Increased Penetration of Paclitaxel into the Brain by Inhibition of P-Glycoprotein

E. Marleen Kemper, A. Erik van Zandbergen, Cindy Cleypool, Henk A. Mos, Willem Boogerd, Jos H. Beijnen, and Olaf van Tellingen

The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, 1066 CX Amsterdam, the Netherlands [J. H. B., A. E. v. Z., C. C., W. B., J. H. B., O. v. T.]; GlaxoSmithKline BV, 3705 LZ Zeist, the Netherlands [H. A. M.]; Department of Neurology, Slotervaart Hospital, 1066 EC Amsterdam, the Netherlands [W. B.]; Department of Pharmacy and Pharmacology, The Netherlands Cancer Institute/Slotervaart Hospital, 1066 EC Amsterdam, the Netherlands [J. H. B.]; and Division of Drug Toxicology, Faculty of Pharmaceutical Sciences, Utrecht University, 3584 CA Utrecht, the Netherlands [J. H. B.]

ABSTRACT

P-Glycoprotein (Pgp) in the blood-brain barrier limits the uptake of substrate drugs into the brain. We have determined the efficacy of several (putative) inhibitors of Pgp (cyclosporin A, PSC833, GF120918, and Cremophor EL) on the penetration of paclitaxel into the mouse brain. Pgp inhibitors were administered p.o. before i.v. paclitaxel. Plasma and tissues were collected at 1, 4, 8, and 24 h and analyzed for paclitaxel by high-performance liquid chromatography. Pgp knockout mice were used as reference for complete blockade of Pgp and to determine the selectivity of Pgp inhibitors on the pharmacokinetics of paclitaxel. Cremophor EL had no effect at all. Increased brain uptake was observed with cyclosporin A (3-fold), PSC833 (6.5-fold), and GF120918 (5-fold), although the levels were lower than that observed in Pgp knockout mice (11-fold increase). Both cyclosporin A and PSC833 also markedly increased the plasma levels of paclitaxel in contrast to GF120918. Obviously, cyclosporin A and PSC833 markedly inhibited several elimination pathways of paclitaxel, whereas the reduced clearance of paclitaxel by GF120918 was most probably related to the inhibition of Pgp alone. After further optimization of the dose and schedule of GF120918, we could achieve paclitaxel brain levels of about 80–90% of those reached in Pgp knockout mice. It is warranted to test paclitaxel in combination with GF120918 in experimental brain tumor models and in clinical trials.

INTRODUCTION

Although the brain is among the best perfused organs in the body, most drugs do not accumulate into this tissue to levels that are therapeutically relevant. Effective drug accumulation into the brain is prevented by the BBB, which is physically located in the brain endothelial cells. In contrast to endothelial cells in most other organs, brain endothelial cells possess several barrier properties including close linkage by tight junctions, absence of fenestrations, and low pinocytic activity (1). As a consequence, substances can enter the brain only by passive transcellular diffusion or by selective carrier transport through the endothelial cells. Strong hydrophobicity, as defined by a high octanol-water partition coefficient, is an essential characteristic of a substance to cross the BBB (2, 3). However, there are many examples of relatively hydrophobic substances, including a broad range of potent anticancer drugs (e.g., Vinca alkaloids, taxanes, anthracyclines, and epipodophyllotoxins), that are unable to gain access to the brain. The presence of the multidrug transporter Pgp at the luminal side of the endothelial cells of the blood capillaries in the brain provides an explanation for these observations (4–6). Initially, Pgp was discovered by its ability to confer multidrug resistance in mammalian tumor cells by active extrusion of a wide range of cytotoxic drugs (7). Subsequent studies have revealed that Pgp is also present in many normal tissues, including the liver, kidney, intestines, and brain (8). The generation of mice with disrupted Pgp genes (Pgp knockout mice) confirmed the important protective pharmacological function of Pgp in the BBB (9, 10). In those mice, the penetration of vinblastine in the brain was 7–46-fold higher than that in the wild-type controls (11), showing that Pgp restricts the entry of its substrates into the brain. These results suggest that the lack of efficacy of chemotherapy in the treatment of brain tumors may be, at least in part, a pharmacokinetic problem. The pivotal role of Pgp in this matter does suggest that inhibition of this drug transporter may be an attractive mode to increase intracerebral penetration of cytotoxic agents and consequently to increase the efficacy of chemotherapy against CNS tumors. Arboix et al. (12) examined the influence of the Pgp inhibitors trifluoperazine, cyclosporin A, amiodaron, quinidine, Bay K8644, and verapamil on the brain penetration of vinblastine. They showed that even high doses of these inhibitors did not substantially increase the accumulation of vinblastine into the brain. Moreover, several inhibitors enhanced exposure of other tissues to vinblastine and potentially increase the toxic side effects of vinblastine. In recent years, more potent and selective inhibitors of Pgp have become available, such as the cyclosporin A.
Inhibition of Pgp in the Blood-Brain Barrier

Inhibition of Pgp in the Blood-Brain Barrier

-methylpaclitaxel were within the brain (17). It helps to increase its efficacy in patients with malignant tumors because it is a good Pgp substrate and an effective drug against a variety of neoplastic disorders growing outside the brain (15, 16). A double amount of Cremophor EL was prepared by dilution of Taxol® with a solution of Cremophor EL:ethanol: saline (1:1:4, v/v) to final concentrations of 1.5 mg/ml paclitaxel, thus containing 180 mg/ml Cremophor EL. Cyclosporin A (50 mg/ml) was diluted to 5 mg/ml on the day of administration with sterile saline. A 50 mg/ml stock solution of PSC833 was prepared by dissolving 250 mg of PSC833 in 2.5 ml of ethanol and 2.5 ml of Cremophor EL. On the day of administration, this solution was diluted further with sterile saline to final concentrations of 1.25 and 2.5 mg/ml. GF120918 (base) suspensions of 2.5 and 10 mg/ml were prepared by accurately weighing 40 or 160 mg of GF120918 (salt) and suspending this in 7.5 ml of water for injection (Braun, Emmer-Compascuum) and 7.5 ml of concentrated stock vehicle [10 g/liter hydroxypropyl methyl cellulose (100 centipoises; Sigma) and 2% Tween 80 in water for injection]. The suspension was mixed for 10 min and then further dispersed using a Polytron PT1200 homogenizer for 2 min. The suspension was kept protected from light and was stirred continuously.

### Table 1

AUCs (mean ± SE) of paclitaxel in plasma (µg/ml) and tissues (µg/g) from 0–8 h in plasma and heart and from 0–24 h in the other tissues.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Dose (mg/kg)</th>
<th>Administration inhibitor (h)</th>
<th>Plasma</th>
<th>Brain</th>
<th>Liver</th>
<th>Kidneys</th>
<th>Lungs</th>
<th>Heart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type mice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>90</td>
<td>0</td>
<td>3.2 ± 0.4</td>
<td>1.6 ± 0.2</td>
<td>126 ± 6</td>
<td>48.1 ± 2.3</td>
<td>34.9 ± 2.5</td>
<td>18.4 ± 1.0</td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>50</td>
<td>1</td>
<td>6.9 ± 0.8</td>
<td>1.8 ± 0.1</td>
<td>124 ± 7</td>
<td>34.7 ± 1.8</td>
<td>22.0 ± 0.9</td>
<td>15.4 ± 1.1</td>
</tr>
<tr>
<td>PSC833</td>
<td>25</td>
<td>1</td>
<td>5.8 ± 0.8</td>
<td>0.5 ± 0.1</td>
<td>290 ± 18</td>
<td>88.6 ± 6.5</td>
<td>41.9 ± 2.1</td>
<td>28.2 ± 1.6</td>
</tr>
<tr>
<td>GF120918</td>
<td>25</td>
<td>2</td>
<td>13.3 ± 0.7</td>
<td>4.5 ± 0.2</td>
<td>261 ± 14</td>
<td>206 ± 9</td>
<td>194 ± 7</td>
<td>127 ± 6</td>
</tr>
<tr>
<td>Knockout mice</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>12.5</td>
<td>4, –1, 2, 10, 20, and 44</td>
<td>9.2 ± 0.4</td>
<td>11.2 ± 1.3</td>
<td>176 ± 6</td>
<td>161 ± 5</td>
<td>138 ± 5</td>
<td>97.0 ± 4.0</td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>100</td>
<td>2</td>
<td>4.8 ± 0.4</td>
<td>11.6 ± 0.6</td>
<td>242 ± 6</td>
<td>68.0 ± 2.5</td>
<td>67.6 ± 3.6</td>
<td>31.4 ± 0.8</td>
</tr>
<tr>
<td>PSC833</td>
<td>100 (50)</td>
<td>2 (2 and 8)</td>
<td>6.2 ± 0.6</td>
<td>16.1 ± 1.1</td>
<td>292 ± 9</td>
<td>104 ± 3</td>
<td>85.1 ± 3.3</td>
<td>39.6 ± 1.3</td>
</tr>
<tr>
<td>GF120918</td>
<td>25</td>
<td>25</td>
<td>4.7 ± 0.2</td>
<td>18.6 ± 0.6</td>
<td>203 ± 10</td>
<td>74.5 ± 2.6</td>
<td>76.1 ± 2.1</td>
<td>35.3 ± 1.0</td>
</tr>
</tbody>
</table>

*CrEL, Cremophor EL.*

**MATERIALS AND METHODS**

**Chemicals.** Taxol® [paclitaxel; 6 mg/ml; formulated in Cremophor EL:ethanol, 1:1 (v/v)] and 2′-methylpaclitaxel were obtained from Bristol-Myers Squibb (Princeton, NJ), and paclitaxel pure compound originated from Sankyo (Tokyo, Japan). Cyclosporin A (50 mg/ml) formulated in Cremophor EL:ethanol (67.1:32.9, v/v) was obtained from Novartis Pharma (Basel, Switzerland), and Cremophor EL and Tween 80 were from Sigma (St. Louis, MO). PSC833 (Valspoda) and GF120918-HCl (Elacridar) were kindly provided by Novartis Pharma and Glaxo SmithKline (Research Triangle Park, NC), respectively.

**Preparation of Drug Solutions.** Paclitaxel solutions for i.v. injection were prepared by dissolving 30 mg of pure paclitaxel in 2.5 ml of ethanol and 2.5 ml of Tween 80. Before injection, this stock solution was diluted with sterile saline (Braun, Emmer-Compascuum) to a final drug concentration of 1.5 mg/ml and used within 4 h. The clinical formulation of paclitaxel (Taxol®) was diluted 4-fold with saline to a final concentration of 1.5 mg/ml paclitaxel. A solution containing a double amount of Cremophor EL was prepared by dilution of Taxol® with a solution of Cremophor EL:ethanol: saline (1:1:4, v/v) to final concentrations of 1.5 mg/ml paclitaxel, thus containing 180 mg/ml Cremophor EL. Cyclosporin A (50 mg/ml) was diluted to 5 mg/ml on the day of administration with sterile saline. A 50 mg/ml stock solution of PSC833 was prepared by dissolving 250 mg of PSC833 in 2.5 ml of ethanol and 2.5 ml of Cremophor EL. On the day of administration, this solution was diluted further with sterile saline to final concentrations of 1.25 and 2.5 mg/ml. GF120918 (base) suspensions of 2.5 and 10 mg/ml were prepared by accurately weighing 40 or 160 mg of GF120918 (salt) and suspending this in 7.5 ml of water for injection (Braun, Emmer-Compascuum) and 7.5 ml of concentrated stock vehicle [10 g/liter hydroxypropyl methyl cellulose (100 centipoises; Sigma) and 2% Tween 80 in water for injection]. The suspension was mixed for 10 min and then further dispersed using a Polytron PT1200 homogenizer for 2 min. The suspension was kept protected from light and was stirred continuously.

**Laboratory Animals.** Experiments were carried out with female FVB wild-type and Pgp knockout mice (mdr1ab–/–) between 10 and 14 weeks of age (body weight was between 18 and 28 g). Animals were handled in accordance with Dutch national law. Food (Hope Farms B.V., Woerden, the Netherlands) and acidified water were provided *ad libitum.*

**Study Design.** All animals received 10 mg/kg paclitaxel by i.v. bolus injection in the tail vein. Pgp inhibitors (except Cremophor EL, for which we used Taxol®) were administered p.o. by gavage into the stomach at 1 or 2 h before paclitaxel injection (Table 1), depending on the *t*<sub>max</sub> of the inhibitor. Blood and tissue samples (brain, liver, kidney, heart, and lungs) were collected at 1, 4, 8, 24, and (in some groups) 48 h after paclitaxel administration. Three to five animals were used per time point per treatment group. Blood was obtained by cardiac puncture under anesthesia with methoxyflurane (Medical Developments Australia, Melbourne, Australia) and transferred into tubes containing potassium EDTA as an anticoagulant. Next, animals were killed by cervical dislocation. After centrifugation (10 min,
whereas 25 mg/kg GF120918 and 25 mg/kg p.o. PSC833 re-
sulted in 5- and 6.5-fold higher AUC brain concentrations (P < 0.001), respectively (Table 1). The concentrations of paclitaxel in the brain remained constant after pretreatment with cyclosporin A and PSC833, whereas with GF120918, the concentrations decreased during the 8–24-h period.

Increased paclitaxel concentrations in plasma were observed in the Pgp knockout control mice at 4 and 8 h after drug administration compared with the wild-type control mice (Fig. 2), reflecting a reduced clearance of paclitaxel when Pgp is absent. Overall, it resulted in a 1.5-fold higher AUC brain concentrations (P < 0.01; Table 1). All Pgp inhibitors significantly increased paclitaxel levels in plasma compared with the wild-type control group (P < 0.01). GF120918 raised the plasma levels to those observed in Pgp knockout control mice. When formulated in Cremophor EL, the plasma concentrations of paclitaxel were higher, but mainly during the first hours after drug administration. A more pronounced increase of the plasma AUC values of paclitaxel was observed when using cyclosporin A (4-fold increase) or PSC833 (3-fold increase). Both cyclosporins increased the plasma levels mainly during the elimination phase of paclitaxel.
The paclitaxel concentration-time profiles in liver, kidney, lung, and heart followed a similar pattern as observed in plasma, as illustrated for the kidney (Fig. 1B). The highest concentrations of paclitaxel were found in the liver, followed by kidney, lungs, and heart. Relative to wild-type control mice, the AUCs of paclitaxel in the different organs of Pgp knockout control mice increased by 1.5-fold for kidney, 1.6-fold for liver, 2.2-fold for lung, and 1.9-fold for heart (P < 0.05). In wild-type mice receiving GF120918, the AUCs of paclitaxel in the liver, kidney, lungs, and heart were almost similar to those in Pgp knockout control mice, whereas treatment with cyclosporin A or PSC833 resulted in a further increase of the AUCs in these organs (except the liver) by about 3- and 2-fold, respectively. However, they were in the same range as those in Pgp knockout mice receiving cyclosporin A or PSC833.

Based on the results in Pgp knockout mice, the relationship between the plasma levels and the brain levels appears to be more complex than that for the other tissues. There was no significant difference in the AUCbrain,0–24 h of paclitaxel between Pgp knockout control mice and Pgp knockout mice receiving GF120918, whereas with cyclosporin A or PSC833, the AUCbrain,0–24 h was 1.7–1.8-fold higher. Although this result indicates that the higher plasma levels contribute to higher brain levels, the increased AUCbrain,0–24 h was not proportional to the AUCplasma,0–8 h (Table 1). Looking at this in more detail by calculation of the ratios between the concentrations in brain and plasma at the various time points (Table 2), it becomes clear that, whereas the differences are still small at 1 h after paclitaxel administration, treatment with cyclosporin A and PSC833 resulted in markedly lower ratios at the later time points.

Because complete inhibition of Pgp in the BBB was not achieved, we investigated whether we could further optimize the dosage regimen of the two most effective inhibitors, GF120918 and PSC833, provided that their plasma concentrations would remain within the clinically achievable range. For PSC833, this resulted in a dosage regimen of six repeated administrations of 12.5 mg/kg (t = −4, −1, 2, 8, 20, 32, and 44 h). However, despite the increased dose intensity of PSC833, no further increase in the AUCbrain,0–24 h was observed, and the paclitaxel concentrations in plasma and other tissues were unaffected (Table 1). Administration of a single dose of 100 mg/kg GF120918 resulted in higher paclitaxel concentrations in the brain compared with 25 mg/kg (Fig. 3). However, the brain levels decreased in time, whereas they remained constant in Pgp knockout mice during the 24-h study period. Two subsequent administrations of 50 mg/kg GF120918 at 2 and 8 h after paclitaxel increased the retention of paclitaxel close to that observed in Pgp knockout mice. The AUCbrain,0–24 h of these two groups did not differ significantly (0.1 < P < 0.05). The plasma levels of GF120918 did not exceed 900 ng/ml.

DISCUSSION

Pgp in the BBB is an important factor limiting the entry of many anticancer drugs into the brain (9, 10). This study shows that only potent Pgp inhibitors such as GF120918 and PSC833 resulted in a significantly increased penetration of paclitaxel into the brain. In the case of PSC833, however, this was achieved in parallel with a major decline in clearance of paclitaxel that may limit the usefulness of this combination in patients. After further optimization of dose and schedule, GF120918 was able to increase the brain penetration close to those observed in Pgp knockout mice, rendering this inhibitor the most promising for further clinical trials.

The inhibitors PSC833 and GF120918 increased the concentration of paclitaxel in the brain substantially, although complete inhibition of Pgp after a single dosage was not achieved. The potency of PSC833 observed in this study is in line with previous reports on its effect on the brain penetration of the Pgp substrates digoxin (23), colchicine, and vinblastine (24). For example, treatment with PSC833 resulted in a more than 18-fold increase of [3H]digoxin brain levels at 4 h after injection (23). Similarly, inhibition of Pgp in the BBB by GF120918 has been reported in previous studies, where an increased penetration of morphine into the brain of rats was obtained and resulted in the enhancement of its antinociception effect (25). In contrast, however, cyclosporin A was not very effective in increasing the accumulation of paclitaxel in the brain, whereas it appears to be capable of sensitizing Pgp-mediated multidrug-resistant tumor cells in vivo (26, 27) and also inhibited Pgp in the gut (28). A similar lack of potency of cyclosporin A has been observed in a study investigating the brain penetration of vinblastine (12). However, in the case of [14C]verapamil (29), a virtually complete inhibition of BBB Pgp was reported with cyclosporin A at a similar dose of 50 mg/kg. A possible explanation for this discrepancy may be that paclitaxel and vinblastine have a greater affinity for Pgp than verapamil, therefore requiring a more potent inhibitor to displace these structures from Pgp.

We further investigated whether adjustments in the dose and schedule of the inhibitors PSC833 and GF120918 could help to increase the accumulation and retention of paclitaxel in the brain. It was considered essential that the plasma levels of the inhibitors remained below those known to cause toxicity in humans. In the case of PSC833, ataxia is dose-limiting and occurs at whole blood levels of 2.5 μM and higher (corresponding to plasma levels of about 3.5 μM). A single dose of 25 mg/kg PSC833 already resulted in peak plasma levels that were higher...
than 5 μM. Adjustment to a regimen of repeated 12.5 mg/kg did not cause a significantly different paclitaxel concentration in the brain, plasma, or other tissues. A single dose is probably already sufficient to achieve maximum inhibition of Pgp and other enzymes involved in metabolic elimination of paclitaxel. In the case of GF120918, it was possible to increase the dose to 100 mg/kg (20). It was also possible to give two additional repeated dosages, which was important because this markedly enhanced the retention of paclitaxel in the brain. This repeated-dose regimen of GF120918 resulted in an almost complete inhibition of Pgp in the BBB (values were about 90% of those reached in Pgp knockout mice), with only minimally further increased concentrations of paclitaxel in the other tissues and in plasma. The plasma concentrations of GF120918 in the mice still remained below the 900 ng/ml level, which appears to be well tolerated by patients (30).

An important point of concern is the substantial reduction of paclitaxel clearance, especially with cyclosporin A or PSC833, resulting in substantially higher paclitaxel concentrations in plasma and proportionally increased levels in tissues. It is very likely that the increased systemic exposure to paclitaxel will lead to an enhancement of the toxicity of this drug (e.g., bone marrow suppression and neurotoxicity). The increased paclitaxel levels in Pgp knockout mice receiving cyclosporin A or PSC833 relative to Pgp knockout control animals show that the interaction caused by these compounds and paclitaxel is not due only to inhibition of Pgp but also to other factors (e.g., inhibition of cytochrome P450 isoenzymes and possibly also other transport proteins).

In contrast to the results obtained with both cyclosporins, GF120918 increased the plasma AUC of paclitaxel by 1.5-fold, to levels in the same range as those observed in Pgp knockout control mice. Moreover, the plasma AUC did not increase further when Pgp knockout mice were given GF120918, showing that this compound does not inhibit other pathways that are important in the pharmacokinetic handling of paclitaxel (22). The observed interaction (resulting in increased plasma concentrations) is most likely due to inhibition of Pgp in the canalicular membrane (thereby decreasing biliary excretion) as well as in the intestine (thereby increasing oral reabsorption). In wild-type mice, 40% of the paclitaxel dose was excreted as unchanged drug in the feces, whereas this was reduced to a few percent in Pgp knockout mice (31). Consequently, GF120918 is the most selective inhibitor of Pgp in this series.

Administration of Pgp inhibitors to Pgp knockout mice was also very helpful to address the question to what extent the increased plasma levels contribute to the higher brain levels. It appears that treatment with cyclosporin A or PSC833 resulted in higher brain levels of paclitaxel than those in the Pgp knockout control mice, suggesting that increased plasma levels also contribute to the higher brain levels in wild-type mice receiving cyclosporin A or PSC833. However, the higher plasma concentration during the elimination phase of paclitaxel did not result in proportionally higher concentration in the brain, whereas toxic side effects are strongly related to the duration that plasma levels exceed certain threshold concentrations (15).

The pharmacokinetic interaction when using a selective inhibitor of Pgp such as GF120918 may even be much less in patients than in mice. In contrast to mice, the fecal excretion of unchanged paclitaxel in humans was less than 10%, rendering fecal elimination of unchanged paclitaxel far less important than metabolic degradation (32). In fact, several clinical studies combining paclitaxel with a (presumed) selective and potent Pgp inhibitor have shown that dose reductions of paclitaxel were not necessary (33, 34). This is in contrast to the results of a clinical study with PSC833 (35), where a substantial dose reduction of paclitaxel was necessary. It is obvious that such dose reduction will also negatively affect the levels of paclitaxel entering into the brain.

We have used paclitaxel formulated in Tween 80 in these preclinical studies because Cremophor EL is known to cause

Table 2  Brain versus plasma ratios at 1, 4, and 8 h after paclitaxel administration in Pgp knockout control mice and in Pgp knockout mice receiving cyclosporin A, PSC833, and GF120918

<table>
<thead>
<tr>
<th></th>
<th>Concentration Brain/plasma</th>
<th>Ratio</th>
<th>Concentration Brain/plasma</th>
<th>Ratio</th>
<th>Concentration Brain/plasma</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>623/1747</td>
<td>0.36</td>
<td>798/295</td>
<td>2.7</td>
<td>799/70</td>
<td>11.4</td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>952/3293</td>
<td>0.28</td>
<td>1245/1543</td>
<td>0.81</td>
<td>1473/771</td>
<td>1.9</td>
</tr>
<tr>
<td>PSC833</td>
<td>844/2855</td>
<td>0.30</td>
<td>1146/705</td>
<td>1.6</td>
<td>1414/307</td>
<td>4.6</td>
</tr>
<tr>
<td>GF120918</td>
<td>677/1951</td>
<td>0.34</td>
<td>687/285</td>
<td>2.4</td>
<td>826/90</td>
<td>9.2</td>
</tr>
</tbody>
</table>

Fig. 3  Paclitaxel concentrations in the brain of wild-type mice at 1, 4, 8, and 24 h after paclitaxel administration in combination with 100 mg/kg GF120918 (small-meshed box) and 100 mg/kg GF120918 followed by two subsequent dosages of 50 mg/kg at 2 and 8 h after paclitaxel administration (large-meshed box). Pgp knockout mice were used as a reference for complete blockade of Pgp (□). Mean levels with SE-mean are depicted (n = 4–5 mice).
nonlinear pharmacokinetic behavior of paclitaxel by entrapment of this drug in micelles (36, 37). However, because conflicting data exist on the capability of Cremophor EL to inhibit Pgp (38–40), and because the Cremophor EL-containing formulation is going to be used in future clinical trials, we have included test groups receiving the paclitaxel-Cremophor EL formulation. The results show that Cremophor EL did not increase the brain concentration of paclitaxel. It is unlikely that this lack of efficacy to inhibit Pgp in the BBB is due to low plasma levels of Cremophor EL because the Cremophor EL levels ranged between 10 and 20 g/liter. A similar lack of efficacy of Cremophor EL to inhibit Pgp in the blood-brain barrier in cell culture for studies of drug transport and metabolism. Adv. Drug Delivery Rev., 22: 251–264, 1996.

In conclusion, our results show that GF120918 is the most potent inhibitor of Pgp in the BBB in this series. Paclitaxel levels close to those observed in Pgp knockout mice were achieved at plasma levels of GF120918, which are most likely nontoxic in humans. The findings warrant the clinical investigation of paclitaxel in combination with a selective inhibitor of Pgp, GF120918, for the treatment of brain tumors.

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REFERENCES


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