A PHARMACOKINETIC STUDY OF DIPHENHYDRAMINE TRANSPORT ACROSS THE BLOOD-BRAIN BARRIER IN ADULT SHEEP: POTENTIAL INVOLVEMENT OF A CARRIER-MEDIATED MECHANISM

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ABSTRACT:

The purpose of this study was to examine the disposition of diphenhydramine (DPHM) across the ovine blood-brain barrier (BBB). In six adult sheep, we characterized the central nervous system (CNS) pharmacokinetics of DPHM in brain extracellular fluid (ECF) and cerebrospinal fluid (CSF) using microdialysis in two experiments. In the first experiment, DPHM was administered via a five-step i.v. infusion (1.5, 5.5, 9.5, 13.5, and 17.5 µg/kg/min; 7 h per step). Average steady-state CNS/total plasma concentration ratios (i.e., [CNS]/[total plasma]) for steps 1 to 5 ranged from 0.4 to 0.5. However, average steady-state [CNS]/[free plasma] ratios ranged from 2 to 3, suggesting active transport of DPHM into the CNS. Plasma protein binding averaged 86.1 ± 2.3% (mean ± S.D.) and was not altered with increasing drug dose. Plasma, CSF, and ECF demonstrated biexponential pharmacokinetics with terminal elimination half-lives (t½) of 10.8 ± 5.4, 3.6 ± 1.0, and 5.3 ± 4.2 h, respectively. The bulk flow of CSF and transport-mediated efflux of DPHM may explain the observed higher CNS clearances. In the second experiment, DPHM was coadministered with propranolol (PRN) to examine its effect on blood-brain CSF and blood-brain ECF DPHM relationships. Plasma total DPHM concentration decreased by 12.8 ± 6.3% during PRN, whereas ECF and CSF concentrations increased (81.1 ± 45.4 and 91.6 ± 43.4%, respectively). This increase may be due to the inhibitory effect of PRN on a transporter-mediated efflux mechanism for DPHM brain elimination.

The blood-brain barrier (BBB) is composed of several specialized elements which act together to regulate the internal milieu of the brain (Smith, 1989; Farrell and Risau, 1994; Davson and Segal, 1996) by controlling the exchange of compounds between two barrier structures—one located between the blood and brain extracellular fluid (ECF), termed the blood/brain barrier, and the second between the blood and cerebrospinal fluid (CSF), known as blood/CSF barrier. Diphenhydramine [2-(diphenylmethoxy)-N,N-dimethyl-2-hydroxyethylamine (DPHM)] is a potent histamine H₁-receptor antagonist (Douglas, 1980) widely used for its antiallergic properties, as well as for its antimetic, sedative, local anesthetic, and hypnotic effects (Runge et al., 1992; Ernst et al., 1993; Pontasch et al., 1993). Like other “first-generation” antihistamines, DPHM occupies central H₁-receptors to result in drowsiness, sedation, incoordination and with higher doses, convulsions, and death (Douglas, 1980; Nicholson, 1983; Koppen et al., 1987; Gengo et al., 1989). However, there are limited data on the CNS levels of the drug or on the mechanisms of transfer involved. Results from previous studies in rats, guinea pigs, and rabbits suggest that DPHM enters the brain tissue and CSF extremely rapidly to achieve CNS concentrations exceeding those in plasma (Glazko and Dill, 1949a,b; Takasato et al., 1984; Goldberg et al., 1987). Because only ~2.5% of DPHM (pKₐ ~9.0) is un-ionized at the physiological pH, the above results cannot be explained by the passive diffusion of this un-ionized form through the blood-brain and blood-CSF barriers. Moreover, there is evidence for saturable BBB transporter mechanisms for lipophilic, amine drugs (Pardridge et al., 1973, 1984; Spector, 1988; Yamazaki et al., 1994a,b,c). This includes mepyramine, a histamine H₁-antagonist. The available data suggest that these compounds cross the blood-brain and blood-CSF barriers by both simple diffusion of the un-ionized lipid-soluble form and by carrier-mediated transport of the ionized form (Pardridge et al., 1984; Goldberg et al., 1987; Yamazaki et al., 1994a). In addition, there is evidence that various substances can inhibit the actions of this transport process. In vivo (rat carotid injection technique), brain uptake of mepyramine is inhibited by DPHM (Yamazaki et al., 1994a).

ABBREVIATIONS: BBB, blood-brain barrier; ECF, extracellular fluid; CSF, cerebrospinal fluid; DPHM, diphenhydramine; CNS, central nervous system; PRN, propranolol; MD, microdialysis; AUC, area under the curve; CPₜ, total plasma DPHM concentration; CPᵤ, free plasma DPHM concentration.

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more, both in vivo and in vitro (bovine brain capillary endothelial cells) studies demonstrate that propranolol (PRN) inhibits meperidine uptake (Yamazaki et al., 1994; Yamazaki et al., 1994). Together, these data led us to hypothesize that PRN could inhibit brain (and perhaps CSF) DPHM uptake. The purpose of our studies then was to use in vivo microdialysis (MD) in chronically instrumented adult ewes to investigate the transport processes of DPHM across the adult ovine blood-brain-barrier using two different experiments. The first involved stepped infusions of DPHM at five different dosing rates to assess blood-brain CSF and blood-brain ECF drug concentration relationships in relation to variations in drug dose and hence plasma drug levels. The second involved coadministration of DPHM and PRN to examine whether PRN alters blood-brain CSF and blood-brain ECF DPHM relationships.

Materials and Methods

Animals and Surgical Preparation. A total of six nonpregnant Dorset Suffolk cross-bred ewes were used in these studies. All studies were approved by the University of British Columbia Animal Care Committee, and the procedures performed on sheep conformed to the guidelines of the Canadian Council on Animal Care. The sheep were between 2 to 4 years old with a body weight of 74.6 ± 22.0 kg (mean ± S.D.). Surgery was performed aseptically under isoflurane (1–2%) and nitrous oxide (60%) anesthesia (balance O2) after induction with i.v. sodium pentothal (1 g) and intubation of the ewe. Polyvinyl or silicone rubber catheters (Dow Corning Corp., Midland, MI) were implanted in both the carotid artery and jugular vein. In addition, flexible MD probes (CMA 20; CMA/Microdialysis, Solna, Sweden) were implanted in the lateral ventricle and ipsilateral parietal cortex for collection of CSF and ECF, respectively. The tubing of the MD probes was tunneled subcutaneously and exteriorized via a small incision on the back of the neck of the ewe. The antibiotics Trivetrin (180 mg of trimethoprim, 900 mg of sulfadoxine; Schering Canada Inc., Pointe Claire, QC, Canada) and ampicillin (500 mg) were administered to the ewe on the day of the surgery and for 3 days postoperatively. After surgery, the animals were kept in holding pens with other sheep and were allowed free access to food and water. The ewes were allowed to recover for 3 days before experimentation.

Experimental Protocols. This was a single-site, nonrandomized, open-label, two-period, single sequence study with the stepped infusion experiment followed by the DPHM-PRN coadministration study. There was a washout period of at least 2 days between the study sessions. The details of the two study periods are described below.

DPHM step-infusions. The protocol involved bolus i.v. loading doses of DPHM (to hasten the achievement of steady state), followed by i.v. infusion of the drug using an infusion pump (model 600-000; Harvard Apparatus Inc., Dover, MA) at five different rates, with each infusion rate lasting 7 h. The DPHM loading dose was 0.15 mg/kg, and the infusion rates were 1.5, 5.5, 9.5, 13.5, and 17.5 μg/kg/min. During the infusions, arterial blood samples (3 ml) were collected hourly. MD sampling began at the onset of the infusion. The microdialysis pump (model PHD2000; Harvard Apparatus Inc., Holliston, MA) infusion rate was 2 μl/min, and 60-min cumulative samples of CSF and ECF were collected throughout the duration of the experiment. Both blood and MD samples were collected up to 18 h after the end of the last infusion step.

Coadministration of DPHM and PRN. DPHM was infused at rate 4 (i.e., 13.5 μg/kg/min) as described in DPHM step-infusions above for 8 h. After 4 h, PRN was coinfused (1.5 mg/kg loading dose, 20.0 μg/kg/min) (Jones and Ritchie, 1978; Mihaly et al., 1982; Czuba et al., 1988) for the remaining 4 h of the DPHM infusion. Blood and MD samples were collected as described above during the infusion and for up to 12 h after infusion.

Retrodialysis. MD probe recovery was determined using the retrodialysis technique (De Lange et al., 1998). The MD dialysate (degassed, sterile lactated Ringer solution) contained a calibrator ([1H10]-DPHM) at a concentration of 400.0 ng/ml. The probe recovery rate was determined by comparing the input and output concentrations of the calibrator as follows:

\[
\text{Recovery} = \frac{[\text{Calibrator}_{\text{input}}] - [\text{Calibrator}_{\text{output}}]}{[\text{Calibrator}_{\text{input}}]}\quad (1)
\]

Free-fraction drug concentration (C_{CSF} or C_{ECF}) at the MD sampling site was equal to the diphenhydramine concentration in the output dialysate (DPHM_{(\text{dialysate})}) recovery rate.

Physiological Recording. Arterial pressure was measured using strain-gauge manometers (Ohmeda Inc., Madison, WI) and heart rates from a cardiotachometer (Astro-Med, West Warwick, RI). All variables were recorded on a Grass K2G polygraph (Astro-Med) and on a computerized data acquisition system (chart v4.2; ADInstruments, Grand Junction, CO).

Plasma Protein Binding of DPHM. Determination of plasma protein binding/unbound fraction (C_{pu}) of DPHM was achieved using the equilibrium dialysis procedure described by Yoo et al. (1990) in the 7-h steady-state plasma sample from each infusion step of the five-step infusion studies. In the case of the DPHM-PRN coadministration study, a sample collected at 8 h of the infusion was used for measurement.

Drug Analysis. The concentrations of DPHM (C_{Pp}, C_{ Pu}, C_{CSF}, and C_{ECF}) in all samples were measured using a gas chromatographic-mass spectrometric assay capable of simultaneously measuring DPHM and [1H10]-DPHM with a limit of quantitation of 2.0 ng/ml (Tonn et al., 1993).

Statistical and Data Analysis. All pharmacokinetic modeling was performed using WinNonlin, version 1.1 (Scientific Consulting Inc., Apex, NC).

Five-step infusion study. Volume of distribution (Vd) and total body clearance (Cl) were calculated using the following respective equations (Gibaldi and Perrier, 1982):

\[
\text{Vd} = \text{Rate of DPHM infusion} / (C_{	ext{Pu}} \cdot \beta) \quad (2)
\]

\[
\text{Cl} = \text{Rate of DPHM infusion} / C_{	ext{Pu}} \quad (3)
\]

where C_{Pu} is the plasma total steady-state DPHM concentration, and β is the terminal elimination constant.

Data were plotted using Microsoft Excel 2000 (Microsoft Corporation, Mountain View, CA). All data are reported as mean ± S.D. Statistical analyses were performed using JMP IN, version 3.2.1 (SAS, Cary, NC). The significance level was p < 0.05 in all cases.

Calculation of f_{CSF} and f_{ECF}. The extent of DPHM transfer into the brain in this study was calculated by relating the CSF and ECF total area under the plasma concentration versus time curve (AUC_{0-\text{t}}) values to the plasma AUC_{0-\text{t}} value to yield the f_{CSF} and f_{ECF} ratios. Specifically, using f_{CSF} as an example:

\[
f_{CSF} = \frac{\text{AUC}_{\text{CSF}}}{\text{AUC}_{\text{ECF}}} = \frac{\text{AUC}_{0-\text{t}_{\text{CSF}}}}{\text{AUC}_{0-\text{t}_{\text{ECF}}}} \quad (4)
\]

The f_{ECF} value was calculated in the same manner using total area under the ECF concentration versus time curve (AUC_{0-\text{t}_{\text{ECF}}}). This method of characterizing drug transfer across the BBB has been used in numerous other MD studies for many different drugs, including acetaminophen, atenolol, gabapentin, zidovudine, morphine-6-glucuronide, lamotrigine, phenobarbital, and felbamate (Wang et al., 1993; Wong et al., 1993; de Lange et al., 1994; Luer et al., 1999; Bow et al., 2001; Potschka et al., 2002).

DPHM-PRN coadministration. Vd, Cl, f_{CSF}, f_{ECF}, and f_{CSF} values in these experiments were estimated using the equations listed above. However, for comparisons of the DPHM alone and DPHM-PRN coadministration periods, DPHM concentrations and AUC values for the periods 0 to 4 h and 4 to 8 h, respectively, were used. Thus, to assess the effect of PRN on the f_{CSF} value, for example, area under the CSF concentration versus time curve from 0 to 4 h (AUC_{0-\text{t}_{\text{CSF}}}) was compared with area under the CSF concentration versus time curve from 4 to 8 h (AUC_{4-\text{t}_{\text{CSF}}}).

Results

Five-Step Infusion Study. Probe recovery rates ranged from 40 to 50% in all six animals, and the average values for the DPHM (46.1 ± 3.3%) and DPHM-PRN (44.3 ± 3.7%) experiments are not significantly different (Table 1). In addition, no significant differences in recovery rates were observed among the five infusion steps for both probes (ECF, 46.3 ± 3.3%; CSF, 45.9 ± 3.3%). The steady-state concentrations of DPHM in plasma, CSF, and ECF increased corre-
CCSF/CPu and CECF/CPu ratios ranged from 2 to 3. There was no significant difference between the steady-state CSF and ECF concentrations, as shown by the high Vd value (27.9 l/kg) (Table 1). Two-compartment pharmacokinetic model was based upon the generation of lower Akaike Information Criterion values for a two-compartment model fitting of the postinfusion data. All model fitting was carried out using a weighting factor of 1/predicted y^2 because it provides more accurate estimates at lower DPHM concentrations. The drug was extensively distributed in the animals, as shown by the high Vd value (27.9 ± 17.4 l/kg) (Table 6). Two-compartment pharmacokinetics were observed in the DPHM elimination profiles of all three fluids, with the CNS compartments.

**TABLE 1**

Summary of microdialysis probe recovery rate in the five-step infusion and DPHM-PRN coadministration experiments

<table>
<thead>
<tr>
<th>Step</th>
<th>Probe (%)</th>
<th>CPt</th>
<th>CPu</th>
<th>CCSF/CPt</th>
<th>CECF/CPt</th>
<th>CCSF/CPu</th>
<th>CECF/CPu</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0 ± 0.5</td>
<td>2.4* 0.4</td>
<td>2.2* 0.3</td>
<td>2.2* 0.2</td>
<td>2.3* 0.1</td>
<td>2.1* 0.0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.4 ± 0.4</td>
<td>2.2* 0.3</td>
<td>2.3* 0.2</td>
<td>2.2* 0.2</td>
<td>2.3* 0.1</td>
<td>2.1* 0.0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.6 ± 0.3</td>
<td>2.1* 0.2</td>
<td>2.3* 0.1</td>
<td>2.2* 0.1</td>
<td>2.3* 0.1</td>
<td>2.1* 0.0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3.8 ± 0.2</td>
<td>2.1* 0.0</td>
<td>2.3* 0.0</td>
<td>2.2* 0.0</td>
<td>2.3* 0.0</td>
<td>2.1* 0.0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5.0 ± 0.1</td>
<td>2.0* 0.0</td>
<td>2.3* 0.0</td>
<td>2.2* 0.0</td>
<td>2.3* 0.0</td>
<td>2.1* 0.0</td>
<td></td>
</tr>
</tbody>
</table>

a Probes recovery rates were determined using eq. 1.
b n = 3 because of failure of ECF probes in three of the animals. Otherwise, n = 6.

**FIG. 1**. Plasma, CSF, and ECF DPHM concentrations achieved with the five-step infusion study. DPHM was infused for 8 h at 13.5 μg/kg/min. The ECF curve was based on results from three animals because of failure of ECF probes in three other animals. Both the plasma and CSF curves represent the results from six animals. Error bars are omitted for clarity.

**FIG. 2**. Plasma, CSF, and ECF DPHM concentrations achieved with the DPHM-PRN coadministration study. DPHM was infused for 8 h at 13.5 μg/kg/min, and propranolol was coinfused from 4 to 8 h at 20 μg/kg/min. The ECF curve was based on results from three animals because of failure of ECF probes in three other animals. Both the plasma and CSF curves represent the results from six animals. Error bars are omitted for clarity.

**TABLE 2**

Steady-state DPHM total plasma (C_Pt), unbound plasma (C_Pu), CSF, and ECF concentrations for the five infusion steps

<table>
<thead>
<tr>
<th>Infusion Step</th>
<th>C_Pt*</th>
<th>C_Pu*</th>
<th>C_CSF*</th>
<th>C_ECF*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62.9 ± 18.8</td>
<td>8.7 ± 3.4</td>
<td>20.0 ± 4.2</td>
<td>20.2 ± 5.0</td>
</tr>
<tr>
<td>2</td>
<td>169.3 ± 61.4</td>
<td>18.9 ± 7.0</td>
<td>54.4 ± 15.9</td>
<td>56.7 ± 27.2</td>
</tr>
<tr>
<td>3</td>
<td>306.6 ± 108.7</td>
<td>40.5 ± 18.0</td>
<td>112.8 ± 42.7</td>
<td>119.6 ± 68.8</td>
</tr>
<tr>
<td>4</td>
<td>435.8 ± 203.0</td>
<td>61.8 ± 36.4</td>
<td>158.0 ± 58.0</td>
<td>165.6 ± 78.8</td>
</tr>
<tr>
<td>5</td>
<td>599.3 ± 276.9</td>
<td>104.7 ± 45.3</td>
<td>221.9 ± 89.0</td>
<td>214.0 ± 109.0</td>
</tr>
</tbody>
</table>

a Average concentration for each step was derived from the last sample of each infusion step. Steady state is reached at 4 h of each infusion step.
b Free plasma concentrations were determined by equilibrium dialysis of the last sample of each infusion step.

**TABLE 3**

Steady-state C_CSF/C_Pt and C_ECF/C_Pt ratios for each infusion step

<table>
<thead>
<tr>
<th>Infusion Step</th>
<th>C_CSF/C_Pt</th>
<th>C_ECF/C_Pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.4 ± 0.2*</td>
<td>2.3 ± 1.2*</td>
</tr>
<tr>
<td>2</td>
<td>0.4 ± 0.2*</td>
<td>2.9 ± 2.3*</td>
</tr>
<tr>
<td>3</td>
<td>0.5 ± 0.2*</td>
<td>2.8 ± 2.4*</td>
</tr>
<tr>
<td>4</td>
<td>0.5 ± 0.3*</td>
<td>2.6 ± 1.6*</td>
</tr>
<tr>
<td>5</td>
<td>0.5 ± 0.3*</td>
<td>2.1 ± 2.0*</td>
</tr>
</tbody>
</table>

a The C_CSF/C_Pt ratios were calculated by dividing the concentrations of the last sample of CSF with the last sample of plasma in each step. The same procedure was applied to the calculation of C_ECF/C_Pt ratios.
b The C_ECF/C_Pt ratios were calculated by dividing the concentration of the last sample of CSF with the free plasma concentration (determined by equilibrium dialysis) of the last plasma sample in each step. The same procedure was applied to the calculation of C_ECF/C_Pt ratios.

Significantly different from the value of 1 (paired t test).
In contrast, CECF and CCSF concentrations increased during PRN (Table 4). For both CECF and CCSF, the percentage increases (88.1% for step 4 and 110% for step 5) at the highest infusion rates, the mean arterial pressure (110.98 mm Hg for step 5) was not significantly different from the value obtained during all five infusion steps. During steps 4 and 5, which involved the highest infusion rates, the mean arterial pressure (110.98 mm Hg for step 5) was not significantly different from the value obtained during all five infusion steps.

**Physiological Responses.** In the five-step infusion study, during the administration of infusion steps 4 to 5, three animals showed symptoms of agitation including restlessness, tremor, excessive bleeding, and heavy breathing. These symptoms disappeared 1 to 1.5 h after the end of the infusion. During steps 4 and 5, which involved the highest infusion rates, the mean arterial pressure (110 ± 2.41 mm Hg for step 4 and 110 ± 0.98 mm Hg for step 5) was not significantly different from the mean baseline value of 111 ± 0.41 mm Hg. In terms of mean heart rate, no significant changes from baseline were observed during all five infusion steps.

In the DPHM-PRN study, no significant difference was observed in mean arterial pressure after PRN coinfusion (101 ± 1.47 mm Hg) compared with DPHM administration alone (102 ± 0.86 mm Hg). However, a significant drop in mean heart rate was observed with PRN coadministration (77.7 ± 3.47 beats per minute) compared with DPHM alone (95.5 ± 2.37 beats per minute), and this fall in heart rate persisted for the full 20-h duration of the experiment (Fig. 3).
The postulation of an active transport process is supported by the C_{CSF/C_{pa}} and C_{ECF/C_{pa}} ratios, both ranging from 2 to 3 (Table 3). Transfer of DPHM into the CNS was rapid after administration; this was not a surprising observation considering the highly lipophilic nature of this compound [octanol/water partition coefficient 1862 (Douglas, 1980)]. Other reports also suggest rapid distribution of DPHM into tissues, with the maximum tissue uptake occurring at 1 to 3 min after i.v. injection (Drach et al., 1970). The close similarities between the two CNS drug concentrations (Table 2 and Fig. 1) suggest that drug clearances in the choroid plexus and the cerebral cortex are comparable with each other. This observation can further be assessed by comparing the f_{CSF} and f_{ECF} values (0.4 ± 0.2 and 0.4 ± 0.2, respectively), which were not significantly different from each other. Two-compartment pharmacokinetics were observed in the DPHM elimination profiles of all three fluids in the five-step infusion studies, with the CNS compartments declining at the highest rates (Table 6). This was reflected in the half-life \( t_{1/2_{plasma}} \) 10.8 ± 5.4 versus \( t_{1/2_{ECF}} \) 5.3 ± 4.2 h values. The more rapid elimination of DPHM from the brain compared plasma is associated with higher concentrations of the drug in the CNS compared with the unbound plasma concentration (Table 2). This is probably due to active transport of the ionized DPHM into the brain, as discussed previously, so that more of the total circulating concentration of the drug is available to the brain compared with other organs and tissues.

The rapid efflux of DPHM from CNS could be due to the bulk flow of CSF (sink effect) and also involvement of a transporter-mediated efflux mechanism for the drug. The validity of the above assumption can be assessed by examining the results from the DPHM-PRN experiment. The CSF DPHM concentration increased significantly during PRN coadministration and for both CSF and ECF the percentage increase in drug levels was statistically significant (Table 4). In addition, both the \( f_{CSF} \) and \( f_{ECF} \) increased after the coadministration of propranolol (from 0.40 ± 0.20 to 0.69 ± 0.03 and 0.95 ± 0.05, respectively), with \( f_{ECF} \) being significantly increased. The trend for an increase in the CSF and ECF DPHM elimination half-life after PRN is also consistent with reduced clearance of the drug from the brain. However, these changes were not statistically significant. Although the PRN infusion was not continued into the elimination phase, the persistence of the PRN-elicted bradycardia for the entire duration of the experiment (Fig. 3) indicates that there was sufficient PRN still present during the elimination period for this action and thus perhaps also for an effect on DPHM transfer across the BBB. Overall, the findings suggest lower DPHM clearances from the CNS after PRN coadministration.

As mentioned earlier, besides the bulk flow of CSF, efflux of substances (transporter-mediated or not) can occur via brain or choroidal blood back to the systemic circulation. To date, there is no information showing that PRN lowers CSF formation or its secretion rates and that it has any interference with the passive diffusion process of substances back to the cerebral circulation. In addition, besides a slight decrease in heart rate, PRN causes no systemic or cerebral physiologic changes in sheep (O’Brien et al., 1999). In another study, PRN infusion did not significantly change choroid plexus blood flow in sheep (Townsend et al., 1984). Results from these studies are consistent with our current findings in that only heart rate, but not arterial pressure, was affected by PRN. Therefore, the lowered brain clearances are probably due to lowered rates of efflux of the drug.
Propranolol can be involved in this process in one or both of the following manners—by directly inhibiting the efflux mechanism and/or by competing with DPHM for the efflux process. Both of these actions could be responsible for the observed lowered rates of CNS clearances; however, the exact mechanism cannot be elucidated by our current experiments.

In contrast to the situation with DPHM concentrations in CSF and ECF, the plasma total DPHM level fell by 12.8% during PRN coadministration study suggests that PRN inhibits an efflux rather than influx mechanism. This latter finding was rather unexpected and warrants further investigation.

References


