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Lack of dose-dependent effects of itraconazole on the pharmacokinetic interaction with fexofenadine

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Abbreviations: P-gp, P-glycoprotein; CYP, cytochrome P450; OATP, organic anion transporting polypeptide; HPLC, high-performance liquid chromatography; AUC, area under the plasma concentration-time curve; C<sub>max</sub>, maximum plasma concentration;

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$t_{max}$ , time to reach  $C_{max}$ ;  $k_e$ , elimination rate constant;  $t_{1/2}$ , elimination half-life;  $CL/F$ , apparent oral clearance;  $V_d/F$ , apparent volume of distribution;  $CL_{renal}$ , renal clearance;  $CV$ , coefficients of variation

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### ABSTRACT:

The aim of this study was to determine the inhibitory effect of itraconazole at different coadministered doses on fexofenadine pharmacokinetics. In a randomized 4-phase crossover study, eleven healthy volunteers were administered a 60 mg fexofenadine hydrochloride tablet alone on one occasion (control phase) and with three different doses of 50, 100 and 200 mg of itraconazole simultaneously on other three occasions (itraconazole phase). Although the elimination half-life and the renal clearance of fexofenadine remained relatively constant, a single administration of itraconazole with fexofenadine significantly increased mean area under the plasma concentration-time curve [AUC(0-∞)] of fexofenadine (1701 / 3554, 4308 and 4107 ng hr/mL for control / 50 mg, 100 mg and 200 mg itraconazole, respectively). While mean itraconazole AUC(0-48) from 50 mg to 200 mg increased dose-dependently from 214 to 772 ng hr/mL ( $p = 0.003$ ), no significant difference was noted in the three parameters, AUC ( $p = 0.423$ ), C<sub>max</sub> ( $p = 0.636$ ) and CL<sub>renal</sub> ( $p = 0.495$ ) of fexofenadine between the three doses of itraconazole. Itraconazole exposure at lower dose (50 mg) compared with the clinical dose (200 mg once or twice daily) had the maximal effect on fexofenadine pharmacokinetics even though itraconazole plasma concentrations have gradually increased following higher doses. These findings suggest that the interaction

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may occur at the gut wall before reaching the portal vein circulation, and the inhibitory effect must be saturated by substantial local concentrations of itraconazole in the gut lumen after 50 mg dosing.

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### **Introduction:**

Fexofenadine is a selective histamine H1 receptor antagonist and is clinically effective in the treatment of seasonal allergic rhinitis and chronic urticaria as a first-line agent (Simpson et al., 2000). Although fexofenadine is not metabolized by cytochrome P450s (CYPs), fexofenadine pharmacokinetics depends on the activity of P-glycoprotein (P-gp) (Cvetkovic et al., 1999; Putnam et al., 2002; Perloff et al., 2002), as an efflux transporter expressed in the small intestine, liver, kidney and brain, and depends on several organic anion transporting polypeptide (OATP) family transporters (Cvetkovic et al., 1999; Niemi et al., 2005; Shimizu et al., 2005; Nozawa et al., 2004) as uptake transporters expressed in organs similar to P-gp. Recently, it has become increasingly evident that drug transporters have a pivotal role in pharmacokinetics of numerous drugs with therapeutic implications (Kim, 2002; Lin et al., 2003; Fromm, 2003). Additionally, drug-drug and drug-food interaction reports relevant to fexofenadine have shown that rifampin (INN, rifampicin), St John's wort, fruit juice, and verapamil affected fexofenadine pharmacokinetics (Hamman et al., 2001; Wang et al., 2002; Dresser et al., 2002; Yasui-Furukori et al., 2005; Tannergren et al., 2003; Lemma et al., 2006).

Itraconazole, an antifungal azole, has been used as a first-line treatment for patients

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with extensive or recalcitrant cutaneous fungal infections, mixed dermatophytoses, candidiasis and aspergillosis (Haria et al., 1996). Itraconazole is extensively metabolized in the liver, and only one hydroxyitraconazole in over 30 metabolites has an antifungal activity similar to that of the parent drug (Haria et al., 1996). Since itraconazole is a potent inhibitor of CYP3A activity *in vitro* and *in vivo*, itraconazole coadministration with a CYP3A substrate can result in clinically significant drug interaction (Dresser et al., 2000). Similar to the inhibition of CYP3A-mediated metabolism, itraconazole significantly inhibits the *in vitro* activity of P-gp (Venkatakrisnan et al., 2000; Wang et al., 2002; Keogh et al., 2006), and coadministration of itraconazole has reduced the clearance of poorly metabolized P-gp substrates such as digoxin (Jalava et al., 1997) and celiprolol (Lilja et al., 2003) in volunteer studies. The drug interaction between fexofenadine and itraconazole has been demonstrated in previous volunteer studies (Shon et al., 2005; Shimizu et al., 2006; Shimizu et al., *in press*). We demonstrated that concomitant administration of 100 mg itraconazole with fexofenadine increased fexofenadine AUC by almost 3-fold after 4-day treatment of 100 mg itraconazole twice daily (Shimizu et al., 2006), and the increase of fexofenadine AUC throughout the 6 days of itraconazole treatment at a 200 mg dose once daily was almost constant even though accumulation of plasma

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itraconazole concentration depended on duration of the 6-days treatment (Shimizu et al., *in press*). Interestingly, in these two different studies, no significant changes were found in elimination half-life and renal clearance reflecting elimination rates of fexofenadine. These results therefore imply that the increase in fexofenadine AUC by itraconazole is probably due to the reduced first-pass effect by inhibiting P-gp activity. Furthermore, the higher plasma itraconazole concentrations from higher doses of itraconazole might affect OATP-mediated hepatic uptake and / or P-gp-mediated hepatic excretion of fexofenadine to greater extent, and thus have an increased effect on fexofenadine pharmacokinetics.

The aim of this study was to determine whether or not the extent of drug interaction of fexofenadine resulting from P-gp inhibition by itraconazole is dose dependent. We therefore investigated the effect of single administration of three different itraconazole doses, 50 mg, 100 mg and 200 mg on fexofenadine pharmacokinetics, and compared them with the pharmacokinetics of fexofenadine administered alone. We also evaluated the plasma concentration-time profiles of itraconazole, and examined their influence on fexofenadine pharmacokinetics.

## **METHODS:**



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### *Subjects.*

Eleven healthy Japanese volunteers (6 males and 5 females) were enrolled in this study after giving written informed consent. Each subject was physically normal by clinical examination and routine laboratory testing and had no history of significant medical illness or hypersensitivity to any drugs. The mean ( $\pm$  SD) values of age and body weight of volunteers were 22.0 ( $\pm$  1.2) years (range 20-24 years) and 56.9 ( $\pm$  7.2) kg (range 46 - 66 kg), respectively. This study was approved by the Ethics Committee of Hirosaki University School of Medicine.

### *Study design.*

This randomized open-label study consisted of one control and three itraconazole phases, in which the volunteers received a tablet of 60 mg fexofenadine hydrochloride (Aventis Pharma Ltd., Tokyo, Japan) at 8 AM with 240 mL tap water after overnight fast. In the three itraconazole phases, the volunteers were administered a 60 mg fexofenadine hydrochloride tablet with one, two or four 50mg itraconazole capsules (JANSSEN PHARMACEUTICAL K.K., Tokyo, Japan) simultaneously at 8 AM with 240 mL tap water after overnight fast. The order of the control and the itraconazole phases (50 mg,

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100 mg and 200 mg) for each of the 11 volunteers in the study was randomly determined by the Latin-square method. Three volunteers in 3 groups participated in each respective sequence in the 4 phases of the study, and two volunteers participated in the sequence of 200 mg itraconazole, control, 50 mg itraconazole and 100 mg itraconazole phase. Each phase was separated by more than 2 weeks from other phases of the study as a washout period. The volunteers did not take any medication or fruit juices for at least 7 days before the control or the treatment phases, and no meal or beverages were allowed until 4 hours after the administration of fexofenadine.

### *Plasma and urine collections and determination of fexofenadine, itraconazole, and hydroxyitraconazole.*

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 and 48 hours after administration of fexofenadine, and plasma was separated immediately. Just before fexofenadine administration, a spot of urine was collected as a blank sample. After fexofenadine administration the urine was collected from 0 to 48 hours. The plasma and urine samples were stored at  $-20^{\circ}\text{C}$  until assayed.

Plasma and urine concentrations of fexofenadine were determined by the high-performance liquid chromatography (HPLC) method developed in our laboratory

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(Uno et al., 2004). In brief, 10  $\mu$ L (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. Samples were purified with C18 minicolumns (BondElute C18, 500 mg packing in 3 mL cartridge, Varian, Palo Alto, CA), 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 flow rate was 1.0 mL/min and the column was maintained at 50 °C. The peak was detected with 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 between-day coefficients of variation (CV) and relative errors were 1.3% and -2.7% at 50 ng/mL (n = 5), respectively. The limit of quantification was 1.0 ng/mL. Plasma and urine samples from the itraconazole treatment did not have any interfering peak for the fexofenadine assay, and the plasma and urine samples before each fexofenadine administration had no fexofenadine peak detected in the assay.

Plasma concentrations of itraconazole and hydroxyitraconazole were determined by the HPLC method developed in our laboratory (Uno et al., 2006). In brief, after 30  $\mu$ L of an internal standard (R051012, 10  $\mu$ g/mL) and 0.1 mL of 0.5M disodium hydrogen phosphate were added to 1 mL of plasma, the mixture was extracted with

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*n*-heptane-chloroform (60:40, v/v). The organic phase was evaporated, and the samples were dissolved and injected into a column I (TSK precolumn BSA-ODS/S, 5  $\mu$ m, 10 mm x 4.6 mm i.d.) for clean-up and column II (Develosil C8-5 column, 5  $\mu$ m, 150 mm x 4.6 mm i.d.) for separation. The mobile phase consisted of phosphate buffer - acetonitrile (68:32 v/v, pH6.0) and phosphate buffer - acetonitrile (35:65 v/v, pH6.0) for clean-up and separation, respectively. The peak was detected with an ultraviolet detector set at a wavelength of 263 nm. The validated concentration ranges of this method were 3-500 ng/mL and 3-1000 ng/mL for itraconazole and hydroxyitraconazole, respectively. The between-day coefficients of variation (CV) was 2.3% at 4 ng/mL (n = 6), and 2.4% at 4 ng/mL (n = 6) for itraconazole and hydroxyitraconazole, respectively. The limit of quantification was 2 ng/mL for both itraconazole and hydroxyitraconazole.

### ***Pharmacokinetic data analysis.***

The maximum plasma concentration ( $C_{max}$ ) and the time to reach  $C_{max}$  ( $t_{max}$ ) of fexofenadine, itraconazole, and hydroxyitraconazole were determined directly from the observed data. The elimination rate constant ( $k_e$ ) of fexofenadine was obtained by linear regression analysis by use of at least 3 sampling points of the terminal log-linear declining phase to the last measurable concentration. The elimination half-life ( $t_{1/2}$ )

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was calculated as 0.693 divided by  $k_e$ . The area under the plasma concentration-time curve from time zero to the last sampling time ( $AUC_{0-t}$ ) was calculated by the trapezoidal rule. AUC from zero to infinity ( $AUC_{0-\infty}$ ) was calculated by  $AUC(0\text{-last}) + C_{\text{last}}/k_e$ , where  $C_{\text{last}}$  is the last detectable plasma drug concentration. In itraconazole and hydroxyitraconazole,  $AUC(0\text{-}48)$  was adopted because their plasma concentration-time profiles lacked the terminal log-linear declining phase. The apparent oral clearance ( $CL/F$ ) was obtained from the equation  $CL/F = \text{Dose}/AUC/\text{kg}$  and the apparent volume of distribution ( $V_d/F$ ) was calculated from the equation  $V_d/F = CL/F/k_e$ . The renal clearance ( $CL_{\text{renal}}$ ) was obtained from the following equation:  $CL_{\text{renal}} = A_e / AUC(0\text{-}48)/\text{kg}$ , in which  $A_e$  is the amount of fexofenadine excreted into the urine within 48 hours.

### ***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 phases, and Bonferroni test was used for *post hoc* comparison. All data were analyzed with the statistical program SPSS for Windows, version 11.5J (SPSS Inc. Chicago, III). A *p* value less than .05 was considered statistically significant.

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### RESULTS:

None of the enrolled subjects reported any adverse events during the study and they completed all phases according to the study protocol.

#### *Plasma concentrations and pharmacokinetics of fexofenadine.*

Mean plasma fexofenadine concentration-time profiles following a single oral administration of 60 mg fexofenadine hydrochloride in the control and the three itraconazole phases are shown in Figure 1-A, and the pharmacokinetic parameters are summarized in Table 1. The mean plasma concentrations of fexofenadine in the itraconazole phases were higher than those in the control phase, and itraconazole coadministration significantly increased fexofenadine AUC ( $p = 0.009$ ,  $p < 0.001$  and  $p = 0.002$  for 50 mg, 100 mg and 200 mg itraconazole, respectively) and  $C_{max}$  ( $p = 0.028$ ,  $p = 0.002$  and  $p = 0.011$  for 50 mg, 100 mg and 200 mg itraconazole, respectively), and reduced its  $CL/F$  ( $p < 0.001$  for all itraconazole phases) and  $V_d/F$  ( $p < 0.001$  for all itraconazole phases), compared to those in the control phase. However, no significant difference was noted in these parameters of fexofenadine such as AUC ( $p = 0.423$ ),

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$C_{max}$  ( $p = 0.636$ ) and  $CL_{renal}$  ( $p = 0.495$ ) between the doses of itraconazole. There was no significant difference in  $t_{max}$  or  $t_{1/2}$  of fexofenadine between the phases.

### *Urinary excretion of fexofenadine.*

Although the renal clearance of fexofenadine was relatively constant between the control ( $63.5 \pm 15.8$  mL/hr/kg) and the itraconazole phases ( $58.9 \pm 19.6$ ,  $65.9 \pm 27.0$  and  $64.1 \pm 24.6$  mL/h/kg for 50 mg, 100 mg and 200 mg itraconazole, respectively), there was a significant difference in the amount of fexofenadine excreted into the urine within 48 hours (Table 1). However, the different doses of itraconazole did not affect the amount of fexofenadine excreted into the urine (Table 1).

### *Plasma concentrations and pharmacokinetics of itraconazole and hydroxyitraconazole.*

Mean plasma concentration-time profiles in the itraconazole phase with the dose of 50, 100 and 200 mg administered once daily are shown in Figure 1-B for itraconazole, and their pharmacokinetic parameters are summarized in Table 2. Mean  $C_{max}$  and  $AUC(0-48)$  of itraconazole and hydroxyitraconazole were increased following higher doses of itraconazole administration in a dose-dependent manner, and mean  $AUC(0-48)$

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of itraconazole of 100 mg and 200 mg itraconazole were increased by 1.9-fold and 3.6-fold, respectively, in comparison with that of 50 mg itraconazole ( $p = 0.027$  and  $p = 0.003$  for 100 mg and 200 mg itraconazole, respectively). Similarly, mean AUC(0-48) of hydroxyitraconazole of 100 mg and 200 mg itraconazole were increased by 2.0-fold and 3.9-fold, respectively, in comparison with that of 50 mg itraconazole ( $p=0.021$  and  $p = 0.007$  for 100 mg and 200 mg itraconazole, respectively).

### DISCUSSION:

In this study, we investigated the effect of single administration of three different itraconazole doses, 50 mg, 100 mg and 200 mg on fexofenadine pharmacokinetics. Since our previous findings indicated that the effect of a single dose of 200 mg itraconazole was almost the same as the effect of multiple dosing of 200 mg itraconazole once daily up to 6 days in terms of the effect on fexofenadine pharmacokinetics (Shimizu et al., *in press*), itraconazole was coadministered with fexofenadine simultaneously as a single dose and significant but similar increase in fexofenadine C<sub>max</sub> and AUC(0-∞) was found in any itraconazole phase of the present study. After higher doses of itraconazole administration, itraconazole C<sub>max</sub> and AUC



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were increased, but the increase in plasma itraconazole concentration did not affect fexofenadine pharmacokinetics. These findings are consistent with the results of our previous studies in which the 2-fold increase in fexofenadine C<sub>max</sub> and AUC(0-∞) by the itraconazole coadministration was relatively constant in spite of almost 4-fold increase in itraconazole AUC (0-24) after multiple dosing of itraconazole for 6 days (from 816 ± 415 on day 1 to 3142 ± 1285 ng hr/mL on day 6).

Itraconazole coadministration has been reported to increase serum concentrations of digoxin, a substrate of P-gp, most probably by inhibiting P-gp in the small intestine and kidneys (Partanen et al., 1996; Jalava et al., 1997; Greiner et al., 1999). In the present study, although the itraconazole treatment significantly increased the amount of fexofenadine excreted into the urine within 48 hours, mean CL<sub>renal</sub> of fexofenadine was relatively constant between the control and the itraconazole phases. Therefore, in the interaction between fexofenadine and itraconazole, the effect of itraconazole could be due to a combination of increased bioavailability by inhibiting P-gp and reduced organic clearance without CL<sub>renal</sub> and distribution volume by inhibiting P-gp and / or other transporters, because fexofenadine is a substrate of several OATPs (Cvetkovic et al., 1999; Niemi et al., 2005; Shimizu et al., 2005; Nozawa et al., 2004) as well as P-gp (Cvetkovic et al., 1999; Putnam et al., 2002; Perloff et al., 2002). Itraconazole might

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inhibit OATP-mediated hepatic uptake and lead to reduced biliary excretion and thus increased fexofenadine excretion into urine. While inhibition of uptake transporters should result in a time shift in  $t_{max}$ , no significant difference was noted in  $t_{max}$  between the control and the itraconazole phases. In addition, there is no *in vitro* data on itraconazole as an inhibitor of OATPs to date. Although some OATPs are reported to be the major determinant on fexofenadine disposition (Dresser et al., 2002; Dresser et al., 2005), the role of OATP in the interaction of the present study may be less than that of P-gp in the small intestine.

Comparing with effective levels of itraconazole in clinical situations (trough ITZ > 250 ng/mL, Van Cutsem, 1989), a much lower plasma concentration of itraconazole was potent enough to double the fexofenadine concentrations. However, these assumptions appeared to be unlikely because itraconazole concentrations in the systemic circulation would not play a major role in the interaction between fexofenadine and itraconazole since 10 times difference in itraconazole AUC ( $214 \pm 113$  and  $3142 \pm 1285$  ng hr/mL for a single dose of 50 mg and 6-day treatment of 200 mg daily, respectively) showed little effect on fexofenadine pharmacokinetics. In addition to this result, the similar effect that at each administration of itraconazole had on fexofenadine AUC<sub>(0-∞)</sub> and CL/F without significant change in CL<sub>renal</sub> or  $t_{1/2}$  implied that substantial local

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concentrations of itraconazole in the gut lumen would result in gastrointestinal inhibition of P-gp and an increase in absorption of fexofenadine from the gastrointestinal tract. However, as for this finding, further studies will be required because it is difficult to clarify the first-pass P-gp-inhibition between in the intestine and in the liver because an intravenous fexofenadine preparation is unavailable, as Lemma GL et al. suggested (Lemma et al., 2006).

In conclusion, itraconazole exposure at much lower dose (50 mg) compared with the clinical dose (200 mg once or twice daily) had the maximal effect on fexofenadine pharmacokinetics even though itraconazole plasma concentrations have gradually increased following higher doses. These findings suggest that the interaction may occur at the gut wall before reaching the portal vein circulation, and the inhibitory effect must be saturated by substantial local concentrations of itraconazole in the gut lumen after 50 mg itraconazole was administered. The increase, however, has limited clinical importance because of a relatively wide therapeutic range of fexofenadine.

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### **FOOTNOTES**

#### **Conflict of interest statement**

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

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### Figure legends

Figure 1. **A)** Mean (+ SD) plasma concentration–time curves of fexofenadine following a single oral administration of 60 mg fexofenadine hydrochloride in 11 healthy volunteers during the control phase (open circle) and 50 mg (open triangle), 100 mg (open square) and 200 mg (open diamond) treatment phases of itraconazole administered once daily. **B)** Mean (+ SD) plasma concentration–time curves of itraconazole in 11 healthy volunteers at 50 mg (closed circle), 100 mg (closed triangle) and 200 mg (closed square) of the itraconazole treatments.

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Table 1. Effects of 50 mg, 100 mg and 200 mg itraconazole on pharmacokinetic parameters of fexofenadine after single oral 60 mg administration of fexofenadine hydrochloride. Data represents mean  $\pm$  SD;  $t_{max}$  data are given as median with range.

Parameters	Control	Itraconazole dose					
		50 mg	<i>P</i> -values	100 mg	<i>P</i> -values	200 mg	<i>P</i> -values
$t_{max}$ (hr) (range)	2 (1-4)	2 (1-4)	0.885	2 (1-4)	0.526	2 (1-4)	0.639
$C_{max}$ (ng mL <sup>-1</sup> )	292 $\pm$ 173	525 $\pm$ 168	0.028	598 $\pm$ 194	0.002	592 $\pm$ 185	0.011
The within-subject ratios (treatment / Control) (%)		246 $\pm$ 144		286 $\pm$ 226		230 $\pm$ 119	
$t_{1/2}$ (hr)	6.2 $\pm$ 2.7	6.5 $\pm$ 2.0	0.990	6.6 $\pm$ 1.7	0.977	6.9 $\pm$ 2.0	0.926
AUC(0- $\infty$ ) (ng hr mL <sup>-1</sup> )	1701 $\pm$ 960	3554 $\pm$ 1220	0.009	4308 $\pm$ 1517	<0.001	4107 $\pm$ 1363	0.002
The within-subject ratios (treatment / Control) (%)		270 $\pm$ 167		325 $\pm$ 204		269 $\pm$ 158	
CL/F (mL hr <sup>-1</sup> kg <sup>-1</sup> )	819 $\pm$ 402	344 $\pm$ 155	<0.001	275 $\pm$ 90	<0.001	280 $\pm$ 89	<0.001
Vd/F (mL kg <sup>-1</sup> )	5632 $\pm$ 2773	2449 $\pm$ 1245	<0.001	2054 $\pm$ 786	<0.001	2166 $\pm$ 947	<0.001
Ae (mg)	5.7 $\pm$ 3.4	11.6 $\pm$ 5.7	0.017	14.9 $\pm$ 5.2	<0.001	13.7 $\pm$ 5.3	0.002
CLrenal (mL hr <sup>-1</sup> kg <sup>-1</sup> )	63.5 $\pm$ 15.8	58.9 $\pm$ 19.6	0.871	65.9 $\pm$ 27.0	1.000	64.1 $\pm$ 24.6	1.000

$t_{max}$ , observed time to reach the maximum plasma concentration;  $C_{max}$ , observed maximum plasma concentration;  $t_{1/2}$ , elimination half-life; AUC(0- $\infty$ ), area under plasma drug concentration-time curve from 0 hours extrapolated to infinity; CL/F, apparent oral clearance; Vd/F, apparent volume of distribution; Ae, amount of fexofenadine excreted into urine; CLrenal, the renal clearance.

*P*-values, compared with the control phase.

Not significant differences found in the itraconazole treatments.

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Table 2. Pharmacokinetic parameters of itraconazole and hydroxyitraconazole following a single administration of 50 mg, 100 mg and 200 mg itraconazole. Data represents mean  $\pm$  SD;  $t_{max}$  data are given as median with range.

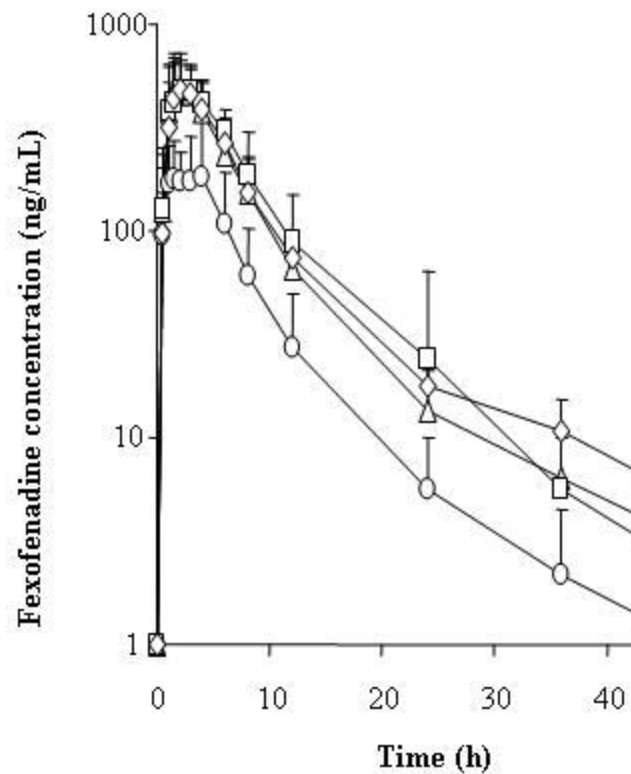
Parameters	Dose 50 mg	100 mg	<i>P</i> -values	200 mg	<i>P</i> -values
<b>Itraconazole</b>					
$t_{max}$ (hr) (range)	4 (3-8)	4 (3-6)	1.000	3 (2-4)	0.175
C <sub>max</sub> (ng/mL)	18 $\pm$ 7	56 $\pm$ 25	0.003	98 $\pm$ 24	<0.001
AUC(0-48) (ng hr mL <sup>-1</sup> )	214 $\pm$ 113	397 $\pm$ 126	0.027	772 $\pm$ 362	0.003
CL/F(mL hr <sup>-1</sup> kg <sup>-1</sup> )	5463 $\pm$ 3077	4798 $\pm$ 1366	1.000	5391 $\pm$ 2049	1.000
<b>Hydroxyitraconazole</b>					
$t_{max}$ (hr) (range)	5 (3-6)	4 (3-6)	0.576	4 (3-8)	0.848
C <sub>max</sub> (ng/mL)	48 $\pm$ 18	120 $\pm$ 34	<0.001	193 $\pm$ 60	<0.001
AUC(0-48) (ng hr mL <sup>-1</sup> )	549 $\pm$ 229	1065 $\pm$ 522	0.021	2048 $\pm$ 1118	0.003

$t_{max}$ , observed time to reach the maximum plasma concentration; C<sub>max</sub>, observed maximum plasma concentration; AUC(0-48), area under plasma drug concentration-time curve from 0 to 48 hours after administration; CL/F, apparent oral clearance.

*P*-values, compared with the 50 mg itraconazole treatment.

Figure 1

**A)**



**B)**

