ROLE OF THE LIVER AND GUT IN SYSTEMIC DIPHENHYDRAMINE CLEARANCE IN ADULT NONPREGNANT SHEEP

SANJEEV KUMAR, K. WAYNE RIGGS, AND DAN W. RURAK

ABSTRACT:

We investigated the contribution of the liver and gut to systemic diphenhydramine (DPHM) clearance in adult nonpregnant sheep in two separate studies. In the first study, a simultaneous 50-mg bolus each of DPHM and its deuterium-labeled analog ([2H10]DPHM) was administered to five sheep via the femoral (i.v.) and the portal venous (p.v.) routes in a randomized manner. Arterial plasma concentrations of DPHM, [2H10]DPHM, and their deaminated metabolites, DPMA (diphenylmethoxyacetic acid) and [2H10]DPMA, were measured using gas chromatography–mass spectrometry. The hepatic first-pass extraction of DPHM after p.v. administration was 94.2±3.7%. However, the area under the plasma concentration versus time profile of the metabolite after i.v. dosing was only 32.5±14.0% relative to that after p.v. administration. Thus, only ~32.5% of the i.v. dose is metabolized in the liver and a significant extrahepatic systemic clearance component is evident. Using the calculated total hepatic blood flow values, it was found that 98.6±9.2% of the i.v. dose eventually was delivered to the “hepatoportal” system. Because the drug delivered to the hepatoportal system is almost completely eliminated in a single pass (hepatic extraction ~94%), this indicates a lack of any significant pulmonary drug uptake. Also, because only ~32.5% of the i.v. dose is metabolized in liver, the gut is most likely responsible for the clearance of the remainder. This gut contribution to systemic DPHM clearance was confirmed in a separate direct study in four sheep where the steady-state DPHM gut extraction ratio was 49.0±3.0%. Thus, gut accounts for a significant proportion (~50%) of DPHM systemic clearance in sheep in spite of a very high hepatic drug extraction efficiency.

Diphenhydramine or 2-(diphenylmethoxy)-N,N-dimethylamine (DPHM) is a potent classical histamine H1 receptor antagonist. It has been widely used during human pregnancy for the treatment of nausea and vomiting, insomnia, allergic rhinitis, and common coughs and colds. For several years, our laboratory has been examining the comparative maternal–fetal pharmacokinetics and metabolism of this drug in chronically instrumented pregnant sheep (Yoo et al., 1990; Kumar et al., 1997). Our current focus is to elucidate the organs and metabolic pathways involved in DPHM clearance in the mother and the fetus.

The major routes of DPHM metabolism in many species (e.g., dog, rhesus monkey, human) include conversion to diphenylmethoxyacetic acid (DPMA) and DPHM-N-oxide metabolites (Drach and Howell, 1968; Drach et al., 1970; Chang et al., 1974). The urinary excretion of DPMA (including its amino acid conjugates) and DPHM-N-oxide may account for ~40 to 60% and ~5 to 15% of the administered dose, respectively, in these species (Drach and Howell, 1968; Drach et al., 1970; Chang et al., 1974). However, we have found that these metabolic pathways collectively account for only ~1 to 2% of total DPHM dose in maternal as well as fetal sheep (unpublished data). This has prompted us to reexamine the role of the liver in DPHM systemic clearance and to study other potential organs of drug clearance in sheep. Hence, in the current study, we have examined the relative importance of the liver and gut in systemic elimination of DPHM in adult sheep.

Materials and Methods

Animals and Surgical Preparation. A total of nine adult female nonpregnant sheep 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. Surgery was performed aseptically under halothane (1–2%) and nitrous oxide (60%) in oxygen anesthesia, after induction with i.v. sodium pentothal (1 g) and intubation of the ewe. Polyvinyl catheters (Dow Corning, Midland, MI) were implanted in a femoral artery and a femoral vein in all nine sheep. In the five sheep (average body weight, 70.1±10.5 kg) used for hepatic DPHM first-pass extraction studies, a sterile catheter was implanted in a branch of one of the mesenteric veins with the catheter tip advanced to the main mesenteric vein in the direction of hepatic portal vein. In the four sheep (average body weight, 64.0±7.9 kg) to be used for DPHM gut uptake studies, a catheter was implanted in the main hepatic portal vein trunk just before its entry into the liver, as described below. A longitudinal abdominal incision was...
made to gain access to various compartments of the ruminant sheep stomach. A prominent branch of the main gastric vein was identified either on the surface of the rumen or the omasum and a segment of the intact vessel was then carefully isolated from the surface of the stomach compartment. An ~12- to 18-inch length of a sterile polyvinyl catheter was then advanced into this vessel toward the direction of liver via the main gastric vein and into the hepatic portal vein. The catheter was secured in place using sterile silk sutures and was anchored to the surface of the rumen or the omasum. All catheters were tunneled s.c. and exteriorized via a small incision on the flank of the ewe and were stored in a denim pouch when not in use. Catheters were flushed daily with approximately 2 ml of sterile 0.9% sodium chloride containing 12 U of heparin/ml to maintain catheter patency. Intramuscular injections of 500 mg of ampicillin were given to the ewe on the day of surgery and for 3 days postoperatively. After surgery, animals were kept in holding pens with other sheep and were given free access to food and water. The sheep were allowed to recover for 3 to 8 days before experimentation. The position of the portal venous catheter was verified in all animals by autopsy at the end of each experiment.

Experimental Protocol. **DPHM hepatic first-pass extraction studies.** Equimolar amounts of DPHM and its deuterium-labeled analog ([2H10]DPHM), equivalent to 50 mg DPHM, were administered simultaneously but separately via the femoral (i.v. route) and mesenteric vein (portal venous (p.v. route) catheters in a randomized manner. Serial samples of femoral arterial plasma (~3 ml) were collected at 5, 10, 20, 30, and 40 min and at 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 h after drug injection.

The deuterium-labeled parent drug ([2H10]DPHM) used in hepatic DPHM uptake studies above was synthesized and purified in our laboratory (Tonn et al., 1993). The doses of [2H10]DPHM were corrected for the mass difference (due to the presence of deuterium labels) compared with the unlabeled drug.

**DPHM gut uptake studies.** DPHM gut uptake was measured under steady-state conditions in four adult sheep with implanted p.v. catheters. For this purpose, a 20-mg i.v. bolus-loading dose of DPHM was administered at the beginning of the experiment via the femoral vein catheter to four sheep. This was followed immediately by an infusion of unlabeled DPHM at a rate of 670 μg/min for 6 h. Simultaneous femoral arterial (before the gut) and p.v. (after the gut) blood samples (~3 ml each) were collected every hour for the entire duration of DPHM infusion (6 h) to estimate the steady-state gut extraction of the drug.

All doses were prepared in sterile water for injection and were sterilized by filtering through a 0.22-μm nylon syringe filter (MSI, Westboro, MA) into a capped empty sterile injection vial.

Blood samples collected above during all experiments were placed into heparinized Vacutainer tubes (Becton Dickinson, Rutherford, NJ) and gently mixed. These samples were then centrifuged at 2000g for 10 min. The plasma supernatant was removed and placed into clean borosilicate test tubes with polytetrafluoroethylene (PTFE)-lined caps. All samples were stored frozen at −20°C until the time of analysis.

**Drug and Metabolite Analysis.** The concentrations of DPHM, [2H10]DPHM, and their corresponding deaminated metabolites, DPMA and [2H10]DPMA, in femoral arterial plasma samples collected during hepatic DPHM uptake studies were measured using previously developed gas chromatographic–mass spectrometric (GC-MS) analytical methods (Tonn et al., 1993, 1995). The femoral arterial and p.v. plasma samples collected during DPHM gut uptake studies were analyzed only for concentrations of the parent drug, i.e., DPHM, using the above GC-MS analytical method (Tonn et al., 1993) The linear calibration range of the above assays is 2.0 to 200.0 ng/ml for DPHM and [2H10]DPHM and 2.5 to 250.0 ng/ml for DPMA and [2H10]DPMA. The inter- and intraday coefficients of variation are <20% at the limit of quantitation and <10% at all other concentrations (Tonn et al., 1993, 1995).

**Pharmacokinetic Analyses.** **DPHM hepatic first-pass uptake studies.** Areas under the plasma drug or metabolite concentration versus time curves (AUCs) from time 0 to the last sampling point were calculated using the linear trapezoidal rule (Gibaldi and Perrier, 1982). This area under the curve was then extrapolated to time infinity by adding the factor, Cinf/K, Cinf is the plasma concentration of the drug or metabolite at the last sampling time, and K is the terminal elimination rate constant (Gibaldi and Perrier, 1982). The total area under the curve up to time infinity is referred to as AUC in the following equations. Subscripts “parent” and “metabolite” stand for parent drug and metabolite, respectively.

The systemic clearance of drug was calculated as:

\[
(CL)_{\text{systemic}} = \frac{(\text{Dose})_{i.v.}}{(AUC_{\text{parent}})_{i.v.}} \tag{1}
\]

where, i.v. refers to i.v. administration of the parent drug.

The hepatic first-pass extraction ratio (Ei.v.) of drug is given by:

\[
E_{i.v.} = 1 - \frac{(AUC_{\text{parent}})_{p.v.}}{(AUC_{\text{parent}})_{i.v.}} \tag{2}
\]

This fraction of the i.v. administered drug metabolized in the liver was calculated from AUCs of the DPMA metabolite after p.v. and i.v. administration of the parent drug, as:

\[
f_i = \frac{(AUC_{\text{metabolite}})_{v}}{(AUC_{\text{metabolite}})_{p.v.}} \tag{3}
\]

This equation assumes linear pharmacokinetics, sole hepatic formation of the metabolite, and complete metabolism of the p.v. dose in the liver.

Total hepatic blood flow (p.v. + hepatic arterial) was estimated from the relationships of the well-stirred model of hepatic elimination (Wilkinson and Shand, 1975; Pang and Gillette, 1978):

\[
Q_{ht} = \frac{1}{\text{Dose}_{i.v.}} \left[ \frac{AUC_{\text{parent}}}{(C_{ss})_{\text{MA}}} - \frac{AUC_{\text{parent}}}{(C_{ss})_{\text{PV}}} \right] \tag{4}
\]

where, i.v. and p.v. refer to the doses and respective AUCs during i.v. or p.v. administration of the parent drug.

The amount of i.v. administered drug eventually delivered to the hepatoportal system (gut + liver) was calculated from estimated hepatic blood flow and its systemic arterial AUC (Wilkinson and Shand, 1975):

\[
\text{Amount delivered to the hepatoportal system} = Q_{ht} \times (AUC_{\text{parent}})_{i.v.} \tag{5}
\]

This subsequently was converted to the percentage of administered dose delivered to the hepatoportal system. **DPHM gut uptake studies.** Steady-state systemic clearance of the drug is calculated as:

\[
(\text{CL})_{\text{systemic}} = \frac{k_{\text{o}}}{(C_{ss})_{\text{MA}}} \tag{6}
\]

where k_o is the DPHM infusion rate and (C_{ss})_{MA} is the steady-state femoral arterial plasma DPHM concentration during gut uptake studies.

The steady-state gut extraction of the drug (E_{g}) is calculated as (du Souich et al., 1995):

\[
E_{g} = 1 - \frac{(C_{\text{inj}})_{\text{PV}}}{(C_{ss})_{\text{MA}}} \tag{7}
\]

where (C_{ss})_{MA} is the steady-state DPHM concentration in femoral arterial plasma (before the gut) and (C_{\text{inj}})_{PV} is the steady-state DPHM concentration in the p.v. plasma (after the gut).

**Statistical Analyses.** All data are reported as the mean ± S.D. The femoral arterial plasma AUCs of the parent drug and metabolite after i.v. and p.v. DPHM administration were compared using a paired t-test. The achievement of steady-state in plasma was established according to two criteria: 1) the slope of plasma concentration versus time curve should not be significantly different from zero and 2) the coefficient of variation of the measured concentrations should be <15%. The steady-state DPHM concentrations in femoral arterial...
and p.v. plasma during gut uptake studies also were compared against each other using a paired \( t \) test. The significance level was \( p < .05 \) in all cases.

**Results**

**DPHM Hepatic First-Pass Uptake Studies.** Figure 1 shows the typical femoral arterial plasma concentration versus time profiles of the parent drug and metabolite after simultaneous and randomized administration of DPHM and \([^{2}H_{10}]{\text{DPHM}}\) via i.v. and p.v. routes in two sheep. In E1154, DPHM was given via the p.v. route and \([^{2}H_{10}]{\text{DPHM}}\) via the i.v. route. In E102, the order of administration was reversed, i.e., DPHM was administered i.v. and \([^{2}H_{10}]{\text{DPHM}}\) was administered via the portal route. The average maximal plasma concentrations \( (C_{\text{max}}) \) of the metabolite generated from the form of drug administered via the p.v. route were significantly higher compared with the \( C_{\text{max}} \) of metabolite generated from the form of drug given i.v. (447.8 ± 175.9 versus 90.7 ± 75.8 ng/ml; paired \( t \) test, \( p < .005 \)). The times of occurrence of plasma \( C_{\text{max}} \) of the metabolite \( (T_{\text{max}}) \) after p.v. administration ranged from 5 to 20 min compared with 10 to 90 min after i.v. administration. Table 1 presents the calculated femoral arterial AUCs of the parent drug and metabolite, hepatic first-pass extraction ratios, and the fraction of i.v. administered dose metabolized in liver. The AUC of the form of parent drug administered via the p.v. route was smaller compared with that of the form administered i.v. (paired \( t \) test, \( p < .005 \)). The AUC of the metabolite generated from the form of parent drug administered via the p.v. route, however, was significantly larger compared with that generated from the form administered via the i.v. route (paired \( t \) test, \( p < .01 \)). The hepatic first-pass extraction of the drug was high and ranged from 90.4 to 99% (mean 94.2 ± 3.7%; Table 1). The fraction of i.v. parent drug dose metabolized in liver ranges from 18.2 to 50.4% (mean 32.5 ± 14.0%; Table 1). Thus, the fraction of drug metabolized/eliminated by extrahepatic tissues will be 49.6 to 81.8% (mean 67.5 ± 14.0%).

**Table 2** presents the estimates of systemic clearance, total hepatic blood flow, and percentage of i.v. dose that is eventually delivered to the hepatoporal system (gut and liver). The average percentage of the i.v. dose delivered to the hepatoporal system was not significantly different from 100% (unpaired \( t \) test, \( p > .3 \)).

**DPHM Gut Uptake Studies.** Figure 2 shows the average concentration versus time profiles of DPHM in femoral arterial and p.v. plasma in four sheep during the 6-h DPHM infusion period. DPHM was at steady-state during the 2- to 6-h DPHM infusion period in both femoral arterial and p.v. plasma according to the established criteria. The steady-state femoral arterial and p.v. plasma concentrations, systemic clearance, and estimates of gut extraction of DPHM in four sheep are presented in Table 3. The p.v. plasma concentrations of DPHM were significantly lower compared with its femoral arterial plasma concentrations throughout the experimental period in all animals (paired \( t \) test, \( p < .005 \) in all cases). The gut extraction of the
The route of drug administration (Pang, 1981). Thus, a significantly higher $C_{\text{max}}$ of the metabolite was observed after p.v. dosing as compared with that after i.v. administration. Also, the $C_{\text{max}}$ values of the former metabolite tended to occur at earlier times compared with those of the latter. This is because p.v. administration results in an almost instantaneous metabolism of ~94.2% of the administered dose (see above) and an apparent “bolus” injection of large amounts of the generated metabolite into the circulation. In contrast, the drug administered i.v. is more gradually metabolized and leads to a slower increase in metabolite plasma concentrations.

It has been suggested that the arterial AUCs of the metabolite after p.v. and i.v. administration of equal doses of the drug should be relatively equal, provided the contribution of renal or peripheral elimination to total clearance is <10% and linear pharmacokinetics exist (Pang, 1981; Houston and Taylor, 1984). This is true in spite of the widely differing shapes of metabolite plasma profiles obtained after these routes of administration (see above). However, if renal or peripheral elimination of the drug is >10%, the metabolite AUC after p.v. administration becomes larger compared with that after i.v. administration (Pang, 1981; Houston and Taylor, 1984). This is because if renal or peripheral elimination of the drug is negligible (<10%), the majority of the drug will undergo hepatic metabolism after all routes of administration. Thus, similar amounts of the metabolite eventually will be formed from equal doses of the drug given via the p.v. and i.v. routes, leading to similar arterial metabolite AUCs. However, if renal or peripheral elimination is >10%, a larger fraction of the i.v. dose will be eliminated via this route and less will be available for hepatic metabolism; this then will lead to the formation of smaller amounts of the metabolite after i.v. dosing in comparison with that after p.v. administration.

Earlier we observed that DPHM exhibits linear pharmacokinetics in adult sheep with negligible renal and biliary clearances (<0.5% of total body clearance) over the dose range used in this study (Yoo et al., 1990; Tonn, 1995). Thus, in the absence of any peripheral elimination, the AUCs of the DPHM metabolites after i.v. and p.v. drug administration should be equal. A lower metabolite AUC after i.v. compared with that after p.v. administration in our DPHM hepatic first-pass studies provides clear evidence for significant peripheral drug elimination. Also, the data presented in Table 1 indicate that almost the entire p.v. DPHM dose is metabolized in the liver. This mainly results from the metabolism of ~94.2% of the dose during its first pass through the liver; plus, at least some of the remaining drug undergoes hepatic metabolism during subsequent passes. Thus, from the relative metabolite AUCs after p.v. and i.v. administration, it appears that only 32.5 ± 14.0% of the i.v. administered drug is metabolized in the liver and the rest likely is eliminated via peripheral mechanisms. This analysis assumes sole hepatic formation of the drug in individual animals ranged from 46.3 to 53.4% (mean 49.0 ± 3.0%).

**Discussion**

DPHM was extracted extensively across the sheep liver with an estimated mean hepatic first-pass extraction ratio of 94.2 ± 3.7% (Table 1).

The shape of the metabolite plasma profile is highly dependent on the route of drug administration (Pang, 1981). Thus, a significantly higher $C_{\text{max}}$ of the metabolite was observed after p.v. dosing as compared with that after i.v. administration. Also, the $C_{\text{max}}$ values of the former metabolite tended to occur at earlier times compared with those of the latter. This is because p.v. administration results in an almost instantaneous metabolism of ~94.2% of the administered dose (see above) and an apparent “bolus” injection of large amounts of the generated metabolite into the circulation. In contrast, the drug administered i.v. is more gradually metabolized and leads to a slower increase in metabolite plasma concentrations.

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The average estimate of $Q_H$ obtained in well-stirred model of hepatic clearance (Wilkinson and Shand, 1975; Pang and Gillette, 1978) found that almost the entire i.v. dose (98.6%) is hepatic extraction of DPHM is high (1%, unpublished data). Because the fraction of dose metabolized via a particular metabolic pathway is constant in a linear pharmacokinetic system, the plasma concentration-time profiles of all other metabolites also will exhibit a similar behavior (Houston and Taylor, 1984).

The parent drug pharmacokinetic data after i.v. and p.v. administration can be used to estimate total hepatic blood flow ($Q_H$) using the well-stirred model of hepatic clearance (Wilkinson and Shand, 1975; Pang and Gillette, 1978). The average estimate of $Q_H$ obtained in these studies (62.6 ± 14.7 ml/min/kg; Table 2) is in excellent agreement with the reported values for adult nonpregnant sheep (56.6 ± 18.0 ml/min/kg, Katz and Bergman, 1969; 48.6 ml/min/kg, Boxenbaum, 1980). It should be emphasized that the above estimation of $Q_H$ assumes a lack of significant DPHM uptake by the gut. However, the hepatic extraction of DPHM is high (94%), and, thus, the presence of any gut drug uptake will not alter significantly the overall DPHM extraction across the hepatoportal system (i.e., observed 94% versus maximum possible 100%). Using these $Q_H$ estimates and eq. 5, we predicted contribution of the liver appears to be near the high end (18.2–50.4%). Also, the systemic clearances of DPHM during the gut uptake study appear to be somewhat lower compared with those during the hepatic first-pass experiments. These may be related to interanimal variability and the small number of animals used in these two studies. The overall combined data indicate that gut uptake of the drug may account for ~50 to 80% of DPHM systemic clearance. The mechanism of this DPHM gut uptake remains unknown and may involve simple binding of the drug to tissue components, its secretion into the lumen via specific transporters (e.g., P-glycoprotein), or metabolism via pathways other than the formation of DPMA.

Lately, there has been an increased interest in the detailed study of the underlying mechanisms of gut uptake/metabolism of drugs and its role in determining drug absorption and bioavailability. Oral bioavailability of midazolam, cyclosporine, verapamil, and nifedipine in humans appears to be highly dependent on their CYP3A-mediated metabolism in the gut mucosa (Hebert et al., 1992; Paine et al., 1996; Thummel et al., 1996; Fromm et al., 1996; Holtebecker et al., 1996; Wandel et al., 1998). Polarized basolateral-to-apical drug transport/secretion in the intestine, mediated via P-glycoprotein, also has been demonstrated to be an important factor in determining the absorption and bioavailability of cyclosporine and paclitaxel (Asperen et al., 1997; Lown et al., 1997; Sparreboom et al., 1997). The majority of the above studies have assessed the effect of gut uptake/metabolism/secretion on the bioavailability of the drug after oral administration. Apart from a few isolated attempts (du Souich et al., 1995), there appear to be few systematic studies on the extent of gut uptake of drugs from the systemic circulation and its role in systemic drug clearance. For midazolam, gut drug uptake from the systemic circulation was negligible, presumably because of inaccessibility of the intestinal CYP3A to the circulating drug (Paine et al., 1996). Other investigators have assumed that the gut drug uptake from the systemic circulation is insignificant (Hebert et al., 1992; Holtebecker et al., 1996). Our data with DPHM show that this assumption may not necessarily be true for all drugs. Thus, pharmacokinetic analyses of hepatoporal drug disposition based on this assumption may not be entirely accurate, as was previously argued by Lin et al. (1997).

In summary, our studies demonstrate that gut drug uptake from the systemic circulation is responsible for ~50 to 80% of DPHM systemic clearance in adult sheep and the liver accounts for the remainder. These data also indicate that the assumption of negligible gut drug uptake from the systemic circulation may not be universally true and that it should be explicitly examined in pharmacokinetic studies designed to assess the role of the gut in drug bioavailability and clearance.

**Acknowledgments.** We thank Eddie Kwan for his help with the animal surgeries.

**TABLE 3**

<table>
<thead>
<tr>
<th>Ewe</th>
<th>Steady-State Plasma Concentration</th>
<th>Systemic Clearance</th>
<th>Gut Extraction ($E_p$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Femoral Arterial</td>
<td>p.v.</td>
<td>ml/min/kg</td>
</tr>
<tr>
<td>E0224</td>
<td>296.7</td>
<td>148.2</td>
<td>40.3</td>
</tr>
<tr>
<td>E4140</td>
<td>197.3</td>
<td>105.9</td>
<td>50.0</td>
</tr>
<tr>
<td>E1225A</td>
<td>451.7</td>
<td>210.5</td>
<td>20.3</td>
</tr>
<tr>
<td>E6216</td>
<td>323.3</td>
<td>173.7</td>
<td>35.1</td>
</tr>
<tr>
<td>Mean ± S.D.</td>
<td>317.2 ± 104.8</td>
<td>159.6 ± 44.0*</td>
<td>36.4 ± 12.4</td>
</tr>
</tbody>
</table>

*Significantly lower compared with femoral arterial plasma concentrations.

metabolite; if the metabolite is also formed in peripheral organs, the percentage metabolized in the liver will be overestimated using this approach (eq. 3). This is because peripheral metabolite formation will contribute more toward the metabolite AUC after i.v. than after p.v. administration because of the much higher parent drug concentrations after i.v. dosing. It should be noted that the above conclusions are valid in spite of the fact that the DPMA metabolite is not the only contributor to DPHM clearance; it actually accounts for only a very small fraction of DPHM elimination (~1%, unpublished data). Because the fraction of dose metabolized via a particular metabolic pathway is constant in a linear pharmacokinetic system, the plasma concentration-time profiles of all other metabolites also will exhibit a similar behavior (Houston and Taylor, 1984).

The parent drug pharmacokinetic data after i.v. and p.v. administration can be used to estimate total hepatic blood flow ($Q_H$) using the well-stirred model of hepatic clearance (Wilkinson and Shand, 1975; Pang and Gillette, 1978). The average estimate of $Q_H$ obtained in these studies (62.6 ± 14.7 ml/min/kg; Table 2) is in excellent agreement with the reported values for adult nonpregnant sheep (56.6 ± 18.0 ml/min/kg, Katz and Bergman, 1969; 48.6 ml/min/kg, Boxenbaum, 1980). It should be emphasized that the above estimation of $Q_H$ assumes a lack of significant DPHM uptake by the gut. However, the hepatic extraction of DPHM is high (94%), and, thus, the presence of any gut drug uptake will not alter significantly the overall DPHM extraction across the hepatoportal system (i.e., observed 94% versus maximum possible 100%). Using these $Q_H$ estimates and eq. 5, we predicted contribution of the liver appears to be near the high end (18.2–50.4%). Also, the systemic clearances of DPHM during the gut uptake study appear to be somewhat lower compared with those during the hepatic first-pass experiments. These may be related to interanimal variability and the small number of animals used in these two studies. The overall combined data indicate that gut uptake of the drug may account for ~50 to 80% of DPHM systemic clearance. The mechanism of this DPHM gut uptake remains unknown and may involve simple binding of the drug to tissue components, its secretion into the lumen via specific transporters (e.g., P-glycoprotein), or metabolism via pathways other than the formation of DPMA.

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