Involvement of Breast Cancer Resistance Protein (ABCG2) in the Biliary Excretion Mechanism of Fluoroquinolones

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ABSTRACT:

Fluoroquinolones are effective antibiotics for the treatment of bile duct infections. It has been shown that the biliary excretion of grepafloxacin is partly accounted for by multidrug resistance-associated protein 2 (MRP2/ABCC2), whereas neither MRP2 nor P-glycoprotein is involved in the biliary excretion of ulifloxacin. In the present study, we examined the involvement of breast cancer resistance protein (BCRP/ABCG2) in the biliary excretion of fluoroquinolones (grepafloxacin, ulifloxacin, ciprofloxacin, and ofloxacin). In Madin-Darby canine kidney II cells expressing human BCRP or mouse Bcrp, the basal-to-apical transport of grepafloxacin and ulifloxacin was greater than that of the mock control, which was inhibited by a BCRP inhibitor, 3-[6-isobutyl-9-methoxy-1,4-dioxo-1,2,3,4,6,7,12a-octahydropyrazino[1/2/1,6]pyrido[3,4-b]indol-3-yl]-propionic acid tert-butyl ester (Ko143). Plasma and bile concentrations of fluoroquinolones were determined in wild-type and Bcrp(−/−) mice after i.v. bolus injection. The cumulative biliary excretion of fluoroquinolones was significantly reduced in Bcrp(−/−) mice, resulting in a reduction of the biliary excretion clearances to 86, 50, 40, and 16 of the control values, for ciprofloxacin, grepafloxacin, ofloxacin, and ulifloxacin, respectively. Preinclusion of sulfobromophthalein significantly inhibited the biliary excretion of grepafloxacin in Bcrp(−/−) mice. There was no change in the tissue/plasma concentration ratios of fluoroquinolones in the liver or brain, whereas those in the kidney were increased 3.6- and 1.5-fold for ciprofloxacin and grepafloxacin, respectively, in Bcrp(−/−) mice but were unchanged for ofloxacin and ulifloxacin. The present study shows that BCRP mediates the biliary excretion of fluoroquinolones and suggests that it is also involved in the tubular secretion of ciprofloxacin and grepafloxacin.

Fluoroquinolones, inhibitors of bacterial DNA gyrase, exhibit strong antibacterial activities against a variety of bacteria, especially aerobic Gram-negative organisms. Orally administered fluoroquinolones are widely distributed throughout the body after rapid absorption from the intestine. Many fluoroquinolones undergo either hepatic or renal elimination. Metabolism accounts for the hepatic elimination of fluoroquinolones, and biliary excretion is usually a minor elimination pathway. However, it has been reported that the concentrations of ciprofloxacin in the bile are far greater than the usual minimal inhibitory concentration of common biliary pathogens in humans, presumably because of active transport as the ratio of the concentrations of ciprofloxacin in bile/liver was greater than unity (Dan et al., 1987). Prulifloxacin, an ester type prodrug of ulifloxacin, is immediately metabolized to ulifloxacin in the intestine, and 10% is recovered in the bile (Nakashima et al., 1994). Grepafloxacin and sparfloxacin are mainly eliminated from the liver by metabolism and biliary excretion, but very little is excreted into urine (Efthymiopoulos et al., 1997; Kamberi et al., 1998).

Although their ability to undergo biliary excretion is one of the crucial factors for their therapeutic efficacy against bile duct infections, the underlying mechanism of fluoroquinolones has not been fully investigated. A number of reports have shown that several kinds of transporters are expressed on the canalicular membrane in the liver and are responsible for the efficient elimination of drugs into the bile (Chandra and Brouwer, 2004; Pauli-Magnus and Meier, 2006; Shitara et al., 2006). It is generally accepted that the transport of a variety of anionic drugs across the canalicular membrane is mainly mediated by multidrug resistance-associated protein 2 (MRP2/ABCC2), and some hydrophobic cationic drugs are eliminated into the bile by P-glycoprotein (Schinkel et al., 1995; Chandra and Brouwer, 2004). The biliary excretion of grepafloxacin is partly mediated by MRP2 as the biliary excretion of grepafloxacin was significantly reduced in MRP2-deficient mice after i.v. bolus injection. The cumulative biliary excretion of fluoroquinolones was significantly reduced in Bcrp(−/−) mice, resulting in a reduction of the biliary excretion clearances to 86, 50, 40, and 16 of the control values, for ciprofloxacin, grepafloxacin, ofloxacin, and ulifloxacin, respectively. Preinclusion of sulfobromophthalein significantly inhibited the biliary excretion of grepafloxacin in Bcrp(−/−) mice. There was no change in the tissue/plasma concentration ratios of fluoroquinolones in the liver or brain, whereas those in the kidney were increased 3.6- and 1.5-fold for ciprofloxacin and grepafloxacin, respectively, in Bcrp(−/−) mice but were unchanged for ofloxacin and ulifloxacin. The present study shows that BCRP mediates the biliary excretion of fluoroquinolones and suggests that it is also involved in the tubular secretion of ciprofloxacin and grepafloxacin.

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ABBREVIATIONS: MRP (Mrp), multidrug resistance-associated protein; EHBR, Eisai hyperbilirubinemic rat; P-gp, P-glycoprotein; UFX, ulifloxacin; GPFX, grepafloxacin; BCRP (Bcrp), breast cancer resistance protein; CPFX, ciprofloxacin; OFX, ofloxacin; Ko143, 3-[6-isobutyl-9-methoxy-1,4-dioxo-1,2,3,4,6,7,12a-octahydropyrazino[1/2/1,6]pyrido[3,4-b]indol-3-yl]-propionic acid tert-butyl ester; MDCK, Madin-Darby canine kidney; GFP, green fluorescent protein; h, human; m, mouse; LC, liquid chromatography; MS, mass spectrometry; BSP, sulfobromophthalein; BBB, blood-brain barrier.
cient mutant rats (EHBRs) (29% of normal rats) (Sasabe et al., 1998).

Although grepafloxacin is a substrate of P-gp, its biliary excretion is unchanged in Mdr1a/1b(−/−) mice, excluding the involvement of P-gp (Sasabe et al., 2004). For ulifloxacin, neither MRP2 nor P-gp is involved in its biliary excretion (Yagi et al., 2003). Therefore, other transporters have been hypothesized to account for the biliary excretion of UFX and GPFX.

Breast cancer resistance protein (BCRP/ABCG2) is the half-size ATP-binding cassette transporter identified on the bile canalicular membrane (Maliepaard et al., 2001; Jonker et al., 2002). In vivo studies using Bcrp(−/−) mice have shown that BCRP accounts for the biliary excretion of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, pitavastatin, and methotrexate (Hirano et al., 2005; Mao and Unadkat, 2005). Merino and colleagues (Merino et al., 2006; Pulido et al., 2006) demonstrated that fluoroquinolones, such as ciprofloxacin (CPFX), ofloxacin (OFX), enrofloxacin, and norfloxa-

Materials and Methods

Animals. Male Bcrp(−/−) and wild-type FVB mice (16–18 weeks old) were used in the present study. Bcrp(−/−) mouse lines were established previously (Jonker et al., 2002). All animals were maintained under standard conditions with a reverse dark/light cycle and were treated humanely. Food and water were available ad libitum. The studies reported in this article were performed in accordance with the guidelines provided by the Institutional Animal Care Committee (Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan).

Materials. UFX was a gift from Meiji Seika (Tokyo, Japan). GPFX and OFX were gifts from Otsuka Pharmaceutical Company (Tokyo, Japan). CPFX and sulfobromophthalein were purchased from MP Biomedicals Inc. (Irvine, CA) and Sigma-Aldrich (St. Louis, MO), respectively. Ko143 was supplied from Dr. A. H. Schinkel (The Netherlands Cancer Institute, Amsterdam, The Netherlands).
Netherlands) (Allen et al., 2002). Parent MDCK II cells were kindly provided by Dr. Piet Borst (The Netherlands Cancer Institute, Amsterdam, The Netherlands). All other chemicals were of analytical grade and were commercially available.

Cell Culture. MDCK II cells (Matsushima et al., 2005) were grown in Dulbecco’s modified Eagle’s medium low glucose (Invitrogen, Carlsbad, CA) supplemented with 10% fetal bovine serum (Sigma-Aldrich, St. Louis, MO), 100 U/ml penicillin, and 100 μg/ml streptomycin at 37°C with 5% CO2 and at 95% humidity.

Transcellular Transport Study. MDCK II cells were seeded in 24-well plates at a density of 1.4 × 10⁵ cells/well (Matsushima et al., 2005). For constructing MDCK II cells expressing human and mouse BCRP, and GFP as a negative control (hBCRP-MDCK, mBcrp-MDCK, and GFP-MDCK, respectively), MDCK II cells were infected with recombinant adenovirus containing human and mouse BCRP and GFP cDNA (200 multiplicity of infection), 48 h before all experiments (Matsushima et al., 2005). Krebs-Henseleit buffer consisted of 142 mM NaCl, 23.8 mM Na₂CO₃, 4.83 mM KCl, 0.96 mM KH₂PO₄, 1.20 mM MgSO₄, 12.5 mM HEPES, 5 mM glucose, and 1.53 mM CaCl₂, adjusted to pH 7.4. The experiments were initiated by replacing the medium on either the apical or basal side of the cell layer with complete medium containing fluoroquinolone (10 μM) with or without Ko143 (1 μM). The cells were incubated at 37°C, and aliquots of medium were taken from each compartment at designated time points. The medium (100 μl) was mixed with 50 μl of methanol containing 0.15% formic acid, followed by centrifugation at 4°C and 10,000g for 10 min. The supernatant was subjected to analysis by LC/MS. At the end of the experiments, the cells were solubilized in 450 μl of 0.2 N NaOH. After the addition of 225 μl of 0.4 N HCl, aliquots of cell lysate were used to determine protein concentrations. Protein concentrations were determined by the method of Lowry et al. (1951), and bovine serum albumin was used as a standard.

In Vivo Study in Mice. Male FVB and Bcrp(−/−) mice weighing approximately 25 to 36 g were used throughout these experiments. Under urethane anesthesia (1.5 mg/kg), the gallbladder was ligated, and the bile duct was cannulated with a Teflon catheter (UT-03; Unique Medical Co., Ltd, Tokyo, Japan) for bile collection. The mice received a bolus administration of each fluoroquinolone at a dose of 1 mg/kg via the jugular vein. Blood samples were collected from the opposite jugular vein at 7.5, 15, 30, 60, and 120 min. Bile was collected in preweighed test tubes at 30-min intervals throughout the experiments. Plasma was prepared by centrifugation of the blood samples. The mice were sacrificed after 120 min, and the entire liver, kidney, and brain were excised immediately. The tissues were weighed and stored at −80°C until quantification. Portions of liver, kidney, and brain were added to 2 volumes of phosphate-buffered saline (w/v) and homogenized. Plasma (25 μl), bile (10 μl), or tissue homogenate (100 μl) was deproteinized with 2 volumes of methanol containing 0.15% formic acid (w/v), followed by centrifugation at 4°C and 10,000g for 10 min. The supernatant was diluted with 0.05% formic acid and analyzed by LC/MS.

FIG. 2. Time profiles of transcellular transport of UFX across MDCK II monolayers expressing transporters. Transcellular transport of UFX (10 μM) with or without Ko143 (1 μM) across MDCK II monolayers expressing hBCRP (A and B) and mBcrp (C and D) was compared with that across control MDCK II monolayers expressing GFP (E and F). ○ and ●, transcellular transport with or without Ko143 (1 μM), respectively. A, C, and E represent the transcellular transport in the apical-to-basal direction, and B, D, and F represent that in the basal-to-apical direction. Each point plotted, with its vertical bar, represents the mean ± S.E. (n = 4). *, P < 0.05; ***, P < 0.01 versus control values.
Transcellular transport of fluoroquinolones across MDCK II monolayers expressing transporters and inhibition of transcellular transport by Ko143

<table>
<thead>
<tr>
<th></th>
<th>Apical to Basal (A to B)</th>
<th>Basal to Apical (B to A)</th>
<th>Ratio (B to A/A to B)</th>
<th>µg/mg protein</th>
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<tr>
<td><strong>GPFX</strong></td>
<td></td>
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<tr>
<td>GF</td>
<td>84.3 ± 14.6</td>
<td>91.4 ± 7.5</td>
<td>1.08 ± 0.21</td>
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<tr>
<td>hBCRP</td>
<td>25.4 ± 3.3</td>
<td>251 ± 38</td>
<td>9.87 ± 1.98**††</td>
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<td>mBcrp</td>
<td>43.8 ± 6.5</td>
<td>178 ± 25</td>
<td>4.05 ± 0.82**</td>
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<tr>
<td>GPFX + Ko143</td>
<td></td>
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<tr>
<td>GF</td>
<td>102 ± 3</td>
<td>113 ± 2</td>
<td>1.10 ± 0.04</td>
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<tr>
<td>hBCRP</td>
<td>115 ± 8</td>
<td>135 ± 12</td>
<td>1.17 ± 0.13</td>
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<tr>
<td>mBcrp</td>
<td>108 ± 5</td>
<td>118 ± 5</td>
<td>1.09 ± 0.06</td>
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<td><strong>UFX</strong></td>
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<tr>
<td>GF</td>
<td>76.9 ± 15.6</td>
<td>47.8 ± 5.1</td>
<td>0.62 ± 0.14</td>
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<td>hBCRP</td>
<td>90.7 ± 3.5</td>
<td>166 ± 25</td>
<td>1.84 ± 0.28**</td>
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<td>mBcrp</td>
<td>53.4 ± 7.4</td>
<td>78.3 ± 11.5</td>
<td>1.46 ± 0.30††</td>
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<tr>
<td>UFX + Ko143</td>
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<tr>
<td>GF</td>
<td>101 ± 15</td>
<td>70.0 ± 18.4</td>
<td>0.69 ± 0.21</td>
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<td>hBCRP</td>
<td>114 ± 24</td>
<td>95.1 ± 30.2</td>
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<tr>
<td>mBcrp</td>
<td>83.0 ± 11.2</td>
<td>38.6 ± 3.8</td>
<td>0.47 ± 0.08</td>
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*Transcellular transport in the apical-to-basal direction at 180 min.
†Transcellular transport in the basal-to-apical direction at 180 min.
**P < 0.05, significantly different from the corresponding parameters in GPFX expressing cells.
††P < 0.01.
†††P < 0.05, significantly different from the corresponding parameters with 1 µM Ko143.

Pharmacokinetic Analysis. The total plasma clearance (CL$_{total}$), biliary excretion clearance normalized by circulating plasma (CL$_{bile, plasma}$), and apparent intrinsic biliary excretion clearance (CL$_{bile, liver, app}$) were calculated using the following equations:

$$CL_{total} = \frac{Dose}{AUC_{inf}}$$

(1)

$$CL_{bile, plasma} = \frac{X_{bile}}{AUC_{0-120}}$$

(2)

$$CL_{bile, liver, app} = \frac{X_{bile}}{AUC_{0-120}/K_{plasma, liver, app}}$$

(3)

where dose, AUC$_{inf}$, AUC$_{0-120}$, X$_{bile}$, and K$_{plasma, liver, app}$ represent the dosage (in milligrams per kilogram), the area under the plasma concentration-time curve from 0 to $\infty$ min and 0 to 120 min (in micromolar units multiplied by the time in minutes), the amount excreted into the bile (in nanomoles per kilogram), and the liver/plasma concentration ratio at 120 min (in grams per milliliter), respectively. AUC was calculated using the trapezoidal method. The plasma concentration at 0 min and the time when the plasma concentration was diminished were acquired by the extrapolation.

Determination of Fluoroquinolones in the Specimens. The LC/MS system consisted of LC-20AD dual micro-plunger pumps, a SIL-20AC autosampler, a CTO-20AC column oven, and an LCMS-2010EV mass spectrometer (Shimadzu Corporation, Kyoto, Japan). The LC/MS analysis of fluoroquinolones was performed using an MHS C$^{18}$ column (50 × 2.1 mm; particle size, 3 µm) at the flow rate of 0.5 ml/min (Shiseido Co., Ltd, Tokyo, Japan). Two mobile phases were used for gradient elution as follows: for CPFX and OFX, 0.05% formic acid-acetonitrile 92.5%/7.5% at 0 to 0.5 min, 80%/20% at 0.5 to 2.5 min, and 92.5%/7.5% at 2.5 to 6.0 min. For GPFX and UFX, 0.05% formic acid-acetonitrile 88.5%/11.5% at 0 to 0.5 min, 80%/20% at 0.5 to 2.5 min, and 88.5%/11.5% from 2.5 min. The MS instrument used for this work was an LCMS-2010EV mass spectrometer (Shimadzu Corporation), which was operated in the positive-ion electrospray ionization mode. The m/z values monitored were 332, 360, 362, and 360 for CPFX, GPFX, OFX, and UFX, respectively. The retention times of CPFX, GPFX, OFX, and UFX were 2.5, 2.9, 2.2, and 2.7 min, respectively. The detection limits for these fluoroquinolones were 0.01 µg/mg in the transport buffer and plasma and 0.03 µg/mg in bile and tissue homogenates.

Statistical Analysis. Statistically significant differences in this study were determined using two-tailed unpaired t-tests. Differences were considered to be significant at P < 0.05.

Results

Transcellular Transport Of Fluoroquinolones across Monolayers of MDCK II Cells Expressing Human and Mouse BCRP. The transcellular transports of GPFX and UFX across the monolayers of hBCRP-, mBcrp- and GMPDCK were determined. Expression of human and mouse BCRP induced asymmetric transethelial transport of GPFX, enhanced the basal-to-apical transport, and reduced the apical-to-basal transport (Fig. 1). We compared the translocation of GPFX in the basal-to-apical direction for 120 min, which was approximately 10- and 4.0-fold greater than that in the opposite direction in hBCRP- and mBcrp-MDCK, respectively, and was identical in GMPDCK (Fig. 1). The translocation of UFX in the basal-to-apical direction for 120 min was slightly increased: 1.8- and 1.5-fold that in the opposite direction in hBCRP- and mBcrp-MDCK cells, respectively (Fig. 2), whereas that in the control was 0.6-fold. The ratio of the transcellular transport at 180 min (basal-to-apical/apical-to-basal) was greater than that in the presence of Ko143: 9.1- and 3.8-fold for GPFX and 3.0- and 2.4-fold for UFX, respectively, 9.87 versus 1.17, 4.05 versus 1.09, 1.84 versus 0.84, and 1.46 versus 0.47 (Table 1). Ko143 (1 µg/mg), an inhibitor of BCRP, reduced the directional transport of the fluoroquinolones observed in MDCK II cells expressing hBCRP and mBcrp.

Plasma Concentrations and Biliary Excretion Time Profiles and Liver Concentration in Mice after Bolus Administration of Fluoroquinolones. Male Bcrp(−/−) and FVB mice received a bolus administration of each fluoroquinolone antibiotic at a dose of 1 mg/kg via the jugular vein. Blood and bile were collected at designated time points. Plasma concentration time profiles of all fluoroquinolones were similar in Bcrp(−/−) and FVB mice, but the cumulative biliary excretion of all fluoroquinolones was significantly reduced in Bcrp(−/−) mice (Fig. 3). The pharmacokinetic parameters are summarized in Table 2. There was no significant difference in the plasma clearance of all fluoroquinolones in Bcrp(−/−) and FVB mice. The CL$_{bile, plasma}$ of CPFX, GPFX, and UFX was significantly reduced, but the reduction in the CL$_{bile, plasma}$ of OFX was not statistically significant.

The tissue/plasma concentration ratios in BCRP-expressing tissues such as liver, brain, and kidney were determined. In the liver and brain, the tissue-to-plasma concentration ratios of all fluoroquinolones were unchanged, whereas those of CPFX and GPFX in kidney were increased in Bcrp(−/−) mice (Table 2).

Inhibition Study of MRP2-Mediated Biliary Excretion of GPFX in Bcrp(−/−) Mice Using BSP Infusion. BSP administration caused no significant differences in the plasma total body clearance in Bcrp(−/−) mice with and without BSP infusion, but the cumulative biliary excretion of GPFX was reduced by BSP (Fig. 4). The CL$_{bile, plasma}$ of GPFX was slightly changed, but this was not statistically signifi-
The liver/plasma concentration ratio of GPFX was higher in the BSP-treated group, whereas the \( \text{CL}_{\text{bile, liver, app}} \) was significantly reduced in the BSP-treated group (Table 3).

**Discussion**

In this study, we investigated the involvement of BCRP in the biliary excretion and tissue distribution of fluoroquinolones using 

\[ \text{BCRP}^{-/-} \]

mice. To show that they are substrates of BCRP, their transcellular transport across monolayers of MDCK II cells was determined. BCRP is expressed on the apical membrane of MDCK II cells (Matsushima et al., 2005), and Merino et al. (2006) reported that the basal-to-apical transport of CPFX and OFX was increased in hBCRP- and mBcrp-MDCK and was reduced in the presence of Ko143, a BCRP specific inhibitor. Consistent with other fluoroquinolones, exogenous expression of hBCRP/mBcrp induced directional transport of GPFX in the basal-to-apical direction, which was reduced by a BCRP inhibitor, Ko143 (Fig. 1). Expression of hBCRP/mBcrp also significantly increased the Ko143-sensitive basal-to-apical transport of UFX (Fig. 2). The ratios of the transcellular transport of UFX in hBCRP/mBcrp-expressing cells were smaller than those of GPFX (Table 1), indicating that GPFX is a better hBCRP/mBcrp substrate with greater transport activities. Unlike GPFX, the apical-to-basal transport of UFX was greater than its basal-to-apical transport in control MDCK cells, suggesting that endogenous transporter(s) facilitate the apical-to-basal transport (Table 1).

The biliary excretion clearance of fluoroquinolones was compared between wild-type and 

\[ \text{BCRP}^{-/-} \]

mice. The cumulative biliary excretion of the fluoroquinolones, particularly UFX, was significantly reduced in 

\[ \text{BCRP}^{-/-} \]

mice, suggesting that BCRP plays a major role in the biliary excretion of UFX and partly accounts for the biliary excretion of other fluoroquinolones. The plasma concentration-time profiles of the fluoroquinolones were not affected by knockout of...
to the total sequestration pathways from the liver. Indeed, Sasabe et al. (1997) suggested that sinusoidal efflux is the major elimination pathway from the liver in rats in a study in which the hepatic clearance of GPFX was compared with the hepatic uptake clearance.

Although GPFX is a mBcrp substrate with greater transport activity than UFX, the magnitude of the reduction in the biliary excretion clearance of GPFX was lower than that of UFX. Because involvement of MRP2 in the biliary excretion of GPFX has been suggested by in vivo kinetic analysis using EHBR, the discrepancy may be explained by the smaller contribution of mBcrp to the net canalicular efflux process of GPFX. This possibility was investigated by examining an inhibitory effect of BSP on the biliary excretion of GPFX. BSP caused only a minimal difference in the CL_{bile, plasma} in Bcrp(−/−) mice. However, taking the greater hepatic concentration in the BSP-treated group into consideration, the biliary excretion clearance will be significantly inhibited with regard to the hepatic concentration, suggesting an involvement of BSP-sensitive efflux transporter at the canalicular membrane, presumably MRP2. The increased concentration produced by BSP may be ascribed to an inhibition of hepatic metabolism and/or sinusoidal efflux of GPFX. Considering the kinetic analyses by Sasabe et al. (1997), it can be speculated that BSP inhibits the sinusoidal efflux of GPFX. This hypothesis should be investigated using the in situ perfusion technique to compare the concentration time profile in the outflow in mice treated with and without BSP.

In addition to the liver, we observed that the kidney/plasma concentration ratios of CPFX and GPFX are 3.6 and 1.5 times higher in Bcrp(−/−) mice than that in FVB mice. Although very little GPFX is excreted into the urine in rats (Sasabe et al., 1998), the urinary excretion accounts for the 50% of the total body clearance in EHBRs (Nouaille-Degorce et al., 1998). BCRP may play a significant role in the urinary excretion of CPFX as well as in its biliary excretion. It should be noted that the protein expression of BCRP was below the limit of detection in human kidney (Maliepaard et al., 2001). Because CPFX undergoes tubular secretion in humans, which is inhibited by probenecid (Jaehde et al., 1995), other transporters will account for the luminal efflux of CPFX in humans.

Epileptogenic neurotoxicity is a well known central nervous system side effect of fluoroquinolones and, thus, transport of the BBB is a critical factor for this adverse effect together with the inhibition...
potency of GABA receptors. Fluoroquinolones have been suggested to undergo active efflux at the BBB because the steady-state brain interstitial space concentration of fluoroquinolones was markedly lower than their plasma unbound concentrations (Ooie et al., 1997b), and the permeability surface area product of the efflux transport was 10- to 300-fold greater than the uptake clearance (Ooie et al., 1997a). Using P-gp knockout mice, P-gp has been shown to limit the brain uptake of GPFX and UFHX (Murata et al., 1999; Sasabe et al., 2004). The present study has demonstrated the limited role of Bcrp in the efflux transport of fluoroquinolones at the BBB, and, unlike the liver, P-gp is probably responsible for major efflux transport of fluoroquinolones at the BBB. The mRNA quantification of Mdr1a showed more abundant expression in the cerebral cortex than in the liver (Brady et al., 2002) and vice versa for Bcrp (Tanaka et al., 2005). This observation may explain the tissue-selective contribution of P-gp and Bcrp to the net efflux process in the liver and brain.

This study showed that Bcrp is involved in the biliary excretion of CPFX, GPFX, OFX, and UFX. The hepatic expression of BCRP is dependent on gender (Merino et al., 2002) and vice versa for Bcrp (Tanaka et al., 2005). This observation suggests that the tissue-selective contribution of P-gp and Bcrp contributes to the tissue distribution and pharmacokinetics of dexamethasone, digoxin, and cyclosporin A. P-glycoprotein in mice affects tissue distribution and pharmacokinetics of dexamethasone, digoxin, and cyclosporin A.

References


