Effect of *OATP1B1* (*SLCO1B1*) variant alleles on the pharmacokinetics of pitavastatin in healthy volunteers

Background: **Pitavastatin is a potent, newly developed 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitor for the treatment of hyperlipidemia. We characterized the effects of organic anion transporting polypeptide 1B1 (*OATP1B1*) alleles **1a*, **1b*, and **15* on the pharmacokinetics of pitavastatin.**

Methods: **Twenty-four healthy Korean volunteers who had previously participated in a pharmacokinetic study of pitavastatin (single oral dose, 1-8 mg) were further investigated. Subjects were grouped according to *OATP1B1* genotype. Dose-normalized area under the plasma concentration–time curve (AUC) and peak plasma concentration (C_{max}) values were analyzed, because different dosages were administered to subjects, whereas the pharmacokinetics showed linear characteristics.**

Results: **Dose-normalized pitavastatin AUCs for **1b/*1b* (group 1), **1a/*1a* or **1a/*1b* (group 2), and **1a/*15* or **1b/*15* (group 3) were 38.8 ± 13.3, 54.4 ± 12.4, and 68.1 ± 16.3 ng · h · mL^{-1} · mg^{-1} (mean ± SD), respectively, with significant differences between all 3 groups ($P = .008$) and between subjects carrying and those not carrying the **15* allele ($P = .004$). Dose-normalized pitavastatin C_{max} values were 13.2 ± 3.3, 18.2 ± 5.7, and 29.4 ± 9.6 ng · mL^{-1} · mg^{-1} in groups 1, 2, and 3, respectively, and also showed significant differences ($P = .003$) in a manner similar to that shown by AUC. No significant differences were found between the genotype groups in terms of dose-normalized AUC or C_{max} values of pitavastatin lactone.**

Conclusion: ***OATP1B1* variant haplotypes were found to have a significant effect on the pharmacokinetics of pitavastatin. These results suggest that the **15* allele is associated with decreased pitavastatin uptake from blood into hepatocytes and that *OATP1B1* genetic polymorphisms have no effect on the pharmacokinetics of pitavastatin lactone. (Clin Pharmacol Ther 2005;78:342-50.)**

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Pitavastatin is a potent inhibitor of 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase and was developed for the treatment of hypercholesterolemia.[1] In humans, pitavastatin is only minimally metabolized by the cytochrome P450 2C9 isozyme.[2] The major metabolic pathway of pitavastatin involves its initial glucuronidation by uridine diphosphate–glucuronosyltransferase and then spontaneous lactonization by the elimination of the glucuronide moiety.[3] Moreover, the lactone form can be reversibly converted to the parent drug.[4] Given the specific distribution of pitavastatin in the liver,[5] the hepatic uptake of pitavastatin through membrane transporters is likely to be a major determinant of drug disposition, as is the case for other HMG-CoA reductase inhibitors (pravastatin, rosuvastatin, and cerivastatin).

Human organic anion transporting polypeptide 1B1 (OATP1B1/OATP-C/OATP2, *SLCO1B1*) is expressed at the basolateral membrane of hepatocytes, and OATP1B1 plays an important role in transporting a broad range of compounds including bile acids, sulfate,

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and glucuronide conjugates. Moreover, it makes a substantial contribution to the hepatic uptake of HMG-CoA reductase inhibitors (statins).[6] Recently, the transporter responsible for the hepatic uptake of pitavastatin in humans was identified as OATP1B1, which could account for 90% of the total hepatic uptake of pitavastatin.[7]

Because the OATP1B1-mediated hepatic uptake of statins is important in terms of enhancing therapeutic efficacy and minimizing excess systemic exposure, which could cause adverse reactions, the presence of a functionally deleterious polymorphism in the *OATP1B1* gene may increase the risk of statin-mediated rhabdomyolysis.[8] Recently, a number of single-nucleotide polymorphisms (SNPs) were identified in this gene,[9,10] and most of these SNPs were associated with a significant reduction in transporter activity in vitro.[9] Moreover, commonly occurring SNPs such as A388G (N130D) and T521C (V174A) were found to cause a marked alteration in the disposition of pravastatin in several in vivo studies.[11,12] Specifically, the *OATP1B1*15* (A388G and T521C) allele was associated with increased pravastatin plasma levels in humans as compared with the *OATP1B1*1b* (A388G) allele, which is most common (approximately 46%) in Japanese subjects.[11] In another study the *OATP1B1*5* (T521C) allele, a variant seen in European Americans, was found to have delayed pravastatin hepatocellular uptake and increased plasma levels, whereas the *OATP1B1*1b* allele showed accelerated transporter activity versus the **1a* allele, also known as the wild type.[12]

Although pitavastatin is less hydrophilic than pravastatin or rosuvastatin,[13] genetic polymorphisms of *OATP1B1* would be expected to affect the pharmacokinetics of pitavastatin because of its high liver specificity and OATP1B1-dependent hepatic uptake. In this study we investigated the relationships between polymorphisms in the *OATP1B1* gene and the pharmacokinetics of pitavastatin (and pitavastatin lactone) in healthy Korean subjects to determine to what extent its pharmacokinetic (PK) variability is explained by known *OATP1B1* alleles.

METHODS

Subjects. Twenty-four healthy, unrelated Korean male subjects were enrolled in a PK study, in which subjects were randomly allocated to 1 of 4 groups as follows: 1 mg, 2 mg, 4 mg, or 8 mg pitavastatin (n = 6 for each group). Genotypes were assessed retrospectively and were related to the PK results. All subjects were ascertained to be healthy by medical history, a physical examination, vital signs, 12-lead electrocardiography, and routine clinical laboratory tests performed within 3 weeks before the start of this study. Regular heavy drinkers, smokers of more than 10 cigarettes per day, and subjects with a body weight differing by more than 20% from the ideal weight were excluded. A urinary drug-screening analysis by use of REMEDi HS (Bio-Rad Laboratories, Hercules, Calif) was used to exclude drug abusers. No medications, herbal drugs, alcohol, beverages containing caffeine, or grapefruit products were permitted from 7 days before the study and for the duration of the study. This study was approved by the Institutional Review Board of Seoul National University Hospital, Seoul, Korea. All procedures were performed in accordance with the recommendations of the Declaration of Helsinki on biomedical research involving human subjects and with the International Conference on the Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use–Good Clinical Practice guidelines. Written informed consent for participation in the study and genotyping was obtained from all subjects before enrollment.

Clinical study. This was a dose-rising, parallel-group study. Subjects were randomly assigned to 1 of 4 dose groups taking 1, 2, 4, or 8 mg. After an overnight fast, all subjects were given a single dose of pitavastatin (Libalo tablet; Choongwae Pharma, Seoul, Korea) or a placebo with 200 mL water at approximately 9 AM. Subjects were kept in a fasting state until 4 hours after drug administration, except for 200 mL water at 2 and 4 hours after dosing. Venous blood samples for PK analysis (8 mL) were collected via an intravenous catheter before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 32 hours after dosing. Blood sampling for genotyping was also done before drug administration, and *OATP1B1* genotyping was done after the end of the study. Alcohol, soft drinks, smoking, drugs, and beverages containing caffeine were prohibited during the study.

OATP1B1 genotyping. Genomic deoxyribonucleic acid (DNA) was extracted from ethylenediaminetetraacetic acid–treated venous blood by use of a QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). The National Center for Biotechnology Information reference sequence used for the *OATP1B1* (*SLCO1B1*) gene was NM_006446. To determine the presence or absence of the 3 alleles, *OATP1B1*1a*, **1b*, and **15*, DNA near 2 polymorphic sites, A388G and T521C, was amplified by polymerase chain reaction (PCR), which was followed by SNaPshot analysis (Applied Biosystems, Foster City, Calif). The sequences of the

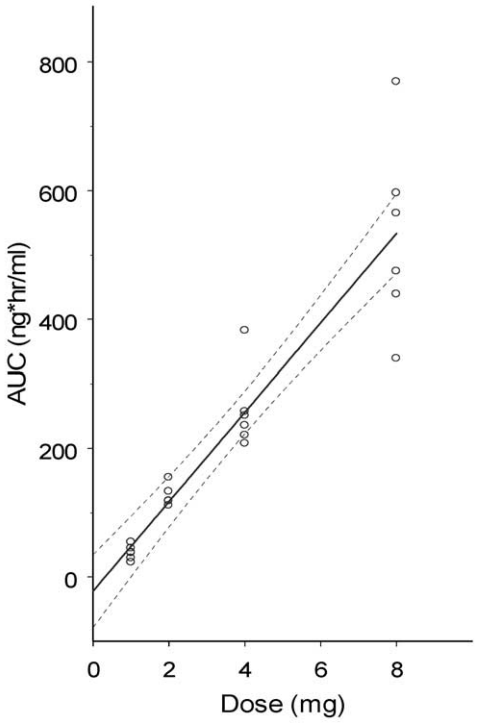

Fig 1. Linear regression of pharmacokinetic parameter (area under plasma concentration–time curve [AUC]) of pitavastatin versus dose. *Dashed lines* represent 95% confidence intervals including 0 at 0-mg dose. The slope is significantly different from 0 ($R^2 = 0.8614$).

forward and reverse primers used were as follows: 5′-GGGGAAGATAATGGTGCAAA-3′ and 5′-CGGCAGGTTTATCATCCAGT-3′, respectively, for A388G SNP and 5′-CAGCATAAGAATGGACTAATACACC-3′ and 5′-TGGACCAATCATTGCTATTG-3′, respectively, for T521C SNP. PCR reactions were performed in a volume of 20 μL consisting of 1.5-mmol/L magnesium chloride, 250-μmol/L deoxyribonucleoside triphosphates, 0.5 pmol of each primer, and 0.25 U of AmpliTaq DNA polymerase (Applied Biosystems). After an initial denaturation at 94°C for 10 minutes, DNA was amplified over 30 cycles (denaturation at 95°C for 30 seconds, annealing at 60°C for 1 minute, and extension at 72°C for 1 minute), and this was followed by an extension at 72°C for 7 minutes. For SNaPshot analysis, PCR products were purified with exonuclease I and shrimp alkaline phosphatase (USB, Cleveland, Ohio) and mixed with AmpliTaq DNA polymerase and 4 fluorescently labeled dideoxynucleoside triphosphates in the reaction buffer contained in an ABI Prism SNaPshot multiplex kit (Applied Biosystems) according to the manufacturer's protocol. The internal reverse primer sequences used for the single-base extension were 5′-GTCGATGTTGAATTTTCTGATGAAT-3′ and 5′-TCCACGAAGCATATTACCCATGAAC-5′ to detect A388G and T521C, respectively. The primers were extended over 25 cycles of 96°C for 10 seconds, 50°C for 5 seconds, and 60°C for 30 seconds. Amplicons were then purified by use of exonuclease I and shrimp alkaline phosphatase and analyzed on an ABI Prism 3700 Automated Sequencer (Applied Biosystems). DNA sequences near polymorphic sites were confirmed by direct sequencing.

Drug concentration analysis and pharmacokinetics. Plasma concentrations of pitavastatin were determined by HPLC with ultraviolet detection. An aliquot of 1 mL plasma was mixed with 225 μL 2N potassium phosphate and 6 mL methyl *tert*-butyl ether, which included 100 μL of internal standard (isopropyl pitavastatin at 0.1 μg/mL). After centrifugation for 10 minutes, 100 μL of the supernatant was injected into an HPLC system (Nanospace SI-2; Shiseido Fine Chemicals, Tokyo, Japan). A mobile phase of 0.2-mol/L acetate/acetonitrile (50:50 [vol/vol], pH 4.0) was used at a flow rate of 0.8 mL/min through a C18 column (150 × 4.6–mm internal diameter, 5.0-μm particle size) (Cosmosil AR-II; Nacalai Tesque, Kyoto, Japan). The lower limit of quantification was 0.5 ng/mL, and calibration curves were linear over the concentration range 0.5 to 200 ng/mL ($r > 0.98$). The accuracy of this assay was within the range of 96.4% to 116.8%, and the interbatch coefficient of variation was less than 9.2% over the calibrated range.

PK parameters were calculated by use of actual sampling times. The maximum drug concentration in plasma (C_{max}) was determined from the observed values. Plasma concentrations of the terminal phase were fitted to a log-linear line by the least squares method to obtain the terminal half-life. The area under the time-concentration curve (AUC) was calculated by use of a combination of the trapezoidal rule and extrapolation to infinity by use of the elimination rate constant. AUC and C_{max} were normalized with respect to administered dose to allow PK parameters to be compared for the different genotypes. Linear dose proportionality of dose-normalized PK parameters was confirmed by 1-way ANOVA ($P > .05$) and linear regression (Fig 1). WinNonlin, version 4.0.1 (Pharsight, Mountain View, Calif) was used for the PK analysis.

Statistical analysis and modeling. Comparisons of the PK parameters between genotype groups were made nonparametrically by use of the Kruskal-Wallis test for multigroup comparisons and the Mann-Whitney test for 2-group comparisons. $P < .05$ was considered statistically significant.

Table I. Demographic summary of subjects according to *OATP1B1* genotype

	Genotype group				*SNP T521C*		
	1	*2*	*3*	*P value†*	*TT*	*TC*	*P value‡*
Genotype	**1b/*1b* (n = 4)	**1a/*1a* (n = 1) **1a/*1b* (n = 8)	**1a/*15* (n = 5) **1b/*15* (n = 6)		521TT (n = 13)	521TC (n = 11)	
Dose (No.)				.081§			.077§
1 mg	3	3	0		6	0	
2 mg	1	1	4		2	4	
4 mg	0	3	3		3	3	
8 mg	0	2	4		2	4	
Age (y)	22.5 ± 1.7	23.8 ± 2.3	24.4 ± 2.9	.366†	23.4 ± 2.2	24.4 ± 2.9	.360‡
Height (cm)	177 ± 2.4	173 ± 3.9	174 ± 4.0	.296†	174 ± 3.8	174 ± 4.0	.929‡
Weight (kg)	70.9 ± 6.5	65.9 ± 6.0	69.5 ± 10.3	.315†	67.4 ± 6.3	69.5 ± 10.3	.549‡

Data are given as mean ± SD. Haplotypes **1a*, **1b*, and **15* are determined by SNPs 388A and 521T, 388G and 521T, and 388G and 521C, respectively.
OATP1B1, Organic anion transporting polypeptide 1B1; SNP, single-nucleotide polymorphism.
†ANOVA for 3 groups.
‡Two-sample *t* test.
§Fisher exact test.

To quantify the proportional contributions made by the individual alleles to PK parameters, we constructed a linear additive model as follows:

$$AUC = Q1 \cdot \theta_{*1a} + Q2 \cdot \theta_{*1b} + Q3 \cdot \theta_{*15} \qquad (1)$$

in which Q1, Q2, and Q3 are variables dependent on genotypes. The AUC of the 5 *OATP1B1* genotypes (**1a/*1a*, **1a/*1b*, **1b/*1b*, **1a/*15*, and **1b/*15*) was modeled as the sum of 2 partial THETAs values of the 3 alleles (θ_{*1a}, θ_{*1b}, and θ_{*15} for the *OATP1B1 *1a*, **1b*, and **15* allele–related AUC, respectively). For example, for genotype **1a/*1a*, Q1 equals 2, Q2 equals 0, and Q3 equals 0, and for genotype **1b/*15*, Q1 equals 0, Q2 equals 1, and Q3 equals 1. In this manner we calculated the proportional contribution to AUC made by each allele. In the case of C_{max}, the same method was applied in the analysis. Model fitting was done by use of NONMEM, version V (GloboMax, Hanover, Md), by use of PRED, which enables flexible model coding.

RESULTS

Subjects were grouped by allele pairs of *OATP1B1*1a*, **1b*, or **15* or by *OATP1B1* T521C SNP pairs to investigate the effect of the *OATP1B1* genotypes (Table I). Subjects were grouped into 3 groups according to allele pairs (**1b* homozygous, **1a/*1b* heterozygous + **1a* homozygous [only 1 subject], and **15* heterozygous) or into 2 groups by T512C SNP (TT or TC). These groupings were based on the fact that only 1 subject with **1a/*1a* was studied, and considerations of statistical comparative power were taken into account. Also, it had been previously reported that the **15* allele (or T512C SNP) has a significant impact on the pharmacokinetics of pravastatin.[12]

Demographic characteristics of subjects and dosages administered were not significantly different among the genotype groups according to *OATP1B1* haplotype pairs or T512C SNP. Representative pitavastatin and pitavastatin lactone plasma concentration–time profiles versus genotypes are shown in Fig 2.

Mean dose-normalized AUC and C_{max} values in genotype group 3 (*OATP1B1*15/*1a* or *OATP1B1*15/*1b*) were 68.1 $ng \cdot h \cdot mL^{-1} \cdot mg^{-1}$ and 29.4 $ng \cdot mL^{-1} \cdot mg^{-1}$, respectively, which were 1.8- and 2.2-fold higher than those values (38.8 $ng \cdot h \cdot mL^{-1} \cdot mg^{-1}$ and 13.2 $ng \cdot mL^{-1} \cdot mg^{-1}$, respectively) in group 1 (*OATP1B1*1b/*1b*) (Table II and Fig 3). Tendencies toward an increase in AUC and C_{max}, as well as a decreasing trend in the volume of distribution, were noted on moving from genotype group 1 to 2 to 3 in sequence, although no significance difference was observed between groups 1 and 2.

Statistically significant differences for dose-normalized AUC and C_{max} values of pitavastatin were found among the 3 genotype groups ($P = .008$ and $P = .003$, respectively), between groups 1 and 3 ($P = .003$ and $P = .006$, respectively), and between groups 2 and 3 ($P = .038$ and $P = .009$, respectively). A statistically significant difference was also found between *OATP1B1* 512TC and TT groups (AUC, 46.6 ± 14.3 $ng \cdot h \cdot mL^{-1} \cdot mg^{-1}$ and 68.1 ± 16.3 $ng \cdot h \cdot mL^{-1} \cdot mg^{-1}$ [$P = .004$], respectively; C_{max}, 16.5 ± 5.5 $ng \cdot mL^{-1} \cdot mg^{-1}$ and 29.4 ± 9.6 $ng \cdot mL^{-1} \cdot mg^{-1}$ [$P = .001$], respectively). No significant difference was observed between groups 1 and 2 (Table II).

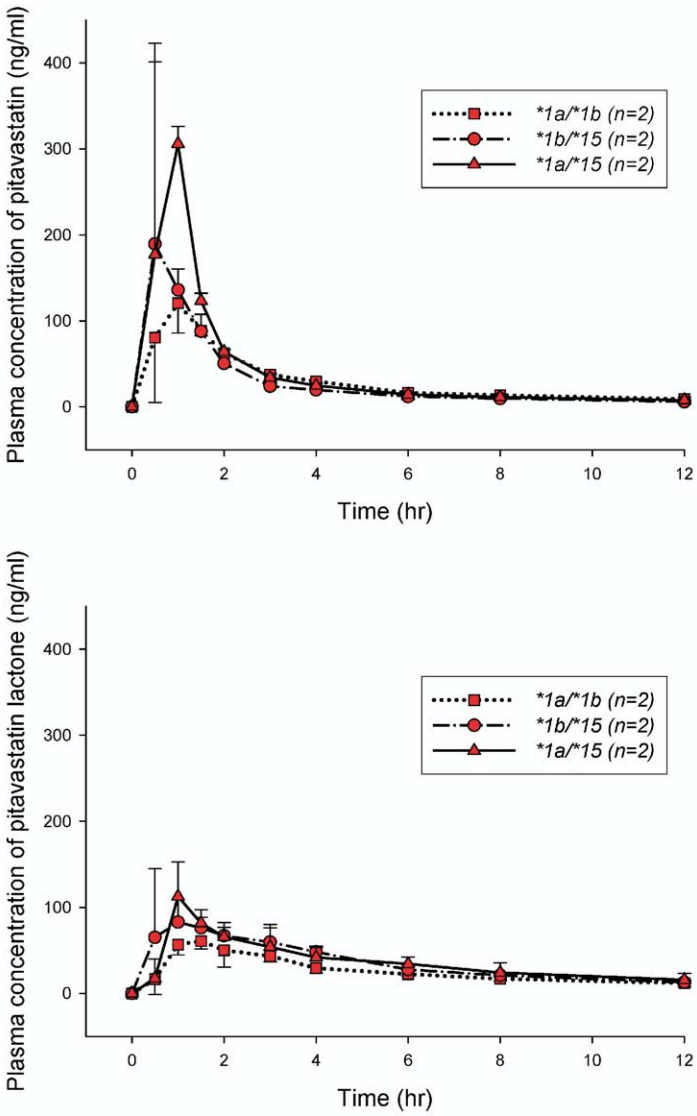

Fig 2. Representative mean plasma concentration–time profiles of pitavastatin (*top*) and pitavastatin lactone (*bottom*) by genotypes after oral administration of 8 mg pitavastatin.

In the case of pitavastatin lactone, no significant difference were observed for dose-normalized AUC and C_{max} values among the 3 genotype groups or between the *OATP1B1* 512TC and TT groups (Table III).

Estimated allele- and genotype-specific PK parameters were obtained for all possible genotypes. The SEs of parameter estimations were less than 20% in terms of coefficient of variation in all cases. All estimated genotype-specific values were consistent with actual mean values according to genotypes (R^2 = 0.85 and 0.52 for AUC and C_{max}, respectively, by linear regression). Mean estimated values of AUC and C_{max} for the *OATP1B1*15/*15* genotype (simulated), which were the highest recorded, were 2.1- and 3.4-fold higher than those of the *OATP1B1*1b/*1b* genotype, respectively, which were the lowest recorded (Table IV).

DISCUSSION

We investigated the functional significance of the *OATP1B1* genetic polymorphism on the pharmacokinetics of pitavastatin in humans. Significant PK differences were observed according to *OATP1B1* genotype. The dose-normalized AUC and C_{max} of pitavastatin were 1.4- and 1.8-fold higher, respectively, in subjects

Table II. Effects of *OATP1B1* genotypes on pharmacokinetic parameters of pitavastatin in 24 healthy Korean male subjects

	*Group 1: *1b/*1b (n = 4)*	*Group 2: *1a/*1a (n = 1)*	*Group 2: *1a/*1b (n = 8)*	*Group 3†: *1a/*15 (n = 5)*	*Group 3†: *1b/*15 (n = 6)*	*P value: All groups‡*	*P value§: Group 1 versus group 2*	*P value§: Group 1 versus group 3*	*P value§: Group 2 versus group 3*
DNAUC ($ng \cdot h \cdot mL^{-1} \cdot mg^{-1}$)	38.8 ± 13.3	45.1	55.6 ± 12.7	68.8 ± 15.6	67.4 ± 18.3	.008	NS	.003	.038
		54.4 ± 12.4		68.1 ± 16.3					
DNC_{max} ($ng \cdot mL^{-1} \cdot mg^{-1}$)	13.2 ± 3.3	15.3	18.5 ± 6.0	34.4 ± 6.9	25.2 ± 10.0	.003	NS	.006	.009
		18.2 ± 5.7		29.4 ± 9.6					
Half-life (h)	7.7 ± 1.3		10.6 ± 2.9		10.0 ± 0.9	.017	NS	.002	NS
Vz/F (L)	212.2 ± 66.2		194.8 ± 41.2		153.7 ± 34.9	NS	NS	.041	.027

Data are given as arithmetic mean ± SD.

DNAUC, Dose-normalized area under plasma concentration–time curve from time 0 to infinity; DNC_{max}, dose-normalized peak plasma concentration; NS, not significant; Vz/F, volume of distribution based on terminal phase.

†Comparison between **1a/*15* and **1b/*15* within group 3 by Mann-Whitney test; $P > .99$ for DNAUC, and $P = .126$ for DNC_{max}.

‡Kruskal-Wallis test for differences across all 3 groups.

§Mann-Whitney test for 2 groups.

heterozygous for the *OATP1B1*15* allele (or 521T>C SNP) versus subjects not carrying this allele (or SNP). We estimated values of the PK parameters in all possible haplotype pairs, and dose-normalized AUC and C_{max} were predicted to be 2- to 3-fold higher for the *OATP1B1*15/*15* genotype than for the *OATP1B1*1b/*1b* genotype.

In a recent in vitro study, OATP1B1 was suggested to be the most important transporter with respect to the hepatic uptake of pitavastatin in humans.[7] OATP1B1 is a major hepatic statin transporter and is known to act on pravastatin, cerivastatin, and rosuvastatin.[6,14,15] However, only the association between polymorphisms in *OATP1B1* and the pharmacokinetics of pravastatin has been reported. In recent studies in humans, significantly higher systemic exposures to pravastatin were identified in subjects carrying the *OATP1B1*15* allele (containing 388A>G and 521T>C SNPs) in Japanese subjects[11] or the *OATP1B1*5* (521T>C SNP) allele[12] and *OATP1B1* −11187G>A and 521T>C SNPs in white subjects.[10] These findings are consistent with the results of our study.

No subjects carrying the *OATP1B1*5* allele were found among our Korean subjects, which is consistent with the results of the previously mentioned Japanese study.[11] The allele frequency of *OATP1B1*5* was 0% in 120 Japanese subjects,[11] whereas it was 14% in European Americans and 0.02% in black subjects.[9] However, both *OATP1B1*5* and **15* contain 521T>C SNP, and the sum of these allele frequencies was found to be similar in Asian and white subjects (15% in Japanese, 20% in Koreans, and 14% in European Americans), implying an ethnic insensitivity with regard to pitavastatin in these 2 ethnic groups. The pharmacokinetics of pitavastatin appear to be similar among Asian ethnic groups. The geometric mean AUC values after a 2-mg oral dose of pitavastatin in healthy volunteers were 118.0 ng · h/mL in Korean subjects, 121.2 ng · h/mL in Chinese subjects,[16] and 104.7 ng · h/mL in Japanese subjects (unpublished data), respectively. More studies are needed on OATP1B1 in black subjects to determine the impact of 521T>C SNP and ethnic differences on pitavastatin and other statins.

The pharmacokinetics of pitavastatin lactone showed no difference for the *OATP1B1* genotype groups, although the plasma lactone level is determined by complex processes, perhaps because both intracellular transportation and the metabolism (glucuronidation and lactonization) of pitavastatin are not associated with *OATP1B1* genotypes.

This study was conducted in a relatively small group of subjects, at different dosages, and the haplotype-pair genotype groupings adopted appear to be somewhat arbitrary, because this study was not prospectively designed to evaluate the effects of *OATP1B1* genotypes. Nevertheless, the effects of *OATP1B1*15* or T512C SNP were clearly observed with statistical significance. The dose normalizations of PK parameters are probably biased; however, we believe that this is justified because pitavastatin PK parameters show a linear dose proportionality, which was confirmed by linear regression and ANOVA.

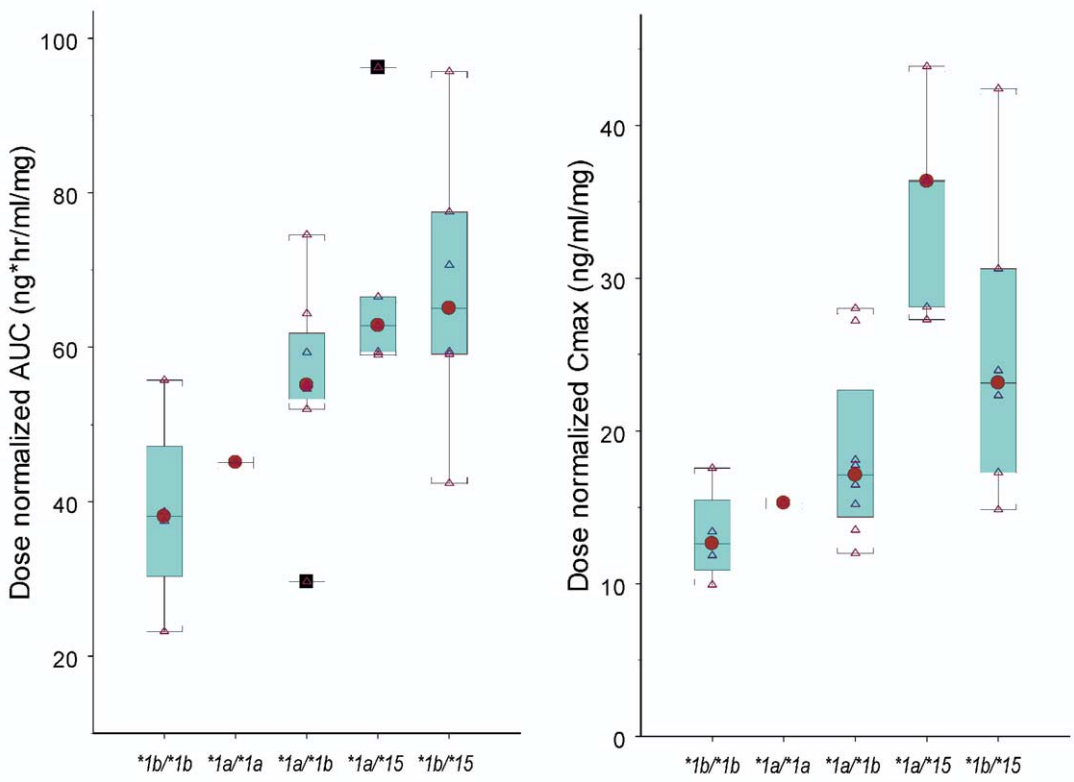

Fig 3. Box-and-whiskers plot of pharmacokinetic parameters of pitavastatin grouped by *OATP1B1* genotypes. The *horizontal lines with solid circles* within each *box* represent the median. The *box edges* show lower (25th) and upper (75th) quartiles, respectively. The *whiskers* extend from the 25th and 75th quartiles to the furthest data points within a distance of 1.5 interquartile ranges from the 25th and 75th quartiles. Individual data points are given as *triangles*. The *horizontal lines with solid boxes outside whiskers* represent outliers.

Table III. Effects of *OATP1B1* genotypes on pharmacokinetic parameters of pitavastatin lactone in 24 healthy Korean male subjects

	Group 1	*Group 2*	*Group 3*	*P value: All groups†*	*P value‡: Group 1 versus group 2*	*P value‡: Group 1 versus group 3*	*P value‡: Group 2 versus group 3*
Genotype	**1b/*1b* (n = 4)	**1a/*1a* (n = 1) or **1a/*1b* (n = 8)	**1a/*15* (n = 5) or **1b/*15* (n = 6)				
DNAUC ($ng \cdot h \cdot mL^{-1} \cdot mg^{-1}$)	55.2 ± 13.5	98.4 ± 52.3	72.3 ± 25.5	.26	.14	.34	.41
DNC_{max} ($ng \cdot mL^{-1} \cdot mg^{-1}$)	9.4 ± 3.1	12.2 ± 4.1	11.7 ± 2.9	.63	.41	.49	.88

†Kruskal-Wallis test for differences across all 3 groups.
‡Mann-Whitney test for 2 groups.

Table IV. Estimated allele- and genotype-specific pharmacokinetic parameters

	AUC estimate ($ng \cdot h \cdot mL^{-1} \cdot mg^{-1}$)		*C_{max} estimate* ($ng \cdot mL^{-1} \cdot mg^{-1}$)	
	Mean	*SE†*	*Mean*	*SE†*
Allele-specific parameter				
θ_{*1b}	22.1	3.1	6.5	0.7
θ_{*1a}	28.9	4.3	11.4	2.2
θ_{*15}	43.1	5.2	20.4	3.0
Genotype				
**1b/*1b*	44.1		13.0	
**1a/*1b*	51.0		17.9	
**1a/*1a*	58.8		22.8	
**1b/*15*	65.2		26.9	
**1a/*15*	72.0		31.8	
**15/*15*	86.2		40.4	

†Asymptotic SE as calculated by NONMEM.

To the best of our knowledge, this is the first study on the association between genetic polymorphisms of *OATP1B1* and the pharmacokinetics of pitavastatin in humans. No in vitro data are available on the transport function of the *OATP1B1* variant with the use of pitavastatin as substrate. However, Iwai et al[17] recently investigated the in vitro function of the 4 major OATP1B1 alleles (*OATP1B1*1a*, **1b*, **5*, and **15*) constructed by the 2 SNPs (A388G and T521C). The normalized V_{max} (concentration/time) value (picomoles per minute per milligram of protein) for *OATP1B1*15* was decreased to less than 30% compared with *OATP1B1*1a*, which is consistent with our results. Further in vitro functional studies may clarify the mechanism underlying the in vivo PK results obtained.

In conclusion, the *OATP1B1*15* allele (containing the 388A>G and 521T>C SNPs) and 521T>C SNP were identified as single major determinants of the pharmacokinetics of pitavastatin. About 2-fold higher pitavastatin concentrations were observed in subjects carrying the *OATP1B1*15* or *OATP1B1* 512C alleles than in those without them. These results suggest that the **15* allele is associated with the reduced uptake of pitavastatin by OATP1B1 from blood. No significant effects of *OATP1B1* genetic polymorphisms were observed on pitavastatin lactone formation, which implies that pitavastatin has a similar therapeutic efficacy for all *OATP1B1* genotype groups. However, plasma concentration–dependent adverse events such as rhabdomyolysis may be related to the *OATP1B1* polymorphism, especially in the presence of a drug interaction; for example, it was reported that gemfibrozil increases plasma pitavastatin concentrations when the 2 drugs are concomitantly administered.[18] A large-scale study including a patient population is necessary to confirm the effect of the *OATP1B1* polymorphisms on the clinical efficacy and adverse events associated with pitavastatin treatment.

All authors have no conflict of interest regarding this study.

References

1. Aoki T, Nishimura H, Nakagawa S, Kojima J, Suzuki H, Tamaki T, et al. Pharmacological profile of a novel synthetic inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. Arzneimittelforschung 1997;47: 904-9.
2. Fujino H, Yamada I, Shimada S, Nagao T, Yoneda M. Metabolic fate of pitavastatin (NK-104), a new inhibitor of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase. Effects on drug-metabolizing systems in rats and humans. Arzneimittelforschung 2002;52:745-53.
3. Fujino H, Yamada I, Shimada S, Yoneda M, Kojima J. Metabolic fate of pitavastatin, a new inhibitor of HMG-CoA reductase: human UDP-glucuronosyltransferase enzymes involved in lactonization. Xenobiotica 2003;33: 27-41.
4. Kojima J, Fujino H, Abe H, Yosimura M, Kanda H, Kimata H. Identification of metabolites of NK-104, an HMG-CoA reductase inhibitor, in rat, rabbit and dog bile. Biol Pharm Bull 1999;22:142-50.
5. Kajinami K, Mabuchi H, Saito Y. NK-104: a novel synthetic HMG-CoA reductase inhibitor. Expert Opin Investig Drugs 2000;9:2653-61.
6. Hsiang B, Zhu Y, Wang Z, Wu Y, Sasseville V, Yang WP, et al. 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 1999;274:37161-8.
7. Hirano M, Maeda K, Shitara Y, Sugiyama Y. Contribution of OATP2 (OATP1B1) and OATP8 (OATP1B3) to the hepatic uptake of pitavastatin in humans J Pharmacol Exp Ther 2004;311:139-46.
8. Simonson SG, Raza A, Martin PD, Mitchell PD, Jarcho JA, Brown CD, et al. Rosuvastatin pharmacokinetics in heart transplant recipients administered an antirejection regimen including cyclosporine. Clin Pharmacol Ther 2004;76:167-77.
9. Tirona RG, Leake BF, Merino G, Kim RB. Polymorphisms in *OATP-C*. Identification of multiple allelic variants associated with altered transport activity among European- and African-Americans. J Biol Chem 2001; 276:35669-75.

10. Niemi M, Schaeffeler E, Lang T, Fromm MF, Neuvonen M, Kyrklund C, et al. High plasma pravastatin concentrations are associated with single nucleotide polymorphisms and haplotypes of organic anion transporting polypeptide-C (OATP-C, SLCO1B1). Pharmacogenetics 2004;14:429-40.
11. Nishizato Y, Ieiri I, Suzuki H, Kimura M, Kawabata K, Hirota T, et al. Polymorphisms of OATP-C (SLC21A6) and OAT3 (SLC22A8) genes: consequences for pravastatin pharmacokinetics. Clin Pharmacol Ther 2003;73:554-65.
12. Mwinyi J, Johne A, Bauer S, Roots I, Gerloff T. Evidence for inverse effects of OATP-C (SLC21A6) 5 and 1b haplotypes on pravastatin kinetics. Clin Pharmacol Ther 2004;75:415-21.
13. Iglesias P, Diez JJ. New drugs for the treatment of hypercholesterolaemia. Expert Opin Investig Drugs 2003;12:1777-89.
14. Brown CDA, Windass A, Bleasby K, Lauffart B. Rosuvastatin is a high affinity substrate of hepatic organic anion transporter OATP-C. Atherosclerosis 2001;(Suppl 2):90.
15. Nakai D, Nakagomi R, Furuta Y, Tokui T, Abe T, Ikeda T, et al. Human liver-specific organic anion transporter, LST-1, mediates uptake of pravastatin by human hepatocytes. J Pharmacol Exp Ther 2001;297:861-7.
16. Hui CK, Cheung BM, Lau GK. Pharmacokinetics of pitavastatin in subjects with Child-Pugh A and B cirrhosis. Br J Clin Pharmacol 2005;59:291-7.
17. Iwai M, Suzuki H, Ieiri I, Otsubo K, Sugiyama Y. Functional analysis of single nucleotide polymorphisms of hepatic organic anion transporter OATP1B1 (OATP-C). Pharmacogenetics 2004;14:749-57.
18. Mathew P, Cuddy T, Tracewell WG, Salazar D. An open-label study on the pharmacokinetics (PK) of pitavastatin (NK-104) when administered concomitantly with fenofibrate or gemfibrozil in healthy volunteers [abstract]. Clin Pharmacol Ther 2004;75:P33.