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ORIGINAL RESEARCH

Association of genetic variations with pharmacokinetics and lipid-lowering response to atorvastatin in healthy Korean subjects

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Hye In Woo[1]
Suk Ran Kim[2]
Wooseong Huh[3,4]
Jae-Wook Ko[4]
Soo-Youn Lee[4,5]

[1]Department of Laboratory Medicine, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Korea; [2]Clinical Research and Development, Hanmi Pharm. Co., Ltd., Seoul, Korea; [3]Department of Medicine, [4]Department of Clinical Pharmacology and Therapeutics, [5]Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Background: Statins are effective agents in the primary and secondary prevention of cardiovascular disease, but treatment response to statins varies among individuals. We analyzed multiple genetic polymorphisms and assessed pharmacokinetic and lipid-lowering responses after atorvastatin 80 mg treatment in healthy Korean individuals.

Methods: Atorvastatin 80 mg was given to 50 healthy Korean male volunteers. Blood samples were collected to measure plasma atorvastatin and lipid concentrations up to 48 hours after atorvastatin administration. Subjects were genotyped for 1,936 drug metabolism and transporter genetic polymorphisms using the Affymetrix DMET plus array.

Results: The pharmacokinetics and lipid-lowering effect of atorvastatin showed remarkable interindividual variation. Three polymorphisms in the *SLCO1B1*, *SLCO1B3*, and *ABCC2* genes were associated with either the maximum concentration (C_{max}) of atorvastatin or changes in total cholesterol or low-density lipoprotein cholesterol (LDL-C). Minor homozygotes (76.5 ng/mL) of *SLCO1B1* c.-910G>A showed higher C_{max} than heterozygotes (34.0 ng/mL) and major homozygotes (33.5 ng/mL, false discovery rate P=0.040). C_{max} and the area under the plasma concentration curve from hour 0 to infinity (AUC_{∞}) were higher in carriers of the *SLCO1B1**17 haplotype that included c.-910G>A than in noncarriers (46.1 vs 32.8 ng/mL for C_{max}; 221.5 vs 154.2 ng/mL for AUC_{∞}). *SLCO1B3* c.334G>T homozygotes (63.0 ng/mL) also showed higher C_{max} than heterozygotes (34.7 ng/mL) and major homozygotes (31.4 ng/mL, FDR P=0.037). A nonsynonymous *ABCC2* c.1249G>A was associated with small total cholesterol and LDL-C responses (0.23% and −0.70% for G/A vs −11.9% and −17.4% for G/G). The C_{max} tended to increase according to the increase in the number of minor allele of *SLCO1B1* c.-910G>A and *SLCO1B3* c.334G>T.

Conclusion: Genetic polymorphisms in transporter genes, including *SLCO1B1*, *SLCO1B3*, and *ABCC2*, may influence the pharmacokinetics and lipid-lowering response to atorvastatin administration.

Keywords: atorvastatin, pharmacokinetics, pharmacogenomics, *SLCO1B1*, *SLCO1B3*, *ABCC2*

Introduction

As therapeutic agents administered to reduce the risk of cardiovascular disease and manage hypercholesterolemia,[1] statins upregulate low-density lipoprotein (LDL) receptors, increase plasma clearance of LDL, and reduce hepatic secretion of apolipoprotein B (ApoB)-containing lipoproteins, very low-density lipoprotein (VLDL), and LDL. Statins can reduce the plasma concentration of low-density lipoprotein cholesterol (LDL-C) by as much as 50% as well as triglycerides.[2]

Atorvastatin is a potent competitive inhibitor of 3-hydroxy-3-ethylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme that catalyzes conversion of

Correspondence: Soo-Youn Lee
Department of Laboratory Medicine and Genetics, Samsung Medical Center, #50, Irwon-dong, Gangnam-gu, Seoul, 135-710, Korea
Tel +82 2 3410 1834
Fax +82 2 3410 2719
Email sy117.lee@samsung.com

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HMG-CoA to mevalonate, an early rate-limiting step in cholesterol synthesis. In spite of the beneficial effects of statin treatment in cardiovascular disease prevention,[1] responses to statin therapy show considerable interindividual variation,[3,4] and some patients may not achieve sufficient LDL-C reduction even with the most efficacious statins.[5]

Genetic factors are expected to be part of the interindividual variation in the pharmacokinetic and pharmacodynamic response to statins.[6,7] Various genes encoding for enzymes and transporters that influence pharmacokinetics and the targets of pathways on which a drug acts, as well as those involved in related disease conditions, have been evaluated in candidate gene studies and hypothesis-free genome-wide investigations.[6–12] Genetic variations on drug transporter genes, *ABCB1* and *SLCO1B1*; P450 system genes, *CYP3A4*, *CYP3A5*, and *CYP2D6*; and other genes encoding lipoproteins and enzymes of lipid metabolic pathways such as *APOE* and *HMACR*, have been suggested to have associations with statin responsiveness.[6,8,9] Genetic variations that affect pharmacokinetics of statins may modify atorvastatin disposition and hence its efficacy and toxicity.[8,13] However, the effects of genetic variations have been inconsistently replicated, and there are relatively few data available in Asian populations.[14] In addition, there are lots of variations in metabolic processes according to statin type, and in the frequency of genetic variations and responsiveness to statins according to ethnic background.[6,15]

Accordingly, we investigated pharmacokinetic and pharmacodynamic changes in healthy Korean individuals after high-dose atorvastatin administration through serial plasma measurements of drug and lipid concentrations. We assessed associations between genetic variations and pharmacokinetics or lipid-lowering effects of atorvastatin using a predesigned gene panel including genes related to absorption, distribution, metabolism, and elimination.

Materials and methods

Subjects and study design

This study enrolled 50 healthy Korean male subjects. All subjects were from unrelated families and were ascertained to be healthy by medical history, physical examination, vital signs, electrocardiography, and routine clinical laboratory tests. Subjects were given a single oral dose of 80 mg atorvastatin calcium at 08:00 am with 240 mL of water in the overnight fasting state. Subjects fasted for 4 hours after atorvastatin administration, then lunch and dinner were served. Venous blood samples for pharmacokinetic analysis were collected via an intravenous catheter at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours after dosing. Plasma concentrations of total cholesterol, LDL-C, and triglycerides were measured before and at 24 and 48 hours after atorvastatin administration. Blood sampling for genotyping was performed before drug administration. The study protocol was approved by the Institutional Review Board of Dankook University and Samsung Medical Center, Korea. Written informed consent was obtained from each participant.

Pharmacokinetic and pharmacodynamic measurements

Plasma concentrations of atorvastatin were determined by liquid chromatography–tandem mass spectrometry (LC–MS/MS) using a TSQ Quantum Discovery mass spectrometer (Thermo Electron, San Jose, CA, USA). The ion transitions monitored were *m/z* 559.2 → 440. Pharmacokinetic parameters were determined by BA-Calc software (Korea Food and Drug Administration, Korea) using actual sampling times. Plasma concentrations of the terminal phase were fitted to a log-linear line by the least squares method to obtain the elimination rate constant. The area under the plasma concentration curve from hour 0 to infinity (AUC_{∞}) was calculated using a combination of the trapezoidal rule and extrapolation to infinity by the elimination rate constant. The maximum drug concentration in plasma (C_{max}) and time to C_{max} (t_{max}) were determined from observed values. Clearance (CL) of atorvastatin was adjusted according to the body weight of each subject. Plasma lipid concentrations were measured with an Hitachi 7600-110 chemistry analyzer (Hitachi, Tokyo, Japan).

Genotyping

Genomic DNA was isolated from peripheral blood samples using the Wizard Genomic DNA Purification Kit (Promega, Madison, WI, USA). Genotyping was performed using the Affymetrix drug-metabolizing enzyme and transporter (DMET) Plus array (Affymetrix, Santa Clara, CA, USA), which gauges 1,936 polymorphisms from 225 genes encoding phase I and phase II drug metabolism enzymes as well as drug transporters.[16,17] Briefly, we determined the yields of pure double-stranded genomic DNA samples before genotyping. Samples were adjusted to concentrations of 60 ng/μL. Normalized genomic DNA (17 μL) was used as a template for DMET arrays. For loci that had pseudogenes and close homologs, initial genomic amplification using locus-specific primers in a multiplex polymerase chain reaction (mPCR) was performed. By hybridization of highly

selective molecular inversion probes (MIPs) to their complementary genomic templates, sequences containing polymorphisms of interest were amplified and then fragmented to improve hybridization onto DMET arrays. Hybridized DMET arrays were scanned with an Affymetrix GeneChip Scanner 3000 7G. Genotyping was performed according to the predefined software algorithms of the manufacturer using DMET Console version 1.0.[16,18]

Statistical analyses

Of 1,936 polymorphisms in 225 genes screened, 519 non-monomorphic polymorphisms in 181 genes were identified with a ≥90% call rate, ≥5% minor allele frequency, and nonsignificant deviation from Hardy–Weinberg equilibrium ($P \geq 0.001$). Analysis of variance (ANOVA) or Kruskal–Wallis tests were used to test for associations between genotypes and pharmacokinetic parameters or lipid concentration changes from baseline to 48 hours after atorvastatin administration. Pharmacokinetic parameters included AUC_{∞}, C_{max}, and clearance adjusted with body weight (CL_{adj}). An ANOVA test was applied for polymorphisms that satisfied the assumptions of normality and homogeneity of variances in phenotype distribution. A *P*-value less than 0.050 was considered statistically significant. For statistically significant associations, the Jonckheere–Terpstra test was performed to test for ordered differences among genotypes. Corrected *P*-values were obtained using the Benjamini–Hochberg false discovery rate (FDR) approach. Statistical analyses were conducted using R, version 2.9.1 (R Foundation for Statistical Computing, Vienna, Austria), and IBM SPSS Statistics version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Participant demographics

A total of 50 healthy individuals were included in this study. Baseline characteristics are presented in Table 1. All subjects were male with a mean age of 24 years (range, 20–27 years) and a mean body weight of 69 kg (50–98 kg). Mean plasma concentrations of total cholesterol, LDL-C, and triglycerides were 150, 72.6, and 110 mg/dL, retrospectively.

Table 1 Demographics and baseline characteristics (n=50)

Variable	Mean (range)
Age (years)	24 (20–27)
Gender, n (%)	
Male	50 (100.0)
Female	0 (0.0)
Body weight (kg)	69 (50–98)
Baseline lipid concentration (mg/dL)	
Total cholesterol, n (%)	150 (101–212)
≥200	2 (4.0)
<200	48 (96.0)
LDL-C, n (%)	72.6 (42–108)
≥130	0 (0.0)
<130	50 (100.0)
Triglycerides, n (%)	110 (52–233)
≥150	9 (18.0)
<150	41 (82.0)
Genotype, n (%)	
SLCO1B1 c.-910G>A	
G/G	33 (66.0)
G/A	14 (28.0)
A/A	3 (6.0)
SLCO1B3 c.334G>T	
G/G	28 (56.0)
G/T	16 (32.0)
T/T	6 (12.0)
ABCC2 c.1249G>A	
G/G	43 (86.0)
G/A	7 (14.0)

Abbreviation: LDL-C, low-density lipoprotein cholesterol.

Atorvastatin pharmacokinetics and pharmacodynamics

Pharmacokinetic properties of atorvastatin are summarized in Table 2. The mean AUC_{∞}, C_{max}, t_{max}, CL, CL_{adj}, and half-life ($t_{1/2}$) were 172 ng·h/mL, 36.2 ng/mL, 1.07 h, 603 L/h, 8.85 L/(h·kg), and 7.75 h, respectively. Pharmacokinetic parameters showed marked interindividual variability, with a coefficient of variation (CV) ranging from 33.3% to 81.8%. The mean and standard deviation (SD) of the plasma concentration–time profile for atorvastatin after a single oral administration in all participants are shown in Figure 1A. The mean dose-per-body weight normalized AUC_{∞} and C_{max} were 148 ng·h/mL per mg/kg and 31.0 ng/mL per mg/kg, respectively. The CVs of dose-per-body weight normalized AUC_{∞} and C_{max} were 59.0% and 54.4%.

Table 2 Atorvastatin pharmacokinetics in 50 healthy individuals

Parameter	Mean	SD	CV	Range
AUC_{∞} (ng·h/mL)	172	94.9	55.3%	48.9–508.8
C_{max} (ng/mL)	36.2	19.3	53.3%	9.5–92.2
t_{max} (h)	1.07	0.89	81.8%	0.5–4.0
CL (L/h)	603	310	51.3%	157–1,636
CL_{adj} (L/(h·kg))	8.85	4.54	51.1%	2.5–25.2
$t_{1/2}$ (h)	7.75	2.56	33.3%	2.1–17.0

Abbreviations: AUC_{∞}, area under the plasma concentration curve from hour 0 to infinity; CL, clearance; CL_{adj}, clearance adjusted with body weight; C_{max}, maximum drug concentration in plasma; CV, coefficient of variation; SD, standard deviation; $t_{1/2}$, half-life; t_{max}, time to C_{max}.

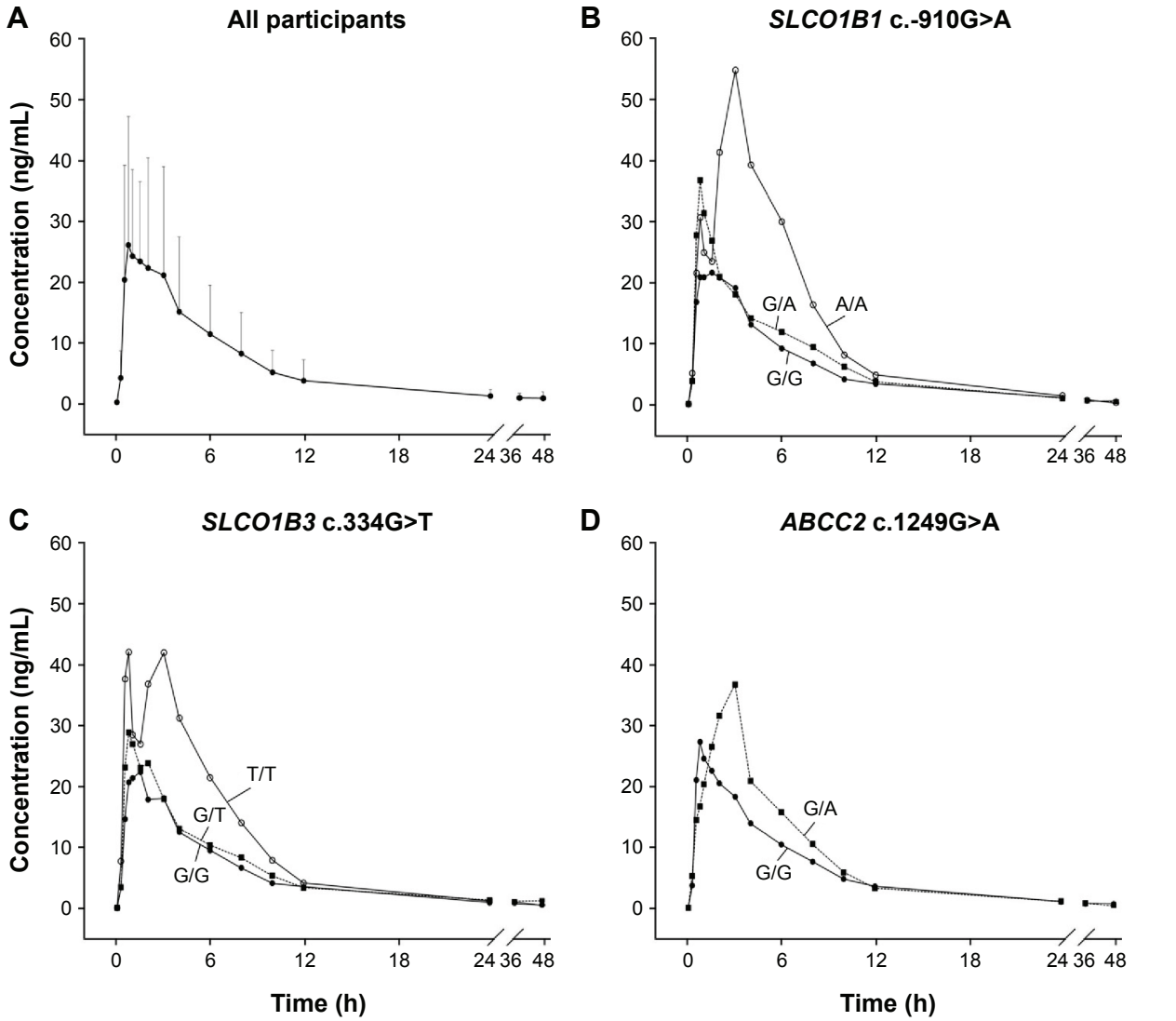

Figure 1 Plasma concentration vs time curve of atorvastatin in healthy subjects receiving a single dose of 80 mg atorvastatin.
Notes: (**A**) A plot of all participants. Solid circles represent mean concentrations of plasma atorvastatin, and the bars correspond to standard deviations. (**B**) A plot according to *SLCO1B1* c.-910G>A genotypes. (**C**) A plot according to *SLCO1B3* c.334G>T genotypes. (**D**) A plot according to *ABCC2* c.1249G>A genotypes. Solid circles correspond to mean concentrations of major homozygotes, quadrangles to heterozygotes, and open circles to minor homozygotes.

Lipid concentration changes at 24 and 48 hours from baseline are summarized in Table 3. Mean total cholesterol and LDL-C concentrations at 48 hours after single atorvastatin administration were decreased by 10.2% and 15.1%, respectively. Triglyceride concentrations did not show any statistically significant change. There was no correlation between baseline plasma concentrations or pharmacokinetic parameters of atorvastatin and changes in lipid concentrations.

Genetic polymorphisms associated with pharmacokinetic/pharmacodynamic variables

Sixty-four polymorphisms from 47 genes were associated with pharmacokinetic variables or lipid concentration changes according to genotype ($P<0.050$ in ANOVA or Kruskal–Wallis tests; Table S1). Seventeen polymorphisms were associated with AUC_{∞}, 26 polymorphisms with C_{max}, and 16 polymorphisms with CL_{adj}. In terms of a lipid-lowering effect, 16 polymorphisms were associated with LDL-C, and 12 polymorphisms with total cholesterol. The 13 genes related to variance in LDL-C lowering included *ABCB11*, *ABCC1*, *ABCC2*, *AHR*, *CBR1*, *CYP19A1*, *CYP1B1*, *CYP4F11*, *NAT2*, *SLC10A2*, *SLC5A6*, *SLC7A8*, and *SULT1B1*.

Among these 64 polymorphisms, 3 in the *SLCO1B1*, *SLCO1B3*, and *ABCC2* genes showed ordinal associations with C_{max}, or changes in total cholesterol or LDL-C (Tables 4 and S2). The mean of the plasma concentration–time profile for atorvastatin according to each genotype is

Table 3 Lipid concentrations (mg/dL) and percentage changes (%Δ) from baseline to 24 and 48 hours after atorvastatin administration

Lipid profile	Baseline	24 hours after				48 hours after			
	Mean (range)	Mean (range)	%Δ mean (95% CI)	%Δ SD (CV%)	*P*-value	Mean (range)	%Δ mean (95% CI)	%Δ SD (CV%)	*P*-value
Total cholesterol	150 (101–212)	141 (85–209)	−5.13 (−8.44 to −1.81)	11.7 (−228)	0.001	133.8 (91–189)	−10.2 (−13.1 to −7.22)	10.4 (−102)	<0.001
LDL-C	72.6 (42–118)	64.0 (30–114)	−9.31 (−16.3 to −2.31)	24.7 (−265)	0.001	60.4 (26–104)	−15.1 (−21.0 to −9.22)	20.7 (−137)	<0.001
Triglycerides	110 (52–233)	115 (56–246)	12.0 (0.92–23.0)	38.9 (325)	0.280	110.4 (39–646)	4.93 (−13.3 to 23.2)	64.3 (1,304)	0.975

Abbreviations: CI, confidence interval; CV, coefficient of variation; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

shown in Figure 1B–D. For c.-910G>A (rs4149015) in the *SLCO1B1* gene, 33 subjects were G/G homozygotes, 14 were G/A heterozygotes, and 3 were A/A homozygotes. The mean C_{max} was 76.5 ng/mL for A/A, 34.0 ng/mL for G/A, and 33.5 ng/mL for G/G (Figure 2). In the analysis of haplotypes that included rs4149015, carriers possessing the *SLCO1B1**17 variant allele (rs2306283, rs4149056, and rs4149015) showed higher C_{max} and AUC_{∞} compared to noncarriers (46.1 vs 32.8 ng/mL, P=0.032 for C_{max}; 222 vs 154 ng/mL, P=0.026 for AUC_{∞}). The *SLCO1B3* c.334G>T (p.Ala112Ser, rs4149117) also influenced the C_{max} of atorvastatin. Mean C_{max} for 6 subjects with T/T (63.0 ng/mL) was higher than that in 16 with G/T (34.7 ng/mL) and 28 with G/G (31.4 ng/mL, FDR P=0.037). In genotype combination analysis of *SLCO1B1* c.-910G>A and *SLCO1B3* c.334G>T, major homozygous individuals of both polymorphisms showed the lowest mean C_{max} (30.7 ng/mL), and the C_{max} tended to increase according to the increase in the number of minor alleles (P=0.011, Figure 3); 39.3 ng/mL for 1 minor allele, 29.0 ng/mL for 2 minor alleles, 56.0 ng/mL for 3 minor alleles, and 76.5 for 4 minor alleles. *ABCC2* c.1249G>A (p.Val417Ile, rs2273697) was associated with changes in total cholesterol and LDL-C at 48 hours after atorvastatin administration. In particular, the decrease in total cholesterol and LDL-C was smaller in those with G/A (n=7) than in the 43 subjects with G/G. There was no A/A homozygote identified. The mean percentage changes in total cholesterol and LDL-C in subjects with G/A were 0.23% and −0.70%, compared to −11.9% and −17.4% for those with G/G.

Discussion

This study investigated pharmacokinetic characteristics and lipid-lowering response following high-dose atorvastatin treatment in young, healthy Korean males in association with genotypes in genes related to absorption, distribution, metabolism, and elimination of drugs.

Statins are known to produce immediate biochemical changes.[19,20] We showed that atorvastatin achieved C_{max} at around 1.07 hours. Dose-per-body weight normalized AUC_{∞} and C_{max} were comparable to the results from previous studies in Asians and Caucasians.[14] Interindividual variability of pharmacokinetic parameters was observed in spite of the uniformity of the enrolled subjects, who were all young and healthy males, and controlled conditions. This finding suggests that much of the pharmacokinetic variability is caused by innate or underlying conditions such as genetic factors and the gut microbiome, instead of controllable environmental factors such as concomitant medicines and compliance.

Table 4 Genetic polymorphisms associated with pharmacokinetic parameters and lipid-lowering response

Gene	rs no	Nucleotide change	MAF	Variable	Mean			Unit	*P*-value	FDR *P*
					A/A[a]	A/B	B/B			
SLCO1B1	rs4149015	c.-910G>A	0.177	C_{max}	33.5	34.0	76.5	ng/mL	0.021	0.040
SLCO1B3	rs4149117	c.334G>T	0.310	C_{max}	31.4	34.7	63.0	ng/mL	0.010	0.037
ABCC2	rs2273697	c.1249G>A	0.113	%ΔTC	−11.9	0.23	–	%	0.003	0.019
				%ΔLDL-C	−17.4	−0.70	–	%	0.023	0.048

Notes: [a]A/A, major homozygote; A/B, heterozygotes; B/B, minor heterozygotes.
Abbreviations: C_{max}, maximum drug concentration in plasma; FDR, false discovery rate; %ΔLDL-C, percentage change in low-density lipoprotein cholesterol from baseline to 48 hours after atorvastatin administration; MAF, minor allele frequency; %ΔTC, percentage change in total cholesterol from baseline to 48 hours after atorvastatin administration.

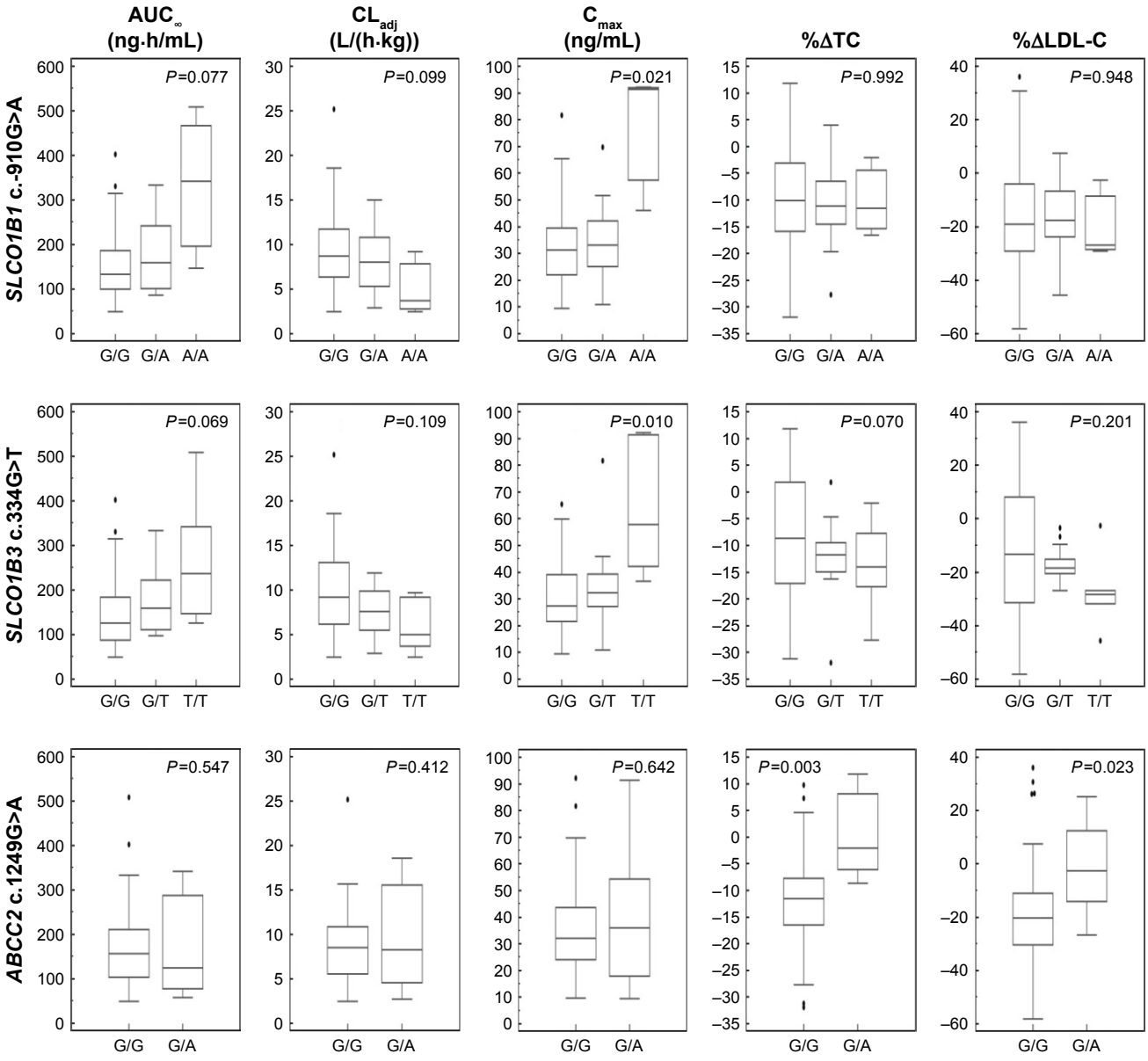

Figure 2 The pharmacodynamic and pharmacokinetic differences according to each genotype of *SLCO1B1* c.-910G>A, *SLCO1B3* c.334G>T, and *ABCC2* c.1249G>A.
Notes: The box-and-whisker plots of the area under the plasma concentration curve from hour 0 to infinity (AUC_{∞}), clearance adjusted with body weight (CL_{adj}) and maximum concentration (C_{max}) of atorvastatin, and percentage changes in total cholesterol (%ΔTC) and LDL-C (%ΔLDL-C) from baseline to 48 hours after atorvastatin administration according to genetic polymorphisms, are presented. There were differences in C_{max} according to *SLCO1B1* c.-910G >A and *SLCO1B3* c.334G>T genotypes, and %ΔTC and %ΔLDL-C between G/G and G/A genotypes of *ABCC2* c.1249G>A.

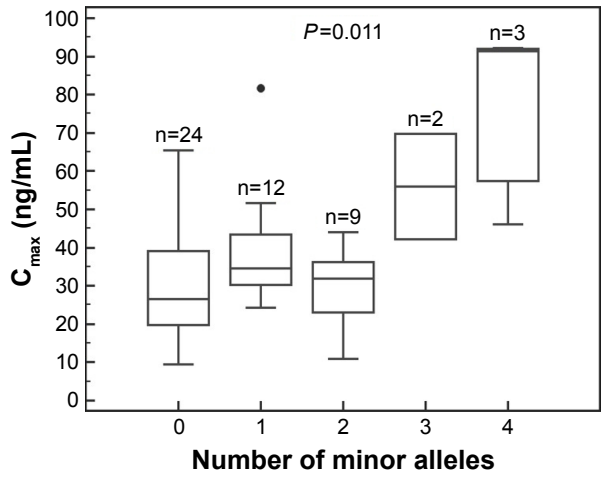

Figure 3 The maximum concentration (C_{max}) of atorvastatin according to the genotype combination of *SLCO1B1* c.-910G>A and *SLCO1B3* c.334G>T.

The lipid-lowering effect of atorvastain also showed interindividual variation. In agreement with previous studies, there were no pharmacokinetic parameters associated with the lipid-lowering effect of atorvastatin.[19,20]

Because the pharmacokinetic and pharmacodynamic changes in this study were as expected, we next inspected their association with multiple genetic polymorphisms. Polymorphisms in the *SLCO1B1*, *SLCO1B3*, and *ABCC2* genes were ordinally associated with pharmacokinetic properties or lipid-lowering responses. *SLCO1B1* c.-910G>A, identified in 17 subjects, was associated with C_{max}, and the *SLCO1B1**17 haplotype including this polymorphism was also related to C_{max} and AUC_{∞}. The S*LCO1B1* gene encodes the organic anion transporting polypeptide (OATP) 1B1, which facilitates hepatic uptake of statins on the sinusoidal membrane of hepatocytes.[21,22] Variations in *SLCO1B1*, c.-910G>A and c.521T>C (rs4149056), and haplotypes, *5, *15, and *17, have been reported to be associated with pharmacokinetic and lipid-lowering responses in previous studies.[6–8,23] In addition, a loss-of-function variation, c.521T>C, which reduced liver influx of the statins, has a potent effect on myalgia, one adverse effect of statins.[8] Similar findings have been reported in individuals who received atorvastatin, including Asians.[8,24,25]

SLCO1B3 c.334G>T was associated with a higher C_{max} in this study. The OATP 1B3 encoded by the *SLCO1B3* gene is one of the major hepatic OATPs and has a potent function as an active transporter of atorvastatin, following the OATP 1B1.[26,27] Several genetic polymorphisms in the *SLCO1B3* gene have been investigated in previous in vitro studies.[28,29] A preclinical study showed no effect of c.334G>T on cellular uptake of atorvastatin,[28] which suggests the minor effect of the *SLCO1B3* gene on the distribution of atorvastatin. As previous studies suggested the aggregate effect of top-associated polymorphisms,[30,31] we evaluated the genotype combination effect. We observed the genotype combination effect of *SLCO1B1* c.-910G>A and *SLCO1B3* c.334G>T; thus, further in vivo analysis of the role of transporter enzymes on the metabolism of statins is needed to clarify the interaction.

c.1249G>A in the *ABCC2* gene was associated with a small lipid-lowering response in this study. Multidrug resistance-associated protein 2 (MRP2/ABCC2) is an efflux transporter expressed in various types of cells, including hepatocytes, enterocytes, and proximal renal tubular cells,[32] and plays an important role in reducing gastrointestinal absorption and facilitating the biliary and urinary excretion of its substrates, including pravastatin and fluvastatin.[32–34] A polymorphism in the *ABCC2* gene has been related to low plasma concentrations of pravastatin,[33] as well as dose decreases or switches to other cholesterol-lowering agents during simvastatin and atorvastatin therapy.[35] In addition, after atorvastatin administration, mRNA levels of transporters, including MRP2/ABCC2, are downregulated and positively correlated with the percentage of reduction in LDL-C.[36] Collectively, these data indicate that the *ABCC2* gene might affect the lipid-lowering response to atorvastatin treatment.

In this prospective study, we performed a pharmacokinetic and pharmacodynamic analysis in healthy Korean individuals following high-dose atorvastatin administration. However, we should acknowledge the limitation of our study. Because of the relatively small sample size, some associations may have been missed or noticed only by chance, and also the aggregate effect of polymorphisms was partially evaluated. Our study findings should be confirmed through future large prospective studies in various ethnic populations. The strength of our study is that we provided prospective data about pharmacokinetics and the lipid-lowering response after atorvastatin 80 mg administration for a hypothesis-free genetic association study in healthy, young male Asian subjects; a population that has not been studied in this context before.[25] Our findings support the value of further studies investigating factors that affect interindividual atorvastatin treatment variability, such as genes related to pharmacodynamics, and the contribution to the risk of adverse effects of polymorphisms identified as associated with the C_{max} of atorvastatin.

Conclusion

In conclusion, we genotyped multiple polymorphisms in genes related to phase I and II drug metabolism enzymes and drug transporters, and evaluated the association of these

with pharmacokinetic properties and lipid-lowering response following atorvastatin administration. Our findings describe pharmacokinetic and pharmacodynamic changes with variations among individuals after high-dose atorvastatin treatment in healthy Korean subjects. We also identified various genetic polymorphisms related to the response to atorvastatin treatment, including the association between polymorphisms in the transporter genes, *SLCO1B1*, *SLCO1B3*, and *ABCC2*, and either C_{max} of atorvastatin or lipid-lowering response. These findings contribute to the understanding of interindividual variation in atorvastatin treatment.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Genotypes associated with atorvastatin pharmacokinetics and lipid-lowering response

Category	Gene	rs number	Nucleotide (AA) change	Call rate (%)	MAF	Major/minor allele	Associated variable	*P*-value
Phase I	*ADH6*	rs10002894	c.-931C>T	98.3	0.155	T/C	C_{max}	0.028
	ALDH2	rs671	c.1369G>A (p.Glu504Lys)	100	0.076	G/A	CL_{adj}	0.010
	ALDH3A1	rs2072330	c.741T>A (p.Pro247=)	96.6	0.342	T/A	C_{max}	0.015
	CBR1	rs1005695	c.397+210G>C	98.3	0.379	G/C	%ΔTC	0.011
							%ΔLDL-C	0.005
		rs998383	c.*559C>G	100	0.356	C/G	%ΔTC	0.011
							%ΔLDL-C	0.005
	CYP1B1	rs1056837	c.1347T>C (p.Asp449=)	100	0.127	C/T	%ΔLDL-C	0.048
	CYP2B6	rs2279344	c.822+183G>A	100	0.395	A/G	CL_{adj}	0.046
	CYP2E1	rs3813867	c.-1295G>C	100	0.234	G/C	C_{max}	0.024
		rs2031920	c.-1055C>T	100	0.218	C/T	C_{max}	0.040
	CYP4F2	rs2074900	c.1029C>T (p.His343=)	100	0.169	C/T	C_{max}	0.024
	CYP4F8	rs4239614	c.*52C>T	98.3	0.224	T/C	AUC_{∞}	0.049
							C_{max}	0.032
	CYP4F11	rs3765070	c.318T>C (p.Ile106=)	100	0.424	T/C	%ΔLDL-C	0.019
		rs1060463	c.1336G>A (p.Asp446Asn)	100	0.407	G/A	%ΔLDL-C	0.019
	CYP11B1	rs4534	c.128G>A (p.Arg43Gln)	100	0.381	G/A	AUC_{∞}	0.027
							C_{max}	0.047
							CL_{adj}	0.038
	CYP11B2	rs4536	c.873G>A (p.Ala291=)	100	0.441	A/G	AUC_{∞}	0.010
							CL_{adj}	0.010
	CYP19A1	rs700519	c.790C>T (p.Arg264Cys)	100	0.136	C/T	%ΔLDL-C	0.031
		rs4646	c.*161T>G	100	0.093	G/A	AUC_{∞}	0.010
	EPHX1	rs1051740	c.337T>C (p.Tyr113His)	100	0.373	T/C	CL_{adj}	0.012
	FMO3	rs1736557	c.769G>A (p.Val257Met)	98.3	0.129	G/A	C_{max}	0.026
		rs2266780	c.923A>G (p.Glu308Gly)	100	0.203	A/G	CL_{adj}	0.014
							%ΔTC	0.031
Phase II	*CHST10*	rs4149521	c.*39T>C	100	0.059	T/C	AUC_{∞}	0.029
							C_{max}	0.007
							%ΔTC	0.007
	CHST13	rs3856650	c.97+3926T>A	98.3	0.267	T/A	AUC_{∞}	0.019
							C_{max}	0.003
							CL_{adj}	0.043
		rs4305381	c.98-5237A>C	98.3	0.216	A/C	C_{max}	0.045
							%ΔTC	0.034
		rs1873397	c.180+2676C>G	100	0.229	G/C	C_{max}	0.007
	GSTA3	rs512795	c.272+161A>G	100	0.339	A/G	C_{max}	0.045
	GSTA4	rs367836	c.*137C>A	98.3	0.172	A/C	%ΔTC	0.010
	NAT2	rs1799931	c.857G>A (p.Gly286Glu)	100	0.144	G/A	%ΔTC	0.030
							%ΔLDL-C	0.047
	SULT1B1	rs11731028	c.376-2858G>A	100	0.220	G/A	%ΔLDL-C	0.037
	SULT1C2	rs17036104	c.796T>G (p.Ser266Ala)	96.6	0.105	T/G	AUC_{∞}	0.006
							CL_{adj}	0.007
	UGT2B4	rs1966151	c.*225T>C	94.9	0.491	T/C	AUC_{∞}	0.027
							CL_{adj}	0.040
	UGT2B15	rs3100	c.*168C>T	100	0.212	C/T	C_{max}	0.014
		rs4148271	c.*185A>T	98.3	0.181	A/T	AUC_{∞}	0.045
							C_{max}	0.007
	UGT8	rs4148254	c.677C>T (p.Pro226Leu)	100	0.085	C/T	AUC_{∞}	0.018
							CL_{adj}	0.031

(*Continued*)

Table S1 (*Continued*)

Category	Gene	rs number	Nucleotide (AA) change	Call rate (%)	MAF	Major/minor allele	Associated variable	*P*-value
Transporter	*ABCB1*	rs10276036	c.1000-44G>A	98.4	0.451	G/A	AUC_{∞}	0.040
		rs2235033	c.1554+24T>C	100	0.444	T/C	AUC_{∞}	0.028
	ABCB11	rs2287622	c.1331T>C (p.Val444Ala)	100	0.271	C/T	%ΔLDL-C	0.037
	ABCB4	rs2302387	c.175C>T (p.Leu59=)	100	0.220	C/T	C_{max}	0.029
	ABCC1	rs246221	c.825T>C (p.Val275=)	100	0.441	T/C	%ΔLDL-C	0.005
		rs4148380	c.*1293G>A	100	0.093	G/A	%ΔLDL-C	0.043
	ABCC2	rs2273697	c.1249G>A (p.Val417Ile)	100	0.113	G/A	%ΔTC	0.003
							%ΔLDL-C	0.023
	ABCG2	rs2231142	c.421C>A (p.Gln141Lys)	100	0.250	C/A	CL_{adj}	0.025
	SLC5A6	rs1395	c.1442C>T (p.Ser481Phe)	100	0.127	T/C	%ΔLDL-C	0.029
	SLC7A7	rs2281677	c.-86T>C	100	0.364	C/T	AUC_{∞}	0.029
							C_{max}	0.021
	SLC7A8	rs7141505	c.-1065G>T	98.3	0.155	T/G	C_{max}	0.034
		rs2268877	c.152-1008T>C	98.3	0.371	T/C	CL_{adj}	0.038
		rs910795	c.508+1988T>C	98.3	0.293	T/C	%ΔLDL-C	0.043
	SLC10A2	rs7987433	c.-457A>G	100	0.085	A/G	%ΔLDL-C	0.045
		rs279942	c.*373C>G	100	0.212	C/G	%ΔTC	0.041
	SLC25A27	rs9381468	c.299-1425A>G	100	0.483	G/A	%ΔTC	0.043
	SLCO1A2	rs7957203	c.61-5605T>A	100	0.271	T/A	AUC_{∞}	0.039
	SLCO1B1	rs4149015	c.-910G>A	100	0.177	G/A	C_{max}	0.021
		rs4149056	c.521T>C (p.Val174Ala)	100	0.177	T/C	C_{max}	0.023
	SLCO1B3	rs4149117	c.334G>T (p.Ala112Ser)	98.4	0.320	G/T	C_{max}	0.010
		rs7311358	c.699G>A (p.Met233Ile)	100	0.306	A/G	C_{max}	0.010
		rs2053098	c.1557A>G (p.Ala519=)	100	0.314	G/A	C_{max}	0.010
	SLCO3A1	rs2283458	c.1513-1102A>G	100	0.398	G/A	C_{max}	0.025
	SLCO4A1	rs2236553	c.797-286C>T	100	0.195	T/C	AUC_{∞}	0.010
							CL_{adj}	0.017
	SLCO5A1	rs16936279	c.*295A>C	100	0.254	A/C	C_{max}	0.030
							CL_{adj}	0.043
Others	*AHR*	rs2066853	c.1661G>A (p.Arg554Lys)	100	0.415	G/A	%ΔLDL-C	0.028
	ATP7B	rs2277448	c.-75C>A	100	0.390	A/C	C_{max}	0.031
	COMT	rs4633	c.36C>T (p.His12=)	100	0.254	C/T	%ΔTC	0.006
		rs4680	c.322G>A (p.Val108Met)	100	0.263	G/A	%ΔTC	0.007
	NR1I2	rs3814055	c.-1135C>T	98.3	0.302	C/T	AUC_{∞}	0.023
							CL_{adj}	0.022
	PGAP3	rs2952151	c.*560T>C	100	0.458	T/C	AUC_{∞}	0.010
							CL_{adj}	0.012

Abbreviations: AA, amino acid; AUC_{∞}, area under the plasma concentration curve from hour 0 to infinity; CL_{adj}, clearance adjusted with body weight; C_{max}, maximum drug concentration in plasma; %ΔLDL-C, percentage change in low-density lipoprotein cholesterol from baseline to 48 hours after atorvastatin administration; MAF, minor allele frequency; %ΔTC, percentage change in total cholesterol from baseline to 48 hours after atorvastatin administration.

Table S2 Pharmacokinetic parameters and lipid-lowering response of *SLCO1B1* c.-910G>A, *SLCO1B3* c.334G>T, and *ABCC2* c.1249G>A

Variable	Unit	Genotype			FC (95% CI)	*P*-value
***SLCO1B1* c.-910G>A**		**G/G**	**G/A**	**A/A**		
n		33	14	3		
AUC_{∞}	ng·h/mL	156±80.5[a] (51.5%) (48.9–403)	173±79.7 (46.0%) (86.2–334)	333±181 (54.4%) (147–509)	1.00 (0.77–1.31)[b] 1.89 (0.39–9.10)[c]	0.077
CL_{adj}	L/(h·kg)	9.54±4.90 (51.4%) (2.48–25.2)	8.01±3.38 (42.3%) (2.85–15.0)	5.11±3.61 (70.6%) (2.46–9.22)	0.77 (0.59–1.00) 0.46 (0.08–2.46)	0.099
C_{max}	ng/mL	33.5±16.7 (49.7%) (9.50–81.6)	34.0±14.9 (43.8%) (10.9–69.7)	76.5±26.4 (34.4%) (46.1–92.2)	0.92 (0.71–1.21) 2.18 (0.81–5.84)	0.021
%ΔTC	%	−10.0±11.6 (−117%) (−31.9 to 11.8)	−10.7±8.23 (−76.9%) (−27.7 to 4.00)	−10.1±7.36 (−73.1%) (−16.6 to −2.10)		0.992
%ΔTG	%	14.4±74.3 (518%) (−68.1 to 258)	−16.6±34.5 (−208%) (−62.5 to 34.4)	1.70±16.8 (986%) (−10.6 to 20.8)		0.659
%ΔLDL-C	%	−13.7±23.5 (−172%) (−58.2 to 36.0)	−17.6±14.5 (−82.4%) (−45.6 to 7.40)	−19.5±14.8 (−75.7%) (−29.1 to −2.50)		0.948
***SLCO1B3* c.334G>T**		**G/G**	**G/T**	**T/T**		
n		28	16	6		
AUC_{∞}	ng·h/mL	151±86.8 (57.4%) (48.9–403)	172±68.9 (40.1%) (97.6–334)	267±142 (53.2%) (126509)	1.06 (0.86–1.30)[b] 1.57 (0.91–2.72)[c]	0.069
CL_{adj}	L/(h·kg)	10.1±5.27 (52.0%) (2.48–25.2)	7.72±2.55 (33.0%) (2.85–11.9)	5.85±3.00 (51.3%) (2.46–9.74)	0.72 (0.59–0.88) 0.51 (0.29–0.90)	0.109
C_{max}	ng/mL	31.4±15.7 (49.9%) (9.50–65.4)	34.7±15.5 (44.6%) (10.9–81.6)	63.0±25.0 (39.6%) (36.6–92.2)	1.01 (0.80–1.28) 1.88 (1.21–2.87)	0.010
%ΔTC	%	−8.27±12.1 (−147%) (−31.2 to 11.8)	−12.1±6.93 (−57.1%) (−31.9 to 1.80)	−13.9±8.90 (−64.1%) (−27.7 to −2.10)		0.070
%ΔTG	%	12.5±78.3 (625%) (−68.1 to 257.5)	−0.79±43.4 (−5,470%) (−62.5 to 128)	−15.3±28.5 (−187%) (−57.7 to 20.8)		0.770
%ΔLDL-C	%	−11.4±25.9 (−227%) (−58.2 to 36.0)	−16.9±6.05 (−35.7%) (−26.8 to −3.40)	−27.3±14.0 (−51.2%) (−45.6 to −2.50)		0.201
***ABCC2* c.1249G>A**		**G/G**	**G/A**			
n		43	7			
AUC_{∞}	ng·h/mL	172±92.1 (53.6%) (48.9–509)	170±119 (69.7%) (58.2–342)		0.80 (0.42–1.53)[b]	0.547
CL_{adj}	L/(h·kg)	8.69±4.30 (49.5%) (2.46–25.2)	9.81±6.15 (62.7%) (2.71–18.6)		0.92 (0.47–1.81)	0.412
C_{max}	ng/mL	35.7±17.9 (50.3%) (9.70–92.2)	39.8±28.1 (70.6%) (9.50–91.3)		0.88 (0.43–1.81)	0.642
%ΔTC	%	−11.9±9.81 (−82.7%) (−31.9 to 9.80)	0.23±8.11 (3,549%) (−8.70 to 11.8)			0.003
%ΔTG	%	1.30±62.3 (4,789%) (−68.1 to 258)	27.2±77.0 (283%) (−62.5 to 156)			0.452
%ΔLDL-C	%	−17.4±20.3 (−117%) (−58.2 to 36.0)	−0.70±18.0 (−2,565%) (−26.6 to 25.2)			0.023

Notes: [a]Mean ± SD (CV) (range) of each variable according to genotype. [b]Fold change in heterozygotes compared to major homozygotes. [c]Fold change in minor homozygotes compared to major homozygotes.

Abbreviations: AUC_{∞}, area under the plasma concentration curve from hour 0 to infinity; CI, confidence interval; CL_{adj}, clearance adjusted with body weight; C_{max}, maximum drug concentration in plasma; CV, coefficient of variation; FC, fold change; %ΔLDL-C, percentage change in low-density lipoprotein cholesterol from baseline to 48 hours after atorvastatin administration; SD, standard deviation; %ΔTC, percentage change in total cholesterol from baseline to 48 hours after atorvastatin administration; %ΔTG, percentage change in triglycerides from baseline to 48 hours after atorvastatin administration.