ORIGINAL ARTICLE

Pharmacokinetic interaction between pravastatin and olmesartan in relation to *SLCO1B1* polymorphism

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Abstract The impact of *SLCO1B1* polymorphism on the pharmacokinetics of olmesartan and on the pharmacokinetic interaction between pravastatin and olmesartan was investigated. On day 1, ten healthy volunteers took an oral dose (10 mg) of pravastatin. After a 3-day washout period, each subject received olmesartan medoxomil (10 mg) for 3 days. On day 8, they received olmesartan medoxomil (10 mg) and pravastatin (10 mg) concurrently, and pharmacokinetic profiles were compared with those in each single-dose phase with regard to the *SLCO1B1* genotypes (*1b/*1b, *1b/*15, and *15/*15). In the single-dose phase, the mean C_{max} and AUC_{0-24} of olmesartan tended to be higher in *15/*15 subjects than in *1b/*1b subjects, while the mean CL_r/F (±SD) in *15/*15 subjects was significantly lower than that in *1b/*1b subjects. No statistically significant differences were observed in any pharmacokinetic parameters between single-dose and co-administration phases for both pravastatin and RMS-416. These results suggest that OATP1B1 plays a role in the pharmacokinetics of olmesartan, and the co-administration of olmesartan does not affect the pharmacokinetics of pravastatin or its metabolite, RMS-416, although larger scale clinical studies are needed to confirm these observations due to the small sample size in the present study.

Keywords Olmesartan · Pravastatin · Pharmacokinetics · Interaction · OATP1B1 · *SLCO1B1* · Polymorphisms

Introduction

As hyperlipemia and hypertension often occur together in the same patients, the combination therapy of lipid-lowering drug and antihypertensive drug is frequently used in clinical situations. Pravastatin is an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase used for the treatment of hypercholesterolemia. Although pravastatin is not significantly metabolized by cytochrome P450 (CYP) isoenzymes, cumulative evidence has suggested that multiple membrane transporters are involved in the absorption (Kobayashi et al. 2003), hepatobiliary excretion (Hirano et al. 2005; Kivistö et al. 2005; Nakai et al. 2001), and renal excretion (Hasegawa et al. 2002) of pravastatin. Organic anion transporting polypeptide (OATP) 1B1 (gene *SLCO1B1*) is an uptake transporter expressed at the sinusoidal membrane of hepatocytes, mediating the uptake of various endogenous and exogenous substances from the blood circulation into hepatocytes in a sodium-independent manner. Previous study has suggested that OATP1B1 is predominantly involved in hepatic uptake of pravastatin in humans (Nakai et al. 2001). Several single-nucleotide polymorphisms (SNPs) have been identified in *SLCO1B1* (Nozawa et al. 2002; Tirona et al. 2001), and some are reported to be associated with alterations in the

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pharmacokinetics of certain substrate drugs, including repaglinide (Niemi et al. 2005a), fexofenadine (Niemi et al. 2005b), pitavastatin (Chung et al. 2005; Ieiri et al. 2007), and pravastatin (Mwinyi et al. 2004; Niemi et al. 2004; Nishizato et al. 2003). Particularly subjects having SLCO1B1*15 allele (possessing both 388A>G and 521T>C) showed elevated systemic exposure of pravastatin as compared to subjects without this allele (Niemi et al. 2004; Nishizato et al. 2003). In contrast, some reports indicated that SLCO1B1*1b allele (possessing 388A>G) showed enhanced transport activity of OATP1B1 as compared with wild-type allele (i.e., *1a allele) (Maeda et al. 2006; Mwinyi et al. 2004).

Olmesartan medoxomil is an angiotensin II receptor blocker used for the treatment of hypertension. Olmesartan medoxomil is completely de-esterified during absorption to form olmesartan, a pharmacologically active metabolite, which is excreted by hepatobiliary and renal systems without further metabolism (Laeis et al. 2001). At least two uptake transporters, OATP1B1 and OATP1B3, have been demonstrated to account for hepatic uptake of olmesartan (Nakagomi-Hagihara et al. 2006; Yamada et al. 2007). As pravastatin and olmesartan share some transporter-mediated transport pathways, such as hepatic uptake via OATP1B1, the co-administration of both drugs may potentially cause drug–drug interactions, which may consequently modulate the pharmacokinetics or pharmacodynamics of either drug. Therefore, this exploratory study was performed to investigate the pharmacokinetic interaction between pravastatin and olmesartan. In addition, since the effects of SLCO1B1 variant on olmesartan pharmacokinetics have not yet been reported, we also evaluated the contribution of SLCO1B1 variants to the pharmacokinetic profiles of olmesartan.

Materials and methods

Subjects and genotyping of SLCO1B1

Ten healthy male volunteers (age range, 20–26 years; weight range, 49.7–96.7 kg) participated in this study. They were grouped based on their SLCO1B1 genotypes into three groups: SLCO1B1*15/*15 ($n = 4$), *1b/*15 ($n = 2$), and *1b/*1b ($n = 4$). They were recruited from a population of 108 male Japanese volunteers whose SLCO1B1 genotype was prescreened after written informed consent was obtained. The individual genotyping for SLCO1B1 was determined using an ABI PRISM® 7000 Sequence Detection System (Applied Biosystems, Foster, CA) with TaqMan® SNP genotyping assays, as recommended by the manufacturer. The accuracy of genotyping was confirmed by direct sequencing. Each subject's health status was ascertained to be normal by medical history

interview, physical examination, electrocardiography, and routine clinical laboratory testing. None was receiving any continuous medications or habitually abusing alcohol/drugs. They were required to refrain from alcohol and caffeine-containing beverages for 2 days before and throughout the study. Drinking grapefruit or orange juice was not permitted during the period of study, and standard meals were served as scheduled.

Study protocol and quantification of drugs

A one-sequence study design with a 3-day washout period was conducted. This study protocol was approved by the Ethics Review Boards of Kyushu University and Kyushu Clinical Pharmacology Research Clinic, Fukuoka, Japan, and written informed consent was obtained from all subjects. On day 1, each subject received 10 mg of pravastatin (Mevalotin®; Daiichi-Sankyo Co. Ltd., Tokyo, Japan) with 150 ml of water after an overnight fast. Peripheral venous blood samples were obtained prior to dosing and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, 12, and 24 h after dosing for pravastatin and its metabolite, RMS-416, single-dose pharmacokinetics. Urine was collected cumulatively over 24 h after dosing. After a 3-day washout period, each subject was given 10 mg of olmesartan medoxomil (Olmetec®; Daiichi-Sankyo) with 150 ml of water once daily at the same time for 3 days (on days 5 through 7). On day 8, subjects received olmesartan medoxomil (10 mg) and pravastatin (10 mg) simultaneously. Plasma and urine samples were collected on day 5 (for olmesartan single-dose pharmacokinetics) and on day 8 (for the pharmacokinetic interaction study) in the same manner as on day 1. The concentrations of all test compounds in plasma and urine were determined by liquid chromatography–tandem mass spectrometry (LC–MS/MS) as described in earlier reports (Kawabata et al. 2005; Nishizato et al. 2003).

Pharmacokinetic and statistical analysis

Peak plasma concentration (C_{max}) was obtained directly from the data. The area under the plasma concentration–time curve from time 0–24 h (AUC_{0-24}) was calculated by the linear trapezoidal rule, and apparent total clearance (CL_t/F) was calculated as follows: $CL_t/F = dose/AUC_{0-24}$. The k_e was determined by log-linear regression analysis. Renal clearance (CLr_{0-24}) was estimated by dividing Ae_{0-24} with AUC_{0-24}, where Ae is the cumulative amount excreted in urine. The statistical differences of parameters among groups were determined by the Kruskal–Wallis or Mann–Whitney U tests. To evaluate the effect of co-administration, within-subject differences of data between single-dose and co-administration phases were analyzed by

the Wilcoxon signed-ranks test. $P < 0.05$ was considered statistically significant.

Results and discussion

All ten participants completed the study according to the protocol without the clinically important adverse events probably due to the administration of pravastatin or olmesartan medoxomil in the single-dose phase as well as in the co-administration phase.

In the single-dose phase, the mean C_{max} and $AUC_{0–24}$ values of olmesartan in *SLCO1B1*15/*15* subjects tended to be higher, and the mean CL_t/F value was significantly lower than those in *SLCO1B1*1b/*1b* subjects (Table 1). Recent in vitro studies using OATP1B1-expressing *Xenopus laevis* oocytes (Nakagomi-Hagihara et al. 2006) and HEK293 cells (Yamada et al. 2007) have indicated that olmesartan is a substrate of OATP1B1. Olmesartan is eliminated from the body through hepatic and renal routes without extensive metabolism (Laeis et al. 2001). Since the uptake of olmesartan into hepatocytes is the first step of hepatobiliary excretion, which is the major elimination route of olmesartan, increased systemic exposures and decreased apparent total clearance of olmesartan observed in subjects with *15 alleles might result from reduced hepatic uptake of olmesartan via OATP1B1. The lack of intergenotypic differences in renal clearance also supports this hypothesis (Table 1). The *SLCO1B1*15* allele, possessing the 521T>C variant, has been consistently associated with reduced transport activity of OATP1B1 both in vitro and in vivo (Chung et al. 2005; Ieiri et al. 2007; Iwai et al. 2004; Kameyama et al. 2005; Nishizato et al. 2003). However, the altered CL_t/F due to change in F

value in our subjects cannot be denied because there is no intravenous data to estimate absolute bioavailability.

In the co-administration phase, the intergenotypic differences in the pharmacokinetic profiles of olmesartan disappeared (Fig. 1; Table 1). After the co-administration of pravastatin, the mean $AUC_{0–24}$ and C_{max} values of olmesartan in *1b/*1b subjects increased, and the mean CL_t/F value decreased by approximately 20%, whereas there were only slight changes in *15/*15 subjects, resulting in comparable values between the two genotype groups (Table 1). Although the small sample size makes it difficult to address the conclusion, these observations might be a consequence of the competitive inhibition of olmesartan hepatic uptake via OATP1B1 by pravastatin, even though no in vitro inhibitory data are currently available.

Very little is known about the metabolism of olmesartan by CYP enzyme systems; no literature reports in this regard. Based on available data, pravastatin is unlikely to be a substrate of CYP3A4 or CYP2C9; the co-administration of CYP3A4 inhibitors (i.e., verapamil, mibefradil, itraconazole, clarithromycin, and grapefruit juice) or CYP2C9 inhibitor (i.e., fluconazole) had no significant effect on the pharmacokinetics of pravastatin (Fukazawa et al. 2003; Jacobson 2004; Kantola et al. 2000). Additionally, in vitro inhibition profiles of major human drug metabolizing CYP isoenzymes (i.e., CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP3A5) by pravastatin showed that both acid and lactone forms of pravastatin had minimal inhibitory effects on metabolic activities of all five CYP isoenzymes with IC_{50} values >100 μM (Sakaeda et al. 2006). Taking these into consideration, increased AUC and decreased CL_t/F of olmesartan in the co-administration phase are unlikely to result from the inhibition of CYP-mediated metabolism of

Table 1 Pharmacokinetic parameters of olmesartan in each *SLCO1B1* genotype group in two administration conditions

Parameter	Single-dose phase[a]			Co-administration phase[b]		
	*15/*15 group ($n = 4$)	*1b/*15 group ($n = 2$)	*1b/*1b group ($n = 4$)	*15/*15 group ($n = 4$)	*1b/*15 group ($n = 2$)	*1b/*1b group ($n = 4$)
C_{max} (ng/ml)	390 ± 110	370	310 ± 59	400 ± 61	380	360 ± 80
$AUC_{0–24}$ (ng h/ml)	$2{,}100 \pm 230$	2,300	$1{,}900 \pm 550$	$2{,}300 \pm 350$	2,100	$2{,}300 \pm 430$
k_e (per h)	0.095 ± 0.008	0.096	0.096 ± 0.017	0.085 ± 0.008	0.10	0.096 ± 0.010
CL_t/F (l/kg/h)	$0.068 \pm 0.009^*$	0.058	0.10 ± 0.041	0.062 ± 0.009	0.060	0.080 ± 0.012
$Ae_{0–24}$ (μg)	830 ± 260	750	740 ± 240	510 ± 130	450	440 ± 141
$CLr_{0–24}$ (l/kg/h)	0.0055 ± 0.0011	0.0046	0.0071 ± 0.0013	0.0032 ± 0.0010	0.0027	0.0034 ± 0.0009

Values are presented as the mean ± SD

* $P < 0.05$ versus values of *1b/*1b group

[a] Ingestion of a single dose of 10 mg olmesartan medoxomil

[b] Ingestion of 10 mg olmesartan medoxomil concomitant with 10 mg pravastatin following administration of 10 mg olmesartan medoxomil alone once daily for 3 days
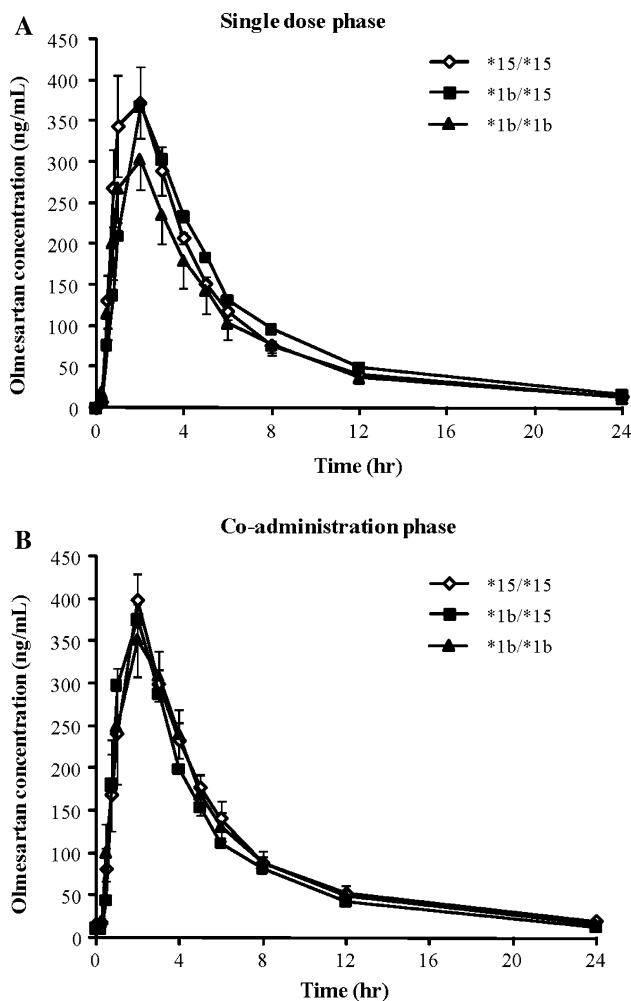
A

B

Fig. 1 Plasma concentrations (mean ± SEM) of olmesartan after oral administration of 10 mg olmesartan medoxomil alone (**a**) and with 10 mg pravastatin (**b**) in *SLCO1B1*15/*15* subjects ($n = 4$), *1b/*15* subjects ($n = 2$), and *1b/*1b* subjects ($n = 4$)

olmesartan by pravastatin. However, possible interaction via other transporters, multidrug resistance-associated protein 2 (MRP2) in particular, cannot be negligible, because pravastatin and olmesartan are also a substrate of MRP2, and this transporter is reported to be involved in their biliary excretion (Kivistö et al. 2005; Nakagomi-Hagihara et al. 2006).

No significant intergenotypic differences in the mean $Ae_{0–24}$ and $CLr_{0–24}$ values of olmesartan were observed in both the single-dose and co-administration phases; however, these values in the single-dose phase were decreased after co-administration of pravastatin, irrespective to *SLCO1B1* status (Table 1). The mechanism by which urinary excretion of olmesartan was reduced after the co-administration of pravastatin is unclear and still needs to be clarified. Recent in vitro studies indicated that organic anion transporter 3 (OAT3) expressed at the basolateral membrane of renal proximal tubule epithelial cells is predominantly involved in renal uptake of both pravastatin

and olmesartan (Hasegawa et al. 2002; Yamada et al. 2007). The drug–drug interaction via OAT3 between pravastatin and olmesartan may account for the reduction of olmesartan renal excretion in the co-administration phase; however, the interaction via MRP2, which also is expressed in the kidney, cannot be ruled out (Kivistö et al. 2005; Nakagomi-Hagihara et al. 2006).

There were no significant differences in any pharmacokinetic parameters of pravastatin among *SLCO1B1* genotypes for both dosing phases (Table 2). In contrast, mean C_{max} and $AUC_{0–24}$ of RMS-416 showed significant differences among *SLCO1B1* genotyping groups; plasma concentrations of RMS-416 were higher in *SLCO1B1*15/ *15* subjects than in *SLCO1B1*1b/*1b* subjects. When we introduced the sum of pravastatin and RMS-416, the mean $AUC_{0–24}$ value in *SLCO1B1*15/*15* subjects was significantly higher than in *SLCO1B1*1b/*1b* subjects for both dosing phases. For urinary data, the mean $Ae_{0–24}$ and $CLr_{0–24}$ values of both pravastatin and RMS-416 were not markedly different between these groups (data not shown). It was somewhat unexpected that there were no significant differences in any pharmacokinetic parameters of pravastatin among *SLCO1B1* genotypes, because previous studies provided accordant evidence that *SLCO1B1*15* is associated with remarkably elevated plasma levels of pravastatin (Niemi et al. 2004; Nishizato et al. 2003). Because of the instability in acid conditions, pravastatin underwent acid-catalyzed conversion to form RMS-416 (3′α-isopravastatin) in the stomach after oral administration, and a considerable amount of RMS-416 was detectable in plasma, urine, and feces (Everett et al. 1991). In this study, we interpreted data in terms of the sum of pravastatin and RMS-416. This method has been suggested previously in a study by Maeda et al. (2006) who demonstrated that RMS-416 is also a substrate of OATP1B1 and assumed that *SLCO1B1* variants would affect the pharmacokinetics of the sum of pravastatin and RMS-416 more markedly than that of pravastatin itself. With this assumption, they could observe an increasing trend in AUC of the sum of pravastatin and RMS-416 in subjects with the *15 allele as compared with subjects without the *15 allele (Maeda et al. 2006). Our present findings are in line with their results that the mean $AUC_{0–24}$ values in single-dose and co-administration phases of *15/*15 group were 96 and 98% higher than those of the *1b/*1b group, respectively, when compared in terms of the sum of pravastatin and RMS-416.

As shown in Table 2, no statistically significant differences were observed in any pharmacokinetic parameters between single-dose and co-administration phases for both pravastatin and RMS-416. Our results show that the co-administration of olmesartan does not affect the pharmacokinetics of pravastatin or its metabolite, RMS-416.

Table 2 Pharmacokinetic parameters of pravastatin and RMS-416 in each *SLCO1B1* genotype group in two administration conditions

Parameter	Single-dose phase[a]			Co-administration phase[b]		
	*15/*15 group (n = 4)	*1b/*15 group (n = 2)	*1b/*1b group (n = 4)	*15/*15 group (n = 4)	*1b/*15 group (n = 2)	*1b/*1b group (n = 4)
C_{max} (ng/ml)						
Pravastatin	19 ± 16	14	20 ± 13	30 ± 29	15	16 ± 8.2
RMS-416	29 ± 4.1*	31	10 ± 7.5	27 ± 13	34	8.9 ± 9.2
AUC_{0-24} (ng h/ml)						
Pravastatin	56 ± 43	38	48 ± 32	64 ± 47	37	43 ± 14
RMS-416	70 ± 15*	60	16 ± 12	56 ± 33	64	18 ± 16
Pravastatin + RMS-416	130 ± 41*	98	64 ± 26	120 ± 33*	100	61 ± 20
k_e (per h)						
Pravastatin	0.31 ± 0.16	0.24	0.22 ± 0.12	0.22 ± 0.13	0.23	0.36 ± 0.18
RMS-416	0.55 ± 0.24	0.17	0.32 ± 0.25	0.37 ± 0.10	0.30	0.50 ± 0.30
CL_r/F [l/(kg h)]						
Pravastatin	3.9 ± 2.5	3.7	6.3 ± 6.0	3.2 ± 1.8	3.6	4.7 ± 2.6

Values are presented as the mean ± SD

* $P < 0.05$ versus values of *1b/*1b group

[a] Ingestion of a single dose of 10 mg olmesartan medoxomil

[b] Ingestion of 10 mg olmesartan medoxomil concomitant with 10 mg pravastatin following administration of 10 mg olmesartan medoxomil alone once daily for 3 days

In this study, OATP1B1 appeared to play a role in the clearance of both olmesartan and pravastatin. However, *SLCO1B1* variants did not have a great impact on the pharmacokinetics of olmesartan, different from the case of previous pravastatin studies (Nishizato et al. 2003; Mwinyi et al. 2004). It is obvious that the small sample size in each genotype group is a limitation of our study, which made it difficult to elucidate the effects of *SLCO1B1* polymorphism; however, this may be explained by the in vitro findings indicating that OATP1B1 accounts for only approximately 40–60% of total hepatic clearance of olmesartan (Yamada et al. 2007). In contrast, OATP1B1 is found to be a predominant transporter responsible for hepatic uptake of pravastatin (Nakai et al. 2001). The relationship between the AUC value of olmesartan and that of pravastatin plus RMS-416 is shown in Fig. 2; although not statistically significant, the AUC of olmesartan tended to correlate with that of pravastatin plus RMS-416 ($R = 0.534$; $P = 0.112$). Since pravastatin and olmesartan are cleared from the body by the liver and kidneys without further metabolism, the correlation between olmesartan and pravastatin plus RMS-416 might be attributed to sharing transporters that mediate their elimination pathways, such as OATP1B1.

In summary, *SLCO1B1* polymorphism could contribute to the interindividual variability in the pharmacokinetics of olmesartan. As pharmacological effects of olmesartan occur in a dose-dependent manner, subjects with *SLCO1B1*15
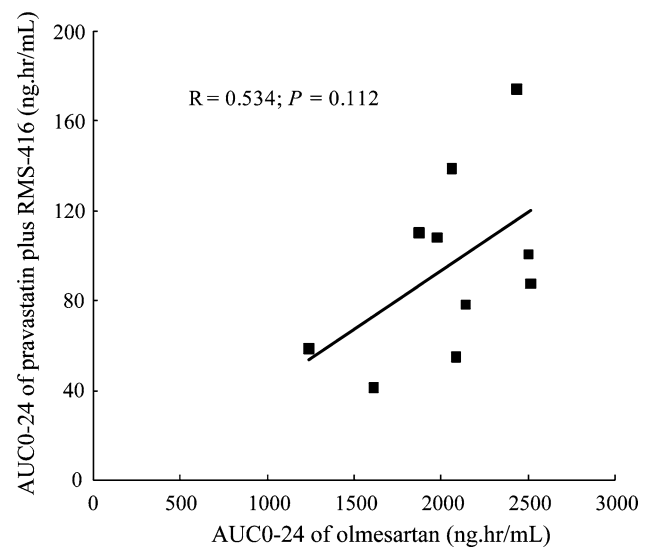

Fig. 2 Correlation between AUC_{0-24} of olmesartan and pravastatin plus RMS-416. Each *point* represents the data of each subject. *Solid line* represents least square linear regression fitting line

haplotypes are predicted to exhibit enhanced therapeutic response to olmesartan, attributed to high plasma levels of olmesartan. On the other hand, these patients may be at risk of dose-dependent adverse effects of olmesartan. However, further clinical studies including a greater number of subjects are needed to confirm these observations.

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