Carbamazepine differentially affects the pharmacokinetics of fexofenadine enantiomers

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- We have shown that P-glycoprotein (P-gp) inhibitors such as itraconazole and verapamil significantly increase the plasma concentrations of fexofenadine enantiomers, and their effects are greater for (S)-fexofenadine compared with the (R)-enantiomer. These mechanisms are likely to be due to inhibition of intestinal P-gp because the $t_{1/2}$ and CL_R were constant during the study, and suggest that intestinal P-gp plays an important role in the pharmacokinetics of fexofenadine enantiomers. To date, there is no information whether the P-gp inducer carbamazepine affects the pharmacokinetics of either fexofenadine enantiomer.

WHAT THIS STUDY ADDS

- This study indicates that the stereoselectivity of fexofenadine pharmacokinetics may be influenced by carbamazepine primarily due to the induction of intestinal P-gp, and this effect may be greater for (S)-fexofenadine compared with (R)-fexofenadine. However, since the inductive effect of carbamazepine did not eliminate the difference between the pharmacokinetics of the fexofenadine enantiomers, it is likely that other transporters, including OATP2B1 and MRP2, also contribute to the stereoselective pharmacokinetics of fexofenadine.

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AIM

This aim of this study was to characterize the impact of the P-glycoprotein (P-gp) inducer, carbamazepine, on fexofenadine enantiomer pharmacokinetics.

METHODS

Twelve healthy volunteers initially received a 60 mg dose of fexofenadine alone. Subsequently, a 100 mg dose of carbamazepine was administered three times daily (300 mg day⁻¹), and on day 7, fexofenadine was co-administered.

RESULTS

Carbamazepine significantly decreased the area under the plasma concentration–time curve and the amount excreted into the urine of (S)- and (R)-fexofenadine. The P-gp inducer showed a greater effect on the pharmacokinetic parameters of (S)-fexofenadine.

CONCLUSION

This study indicates that carbamazepine may alter the pharmacokinetics of fexofenadine enantiomers.

Introduction

Fexofenadine is therapeutically administered as a racemic mixture of (R)- and (S)-enantiomers, with equal clinical efficacy attributed to both enantiomers [1]. However, previous clinical studies have demonstrated that the plasma concentration of (R)-fexofenadine in humans is about 1.5-fold higher than that of the corresponding (S)-enantiomer and indicate that the stereoselective pharmacokinetics of fexofenadine probably results from P-glycoprotein (P-gp)-mediated transport [2] because the metabolic disposition is <1% [3]. Recent *in vivo* studies have reported that P-gp inhibitors such as itraconazole and verapamil significantly increase the plasma concentrations of both enantiomers, and the effect on the P-gp-mediated transport of (S)-fexofenadine is greater in comparison with that of the (R)-enantiomer [2]. Because the peak plasma concentration (C_{max}) and the plasma concentration at the first sample point of both enantiomers were increased, these findings imply that the P-gp-mediated transport of fexofenadine may be primarily inhibited by P-gp inhibitors in the small intestine.

Although carbamazepine is known to be a potent cytochrome P450 (CYP) 3A inducer, several *in vitro* and *in vivo* reports regarding drug–drug interactions have shown that carbamazepine is also a P-gp inducer [4] that can markedly reduce plasma concentrations and the efficacy of talinolol as a P-gp substrate [5]. Therefore, if the stereoselective disposition of fexofenadine is caused by P-gp-mediated transport, carbamazepine may alter the different properties of each fexofenadine enantiomer. To date, no information is available to suggest an *in vivo* contribution of a P-gp inducer in the stereoselective effects of racemic mixtures. Therefore, the principal aim was to evaluate the possible effects of the P-gp inducer, carbamazepine, on fexofenadine enantiomer pharmacokinetics in healthy volunteers. The present results may indicate how the stereoselectivity of fexofenadine will be changed by P-gp inducers and will lead to further research concerning the chirality of racemic mixtures.

Methods

Most of the subjects included in this study had participated in our previous studies [6]. Twelve healthy Japanese volunteers (males) were enrolled in this study after giving informed written consent. Each subject was deemed physically healthy by a clinical examination. The mean ($\pm$ SD) age and body weight of the volunteers were 25.2 ($\pm$ 5.9) years and 62.4 ($\pm$ 4.1) kg, respectively. The study was approved by the Ethics Committee of the Hiroshima University School of Medicine.

This randomized, open-label study consisted of two phases (a control and a 7 day treatment period) and volunteers initially received a 60 mg dose of fexofenadine hydro-

chloride (Aventis Pharma Ltd, Tokyo, Japan) at 09.00 h after an overnight fast. In the treatment phase after a 2 week washout period, volunteers received a 100 mg dose of carbamazepine (Novartis Pharma Ltd, Tokyo, Japan) three times daily (for a total daily dose of 300 mg) for 7 days. On day 7, a single 60 mg dose of fexofenadine was co-administered with a 100 mg dose of carbamazepine at 09.00 h after an overnight fast. The order of the two phases was randomly assigned to each volunteer. Six volunteers started the control phase and the other volunteers started the treatment phase. Volunteers did not take any medication or fruit juices for 7 days before both phases.

Blood and urine samples (10 ml each) were collected during the period of 24 h after the administration of fexofenadine. Samples were stored at -20°C until they were assayed by a developed HPLC method [7].

The peak plasma concentration (C_{max}) and the time to maximal concentration (t_{max}) were obtained directly from the raw data. The area under the plasma concentration–time curve from time zero to infinity ($\text{AUC}(0,\infty)$) was calculated using $\text{AUC}(0,\text{last}) + C_{\text{last}}/\lambda_z$, wherein C_{last} was the last detectable plasma drug concentration. The elimination half-life ($t_{1/2}$) was calculated as 0.693 divided by the elimination rate constant (λ_z) of fexofenadine. The apparent oral clearance (CL/F , F : bioavailability) was obtained from the equation $\text{CL}/F = \text{Dose}/\text{AUC}$. The renal clearance (CL_R) was obtained from the following equation: $\text{CL}_R = \text{Ae}/\text{AUC}$, in which Ae was the amount of fexofenadine that was excreted into the urine.

All data were analyzed via the statistical program SPSS for Windows, version 11.5J (SPSS Inc. Chicago, IL). A P value of less than 0.05 was considered to be statistically significant.

Results

Carbamazepine co-administration significantly decreased plasma concentrations of both fexofenadine enantiomers compared with those of the enantiomers measured during the control phase (Figure 1). All pharmacokinetic parameters except for t_{max} (Table 1) were altered, and the mean $\text{AUC}(0,\infty)$ (95% CI of differences 212, 376; $P < 0.001$ for (S)-fexofenadine, 95% CI of differences 296, 484; $P < 0.001$ for (R)-fexofenadine, respectively) values of both enantiomers were significantly decreased in the carbamazepine phase.

Carbamazepine co-administration significantly decreased the mean $\text{Ae}(0,24\text{ h})$ values of both enantiomers in the carbamazepine phase (95% CI of differences 0.2, 2.1; $P < 0.05$ for (S)-fexofenadine, 95% CI of differences 0.6, 2.1; $P < 0.01$ for (R)-fexofenadine, respectively).

Discussion

We investigated the effects of the P-gp inducer carbamazepine on the pharmacokinetics of fexofenadine enanti-

Figure 1

(A) Mean (+ SE) plasma concentration–time curves of (S)-fexofenadine following a single oral administration of 60 mg fexofenadine hydrochloride in 12 healthy volunteers treated with placebo (○) or carbamazepine (●). (B) Mean (+ SE) plasma concentration–time curves of (R)-fexofenadine following a single oral administration of 60 mg fexofenadine hydrochloride in 12 healthy volunteers treated with placebo (□) or carbamazepine (■).

Table 1

Effect of carbamazepine on pharmacokinetic parameters of fexofenadine enantiomers

Parameters	With control	With carbamazepine	Ratio to control
(S)-fexofenadine			
$t_{1/2}$ (h)	3.7 (2.7, 4.7)	2.5 (2.1, 2.8)*	0.76 (0.57, 0.97)
t_{max} (h) (range)	1.5 (1.0–2.0)	1.1 (0.7–1.4)	0.81 (0.56–1.05)
C_{max} (ng ml ⁻¹)	100 (83, 118)	68 (47, 88)*	0.69 (0.49, 0.88)
AUC(0,∞) (ng ml ⁻¹ h)	481 (410, 552)	187 (153, 222)***	0.40 (0.31, 0.49)
CL/F (l h ⁻¹)	67 (56, 77)	174 (145, 202)***	2.71 (2.28, 3.13)
Ae(0,24 h) (mg)	3.6 (2.5, 4.6)	2.4 (1.8, 3.0)*	0.79 (0.54, 1.05)
CL _R (l h ⁻¹)	7.5 (5.5, 9.6)	13.6 (10.0, 17.3)**	2.20 (1.31, 3.09)
(R)-fexofenadine			
$t_{1/2}$ (h)	4.2 (3.4, 4.9)	3.3 (2.8, 3.9)†††	0.84 (0.71, 0.96)
t_{max} (h) (range)	1.4 (1.1–1.7)	1.1 (0.8–1.5)	0.80 (0.62–1.05)
C_{max} (ng ml ⁻¹)	132 (103, 161)†	85 (64, 107)**†††	0.68 (0.53, 0.82)
AUC(0,∞) (ng ml ⁻¹ h)	749 (656, 842)†††	359 (303, 415)***†††	0.49 (0.40, 0.57)
CL/F (l h ⁻¹)	42 (36, 48)†††	86 (63, 108)***†††	2.00 (1.90, 2.45)
Ae(0,24 h) (mg)	3.4 (2.5, 4.4)	2.1(1.6, 2.6)**†††	0.69 (0.47, 0.92)
CL _R (l h ⁻¹)	4.7 (3.3, 6.0)††	6.1(4.5, 7.7)†††	1.62 (0.89, 2.36)
S : R ratio of AUC	0.64 (0.60, 0.68)	0.52 (0.48, 0.57)**	0.79 (0.75, 0.90)
S : R ratio of CL_R	1.61 (1.48, 1.88)	2.24 (2.05, 2.44)***	1.41 (1.16, 1.65)

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, between control phase and carbamazepine phase. † $P < 0.05$, †† $P < 0.01$, ††† $P < 0.001$, between (S)-fexofenadine and (R)-fexofenadine. Data are shown as mean and 95% confidence interval; t_{max} data are shown as a median with a range.

omers. Similar to the results of previous reports [2], the present study demonstrated that the plasma concentration of (R)-fexofenadine was higher than the corresponding (S)-enantiomer during the control phase, and the stereoselectivity was altered by carbamazepine treatment. Carbamazepine significantly decreased the mean AUC(0,∞) of both enantiomers, but this effect was greater

for (S)-fexofenadine, resulting in a mean decrease in AUC(0,∞) S : R ratio from 0.64 to 0.52 ($P < 0.01$). Previous *in vitro* studies have suggested that P-gp plays a major role in the efflux of fexofenadine in the small intestine, whereas it has a minor role in biliary excretion [8]. Therefore, the present result may suggest that the P-gp-inductive effect of carbamazepine in the small intestine could result in a

decrease of the mean $AUC(0,\infty)$ of both enantiomers and these different effects may be due to the affinity of P-gp for each enantiomer.

Interestingly, the mean S : R ratio of $AUC(0,\infty)$ did not approach 1.0 in the carbamazepine phases, implying that a carbamazepine dose of 300 mg may be insufficient to achieve substantial inductive effects of P-gp-mediated transport. Furthermore, in the present study, although we did not measure carbamazepine concentration, an assessment of the relationship between plasma carbamazepine concentration and fexofenadine pharmacokinetics would be more informative.

Alternatively, the enantioselective disposition of fexofenadine may not be completely explained solely on the basis of chiral discrimination by P-gp, because fexofenadine is also a substrate of other drug transporters, including organic anion-transporting polypeptide (OATP) and multidrug resistance-associated protein (MRP) 2. Consequently, the present results suggest that these drug transporters might play roles in the stereoselective pharmacokinetics of fexofenadine [3]. Additionally, although carbamazepine is also known to be an MRP2 inducer [5], little is known about whether carbamazepine is a substrate or an inducer of OATPs. Therefore, the different effects of carbamazepine on the pharmacokinetics of fexofenadine enantiomers may be partially attributed to MRP2, in addition to P-gp.

On the other hand, although the $t_{1/2}$ values were not different between the (S)- and (R)-enantiomers in the control phase, there were significant differences in the $t_{1/2}$ between both enantiomers in the carbamazepine phases (Table 1). These results may be due to the combinative induction of the intestinal- and hepatic-efflux transport because the about two-thirds of bioavailable fexofenadine is estimated to be excreted into the bile and both MRP2 and P-gp are the efflux-transporters into the bile.

In our recent study, we indicated that SLCO (the gene encoding OATP) polymorphisms were strongly associated with the pharmacokinetics of fexofenadine enantiomers. The pharmacokinetics of (S)-fexofenadine are affected by a polymorphism of *SLCO2B1* [6]. Therefore, these results suggest that OATP2B1 plays an important role in (S)-fexofenadine pharmacokinetics. Our findings suggest that a combination of multiple transporters, including OATP2B1, P-gp and MRP2, may be strongly influenced by fexofenadine exposure and result in different dispositions between the enantiomers.

In conclusion, this study indicates that intestinal P-gp is a key determinant for the stereoselective pharmacokinetics

of fexofenadine, and such stereoselectivity is altered by carbamazepine, a recognized inducer of P-gp. In addition, because the inductive effect of carbamazepine did not eliminate the pharmacokinetic difference between the fexofenadine enantiomers, it is likely that other transporters, including OATP2B1 and MRP2, also contribute to the stereoselective pharmacokinetics of fexofenadine.

Competing Interests

There are no competing interests to declare.

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