No significant effect of *ABCB1* haplotypes on the pharmacokinetics of fluvastatin, pravastatin, lovastatin, and rosuvastatin

Jenni E. Keskitalo, Kaisa J. Kurkinen, Mikko Neuvonen,
Janne T. Backman, Pertti J. Neuvonen & Mikko Niemi

Department of Clinical Pharmacology, University of Helsinki and Helsinki University Central Hospital,
Helsinki, Finland

Correspondence

Dr Mikko Niemi, MD, Department of
Clinical Pharmacology, Helsinki University
Central Hospital, PO Box 705, FI-00029
HUS, Helsinki, Finland.
Tel: +358 9 4717 3592
Fax: +358 9 4717 4039
E-mail: mikko.niemi@helsinki.fi

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- *ABCB1* genotype affects the pharmacokinetics and cholesterol-lowering effects of simvastatin and atorvastatin.
- The cholesterol-lowering effect of fluvastatin has been associated with *ABCB1* genotype, and pravastatin, lovastatin, lovastatin acid, and rosuvastatin are substrates of *ABCB1*.
- However, it is not known whether *ABCB1* genotype affects the pharmacokinetics of fluvastatin, pravastatin, lovastatin, or rosuvastatin.

WHAT THIS STUDY ADDS

- *ABCB1* c.1236C-c.2677G-c.3435C and c.1236T-c.2677T-c.3435T haplotypes have no significant effects on the pharmacokinetics of fluvastatin, pravastatin, lovastatin, or rosuvastatin.

AIMS

This study aimed to investigate possible effects of *ABCB1* genotype on fluvastatin, pravastatin, lovastatin, and rosuvastatin pharmacokinetics.

METHODS

In a fixed-order crossover study, 10 healthy volunteers with the *ABCB1* c.1236C/C-c.2677G/G-c.3435C/C (CGC/CGC) genotype and 10 with the c.1236T/T-c.2677T/T-c.3435T/T (TTT/TTT) genotype ingested a single 20-mg dose of fluvastatin, pravastatin, lovastatin, and rosuvastatin. Plasma fluvastatin, pravastatin, and lovastatin concentrations were measured up to 12 h and plasma and urine rosuvastatin concentrations up to 48 and 24 h, respectively.

RESULTS

The *ABCB1* genotype had no significant effect on the pharmacokinetics of any of the investigated statins. The geometric mean ratio (95% confidence interval) of the area under the plasma concentration–time curve from 0 h to infinity ($AUC_{0-\infty}$) in participants with the TTT/TTT genotype to that in those with the CGC/CGC genotype was 0.96 (0.77, 1.20; $P = 0.737$) for fluvastatin, 0.92 (0.53, 1.62; $P = 0.772$) for pravastatin, 0.83 (0.36, 1.90; $P = 0.644$) for lovastatin, 1.25 (0.72, 2.17; $P = 0.400$) for lovastatin acid, and 1.10 (0.73, 1.65; $P = 0.626$) for rosuvastatin. The $AUC_{0-\infty}$ of lovastatin acid correlated significantly with that of rosuvastatin ($r = 0.570$, $P = 0.009$), but none of the other $AUC_{0-\infty}$ pairs showed a significant correlation.

CONCLUSIONS

These data suggest that the *ABCB1* c.1236C-c.2677G-c.3435C and c.1236T-c.2677T-c.3435T haplotypes play no significant role in the interindividual variability in the pharmacokinetics of fluvastatin, pravastatin, lovastatin, and rosuvastatin.

Introduction

The response to statin therapy shows large variability, due to physiological, pathophysiological and environmental factors, as well as genetics [1–5]. For example, the c.1236T-c.2677T-c.3435T (TTT) haplotype of the *ABCB1* gene, encoding the ATP-binding cassette B1 (ABCB1) transporter, has been associated with increased plasma concentrations and enhanced lipid-lowering response of simvastatin (acid) and atorvastatin, compared with the c.1236C-c.2677G-c.3435C (CGC) haplotype [6–8]. The TTT and CGC haplotypes are common in Whites, with frequencies of 42.7 and 34.4%, respectively, in the Finnish population [8]. The *ABCB1* c.3435T allele has been associated with reduced expression and function of ABCB1, especially when in combination with either the c.1236T or c.2677T allele, or both [9, 10].

ABCB1 is an efflux transporter expressed in tissues with a barrier or excretory function [11]. In addition to simvastatin and atorvastatin, also rosuvastatin, pravastatin, and both parent lovastatin and lovastatin acid are substrates of ABCB1 [12–15]. It is not known whether fluvastatin is a substrate of ABCB1, but certain single nucleotide polymorphisms (SNPs) and haplotypes of *ABCB1* have been associated with the lipid-lowering effect of fluvastatin [16]. Lovastatin is administered in the inactive lactone form, which is reversibly converted into active lovastatin acid intracellularly and in the plasma [17]. Pravastatin, rosuvastatin and fluvastatin are administered in the active acid form. Lovastatin is eliminated mainly by biotransformation via CYP3A4 and fluvastatin via CYP2C9, whereas pravastatin and rosuvastatin are excreted largely in the unchanged form into bile and urine [17].

Our hypothesis was that *ABCB1* genotype affects the pharmacokinetics of fluvastatin, pravastatin, lovastatin and rosuvastatin. Therefore, we investigated the effects of the *ABCB1* c.1236C/C-c.2677G/G-c.3435C/C (CGC/CGC) and c.1236T/T-c.2677T/T-c.3435T/T (TTT/TTT) genotypes on their pharmacokinetics.

Methods

Subjects

Twenty healthy White volunteers participated in this study after giving written informed consent. The subjects had been genotyped for *ABCB1* c.1236C→T (rs1128503), c.2677G→T/A (p.Ala893Ser/Thr; rs2032582) and c.3435C→T (rs1045642) SNPs by TaqMan® allelic discrimination with an Applied Biosystems 7300 Real-Time PCR system (Applied Biosystems, Foster City, CA, USA) [18]. In addition, participants were genotyped for the *ABCB1* c.1199G→A (p.Ser400Asn; rs2229109), *CYP3A5**3 (g.6986A→G; rs776746), *CYP2C9**3 (c.1075A→C, p.Ile359Thr; rs1057910) and *SLCO1B1* c.521T→C (p.Val174Ala; rs4149056) alleles [18–21]. Only noncarriers

of the *ABCB1* c.1199A, *CYP2C9**3 and *CYP3A5* g.6986A alleles and the *SLCO1B1* c.521CC genotype were recruited.

Two women and eight men with the *ABCB1* CGC/CGC genotype (mean $\pm$ SD age 24 ± 3 years, height 179 ± 9 cm, and weight 73 ± 12 kg) and four women and six men with the TTT/TTT genotype (age 23 ± 2 years, height 174 ± 7 cm, and weight 65 ± 9 kg) participated in the study. Two CGC/CGC participants and one TTT/TTT participant had the *SLCO1B1* c.521TC genotype and the other participants had the c.521TT genotype. Each participant's health was ascertained by medical history, physical examination and laboratory tests. None was on any continuous medication and none was a tobacco smoker.

Study design

The study protocol was approved by the Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District, and the National Agency for Medicines in Finland. In a fixed-order crossover study with four phases and a wash-out period of 1 week between the phases, following an overnight fast, the subjects ingested, as a single dose, 20 mg fluvastatin (Lescol; Novartis Farmaceutica S.A., Barcelona, Spain), 20 mg pravastatin (Pravachol; Bristol-Myers Squibb, Epernon, France), 20 mg lovastatin (Lovacol; Orion Pharma, Espoo, Finland), or 20 mg rosuvastatin (Crestor; AstraZeneca GmbH, Plankstadt, Germany) with 150 ml water at 08.00 h. A standardized warm meal was served 4 h after statin ingestion and a standardized light meal after 7 and 10 h. Timed blood samples (5–10 ml each) were drawn prior to and up to 12 h after fluvastatin, pravastatin and lovastatin ingestion and up to 48 h after rosuvastatin ingestion into tubes that contained ethylenediamine tetraacetic acid. The tubes were kept on ice, and plasma was separated within 30 min and stored at -70°C until analysis. Following rosuvastatin intake, the urine was collected from 0 to 12 h and 12 to 24 h. The volume was measured and 5 ml of each fraction was stored at -70°C until analysed. Use of other drugs was prohibited for 1 week and use of grapefruit products for 3 days before statin administration.

Determination of drug concentrations

Plasma fluvastatin and plasma and urine rosuvastatin concentrations were measured using the Applied Biosystems SCIEX Q Trap LC/MS/MS system, plasma pravastatin concentrations using the SCIEX API3000 LC/MS/MS system, and plasma lovastatin and lovastatin acid concentrations using the SCIEX API2000 LC/MS/MS system (Sciex Division of MDS Inc, Toronto, Ontario, Canada) [22–26]. The limit of quantification was 0.25 ng ml^{-1} for plasma fluvastatin, 0.2 ng ml^{-1} for plasma pravastatin, 0.1 ng ml^{-1} for plasma lovastatin, lovastatin acid and rosuvastatin, and 10 ng ml^{-1} for urine rosuvastatin. The between-day coefficients of variation were $<10\%$ at relevant concentrations ($n = 3\text{--}10$).

Pharmacokinetics

Peak concentration in plasma (C_{max}), time to C_{max} (t_{max}), elimination half-life ($t_{1/2}$), and areas under the plasma

concentration–time curve from 0 to 12 h or 0 to 48 h (AUC_{0-12}), and 0 h to infinity ($AUC_{0-\infty}$) were calculated for the investigated statins [8].

Statistical analysis

The data were analysed with the statistical program SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Results are expressed as estimated marginal mean values adjusting for covariates with 95% confidence intervals (CI) (C_{max} , AUC and Ae), mean values $\pm$ SD ($t_{1/2}$, CL_R , and Figure 1), or median with range (t_{max}). The geometric mean ratio between the TTT/TTT and CGC/CGC genotype groups with 95% CI, based on the estimated marginal means, was calculated for the C_{max} and AUC values and the mean difference with 95% CI for the $t_{1/2}$ values. Logarithmically transformed C_{max} , AUC and Ae values were compared between the ABCB1 genotypes using analysis of variance (ANOVA) with body weight as a covariate for all compounds and the *SLCO1B1* c.521T→C genotype for pravastatin, lovastatin acid and rosuvastatin. The $t_{1/2}$ and CL_R data were analysed using ANOVA without covariates and the t_{max} data with the Mann–Whitney test. Correlations between the $AUC_{0-\infty}$ values of different statins were investigated with the Pearson correlation coefficient. Differences were considered statistically significant when $P < 0.05$. A post hoc power calculation indicated that the study had a power of at least 80% (α -level 5%) to detect a 40, 50, 70 and 80% larger $AUC_{0-\infty}$ of fluvastatin, rosuvastatin, lovastatin acid, and pravastatin, respectively, in individuals with the ABCB1 TTT/TTT genotype than in those with the CGC/CGC genotype.

Results

The ABCB1 genotype had no significant effect on any of the pharmacokinetic variables of any of the investigated statins (Figure 1, Table 1). The $AUC_{0-\infty}$ of fluvastatin varied 3.1-fold between individual participants, that of pravastatin 6.7-fold, that of lovastatin 14.5-fold, that of lovastatin acid 9.8-fold, and that of rosuvastatin 4.5-fold. The estimated marginal mean lovastatin acid/lactone $AUC_{0-\infty}$ ratio was 0.73 (0.45, 1.18) in individuals with the CGC/CGC genotype and 1.08 (0.66, 1.75) in those with the TTT/TTT genotype ($P = 0.258$), and varied 11.0-fold between individual subjects. The mean CL_R of rosuvastatin was 16.1 ± 3.2 l h⁻¹ in participants with the CGC/CGC genotype and 14.9 ± 3.9 l h⁻¹ in participants with the TTT/TTT genotype ($P = 0.455$). The Ae of rosuvastatin was 0.8 mg (0.6, 1.1) in participants with the CGC/CGC genotype and 0.9 mg (0.7, 1.2) in those with the TTT/TTT genotype ($P = 0.765$). The $AUC_{0-\infty}$ of lovastatin acid correlated positively with the $AUC_{0-\infty}$ of rosuvastatin ($r = 0.570$, $P = 0.009$). None of the other $AUC_{0-\infty}$ pairs showed a significant correlation.

Discussion

In the present study, the pharmacokinetics of fluvastatin, pravastatin, lovastatin and rosuvastatin were unaffected by the ABCB1 genotype. This is in contrast to simvastatin acid and atorvastatin, the AUCs of which have been modestly increased in individuals with the ABCB1 TTT/TTT genotype compared with those with the CGC/CGC genotype [8]. Thus, the ABCB1 genotype has different effects on the pharmacokinetics of different statins.

The present results do not necessarily imply that the ABCB1 transporter does not transport fluvastatin, pravastatin, lovastatin or rosuvastatin *in vivo*. In general, ABCB1 genotypes explain only a limited fraction of the overall variability in ABCB1 expression and activity, and the effects of ABCB1 haplotypes on the pharmacokinetics of ABCB1 substrates have been relatively modest [8, 9, 27]. Drugs such as ciclosporin and itraconazole, which inhibit ABCB1, have been shown to increase the plasma concentrations of many statins [17]. However, these drugs are potent inhibitors of CYP3A4 and some other transporters. For example, itraconazole raises the AUC of lovastatin more than 15-fold, but this interaction is mainly due to inhibition of CYP3A4 [28]. Itraconazole has only minor effects on the pharmacokinetics of statins that are not metabolized by CYP3A4, such as pravastatin, fluvastatin and rosuvastatin [28–30], but the slight effects seen might be due to inhibition of ABCB1 or some other transporter(s).

The present study had sufficient power to detect only a relatively large effect (between 40 and 80%) of ABCB1 genotype on the AUC of the different statins, and thus a small effect cannot be ruled out. In any case, the estimated marginal mean AUCs (adjusting for covariates) of fluvastatin, pravastatin, lovastatin acid and rosuvastatin were no more than 25% different between the TTT/TTT and CGC/CGC genotype groups. Thus, it is unlikely that possible small differences in the AUCs of the investigated statins would be of clinical importance.

To allow comparing possible effects of ABCB1 haplotypes on different statins, the four statins were given at 20-mg doses, identical to the doses of simvastatin and atorvastatin in our previous study [8]. However, statins are not equipotent at the 20-mg dose. Moreover, it is possible that the capacity of intestinal ABCB1 is saturated at the 20-mg dose of the statins investigated in the present study, diminishing possible ABCB1 genotype-related differences in their pharmacokinetics. Therefore, it cannot be ruled out that ABCB1 genotypes might have affected the pharmacokinetics of fluvastatin, pravastatin, lovastatin or rosuvastatin at a lower dose, or that ABCB1 genotypes might have affected their transmembrane passage at another site, such as the blood–brain barrier, where statin concentrations are much lower.

The AUCs of lovastatin acid and rosuvastatin (acid) showed a strong correlation. This might be due to interindividual variability in the function of a transporter shared

Figure 1

Mean $\pm$ SD plasma concentrations of fluvastatin, pravastatin, lovastatin, lovastatin acid and rosuvastatin after a single 20-mg oral dose of fluvastatin, pravastatin, lovastatin and rosuvastatin in healthy participants with the *ABCB1* c.1236C/C-c.2677G/G-c.3435C/C ($n = 10$, open circles) or *ABCB1* c.1236T/T-c.2677T/T-c.3435T/T genotype ($n = 10$, solid circles)

by lovastatin acid and rosuvastatin. Rosuvastatin is a substrate of multiple influx and efflux transporters, such as OATP1B1, OATP1B3, OATP2B1, sodium taurocholate co-transporting polypeptide, ABCC2, ABCG2 and ABCB1

[15, 31]. Lovastatin acid is a substrate of OATP1B1 and ABCB1 [13, 32]. However, in the present study the AUCs of both lovastatin acid and rosuvastatin were unaffected by *ABCB1* haplotypes and showed no significant correlation

Table 1

Pharmacokinetic variables of a single 20-mg oral dose of fluvastatin, pravastatin, lovastatin and rosuvastatin in healthy White participants with the *ABCB1* c.1236C/C-c.2677G/G-c.3435C/C (CGC/CGC; *n* = 10) or the c.1236T/T-c.2677T/T-c.3435T/T genotype (TTT/TTT; *n* = 10)

<i>ABCB1</i> genotype	<i>C</i> _{max} (ng ml ⁻¹)	<i>t</i> _{max} (h)	<i>t</i> _{1/2} (h)	<i>AUC</i> _{0–t} (ng ml ⁻¹ h)	<i>AUC</i> _{0–∞} (ng ml ⁻¹ h)
Fluvastatin					
CGC/CGC	137.2 (106.3, 177.0)	0.5 (0.5–2.0)	3.0 ± 0.9	199.5 (172.7, 230.5)	203.9 (175.1, 237.5)
TTT/TTT	124.0 (96.0, 159.9)	0.75 (0.5–1.5)	3.0 ± 1.0	192.5 (166.6, 222.4)	196.8 (168.9, 229.2)
Mean ratio/difference*	0.90 (0.62, 1.31)		0.0 (–0.9, 0.9)	0.96 (0.78, 1.19)	0.96 (0.77, 1.20)
<i>P</i> -value	0.572	0.616	0.990	0.725	0.737
Pravastatin					
CGC/CGC	24.0 (16.3, 35.3)	1.0 (1.0–1.0)	1.8 ± 0.5	51.2 (34.9, 75.0)	51.7 (35.2, 75.9)
TTT/TTT	22.1 (15.0, 32.6)	1.0 (1.0–1.5)	1.9 ± 0.5	47.5 (32.4, 69.6)	47.8 (32.6, 70.2)
Mean ratio/difference*	0.92 (0.52, 1.63)		0.1 (–0.4, 0.5)	0.93 (0.53, 1.62)	0.92 (0.53, 1.62)
<i>P</i> -value	0.768	>0.999	0.696	0.782	0.772
Lovastatin (lactone)					
CGC/CGC	1.3 (0.8, 2.2)	1.5 (0.5–7.0)	13.1 ± 11.6	8.0 (5.2, 12.2)	17.2 (9.7, 30.3)
TTT/TTT	1.4 (0.8, 2.5)	1.5 (1.0–5.0)	9.3 ± 4.7	8.0 (5.2, 12.3)	14.3 (8.1, 25.2)
Mean ratio/difference*	1.11 (0.51, 2.43)		–3.7 (–12.0, 4.5)	1.00 (0.54, 1.87)	0.83 (0.36, 1.90)
<i>P</i> -value	0.769	0.726	0.354	0.987	0.644
Lovastatin acid					
CGC/CGC	1.9 (1.3, 2.9)	4.0 (3.0–5.0)	3.1 ± 1.2	10.7 (7.4, 15.4)	12.4 (8.5, 17.8)
TTT/TTT	2.2 (1.4, 3.3)	3.5 (3.0–7.0)	4.3 ± 2.7	12.3 (8.5, 17.8)	15.5 (10.7, 22.6)
Mean ratio/difference*	1.14 (0.62, 2.08)		1.2 (–0.7, 3.1)	1.15 (0.67, 1.97)	1.25 (0.72, 2.17)
<i>P</i> -value	0.655	0.419	0.209	0.587	0.400
Rosuvastatin					
CGC/CGC	6.4 (4.7, 8.6)	5.0 (2.0–5.0)	10.9 ± 1.6	54.5 (41.2, 72.0)	56.3 (42.7, 74.4)
TTT/TTT	7.1 (5.3, 9.6)	5.0 (4.0–5.0)	13.2 ± 3.8	59.1 (44.7, 78.1)	62.0 (46.9, 81.8)
Mean ratio/difference*	1.12 (0.72, 1.73)		2.3 (–0.4, 5.0)	1.08 (0.72, 1.63)	1.10 (0.73, 1.65)
<i>P</i> -value	0.592	0.512	0.090	0.679	0.626

*These data are geometric mean ratio (95% CI) for the *C*_{max} and *AUC* values and mean difference (95% CI) for the *t*_{1/2} values. *C*_{max} and *AUC* data are estimated marginal mean (95% CI) adjusting for weight for all compounds and for the *SLCO1B1* c.521T→C genotype for pravastatin, lovastatin acid and rosuvastatin; *t*_{max} are median (range); *t*_{1/2} are mean ± SD. *C*_{max}, peak plasma concentration; *t*_{max}, time to *C*_{max}; *t*_{1/2}, elimination half-life; *AUC*_{0–t}, area under the plasma concentration–time curve from 0 h to 12 h (fluvastatin, pravastatin, lovastatin and lovastatin acid) or to 48 h (rosuvastatin); *AUC*_{0–∞}, area under the plasma concentration–time curve from 0 h to infinity.

with the *AUC* of pravastatin, a known OATP1B1 substrate [32]. Another possibility is that the correlation is caused by variability in the expression or activity of a transcription factor, such as the pregnane X receptor, which affects the expression of both drug-metabolizing enzymes and transporters [33].

As the use of statins becomes more common [34], optimizing the safety of statin therapy becomes a major issue. One way to achieve this is through genotype-guided selection of a statin and its dose [2]. The present data suggest that the investigated *ABCB1* haplotypes are unlikely to explain differences in the response to fluvastatin, pravastatin, lovastatin or rosuvastatin, unlike in the case of simvastatin and atorvastatin [8]. However, in one study with 76 patients with familial hypercholesterolaemia treated with 40 mg daily fluvastatin for 20 weeks, a certain *ABCB1* haplotype (containing the c.2677T allele) was associated with enhanced low-density lipoprotein-cholesterol-lowering response [16]. Moreover, another haplotype (containing the c.2677G allele) was associated with an enhanced triglyceride-lowering response to fluvastatin. However, it is not known whether these associations are reproducible or have a pharmacokinetic basis.

In conclusion, the common *ABCB1* haplotypes c.1236C-c.2677G-c.3435C and c.1236T-c.2677T-c.3435T have no

clinically meaningful effects on the pharmacokinetics of fluvastatin, pravastatin, lovastatin and rosuvastatin.

Competing interests

None to declare.

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