Pharmacokinetics and Pharmacodynamics of Alfentanil in P-Glycoprotein-Competent and P-Glycoprotein-Deficient Mice: P-Glycoprotein Efflux Alters Alfentanil Brain Disposition and Antinociception

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ABSTRACT:

Previous studies have indicated that P-glycoprotein (P-gp) attenuates the central nervous system penetration and central activity of some opioids. The impact of P-gp-mediated efflux on the disposition and efficacy of the synthetic opioid alfentanil currently is unknown. In this study, P-gp-competent [mdr1a(+/+) ] and P-gp-deficient [mdr1a(−/−) ] mice were used to investigate the impact of P-gp-mediated efflux on the systemic pharmacokinetics, brain disposition, and central activity of alfentanil. Equimolar doses of alfentanil were administered to mdr1a(+/+) and mdr1a(−/−) mice (0.2 and 0.067 mg/kg, respectively), and the time course of brain and serum concentrations as well as antinociception were determined. A pharmacokinetic-pharmacodynamic (PK-PD) model was fit to the data and used to assess the impact of P-gp on parameters associated with alfentanil disposition and action. The mdr1a(+/+) mice were less sensitive to alfentanil than mdr1a(−/−) mice, requiring a 3-fold higher dose to produce similar antinociception. PK-PD modeling revealed no differences in alfentanil systemic pharmacokinetics between P-gp expressers and nonexpressers. However, the steady-state brain-to-serum concentration ratio (Kp,brain,ss) was ~3-fold lower in mdr1a(+/+) mice compared with mdr1a(−/−) mice (0.19 ± 0.01 versus 0.54 ± 0.04, respectively). Consistent with the ~3-fold lower Kp,brain,ss, the antinociception versus serum concentration relationship in mdr1a(+/+) mice was shifted ~3-fold rightward compared with mdr1a(−/−) mice. However, there was no difference in the antinociception versus brain concentration relationship, or in the brain tissue EC50 (11 ± 1.8 versus 9.2 ± 1.7 ng/g), between mdr1a(+/+) and mdr1a(−/−) mice. These results indicate that alfentanil is an in vivo P-gp substrate and are consistent with the hypothesis that P-gp-mediated efflux attenuates antinociception by reducing alfentanil Kp,brain,ss.

P-glycoprotein (P-gp) is the 170-kDa protein product of the multidrug resistance gene (mdr1) first identified for its ability to confer multidrug resistance in tumor cells (Juliano, 1976; Gros et al., 1986). P-gp mediates excretory and barrier functions in several tissue (e.g., proximal tubular cells of the kidneys, the canicular membrane of hepatocytes in the liver, the apical membrane of intestinal enterocytes, and the luminal membrane of brain capillary endothelial cells) (Thiebault et al., 1987; Cordon-Cardo et al., 1989, 1990). P-gp seems to play a protective role in intact mammals by attenuating absorption, facilitating excretion, and restricting distribution to several tissue sites, including the central nervous system, of many structurally diverse xenobiotics, including calcium channel blockers, human immunodeficiency virus protease inhibitors, immunosuppressants, and opioids (Matheny et al., 2001).

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ABBREVIATIONS: P-gp, P-glycoprotein; BBB, blood-brain barrier; GF120918, N-[4-[1-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethyl]phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridine carboxamide; PK-PD, pharmacokinetic-pharmacodynamic; MPR, maximum possible response; HPLC, high-performance liquid chromatography; CI, clearance.

Concomitant administration of P-gp inhibitors with P-gp substrates may lead to clinically significant drug interactions (Ho and Kim, 2005). For example, although the antidiarrheal agent loperamide is a potent opioid agonist, it is not centrally active due, in part, to P-gp-mediated efflux at the blood-brain barrier (BBB) (Schinkel et al., 1996). However, when loperamide and the P-gp inhibitor quinidine were coadministered to subjects, respiratory depression was observed, which was attributed to an increase in loperamide brain concentration caused by P-gp inhibition (Sadeque et al., 2000). Although the precise mechanism of this interaction has not been verified, the potential for enhanced central effects of P-gp substrates due to P-gp inhibition is nonetheless clear.

Studies have demonstrated that P-gp attenuates the brain distribution and central activity of several opioids. For example, Thompson et al. (2000) showed that fentanyl, morphine, and methadone resulted in increased and prolonged antinociception in mdr1a(−/−) mice compared with mdr1a(+/+) mice. Likewise, the cyclic peptide opioid [d-Pen2,d-Pen5]-enkephalin produced increased antinociception in mdr1a(−/−) mice as opposed to their P-gp-expressing counterparts (Chen and Pollack, 1998). The P-gp inhibitor GF120918 was able to restore [d-Pen2,d-Pen5]-enkephalin-mediated antinociception in
mdr1a(+/+) mice to levels observed in the mdr1a(−/−) mice (Chen and Pollack, 1999). The P-gp inhibitor verapamil also was capable of increasing morphine brain concentrations and morphine-associated antinociception in mdr1a(+/+) mice (Zong and Pollack, 2000).

Alfentanil is a synthetic opioid used for the induction of surgical anesthesia and the management of postsurgical pain. The alfentanil dose needs to be individualized based on numerous factors, including pathological condition, use of other medicines, and the type and duration of the surgical procedure (Scholz et al., 1996). Because alfentanil is a CYP3A4 substrate, CYP3A4 activity is another important determinant of the required alfentanil dose (Kharasch and Thummel, 1993). Many compounds are substrates of both CYP3A4 and P-gp. If alfentanil is a P-gp substrate, P-gp may be a determinant of the required alfentanil dose, a possible source of interpatient variability, and a potential locus of drug-drug interactions.

The impact of P-gp-mediated efflux on the pharmacokinetics and central pharmacodynamics of alfentanil is unknown. Initial pilot experiments in this laboratory indicated P-gp-mediated efflux reduces alfentanil-associated antinociception. To investigate these observations further, and to evaluate whether P-gp efflux activity may contribute to interpatient variability in alfentanil response or serve as a locus of drug-drug interactions, the present study was undertaken to determine the impact of P-gp-mediated efflux on the systemic pharmacokinetics, brain disposition, and central activity of alfentanil. A PK-PD modeling approach was used to assess the mechanism(s) by which P-gp-mediated efflux influences alfentanil-associated antinociception.

Materials and Methods

Materials. Alfentanil was obtained from Taylor Pharmaceuticals (Decatur, IL), and loperamide was purchased from Sigma-Aldrich (St. Louis, MO). All other reagents were obtained from common sources and were of reagent grade or better.

Animals. Male CF-1 mdr1a(+/+) and mdr1a(−/−) mice (30–40 g; Charles River Laboratories, Inc., Wilmington, MA) were maintained on a 12-h light/dark cycle in a temperature- and humidity-controlled room with access to water and food ad libitum. All procedures involving mice were approved by The Institutional Animal Care and Use Committee of the University of North Carolina and were conducted in accordance with Principles of Laboratory Animal Care (National Institutes of Health Publication 85-23, revised in 1985).

PK-PD Study. Based on the results of pilot studies, 36 mdr1a(−/−) and 36 mdr1a(+/+) mice received equipotent subcutaneous doses of alfentanil in physiological saline (0.067 and 0.2 mg/kg, respectively). At 0.5, 1, 2, 4, 8, 15, 30, 45, and 60 min postadministration, antinociception was assessed, and four mdr1a(−/−) and four mdr1a(+/+) mice were sacrificed by decapitation for collection of brain tissue and trunk blood. Trunk blood was collected in 1.5-ml microcentrifuge tubes and was allowed to clot for 30 min at room temperature. Serum was harvested following centrifugation. Serum and brain samples were stored at −20°C until analysis by HPLC-tandem mass spectrometry.

Assessment of Antinociception. Antinociception was assessed with the hot-plate latency test as described previously (Chen and Pollack, 1997). Before administration of alfentanil, baseline hot-plate latency was determined for each animal in triplicate. Hot-plate latency was defined as the time interval between placement on the hot-plate (55°C; Columbus Instruments, Columbus, OH) and first observation of a jump or lick of the hind limb(s). Animals with an average baseline latency <25 s were used in the study. A cut-off latency of 60 s was used to avoid tissue damage. The degree of antinociception was calculated as follows:

\[
\%\text{MPR} = \frac{\text{test latency} - \text{control latency}}{\text{control latency}} \times 100\%
\]

Quantitation of Alfentanil in Serum and Brain. Brain samples were homogenized in water (1:2, v/v) with a sonic probe. A 25-μl aliquot of homogenate or serum was transferred to an HPLC vial, and protein was precipitated with 100 μl of methanol containing internal standard (5 ng/ml loperamide). The sample was vortex-mixed and centrifuged, and the supernatant was analyzed by HPLC-tandem mass spectrometry. Samples (3 μl) were injected (autosampler; CTC Analytics, Zwingen, Switzerland) onto a Gemini 110A column (2.0 by 30 mm, 5 μm; Phenomenex, Torrance, CA) maintained at 60°C. The total run time was 2 min. Analyses were eluted with a linear gradient consisting of 10 mM ammonium acetate, pH 6.8 (A) and methanol (B) produced by two Shimadzu LC-10ADVP binary pumps. An initial condition of 5% B was ramped to 95% B over 2 min, held for 0.5 min, and then returned initial condition of 5% B in a single step to re-equilibrate the column. During the run, the flow rate was increased from 750 to 1500 μl/min over the first 2 min, held at 1500 μl/min for 1 min, and then returned to the initial flow rate of 750 μl/min in a single step. The entire column effluent was diverted from the source of the API-4000 quadrupole mass spectrometer (Turbo V ionspray source, 700°C; PerkinElmerSciex Instruments, Boston, MA) for the first 1 min and last 0.5 min of the run. Alfentanil and loperamide were measured in positive ionization mode using multiple reaction monitoring (417.3→268.3 and 477.4→266.0, respectively). Standards were prepared in brain homogenate and serum and fitted with a quadratic equation with 1/2 weighting (0.1–500 ng/ml). Accuracy of standards was within ±15%.

Pharmacokinetic-Pharmacodynamic Analysis. A compartmental modeling approach with distribution between serum and brain tissue was used to describe alfentanil pharmacokinetics. The pharmacokinetic model shown schematically in Fig. 1 was fit simultaneously to the serum and brain concentration data from both mdr1a(−/−) and mdr1a(+/+) mice using nonlinear least-squares regression (WinNonlin 4.1; Pharsight, Mountain View, CA). The absorption rate constant (Kph), central volume (Vc), and systemic clearance (Cl) did not differ between mdr1a(−/−) and mdr1a(+/+) mice; therefore, they were assumed to be identical when fitting the model to the data from both mouse strains simultaneously. The brain uptake (Clup) and brain efflux (Clefflux) clearances were allowed to vary between mdr1a(−/−) and mdr1a(+/+) mice. The brain volume (Vb) was determined experimentally as 13.4 ml/kg−1.
Dashed and solid lines represent the fit of the PK model to the concentration data for \( mdr1a(-/-) \) and \( mdr1a(+/-) \) mice, respectively. Data are presented as mean ± S.E. (\( n = 3 \)). Dashed and solid lines represent the fit of the PK model to the concentration data for \( mdr1a(-/-) \) and \( mdr1a(+/-) \) mice, respectively.

Assuming a specific gravity of 1.0 ml. The pharmacodynamic parameters EC\( _{50} \) and \( \gamma \) were determined directly from fitting a sigmoidal \( f_{\text{max}} \) model to the antinociception versus concentration data (C) data:

\[
\% \text{MPR} = \frac{f_{\text{max}} \times C}{EC_{50} + C^2}
\]

Where \( f_{\text{max}} \) was defined as 100%, and \( \gamma \) was constrained to the same value for \( mdr1a(-/-) \) and \( mdr1a(+/-) \) mice. The time course of the brain-to-serum concentration ratio (\( K_{\text{p,brain}} \)) was used to estimate the brain equilibration rate constant (\( k_{eq} \)) and steady-state brain-to-serum ratio (\( K_{\text{p,brain,ss}} \)) according to the following:

\[
K_{\text{p,brain}} = K_{\text{p,brain,ss}}(1 - e^{-t_{1/2eq,brain}})
\]

The brain equilibration half-life (\( t_{1/2eq,brain} \)) was obtained from \( k_{eq} \):

\[
t_{1/2eq,brain} = \frac{\ln(2)}{k_{eq}}
\]

### Results

#### Alfentanil Pharmacokinetics

Alfentanil was absorbed rapidly following subcutaneous administration, with peak serum and brain concentrations achieved in less than 10 min (Fig. 2). Alfentanil clearance was high (approximately equivalent to hepatic blood flow), assuming complete absorption from the subcutaneous site, and half-life was short (\( t_{1/2} < 15 \) min). Alfentanil serum concentrations were 3-fold lower in the \( mdr1a(-/-) \) mice, consistent with those animals receiving a 3-fold lower dose than their transporter-competent counterparts. However, the time course of brain concentrations in the \( mdr1a(-/-) \) and \( mdr1a(+/-) \) mice were nearly superimposable (Fig. 2). Both the systemic and brain tissue pharmacokinetics were capable of being described by the pharmacokinetic model (Fig. 2; Table 1). Parameter estimates obtained from the pharmacokinetic model are reported in Table 1.

#### Alfentanil Pharmacodynamics

Pilot experiments indicated that, at equivalent doses, antinociceptive activity was lower in \( mdr1a(+/-) \) mice than in \( mdr1a(-/-) \) mice (data not shown). However, at a 3-fold higher dose (0.20 versus 0.067 mg/kg), the magnitude and duration of antinociception in \( mdr1a(+/-) \) were identical to those in \( mdr1a(-/-) \) mice (Fig. 3). In both \( mdr1a(+/-) \) and \( mdr1a(-/-) \) mice, alfentanil had a rapid onset of antinociception, a peak effect of ~85% MPR, and a rapid offset of action with nociceptive response returning to baseline within 60 min of administration. Consistent with a lower alfentanil potency in \( mdr1a(+/-) \) mice (due to P-gp-mediated efflux from the brain), there was a 3-fold rightward shift in the serum concentration-effect relationship in transporter-competent versus transporter-deficient mice (Fig. 4). There was no difference in the brain concentration-effect relationship or brain EC\( _{50} \) values between the \( mdr1a(+/-) \) and \( mdr1a(-/-) \) mice (Fig. 5; Table 1). The PK-PD model adequately described the time course of antinociception, the serum concentration-effect relationships, and the brain concentration-effect relationships in both mouse strains (Figs. 3–5, respectively). The PK-PD model indicated the presence of a slight counterclockwise hysteresis in the antinociceptive effect versus serum concentration relationship (Fig. 4). However, there was no hysteresis in the antinociceptive effect versus brain concentration relationship (Fig. 5). Pharmacodynamic parameter estimates obtained from the PK-PD model are reported in Table 1.

### Alfentanil Brain Disposition

Equilibration of alfentanil between brain and serum occurred rapidly, with state-steady \( K_{\text{p,brain}} \) reached within approximately 4 min. The time course of alfentanil \( K_{\text{p,brain}} \) is shown in Fig. 6. The \( K_{\text{p,brain,ss}} \) was less than unity for both \( mdr1a(+/-) \) and \( mdr1a(-/-) \) mice, and the \( K_{\text{p,brain}} \) was less than unity for both \( mdr1a(+/-) \) and \( mdr1a(-/-) \) mice (Fig. 2; Table 1). The PK-PD model adequately describes the time course of antinociception, the serum concentration-effect relationships, and the brain concentration-effect relationships in both mouse strains (Figs. 3–5, respectively). The PK-PD model indicated the presence of a slight counterclockwise hysteresis in the antinociceptive effect versus serum concentration relationship (Fig. 4). However, there was no hysteresis in the antinociceptive effect versus brain concentration relationship (Fig. 5). Pharmacodynamic parameter estimates obtained from the PK-PD model are reported in Table 1.

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### Table 1

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Weighting</th>
<th>mdr1a(-/-)</th>
<th>mdr1a(+/-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( K_{\text{p,brain}} ) (min(^{-1}))</td>
<td>0.35 ± 0.03</td>
<td>0.35 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>( V_{\text{C}} ) (ml·kg(^{-1})·h(^{-1}))</td>
<td>82 ± 3</td>
<td>82 ± 3</td>
<td></td>
</tr>
<tr>
<td>( t_{1/2} ) (min)</td>
<td>12 ± 0.6(^a)</td>
<td>12 ± 0.6(^a)</td>
<td></td>
</tr>
<tr>
<td>EC( _{50} ) (ng/g)</td>
<td>9.2 ± 1.7</td>
<td>11 ± 1.8</td>
<td></td>
</tr>
<tr>
<td>( K_{\text{p,brain}} ) (h)</td>
<td>0.54 ± 0.04</td>
<td>0.195 ± 0.008</td>
<td></td>
</tr>
<tr>
<td>( K_{eq} ) (min(^{-1}))</td>
<td>0.46 ± 0.10</td>
<td>0.64 ± 0.09</td>
<td></td>
</tr>
<tr>
<td>( t_{1/2eq,brain} ) (min)</td>
<td>1.5 ± 0.3</td>
<td>1.08 ± 0.16</td>
<td></td>
</tr>
</tbody>
</table>

*Parameter estimate ± S.E. from nonlinear least-squares regression analysis of pooled \( mdr1a(-/-) \) or \( mdr1a(+/-) \) mouse data. \( K_{\text{p}}, V_{\text{C}}, V_{\text{p}}, \) and \( \gamma \) were constrained to the same value for \( mdr1a(-/-) \) or \( mdr1a(+/-) \) mice. \( t_{1/2} \) and \( t_{1/2eq,brain} \) were calculated from 0.693/\( V/C_0 \) and 0.693/\( K_{\text{p,brain}} \), respectively.

А propagation of error was used to calculate S.E.
mice, respectively) were comparable with the respective $K_{p,brain,ss}$ values (Table 1).

Discussion

The ATP-dependent efflux transporter P-gp is the protein product of the mdr1 gene, and it is expressed in a variety of tissues, including the luminal membrane of the BBB (Cordon-Cardo et al., 1989, 1990). Several studies have indicated that some opioids have reduced brain penetration and attenuated central activity due to P-gp-mediated efflux (Chen and Pollack, 1998; Thompson et al., 2000; Zong and Pollack, 2000; Dagenais et al., 2004). The influence of P-gp on the pharmacokinetics and central pharmacodynamics of the synthetic opioid alfentanil had not been explored previously. Pilot experiments in this laboratory indicated that alfentanil produced less antinociception in mdr1a(−/−) mice than in mdr1a(+/+) mice, consistent with P-gp-mediated efflux at the BBB. In this study, the time course of antinociception as well as serum and brain concentrations of alfentanil were evaluated in mdr1a(+/+) and mdr1a(−/−) mice to investigate the impact of P-gp-mediated efflux on the systemic pharmacokinetics, brain disposition, and central activity of alfentanil.

To achieve a similar degree of antinociception in both mdr1a(+/+) and mdr1a(−/−) mice, the dose administered to mdr1a(+/+) mice was 3-fold higher than that in transporter-deficient animals. Even though the doses were different, pharmacokinetic modeling indicated no difference in systemic pharmacokinetics between mdr1a(+/+) and mdr1a(−/−) mice (Table 1). This result was not unexpected, because P-gp often has minimal impact on systemic pharmacokinetics following subcutaneous or intravenous administration (Chen et al., 2003).

In contrast to the serum pharmacokinetics, P-gp had a pronounced effect on alfentanil brain pharmacokinetics. The $K_{p,brain,ss}$ of mdr1a(+/+) mice was ~3-fold lower compared with mdr1a(−/−) mice (0.19 versus 0.54). The decrease in $K_{p,brain,ss}$ was accompanied by a ~1.6-fold decrease in $C_{up}$ and ~1.6-fold increase in $C_{efflux}$. These observations are consistent with the hypothesis that P-gp decreases $K_{p,brain,ss}$ by both attenuating brain uptake and enhancing brain efflux. Similar observations have been reported for other P-gp substrates (Kusuhara et al., 1997). The brain and serum concentrations of alfentanil equilibrated rapidly, with a $t_{1/2,eq,brain} \leq 1.5$ min. This value is similar to previously reported estimates from humans (Lotsch, 2005). Unexpectedly, the $t_{1/2,eq,brain}$ was shorter in the mdr1a(+/+) mice (Table 1). This observation may be explained by the fact that $t_{1/2,eq,brain}$ is inversely proportional to $C_{efflux}$ and that P-gp increased $C_{efflux}$ (~1.6-fold), thereby causing a proportional decrease in the $t_{1/2,eq,brain}$ in mdr1a(+/+) mice (~1.4-fold). Interestingly, this result implies that P-gp-mediated efflux may reduce equilibration time between brain and systemic concentrations. Previously, the short $t_{1/2,eq,brain}$ of alfentanil had been attributed in part to a small $K_{p,brain,ss}$ (Upton et al., 1997). In this study, the $K_{p,brain,ss}$ of alfentanil was less than unity for both mdr1a(+/+) and mdr1a(−/−) mice, indicating two important points: first, that a small $K_{p,brain,ss}$ may indeed facilitate rapid equilibrium between systemic and brain concentration, and second, that a $K_{p,brain,ss}$ greater than unity may not be needed, or even desirable, for a central nervous system drug with rapid onset and offset of action.

PK-PD modeling indicated an ~3-fold rightward shift in the antinociception versus serum concentration relationship for mdr1a(+/+) mice compared with mdr1a(−/−) mice. PK-PD modeling also revealed a slight counterclockwise hysteresis in the antinociception versus serum concentration relationship for both mdr1a(+/+) and mdr1a(−/−) mice. However, there was no hysteresis in the antinociception versus brain concentration relationship, and the brain tissue EC$_{50}$ values between mdr1a(+/+) and mdr1a(−/−)
mice were not different. These observations are consistent with brain concentrations driving antinociception, and they provide compelling evidence that P-gp efflux attenuates alfentanil antinociception by reducing $K_{p,brain}$. This study is the first to show that alfentanil is a P-gp substrate. In contrast, an earlier study that examined the transcellular flux of alfentanil across L-MDR1 (expressing P-gp) and LLC-PK1 cell monolayers concluded alfentanil was not a P-gp substrate and had low affinity toward P-gp (IC$_{50} > 50$ µM) (Wandel et al., 2002). There are at least two possible explanations for the difference in results between these two studies. First, even though murine-human differences in P-gp substrate recognition and transport seem modest for most substrates (Yamazaki et al., 2001; Hochman et al., 2002; Takeuchi et al., 2006), there might be species differences in the P-gp-mediated transport of alfentanil. This study evaluated the in vivo effects of murine P-gp (mdr1a), whereas the previous work studied the human form of P-gp (MDR1) in vitro. Second, in vitro systems often are less sensitive than intact animal models for identifying weak P-gp substrates (Polli et al., 2001). In the Wandel et al. (2002) study, the basolateral-to-apical orientation in both the P-gp-expressing L-MDR1 and control LLC-PK1 cell monolayers. Alfentanil is a CYP3A4 substrate in humans, and it has been used as a noninvasive clinical probe to evaluate CYP3A4 activity (Kharasch et al., 2005). The degree of miosis produced by alfentanil has been shown to correlate well with alfentanil plasma concentrations, and as such alfentanil-pupillometry studies have been used to evaluate CYP3A4 activity and to conduct drug-drug interaction studies. An assumption of such studies is that any increase or decrease in alfentanil-induced miosis is due primarily to changes in CYP3A4 activity (inhibition or induction). The present results showing that alfentanil is a P-gp substrate indicate that alfentanil-pupillometry studies may have the potential to detect alterations in P-gp activity. Previous pupillometry studies conducted with the P-gp substrates morphine, fentanyl, methadone, and loperamide have shown that inhibition of P-gp at the BBB by the P-gp inhibitor quinidine is modest (Kharasch et al., 2003, 2004a,b; Skarke et al., 2003). Because quinidine is one of the most potent compounds capable of inhibiting P-gp that is in clinical use, the likelihood of significant inhibition of P-gp at the BBB seems remote. However, future drug-drug interaction studies conducted with alfentanil should be assessed carefully to ensure that any observed drug-drug interaction is not caused by P-gp inhibition. The clinical significance of alfentanil being a P-gp substrate is not known, but it may be modest considering that only a 3-fold P-gp effect was observed in mice, that all human MDR1 polymorphisms identified to date retain most functional activity, and that clinically significant inhibition of P-gp at the BBB has not been well documented (Ho and Kim, 2005; Kerb, 2006). In summary, the present study indicated that alfentanil is a P-gp substrate, and that P-gp-mediated efflux attenuates alfentanil antinociception by reducing $K_{p,brain}$. These observations may have important implications regarding interindividual differences in alfentanil pharmacodynamics and for the risk of drug-drug interactions. Additional studies may be warranted to assess the clinical relevance of P-gp efflux as a determinant of alfentanil pharmacotherapy.

References


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