Bupivacaine Transfer across the Human Term Placenta

A Study Using the Dual Perfused Human Placental Model

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Background: Bupivacaine is widely used for obstetric analgesia, yet published information on the mechanism of human placental bupivacaine transfer is sparse. The dual perfused human placental model was used to elucidate the factors governing the placental transfer of bupivacaine.

Methods: Bupivacaine transfer was studied using the recirculating (closed) model and the single pass (open) model. Single placental cotyledons were perfused with either heparinized Krebs-Ringer's buffer (KRB) supplemented with human albumin (fetal and maternal circuits) or 100% fresh frozen plasma (maternal circuit) to control the bupivacaine protein binding in those circuits. In the open model, bupivacaine clearance was compared before and after being subjected to either increasing concentrations of bupivacaine or its structural analog, mepivacaine.

Results: For those studies in which the maternal and fetal protein binding was equal, the maternal to fetal (M → F) transfer was significantly greater (P < 0.05) than that in the fetal to maternal (F → M) direction. When the perfusates were modified to simulate actual in vivo plasma protein concentrations, bupivacaine transfer was shown to be related to the degree of protein binding found in the two circuits. In the open studies, bupivacaine transfer was similar at all concentrations investigated, unaffected by mepivacaine, and related to the pH of the fetal perfusate. A concentration effect was seen within the placental tissue at the end of the experiment.

Conclusions: Bupivacaine placental transfer characteristics suggest passive diffusion rather than active drug transport and appear to be influenced by the maternal and fetal plasma protein binding, fetal pH, and placental uptake. (Key words: Anesthetics, local; bupivacaine. Pharmacokinetics: placental accumulation; placental transfer; protein binding.)

MANY women receive epidural analgesia for childbirth. Currently, epidural analgesia for labor and delivery involves an initial incremental injection of 8–12 ml of a relatively dilute local anesthetic solution. This is followed by either repeated bolus doses of the same local anesthetic concentration when pain recurs or a continuous infusion of an even more dilute local anesthetic solution into the epidural space. Despite the frequent use of local anesthetics in obstetrics, published information concerning the mechanism(s) governing their transfer across the human placenta, ultimately leading to fetal exposure by these agents is sparse. Most of the available information has been derived from single-point determinations of blood concentration in maternal, umbilical cord, and neonatal blood samples taken at birth from multiple subjects after variable periods of drug exposure.1-3 These single-point determination studies provide valuable data on fetal exposure and net placental transfer over time. However, it is difficult to reach meaningful conclusions as to the direction (i.e., M → F or F → M) and rate of local anesthetic transfer across the placenta from such studies.

Animal models have been used to assess transplacental drug passage but interspecies differences in anatomy and physiology have prevented general acceptance of animal studies as they relate to humans.4-6 A wide gap thus exists in our knowledge and understanding of the mechanisms and rates of M → F and especially F → M
transport of bupivacaine and other local anesthetics across the placenta and the role that placental sequestration and metabolism might play in influencing fetal drug exposure to these commonly used agents.

An isolated, dual perfusion, human placental model was developed in the 1970s and has been well validated through studies of the transfer of several different substances. However, its use to study the transplacental passage of anesthetic agents has been limited because there is considerable individual variability among placentas, differences in lobule sizes and flow rates between placental studies can be normalized by relating the transfer rates of bupivacaine to that of the freely diffusible, flow limited, compound antipyrine.

The objectives of the current investigation were to determine the bidirectional rates of bupivacaine transfer across the placenta and to what degree protein binding affects these rates; to ascertain whether bupivacaine transfer exhibits saturation kinetics or is effected by a structural analog, mepivacaine; to examine the relationship of bupivacaine clearance to fetal perfusate pH; and to assess the ability of the placenta to sequester bupivacaine.

Methods and Materials

Placental Perfusions

After IRB approval and informed, written consent, normal term placentas were obtained from parturients within 5–10 min after either vaginal or cesarean section delivery. Each placenta was immediately perfused via an umbilical artery and direct injection of the intervillous space with cold heparinized Krebs-Ringer’s buffer (KRB) at pH 7.4 to preserve placental function and prevent clotting. A fetal artery and vein supplying a single cotyledon were cannulated (fig. 1) with polyethylene infant feeding tubes, 5 or 8 Fr depending on vessel size (Sherwood Medical, St. Louis, MO), and perfused with KRB. After insuring complete recovery of all arterially infused perfusate from the venous catheter (i.e., there were no placental leaks), the placenta was placed into a plexiglass chamber, maternal side upward, and the intervillous space perfused by three blunt tip 19-G needles, inserted into the area discolored by the washout of erythrocytes by the perfusion of the fetal vessels. Maternal and fetal circulatory temperature and pH were maintained at constant 37°C and 7.4 ± 0.05, except in a series of seven experiments in which fetal perfusate pH was adjusted in intervals from 7.4 to 7.2, 7.0, and 6.8. The maternal flow rate was maintained at 12 to 15 ml/min producing perfusion pressures of 25–35 mmHg. The fetal flow rate was adjusted to provide fetal perfusion pressures of 65–75 mmHg resulting in flow rates of 1.5–3.0 ml/min. Pressure, pH, and temperature were electronically recorded using a specific software package (Anesthesiology Research Department, Vanderbilt University) for the duration of the experiment. The perfusate was equilibrated with 21% O2 and the concentration of carbon dioxide needed to maintain the desired pH (7.4 ± 0.05). Viability of the placenta was monitored by longitudinal measurement of glucose consumption and lactate production.

In 29 studies, the perfusate consisted of KRB supplemented with 2 g/100 ml or 0.2 g/100 ml human albumin and 150 mg/100 ml glucose. In ten experiments, the perfusates were altered to better simulate the in vivo protein binding by using 100% fresh frozen plasma (FFP, Vanderbilt Hospital blood bank) on the maternal side and KRB with 4 g/100 ml human albumin on the fetal side.

Specific Experiments

Experiments were performed using either the closed (recirculating) method (fig. 2) or the open (single pass or nonrecirculating) method (fig. 3). In the closed model, both the maternal and fetal perfusate (250 ml and 100 ml, respectively) were recirculated. After a 30-min equilibration period, bupivacaine (1 or 4 µg/ml, 3.5 or 14 µM, respectively) and antipyrine (10 µg/ml, 53 µM) were added to either the maternal or fetal reservoir and allowed to equilibrate for 3 h. Samples (1 ml) were taken from the maternal and fetal circuits at 15–30-min intervals for the duration of the experiment (3 h) for the measurement of bupivacaine, antipyrine, lactate production, and glucose consumption. Eight closed experiment were performed using KRB with 2 g/100 ml albumin in both reservoirs and bupivacaine concentration of 4 µg/ml (14 µM), four in the M → F direction and four in the F → M direction. Ten additional M → F (n = 6) and F → M (n = 4) closed experiments were accomplished using human FFP as perfusate within the maternal circuit and KRB with 4 g/100 ml albumin in the fetal circuit and a bupivacaine concentration of 1 µg/ml (3.5 µM) to simulate protein binding of bupivacaine as seen in vivo.

Twent-one open experiments were completed, all using KRB with 0.2 g/100 ml albumin in both circuits. At 15-min intervals during the 3-h study, 2-ml samples
were taken from the "donor circuit" reservoir and, at the same time, a 2-min collection from the venous outflow was obtained. From these samples and the resulting flow rate determination, clearance was calculated. In ten of these open studies, progressively increasing concentrations of bupivacaine (4, 20, 40, and 80 µg/ml and 14, 70, 140, and 280 µm, respectively) were presented to the placenta in either the M → F direction (n = 5) or the F → M direction (n = 5). In four M → F experiments, the concentration of bupivacaine was held constant at 4 µg/ml (14 µm) and mepivacaine, a structurally analogous local anesthetic, was added in increasing concentration of 4, 40, and 80 µg/ml (16, 162, and 325 µm, respectively) to assess for the presence of a specific placental carrier for these amide local anesthetics. In the remaining seven experiments, the effect of fetal pH on M → F bupivacaine clearance was investigated. Bupivacaine clearance was initially determined at equal pH (7.4) in both circuits, after which clearance was measured while fetal perfusate pH was changed in 30-min intervals to 7.2, 7.0, 6.8 and back to 7.4. These pH adjustment were achieved by addition of dilute hydrochloric acid.

**Placental Uptake**

At the end of the experiment, a solution of Malachite green was injected through the fetal artery catheter, thereby demarcating the boundaries of the placental cotyledon perfused. This stained lobule was dissected from surrounding unstained placenta, weighed, and then homogenized in KRB (1 g/10 ml). In addition, in a few experiments, adjacent nonperfused lobules were excised and similarly analyzed to examine for potential drug loss to adjacent lobules. Because the population of patients from which the study placentas were chosen generally deliver under regional anesthesia, a series of five placentas were studied to check for possible contamination of the placental tissue with preexisting bupivacaine from the clinically administered epidural doses. These placentas were prepared as if for perfusion, however, at the point when bupivacaine was to be added, the study was aborted and the lobule was stained, removed, and homogenized as described above. These homogenates were assayed for bupivacaine concentration.

**High Performance Liquid Chromatographic Analysis**

Bupivacaine and antipyrine concentrations were measured in perfusate samples and placental homogenates using a modified HPLC method, as described by Huy-Riem et al. A µBondapakC18 (10 µm, 3.9 × 150 mm HPLC column, Millipore, Milford, MA) was equilibrated at 1 ml/min with the mobile phase, which consisted of acetonitrile and 0.05 M Na2HPO4 pH 5.80 (35:65 wt/vol). UV absorbance was monitored at 210 nm using a variable wavelength UV detector (Waters 486, Millipore). Butorphanol was used as internal marker because of its similar extraction and chromatographic qualities to bupivacaine and antipyrine. Samples (0.5 ml) were made basic with 2 N NaOH (0.2 ml) and extracted with ethyl ether (5 ml). They were
then vaporized to dryness, redissolved in 150 μl mobile phase, and introduced onto the HPLC column using an automated injection system (Waters Wisp 712, Millipore). Bupivacaine and antipyrine concentrations were ascertained from peak-height ratios with the internal standard butorphanol and subsequent comparisons to a calibration curve run concurrently with known bupivacaine and antipyrine concentrations. Calibration curves were linear from 0.1 μg to 10.0 μg/ml and exhibited a interday and intraday coefficient of variation of 6.07 and 5.9, respectively.

Equilibrium Dialysis

The protein binding of bupivacaine to the different perfusate preparation was determined using Spectrum Equilibrium Dialyzer (Spectrum Medical Industries, Los Angeles, CA) equipped with Spectrapore 2 dialysis tubing with a molecular cutoff of 12,000. Perfusate samples were dialyzed against phosphate buffer at pH 7.4 for 3 h at 37°C. Concentrations on both sides of the membrane were measured by HPLC.

Calculations

The nature of recirculating studies make it difficult to assess meaningful clearance data because it changes over time as more drug is transferred and accumulates toward equilibrium between the circuits. Instead, data are expressed in terms of a percent transfer of the drug during the period of greatest transport (i.e., on the steepest aspect of the exponential decline curve of the donor circuit). Percentage transfer in closed M → F perfusions was calculated from the equation:

\[
\% \text{ transfer}_{M\rightarrow F} = \frac{(C_F \times V_F)}{(C_M \times V_M) + (C_M \times V_M)} \times 100,
\]

where \( C_F \) and \( V_F \) represent the concentration of drug and volume of perfusate found in the fetal circuit, respectively, and \( C_M \) and \( V_M \) equal those values found in the maternal circuit. \( F \rightarrow M \)/% transfer was expressed in terms of the equation:

\[
\% \text{ transfer}_{F\rightarrow M} = \frac{(C_M \times V_M)}{(C_F \times V_F) + (C_M \times V_M)} \times 100.
\]

In open perfusions, after a period of equilibration, a steady state is attained. \( M \rightarrow F \) drug clearance (Cl) was calculated using the formula:

\[
\text{Cl}_{M\rightarrow F} = \frac{(C_{PV} \times Q_F)}{C_{MA}},
\]

where \( C_{PV} \) = drug concentration in fetal vein, \( C_{MA} \) = drug concentration in the “maternal artery”, and \( Q_F \) = fetal perfusate flow rate. In F → M open perfusions, clearance was calculated using the equation:

\[
\text{Cl}_{F\rightarrow M} = \frac{(C_{MV} \times Q_M)}{C_{FA}},
\]

where \( Q_M \) = maternal perfusate flow, \( C_{MV} \) = drug concentration in the “maternal vein,” and \( C_{FA} \) = drug concentration in the fetal artery. In five open M → F experiments, maternal clearance was calculated by altering the equation as follows:

\[
\text{Cl}_M = \frac{(C_{MA} - C_{MV}) \times Q_M}{C_{MA}}.
\]

Antipyrine, a freely diffusible flow-limited control marker, was used to remove interplacental variability.
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in lobule size and flow by expressing data as the bupivacaine/antipyrine transfer or clearance ratio. Reporting placental transfer or clearance in terms of antipyrine transfer or clearance has been employed since the early 1970s and is widely accepted as a useful tool in comparing rates of placental transfer for different compounds or in different directions (M → F or F → M). In the closed experiments, because the rate of transfer changes as the maternal and fetal drug concentration approaches equilibrium, the transfer ratios were reported at the 90-min point as neither bupivacaine nor antipyrine had reached equilibrium.

Statistics
The transfer or clearance ratios derived from M → F and F → M perfusions were compared using the unpaired t test. Clearances observed at varying fetal pH were examined using paired t test for significance. Regression analysis was used to assess correlation between bupivacaine concentrations occurring in the supplying reservoir and the recipient venous outflow as observed in open experiments demonstrating lack of saturation of placental clearance. Data is expressed as mean ± SE. A P value of ≤0.05 was considered significant.

Results

Closed Studies
When the albumin concentration (2 g/100 ml) was identical in both circuits (fig. 4), bupivacaine crossed the placental rapidly in the M → F direction with a transfer ratio at 90 min of 0.87 ± 0.05 (mean ± SEM). This ratio was significantly higher than was observed in the F → M direction at that time (0.57 ± 0.07, P < 0.05). When 100% FFP and KRB with 4 g/100 ml was substituted as the maternal and fetal perfusates, respectively, the transfer ratio at 90 min was reduced to 0.56 ± 0.05 in the M → F direction, while in the F → M direction, the ratio increased to 1.03 ± 0.04. Bupivacaine protein binding to KRB with 2 g/100 ml, KRB with 4 g/100 ml, and 100% FFP was shown to be 32.1 ± 2.8%, 54.2 ± 2.7%, and 79.5 ± 1.7%, respectively. As shown in table 1, when the terminal (3 h) maternal and fetal perfusate bupivacaine concentrations were corrected to express the amount of free (unbound) drug present, similar maternal/fetal ratios were observed in both the KRB and FFP experiments. In all closed experiments, the bupivacaine concentrations found in the perfused placental tissue at the end of the experiments averaged 5.13 ± 0.93 times the concentration found in the terminal perfusate samples. No bupivacaine was detected in experiments in which placentas were examined for residual bupivacaine from maternal epidural administration or in adjacent non-perfused lobules.

Open Studies
Bupivacaine and antipyrine clearance values observed in the open system are presented in table 2. When bupivacaine transfer was assessed in the open system using KRB with 2 g/100 ml, bupivacaine/antipyrine clear-

Fig. 3. The isolated dual circuit placental perfusion model, "open system." The "open" nonrecirculating perfusion model in which perfusates take a single pass through the placental lobule. With this modification, steady-state clearance of a drug can be measured.
Bupivacaine clearance was not diminished by increasing concentrations of its structural analog mepipacaine (fig. 6). A significant increase ($P < 0.01$) in bupivacaine clearance was observed as the fetal perfusate $\text{pH}$ was acidified. $\text{M} \rightarrow \text{F}$ clearance was shown to be 1.37, 1.64, and 1.85 times the baseline clearance when the fetal perfusate $\text{pH}$ was adjusted to 7.2, 7.0, and 6.8, respectively (fig. 7). Clearance values were similar before and after $\text{pH}$ adjustment of the fetal circulation when the $\text{pH}$ of both circuits were maintained at 7.4.

**Viability Parameters**

Lactate production was $0.157 \pm 0.04 \mu\text{mol/min/g}$ and glucose consumption measured $0.08 \pm 0.02 \mu\text{mol/min/g}$, which were similar to values associated with oxygenated systems as observed by others. In addition, no significant fluid shift was observed from the maternal circuit to the fetal circuit.

**Discussion**

The purpose of this study was to elucidate the factors that regulate the transfer of bupivacaine from mother to fetus. Investigators, using single-point determinations of maternal and umbilical cord blood samples at birth, have revealed a relatively low fetal:maternal distribution of bupivacaine with concentration ratios of $0.31^{1,2,20}$ as compared to lidocaine's $0.5^{2,21,22}$ after epidural administration. Possible explanations for this transfer differential include different transfer mechanism (active transport or passive diffusion), tissue accumulation, and unequal maternal and fetal protein binding. In addition, investigators, using the animal model, have demonstrated a relationship of bupivacaine and/or lidocaine clearance to the $\text{pH}$ of fetal circulation.^{23-25} By applying the dual perfused human placental model to this question, these hypotheses were investigated. This unique model system has the advantage of allowing the examination of each variable independently.

**Transfer Mechanism**

With low and equal protein binding on both sides of the placenta, transfer was shown to be rapid and unaffected by increasing concentrations of bupivacaine or the addition of its analog, mepipacaine. This absence of saturation kinetics and competitive inhibition, within the limited range studied, suggest that the trans-
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Table 1. Relationship of Total and Unbound Bupivacaine Concentrations (μg/ml) Observed in the Maternal and Fetal Circuits at the End of the Experiments

<table>
<thead>
<tr>
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<th>Total Drug</th>
<th>Unbound Drug</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Maternal</td>
<td>Fetal</td>
<td>M:F or F:M Ratio (Donor−Recipient)</td>
</tr>
<tr>
<td>KRB experiments*</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Maternal to fetal</td>
<td>1.34</td>
<td>1.11</td>
<td>0.81</td>
</tr>
<tr>
<td>Fetal to maternal</td>
<td>1.12</td>
<td>2.63</td>
<td>0.43</td>
</tr>
<tr>
<td>FFP experiments†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal to fetal</td>
<td>1.27</td>
<td>0.65</td>
<td>0.51</td>
</tr>
<tr>
<td>Fetal to maternal</td>
<td>0.30</td>
<td>0.30</td>
<td>1.02</td>
</tr>
</tbody>
</table>

KRB = Krebs-Ringer's buffer; FFP = fresh frozen plasma.
* Protein binding averaged 32.1% in both the maternal and fetal circuits.
† Protein binding averaged 79.5% and 54.2% in the maternal and fetal circuits, respectively.

fer of bupivacaine across the human placenta is by passive diffusion, whereas the drug’s speed of transport relates to its molecular weight and lipid solubility. The reduced F → M transfer rate as compared with the M → F rate is not entirely consistent with the previous hypothesis, however other factors may be involved in its transplacental passage. Using the same placental model, this asymmetric transfer has been demonstrated with two highly lipophilic intravenous anesthetics, thiopental and methohexital.13 This transfer differential for bupivacaine may not be present when normal maternal and fetal physiologic concentrations of serum proteins exist in vivo. This, however, does not necessarily rule out the existence of a placental transport mechanism leading to the asymmetry now observed under conditions of equal protein concentrations in both circuits. It is possible that this transport difference is a function of the low fetal perfusion versus the maternal circuit perfusion rate (1–3 ml/min vs. 12–15 ml/min) coupled with the high placental uptake of bupivacaine, in that it simply takes longer to saturate the placenta at the lower rate of perfusion on the fetal side.

Placental Accumulation

The ability for the placenta to accumulate bupivacaine was shown clearly as maternal clearance of bupivacaine in the open perfusion model was found to be much higher than maternal to fetal clearance and must be due to the placental tissue uptake of the drug. In addition, in the closed perfusion system, placental tissue concentration measured at the end of the experiment averaged five times the concentration observed in the perfusate at that time and was not related

Table 2. Bupivacaine and Antipyrine Clearances as Observed in the Open Placental Perfusion Model

<table>
<thead>
<tr>
<th></th>
<th>Cl(M→F)</th>
<th>Cl(F→M)</th>
<th>Cl(maternal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine clearance*</td>
<td>2.17 ± 0.3</td>
<td>3.27 ± 0.7</td>
<td>14.36 ± 1.1</td>
</tr>
<tr>
<td>Antipyrine clearance*</td>
<td>3.57 ± 0.8</td>
<td>4.29 ± 0.7</td>
<td>14.21 ± 2.1</td>
</tr>
<tr>
<td>Bupivacaine/antipyrine</td>
<td>0.58</td>
<td>0.73</td>
<td>1.01</td>
</tr>
<tr>
<td>clearance ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cl(M→F) = clearance (fetal to maternal); Cl(F→M) = clearance (maternal to fetal).
* Clearances (ml·h⁻¹·g⁻¹ placenta) expressed as the mean ± SE of five experiments.

Fig. 5. Correlation of bupivacaine transferred into the recipient circuit at increasing donor circuit concentrations. Data are given as mean ± SEM. A linear upward response in transfer rate was seen with increasing donor circuit concentrations, consistent with passive transfer of bupivacaine. Placental bupivacaine transfer in both the M → F (closed triangles) and F → M direction (open triangles) is shown.
Fig. 6. Absence of inhibitory effects of mepivacaine on placental transfer of bupivacaine. Steady-state bupivacaine transfer was established with a maternal bupivacaine concentration of 4 μg/ml, after which mepivacaine, a structurally analogous amide LA, was added in 45-min intervals at the concentrations of 4, 40, and 80 μg/ml. No significant decrease in bupivacaine clearance was seen. These data are consistent with passive diffusion. Data expressed as mean ± SEM of 16 clearance observations at each concentration during four open placental perfusions.

to the degree of protein binding or direction of transfer. This concentration effect might account for the increased maternal clearance as compared to the M → F clearance, as such a rate is necessary to achieve these placental tissue concentrations.

**Protein Binding**

Mather et al. demonstrated increased bupivacaine protein binding in maternal plasma as compared to fetal blood or human albumin and suggested that this binding differential affects bupivacaine placental transfer. To investigate this possibility using the dual perfused placental model, the protein binding potentials of both circuits were altered to match the normal physiologic serum protein levels by employing FFP as the maternal perfusate and KRB with 4 g/100 ml human albumin as the fetal perfusate. In addition, the initial concentration of bupivacaine was reduced to 1 μg/ml, a concentration within the clinical range normally achieved after epidural administration. Using these perfusates, bupivacaine protein binding was increased to values similar to those observed in vivo. As a result of these perfusate alterations, M → F bupivacaine transfer ratio decreased, but F → M transfer increased to a rate similar to that of antipyrine. These differences in transfer as compared to the perfusions with equal concentrations of albumin in both maternal and fetal circuits relate to free fraction of drug available for transfer across the placenta and can be negated if the gradient of unbound drug is examined (table 1). These studies clearly demonstrate that substances that exhibit higher protein binding potentials reflect these factors in the maternal-fetal gradient. This phenomenon of enhanced placental transfer driven by increased protein binding was also documented by Hamshaw-Thomas et al., who showed that placental bupivacaine transfer increased as the amount of plasma in the receiving perfusate was increased.5

**pH Effects**

Using the pregnant ewe and rabbit model, investigators have related increased umbilical vein bupivacaine concentrations to the pH of the media perfusing the umbilical vessels. The mechanism proposed resulting in the observed increased fetal bupivacaine concentrations is ion trapping as a result of the decreasing fetal pH. In addition, it has been proposed that decreased local anesthetic clearance by the fetus or changes in the tissue distribution might explain these increases in local anesthetic concentrations. Whatever the mechanism, this observation may be of critical importance to the safety of the preterm fetus as investigators have demonstrated increased sensitivity of the asphyxiated fetus to the deleterious effects of local anesthetics. In the current investigation, when experiments using pH values similar to those seen in the animal model were performed, an increase in M → F clearance was demonstrated. Unlike the animal model,
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in the open perfusion model, bupivacaine cannot accumulate in fetal circulation as the flow is not recirculated. Fetal drug clearance and fetal tissue distribution changes are not applicable to our model, therefore the increased bupivacaine clearance across the placenta we observed was related to changes in the maternal:fetal gradient of unionized bupivacaine.

In summary, this study suggests that bupivacaine crosses the human placenta by passive diffusion rather than active transport and is influenced by the degree of maternal and fetal protein binding differences and quite possibly by placental accumulation. It is highly probable that these transfer factors play an important role in producing the lower fetal:maternal plasma concentrations ratio for bupivacaine as compared to lidocaine seen clinically. This relationship of protein binding to placental transfer has important clinical implications, especially under pathologic circumstances, when either maternal or fetal serum protein concentrations might vary widely from normal. For example, in severe preeclampsia with reduced maternal protein binding, greater placental transfer of bupivacaine might occur. Also, it is quite clear that, during the period of fetal acidosis, bupivacaine transfer might be increased by a large factor. In addition, the placenta’s ability to sequester bupivacaine in large quantities may allow it to act as a depot to expose the fetus to concentrations of bupivacaine well after maternal concentrations have disappeared. Further studies are warranted to investigate the phenomenon of asymmetric transfer observed in the current bupivacaine study and for other lipophilic agents. Data from placental perfusion studies investigating drugs that exhibit lower protein binding and lipophilicity, such as lidocaine, are required to further elucidate these transfer processes.

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