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Pharmacokinetics of Fexofenadine Enantiomers in Healthy Subjects

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ABSTRACT Fexofenadine, a substrate of P-glycoprotein and an organic anion transporter polypeptide, is commonly used to assess P-glycoprotein activity in vivo. The purpose of this study was to elucidate the pharmacokinetics of each fexofenadine enantiomer. After a single oral dose of racemic fexofenadine (60 mg), the plasma and urine concentrations of fexofenadine enantiomers were measured over the course of 24 h in six healthy subjects. The mean plasma concentration of *R*(+)-fexofenadine was higher than that of *S*(−)-fexofenadine. The area under the plasma concentration-time curve ($AUC_{0-\infty}$) and the maximum plasma concentration (C_{max}) of *R*(+)-fexofenadine were significantly greater than those of the *S*(−)-enantiomer ($P = 0.0018$ and 0.0028, respectively). The *R*/*S* ratios of AUC and C_{max} of fexofenadine were 1.75 and 1.63, respectively. The oral clearance and renal clearance of *S*(−)-fexofenadine were significantly greater than that of *R*(+)-fexofenadine ($P = 0.0074$ and 0.0036). On the other hand, the stereoselective metabolism of fexofenadine using recombinant CYP3A4 was investigated; however, fexofenadine enantiomers were not metabolized by CYP3A4. Fexofenadine is transported by both P-glycoprotein and OATP and is not metabolized by intestinal CYP3A. Our findings suggest that the affinity of P-glycoprotein for *S*(−)-fexofenadine is greater than its affinity for the *R*(+)-enantiomer. Thus, P-glycoprotein is likely to have chiral discriminatory abilities. *Chirality 19:223–227, 2007.*

KEY WORDS: fexofenadine; enantiomer; P-glycoprotein; pharmacokinetics

INTRODUCTION

Fexofenadine ((±)-2-[4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)piperidino]butyl] phenyl]-2-methylpropanoic acid) is a nonsedating histamine H_1 antagonist. The contribution of fexofenadine metabolism is less than 1% to its elimination process since about 95% of this drug is excreted in both urine and feces in its original form.[1,2] Therefore, fexofenadine has been proposed as a probe drug to quantify the modulation of P-glycoprotein. In addition, fexofenadine is a substrate of the intestinal uptake transporters organic anion transporter polypeptide (OATP).[1] P-glycoprotein is a membrane efflux transporter normally expressed in human tissues, such as the small intestine, biliary canalicular front of hepatocytes, and renal proximal tubules.[3] Moreover, OATPs are also expressed in the gastrointestinal tract, liver, kidney, and blood-brain barrier, suggesting that they play an important role in drug absorption, elimination, and tissue penetration.[4]

An in vivo study reported that cytochrome P450 (CYP) 3A4 is involved in the metabolism of fexofenadine.[5] Many clinical studies on fexofenadine pharmacokinetics have been performed on the basis of several in vitro studies[1,6]; however, critical details about fexofenadine pharmacokinetics are still unknown, because the intervention of plural transporters and the slight involvement of CYP3A4 in fexofenadine pharmacokinetics make it difficult to investigate its transport mechanisms in humans. In addition until now, all clinical studies have been carried out using a racemic mixture of fexofenadine. Fexofenadine contains an asymmetric carbon in its chemical structure and is administered clinically as a racemic mixture of *R*(+)- and *S*(−)-enantiomers. To date, there has been only one clinical study on the pharmacokinetics of fexofenadine enantiomers.[7] Though the plasma concentration of *R*(+)-fexofenadine in humans is about twofold higher than that of the corresponding *S*(−)-enantiomer, the two enantiomers in human urine have been reported in almost identical ratios.[7] However, the pharmacokinetic parameters of fexofenadine enantiomers were not assessed by Robbins et al.[7] In addition, both P-glycoprotein and OATPs are able to transport fexofenadine, but the role of chirality has not been addressed.

In the present study, we carried out a clinical study to elucidate the pharmacokinetics of fexofenadine enantiomers and to understand transport mechanisms involved in the intestinal absorption and extraction of fexofenadine. Furthermore, we investigated in vitro the contribution of

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CYP3A4 to fexofenadine enantiomer metabolism and the stereoselectivity in CYP3A4-mediated metabolism of fexofenadine. The results of these studies should lead to better definition of the pharmacokinetics of racemic fexofenadine.

MATERIALS AND METHODS

Reagents and Chemicals

Fexofenadine and diphenhydramine were donated by Sanofi Aventis (Tokyo, Japan) and Tanabe Pharmaceutical Company Ltd. (Osaka, Japan), respectively. An Oasis HLB extraction cartridge was purchased from Waters (Milford, MA). All other reagents were purchased from Nacalai Tesque (Kyoto, Japan). All solvents were HPLC grade. The cofactors (nicotinamide adenine dinucleotide phosphate [$NADP^+$], glucose-6-phosphate dehydrogenase, and glucose-6-phosphate) were purchased from Sigma (St. Louis, MO, USA). Microsomes prepared from human B lymphoblastoid cells expressing human CYP3A4 were purchased from GENTEST Corporation (Woburn, MA, USA).

Subjects

Six healthy Japanese subjects (3 males and 3 females) were selected for this study. Their mean age was 21.2 ± 0.8 yr (range 20–22 yr) and their mean weight was 57.8 ± 8.4 kg (range 46–67 kg). None of the subjects had a history of significant medical illness or drug hypersensitivity. All subjects were nonsmokers. None had taken any drug for at least 1 wk before and during the study. The study protocol was approved by the Ethics Committee of Hirosaki University Hospital, and all subjects gave their written informed consent before participating.

Study Protocols

Each subject received an oral dose of 60 mg of racemic fexofenadine (Allegra®, Sanofi Aventis, Tokyo, Japan) with a glass of tap water at 9 A.M. Venous blood samples were used to determine the plasma concentration of fexofenadine enantiomers and were taken before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after ingestion of recemic fexofenadine. Urine samples were collected from 0 to 6 h, 6 to 12 h, and 12 to 24 h after ingestion. The plasma samples were subjected to centrifugation at 3000*g* immediately after the collection and stored at −80°C until analyzed. A portion of the urine sample (30 ml) was stored at −80°C until analyzed. All subjects fasted for 10 h before administration of fexofenadine and had a standard meal 4 h after ingestion of fexofenadine. Beverages containing alcohol, caffeine, tea, and fruit juice were forbidden during the test period.

Time Course of Fexofenadine Metabolism by Recombinant CYP3A4

Incubations were carried out in duplicate with recombinant CYP3A4 in 5-ml test tubes three independent times ($n = 3$) using a shaking water bath at 37°C. A typical incubation mixture consisted of a cofactor solution (100 μl), microsomal preparation (50 μl of 0.5 mg of microsomal protein), and substrate (5 μl of 4.65 μM for racemic fexofenadine) in a total volume of 0.2 ml. The cofactor solution consisted of $NADP^+$ (1.3 mM), glucose-6-phosphate (3.3 mM), glucose-6-phosphate dehydrogenase (0.4 U), and magnesium chloride (3.3 mM) in sodium phosphate buffer (0.1 M, pH 7.4). Controls for human CYP enzymes were expressed in a cell line containing control microsomes (i.e. a cell line transfected with a control vector). The metabolic reaction was initiated by the addition of the cofactor solution and terminated by immersing in an ice bath and the addition of 5.0 ml of 1.0 M sodium chloride. Before extraction, diphenhydramine (50 ng) in methanol (10 μl) was added as an internal standard to the incubation mixture.

Analysis of Fexofenadine Enantiomers in Plasma and Urine

The plasma concentration of fexofenadine enantiomers was determined according to the HPLC method of Miura et al.[8] In brief, following the addition of diphenhydramine (50 ng) in methanol (10 μl) as an internal standard to a 400 μl plasma sample, the plasma sample was diluted with 600 μl water and vortexed for 30 sec. A urine sample (100 μl) was diluted with 900 μl water after diphenhydramine (50 ng) in methanol (10 μl) was added. These mixtures were applied to an Oasis HLB extraction cartridge that had been activated previously with methanol and water (1.0 ml each). The cartridge was then washed with 1.0 ml water and 1.0 ml 40% methanol in water, and eluted with 1.0 ml 100% methanol. Eluates were evaporated to dryness in a vacuum at 40°C using a rotary evaporator (Iwaki, Tokyo, Japan). The resulting residues were then dissolved in 50 μl methanol and vortex-mixed for 30 sec; 50 μl mobile phase was added to each sample and samples were vortex-mixed for another 30 sec. An aliquot of 50 μl from each sample was then processed by HPLC. A Model 510 chromatography pump (Waters) equipped with a Waters 486 ultraviolet detector was used for HPLC analysis. The HPLC column was a Chiral CD-Ph (250 × 4.6 mm I.D., Shiseido, Tokyo, Japan). The mobile phase was 0.5% KH_2PO_4 (pH 3.5)-acetonitrile (65:35, v/v), which was degassed in an ultrasonic bath prior to use. Before mixing with acetonitrile, the pH of the 0.5% KH_2PO_4 was adjusted with 50% phosphoric acid. The flow-rate was 0.5 ml/min at ambient temperature and sample detection was carried out at 220 nm. The lower limit of quantification of this assay was 25 ng/ml for each fexofenadine enantiomer. The coefficient of variation for inter- and intra-day assays was less than 13.6% and accuracies were within 8.8% for both analytes (concentration range 25–625 ng/ml).

Pharmacokinetic Analysis

Pharmacokinetic analysis of fexofenadine enantiomers was done according to a standard non-compartmental method using WinNonlin software (Pharsight, Mountain View, CA, version 4.0.1). The terminal elimination rate constant (λ) was estimated from the least-squares regression slope of the terminal phase concentration. The terminal elimination half-life was calculated as $\ln 2/\lambda$. The total area under the observed plasma concentration-time curve (AUC) was calculated using the linear trapezoidal rule.

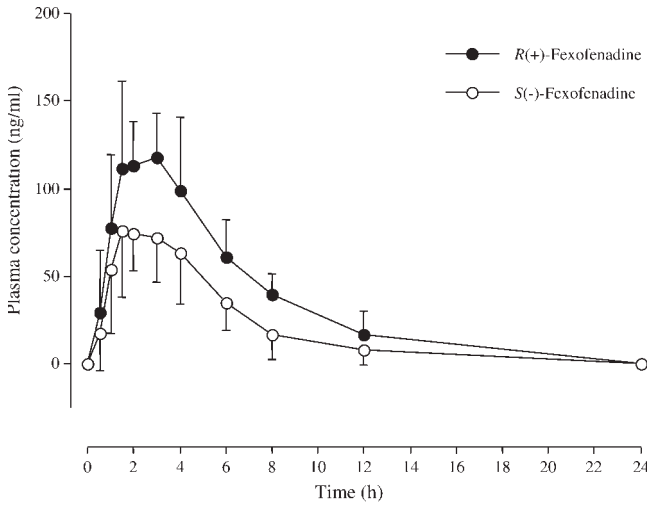

Fig. 1. Mean ± SD of the plasma concentration-time profiles of *R*(+)-fexofenadine (solid circles) and *S*(−)-fexofenadine (open circles) after a 60 mg oral dose of racemic fexofenadine.

The maximum plasma concentration (C_{max}) and time required to reach the peak (t_{max}) were directly obtained from the profile. Oral clearance (CL/F) was calculated with the equation: $CL/F = dose/AUC_{0-\infty}$. The renal clearance ($CL_R$) was calculated by $CL_R = Xu_{0-24}/AUC_{0-\infty}$, where Xu_{0-24} represents the amount of fexofenadine excreted in urine. Urinary excretion of fexofenadine is nearly completed 24 h after fexofenadine administration.[9]

Statistical Analysis

All results were expressed as the mean ± SD. Statistical comparisons of the parameters were implemented with the paired Student's *t*-test using Stat View (SAS Institute, Cary, NC, version 5.0). A *P*-value less than 0.05 was considered statistically significant.

RESULTS

In Vivo Study

The mean plasma concentration of *R*(+)-fexofenadine was higher than that of *S*(−)-fexofenadine (Fig. 1). The $AUC_{0-\infty}$ and C_{max} of (*R*)-fexofenadine were significantly greater than those of the *S*(−)-enantiomer ($P = 0.0018$ and 0.0028, respectively) (Table 1). The *R/S* ratios of AUC and C_{max} of fexofenadine were 1.75 ± 0.34 and 1.63 ± 0.56, respectively. On the other hand, the oral clearance (CL/F) of *S*(−)-fexofenadine was significantly greater than that of *R*(+)-fexofenadine ($P = 0.0074$). Although the elimination half-life of *S*(−)-fexofenadine was shorter than that of the *R*(+)-enantiomer, there were no significant differences between fexofenadine enantiomers. The *R/S* enantiomer ratio in plasma from each time point ranged from 1.42 to 1.88, whereas the *R/S* enantiomer ratio from the urinary excretion rate of fexofenadine was 0.89 ± 0.05 and 0.90 ± 0.05 at 0–6 h and 6–12 h, respectively (Fig. 2). The amount of urinary excretion of *S*(−)-fexofenadine was slightly higher than that of *R*(+)-fexofenadine (Fig. 3), but not significantly different. Renal clearance (CL_R) of *S*(−)-fexofenadine was significantly greater than that of *R*(+)-fexofenadine ($P = 0.0036$) (Table 1).

In Vitro Study with Recombinant CYP3A4

As shown in Figure 4, recombinant CYP3A4 was not involved in the metabolism of each fexofenadine enantiomer. In addition, the stereoselective metabolism of fexofenadine by CYP3A4 was not observed.

DISCUSSION

In the present study, we examined the pharmacokinetics of fexofenadine enantiomers by administering 60 mg of racemic fexofenadine. Until now, information on the pharmacokinetic parameters of fexofenadine enantiomers has been lacking. Our results showed statistically significant differences in the pharmacokinetics between *R*(+)- and *S*(−)-fexofenadine. The plasma concentration of *R*(+)-fexofenadine for all time points was higher compared with those of the corresponding *S*(−)-enantiomer. The $AUC_{0-\infty}$ and C_{max} of *R*(+)-fexofenadine were significantly greater than those of the *S*(−)-enantiomer. However, the stereoselective metabolism of fexofenadine by recombinant human CYP3A4 was not observed. Fexofenadine is transported by both P-glycoprotein and OATP and is not metabolized by intestinal CYP3A. In the present study, stereoselective absorption by transporters of fexofenadine was observed. This indicates that P-glycoprotein or OATP might have the ability for chiral discrimination. On the basis of these observations the following two hypotheses are considered: (1) The P-glycoprotein efflux for *S*(−)-fexofenadine is greater than that for the *R*(+)-enantiomer. (2) The OATP uptake for *R*(+)-fexofenadine is greater than that for the *S*(−)-enantiomer.

Similar to the results of Robbins et al.[7] our present study also showed that the urinary excretion rate of fexo-

TABLE 1. Pharmacokinetic parameters of fexofenadine enantiomers in six healthy subjects

Parameter	*R*(+)-Fexofenadine	*S*(−)-Fexofenadine	*P* value
C_{max} [ng/ml]	153 ± 17	101 ± 27	0.0028
t_{max} [h]	2.4 ± 1.1	2.4 ± 1.1	
Elimination half-life [h]	3.4 ± 0.6	2.9 ± 0.8	0.2406
$AUC_{0-\infty}$ [(ng h)/ml]	843 ± 153	496 ± 131	0.0018
CL/F [ml/(min kg)]	10.8 ± 2.9	18.7 ± 5.0	0.0074
CL_R [ml/(min kg)]	1.4 ± 0.4	2.7 ± 0.8	0.0036

Values are the mean ± SD of six subjects.

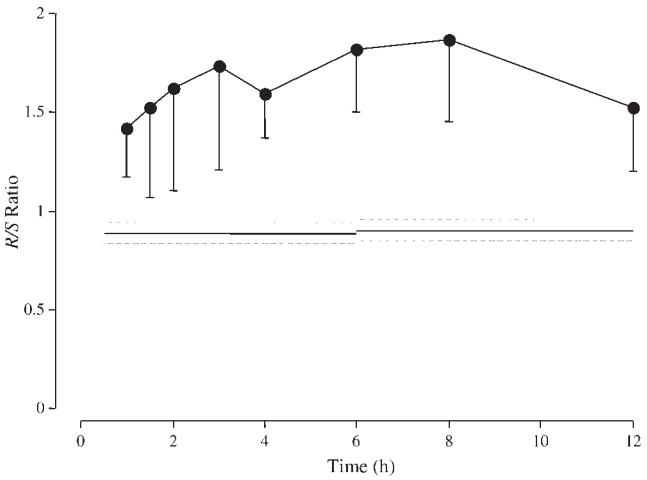

Fig. 2. Mean ± SD of the *R/S* ratios of fexofenadine plasma concentration (solid circles) and urinary excretion rate (solid lines with gray lines indicating the standard deviation) after a 60 mg oral dose of racemic fexofenadine.

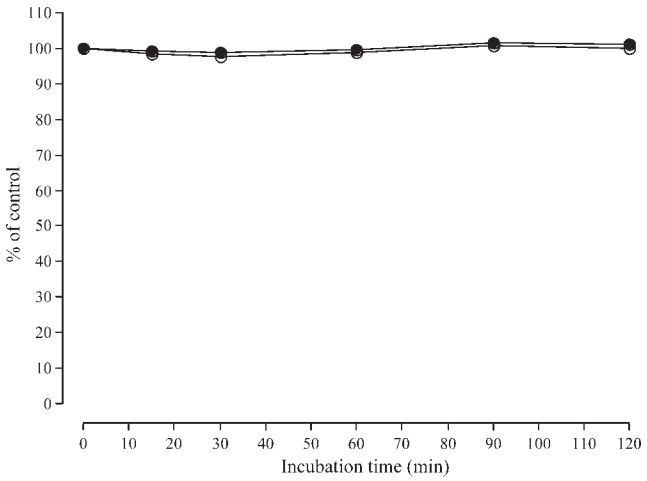

Fig. 4. Time course of *R*(+)-fexofenadine (solid circles) and *S*(−)-fexofenadine (open circles) metabolism by recombinant CYP3A4. Incubations were carried out in duplicate three separate times. Each point represents the mean ± SD of each time point (0, 15, 30, 60, 90, and 120 min).

fenadine enantiomers is similar. However, the urinary excretion rate of *S*(−)-fexofenadine in all urine collection points was higher than that of *R*(+)-fexofenadine. Accordingly, the renal clearance of *S*(−)-fexofenadine was significantly greater than that of *R*(+)-fexofenadine. In addition, the elimination half-life of *S*(−)-fexofenadine in all subjects was shorter than that of the *R*(+)-enantiomer, but not significantly (2.9 vs. 3.4 h). Hence, hypothesis 2 is negative; however, the contribution for fexofenadine of P-glycoprotein might be greater than that of OATP. If the OATP uptake for *R*(+)-fexofenadine is greater than that for the *S*(−)-enantiomer, the elimination half-life and renal clearance of *R*(+)-fexofenadine should be shorter and greater, respectively, than those of the *S*(−)-enantiomer. Yasui-Furukori et al. reported that the renal clearance of fexofenadine is decreased to 27% by probenecid, a potent inhibitor of OATP.[9] The finding suggests that fexofenadine in the kidney was inhibited by probenecid through OATP inhibition, resulting in an increased plasma concentration of fexofenadine.[9–11]

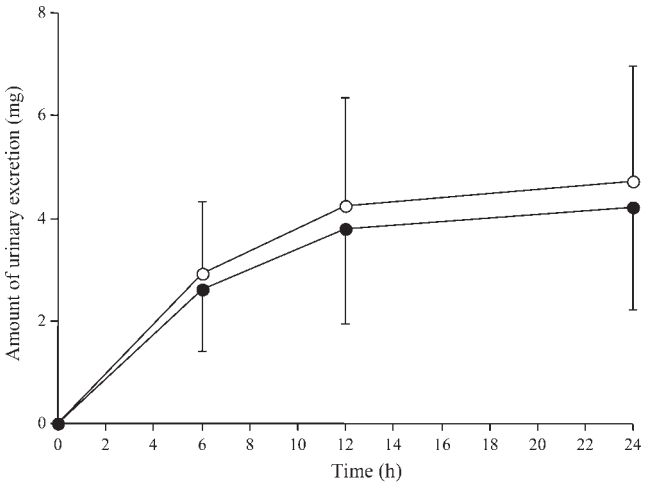

Fig. 3. Mean ± SD of the amount of urinary excretion of *R*(+)-fexofenadine (solid circles) and *S*(−)-fexofenadine (open circles) after a 60 mg oral dose of racemic fexofenadine. Time points consisted of 0, 6, 12, and 24 h after fexofenadine administration.

Our findings shows that the P-glycoprotein efflux for *S*(−)-fexofenadine in the kidney seems to be greater than that for the *R*(+)-enantiomer. Consequently, our finding suggests that the affinity of P-glycoprotein for *S*(−)-fexofenadine is likely to be greater than that for the *R*(+)-enantiomer. However, our results were not sufficient to explain the stronger affinity of P-glycoprotein for *S*(−)-fexofenadine and the stereoselective P-glycoprotein transport of fexofenadine. Because the regulation of transporters such as P-glycoprotein and OATPs is complex and the contribution of P-glycoprotein and OATPs in the small intestine or kidney is unclear. Furthermore, we did not confirm our finding using transporter inhibitors. Fruit juices such as grapefruit, orange, and apple juice decrease the oral bioavailability of fexofenadine by inhibiting the activity of OATPs.[12,13] P-glycoprotein inducers such as rifampin, troglitazone, and St. John's wort pretreatment decrease the plasma concentrations of fexefenadine.[2,14–16] Verapamil and itraconazole increase the plasma concentration of fexofenadine by inhibiting the P-glycoprotein activity.[5,9,17,18] Therefore, further studies are required to characterize the interaction between each fexofenadine enantiomer and these inducers and inhibitors.

Until now, stereoselective differences in the pharmacologic effects and safety for each fexofenadine enantiomer have not been established. Therefore, the clinical significance of our results is currently unknown. However to our knowledge, this is the first report that P-glycoprotein might have the ability of chiral discrimination. In addition, the higher affinity of P-glycoprotein for *S*(−)-fexofenadine may induce absorption in the small intestine or first-pass liver extraction and re-absorption in the kidney of *R*(+)-fexofenadine, resulting in increased plasma concentrations of *R*(+)-fexofenadine. Verapamil, a short-term inhibitor

and substrate of mainly P-glycoprotein, has also been used clinically as a racemic mixture of *R*- and *S*-enantiomers. However, (*R*)- and (*S*)-verapamil have been previously reported to equally transport by P-glycoprotein.[19–24] Therefore, these results indicate that P-glycoprotein does not discriminate between the enantiomers of chiral compounds. From the verapamil data it is impossible to draw any conclusion for fexofenadine because fexofenadine is subjected to minor metabolism differences as compared to verapamil. In addition, the exact mechanisms as to how P-glycoprotein recognizes substrates remain to be elucidated. Therefore, further studies are required to explain the stereoselective P-glycoprotein dependent transport of fexofenadine.

In conclusion, the present study indicates that the affinity of P-glycoprotein for *S*(−)-fexofenadine is likely to be greater than that for *R*(+)-enantiomer. The *R*/*S* ratio for AUC of fexofenadine at a clinical dose is 1.75. Lastly, P-glycoprotein is likely to have the ability of chiral discrimination.

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