P-GLYCOPROTEIN PLAYS A MAJOR ROLE IN THE EFFLUX OF FEXOFENADINE IN THE SMALL INTESTINE AND BLOOD-BRAIN BARRIER, BUT ONLY A LIMITED ROLE IN ITS BILIARY EXCRETION

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Received February 11, 2005; accepted March 31, 2005

ABSTRACT:
Fexofenadine is a selective, non-sedating H1-receptor antagonist approved for symptoms of allergic conditions, which is mainly excreted into feces via biliary excretion. The purpose of this study is to investigate its pharmacokinetics in mice and rats to determine the role of P-glycoprotein (P-gp) in its biliary excretion. In mice, bile excretion clearance (17 ml/min/kg) accounted for almost 60% of the total body clearance (30 ml/min/kg). Comparing the pharmacokinetics after intravenous and oral administration indicated that the bioavailability of fexofenadine was at most 2% in mice. Knockout of Mdr1a/1b P-gp did not affect the biliary excretion clearance with regard to both plasma and liver concentrations, whereas the absence of P-gp caused a 6-fold increase in the plasma concentration after oral administration. In addition, the steady-state brain-to-plasma concentration ratio of fexofenadine was approximately 3-fold higher in Mdr1a/1b P-gp knockout mice than in wild-type mice. Together, these results show that P-glycoprotein plays an important role in efllux transport in the brain and small intestine but only a limited role in biliary excretion in mice. In addition, there was no difference in the biliary excretion between normal and hereditarily multidrug resistance-associated protein 2 (Mrp2)-deficient mutant rats (Eisai hyperbilirubinemic rats) and between wild-type and breast cancer resistance protein (Bcrp) knockout mice. These results suggest that the biliary excretion of fexofenadine is mediated by unknown transporters distinct from P-gp, Mrp2, and Bcrp.

Fexofenadine is an orally active nonsedating histamine H1-receptor antagonist that is prescribed for oral treatment of allergic rhinitis and chronic idiopathic urticaria. After oral administration of [14C]fexofenadine, the radioactivity was recovered in the urine (2.5%), bile (28%), and feces (69%) of rats whose bile duct had been cannulated, and thus, its oral absorption is at most 30%, and biliary excretion likely plays a major role in its elimination (Common Technical Document for the Registration of Pharmaceuticals for Human Use).

It has been suggested that transporters play important roles in the disposition of fexofenadine. Fexofenadine has been shown to be a substrate of P-glycoprotein (P-gp) (Cvetkovic et al., 1999; Perloff et al., 2002). Vectorial transport of fexofenadine in the basolateral-apical direction was observed in Caco-2 cells, and this was inhibited by inhibitors of P-gp, such as ritonavir and verapamil (Perloff et al., 2002). Transfection of MDRI P-gp cDNA into LLC-PK1 cells increased the vectorial transport of fexofenadine in the basolateral-apical direction (Cvetkovic et al., 1999). Furthermore, knockout of Mdr1a P-gp caused a significant increase in the plasma concentration of fexofenadine at 4 h after intravenous and oral administration. In addition, among the tissues examined, the brain-to-plasma concentration ratio of [14C]fexofenadine compared with that in wild-type mice was also increased (Cvetkovic et al., 1999). Therefore, P-gp limits the bioavailability and brain uptake of fexofenadine. It has been reported that nonsedating H1-receptor antagonists, such as loratadine, cetirizine, and desloratadine, are P-gp substrates, and their distribution in the brain is clearly increased in Mdr1a/1b P-gp knockout mice compared with wild-type, whereas there was no increase in the brain concentration of sedating H1-receptor antagonists (Chen et al., 2003). It is likely that P-gp acts as gatekeeper against nonsedating H1-receptor antagonists to prevent their adverse effects in the central nervous system (Chen et al., 2003). Fexofenadine is also transported by human and rat organic anion transporting polypeptides; OATP-A and OATP-B in humans and Oatp1, Oatp2, and Oatp3 in rats (Cvetkovic et al., 1999; Dresser et al., 2002). These transporters have been proposed as candidate transporter involved in the hepatic and intestinal uptake of fexofenadine (Cvetkovic et al., 1999; Milne et al., 2000). Especially, grapefruit juice reduced the bioavailability of fexofenadine, and this interaction has been proposed to be caused by an inhibition of intestinal uptake process mediated by OATP-B (Dresser et al., 2002; Nozawa et al., 2004).

Coperfusion of erythromycin caused a reduction in the biliary...
excretion clearance (Milne et al., 2000). Since erythromycin did not affect the liver/perfusate concentration ratio of fexofenadine, but decreased the bile/liver concentration ratio (Milne et al., 2000), the effect is ascribed to an inhibition of biliary excretion. Taking into consideration the fact that fexofenadine is a substrate of P-gp, it is possible that the biliary excretion of fexofenadine is mediated by P-gp. The primary purpose of the present study is to examine the involvement of P-gp in the biliary excretion of fexofenadine. In vivo pharmacokinetic studies were carried out under steady-state conditions using Mdr1a/1b double knockout mice. Export of xenobiotic compounds across the canalicular membrane is carried out by a number of transporters. In addition to P-gp, there are two other ABC transporters: multidrug resistance-associated protein 2 (Mrp2/AhcC2) and breast cancer resistance protein (BCRP/ABCG2). It is generally accepted that Mrp2 plays a major role in the biliary excretion of various kinds of glutathione and glucuronide conjugates and nonconjugated amphipathic organic anions (Suzuki and Sugiyama, 2002). Bcrp/BCRP is an ATP-binding cassette half-transporter originally identified in mitoxantrone-resistant tumor cells (MCF-7) (Doyle et al., 1998; Ross et al., 1999). Recently, it was shown that murine Bcrp is involved in the hepatobiliary excretion of a food-derived carcinogen, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, and its biliary excretion was markedly reduced in Bcrp knockout mice (van Waarden et al., 2003). These transporters may be involved in the biliary excretion of fexofenadine. Therefore, their involvement was also investigated using knockout mice and Mrp2-deficient mutant rats (Eisai hyperbilirubinemic rats; EHBRs).

Materials and Methods

Materials. Fexofenadine hydrochloride was purchased from Toronto Research Chemicals (North York, ON, Canada). All other chemicals and reagents were obtained from Kanto Kagaku (Tokyo, Japan) or Wako Pure Chemicals (Osaka, Japan) and were of the highest grade available.

Animals. Male FVB mice (wild type) and Mdr1a/1b P-gp knockout mice were obtained from Taconic Farms (Germantown, NY). Male Bcrp knockout mice were previously established by Jonker et al. (2002) and were a gift from Dr. A. H. Shinkel (Division of Experimental Therapy, The Netherlands Cancer Institute, Amsterdam, The Netherlands). Male SDRs and EHBRs were purchased from SLC (Shizuka, Japan) and maintained under standard conditions with a reverse dark/light cycle. Food and water were available ad libitum.

Intravenous Infusion. Mice of both strains, weighing approximately 25 to 35 g, were used throughout the experiments. Under anesthesia with pentobarbital sodium (Nembutal; Dainippon Pharmaceutical, Osaka, Japan), the tail vein was cannulated with a needle catheter for the injection of fexofenadine. Blood samples (approximately 100 μl) were collected from the tail vein at 105, 135, 165, and 215 min after starting the infusion. Plasma was prepared by centrifuging the blood samples (3000g). The rats were sacrificed after 215 min, and the entire liver was excised immediately. The tissues were weighted and stored at −80°C until required for assay. The protocols for the animal experiments were approved by Tokyo University Animal Care Committee.

Oral Administration. Both wild-type and Mdr1a/1b P-gp knockout mice, weighing approximately 27 to 31 g, were used throughout the experiments. The mice received a 10-mg/kg oral dose of fexofenadine (1 mg/ml in 0.5% vol methylcellulose; Wako Pure Chemicals). Blood samples (approximately 30 μl) were collected from the tail vein at the dose of 1 mg/kg, 1, 2, 4, 6, and 8 h after oral administration under light ether anesthesia. Plasma was prepared by centrifuging the blood samples (3000g). The plasma was stored at −80°C until required for assay.

Kinetic Analysis. The steady-state plasma concentration (C_{ss}) was assessed as the mean plasma concentration at 75, 105, 135, and 150 min for mice, and 105, 135, 165, 195, and 205 min for rats, whereas the steady-state liver (C_{liver}^{\text{ss}}) and steady-state brain (C_{brain}^{\text{ss}}) concentrations were determined at 150 min for mice and 205 min for rats, respectively. The total plasma clearance (CL_{plasma}) was obtained by dividing the infusion rate by C_{ss}. The bile clearance (CL_{bile,plasma}) gave the mean clearance value calculated by dividing the biliary excretion rates (V_{bile}) by CL_{plasma}. CL_{bile,liver} was the biliary clearance based on the liver concentration, which was obtained by dividing the biliary excretion rates by C_{liver}. The K_{bile,liver} and K_{bile,brain} represented the ratio of C_{liver} to C_{ss} and C_{brain} to C_{ss}, respectively. The area under the plasma concentration-time curve from time 0 to infinity (AUC_{0-\infty}) of fexofenadine was calculated using the linear trapezoidal rule. The plasma AUC beyond the last time point to infinity was estimated by dividing the predicted plasma concentration at the last time point by the calculated terminal elimination rate constant (\lambda_{e}). The k_{e} was obtained from a log linear regression analysis of the last three data points of the plasma concentration-time curve. The terminal elimination half-life (t_{1/2}\_e) was obtained from ln2/k_{e}.

Quantitation of Fexofenadine in Plasma, Bile, Liver, and Brain. Sample Pretreatment. Plasma (5 μl) was mixed with 15 μl of 0.05% vol formic acid and precipitated with methanol (40 μl) containing midazolam (500 ng/ml) as the internal standard (I.S.). Bile (5 μl) was mixed with 15 μl of 0.05% vol formic acid and precipitated with methanol (200 μl) containing I.S. After centrifugation (15,000g; 10 min) of the mixture, 50 μl of 0.05% formic acid was added to the 50 μl of supernatant. Liver and brain were added to a 3-fold volume of 80% vol methanol containing I.S. and homogenized with a handy type homogenizer (Miltiporo 395; Dorem Corp, Racine, WI). After centrifugation (15,000g; 10 min) of the homogenate, the supernatant was diluted with an equal volume of 0.05% vol formic acid. In all cases, an aliquot of the supernatant was transferred to a new tube after centrifugation. The resulting supernatant fractions from plasma (10 μl), bile (5 μl), liver (10 μl), and brain (40 μl) were subjected to LC/MS analysis to determine the concentration of fexofenadine.

LC/MS Instrumentation and Operating Conditions. A sensitive method was developed to determine fexofenadine in plasma, bile, and tissues by high-performance liquid chromatography-electrospray ionization mass spectrometry with midazolam as the internal standard. The LC/MS consisted of an Alliance HT 2790 separation module with an autosampler (Waters, Milford, MA) and Micromass ZQ mass spectrometer with an electro ion spray interface (Waters). The optimum operating conditions used were as follows: electrospray probe (capillary) voltage, 2.7 kV; sample cone voltage, 35 V; and source temperature, 100°C. The spectrometer was operated at a drying desolvation gas flow rate of 300 l/h. The mass spectrometer was operated in the selected ion monitoring mode using the respective MH+ ions m/z 502.3 for fexofenadine and m/z 326.3 for the internal standard. The mobile phase used for high-performance liquid chromatography was methanol (A) and 0.05% formic acid (B). Chromatographic separation was achieved on a C18 column (Capcell pak C18, MG, 3 mm, 4.6 mm i.d. × 75 mm, particle size 3 μm; Shiseido, Tokyo, Japan).
Japan) using a linear gradient from 55% A to 70% A over 5 min and returning to 55% A within 2 min.

The quantification limits of this method were 2 to 500 ng/ml in plasma, 5 to 200 μg/ml in bile, 0.5 to 10 μg/g in liver, and 5 to 100 ng/g in brain, respectively. Instrument control and data analysis were performed using Mass Lynx application software (Waters).

Results

Steady-State Pharmacokinetics of Fexofenadine in Mdr1a/1b P-gp Knockout Mice. Plasma concentrations and biliary excretion rates of fexofenadine at steady state in Mdr1a/1b P-gp knockout mice are shown in Fig. 1. The pharmacokinetic parameters are summarized in Table 1. The plasma concentrations of fexofenadine reached steady state within the 75 min during the constant infusion of fexofenadine to both strains of mice (Fig. 1A). The CL\textsubscript{plasma} of fexofenadine was similar in wild-type and Mdr1a/1b P-gp knockout mice, 30.1 ± 2.4 versus 30.7 ± 5.4 ml/min/kg, respectively. The CL\textsubscript{bile,plasma} accounts for 56 and 72% of the total body clearance in wild-type and Mdr1a/1b P-gp knockout mice (Table 1) and was slightly greater in Mdr1a/1b P-gp knockout mice. The intrinsic biliary excretion clearance of fexofenadine with respect to its liver concentration (CL\textsubscript{bile,liver}) was similar for wild-type and Mdr1a/1b P-gp knockout mice (Table 1). A significant increase was observed in the K\textsubscript{p,brain} between wild-type (0.0394 ± 0.0033 ml/g brain) and Mdr1a/1b P-gp knockout (0.130 ± 0.021 ml/g brain) mice (p < 0.01; Fig. 1C).

Oral Administration of Fexofenadine in Mdr1a/1b P-gp Knockout Mice. Plasma concentrations of fexofenadine after oral administration to Mdr1a/1b P-gp knockout and wild-type mice at a dose of 10 mg/kg are shown in Fig. 2. The plasma concentration and AUC\textsubscript{0-inf} of fexofenadine were significantly increased in Mdr1a/1b P-gp knockout mice compared with wild-type mice after oral administration (p < 0.01). The times to reach the peak plasma concentration were 1.50 ± 0.71 and 4.0 ± 0.0 h, and the peak serum concentrations (C\textsubscript{max}) were 73.6 ± 5.9 and 303 ± 71 nM for wild-type and Mdr1a/1b P-gp knockout mice, respectively. Knockout of Mdr1a/1b caused a 6-fold increase in the AUC\textsubscript{0-inf} from 243 ± 37 to 1543 ± 223 nmol · h/ml. The terminal half-lives in wild-type and Mdr1a/1b P-gp knockout mice were 1.49 ± 0.21 and 1.54 ± 0.04 h, respectively, and this difference was not significant. The bioavailability calculated from the pharmacokinetic parameters obtained from in vivo studies was 2.38 ± 0.37 and 15.5 ± 2.2% in wild-type and Mdr1a/1b P-gp knockout mice, respectively.

Steady-State Pharmacokinetics of Fexofenadine in EHBRs. Plasma concentration and biliary excretion rates of fexofenadine at steady state in EHBRs are shown in Fig. 3. The pharmacokinetic parameters are summarized in Table 2. The plasma concentrations of fexofenadine reached equilibrium at approximately 75 min during the constant infusion of fexofenadine to both normal rats and EHBRs (Fig. 3A). The CL\textsubscript{plasma} values of fexofenadine in SDRs and EHBRs were 28.3 ± 2.1 and 27.2 ± 1.8 ml/min/kg, respectively, and the CL\textsubscript{bile,liver} values were similar in SDRs and EHBRs (Table 2). Pravastatin was used as positive control, and its biliary clearance was markedly reduced in EHBRs compared with SDRs (data not shown).

Steady-State Pharmacokinetics of Fexofenadine in Bcrp Knockout Mice. Plasma concentrations and biliary excretion rate of fexofenadine at steady state in Bcrp knockout mice are shown in Fig. 4. The pharmacokinetic parameters are summarized in Table 3. The plasma concentration reached steady state within approximately 75 min during the constant infusion of fexofenadine to both strains of mice (Fig. 4A). The CL\textsubscript{plasma} values of fexofenadine in wild-type and Bcrp knockout mice were 27.0 ± 4.7 and 29.9 ± 2.1 ml/min/kg, respectively. There was no statistical difference in the CL\textsubscript{bile,plasma} or CL\textsubscript{bile,liver} between wild-type and Bcrp knockout mice (Table 3). The K\textsubscript{p} values in the liver and brain were also comparable in wild-type and Bcrp knockout mice (Fig. 4, C and D).

Discussion

In vivo steady-state pharmacokinetic analyses were carried out to determine quantitatively the importance of P-gp in the biliary excretion of fexofenadine at the canalicular membrane using Mdr1a/1b P-gp knockout mice. A previous study had been carried out in Mdr1a P-gp knockout mice (Cvetkovic et al., 1999). Knockout of Mdr1a causes absence of P-gp at the blood-brain barrier and small intestine; however, it induces the expression of another isoform of Mdr1b P-gp in the liver and kidney (Schinkel et al., 1994). Therefore, the Mdr1a P-gp knockout mouse is not appropriate to investigate an involvement of P-gp in the biliary and urinary excretion.

The total body clearance and biliary clearance of fexofenadine with regard to the plasma concentration were determined in mice at steady-
Since Cvetkovic et al. (1999) determined the plasma concentration at 4 h after administration, it may be possible that reabsorption of fexofenadine excreted into the intestine occurs. Alternatively, it is also possible that the total radioactivity in the plasma might include metabolites of fexofenadine as well as its intact form since Cvetkovic et al. (1999) determined the plasma concentration by measuring the radioactivity without separation, and according to our kinetic study, the metabolic clearance accounts for a substantial fraction of the total body clearance (~30–50%), at least in mice (Table 1).

Fexofenadine was concentrated in the bile, even compared with the total concentration in the liver, about 10-fold, and a similar value has been reported by Milne et al. (2000). Absence of the effect of P-gp knockout on the biliary excretion of fexofenadine suggests an involvement of another efflux transporter(s). Two ABC transporters, Mdr1a and Bcrp, are alternative candidates, and their involvement was investigated using Mdr2-deficient mutant rats and Bcrp knockout mice. The kinetic parameters for the biliary excretion clearance (CLbile) of fexofenadine in EHBs were comparable with those in SDRs between SDR and EHB (Table 2). Similar results were obtained for the comparison of the kinetic parameters between wild-type and Bcrp knockout mice (Fig. 3; Table 3). Absence of Mdr2 and Bcrp did not affect the biliary excretion of fexofenadine. Finally, we were able to exclude the involvement of P-gp, Mdr2, and Bcrp in the biliary excretion of fexofenadine. Multiplicity of canalicular transporters has been proposed for the biliary excretion of pravastatin, telmisartan, E3040-glucuronide, E3040-sulfate, grepafloxacin, the taurine conjugate of Z-335 (Z-335-tau), and the active metabolite of prurifloxacin (Takenaka et al., 1995; Yamazaki et al., 1996; Sasabe et al., 1998; Nishino et al., 2000; Kawabata et al., 2004). Of these compounds, the biliary excretion of Z-335-tau has been suggested to be mediated by ABC transporters (Kawabata et al., 2004). ATP-dependent uptake of Z-335-tau was still observed in the membrane vesicles from EHBs and inhibited by digoxin P-gp inhibitor taurocholate, estrone sulfate estradiol 17β-glucuronide, and bromosulfophthalein, although their inhibition constants were greater than their own Km values. In addition to Z-335-tau, neither Mdr2 nor P-gp is a major transporter governing the biliary excretion of the active metabolite of prurifloxacin, although the brain distribution is limited by P-gp (Yagi et al., 2003). Further studies are required to clarify the multiplicity of canalicular transport mechanisms for xenobiotics.

The present study provides evidence that P-gp restricts the brain penetration and intestinal absorption, but it plays only a minor role in the pharmacokinetics of fexofenadine in blood in mice. In contrast to the observations in mice, it is unlikely that P-gp plays an important role in limiting the oral absorption in humans under normal conditions since verapamil treatment did not affect the intestinal absorption rate (Tannergren et al., 2003), and the C3435T polymorphism, which is associated with lower intestinal P-glycoprotein expression, has no effect on the disposition of fexofenadine (Drescher et al., 2002). However, treatment of rifampicin (Hamman et al., 2001) or St John’s wort (Wang et al., 2002) caused an increase in oral clearance, which

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**TABLE 1**

<table>
<thead>
<tr>
<th>CL</th>
<th>Mdr1a/1b P-gp knockout</th>
<th>Wild-type mice</th>
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</thead>
<tbody>
<tr>
<td>CLbile &amp; liver</td>
<td>17.0 ± 2.1</td>
<td>6.94 ± 0.092</td>
</tr>
<tr>
<td>CLbile</td>
<td>22.2 ± 2.1</td>
<td>7.86 ± 1.45</td>
</tr>
<tr>
<td>Vbile</td>
<td>8.28 ± 1.13</td>
<td>2.33 ± 0.34</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01.
may be accounted for by an induction of intestinal P-gp through a nuclear receptor pregnane X receptor (Geick et al., 2001). Under such circumstances, P-gp is likely to become one of determinant factors limiting the oral absorption of fexofenadine as observed in mice. Whether P-gp limits the brain uptake of fexofenadine in human remains unknown. Sadeque et al. (2000) have reported an interaction between quinidine and loperamide, which resulted in loperamide respiratory depression. This interaction has been interpreted as the inhibition of P-gp-mediated efflux of loperamide by quinidine at the BBB. Taking into consideration the fact that nonsedating H1-receptor

### TABLE 2
Pharmacokinetic parameters of fexofenadine during constant infusion to EHBRs and SDRs

<table>
<thead>
<tr>
<th></th>
<th>C_{ss} (nmol/l)</th>
<th>C_{liver} (nmol/l)</th>
<th>CL_{total} (ml/min/kg)</th>
<th>CL_{bile,plasma} (ml/min/kg)</th>
<th>CL_{bile,liver} (ml/min/kg)</th>
<th>V_{bile} (nmol/min)</th>
<th>Bile Flow (µl/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDR</td>
<td>680 ± 51</td>
<td>13.5 ± 1.4</td>
<td>28.3 ± 2.1</td>
<td>11.4 ± 1.6</td>
<td>0.537 ± 0.033</td>
<td>7.73 ± 0.78</td>
<td>22.6 ± 0.7</td>
</tr>
<tr>
<td>EHBR</td>
<td>675 ± 56</td>
<td>13.2 ± 0.8</td>
<td>27.2 ± 1.8</td>
<td>10.7 ± 1.9</td>
<td>0.496 ± 0.027</td>
<td>7.27 ± 0.69</td>
<td>14.5 ± 0.66**</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01.

### TABLE 3
Pharmacokinetic parameters of fexofenadine during constant infusion to Bcrp knockout and wild-type mice

<table>
<thead>
<tr>
<th></th>
<th>C_{ss} (nmol/l)</th>
<th>C_{liver} (nmol/l)</th>
<th>CL_{total} (ml/min/kg)</th>
<th>CL_{bile,plasma} (ml/min/kg)</th>
<th>CL_{bile,liver} (ml/min/kg)</th>
<th>V_{bile} (nmol/min)</th>
<th>Bile Flow (µl/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>bcrp(+/+)</td>
<td>354 ± 55</td>
<td>8.59 ± 0.99</td>
<td>27.0 ± 4.7</td>
<td>12.0 ± 0.8</td>
<td>0.444 ± 0.051</td>
<td>4.08 ± 1.02</td>
<td>2.54 ± 0.16</td>
</tr>
<tr>
<td>bcrp(-/-)</td>
<td>348 ± 41</td>
<td>8.49 ± 1.45</td>
<td>29.9 ± 2.1</td>
<td>14.5 ± 1.0</td>
<td>0.550 ± 0.060</td>
<td>4.19 ± 1.20</td>
<td>2.19 ± 0.19</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01.

FIG. 3. Plasma concentration-time profile (A) and biliary excretion rate (B) of fexofenadine during constant infusion to SDRs and EHBRs during the constant infusion of fexofenadine. The infusion rates of fexofenadine in SDR (open circles) and EHBR (closed circles) were 1.08 ± 0.02 and 1.14 ± 0.07 µmol/h/kg, respectively. Each point represents the mean ± S.E. (n = 4).

FIG. 4. Plasma concentration-time profile (A), biliary excretion rate (B), brain-to-plasma (K_{p,brain}) (C), and liver-to-plasma (K_{p,liver}) (D) concentrations ratios of fexofenadine in Bcrp knockout and wild-type mice during the constant infusion of fexofenadine. The infusion rates of fexofenadine in Bcrp knockout (open circles) and wild-type (closed circles) mice were 0.614 ± 0.037 and 0.554 ± 0.038 µmol/h/kg, respectively. Statistical differences between Bcrp knockout mice and wild-type mice were calculated by a two-sided unpaired Student’s t test with p < 0.05 as the limit of significance (+, p < 0.05; **, p < 0.01). Each point represents the mean ± S.E. (n = 3).
antagonists are substrates of P-gp, it presumably acts as a gatekeeper for fexofenadine and other nonselecting H₁-receptor antagonists at the BBB.

In conclusion, P-gp is involved in the efflux transport of fexofenadine in the small intestine and BBB in mice; however, other unknown efflux transporters will be a determinant factor of the biliary excretion.

References


References


