Effects of itraconazole and diltiazem on the pharmacokinetics of fexofenadine, a substrate of P-glycoprotein

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Aims

Fexofenadine is a substrate of several drug transporters including P-glycoprotein. Our objective was to evaluate the possible effects of two P-glycoprotein inhibitors, itraconazole and diltiazem, on the pharmacokinetics of fexofenadine, a putative probe of P-glycoprotein activity *in vivo*, and compare the inhibitory effect between the two in healthy volunteers.

Methods

In a randomized three-phase crossover study, eight healthy volunteers were given oral doses of 100 mg itraconazole twice daily, 100 mg diltiazem twice daily or a placebo capsule twice daily (control) for 5 days. On the morning of day 5 each subject was given 120 mg fexofenadine, and plasma concentrations and urinary excretion of fexofenadine were measured up to 48 h after dosing.

Results

Itraconazole pretreatment significantly increased mean ($\pm$ SD) peak plasma concentration ($C_{\max}$) of fexofenadine from 699 ($\pm$ 366) ng ml⁻¹ to 1346 ($\pm$ 561) ng ml⁻¹ (95% CI of differences 253, 1040; $P < 0.005$) and the area under the plasma concentration-time curve [AUC(0, ∞)] from 4133 ($\pm$ 1776) ng ml⁻¹ h to 11287 ($\pm$ 4552) ng ml⁻¹ h (95% CI 3731, 10575; $P < 0.0001$). Elimination half-life and renal clearance in the itraconazole phase were not altered significantly compared with those in the control phase. In contrast, diltiazem pretreatment did not affect $C_{\max}$ (704 $\pm$ 316 ng ml⁻¹, 95% CI –145, 155), AUC(0, ∞) (4433 $\pm$ 1565 ng ml⁻¹ h, 95% CI –1353, 754), or other pharmacokinetic parameters of fexofenadine.

Conclusions

Although some drug transporters other than P-glycoprotein are thought to play an important role in fexofenadine pharmacokinetics, itraconazole pretreatment increased fexofenadine exposure, probably due to the reduced first-pass effect by inhibiting the P-glycoprotein activity. As diltiazem pretreatment did not alter fexofenadine pharmacokinetics, therapeutic doses of diltiazem are unlikely to affect the P-glycoprotein activity *in vivo*.

Introduction

There is growing evidence of various membrane transporters playing an important role in the absorption and disposition of many drugs and affecting their clinical effect [1, 2]. Among these transporters, the efflux transporter P-glycoprotein, the product of the human *MDR1* gene, has been particularly investigated. P-glycoprotein transports numerous structurally and therapeutically unrelated compounds, and limits intestinal absorption and tissue distribution and facilitates the excretion of many drugs [3, 4]. In *in vitro* models, P-glycoprotein has been reported to transport fexofenadine, a selective histamine H₁-receptor antagonist [5–7]. To date, fexofenadine is also known to be a substrate of several organic anion transporting polypeptide (OATP) family transporters such as OATP1A2 (OATP-A) [5], OATP1B1 (OATP-C/OATP2) [8], OATP1B3 (OATP8) [9], and OATP2B1 (OATP-B) [10], and some of them play an important role in fexofenadine pharmacokinetics. Food components decreased its oral bioavailability, probably due to inhibition of OATP1A2 activity [11, 12]. Subjects with the 521CC genotype in the *SLCO1B1* gene encoding OATP1B1 had higher fexofenadine AUC than those with other genotypes [8]. In spite of these findings, the co-administration of drugs such as azithromycin [13], rifampicin [14] and verapamil [15], which modify the P-glycoprotein activity *in vivo*, has been reported to alter the absorption and disposition of fexofenadine, and P-glycoprotein is considered to be an important determinant of fexofenadine pharmacokinetics [16, 17].

Itraconazole, an antifungal azole, inhibits the activity of P-glycoprotein as well as CYP3A in *in vitro* models [18], and the co-administration of itraconazole reduces the clearance of P-glycoprotein substrates such as digoxin [19], celiprolol [20] and quinidine [21] in volunteer studies. Therefore, a possible effect of itraconazole on fexofenadine pharmacokinetics can be expected. Diltiazem, a calcium channel antagonist, is also known to inhibit the *in vitro* activity of CYP3A [22] and P-glycoprotein [23], and co-administration of diltiazem affects the pharmacokinetics of many drugs [24, 25]. As the majority of affected drugs are substrates of both CYP3A and P-glycoprotein, it is difficult to say whether CYP3A or P-glycoprotein is mainly involved in the pharmacokinetic interaction induced by diltiazem. If comparing the effect on fexofenadine pharmacokinetics between itraconazole and diltiazem in the same subjects, relative potency of the inhibitory effect of diltiazem on the *in vivo* activity of P-glycoprotein would be evaluated.

In this study with healthy volunteers, we used fexofenadine as a putative probe of P-glycoprotein activity

in vivo. The aim was to evaluate the possible effects of the P-glycoprotein inhibitors, itraconazole and diltiazem, on the pharmacokinetics of fexofenadine and compare the effects between these two inhibitors in humans.

Methods

Subjects

This study was designed to have 80% power at the 5% significance level to detect a minimum 75% difference in fexofenadine AUC(0, ∞) between three phases because our previous study showed that the co-administration of verapamil increased fexofenadine AUC(0, ∞) by about 150% [15], assuming a sample size of seven subjects. Nine healthy Japanese volunteers (seven men and two women) were enrolled in this study after giving written informed consent. Each subject was physically normal and had no history of significant medical illness or hypersensitivity to any drugs and his/her biochemistry and haematology values were within normal limits. After the first phase was finished, one male volunteer withdrew from the study for personal reasons. The data from the eight volunteers were subjected to statistical analysis. The mean (± SD) values of age and body weight of the eight volunteers were 22.8 (± 1.4) years (range 21–25 years) and 57.1 (± 7.7) kg (range 46–65 kg), respectively. This study was approved by the Ethics Committee of Hirosaki University School of Medicine.

Study design

A randomized, open-label, Latin-square study design with three phases was used at intervals of 2 weeks. In each phase, the volunteers received one of three pretreatment drugs in a randomized order, a 100 mg slow-release diltiazem capsule (Nichi-iko Pharmaceutical Co. Ltd, Toyama, Japan), two 50 mg itraconazole capsules (Janssen Pharmaceutical K.K., Tokyo, Japan), or a placebo capsule orally twice daily for 5 days. On the 5th day, after we checked the number of remaining pretreatment capsules, the volunteers received, after an overnight fast, two 60 mg fexofenadine hydrochloride tablets (Aventis Pharma Ltd, Tokyo, Japan) with the pretreatment drug at 09.00 h with 250 ml water. In our previous study [15], AUC(0,24 h) and cumulative urinary amount of fexofenadine from 0–24 h accounted for 95.6% (95% CI 94.3, 96.9) and 94.9% (95% CI 93.4, 96.5) of AUC(0,48 h) and urinary amount from 0 to 48 h, respectively, and therefore the last dose of the pretreatment was administered at 21.00 h on day 5. The volunteers did not take any medication or fruit juice for at least 7 days before the

study, and no meals or beverages were allowed until 3 h after administration.

Plasma and urine collections and determination of fexofenadine

Blood samples (10 ml each) were drawn into heparinized tubes before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and 48 h after administration of fexofenadine, and plasma was separated immediately. The urine was collected cumulatively from 0 to 48 h in fractions from 0–4 h, 4–8 h, 8–12 h, 12–24 h, 24–36 h and 36–48 h. The plasma and urine samples were stored at -20°C until assayed. Plasma and urine concentrations of fexofenadine were determined by the HPLC method developed in our laboratory [26]. In brief, 10 μl (100 ng) of diphenhydramine as an internal standard and 1 ml of 0.2 M acetate buffer (pH 4.0) were added to 1 ml of plasma or urine. Samples were purified with C18 minicolumns (BondElute C18, 500 mg packing in 3 ml cartridge, Varian, Palo Alto, California, USA), and fexofenadine and the internal standard were eluted in 1 ml methanol. After the eluates were evaporated with air, the residues were dissolved with a HPLC mobile phase. The HPLC system consisted of two LC-10AD pumps, a SIL-10 A autoinjector, an Inertsil DS-80 A column (4.6×150 mm i.d., particle size 5 μm , GL Science Inc., Tokyo, Japan), a RF-10AXL fluorescence detector monitored at an excitation wavelength of 220 nm and an emission wavelength of 290 nm, and a CLASS-VP integrator (Shimadzu Co., Kyoto, Japan). The flow rate was 1.0 ml min^{-1} and the column was maintained at 50°C . The between-day coefficients of variation (CV) and relative errors were 8.0% and 4.3% at 5 ng ml^{-1} ($n = 5$), 1.3% and -2.7% at 50 ng ml^{-1} ($n = 5$), and 2.2% and -0.5% at 500 ng ml^{-1} ($n = 5$), respectively. The limit of quantification was 1.0 ng ml^{-1} . Plasma and urine samples from the diltiazem or itraconazole phases did not have any interfering peak for the fexofenadine assay.

Pharmacokinetic data analysis

The maximum plasma concentration (C_{max}) and the time to reach C_{max} (t_{max}) of fexofenadine were determined directly from the observed data. The elimination rate constant (λ_z) was obtained by linear regression analysis by use of at least three sampling points of the terminal log-linear declining phase to the last measurable concentration. The elimination half-life ($t_{1/2}$) was determined from the equation $t_{1/2} = \ln 2 / \lambda_z$. The area under the plasma concentration-time curve was calculated by the trapezoidal rule from 0 h to the last sampling point of plasma fexofenadine concentration

detected [$\text{AUC}(0, t)$] and then extrapolated to infinity using (λ_z [$\text{AUC}(0, \infty)$]). The apparent oral clearance (CL/F) was obtained from the equation $\text{CL}/F = \text{Dose}/\text{AUC}(0, \infty)/\text{kg}$ and the apparent volume of distribution (V/F) was calculated from the equation $V/F = \text{CL}/F/\lambda_z$. The renal clearance (CL_r) was obtained from the equation $\text{CL}_r = \text{Ae}/\text{AUC}(0, t)$, in which Ae is the amount of fexofenadine excreted into the urine within 48 h.

Statistical analysis

The results are expressed as mean $\pm$ SD. Repeated-measures ANOVA was used for statistical differences in the mean pharmacokinetic parameters between the three phases of control, diltiazem and itraconazole, and the Bonferroni test was used for *post hoc* comparison. The cumulative amount of fexofenadine excreted into the urine was compared by two-way ANOVA (treatment $\times$ time), and the Bonferroni test was used for *post hoc* comparison. All data were analysed with the statistical program SPSS for Windows, version 11.5 J (SPSS Inc. Chicago, III). A *P* value of less than 0.05 was considered statistically significant.

Results

Including the volunteer who dropped out, all enrolled subjects reported no adverse events during the study and eight subjects completed each of three phases according to the study protocol.

Plasma concentrations and pharmacokinetics of fexofenadine

Mean plasma fexofenadine concentration-time profiles following single-dose oral administration of 120 mg fexofenadine hydrochloride in the control, diltiazem and itraconazole phase are shown in Figure 1, and the effect of the pretreatment on fexofenadine $\text{AUC}(0, \infty)$ and C_{max} in each subject is illustrated in Figure 2. Itraconazole pretreatment significantly increased mean ($\pm$ SD) $\text{AUC}(0, \infty)$ from $4133 (\pm 1776)$ to $11287 (\pm 4552)$ $\text{ng ml}^{-1} \text{ h}$ (95% CI of differences 3731, 10575; $P < 0.0001$) and mean C_{max} ($\pm$ SD) from $699 (\pm 366)$ to $1346 (\pm 561)$ ng ml^{-1} (95% CI of differences 253, 1040; $P < 0.005$). In contrast, diltiazem pretreatment affected neither $\text{AUC}(0, \infty)$ ($4433 \pm 1565 \text{ ng ml}^{-1} \text{ h}$, 95% CI of differences $-1353, 754$) nor C_{max} ($704 \pm 316 \text{ ng ml}^{-1}$, 95% CI of differences $-145, 155$). Other pharmacokinetic parameters from plasma fexofenadine concentrations are shown in Table 1. Although significant difference was found in CL/F and V/F , there was no significant change in t_{max} or $t_{1/2}$ of fexofenadine between the three pretreatment groups.

Urinary excretion of fexofenadine

Mean ($\pm$ SD) cumulative amounts of fexofenadine excreted into urine are shown in Figure 3. Up to 48 h after administration, 11.4 ($\pm$ 5.4) and 10.7 ($\pm$ 5.0) mg of fexofenadine were excreted into urine in the control and the diltiazem phase (mean $\pm$ SD, 95% CI of differences between control and diltiazem -2.6 , 4.1), respectively, but the amount excreted significantly increased in the itraconazole phase (33.9 ± 13.9 mg, 95% CI of differences between control and itraconazole 10.4 , 34.5 ; $P < 0.0001$). Mean ($\pm$ SD) CL_r of fexofenadine in fractions from 0 to 4 h, 4–8 h, 8–12 h, 12–24 h, 24–36 h and 36–48 h are shown in Figure 4, and no significant difference in CL_r of fexofenadine was found in each fraction between three groups.

Figure 1

Mean ($\pm$ SD) plasma concentration–time curves of fexofenadine following single dose oral administration of 120 mg fexofenadine hydrochloride to eight healthy volunteers in the control (open circle), diltiazem (open triangle) and itraconazole (open square) phases

Figure 2

Individual and mean ($\pm$ SD) (A) $AUC(0, \infty)$ and (B) C_{max} in the control, diltiazem and itraconazole phases. $AUC(0-\infty)$ denotes area under plasma drug concentration–time curve from 0 h extrapolated to infinity. C_{max} denotes the maximum plasma concentration.

* $P < 0.0001$ for itraconazole vs. placebo and diltiazem. # $P < 0.005$ for itraconazole vs. placebo and diltiazem

Discussion

We investigated the effect of pretreatment with diltiazem or itraconazole on the pharmacokinetics of fexofenadine, a putative probe of P-glycoprotein activity *in vivo*. The results of our study demonstrated that pretreatment with itraconazole altered the pharmacokinetics of fexofenadine, whereas that with diltiazem did not.

Itraconazole is a potent inhibitor of P-glycoprotein [18], and co-administration with itraconazole is reported to increase the $AUC(0, \infty)$ of digoxin, which is a poorly metabolized substrate of P-glycoprotein, by 68% due to a reduction of its renal clearance [19]. In this study, itraconazole pretreatment increased the C_{max} and $AUC(0, \infty)$ of fexofenadine by two- and threefold, respectively, and reduced both CL/F and V/F of fexofenadine without change in CL_r and $t_{1/2}$. The effect of itraconazole could be a combination of increased bioavailability via P-glycoprotein and reduced clearance and distribution volume via P-glycoprotein and/or other transporters, because fexofenadine is a substrate of several OATPs [5, 8–12] as well as P-glycoprotein [5–7]. Itraconazole might inhibit OATP-mediated hepatic uptake of fexofenadine, leading to reduced biliary excretion and thus increased fexofenadine excretion into urine. To our knowledge, however, no *in vitro* data are available on itraconazole as an inhibitor of OATPs, and the increase in fexofenadine $AUC(0, \infty)$ by itraconazole would be in part due to inhibition of P-glycoprotein activity in the intestinal wall and increase in absorption of fexofenadine from the gastrointestinal tract. Inhibition of hepatic P-glycoprotein activity should be also taken into account because the activities in the intestinal wall and the liver cannot be separated when a drug absorbed from the gut lumen passes through the intestinal wall and the liver before entering the general cir-

Table 1

Effects of diltiazem and itraconazole treatment on the pharmacokinetics of fexofenadine after single oral 120 mg administration of fexofenadine to eight healthy volunteers

Parameter	Placebo (control) phase	Diltiazem phase Itraconazole phase	Mean difference between control and diltiazem or itraconazole (95% CI)
$t_{\max}$ (h)	1 (0.5–6)	1 (1–4) 2 (1–4)	
$t_{1/2}$ (h)	10.1 $\pm$ 5.3	10.4 $\pm$ 4.4 10.3 $\pm$ 4.3	0.263 (–2.75, 3.28) 0.125 (–1.45, 1.70)
CL/F (ml h ^{–1} kg ^{–1})	591.6 $\pm$ 236.3	554.0 $\pm$ 257.6 223.4 $\pm$ 112.5#	–37.6 (–239.9, 164.6) –368.3 (–530.4, –206.1)
V/F (ml kg ^{–1})	8890 $\pm$ 6849	9096 $\pm$ 7794 3045 $\pm$ 1144*	205 (–3670, 4080) 5845 (–11195, –496)

Data represent mean $\pm$ SD; $t_{\max}$ data are given as median with range. $t_{\max}$, observed time to reach the maximum plasma concentration; $t_{1/2}$, elimination half-life; CL/F, apparent oral clearance; V/F, apparent volume of distribution. # $P < 0.005$ for itraconazole vs. placebo and diltiazem. $P < 0.05$ for itraconazole vs. placebo and diltiazem.

Figure 3

Mean ($\pm$ SD) cumulative amount of fexofenadine excreted into urine during 48 h following single dose oral administration of 120 mg fexofenadine hydrochloride to eight healthy volunteers in the control (open circle), diltiazem (open triangle) and itraconazole (open square) phases.

* $P < 0.0001$ for itraconazole vs. placebo and diltiazem

Figure 4

Mean ($\pm$ SD) CL_r in fractions from 0–4 h, 4–8 h, 8–12 h, 12–24 h, 24–36 h and 36–48 h, following single dose oral administration of 120 mg fexofenadine hydrochloride to eight healthy volunteers in the control (open circle), diltiazem (open triangle) and itraconazole (open square) phases. CL_r denotes the renal clearance. There was no significant difference in each fraction between three phases

culatation. The reduced activity of P-glycoprotein in both organs would lessen the first-pass effect and, subsequently, increase the fexofenadine bioavailability. Although the MDR1 haplotype was not determined in this study, the recent study reported that the increase in fexofenadine AUC by itraconazole pretreatment was greater in subjects with the 2677TT/3435TT haplotype

than those with the 2677GG/3435CC haplotype [27], and the effect of itraconazole on P-glycoprotein activity would be MDR1 genotype dependent.

In the present study, mean CL_r of fexofenadine was 47.3 ± 16.7 ml min^{–1}, which was relatively constant between the three phases and in line with previous studies reporting from 43 to 87 ml min^{–1} [11, 17, 28]. As the

binding fraction of fexofenadine is reported to be $69.4 \pm 5.9\%$ for plasma fexofenadine concentrations ranging from 13 to 7359 ng ml⁻¹ (data on the file ALE-14, Aventis Pharma Ltd, Tokyo, Japan) and CL_r of fexofenadine is approximately GFR × unbound fraction, its secretion through the P-glycoprotein in renal tubules should be of little importance in the elimination of fexofenadine from the body. Pretreatment with rifampin was reported to reduce fexofenadine AUC(0, ∞) and C_{max}, which presumably resulted from inducing P-glycoprotein activity, but CL_r remained unchanged [14]. These findings are consistent with what we found in the present study, and may support the idea of a small contribution from P-glycoprotein in fexofenadine renal elimination.

Diltiazem has been reported to inhibit P-glycoprotein activity in various *in vitro* models [23, 29, 30] as well as CYP 3A [22]. In clinical studies, co-administration with diltiazem increased plasma concentrations of digoxin at steady state [31] or after single administration [32]. However, the 4-day pretreatment with 100 mg diltiazem twice daily seems to have had little effect on fexofenadine pharmacokinetics. Naturally, the relatively small number of subjects hindered us finding a difference, and a sample size of 25 subjects would be required to detect a 25% shift in fexofenadine AUC(0, ∞). A slow-release formulation of diltiazem at moderate doses might contribute to the absence of a clinically relevant impact of diltiazem on fexofenadine pharmacokinetics. Co-administration of an instant release formulation at higher doses would result in much higher local concentration in the gut lumen and might affect absorption of fexofenadine. Co-administration with diltiazem is known to affect the pharmacokinetics of many drugs [24, 25], most of which are substrates for CYP3A and P-glycoprotein. Our results, showing little effect of diltiazem pretreatment on the P-glycoprotein activity *in vivo*, suggest that CYP3A would play a major role in the pharmacokinetic interaction by co-administration of a slow-release formulation of diltiazem in a clinical situation.

In conclusion, this study indicates that itraconazole increases fexofenadine exposure, probably due to the reduced first-pass effect by inhibiting P-glycoprotein activity, whereas therapeutic doses of diltiazem did not alter fexofenadine pharmacokinetics, suggesting it has little effect on P-glycoprotein activity *in vivo*. The pharmacokinetic interaction between itraconazole and fexofenadine has limited clinical importance because fexofenadine has a relatively wide therapeutic range.

The authors have no conflicts of interest in relation to this paper.

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