Letter to the Editors

Fexofenadine pharmacokinetics are associated with a polymorphism of the *SLCO1B1* gene (encoding OATP1B1)

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The H_1-receptor antagonist fexofenadine is a P-glycoprotein substrate [1]. However, the effects of genetic polymorphisms of the *MDR1* (*ABCB1*) gene, which codes for P-glycoprotein on the disposition of fexofenadine are unclear [2, 3]. In addition, fexofenadine is a substrate of the intestinal uptake transporters organic anion transporting polypeptide 1A2 (OATP1A2, OATP-A) and 2B1 (OATP2B1, OATP-B) [1, 4]. Fruit juices such as grapefruit, orange and apple juice may decrease the oral bioavailability of fexofenadine by inhibiting the activity of OATP1A2 [5]. There seems to be no published data on whether fexofenadine is a substrate of the hepatic uptake transporter OATP1B1 (also known as OATP-C and OATP2), encoded by *SLCO1B1*. It has been recently demonstrated that certain single-nucleotide polymorphisms (SNP) of *SLCO1B1* are associated with a decreased function of OATP1B1 *in vitro*. For example healthy carriers of the 521T > C allele [6] have an increased systemic exposure to pravastatin [7]. The aim of the present study was to characterize possible relationships between polymorphisms in the *SLCO1B1* gene and the pharmacokinetics of fexofenadine in healthy Caucasian subjects. To this end, 20 Caucasian volunteers who had previously participated in a pharmacokinetic study with fexofenadine [3] were genotyped by Taq-Man® 5′nuclease assays for the two *SLCO1B1* SNPs that were significantly associated with increased pravastatin concentrations in our previous study [7], 521T > C (Val174Ala) and for the promoter SNP −11187G > A.

Of the 20 subjects, two were homozygous and eight were heterozygous for the *SLCO1B1*521T > C SNP, the remaining 10 subjects having the reference genotype (521TT). Two subjects were heterozygous for the *SLCO1B1*−11187G > A polymorphism, and the remaining subjects had the reference (−11187GG) genotype. Both heterozygotes for the −11187G > A SNP were also heterozygous for the 521T > C SNP.

In the two subjects with the 521CC (and −11187GG) genotype, the mean total AUC of fexofenadine was 76.0% higher (P < 0.05; ANOVA followed by the Tukey test) than in the eight subjects with the 521TC genotype and 127% higher (P < 0.01) than in the 10 subjects with the 521TT genotype (Figure 1). The *SLCO1B1*521T > C polymorphism had no significant influence on the C_{max} or $t_{1/2}$ of fexofenadine. There was a trend (P = 0.13) towards a gene-dose effect regarding the influence of the 521T > C SNP on the apparent nonrenal clearance of fexofenadine. Thus, it was lowest (389 ± 185 ml min^{-1}) in subjects with the 521CC genotype, intermediate (775 ± 401 ml min^{-1}) in those with the 521TC genotype
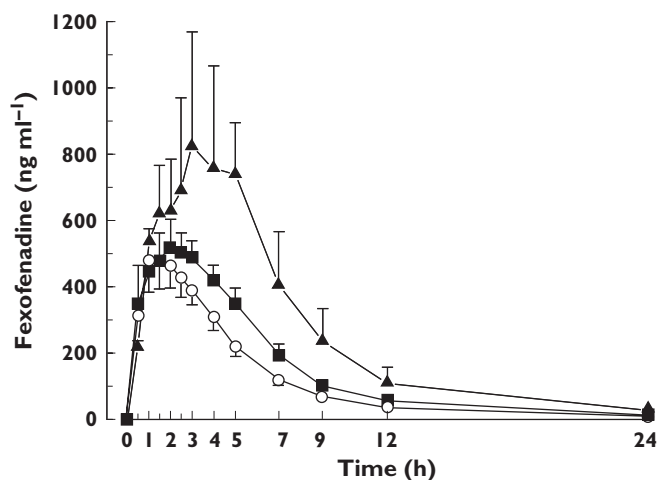
Figure 1

Mean (± SEM) plasma concentrations of fexofenadine in 20 healthy subjects with different *SLCO1B1* 521T > C genotypes after a single 180 mg oral dose of fexofenadine HCl. *SLCO1B1* 521CC subjects (n = 2) (▲); *SLCO1B1* 521TC subjects (n = 8) (■); *SLCO1B1* 521TT subjects (n = 10) (○)

and highest in those with the reference genotype (957 ± 325 ml min^{-1}).

A stepwise multiple regression analysis of data from subjects carrying the *SLCO1B1*521T > C and −11187G > A SNPs and the *MDR1*3435C > T (exon 26), 2677G > T/A (exon 21), 1236C > T (exon 12) and 61 A > G (exon 2) SNPs indicated that only the *SLCO1B1*521T > C SNP was an independent predictor of the total AUC of fexofenadine ($P < 0.01$, $r^2 = 0.347$). The *MDR1* SNPs 2677G > T and 3435C > T were assigned into haplotype pairs according to Johne *et al.* [8] and data from subjects with these haplotypes were put into a stepwise multiple regression analysis with the *SLCO1B1* SNP data. It was found that the *MDR1* haplotypes had no independent effect on the AUC of fexofenadine (haplotype 2677T/3435C was present in one subject only).

The results of this retrospective study demonstrated that the pharmacokinetics of fexofenadine were influenced by the *SLCO1B1* genotype. Fexofenadine has been previously shown to be a substrate of OATP1A2 [1] and OATP2B1 [4].

Tamai *et al.* reported that OATP1A2 was not expressed in a single sample of human small intestine as analyzed by RT-PCR [9]. However, more recently, expression of OATP1A2 in human intestine was demonstrated [10], a finding supported indirectly by the work of Dresser *et al.* [5]. These investigators showed that certain fruit juices at 5% of normal strength markedly inhibited OATP1A2 mediated fexofenadine uptake *in vitro* and that the same juices considerably decreased the oral bioavailability of fexofenadine *in vivo*. A nonsynonymous SNP associated with a markedly impaired capacity for mediating the cellular uptake of fexofenadine was recently identified within the coding region of the *SLCO1A2* gene (encoding for OATP1A2) [10]. Expression of OATP2B1 has been shown immunohistochemically at the apical membrane of human intestinal epithelial cells [11]. Known functionally significant *SLCO2B1* SNPs are rare in Caucasians [7], and *SLCO2B1* genotypes were not determined in the present study. OATP1B1 is exclusively expressed in the liver [12, 13].

That the *SLCO1B1*−11187G > A and 521T > C SNPs are associated with a higher pravastatin AUC [7] may be explained by decreased hepatic uptake of the drug, resulting in its slower elimination and lower systemic clearance. The pharmacokinetics of pravastatin and fexofenadine are similar in that these drugs do not undergo significant CYP-mediated biotransformation and are eliminated from the body unchanged mainly by biliary and urinary excretion [14, 15]. The influence of the *SLCO1B1*521T > C polymorphism on the AUC of fexofenadine suggests that the OATP1B1-mediated uptake of the drug into the liver is a prerequisite for its biliary elimination. This hypothesis is also supported by the trend towards a lower apparent nonrenal clearance of fexofenadine in subjects with the 521CC or 521TC genotype compared with those with the reference genotype.

Studies on the effect of the 3435C > T SNP in the exon 26 of *MDR1* on intestinal P-glycoprotein expression and on the disposition of P-glycoprotein substrates, including fexofenadine, have yielded conflicting results [16]. These might be partly explained by the influence of the *SLCO1B1* genotype on fexofenadine disposition [2, 3].

In conclusion, we have demonstrated that the pharmacokinetics of fexofenadine are associated with a polymorphism of the *SLCO1B1* gene (encoding OATP1B1). Further studies are required to characterize the interaction between fexofenadine and the hepatic uptake transporter OATP1B1.

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