The Effect of Bcrp1 (Abcg2) on the *In vivo* Pharmacokinetics and Brain Penetration of Imatinib Mesylate (Gleevec): Implications for the Use of Breast Cancer Resistance Protein and P-Glycoprotein Inhibitors to Enable the Brain Penetration of Imatinib in Patients

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Abstract

Imatinib mesylate (signal transduction inhibitor 571, Gleevec) is a potent and selective tyrosine kinase inhibitor, which was shown to effectively inhibit platelet-derived growth factor–induced glioblastoma cell growth preclinically. However, in patients, a limited penetration of imatinib into the brain has been reported. Imatinib is transported *in vitro* and *in vivo* by P-glycoprotein (P-gp; ABCB1), which thereby limits its distribution into the brain in mice. Previously, imatinib was shown to potently inhibit human breast cancer resistance protein (BCRP; ABCG2). Here, we show that imatinib is efficiently transported by mouse Bcrp1 in transfected Madin-Darby canine kidney strain II (MDCKII) monolayers. Furthermore, we show that the clearance of i.v. imatinib is significantly decreased 1.6-fold in *Bcrp1* knockout mice compared with wild-type mice. At $t = 2$ hours, the brain penetration of i.v. imatinib was significantly 2.5-fold increased in *Bcrp1* knockout mice compared with control mice. We tested the hypothesis that P-gp and BCRP inhibitors, such as elacridar and pantoprazole, improve the brain penetration of imatinib. Firstly, we showed *in vitro* that pantoprazole and elacridar inhibit the Bcrp1-mediated transport of imatinib in MDCKII-*Bcrp1* cells. Secondly, we showed that co-administration of pantoprazole or elacridar significantly reduced the clearance of i.v. imatinib in wild-type mice by respectively 1.7-fold and 1.5-fold. Finally, in wild-type mice treated with pantoprazole or elacridar, the brain penetration of i.v. imatinib significantly increased 1.8-fold and 4.2-fold, respectively. Moreover, the brain penetration of p.o. imatinib increased 5.2-fold when pantoprazole was co-administered in wild-type mice. Our results suggest that co-administration of BCRP and P-gp inhibitors may improve delivery of imatinib to malignant gliomas. (Cancer Res 2005; 65(7): 2577-82)

Introduction

Imatinib mesylate (signal transduction inhibitor 571, Gleevec) has shown marked clinical efficacy and safety in Bcr/Abl-expressing chronic myeloid leukemia and c-Kit–expressing gastrointestinal stromal tumors (1, 2). In addition, preclinical *in vitro* and *in vivo* studies have shown that imatinib effectively inhibits platelet-derived growth factor-induced glioblastoma cell growth (3, 4).

Primary tumors of the central nervous system (CNS; e.g., glioblastoma multiforme) are, respectively, the third and fourth leading cause of cancer-related death among male and female young adults. Moreover, primary brain tumors are the most common solid tumor of childhood and the second leading cause of cancer death in children after leukemia. Unfortunately, the treatment of primary CNS tumors is often limited by low distribution of antitumor agents into the brain as a result of a proficient blood–brain barrier containing various efflux transporters. These include P-glycoprotein (P-gp; MDR1, ABCB1) and Breast Cancer Resistance Protein (BCRP; ABCG2), which can eliminate xenobiotics from the brain against a concentration gradient, thereby limiting CNS exposure to these compounds (5–7). A limited penetration of imatinib into the cerebrospinal fluid of humans and nonhuman primates has been reported (8–10). Preclinical *in vitro* and *in vivo* studies have shown that P-gp plays an important role in the transport of imatinib and limits the distribution of imatinib to the brain (11, 12). These studies also showed that P-gp inhibitors, like cyclosporin A and zosuquidar (LY335979), can effectively block the P-gp–mediated transport of imatinib *in vitro* and improve the brain penetration of imatinib in mice. Houghton et al. (13) recently showed that imatinib mesylate potently reverses BCRP-mediated resistance, but they concluded that it is not a BCRP substrate for efflux. However, as imatinib is a lipophilic drug, we hypothesized that imatinib is also a BCRP substrate. To test this hypothesis and extend the observations of Houghton et al. (13) and the recent finding of Burger et al. (14) that imatinib is a BCRP substrate in drug accumulation assays, we first investigated in Sf9-BCRP membrane vesicles whether imatinib could inhibit the BCRP-mediated transport of methotrexate (MTX; ref. 15). Secondly, we studied in Madin-Darby canine kidney strain II (MDCKII)-*Bcrp1* monolayers whether imatinib is transported by Bcrp1. In addition, we studied in the MDCKII-*Bcrp1* monolayers the effect of the P-gp and BCRP inhibitors elacridar and pantoprazole (15) on the transport of imatinib. Finally, we studied in *Bcrp1* knockout, *Mdr1a/1b* knockout, and wild-type mice the role of Bcrp1, relative to P-gp, in the *in vivo* pharmacokinetics and brain penetration of i.v. and p.o. imatinib in the absence or presence of P-gp and BCRP inhibitors.

Materials and Methods

Materials. Imatinib (signal transduction inhibitor 571) and [^{14}C]imatinib (both as the mesylate salt) were kindly provided by Novartis Pharma AG

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(Basel, Switzerland). Pantoprazole (Pantozol, 40 mg i.v., Altana Pharma, Hoofddorp, the Netherlands) was obtained from the pharmacy of the Netherlands Cancer Institute. Elacridar (GF120918) was a generous gift from Glaxo Wellcome (Research Triangle Park, NC).

Preparation of membrane vesicles and vesicular transport assays. Membrane vesicles from Sf9 cells and HEK293 cells were prepared and vesicular transport assays done as described before (15, 16). The ATP-dependent uptake of [^{3}H]MTX into Sf9-*BCRP*, and of [^{3}H]$E_2$17βG into Sf9-*MRP1-3* and HEK293-*MRP4* membrane vesicles, and of [^{3}H]alaninyl-d4TMP into HEK293-*MRP5* membrane vesicles in the absence and presence of varying concentrations of imatinib mesylate was studied following the rapid filtration method as previously described (15, 16).

Transport across Madin-Darby canine kidney strain II monolayers. The MDCKII cells were cultured in DMEM supplemented with 10% FCS and 100 units penicillin/streptomycin per milliliter. Cells were grown at 37°C with 5% CO_2 under humidifying conditions. Polarized MDCKII cells stably expressing human *MRP2* (*ABCC2*) or murine *Bcrp1* (*Abcg2*) cDNA have been described before (15, 17). Transepithelial transport assays were done as previously described (15).

Animals. Animals used in this study were male *Bcrp1*$^{-/-}$ (Bcrp1 knockout), *Mdr1a/1b*$^{-/-}$ (P-gp knockout), and wild-type mice of a comparable genetic background (FVB) between 9 and 14 weeks of age. Mice were housed and handled according to institutional guidelines complying with Dutch legislation as described before (15).

Drug solutions. A mixture of imatinib mesylate and [^{14}C]imatinib (~3 μCi) was diluted with 0.9% NaCl to a final concentration of 1.6 mg/mL for i.v. administration or to a final concentration of 12.8 mg/mL for p.o. administration. A vial of pantoprazole (Pantozol, 40 mg) was diluted with 0.9% NaCl to a final concentration of 8 mg/mL. Elacridar was suspended at 10 mg/mL in a mixture of hydroxypropylmethylcellulose (10 g/L)/2% Tween 80/H_2O [0.5:1:98.5 (v/v/v)] for p.o. administration.

Drug administration and analysis. All mice received [^{14}C]imatinib mesylate either by i.v. administration in the tail vein at a dose of 12.5 mg/kg or by p.o. administration at a dose of 100 mg/kg. The study comprised nine different study groups:

1. Wild-type control mice, receiving i.v. NaCl 0.9% 3 minutes before i.v. imatinib.
2. *Bcrp1* knockout mice, receiving i.v. NaCl 0.9% 3 minutes before i.v. imatinib.
3. *Mdr1a/1b* knockout mice, receiving i.v. NaCl 0.9% 3 minutes before i.v. imatinib.
4. Wild-type mice, receiving p.o. elacridar (100 mg/kg; ref. 18) 2 hours before i.v. imatinib.
5. Wild-type mice, receiving i.v. pantoprazole (40 mg/kg; ref. 15) 3 minutes before i.v. imatinib.
6. *Bcrp1* knockout mice, receiving i.v. pantoprazole (40 mg/kg; ref. 15) 3 minutes before i.v. imatinib.
7. *Mdr1a/1b* knockout mice, receiving i.v. pantoprazole (40 mg/kg; ref. 15) 3 minutes before i.v. imatinib.
8. Wild-type control mice, receiving p.o. NaCl 0.9% 5 minutes before p.o. imatinib and 1 hour after administration of imatinib.
9. Wild-type mice, receiving p.o. pantoprazole (40 mg/kg) 5 minutes before p.o. imatinib and 1 hour after administration of imatinib.

Blood samples (30 μL) were taken from the tail vein at 5, 15, 30, 60, 90, and 120 minutes after i.v. administration of imatinib, or at 10, 20, 40, 60, 120, 180, and 240 minutes after p.o. administration of imatinib. After the last sampling time point, animals were anesthetized with methoxyflurane, their remaining blood collected by cardiac puncture, and organs were removed after sacrifice by cervical dislocation. Coagulation of blood was prevented by use of heparinized capillaries for blood sampling. The plasma fraction of the blood samples was collected after centrifugation at 3,000 × *g* for 5 minutes. The organs were homogenized in 4% (w/v) bovine serum albumin. Radioactivity in the plasma samples and the tissue homogenates was determined by liquid scintillation counting (Tri-Carb 2100 CA Liquid Scintillation analyzer, Canberra Packard, Groningen, the Netherlands).

Pharmacokinetic and statistical analyses. Pharmacokinetic parameters after administration of imatinib were calculated by noncompartmental methods using the software package MW (version 3.02, MediWare, Groningen, the Netherlands).

The area under the plasma concentration–time curve (AUC) was calculated from 0 to 120 minutes (i.v. imatinib) or from 0 to 240 minutes (p.o. imatinib) using the linear-logarithmic trapezoidal method. The clearance was calculated by the formula Cl = dose / AUC (15).

The two-sided unpaired Student's *t* test was used to assess the statistical significance of difference between two sets of data. Results are presented as means ± SD. Differences were considered to be statistically significant when $P < 0.05$.

Calculation of brain penetration of imatinib. We determined the brain concentration of imatinib by measuring the radioactivity in whole brain homogenates, which were collected 2 hours after administration of i.v. imatinib or 4 hours after administration of p.o. imatinib. Because imatinib has a low CNS distribution (8–10), we subtracted the concentration of imatinib in the brain vascular space (i.e., 1.4% of the plasma concentration at $t = 2$ hours for i.v. imatinib or at $t = 4$ hours for p.o. imatinib) from the brain concentration found in whole brain homogenates (11). We then calculated the brain penetration of i.v. imatinib by determining the imatinib brain concentration at $t = 2$ hours relative to the plasma AUC (0-2 hours), as the AUC better reflects the overall imatinib exposure to the brain than the plasma concentration at 2 hours after administration. The brain penetration of p.o. imatinib was calculated in the same manner using the AUC (0-4 hours).

Results and Discussion

Effect of imatinib on BCRP-mediated transport of methotrexate in Sf9-membrane vesicles. Using Sf9-*BCRP* membrane vesicles, we studied the effect of imatinib mesylate on the transport of 100 μmol/L MTX. The ATP-dependent transport of MTX by BCRP was inhibited by imatinib in a concentration-dependent manner, as shown in Fig. 1 (IC_{50} value ~0.2 μmol/L), confirming that imatinib potently inhibits BCRP-mediated transport, as shown by Houghton et al. (13). Imatinib (up to 10 μmol/L concentrations) did not affect the MRP-mediated transport of $E_2$17βG, neither in Sf9 membrane vesicles, containing MRP1, 2, or 3, nor in HEK293 membrane vesicles, containing MRP4 (data not shown). The MRP5-mediated transport of alaninyl-d4TMP (16) was not affected either in membrane vesicles from HEK293 cells, stably overexpressing MRP5 (data not shown).

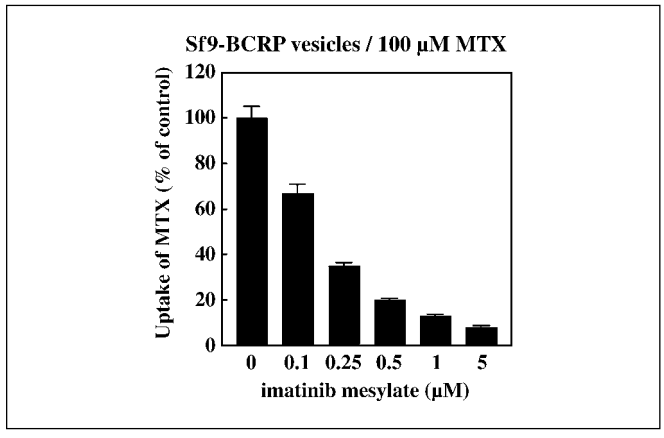

Figure 1. Effect of imatinib mesylate on ATP-dependent transport of MTX by BCRP. Sf9-BCRP membrane vesicles were incubated with 100 μmol/L [^{3}H]MTX for 5 minutes at 37°C in the absence or presence of the indicated concentrations of imatinib mesylate. The ATP-dependent transport is plotted as percentage of the control value. *Columns,* means of each experiment in triplicate; *bars,* SE.

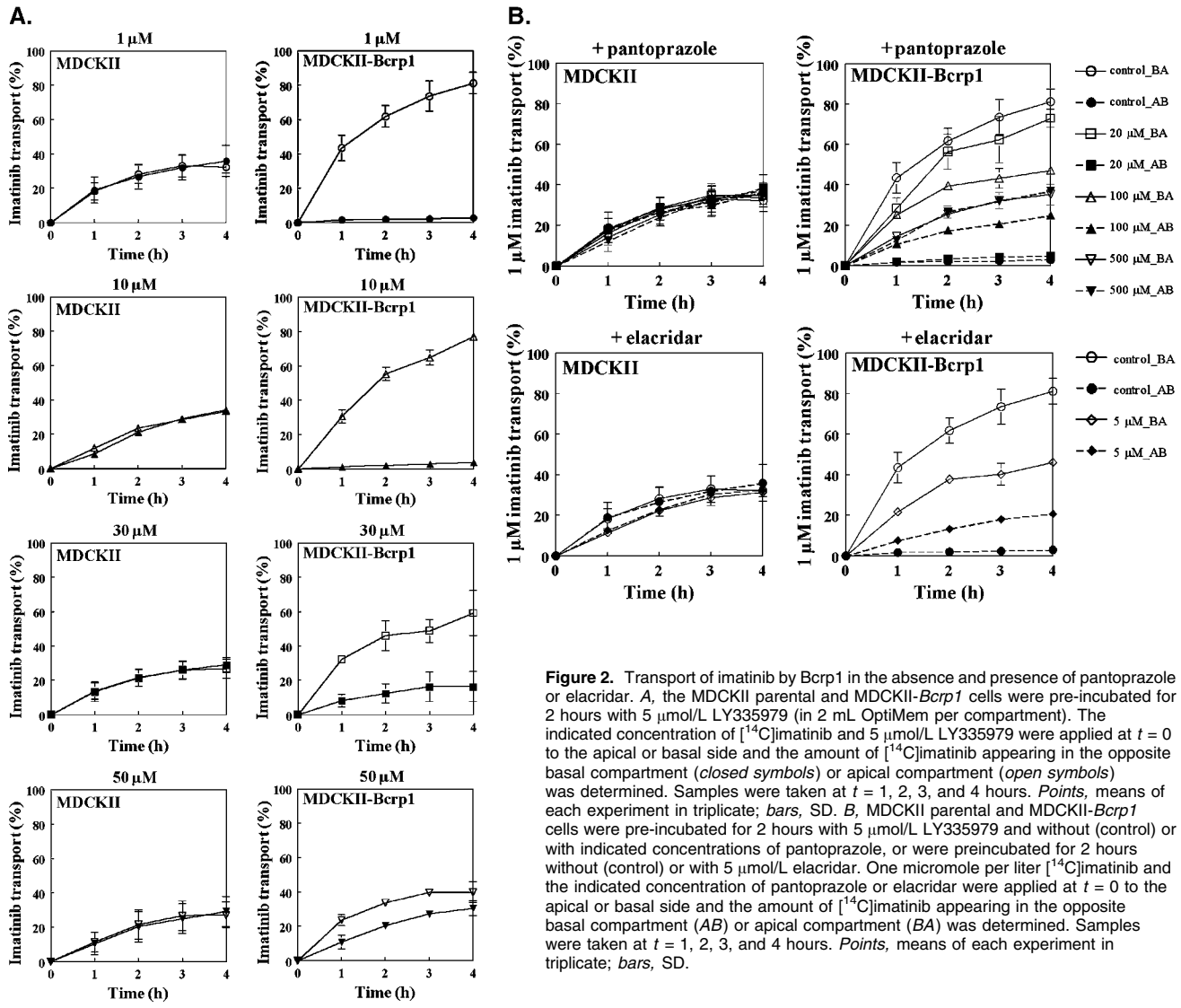

Figure 2. Transport of imatinib by Bcrp1 in the absence and presence of pantoprazole or elacridar. *A,* the MDCKII parental and MDCKII-*Bcrp1* cells were pre-incubated for 2 hours with 5 μmol/L LY335979 (in 2 mL OptiMem per compartment). The indicated concentration of [^{14}C]imatinib and 5 μmol/L LY335979 were applied at $t = 0$ to the apical or basal side and the amount of [^{14}C]imatinib appearing in the opposite basal compartment (*closed symbols*) or apical compartment (*open symbols*) was determined. Samples were taken at $t = 1$, 2, 3, and 4 hours. *Points,* means of each experiment in triplicate; *bars,* SD. *B,* MDCKII parental and MDCKII-*Bcrp1* cells were pre-incubated for 2 hours with 5 μmol/L LY335979 and without (control) or with indicated concentrations of pantoprazole, or were preincubated for 2 hours without (control) or with 5 μmol/L elacridar. One micromole per liter [^{14}C]imatinib and the indicated concentration of pantoprazole or elacridar were applied at $t = 0$ to the apical or basal side and the amount of [^{14}C]imatinib appearing in the opposite basal compartment (*AB*) or apical compartment (*BA*) was determined. Samples were taken at $t = 1$, 2, 3, and 4 hours. *Points,* means of each experiment in triplicate; *bars,* SD.

Transport of imatinib across MDCKII-monolayers. Transport of imatinib by Bcrp1 was studied in MDCKII-*Bcrp1* and MDCKII parental cells (15). To exclude any contribution of P-gp (12), the P-gp inhibitor zosuquidar (5 μmol/L) was added (18). We found efficient transport of 1 and 10 μmol/L imatinib by Bcrp1 (~20% net active transport per h), which was saturable at concentrations above 10 μmol/L (Fig. 2*A*). Imatinib was not transported by MRP2 (data not shown). As shown by Dai et al. (11), the net active transport of 1.9 μmol/L imatinib by P-gp in MDCKII cells was ~6% per hour; thus, Bcrp1 seems to transport imatinib at least as efficiently as P-gp.

Effect of pantoprazole and elacridar on Bcrp1-mediated transport of imatinib *in vitro*. The effect of pantoprazole and elacridar on the transport of 1 μmol/L imatinib was also investigated in MDCKII-transfected cells. In the experiments in which the effect of pantoprazole was studied, we also added the P-gp inhibitor zosuquidar (5 μmol/L) to exclude any contribution of P-gp (11, 12). Pantoprazole and elacridar inhibited the Bcrp1-mediated transport of imatinib (Fig. 2*B*).

Role of Bcrp1 in the clearance of imatinib in mice. In cancer patients, imatinib is administered p.o., but to exclude any variation at the absorption level, we initially administered [^{14}C]imatinib mesylate (12.5 mg/kg) i.v. to *Bcrp1*$^{-/-}$ (*Bcrp1* knockout), *Mdr1a/1b*$^{-/-}$ (*P-gp* knockout), and wild-type mice. We determined the clearance after measurement of imatinib plasma concentrations by total radioactivity over a 120-minute time period. As shown in Fig. 3*A*, the clearance of i.v. imatinib was 1.6-fold decreased in *Bcrp1* knockout mice compared with control mice ($P < 0.01$). In *P-gp* knockout mice, the clearance of i.v. imatinib was 1.25-fold decreased compared with control mice ($P < 0.01$). These results show that Bcrp1 plays an important, and maybe even a more prominent role than P-gp, in the clearance of i.v. imatinib in mice.

Effect of P-glycoprotein and Bcrp1 inhibitors on the clearance of intravenous imatinib in mice. We administered i.v. [^{14}C]imatinib mesylate (12.5 mg/kg) to mice, which were pretreated either with p.o. elacridar (17, 18), or with i.v. pantoprazole (15), or with solvent only as control. As shown in Fig. 3*B*, the clearance of i.v. imatinib in wild-type mice pretreated with elacridar was 1.5-fold

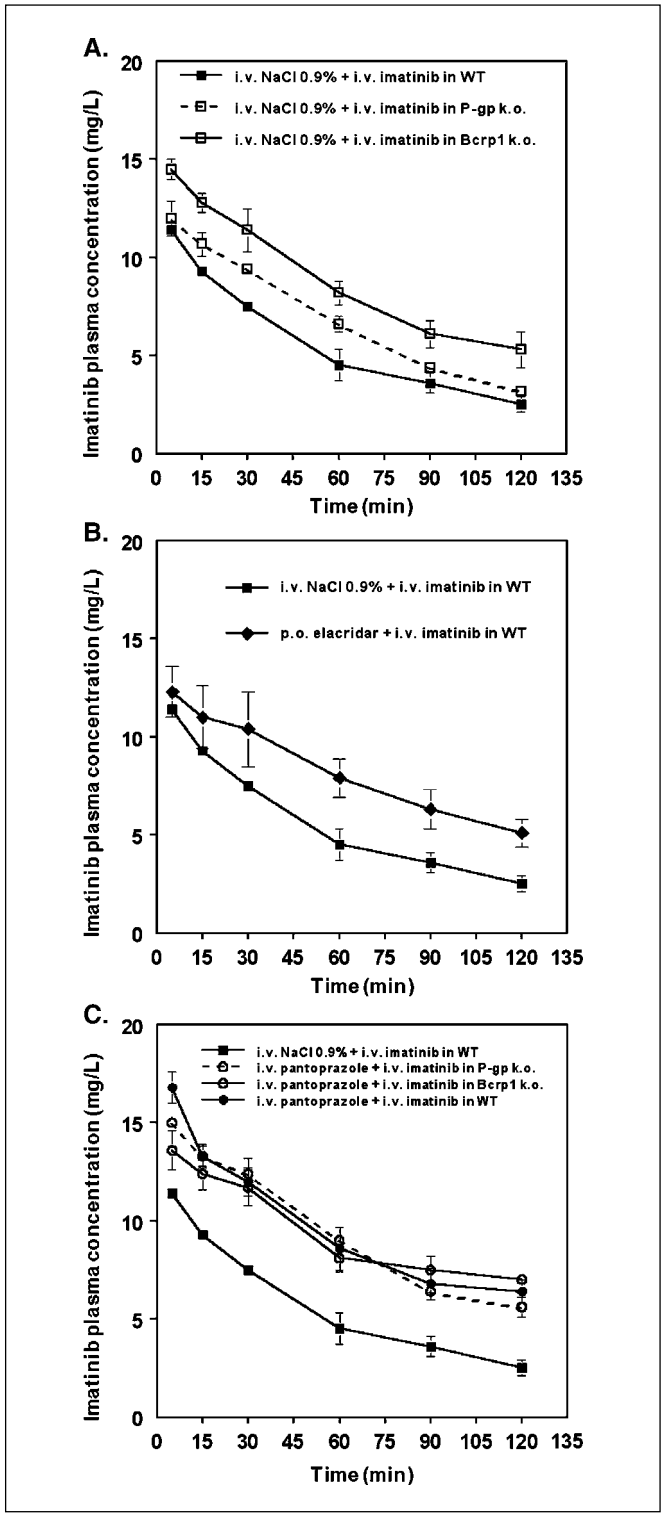

Figure 3. Linear plots of [^{14}C]imatinib plasma concentration versus time curves in mice. *Bcrp1* knockout (*k.o.*) mice, *P-gp* knockout (*k.o.*) or wild-type mice (*WT*) were treated with i.v. NaCl 0.9% (control) 3 minutes before an i.v. dose of [^{14}C]imatinib mesylate (12.5 mg/kg), or with i.v. pantoprazole (40 mg/kg) 3 minutes before an i.v. dose of [^{14}C]imatinib mesylate, or wild-type mice were pretreated with p.o. elacridar (100 mg/kg) 2 hours before an i.v. dose of [^{14}C]imatinib mesylate. *A,* role of Bcrp1 and P-gp in the pharmacokinetics of i.v. imatinib, as determined in knockout mice. *B,* effect of the P-gp and BCRP inhibitor elacridar on the pharmacokinetics of i.v. imatinib. *C,* effect of pantoprazole on the pharmacokinetics of i.v. imatinib. Plasma levels of radiolabeled imatinib were determined by liquid scintillation counting at t = 5, 15, 30, 60, 90, and 120 minutes. *Points,* means; *bars,* SD (n = 3).

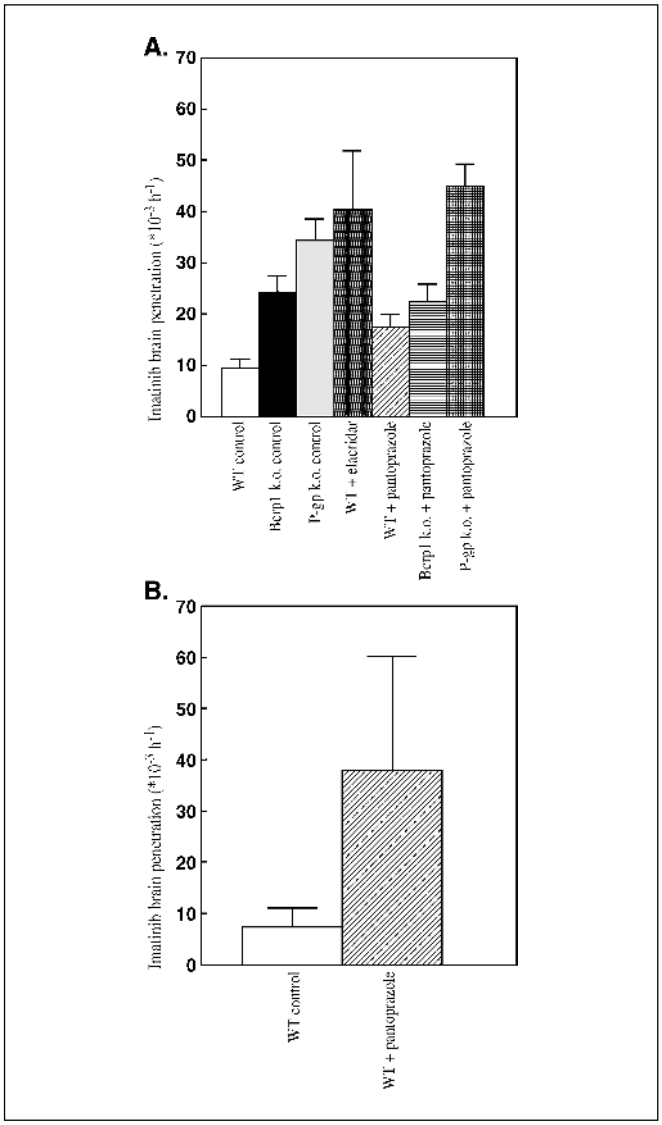

Figure 4. Brain penetration of [^{14}C]imatinib mesylate in mice. *A,* control wild-type mice were treated with i.v. NaCl 0.9% 3 minutes before an i.v. dose of [^{14}C]imatinib mesylate (12.5 mg/kg). To determine the role of Bcrp1 relative to P-gp in the brain penetration of imatinib, *Bcrp1* knockout and *P-gp* knockout mice were pretreated with i.v. NaCl 0.9% (control) and compared with control mice ($P < 0.01$). To determine the effect of a P-gp and BCRP inhibitor on the brain penetration of imatinib, wild-type mice were treated with p.o. elacridar (100 mg/kg) 2 hours before an i.v. dose of [^{14}C]imatinib mesylate and compared with control wild-type mice ($P < 0.05$) and with control *Bcrp1* knockout ($P = 0.08$) and control *P-gp* knockout mice ($P = 0.45$). To determine the effect of pantoprazole on the brain penetration of imatinib, wild-type, *Bcrp1* knockout, and *P-gp* knockout mice were treated with i.v. pantoprazole (40 mg/kg) 3 minutes before an i.v. dose of [^{14}C]imatinib mesylate and compared with control ($P < 0.05$). At 2 hours postdose, the plasma and whole brain tissue homogenate were collected and counted for radioactivity. The brain penetration, calculated as the brain concentration at t = 2 hours to plasma AUC (0-2 hours) ratio of each test group, is plotted (the brain concentration is corrected for the brain vascular space, i.e., 1.4% of plasma concentration at t = 2 hours). *Columns,* mean; *bars,* SD (n = 3). *B,* control wild-type mice were treated with p.o. NaCl 0.9% 5 minutes before a p.o. dose of [^{14}C]imatinib mesylate (100 mg/kg) and with a second dose of p.o. NaCl 0.9% 1 hour after administration of imatinib. To determine the effect of p.o. pantoprazole on the brain penetration of p.o. imatinib, wild-type mice were treated with p.o. pantoprazole (40 mg/kg) 5 minutes before a p.o. dose of [^{14}C]imatinib mesylate (100 mg/kg) and with a second dose of p.o. pantoprazole (40 mg/kg) 1 hour after administration of imatinib and compared with control mice ($P < 0.05$). At 4 hours postdose, the plasma and whole brain tissue homogenate were collected and counted for radioactivity. The brain penetration, calculated as the brain concentration at t = 4 hours to plasma AUC (0-4 hours) ratio of each test group, is plotted (the brain concentration is corrected for the brain vascular space, i.e., 1.4% of plasma concentration at t = 4 hours). *Columns,* mean; *bars,* SD (n = 5).

decreased compared with control mice ($P < 0.05$) and was not significantly different from the clearance in *Bcrp1* knockout and *P-gp* knockout mice (Fig. 3*A* and *B*). As shown in Fig. 3*C*, the clearance of i.v. imatinib in mice pretreated with pantoprazole was 1.7-fold decreased compared with control mice ($P < 0.001$). In *Bcrp1* knockout mice pretreated with pantoprazole, the clearance of i.v. imatinib was 1.7-fold decreased compared with control wild-type mice ($P < 0.001$) and was not significantly different from control *Bcrp1* knockout mice (Fig. 3*A* and *C*). In *P-gp* knockout mice pretreated with pantoprazole, the clearance of i.v. imatinib was 1.7-fold decreased compared with control mice ($P < 0.001$) and was 1.4-fold decreased compared with control *P-gp* knockout mice ($P < 0.001$; Fig. 3*A* and *C*). These results suggest that co-administration of pantoprazole decreases the clearance of i.v. imatinib by competition for Bcrp1. Overall, these data show that co-administration of a P-gp and BCRP inhibitor reduces the clearance of i.v. imatinib, in line with the results obtained with the knockout mice.

Effect of Bcrp1 on the brain penetration of intravenous imatinib in mice. As shown in Fig. 4*A*, the brain penetration of i.v. imatinib in *Bcrp1* knockout mice was 2.5-fold increased compared with control mice, whereas in *P-gp* knockout mice this was 3.6-fold increased. These results show that Bcrp1 in the blood-brain barrier limits the brain penetration of imatinib, but to a lower extent than P-gp does.

Effect of P-glycoprotein and Bcrp1 inhibitors on the brain penetration of intravenous imatinib in mice. As shown in Fig. 4*A*, co-administration of the P-gp and BCRP inhibitor elacridar in wild-type mice increased the brain penetration of i.v. imatinib 4.2-fold compared with control mice, 1.7-fold compared with *Bcrp1* knockout mice that lack Bcrp1 but have P-gp, and 1.2-fold compared with *P-gp* knockout mice that lack P-gp but have Bcrp1. Taking into account that P-gp inhibition with a single dose of elacridar was ~70% to ~80% (18), the role for Bcrp1 in the brain penetration of imatinib is likely more important than suggested by the 1.2-fold increase in control mice compared with *P-gp* knockout mice. Thus, co-administration of elacridar effectively increases the brain penetration of imatinib, by inhibition of both P-gp and Bcrp1 at the blood-brain barrier.

The brain penetration of i.v. imatinib in wild-type mice pretreated with pantoprazole was 1.8-fold increased compared with control mice (Fig. 4*A*). In *P-gp* knockout mice pretreated with pantoprazole, the imatinib brain penetration was 4.7-fold increased compared with control wild-type mice and 1.3-fold compared with control *P-gp* knockout mice. Thus, when P-gp is absent, additional inhibition of Bcrp1 by pantoprazole further increases the brain penetration of imatinib. In *Bcrp1* knockout mice pretreated with pantoprazole, the brain penetration of imatinib increased 2.3-fold compared with control mice and was not significantly different from control *Bcrp1* knockout mice. These results suggest that co-administration of pantoprazole increases the brain penetration of imatinib in mice by inhibition of Bcrp1 and not by P-gp inhibition.

Effect of pantoprazole on the brain penetration of p.o. imatinib in mice. Both pantoprazole and imatinib are usually given as p.o. formulation to patients. Therefore, we also administered p.o. [^{14}C]imatinib mesylate (100 mg/kg) to wild-type mice, which were treated with p.o. pantoprazole or with p.o. NaCl 0.9% only as control. As shown in Fig. 4*B*, the brain penetration of p.o. imatinib in mice treated with p.o. pantoprazole was 5.2-fold increased compared with control mice. These results suggest that co-administration of p.o. pantoprazole and p.o. imatinib is more effective than co-administration of i.v. pantoprazole and i.v. imatinib to increase the brain penetration of imatinib. However, we cannot exclude that other mechanisms, such as Cyp3a-mediated metabolism, also play a role. Ketoconazole, a potent CYP3A4 inhibitor, was shown to significantly decrease the apparent clearance of p.o. imatinib with a mean reduction of 29% and decrease the AUC (0-24 hours) of the metabolite CGP74588 by 13% in patients (19). As pantoprazole only weakly inhibits human CYP3A4 (20), interference at the CYP3A4 level is most likely less important than for ketoconazole. To further elucidate whether Cyp3a metabolism of imatinib is inhibited in mice when pantoprazole is co-administered, additional studies in which parental imatinib and metabolites are quantitated need to be conducted.

In conclusion, our results show that besides P-gp, Bcrp1 also plays an important role in the pharmacokinetics and brain penetration of imatinib. The brain penetration of imatinib can be improved by the co-administration of P-gp and/or BCRP inhibitors, such as elacridar and pantoprazole. Furthermore, our results suggest that inhibition of both Bcrp1 and P-gp is more effective than inhibition of P-gp alone to increase the brain penetration of imatinib. Moreover, inhibition of Bcrp1 by co-administration of p.o. pantoprazole and p.o. imatinib is even more effective than co-administration of i.v. pantoprazole and i.v. imatinib to increase the brain penetration of imatinib. In view of reported CNS relapses in imatinib-treated patients with acute leukemias, and promising activity of imatinib against glioblastoma, our concept of improved delivery of imatinib to the brain by co-administration of P-gp and BCRP inhibitors warrants further preclinical and clinical investigations (21, 22).

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