PHARMACOGENETICS AND GENOMICS

Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment

Background: **Systemic exposure to rosuvastatin had been observed to be approximately 2-fold higher in Japanese subjects living in Japan compared with white subjects in Western Europe or the United States. The organic anion transporting polypeptide 1B1 contributes to the hepatic uptake of rosuvastatin. Polymorphisms in the *SLCO1B1* gene can lead to reduced transport function in vitro (T521>C). This study was conducted to determine whether the pharmacokinetic differences between Japanese and white subjects extended to other Asian ethnic groups and to determine whether polymorphisms in the *SLCO1B1* gene contribute to any pharmacokinetic differences observed.**

Methods: **Rosuvastatin pharmacokinetics was studied in an open-label, parallel-group, single–oral dose (40 mg) study in 36 white, 36 Chinese, 35 Malay, and 35 Asian-Indian subjects living in Singapore, Singapore. Plasma concentrations of rosuvastatin and metabolites were determined by HPLC–mass spectrophotometry. Two *SLCO1B1* polymorphisms (A388>G and T521>C) were genotyped.**

Results: **Ratios for rosuvastatin area under the plasma concentration–time curve from time 0 to the time of the last quantifiable concentration were 2.31, 1.91, and 1.63 and ratios for maximum plasma concentration were 2.36, 2.00, and 1.68 in Chinese, Malay, and Asian-Indian subjects, respectively, compared with white subjects. Similar increases in exposure to *N*-desmethyl rosuvastatin and rosuvastatin-lactone were observed. *SLCO1B1* genotypes did not account for the observed pharmacokinetic differences between Asians and white subjects.**

Conclusions: **Plasma exposure to rosuvastatin and its metabolites was significantly higher in Chinese, Malay, and Asian-Indian subjects compared with white subjects living in the same environment. (Clin Pharmacol Ther 2005;78:330-41.)**

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Rosuvastatin is a 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitor (statin) that has been developed for the treatment of dyslipidemia. Pharmacokinetic studies conducted in healthy white volunteers living in England or the United States and by Japanese investigators studying healthy Japanese volunteers living in Japan showed an increase of approximately 2-fold in systemic exposure to rosuvastatin in the Japanese subjects compared with the white subjects.[1-3] A population pharmacokinetic analysis showed that rosuvastatin apparent oral clearance was approximately 50% lower in Japanese subjects living in Japan than in white subjects living in Europe or the United States.[4] In

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view of these findings, we carried out a prospective study to determine whether the pharmacokinetic differences between Japanese subjects and white subjects extended to other Asian groups compared with white subjects living in the same environment.

Metabolic transformation plays a minor role in rosuvastatin clearance,[5,6] and 90% of an orally administered dose of rosuvastatin is recovered as unchanged drug primarily in the feces.[5] After intravenous administration, renal clearance and nonrenal (hepatic) clearance account for 28% and 72% of total systemic clearance, respectively.[7] The values for absolute bioavailability of rosuvastatin are 29% (AstraZeneca, data on file) and 20%[7] in Japanese subjects and white subjects, respectively. Thus ethnic differences in metabolism are unlikely to make an important contribution to the observed data.

In humans, organic anion transporting polypeptide C (OATP1B1, also known as OATP-C) is expressed in the basolateral membrane of hepatocytes and contributes to hepatic uptake of statins including rosuvastatin[8] and pravastatin.[9,10] Atorvastatin, simvastatin acid, and lovastatin acid are effective inhibitors of the uptake of pravastatin and rosuvastatin by OATP1B1 and may be substrates for this transporter.[9,11]

Several single-nucleotide polymorphisms (SNPs) in the gene encoding OATP1B1 (*SLCO1B1*) have been described.[12,13] One common SNP in *SLCO1B1*, T521>C, predicts the substitution of alanine for valine at amino acid 174 (Val174Ala). Another prevalent SNP, A388>G, affects the amino acid at position 130 (Asn130Asp). Together, these 2 SNPs define 4 *SLCO1B1* haplotypes (alleles) that code for OATP1B1 peptides containing 130Asn and 174Val (**1a* allele), 130Asp and 174Val (**1b*), 130Asn and 174Ala (**5*), and 130Asp and 174Ala (**15*).

Three in vitro studies have failed to detect a difference in substrate transport between the 2 most prevalent OATP1B1 alleles, **1a* and **1b*.[12-14] A single in vivo study showed a nonsignificant trend toward higher pravastatin exposure in **1b/*1b* and **1a/*1b* subjects.[15] Thus, to date, there is no convincing evidence that the **1b* allele has functional significance.

In contrast, 2 of 3 in vitro studies have shown reduced function of OATP1B1 alleles containing 521C; that is, the **5* and **15* alleles. Transfected HeLa cells showed reduced uptake by the **5* allele (compared with **1a*) of estrone sulfate and estradiol 17β-D-glucuronide.[12] In another study, transfected HEK293 cells showed no difference in the uptake of estrone sulfate by the **5* allele compared with the **1a* and **1b* alleles.[13] More recently, however, experiments with cultured *Xenopus* oocytes expressing OATP1B1 and use of 7-ethyl-10-hydroxycamptothecin, pravastatin, estrone sulfate, and estradiol-17β-glucuronide as substrates showed significantly reduced uptake in cells containing the **15* allele compared with the reference allele (**1a*).[14] This study also showed a nonsignificant trend toward reduced function of the **5* allele for all 4 substrates. Heterozygosity and homozygosity for 521C have also been associated with higher pravastatin plasma concentrations in vivo.[15,16]

The frequency of OATP1B1 521C (ie, the proportion of OATP1B1 alleles containing 521C) has been reported as 11% to 16% in Japanese subjects, 14% in European Americans, and 0.02% in African Americans.[12,13] Among Japanese subjects, most 521C alleles are part of a **15* haplotype.[13] An early survey of genetic variation in OATP1B1 in European Americans and African Americans did not describe the **15* allele[12]; however, it is not clear that the study distinguished persons with haplotype pair **1b/*15* from those with haplotype pair **1a/*5*. A more recent study of 41 Finnish volunteers included Bayesian haplotype estimation and identified 4 **15* alleles and 1 **5* allele.[17] Thus it is not clear from the literature whether the frequency of **15* in white subjects differs from that in Japanese subjects. If so, then genetic variation within OATP-C might be one factor contributing to pharmacokinetic differences in rosuvastatin between Japanese subjects and white subjects. Thus we genotyped subjects in this study to explore the effects of these *SLCO1B1* SNPs on any between- and within-group variation in rosuvastatin pharmacokinetics that might be observed.

METHODS

Human pharmacokinetic trial

Subjects. Subjects were healthy white, Chinese, Malay, and Asian-Indian volunteers identified from their medical history, physical examination, electrocardiogram, clinical chemical, and urinalysis findings. Race and ethnic group were self-reported by the volunteers for both parents and all 4 grandparents. For Singaporean Chinese, Malay, and Asian-Indians, the ethnic group as defined by National Registration Identity Cards provided additional confirmation of ethnicity. One hundred forty-one volunteers entered and completed the trial; all gave informed consent. There were 106 men and 35 women who participated in this study. In white subjects, gender has no significant effect on rosuvastatin pharmacokinetics; therefore no effort was made to balance the study with respect to gender.[18]

Trial design. The trial (AstraZeneca Trial 4522IL/0101) was designed and monitored in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The trial was carried out at 2 centers in Singapore, Singapore (National University Hospital and Changi General Hospital), after protocol approval by their institutional review boards. Volunteers were recruited from the Singapore metropolitan area. White subjects were required to have resided in Singapore for at least 6 months before participation in the trial. Asian subjects were permanent residents of the region.

The trial was an open-label, parallel-group, single-dose study. Volunteers fasted for 8 hours before and 4 hours after administration of a single oral 40-mg dose of rosuvastatin on day 1. They were required to refrain from strenuous exercise, smoking, caffeine-containing drinks and food, alcohol, grapefruit-containing products, and other medications.

To reduce potential dietary influences on rosuvastatin exposure, dietary histories of the subjects were assessed before entry into the study. Subjects on extreme diets such as weight reduction diets were excluded. Subjects with diets in which the percent saturated fat content was less than 10% and daily cholesterol intake was less than 300 mg were also excluded. The intent was to have all subjects on similar diets at the time of dosing. Each subject recorded his or her food intake in a diary for 3 days before rosuvastatin administration. The diet diary records were analyzed with Dietplan5 (Forestfield Software, Horsham, United Kingdom), a validated nutrition analysis software program. Dietary parameters, estimated as the mean of the 3-day evaluation, included daily caloric intake; fraction of caloric intake as protein, carbohydrate, and fat; and daily cholesterol intake.

Blood sampling. Venous blood samples (7 mL) for rosuvastatin, *N*-desmethyl rosuvastatin, and rosuvastatin-lactone assays were taken before and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 48, 72, and 96 hours after rosuvastatin administration. Samples were collected into tubes containing lithium-heparin anticoagulant and centrifuged within 30 minutes; plasma was then harvested and mixed 1:1 with sodium acetate buffer, 0.1 mol/L (pH 4.0), and stored at −70°C until assay.

Determination of plasma rosuvastatin, N-desmethyl rosuvastatin, and rosuvastatin-lactone concentrations. Plasma samples were analyzed for rosuvastatin, *N*-desmethyl rosuvastatin, and rosuvastatin-lactone by use of a method (HPLC with mass spectrometric detection) developed and validated at AstraZeneca, Wilmington, Del (data on file). A robotic liquid-handling system was used to perform the sample preparation in a 96-well format. Plasma proteins were precipitated via simple protein precipitation and filtration. Analysis of the filtrate was accomplished by multiple-reaction monitoring via positive electrospray ionization–tandem mass spectrometric detection.

The lower limit of quantitation for rosuvastatin was 0.100 ng/mL; the upper limit was 100 ng/mL but was extended by dilution. The lower limit of quantitation for *N*-desmethyl rosuvastatin and rosuvastatin-lactone was 0.250 ng/mL; the upper limit was 25.0 ng/mL.

The accuracy and precision of the analytic method were ensured on the basis of the results for spiked quality control samples, which were assayed on each day of trial analysis. For rosuvastatin, accuracy averaged 101% (7.3% relative SD [RSD]) at 0.750 ng/mL, 97.0% (3.9% RSD) at 7.5 ng/mL, and 96.1% (3.4% RSD) at 25 ng/mL. For *N*-desmethyl rosuvastatin, accuracy averaged 102% (6.5% RSD) at 0.750 ng/mL, 95.6% (4.1% RSD) at 7.50 ng/mL, and 99.3% (4.1% RSD) at 15 ng/mL. For rosuvastatin-lactone, accuracy averaged 97.1% (9.6% RSD) at 0.750 ng/mL, 98.3% (7.7% RSD) at 7.50 ng/mL, and 97.5% (8.2% RSD) at 15 ng/mL.

Pharmacokinetic evaluation. The primary pharmacokinetic parameter of this trial was the area under the plasma concentration–time curve (AUC) or, if fewer than 29 subjects per ethnic group had estimable AUC values, the AUC from time 0 to the time of the last quantifiable concentration ($AUC_{0\text{-}t}$). Other pharmacokinetic parameters included maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), and terminal elimination half-life ($t_{½}$) of rosuvastatin and $AUC_{0\text{-}t}$, C_{max}, and $t_{½}$ of *N*-desmethyl rosuvastatin and rosuvastatin-lactone. The apparent terminal half-life was calculated as $0.693/\lambda_z$, where λ_z is the terminal elimination rate constant calculated by log-linear regression of the terminal portion of the plasma concentration–time curve. $AUC_{0\text{-}t}$ was determined by use of the linear trapezoidal rule, and AUC was determined as $AUC_{0\text{-}t} + C_{last}/\lambda_z$ (where C_{last} is the last measurable plasma concentration).

Genotyping of *SLCO1B1* polymorphisms

Deoxyribonucleic acid (DNA) was extracted from blood samples by use of the QIAamp DNA Blood Maxi kit (Qiagen, Hilden, Germany). *SLCO1B1* polymorphisms A388>G and T521>C were genotyped by use of TaqMan MGB technology, marketed as Assays-by-Design (Applied Biosystems, Foster City, Calif). Applied Biosystems–designed and –synthesized primers and probes, supplied at ×40, were diluted in 1× Universal Master Mix (Applied Biosystems), to ×0.5. Primer sequences were as follows (5′-3′): N130D poly-

Table I. Demographic characteristics of volunteers

	White (n = 36)	*Chinese (n = 35)*	*Malay (n = 35)*	*Asian-Indian (n = 35)*
Body weight (kg)	75.1 (10.7)	66.6 (10.3)	62.6 (10.0)	67.7 (9.3)
Height (cm)	178.8 (7.1)	171.4 (8.0)	163.7 (7.4)	170.2 (8.3)
BMI (kg/m^2)	23.4 (2.5)	22.6 (2.9)	23.3 (2.9)	23.4 (2.7)
Age (y)	30.2 (9.0)	29.3 (9.0)	28.3 (9.2)	27.8 (8.3)
Male (No.)	31	32	17	26
Female (No.)	5	3	18	9

Data are presented as mean and SD, unless otherwise indicated.
BMI, Body mass index.

merase chain reaction (PCR) forward TTTAATTCAGTGATGTTCTTACAGTTACAGGT, PCR reverse GAGTGATAAAATTTGATTAATTAAACAAGTGGATAAGGT, FAM probe AAAGAAACTAATATCGATTCAT, and VIC probe CTAAAGAAACTAATATCAATTCAT; and V174A PCR forward AGGTTGTTTAAAGGAATCTGGGTCATAC, PCR reverse CTCCCCTATTCCACGAAGCATATT, FAM probe CCATGAACGCATATAT, and VIC probe CCCATGAACACATATAT. Two microliters of reaction mix was added to dried-down DNA (10 ng/well) in ABgene Thermofast 384-well plates (ABgene, Epsom, United Kingdom). Plates were sealed by use of an ALPS 300 sealer (ABgene) with Clear Seal Strong (ABgene) and cycled in a DT-108 Super-Duncan water bath cycler (KBiosystems, Basildon, United Kingdom). The cycling conditions were 92°C for 10 minutes (92°C for 15 seconds and 57°C for 1 minute) ×45 cycles. After PCR, FAM, VIC, and ROX fluorescence intensities were measured in an ABI 7900HT Sequence Detection System (Applied Biosystems). Cluster analysis was performed manually.

Statistical methods. Differences in diet (total daily caloric intake, daily cholesterol intake, and total fat, saturated fat, carbohydrate, and protein as a percent of total calories) were analyzed by ANOVA and results given as the least squares mean difference and 90% confidence interval (CI) between each Asian ethnic group and the white group.

Summary statistics for $AUC_{0\text{-}t}$ and C_{max} are presented as geometric means and 95% CIs. Half-life values are shown as least square means and SEs, and t_{max} values are given as mean, median, and range. Three primary comparisons of rosuvastatin $AUC_{0\text{-}t}$ were made as follows: Chinese versus white subjects, Asian-Indian versus white subjects, and Malay versus white subjects. A sample comprising 29 volunteers per ethnic group had greater than 90% power to ensure that the 90% CI for the ratio of $AUC_{0\text{-}t}$ for each of the 3 comparisons would be contained within the interval 0.7 to 1.43, with the assumption that the true underlying ratio was 1. No adjustment for multiple comparisons was made.

Rosuvastatin $AUC_{0\text{-}t}$ was log-transformed before analysis. ANOVA was used to determine geometric mean ratios and 90% CIs for each Asian group versus the white group. Rosuvastatin C_{max} and $AUC_{0\text{-}t}$ and C_{max} for *N*-desmethyl rosuvastatin and rosuvastatin-lactone were analyzed in a similar manner. Rosuvastatin and metabolite half-lives (untransformed) were analyzed by ANOVA, and results are given as the least squares mean difference and 90% CI between each Asian ethnic group and the white group.

In contrast to the pharmacokinetic analyses, all pharmacogenetic analyses were post hoc and hence exploratory. Chi-square analysis was used to test for Hardy-Weinberg equilibrium (HWE) for each SNP within each population. *SLCO1B1* haplotypes were assigned by use of an expectation maximization method as implemented in the software package SNPHAP.[19] The pharmacokinetic measurements $AUC_{0\text{-}t}$ and C_{max} of rosuvastatin were log-transformed before analysis, and summary statistics reported are the geometric means and 95% CIs. The effects of the T521>C and A388>G SNPs and of *SLCO1B1* diplotypes on log-transformed C_{max} and $AUC_{0\text{-}t}$ were examined by ANOVA. Tukey-Kramer analysis was used to locate nominally significant genotypic and diplotypic differences within each ethnic group for $\alpha = .05$.

Tolerability. Adverse event reports, medical examinations, and clinical laboratory data were assessed to evaluate tolerability.

RESULTS

Subject demographic characteristics

The demographic characteristics of the volunteers are shown in Table I. Body weight and height were greater in white subjects compared with those in each of the Asian groups. However, body mass index values were similar among the 4 groups. Substantially more

Table II. Dietary characteristics by ethnic group

	White (n = 36)	*Chinese (n = 35)*	*Malay (n = 35)*	*Asian-Indian (n = 35)*
Daily caloric intake (kcal)				
Least squares mean and SD	2732 (953)	3124 (806)	2840 (1079)	2887 (1000)
Difference*		392	108	155
90% CI		16.3 to 768	−270 to 487	−224 to 533
% Total fat†				
Least squares mean and SD	38.38 (7.37)	37.10 (5.27)	37.79 (5.38)	40.25 (9.89)
Difference*		−1.28	−0.60	1.87
90% CI		−4.10 to 1.54	−3.44 to 2.24	−0.97 to 4.71
% Saturated fat†				
Least squares mean and SD	13.44 (2.44)	12.50 (2.36)	13.12 (3.50)	12.81 (3.57)
Difference*		−0.93	−0.31	−0.62
90% CI		−2.11 to 0.24	−1.50 to 0.87	−1.81 to 0.56
% Carbohydrate†				
Least squares mean and SD	46.24 (8.82)	47.81 (5.02)	47.02 (5.72)	44.67 (8.68)
Difference*		1.57	0.78	−1.57
90% CI		−1.26 to 4.41	−2.07 to 3.64	−4.43 to 1.28
% Protein†				
Least squares mean and SD	16.71 (2.54)	16.45 (2.42)	16.51 (2.60)	15.66 (3.56)
Difference*		−0.26	−0.20	−1.05
90% CI		−1.36 to 0.84	−1.31 to 0.90	−2.15 to 0.06
Daily cholesterol intake (mg)				
Least squares mean and SD	425.8 (181.4)	488.1 (163.4)	547.2 (157.8)	475.1 (199.8)
Difference*		62.36	121.42	49.28
90% CI		−6.45 to 131.2	52.1 to 190.7	−20.0 to 118.6

CI, Confidence interval.
*Difference of Asian ethnic group compared with white subjects derived from least squares mean (ethnic group effect).
†Percent of total daily caloric intake.

men than women were enrolled in the white, Chinese, and Asian-Indian groups compared with the Malay group.

Dietary parameters

Total daily caloric intake; total fat, saturated fat, carbohydrate, and protein as a percent of total calories; and daily cholesterol intake in each of the groups are presented in Table II. Total daily caloric intake was 14% higher in the Chinese subjects compared with the white subjects. Cholesterol intake was 29% higher in the Malay subjects compared with the white subjects. No other significant differences were observed between the Asian groups and the white subjects.

Rosuvastatin pharmacokinetic parameters

The mean rosuvastatin plasma concentration–time profiles for each ethnic group are shown in Fig 1. Error bars indicating the SDs for mean plasma concentrations are shown for white subjects and Chinese subjects. SDs were similar among Malay and Asian-Indian subjects but are not shown because of the substantial overlap in variability and resulting lack of clarity in the figure. Rosuvastatin pharmacokinetic parameters are summarized by ethnic group in Table III. The table also presents the statistical comparisons for each Asian ethnic group relative to the white group.

Rosuvastatin geometric mean $AUC_{0\text{-}t}$ was 2.31-fold higher in Chinese subjects, 1.63-fold higher in Asian-Indian subjects, and 1.91-fold higher in Malay subjects compared with white subjects. These differences were all statistically significant. Geometric mean C_{max} was 2.36-fold higher in Chinese subjects, 1.68-fold higher in Asian-Indian subjects, and 2.00-fold higher in Malay subjects compared with white subjects. These differences were also statistically significant. The ANOVA model included weight as a covariate. Adjustment of the pharmacokinetic parameters by weight resulted in less than a 10% change in C_{max} or $AUC_{0\text{-}t}$ in any ethnic group. The terminal slope (λ_z) and $t_{½}$ could not be estimated in all subjects because of either the presence of multiple peaks or insufficient data (or both) in the terminal phase of the plasma concentration–time profiles. Among subjects with reliable estimates, the mean $t_{½}$ values were approximately 3 hours shorter in the Chinese and Asian-Indian groups compared with the

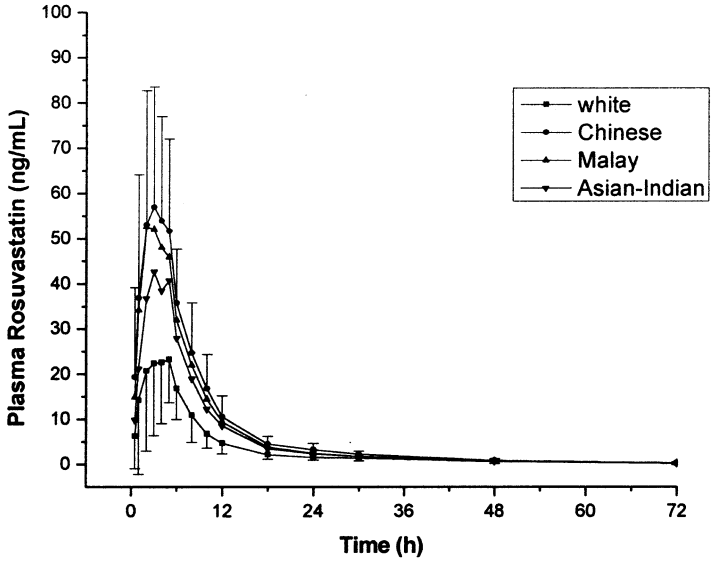

Fig 1. Plasma concentration–time profiles across white and Asian ethnic groups (arithmetic mean ± SD).

value in white subjects, but the difference did not reach statistical significance. The mean $t_{½}$ in the Malay group was similar to that of white subjects.

N-desmethyl rosuvastatin

Systemic exposure to the active metabolite of rosuvastatin mirrored the pattern observed for rosuvastatin. The mean exposure $AUC_{0\text{-}t}$ and C_{max} values (not adjusted for body weight) were highest in Chinese volunteers, followed by Malay, Asian-Indian, and white volunteers. Geometric means for $AUC_{0\text{-}t}$ in these ethnic groups were 61.2 ng · h/mL (95% CI, 50.1-74.7 ng · h/mL), 54.3 ng · h/mL (95% CI, 44.5-66.3 ng · h/mL), 45.1 ng · h/mL (95% CI, 36.6-55.5 ng · h/mL), and 28.3 ng · h/mL (95% CI, 23.2-34.5 ng · h/mL), respectively. Geometric means for C_{max} were 8.08 ng/mL (95% CI, 6.7-9.73 ng/mL), 7.48 ng/mL (95% CI, 6.21-9.01 ng/mL), 5.95 ng/mL (95% CI, 4.89-7.22 ng/mL), and 3.80 ng/mL (95% CI, 3.15-4.58 ng/mL), respectively.

The increase in exposure among Asians relative to white subjects was similar to that observed for rosuvastatin: Geometric mean ratios for $AUC_{0\text{-}t}$ were 2.17 (90% CI, 1.71-2.74), 1.92 (90% CI, 1.52-2.43), and 1.59 (90% CI, 1.25-2.03) in Chinese, Malay, and Asian-Indian subjects respectively. Geometric mean ratios for C_{max} in Asians relative to white subjects were 2.13 (90% CI, 1.70-2.65), 1.97 (90% CI, 1.58-2.45), and 1.56 (90% CI, 1.25-1.96) in Chinese, Malay, and Asian-Indian subjects, respectively.

Values for t_{max} and $t_{½}$ were similar among all 4 ethnic groups.

Rosuvastatin-lactone

Mean $AUC_{0\text{-}t}$ and C_{max} (not adjusted for body weight) for rosuvastatin-lactone were also greater in Asian subjects relative to white subjects. Geometric mean values for $AUC_{0\text{-}t}$ were 112 ng · h/mL (95% CI, 94.0-133 ng · h/mL), 99.1 ng · h/mL (95% CI, 83.4-118 ng · h/mL), 91.9 ng · h/mL (95% CI, 76.7-110 ng · h/mL), and 52.1 ng · h/mL (95% CI, 43.9-61.9 ng · h/mL) in Chinese, Malay, Asian-Indian, and white subjects, respectively. Geometric mean values for C_{max} were 7.53 ng/mL (95% CI, 6.24-9.10 ng/mL), 6.61 ng/mL (95% CI, 5.48-7.98 ng/mL), 5.32 ng/mL (95% CI, 4.37-6.49 ng/mL), and 3.14 ng/mL (95% CI, 2.60-3.79 ng/mL), respectively.

The geometric mean ratios for the relative exposure to the lactone in each Asian group relative to white subjects were 2.14 (90% CI, 1.75-2.63), 1.90 (90% CI, 1.55-2.33), and 1.76 (90% CI, 1.43-2.17) for Chinese, Malay, and Asian-Indian subjects, respectively. The geometric mean ratios for C_{max} in Asians relative to white subjects were 2.40 (90% CI, 1.92-3.00), 2.11 (90% CI, 1.68-2.63), and 1.70 (90% CI, 1.35-2.13) in Chinese, Malay, and Asian-Indian subjects, respectively.

Table III. Summary of rosuvastatin pharmacokinetic parameters (unadjusted for body weight) and statistical comparison in white, Chinese, Malay, and Asian-Indian subjects after administration of a single 40-mg dose of rosuvastatin

	Chinese	*Asian-Indian*	*Malay*	*White*	*Chinese versus white*	*Asian-Indian versus white*	*Malay versus white*
$AUC_{0\text{-}t}$ (ng · h/mL)							
n	35	35	35	36			
Geometric mean	500	353	413	216			
95% CI	428 to 583	302 to 411	354 to 482	186 to 252			
Ratio*					2.31	1.63	1.91
90% CI					1.93 to 2.77	1.36 to 1.96	1.59 to 2.29
P value					<.0001	<.0001	<.0001
C_{max} (ng/mL)							
n	35	35	35	36			
Geometric mean	59.1	42.0	50.0	25.0			
95% CI	49.8 to 70.1	35.4 to 49.9	42.2 to 59.3	21.1 to 29.6			
Ratio*					2.36	1.68	2.00
90% CI					1.93 to 2.89	1.37 to 2.05	1.64 to 2.44
P value					<.0001	<.0001	<.0001
$t_{½}$ (h)†							
n	32	31	31	26			
Least squares mean and SE	14.1 (5.08)	13.8 (4.03)	16.5 (6.96)	16.6 (6.02)			
Difference‡					−2.53	−2.86	−0.15
90% CI					−4.98 to −0.07	−5.33 to −0.39	−2.63 to 2.32
P value					.0907	.0574	.9186
t_{max} (h)§							
n	35	35	35	36			
Mean and SD	3.13 (1.31)	3.94 (1.23)	3.07 (1.20)	4.14 (1.51)			
Median	3.00	4.98	3.00	5.00			
Range	0.50 to 5.00	1.00 to 5.00	0.50 to 5.00	1.00 to 8.00			

$AUC_{0\text{-}t}$, Area under plasma concentration–time curve from time 0 to time of last quantifiable concentration; C_{max}, maximum plasma concentration; $t_{½}$, terminal elimination half-life; t_{max}, time to maximum plasma concentration.
*Ratio of Asian ethnic group to white subjects derived from geometric mean (ethnic group effect).
†Analysis performed on untransformed data.
‡Difference of Asian ethnic group compared with white subjects derived from least squares mean (ethnic group effect).
§Not analyzed for differences between ethnic groups.

Values for t_{max} were similar among the groups. Values for $t_{½}$ were significantly longer in white subjects compared with the Asian groups.

Metabolite ratios

The $AUC_{0\text{-}t}$ ratios for *N*-desmethyl rosuvastatin to rosuvastatin were 0.13, 0.12, 0.13, and 0.13 for white, Chinese, Malay, and Asian-Indian subjects, respectively. For the ratio of rosuvastatin-lactone to rosuvastatin, these values were 0.24, 0.22, 0.24, and 0.26, respectively. Similar results were obtained for C_{max}.

Results of genetic analysis

Tables IV and V present *SLCO1B1* genotype and diplotype frequencies in each of the 4 ethnic groups. The T521>C (Val174Ala) SNP deviated significantly from HWE in the white group ($P = .002$) but not in the other 3 groups. The number of white subjects homozygous for 521C (n = 5) exceeded that expected under HWE (n = 2). No 521C homozygotes were present in the Chinese, Asian-Indian, or Malay groups. Neither the A388>G (Asn130Asp) SNP nor *SLCO1B1* diplotypes showed significant deviation from HWE in any group.

Tables IV and V also show geometric means of $AUC_{0\text{-}t}$ and C_{max} in the 4 study groups according to *SLCO1B1* genotypes (T521>C and A388>G) and diplotypes. Among white subjects, there was a significant effect of T521>C genotype on $AUC_{0\text{-}t}$ ($P = .001$). $AUC_{0\text{-}t}$ was higher in 521C homozygotes (CC) than in heterozygotes (TC) and in 521T homozygotes (TT), but $AUC_{0\text{-}t}$ in heterozygotes did not differ significantly from that of 521T homozygotes (TT) (Table IV and Fig

Table IV. Rosuvastatin pharmacokinetic parameters according to *SLCO1B1* genotype

	T521>C (Val174Ala)			*A388>G (Asn130Asp)*		
	TT	*TC*	*CC*	*AA*	*AG*	*GG*
White (n = 36)						
Count	25	6	5	8	19	9
Frequency	0.69	0.17	0.14	0.22	0.53	0.25
AUC_{0-t}	192*	204†	416‡	183	207	274
	(165 to 224)	(131 to 318)	(257 to 672)	(152 to 221)	(165 to 260)	(182 to 411)
C_{max}	21.4*	23.8†	58.6‡	18.7	24.3	34.4§
	(18.2 to 25.0)	(14.1 to 38.1)	(36.8 to 93.3)	(13.9 to 25.2)	(19.1 to 31.0)	(16.7 to 52.0)
Chinese (n = 35)						
Count	29	6	0	5	13	17
Frequency	0.83	0.17	0	0.14	0.37	0.49
AUC_{0-t}	485	579		538	474	508
	(423 to 555)	(422 to 794)		(260 to 1110)	(398 to 565)	(429 to 603)
C_{max}	56.2	75.6		66.6	55.4	60.0
	(47.8 to 66.0)	(53.3 to 107)		(31.8 to 140)	(45.4 to 67.4)	(47.7 to 75.5)
Malay (n = 35)						
Count	26	9	0	0	12	23
Frequency	0.74	0.26	0	0	0.34	0.66
AUC_{0-t}	400	454			402	419
	(318 to 502)	(316 to 651)			(277 to 584)	(334 to 525)
C_{max}	48.5	54.8			53.0	48.5
	(38.0 to 61.8)	(38.9 to 77.2)			(35.2 to 79.7)	(38.6 to 61.1)
Asian-Indian (n = 35)						
Count	30	5	0	7	18	10
Frequency	0.86	0.14	0	0.20	0.51	0.29
AUC_{0-t}	348	378		322	322	442
	(288 to 421)	(245 to 582)		(256 to 404)	(249 to 417)	(307 to 636)
C_{max}	42.5	39.5		37.6	37.7	55.3
	(34.6 to 52.1)	(22.1 to 70.9)		(28.5 to 49.7)	(28.4 to 49.9)	(37.7 to 81.2)

Summary values of AUC_{0-t} and C_{max} are given as geometric mean and 95% CI calculated from log-transformed data. Differences were tested by use of an ANOVA model; where a genotypic effect was significant ($P < .05$), the Tukey-Kramer test ($\alpha = .05$) was used to identify significant pairwise differences.

*Within TT homozygotes for T521>C, the values in white subjects were lower than those in Chinese, Asian-Indian, and Malay subjects.

†Within TC heterozygotes for T521>C, the values in white subjects were lower than those in Chinese and Malay subjects.

‡Within white subjects values greater than those for T521>C genotypes TT and TC.

§Within white subjects values greater than those for A388>G genotype AA.

2). The effects of the T521>C genotype on C_{max} in white subjects was similar to that seen for AUC_{0-t} ($P < .0001$). There was a marginally significant effect of the A388>G genotype on C_{max} ($P = .0456$), with a higher mean in 388G homozygotes (GG) than in 388A homozygotes (AA).

No effect of the T521>C genotype on systemic exposure to rosuvastatin was evident in the Chinese, Malay, and Asian-Indian subjects. The A388>G genotype also showed no association with AUC_{0-t} or C_{max} in any of the Asian groups (Table IV).

In white subjects analysis of *SLCO1B1* diplotypes showed significant effects on both AUC_{0-t} and C_{max} ($P = .028$ and .002, respectively). AUC_{0-t} and C_{max} were higher among subjects with diplotype **15/*15* (which contains 2 copies of the 521C allele) than in those with wild-type diplotype **1a/*1a*.

A comparison of AUC_{0-t} in all subjects homozygous for 521T (TT) showed a significant effect of race ($P < .0001$), with a lower AUC_{0-t} in white subjects than in Chinese, Malay, and Asian-Indian subjects. There was a similar effect of race on AUC_{0-t} in subjects with the heterozygous (TC) genotype ($P = .001$), with a lower AUC_{0-t} in white heterozygotes than in Chinese and Malay heterozygotes (Fig 2). Similar results were obtained for C_{max}.

Rosuvastatin was well tolerated by all volunteers after administration of the single 40-mg dose, and clin-

Table V. Rosuvastatin pharmacokinetic parameters according to *SLCO1B1* diplotype

	Diplotype						
	**1a/*1a*	**1a/*1b*	**1b/*1b*	**1a/*15*	**1b/*15*	**15/*15*	**15/*5*
White (n = 36)							
Count	8	13	4	5	1	4	1
Frequency	0.22	0.36	0.11	0.14	0.03	0.11	0.03
$AUC_{0\text{-}t}$	183 (152 to 221)	191 (147 to 249)	216 (105 to 445)	214 (122 to 376)	159	397† (200 to 789)	499
C_{max}	18.7 (13.9 to 25.2)	22.2 (17.5 to 28.7)	23.7 (13.1 to 42.8)	23.6 (12.7 to 43.9)	24.9	54.1‡ (29.6 to 98.3)	80.9
Chinese (n = 35)							
Count	5	12	12	1	5	0	0
Frequency	0.14	0.34	0.34	0.30	0.14	0	0
$AUC_{0\text{-}t}$	538 (260 to 1110)	466 (386 to 562)	482 (391 to 594)		577 (380 to 876)	—	—
C_{max}	66.6 (31.8 to 140)	54.4 (44.0 to 67.3)	54.0 (40.7 to 71.7)	68.1	77.2 (48.9 to 122)	—	—
Malay (n = 35)							
Count	0	8	18	4	5	0	0
Frequency	0	0.23	0.51	0.11	0.14	0	0
$AUC_{0\text{-}t}$	—	427 (254 to 718)	388 (295 to 510)	357 (143 to 890)	551 (381 to 796)	—	—
C_{max}	—	58.3 (32.4 to 105)	44.7 (33.9 to 58.9	43.9 (18.7 to 103)	65.5 (44.9 to 95.5)	—	—
Asian-Indian (n = 35)							
Count	7	15	8	3	2	0	0
Frequency	0.20	0.43	0.23	0.08	0.06	0	0
$AUC_{0\text{-}t}$	322 (256 to 404)	325 (238 to 444)	425 (265 to 682)	307 (163 to 577)	516 (113 to 2370)	—	—
C_{max}	37.6 (28.5 to 49.7)	39.8 (28.5 to 55.5)	53.4 (32.4 to 88.1)	28.8 (16.9 to 49.0)	63.5 (9.95 to 405)	—	—

Summary values of $AUC_{0\text{-}t}$ and C_{max} are given as geometric mean and 95% CI calculated from log-transformed data. Differences were tested by use of an ANOVA model; where a diplotypic effect was significant ($P < .05$), the Tukey-Kramer test ($\alpha = .05$) was used to identify significant pairwise differences.

†Within white subjects values greater than those for **1a/*1a* and **1a/*1b* diplotypes.

‡Within white subjects values greater than those for **1a/*1a* diplotypes.

ically significant changes in laboratory parameters were not observed.

DISCUSSION

Plasma exposure to rosuvastatin was significantly increased in the 3 Asian groups compared with the white subjects living in the same environment for at least 6 months. The increases in $AUC_{0\text{-}t}$ were approximately 2.3-fold in Chinese subjects, 2.0-fold in Malay subjects, and 1.6-fold in Asian-Indian subjects. Body weight differences contributed less than 10% to the pharmacokinetic differences noted between the Asian ethnic groups and the white subjects.

Previous phase I studies conducted in Japanese subjects living in Japan suggested that plasma exposure in these subjects is approximately 2-fold greater compared with white subjects living in England or the United States.[1-3] A population pharmacokinetic analysis including dyslipidemic Japanese subjects living in Japan confirmed the approximate 2-fold increase in exposure in these subjects compared with dyslipidemic white subjects living in Europe and the United States.[4] The results of our study and the previously conducted studies indicate that the pharmacokinetic difference between white subjects and Asians extends across several Asian ethnic groups.

Conceivably, differences in specific dietary constituents not captured in the diaries may have contributed to the observed differences in exposure. However, the dietary intake of the Asian groups was similar to that of the white subjects in terms of total calories and fractional contribution of fat, protein, and carbohydrate to total caloric intake. Cholesterol intake was 29% higher in the Malay subjects compared with the white subjects,

but similar cholesterol intake was noted for the Chinese and Asian-Indian groups compared with the white subjects. Thus variation in these parameters cannot account for the differences in exposure observed in our study.

It is of interest to note that the relative increase in plasma concentrations of *N*-desmethyl rosuvastatin and rosuvastatin-lactone was similar to that of rosuvastatin in the Asian groups relative to the white subjects. It is also of interest that the plasma $AUC_{0\text{-}t}$ and C_{max} metabolite/parent ratios were similar across all ethnic groups for each metabolite. *N*-desmethyl rosuvastatin formation is thought to occur primarily in the liver via cytochrome P450 2C9.[5] The lactone may also be formed in the liver.[20] These observations suggest that a greater fraction of the rosuvastatin dose reaches the liver in the Asian groups compared with the white subjects and that the formation and elimination clearances of the metabolites may not differ between groups. Differences in the hepatic clearance of rosuvastatin may also play a role in racial variation in rosuvastatin exposure. Biliary excretion is likely to be the major process for the hepatic clearance of rosuvastatin, and reduced biliary clearance in Asians compared with white subjects could lead to higher systemic plasma concentrations. The identity of the biliary transporter(s) for rosuvastatin has not been defined, but studies to do so are ongoing. The absorptive mechanism for rosuvastatin is unknown, but rosuvastatin is a high-solubility, low-permeability compound (AstraZeneca, data on file) and active transport processes (both uptake and efflux in nature) are likely to be involved. Recently, the organic anion transporter OATP2B1 (OATP-B) has been shown to be expressed in the microvilli of the human small intestine.[21] Pravastatin has been shown in vitro to be a substrate for this transporter.[21,22] The role of this transporter in rosuvastatin absorption has not been established. Rosuvastatin is not a substrate for P-glycoprotein[23]; thus this intestinal transporter is unlikely to affect the absorption of rosuvastatin or account for the pharmacokinetic differences observed in this study. Further studies are required to assess whether variation in intestinal absorption underlies differences in rosuvastatin exposure in Asians compared with white subjects.

The mean renal clearance of rosuvastatin was 13.6 L/h in white volunteers after intravenous administration[7] and 11.6 L/h in Japanese subjects living in Japan (AstraZeneca, data on file). Greater than 90% of the renal clearance was a result of tubular secretion. Differences in the renal clearance of rosuvastatin between Asians and white subjects cannot explain the differences in exposure after oral administration because the kidney is responsible for only about 30% of rosuvastatin systemic clearance and the Japanese renal clearance values are approximately 85% of that of the white subjects.

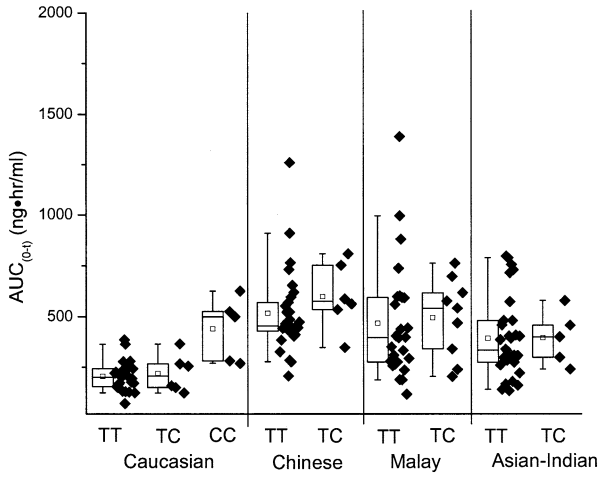

Fig 2. Rosuvastatin area under plasma concentration–time curve from time 0 to time of last quantifiable concentration ($AUC_{0\text{-}t}$) in each group according to *SLCO1B1* single-nucleotide polymorphism T521>C genotype (ie, TT, TC, and CC). For the box-whisker plots, from bottom to top, the *horizontal lines* represent the 5th, 25th, 50th, 75th, and 95th percentiles; the *square within the box* represents the arithmetic mean value.

The inclusion in our study of 5 white subjects homozygous for the *SLCO1B1* 521C allele and the associated deviation from HWE in white subjects are somewhat surprising. Other reports,[12,13] public database information (dbSNP),[24] and our own unpublished data indicate that the homozygous 521C genotype is uncommon (less than 4%) in white subjects and Japanese populations. We suspect that the disproportionate number of white 521C homozygotes in this study reflects random sampling variation. No white subject had a relative who was also enrolled, and we have not been able to identify an alternative, satisfactory explanation for biased recruitment of white subjects with this genotype.

Our observation of higher rosuvastatin exposure in the 5 white subjects with the homozygous 521C genotype compared with that in white heterozygotes and 521T homozygotes is consistent with the finding of Nishizato et al,[16] who studied the effects of *SLCO1B1* SNPs on pravastatin pharmacokinetics. The single 521C homozygote in that study showed a higher C_{max} and a lower estimated nonrenal clearance than the other subjects. In contrast, in the study of Niemi et al,[17]

pravastatin exposure in 521C homozygotes (N = 2) fell between that of TT homozygotes and TC heterozygotes.

The possibility that homozygosity for the 521C allele results in higher exposure to certain drugs, particularly those for which hepatic clearance accounts for a large proportion of systemic clearance, is biologically plausible. However, the genetic results should be interpreted cautiously because of the deviation from HWE in the white group, the small number of white 521C homozygotes, and the post hoc nature of the genetic analysis. This hypothesis could be tested in an adequately powered prospective study, with selection of subjects of known *SLCO1B1* genotype.

We found no significant effect of heterozygosity for the T521>C SNP on rosuvastatin pharmacokinetic parameters in any of the 4 groups. This finding contrasts with the results of several studies of pravastatin in which higher plasma concentrations were seen in heterozygous (TC) subjects compared with homozygotes for the 521T allele.[15-17] Our results, of course, do not exclude the possibility that a larger sample could show an effect of heterozygosity on rosuvastatin plasma concentration. It is also possible that there are significant differences in the hepatic transport of rosuvastatin and pravastatin such that rosuvastatin transport is unaffected by heterozygosity for the T521>C SNP.

Regarding the A388>G SNP, white subjects homozygous for the 388G allele had higher C_{max} but not $AUC_{0\text{-}t}$ values compared with white subjects homozygous for 388A. This influence of the A388>G SNP on C_{max}, however, was less than that described previously for the T521>C SNP, and no effect of the former SNP was seen in the Asian groups. Moreover, we did not detect a significant difference (in any of the study groups) in rosuvastatin pharmacokinetic parameters in subjects with diplotypes **1a/*1b* or **1b/*1b* compared with those with diplotype **1a/*1a*. These observations suggest that the apparent effect of the 388G SNP on rosuvastatin C_{max} in white subjects in our study reflects linkage disequilibrium between the A388>G and T521>C SNPs. This interpretation is consistent with the in vitro findings of Tirona et al,[12] which showed no functional differences between the **1b* and **1a* alleles. It contrasts, however, with the proposal of Mwinyi et al[15] that the **1b* allele is associated with "accelerated uptake" of pravastatin. Their conclusion was prompted by the observation of diminished urinary excretion, as well as a trend toward lower plasma concentrations of pravastatin in subjects with 1 or 2 copies of the **1b* allele (diplotypes **1a/*1b* or **1b/*1b*) compared with **1a/*1a* homozygotes. However, the differences were of marginal statistical significance.

Neither the T521>C nor the A388>G SNPs nor the *SLCO1B1* diplotypes that they define account for the higher rosuvastatin exposure we have observed in Chinese, Malay, and Asian-Indian subjects compared with white subjects. Whether these differences result from additional genetic influences or from environmental factors remains unclear, although the similarities in macroenvironment and in consumption of saturated fat, cholesterol, and other dietary constituents across the 4 groups provide indirect support for additional genetic effects.

The finding of increased exposure to rosuvastatin in Asian subjects relative to white subjects should be considered when rosuvastatin treatment is initiated or doses are increased in dyslipidemic Asian patients.

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