine. *Transplantation 62*, 1559–1564.

Grunden, J. W., & Fisher, K. A. (1997). Lovastatin-induced rhabdomyolysis possibly associated with clarithromycin and azithromycin. *Ann Pharmacother 31*, 859–863.

Grundy, S. M. (1978). Cholesterol metabolism in man. *West J Med 128*, 13–25.

Hare, C. B., Vu, M. P., Grunfeld, C., & Lampiris, H. W. (2002). Simvastatin–nelfinavir interaction implicated in rhabdomyolysis and death. *Clin Infect Dis 35*, e111–e112.

Hasegawa, M., Kusuhara, H., Sugiyama, D., Ito, K., Ueda, S., Endou, H., 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*, 746–753.

Hasunuma, T., Nakamura, M., Yachi, T., Arisawa, N., Fukushima, K., & Iijima, H. (2003). The drug–drug interactions of pitavastatin (NK-104), a novel HMG-CoA reductase inhibitor and cyclosporine. *J Clin Ther Med 19*, 381–389.

Hatanaka, T. (2000). Clinical pharmacokinetics of pravastatin: mechanisms of pharmacokinetic events. *Clin Pharmacokinet 39*, 397–412.

Hichiya, H., Tanaka-Kagawa, T., Soyama, A., Jinno, H., Koyano, S., Katori, N., et al. (2005). Functional characterization of five novel CYP2C8 variants, G171S, R186X, R186G, K247R and K383N, found in a Japanese population. *Drug Metab Dispos 33*, 630–636.

Hirai, S., Jacobson, W., Djuvo, S., Benet, L. Z., & Christians, U. (2001). Comparison of the P-glycoprotein-mediated transport of HMG-CoA reductase inhibitors across MDCK-MDR1 cell monolayers (Abstract). *AAPS PharmSci 3* (online).

Hirano, M., Maeda, K., Shitara, Y., & Sugiyama, Y. (2005a). Contribution of OATP2 (OATP1B1) and OATP8 (OATP1B3) to the hepatic uptake of pitavastatin in humans. *J Pharmacol Exp Ther 311*, 139–146.

Hirano, M., Maeda, K., Matsushima, S., Nozaki, Y., Kusuhara, H., & Sugiyama, Y. (2005b). Involvement of BCRP (ABCG2) in the biliary excretion of pitavastatin. *Mol Pharmacol 68*, 800–807.

Hirano, M., Maeda, K., Hayashi, H., Kusuhara, H., & Sugiyama, Y. (2005). Bile salt export pump (BSEP/ABCB11) can transport a non-bile acid substrate, pravastatin. *J Pharmacol Exp Ther 314*, 876–882.

Hirayama, M., Yoshimura, Y., & Moriyasu, M. (2000). Carrier-mediated uptake of cerivastatin in primary cultured rat hepatocytes. *Xenobio Metabol Dispos 15*, 219–225.

Hochman, J. H., Pudvah, N., Qiu, J., Yamazaki, M., Tang, C., Lin, J. H., et al. (2004). Interactions of human P-glycoprotein with simvastatin, simvastatin acid, and atorvastatin. *Pharm Res 21*, 1686–1691.

Hoffman, W. F., Alberts, A. W., Anderson, P. S., Chen, J. S., Smith, R. L., & Willard, A. K. (1986). 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors: 4. Side chain ester derivatives of mevinolin. *J Med Chem 29*, 849–852.

Holdgate, G. A., Ward, W. H., & McTaggart, F. (2003). Molecular mechanism for inhibition of 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase by rosuvastatin. *Biochem Soc Trans 31*, 528–531.

Hsiang, B., Zhu, Y., Wang, Z., Wu, Y., Sasseville, V., Yang, W. P., 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*, 37161–37168.

Hsyu, P. H., Schultz-Smith, M. D., Lillibridge, J. H., Lewis, R. H., & Kerr, B. M. (2001). Pharmacokinetic interactions between nelfinavir and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors atorvastatin and simvastatin. *Antimicrob Agents Chemother 45*, 3445–3450.

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*, 417–423.

Ishigami, M., Tokui, T., Komai, T., Tsukahara, K., Yamazaki, M., & Sugiyama, Y. (1995). Evaluation of the uptake of pravastatin by perfused rat liver and primary cultured rat hepatocytes. *Pharm Res 12*, 1741–1745.

Ishigami, M., Honda, T., Takasaki, W., Ikeda, T., Komai, T., Ito, K., et al. (2001). A comparison of the effects of 3-hydroxy-3-methylglutaryl-coenzyme a (HMG-CoA) reductase inhibitors on the CYP3A4-dependent oxidation of mexazolam in vitro. *Drug Metab Dispos 29*, 282–288.

Ishikawa, C., Ozaki, H., Nakajima, T., Ishii, T., Kanai, S., Anjo, S., et al. (2004). A frameshift variant of CYP2C8 was identified in a patient who suffered from rhabdomyolysis after administration of cerivastatin. *J Hum Genet 49*, 582–585.

Istvan, E. S., & Deisenhofer, J. (2001). Structural mechanism for statin inhibition of HMG-CoA reductase. *Science 292*, 1160–1164.

Ito, K., Ogihara, K., Kanamitsu, S., & Itoh, T. (2003). Prediction of the in vivo interaction between midazolam and macrolides based on in vitro studies using human liver microsomes. *Drug Metab Dispos 31*, 945–954.

Iwai, M., Suzuki, H., Ieiri, I., Otsubo, K., & Sugiyama, Y. (2004). Functional analysis of single nucleotide polymorphisms of hepatic organic anion transporter OATP1B1 (OATP-C). *Pharmacogenetics 14*, 749–757.

Iwatsubo, T., Hirota, N., Ooie, T., Suzuki, H., & Sugiyama, Y. (1996). Prediction of in vivo drug disposition from in vitro data based on physiological pharmacokinetics. *Biopharm Drug Dispos 17*, 273–310.

Iwatsubo, T., Hirota, N., Ooie, T., Suzuki, H., Shimada, N., Chiba, K., et al. (1997). Prediction of in vivo drug metabolism in the human liver from in vitro metabolism data. *Pharmacol Ther 73*, 147–171.

Johnson, T. E., Zhang, X., Bleicher, K. B., Dysart, G., Loughlin, A. F., Schaefer, W. H., et al. (2004). Statins induce apoptosis in rat and human myotube cultures by inhibiting protein geranylgeranylation but not ubiquinone. *Toxicol Appl Pharmacol 200*, 237–250.

Jokubaitis, L. A. (1994). Updated clinical safety experience with fluvastatin. *Am J Cardiol 73*, 18D–24D.

Kahri, A. J., Valkonen, M. M., Vuoristo, M. K., & Pentikainen, P. J. (2004). Rhabdomyolysis associated with concomitant use of simvastatin and clarithromycin. *Ann Pharmacother 38*, 719.

Kajinami, K., Brousseau, M. E., Ordovas, J. M., & Schaefer, E. J. (2004a). CYP3A4 genotypes and plasma lipoprotein levels before and after treatment with atorvastatin in primary hypercholesterolemia. *Am J Cardiol 93*, 104–107.

Kajinami, K., Takekoshi, N., Brousseau, M. E., & Schaefer, E. J. (2004b). Pharmacogenetics of HMG-CoA reductase inhibitors: exploring the potential for genotype-based individualization of coronary heart disease manegement. *Atherosclerosis 177*, 219–234.

Kajinami, K., Masuya, H., Hoshiba, Y., Takeda, K., Sato, R., Okabayashi, M., et al. (2005). Statin response and pharmacokinetics variants. *Expert Opin Pharmacother 6*, 1291–1297.

Kameyama, Y., Yamashita, K., Kobayashi, K., Hosokawa, M., & Chiba, K. (2005). Functional characterization of SLCO1B1 (OATP-C) variants, SLCO1B1*5, SLCO1B1*15 and SLCO1B1*15+C1007G, by using transient expression systems of HeLa and HEK293 cells. *Pharmacogenet Genomics 15*, 513–522.

Kantola, T., Kivisto, K. T., & Neuvonen, P. J. (1998a). Effect of itraconazole on the pharmacokinetics of atorvastatin. *Clin Pharmacol Ther 64*, 58–65.

Kantola, T., Kivisto, K. T., & Neuvonen, P. J. (1998b). Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther 64*, 177–182.

Kantola, T., Kivisto, K. T., & Neuvonen, P. J. (1998c). Grapefruit juice greatly increases serum concentrations of lovastatin and lovastatin acid. *Clin Pharmacol Ther 63*, 397–402.

Kantola, T., Kivisto, K. T., & Neuvonen, P. J. (1999). Effect of itraconazole on cerivastatin pharmacokinetics. *Eur J Clin Pharmacol 54*, 851–855.

Kikuchi, R., Kusuhara, H., Abe, T., Endou, H., & Sugiyama, Y. (2004). Involvement of multiple transporters in the efflux of 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors across the blood–brain barrier. *J Pharmacol Exp Ther 311*, 1147–1153.

Kirchheiner, J., Kudlicz, D., Meisel, C., Bauer, S., Meineke, I., Roots, I., et al. (2003). Influence of CYP2C9 polymorphisms on the pharmacokinetics and cholesterol-lowering activity of (−)-3S,5R-fluvastatin and (+)-3R,5S-fluvastatin in healthy volunteers. *Clin Pharmacol Ther 74*, 186–194.

Kivisto, K. T., Kantola, T., & Neuvonen, P. J. (1998). Different effects of itraconazole on the pharmacokinetics of fluvastatin and lovastatin. *Br J Clin Pharmacol 46*, 49–53.

Kivisto, K. T., Zukunft, J., Hofmann, U., Niemi, M., Rekersbrink, S., & Schneider, S. (2004a). Characterisation of cerivastatin as a P-glycoprotein substrate: studies in P-glycoprotein-expressing cell monolayers and mdr1a/b knock-out mice. *Naunyn Schmiedeberg's Arch Pharmacol 370*, 124–130.

Kivisto, K. T., Niemi, M., Schaeffeler, E., Pitkala, K., Tilvis, R., Fromm, M. F., et al. (2004b). Lipid-lowering response to statins is affected by CYP3A5 polymorphism. *Pharmacogenetics 14*, 523–525.

Klotz, U. (2003). Pharmacological comparison of the statins. *Arzneimittel-forschung 53*, 605–611.

Kobayashi, D., Nozawa, T., Imai, K., Nezu, J., Tsuji, A., & Tamai, I. (2003). Involvement of human organic anion transporting polypeptide OATP-B (SLC21A9) in pH-dependent transport across intestinal apical membrane. *J Pharmacol Exp Ther 306*, 703–708.

Koga, T., Shimada, Y., Kuroda, M., Tsujita, Y., Hasegawa, K., & Yamazaki, M. (1990). Tissue- selective inhibition of cholesterol synthesis in vivo by pravastatin sodium, a 3-hydroxy-3- methylglutaryl coenzyme A reductase inhibitor. *Biochim Biophys Acta 1045*, 115–120.

Kojima, J., Fujino, H., Abe, H., Yosimura, M., Kanda, H., & Kimata, H. (1999). Identification of metabolites of NK-104, an HMG-CoA reductase inhibitor, in rat, rabbit and dog bile. *Biol Pharm Bull 22*, 142–150.

Kyrklund, C., Backman, J. T., Kivisto, K. T., Neuvonen, M., Laitila, J., & Neuvonen, P. J. (2000). Rifampin greatly reduces plasma simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther 68*, 592–597.

Kyrklund, C., Backman, J. T., Kivisto, K. T., Neuvonen, M., Latila, J., & Neuvonen, P. J. (2001). Plasma concentrations of active lovastatin acid are markedly increased by gemfibrozil but not by bezafibrate. *Clin Pharmacol Ther 69*, 340–345.

Kyrklund, C., Backman, J. T., Neuvonen, M., & Neuvonen, P. J. (2003). Gemfibrozil increases plasma pravastatin concentrations and reduces pravastatin renal clearance. *Clin Pharmacol Ther 73*, 538–544.

Kyrklund, C., Backman, J. T., Neuvonen, M., & Neuvonen, P. J. (2004). Effect of rifampicin on pravastatin pharmacokinetics in healthy subjects. *Br J Clin Pharmacol 57*, 181–187.

Laaksonen, R., Jokelainen, K., Sahi, T., Tikkanen, M. J., & Himberg, J. J. (1995). Decreases in serum ubiquinone concentrations do not result in reduced levels in muscle tissue during short-term simvastatin treatment in humans. *Clin Pharmacol Ther 57*, 62–66.

Laaksonen, R., Jokelainen, K., Laakso, J., Sahi, T., Harkonen, M., Tikkanen, M. J., et al. (1996). The effect of simvastatin treatment on natural antioxidants in low-density lipoproteins and high-energy phosphates and ubiquinone in skeletal muscle. *Am J Cardiol 77*, 851–854.

Lalani, S. R., Vladutiu, G. D., Plunkett, K., Lotze, T. E., Adesina, A. M., & Scaglia, F. (2005). Isolated mitochondrial myopathy associated with muscle coenzyme Q10 deficiency. *Arch Neurol 62*, 317–320.

Lau, Y. Y., Okochi, H., Huang, Y., & Benet, L. Z. (2006). Multiple transporters affect the disposition of atorvastatin and its two active hydroxy metabolites: application of in vitro and ex situ systems. *J Pharmacol Exp Ther 316*, 762–771.

Lee, A. J., & Maddix, D. S. (2001). Rhabdomyolysis secondary to a drug interaction between simvastatin and clarithromycin. *Ann Pharmacother 35*, 26–31.

Lennernas, H. (2003). Clinical pharmacokinetics of atorvastatin. *Clin Pharmacokinet 42*, 1141–1160.

Lennernas, H., & Fager, G. (1997). Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors. Similarities and differences. *Clin Pharmacokinet 32*, 403–425.

Lilja, J. J., Kivisto, K. T., & Neuvonen, P. J. (1998). Grapefruit juice–simvastatin interaction: effect on serum concentrations of simvastatin, simvastatin acid, and HMG-CoA reductase inhibitors. *Clin Pharmacol Ther 64*, 477–483.

Lilja, J. J., Kivisto, K. T., & Neuvonen, P. J. (1999). Grapefruit juice increases serum concentrations of atorvastatin and has no effect on pravastatin. *Clin Pharmacol Ther 66*, 118–127.

Lilja, J. J., Kivisto, K. T., & Neuvonen, P. J. (2000). Duration of effect of grapefruit juice on the pharmacokinetics of the CYP3A4 substrate simvastatin. *Clin Pharmacol Ther 68*, 384–390.

Lilja, J. J., Neuvonen, M., & Neuvonen, P. J. (2004). Effects of regular consumption of grapefruit juice on the pharmacokinetics of simvastatin. *Br J Clin Pharmacol 58*, 56–60.

Lu, P., Schrag, M. L., Slaughter, D. E., Raab, C. E., Shou, M., & Rodrigues, A. D. (2003). Mechanism-based inhibition of human liver microsomal cytochrome P450 1A2 by zileuton, a 5-lipoxygenase inhibitor. *Drug Metab Dispos 31*, 1352–1360.

Martin, P. D., Warwick, M. J., Dane, A. L., Hill, S. J., Giles, P. B., Phillips, P. J., et al. (2003). Metabolism, excretion, and pharmacokinetics of rosuvastatin in healthy adult male volunteers. *Clin Ther 25*, 2822–2835.

Mathew, P., Cuddy, T., & Tracewell, W. G. (2004). An open-label study on the pharmacokinetics (PK) of pitavastatin (NK-104) when administered concomitantly with fenofibrate or gemfibrozil in healthy volunteers (Abstract PI-115). *Clinical Pharmacology and Therapeutics 75*, 33.

Matsushima, S., Maeda, K., Kondo, C., Hirano, M., Sasaki, M., Suzuki, H., et al. (2005). Identification of the hepatic efflux transporters of organic anions using double-transfected Madin-Darby canine kidney II cells expressing human organic anion-transporting polypeptide 1B1 (OATP1B1)/multidrug resistance-associated protein 2, OATP1B1/multidrug resistance 1, and OATP1B1/breast cancer resistance protein. *J Pharmacol Exp Ther 314*, 1059–1067.

Mazzu, A. L., Lasseter, K. C., Shamblen, E. C., Agarwal, V., Lettieri, J., & Sundaresen, P. (2000). Itraconazole alters the pharmacokinetics of atorvastatin to a greater extent than either cerivastatin or pravastatin. *Clin Pharmacol Ther 68*, 391–400.

McCormick, A. D., McKillop, D., Butters, C. J., Miles, G. S., Bab, T., Touchi, A., et al. (2000). ZD4522 – an HMG-CoA reductase inhibitor free metabolically mediated drug interactions: metabolic studies in human in vitro systems. *J Clin Pharmacol 40*, 1055.

McTaggart, F., Buckett, L., Davidson, R., Holdgate, G., McCormick, A., Schneck, D., et al. (2001). Preclinical and clinical pharmacology of rosuvastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. *Am J Cardiol 87*, 28B–32B.

Meadowcroft, A. M., Williamson, K. M., Patterson, J. H., Hinderliter, A. L., & Pieper, J. A. (1999). The effects of fluvastatin, a CYP2C9 inhibitor, on losartan pharmacokinetics in healthy volunteers. *J Clin Pharmacol 39*, 418–424.

Michalski, C., Cui, Y., Nies, A. T., Nuessler, A. K., Neuhaus, P., Zanger, U. M., et al. (2002). A naturally occurring mutation in the SLC21A6 gene causing impaired membrane localization of the hepatocyte uptake transporter. *J Biol Chem 277*, 43058–43063.