Enantioselective disposition of fexofenadine with the P-glycoprotein inhibitor verapamil

Takashi Sakugawa, Masatomo Miura,¹ Nobuo Hokama,
Toshio Suzuki,¹ Tomonori Tateishi² & Tsukasa Uno

Department of Hospital Pharmacy, Faculty of Medicine, University of the Ryukyus, Okinawa,

¹Department of Pharmacy, Akita University Hospital, Akita and ²Department of Clinical Pharmacology, Hirosaki University School of Medicine, Hirosaki, Japan

Correspondence

Professor Tsukasa Uno, PhD, Department of Hospital Pharmacy, Faculty of Medicine, University of the Ryukyus, Okinawa 903-0215, Japan.

Tel: + 81 98 895 1346

Fax: + 81 98 895 1487

E-mail: u370409@med.u-ryukyu.ac.jp

Keywords

enantiomer, fexofenadine, P-glycoprotein, verapamil

Received

25 June 2008

Accepted

11 February 2009

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Recently, we have shown that itraconazole co-administration increases the plasma concentrations of *S*(-)- and *R*(+)-fexofenadine enantiomers, and it appears to affect this P-glycoprotein (P-gp)-mediated transport of *S*(-)-fexofenadine to a greater extent compared with that of *R*(+)-fexofenadine.
- Although verapamil is a P-gp inhibitor and co-administration is known to increase the bioavailability of racemic fexofenadine, little is known about the inhibitory effect of verapamil for each fexofenadine enantiomer.

WHAT THIS STUDY ADDS

- Similar to the drug-interaction study with itraconazole, verapamil altered the stereoselective pharmacokinetics of fexofenadine to a greater extent on *S*(-)-fexofenadine than on *R*(+)-fexofenadine.
- This effect by verapamil may be due to the differing affinities of P-gp for each enantiomer.
- However, since the inhibitory effect of verapamil did not eliminate the difference in pharmacokinetics of fexofenadine enantiomers, it is likely that other mechanisms in addition to P-gp contribute to the stereoselective pharmacokinetics of fexofenadine.

AIMS

The aim was to compare possible effects of verapamil, as a P-glycoprotein (P-gp) inhibitor, on the pharmacokinetics of each fexofenadine enantiomer, as a P-gp substrate.

METHODS

Thirteen healthy Japanese volunteers (10 male and three female) were enrolled. In a randomized, two-phase, crossover design, verapamil was dosed 80 mg three times daily (with total daily doses of 240 mg) for 6 days, and on day 6, a single 120-mg dose of fexofenadine was administered along with an 80-mg dose of verapamil. Subsequently, fexofenadine was administered alone after a 2-week wash-out period. The plasma concentrations of fexofenadine enantiomers were measured up to 24 h after dosing.

RESULTS

During the control phase, the mean $AUC_{0-\infty}$ of *S*(-)- and *R*(+)-fexofenadine was $700 \text{ ng h}^{-1} \text{ ml}^{-1}$ [95% confidence interval (CI) 577, 823] and $1202 \text{ ng h}^{-1} \text{ ml}^{-1}$ (95% CI 1007, 1396), respectively, with a significant difference ($P < 0.001$). Verapamil had a greater effect on the pharmacokinetic parameters of *S*(-)-fexofenadine compared with those of the *R*(+)-enantiomer, and increased $AUC_{0-\infty}$ of *S*(-)-fexofenadine and *R*(+)-fexofenadine by 3.5-fold (95% CI of differences 1.9, 5.1; $P < 0.001$) and by 2.2-fold (95% CI of differences 1.7, 3.0; $P < 0.001$), respectively. The *R/S* ratio for the $AUC_{0-\infty}$ was reduced from 1.76 to 1.32 ($P < 0.001$) by verapamil treatments.

CONCLUSION

This study indicates that P-gp plays a key role in the stereoselectivity of fexofenadine pharmacokinetics, since the pharmacokinetics of fexofenadine enantiomers were altered by the P-gp inhibitor verapamil, and this effect was greater for *S*-fexofenadine compared with *R*-fexofenadine.

Introduction

Fexofenadine (($\pm$)-2-[4-[1-hydroxy-4-[4-(hydroxydiphenyl methyl)piperidino]butyl]phenyl]-2-methylpropanoic acid) is a selective histamine H1 receptor antagonist and is one of the most used seasonal allergic rhinitis and chronic urticaria treatments [1]. Since fexofenadine is scarcely metabolized by cytochrome P450s (CYPs), it has been suggested that transporters play an important role in fexofenadine pharmacokinetics. Fexofenadine is a substrate of P-glycoprotein (P-gp) and its disposition depends in part on the activity of P-gp [2–4], an efflux transporter. Furthermore, several organic anion transporting polypeptides (OATP)1A2 and OATP2B1 [2, 5–7] of uptake transporters also contribute to the disposition of fexofenadine.

Fexofenadine is administered therapeutically as a racemic mixture of *R*(+)- and *S*(–)-enantiomers. In addition, clinical efficacies of both enantiomers possess equal potency [8]. However, the plasma concentration of *R*(+)-fexofenadine in humans is about 1.5-fold higher than that of the corresponding *S*(–)-enantiomer [8]. There have been few studies on the pharmacokinetics of fexofenadine enantiomers [8–10]. Although P-gp and OATPs may be major determinants of fexofenadine pharmacokinetics, it is unclear how these transporters contribute to the enantiomeric disposition of fexofenadine. Recently, we have shown that P-gp is likely to mediate the stereoselective disposition of fexofenadine [10] and itraconazole, a P-gp inhibitor, alters the stereoselective disposition of fexofenadine enantiomers [11].

Similarly, verapamil is a known P-gp inhibitor and has been used to increase the therapeutic effectiveness of cytotoxic anticancer drugs [12–15]. To date, there is no information that verapamil is an inhibitor of OATPs. Therefore, if the stereoselective disposition of fexofenadine enantiomers is due to a contribution from P-gp function, verapamil may alter the different properties of each fexofenadine enantiomer. This study was designed to examine whether and to what extent verapamil affects the pharmacokinetics of fexofenadine enantiomers.

Methods

Subjects

Thirteen healthy Japanese volunteers (10 male and three female) 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 24.6 years ($\pm$ 3.7) (range 22–36 years) and 57.4 kg ($\pm$ 5.5) (range 46–65 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 two (control and 6-day treatments) phases and two study days, in which 120 mg fexofenadine hydrochloride was administered. In the control phase, volunteers received 120 mg of fexofenadine hydrochloride (Aventis Pharma Ltd., Tokyo, Japan) at 09.00 h after an overnight fast. In the treatment phase, verapamil was dosed 80 mg three times daily (with total daily doses of 240 mg) for 6 days, and on day 6 a single 120-mg dose of fexofenadine was co-administered with an 80-mg dose of verapamil at 09.00 h after an overnight fast. On another occasion, fexofenadine was administered alone with a 2-week wash-out period. The order of the two phases was randomly assigned to each volunteer. Seven volunteers started the control phase first, followed by the treatment phase >24 h after the last blood sampling of the control phase. Other volunteers started the treatment phase first, followed by the control phase >2 weeks after the last sampling. Volunteers did not take any medication or fruit juices for at least 7 days before both phases, and no meal or beverages were allowed until 4 h after fexofenadine administration.

Plasma collections and determination of fexofenadine enantiomer concentration

Blood samples (10 ml each) were drawn into heparinized tubes before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h after administration of fexofenadine, and plasma was separated immediately. The plasma samples were stored at -20°C until assayed.

The plasma concentration of fexofenadine enantiomers was determined according to the high-performance liquid chromatography (HPLC) method of Miura *et al.* [9]. In brief, following the addition of diphenhydramine (50 ng) as an internal standard in methanol (10 μl) to 400 μl of plasma, the plasma sample was diluted with 600 μl water and vortexed for 30 s. 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 under vacuum at 40°C using a rotary evaporator (Iwaki, Tokyo, Japan). The residues were then dissolved in 50 μl methanol and vortexed for 30 s; 50 μl mobile phase was added to each sample and samples were vortexed for another 30 s. An aliquot of 50 μl of each sample was then processed on an HPLC apparatus equipped with a Chiral CD-Ph column (250 $\times$ 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). The flow rate was 0.5 ml min^{-1} at ambient temperature and sample detection was carried out at 220 nm. The lower limit of quantification was 25 ng ml^{-1} for *R*(+)- and *S*(–)-fexofenadine. The validated concentration ranges of this method from plasma and urine were 25–625 ng ml^{-1} for both enantiomers. The within- and between-day coeffi-

Figure 1

(a) Mean ($\pm$ SD) plasma concentration–time curves of *S*(–)-fexofenadine following a single oral administration of 120 mg fexofenadine hydrochloride in 13 healthy volunteers treated with control (open circles) or verapamil (closed circles). (b) Mean ($\pm$ SD) plasma concentration–time curves of *R*(+)-fexofenadine following a single oral administration of 120 mg fexofenadine hydrochloride in 13 healthy volunteers treated with control (open circles) or verapamil (closed circles)

cients of variation were $<13.6\%$ and accuracies were within 8.8% over the linear range for both analytes.

Pharmacokinetic data analysis

The maximum plasma concentration ($C_{\max}$) and the time to reach $C_{\max}$ ($t_{\max}$) of fexofenadine enantiomers 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 three sampling points of the terminal log-linear declining phase to the last measurable concentration. The elimination half-life ($t_{1/2}$) was calculated as 0.693 divided by k_e . The area under the plasma concentration–time curve (AUC) from zero to infinity ($0-\infty$) was calculated by $\text{AUC}(0-\text{last}) + C_{\text{last}}/k_e$, where C_{last} is the last detectable plasma drug concentration. The apparent oral clearance (CL/F) was obtained from the equation $\text{CL}/F = \text{Dose}/\text{AUC}_{0-\infty}$, where Dose is 60 mg for each fexofenadine enantiomer. The apparent volume of distribution (V_d/F) was calculated from the equation $V_d/F = \text{CL}/F/k_e$.

Statistical analysis

The results are expressed as mean $\pm$ SD. Differences in pharmacokinetic parameters between *S*(–)- and *R*(+)-fexofenadine, between the control phase and the treatment phase, in the *R/S* ratio of the $\text{AUC}_{0-\infty}$ between the control phase and the treatment phase, and mean difference (%) in the within-subject ratio such as verapamil/control between *S*(–)- and *R*(+)-fexofenadine were

analysed by the paired *t*-test. All data were analysed with the statistical program SPSS for Windows, version 11.5 J (SPSS Inc., Chicago, IL, USA). A *P*-value <0.05 was considered statistically significant.

Results

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

Pharmacokinetics of fexofenadine enantiomers

Plasma concentration–time profiles of fexofenadine enantiomers in both phases are shown in Figure 1, and the pharmacokinetic parameters are summarized in Table 1.

In the control phase, mean plasma concentrations of *R*(+)-fexofenadine were higher than those of *S*(–)-fexofenadine, and the mean $\text{AUC}_{0-\infty}$ and $C_{\max}$ of *R*(+)-fexofenadine were significantly greater than those of the *S*(–)-enantiomer ($P < 0.001$ for both parameters). Mean CL/F and V_d/F of *S*(–)-fexofenadine were significantly greater than those of *R*(+)-fexofenadine ($P < 0.001$ and $P = 0.006$ for CL/F and V_d/F , respectively).

Verapamil co-administration increased plasma concentrations of both fexofenadine enantiomers, compared with those in the control phase (Figure 1), and verapamil treatment significantly altered the pharmacokinetic parameters except for $t_{\max}$ or $t_{1/2}$ of each enantiomer (Table 1).

Table 1

Effects of verapamil on pharmacokinetic parameters of fexofenadine enantiomers after a single oral 120-mg dose of fexofenadine

Parameters	<i>S</i> (-)-fexofenadine Control	Verapamil	<i>P</i> -value	<i>R</i> (+)-fexofenadine Control	Verapamil	<i>P</i> -value
<i>t</i> _{max} (h) (range)	1.8 (0.5–4)	1.5 (1–4)	0.971	1.5 (0.5–4)	1.0 (1–4)	0.900
<i>C</i> _{max} (ng ml ⁻¹)	179 (149, 209)	392 (263, 520)	0.014	223 (194, 252)***	480 (359, 600)+++	0.003
Mean difference (%)		261 (128, 393)			234 (157, 311)	0.439
<i>t</i> _{1/2} (h)	3.0 (2.4, 3.7)	3.5 (2.8, 3.7)	0.436	3.3 (2.8, 3.7)	3.4 (2.8, 4.0)	0.516
Mean difference (%)		131 (88, 174)			110 (88, 132)	0.296
AUC _{0–∞} (ng h ⁻¹ ml ⁻¹)	700 (577, 823)	2006 (1617, 2394)	<0.001	1202 (1007, 1396)***	2632 (2131, 3132)+++	<0.001
Mean difference (%)		348 (190, 505)			238 (172, 304)	0.017
<i>V</i> _d / <i>F</i> (l)	387 (293, 480)	166 (122, 211)	0.004	247 (215, 280)**	125 (97, 154)+++	<0.001
Mean difference (%)		53 (35, 70)			53 (41, 66)	0.938
CL/ <i>F</i> (l h ⁻¹)	93 (70, 116)	33 (27, 39)	<0.001	56 (47, 64)***	26 (20, 32)+++	<0.001
Mean difference (%)		43 (31, 54)			50 (38, 63)	0.018
The <i>R</i> / <i>S</i> ratios of AUC	1.76 (1.61, 1.91) (Control phase)			1.32 (1.22, 1.42) (Verapamil phase)		0.001

Data are shown as mean and 95% confidence interval; *t*_{max} data are shown as a median with a range. ***P* < 0.01, between *R*(+)-fexofenadine and *S*(-)-fexofenadine in the control phase. ****P* < 0.001, between *R*(+)-fexofenadine and *S*(-)-fexofenadine in the control phase. +++*P* < 0.001, between *R*(+)-fexofenadine and *S*(-)-fexofenadine in the verapamil phase. *P*-values, compared with the control phase, and compared with mean difference percentages of *S*(-)-fexofenadine. *t*_{max}, observed time to reach the maximum plasma concentration; *C*_{max}, observed maximum plasma concentration; *t*_{1/2}, elimination half-life; AUC_{0–∞}, area under plasma drug concentration–time curve from 0 to infinity; *V*_d/*F*, apparent volume of distribution; CL/*F*, apparent oral clearance; Mean difference (95% confidence interval), the within-subject ratio (verapamil phase/control phase).

Figure 2

Mean (±SD) *R*/*S* ratios of plasma concentrations following a single oral administration of 120 mg fexofenadine hydrochloride in 13 healthy volunteers after control (open circles) or verapamil administration (closed circles)

The *R*/*S* ratios of plasma concentration at each sampling point ranged from 1.35 to 2.23 in the control phase, but verapamil co-administration decreased the ratios to a range of 1.20–1.55 (Figure 2). The *R*/*S* AUC_{0–∞} ratio was 1.76 ± 0.27 in the control phase, which significantly decreased to 1.32 ± 0.19 in the verapamil phase (*P* = 0.001). In the pharmacokinetic parameters, the mean difference

between control and verapamil phase in AUC_{0–∞} (*P* = 0.017) and CL/*F* (*P* = 0.018) for *S*(-)-fexofenadine was greater than for *R*(+)-fexofenadine.

Discussion

Similar to previous reports [8, 10, 11], stereoselective pharmacokinetics of fexofenadine enantiomers were observed, with an *R*/*S* AUC ratio for fexofenadine enantiomers of 1.76 ± 0.27 in the control phase. Fexofenadine is a known substrate of P-gp [2–4], an efflux transporter expressed in the small intestine, biliary canalicular front of hepatocytes, renal proximal tubules, blood–brain barrier [16] and OATPs [2, 5–7], which are uptake transporters expressed in the gastrointestinal tract, liver, kidney and blood–brain barrier [17]. Previous *in vivo* and *in vitro* studies have suggested that these transporters are key determinants of the bioavailability and disposition of fexofenadine in the small intestine [2–5, 18]. Therefore, the present result implies that stereoselective pharmacokinetics of fexofenadine may occur in the small intestine and may be due to differences in the affinity of P-gp or OATPs for each enantiomer. In addition, the contribution of fexofenadine metabolism to the elimination process is <1% [2, 18]. Lemma *et al.* [19] have reported that verapamil inhibited the CYP3A4-mediated metabolism of fexofenadine in addition to the inhibition of P-gp transport. Therefore, it is possible that CYP3A4 activity can contribute to the stereoselective pharmacokinetics of fexofenadine enantiomers. However, this assumption appears unlikely, since our previous *in vitro* experiments on cDNA-expressed CYP3A4 showed that the

disappearance rates of *S*(-)-fexofenadine and its *R*(+)-enantiomer are similar [10].

In this study, we investigated the effect of verapamil on the pharmacokinetics of fexofenadine enantiomers. The results showed that verapamil increased $C_{\max}$ and $AUC_{0-\infty}$ of both *S*(-)- and *R*(+)-fexofenadine enantiomers. No significant difference was found in the pharmacokinetic parameters involving $t_{\max}$ and $t_{1/2}$ between the two phases. This finding is in accordance with our previous report [20]. Consequently, the present result suggests that P-gp has a key role in the pharmacokinetics of both enantiomers, and verapamil may predominantly inhibit the P-gp-mediated transport of both enantiomers in the small intestine. There are no *in vitro* and *in vivo* data of verapamil as an OATP inhibitor. Furthermore, Tannergren *et al.* [21] have reported that verapamil increased fexofenadine bioavailability because it decreased CL/F and V_d/F without changing $t_{1/2}$, and hypothesized that this might result from a decreased first-pass liver extraction of fexofenadine. However, it is difficult to clarify whether the inhibitory effect of verapamil occurs in the small intestine or liver, because an intravenous fexofenadine formulation necessary for such experiments is unavailable.

In addition, the *R/S* ratios of plasma concentration at each sampling point and AUC for fexofenadine enantiomers decreased with verapamil treatment because the P-gp-inhibition effects for *S*(-)-fexofenadine are greater than those for *R*(+)-fexofenadine. This finding is in accordance with our previous study with itraconazole [11]. Furthermore, OATPs in the small intestine might play some role in the stereoselective pharmacokinetics of fexofenadine, because the inhibition of P-gp-mediated transport was insufficient to mitigate the different pharmacokinetics of fexofenadine enantiomers in both the itraconazole- and verapamil-fexofenadine studies. Therefore, these results imply that the verapamil dose of 240 mg in the present study may not be sufficient to inhibit completely the P-gp effects or that the enantiomeric disposition of fexofenadine may be influenced by OATPs in addition to P-gp. Thus, further *in vivo* studies with fexofenadine will be required to discriminate between these possibilities.

In conclusion, this study has indicated that verapamil, a P-gp inhibitor, alters the stereoselective pharmacokinetics of fexofenadine and appears to affect the P-gp-mediated transport of *S*(-)-fexofenadine to a greater extent compared with *R*(+)-fexofenadine. However, since the inhibitory effect of verapamil did not eliminate the difference between the pharmacokinetics of fexofenadine enantiomers, it is likely that other mechanisms in addition to P-gp also contribute to the stereoselective pharmacokinetics of fexofenadine.

Competing interests

None to declare.

REFERENCES

- Kim RB. Transporters and xenobiotic disposition. *Toxicology* 2002; 181–182: 291–7.
- Cvetkovic M, Leake B, Fromm MF, Wilkinson GR, Kim RB. OATP and P-glycoprotein transporters mediate the cellular uptake and excretion of fexofenadine. *Drug Metab Dispos* 1999; 27: 866–71.
- Putnam WS, Ramanathan S, Pan L, Takahashi LH, Benet LZ. Functional characterization of monocarboxylic acid, large neutral amino acid, bile acid and peptide transporters, and P-glycoprotein in MDCK and Caco-2 cells. *J Pharm Sci* 2002; 91: 2622–35.
- Perloff MD, von Moltke LL, Greenblatt DJ. Fexofenadine transport in Caco-2 cells: inhibition with verapamil and ritonavir. *J Clin Pharmacol* 2002; 42: 1269–74.
- Dresser GK, Bailey DG, Leake BF, Schwarz UI, Dawson PA, Freeman DJ, Kim RB. Fruit juices inhibit organic anion transporting polypeptide-mediated drug uptake to decrease the oral availability of fexofenadine. *Clin Pharmacol Ther* 2002; 71: 11–20.
- Nozawa T, Imai K, Nezu J, Tsuji A, Tamai I. Functional characterization of pH-sensitive organic anion transporting polypeptide OATP-B in human. *J Pharmacol Exp Ther* 2004; 308: 438–45.
- Simpson K, Jarvis B. Fexofenadine: a review of its use in the management of seasonal allergic rhinitis and chronic idiopathic urticaria. *Drugs* 2000; 59: 301–21.
- Robbins DK, Castles MA, Pack DJ, Bhargava VO, Weir SJ. Dose proportionality and comparison of single and multiple dose pharmacokinetics of fexofenadine (MDL 16455) and its enantiomers in healthy male volunteers. *Biopharm Drug Dispos* 1998; 19: 455–63.
- Miura M, Uno T, Tateishi T, Suzuki T. Determination of fexofenadine enantiomers in human plasma with high-performance liquid chromatography. *J Pharm Biomed Anal* 2007; 43: 741–5.
- Miura M, Uno T, Tateishi T, Suzuki T. Pharmacokinetics of fexofenadine enantiomers in healthy subjects. *Chirality* 2007; 19: 223–7.
- Tateishi T, Miura M, Suzuki T, Uno T. The different effects of itraconazole on the pharmacokinetics of fexofenadine enantiomers. *Br J Clin Pharmacol* 2008; 65: 693–700.
- Pauli-Magnus C, von Richter O, Burk O, Ziegler A, Mettang T, Eichelbaum M, Fromm MF. Characterization of the major metabolites of verapamil as substrates and inhibitors of P-glycoprotein. *J Pharmacol Exp Ther* 2000; 293: 376–82.
- Tsuruo T, Iida H, Naganuma K, Tsukagoshi S, Sakurai Y. Promotion by verapamil of vincristine responsiveness in tumor cell lines inherently resistant to the drug. *Cancer Res* 1983; 43: 808–13.

- 14** Tsuruo T, Iida H, Tsukagoshi S, Sakurai Y. Potentiation of vincristine and Adriamycin effects in human hemopoietic tumor cell lines by calcium antagonists and calmodulin inhibitors. *Cancer Res* 1983; 43: 2267–72.
- 15** Belpomme D, Gauthier S, Pujade-Lauraine E, Facchini T, Goudier MJ, Krakowski I, Netter-Pinon G, Frenay M, Gousset C, Marié FN, Benmiloud M, Sturtz F. Verapamil increases the survival of patients with anthracycline-resistant metastatic breast carcinoma. *Ann Oncol* 2000; 11: 1471–6.
- 16** Thiebaut F, Tsuruo T, Hamada H, Gottesman MM, Pastan I, Willingham MC. Cellular localization of the multidrug-resistance gene product P-glycoprotein in normal human tissues. *Proc Natl Acad Sci USA* 1987; 84: 7735–8.
- 17** Kim RB. Organic anion-transporting polypeptide (OATP) transporter family and drug disposition. *Eur J Clin Invest* 2003; 1–5.
- 18** Hamman MA, Bruce MA, Haehner-Daniels BD, Hall SD. The effect of rifampin administration on the disposition of fexofenadine. *Clin Pharmacol Ther* 2001; 69: 114–21.
- 19** Lemma GL, Wang Z, Hamman MA, Zaheer NA, Gorski JC, Hall SD. The effect of short- and long-term administration of verapamil on the disposition of cytochrome P450 3A and P-glycoprotein substrates. *Clin Pharmacol Ther* 2006; 79: 218–30.
- 20** Yasui-Furukori N, Uno T, Sugawara K, Tateishi T. Different effects of three transporting inhibitors, verapamil, cimetidine, and probenecid, on fexofenadine pharmacokinetics. *Clin Pharmacol Ther* 2005; 77: 17–23.
- 21** Tannergren C, Petri N, Knutson L, Hedeland M, Bondesson U, Lennernas H. Multiple transport mechanisms involved in the intestinal absorption and first-pass extraction of fexofenadine. *Clin Pharmacol Ther* 2003; 74: 423–36.