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Uptake and Distribution of Bupivacaine in Fetal Lambs

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Direct continual measurement of placental drug transfer was introduced to evaluate more precisely the fetal uptake of a commonly used local anesthetic in obstetrics. Bupivacaine, 2.7 mg · kg^{-1} (base), was infused at a constant rate over 1 h into a maternal jugular vein of five chronically prepared pregnant ewes. Blood was sampled simultaneously from the umbilical vein (UV), fetal aorta (FA), and a maternal artery (MA). Fetal uptake rate was determined from the product of the bupivacaine UV–FA blood concentration difference and the umbilical flow rate ($\dot{Q}_u$). Total fetal accumulation was determined by integrating uptake rate over 5 h. Correlation of total fetal uptake and the infused mean maternal dose ($r = 0.993$, $P < 0.001$) indicated that during the infusion, mean fetal uptake was a constant fraction (0.16) of the maternal infused dose. Total fetal uptake was linear despite wide individual changes in $\dot{Q}_u$, suggesting that within limits fetal accumulation is not $\dot{Q}_u$-dependent. Mean ovine protein binding of bupivacaine by maternal and fetal whole blood was 85.49% ± 2.61 (SD) and by fetal blood, 40.43% ± 9.60 (SD). Back-transfer of bupivacaine to the mother proceeded against a higher total bupivacaine concentration because unbound unionized drug concentrations in maternal blood were less than in fetal blood. At maternal–fetal equilibrium when UV and FA total blood concentrations were equal, the calculated fetal/maternal concentration ratio (f/m) (0.36) determined from the maternal and fetal protein binding and *p*H closely approximated the observed (0.35). The f/m increased during both fetal uptake and back-transfer and cannot be considered a good index of placental transfer. Back-transfer suggests that following an unintentional intravascular injection, delivery should be delayed for back-transfer to be completed, provided maternal and fetal circulation remain adequate. (Key words: Anesthesia, obstetric. Anesthetic techniques: regional, epidural. Anesthetics, local: bupivacaine. Measurement techniques: high-pressure liquid chromotography. Placenta. Protein, binding: ovine.)

LOW FETAL BLOOD levels associated with maternal bupivacaine administration are well recognized. However, opinions vary regarding the extent of placental transfer and fetal uptake. Low fetal blood concentrations have been attributed to the high maternal plasma protein binding of bupivacaine[1] and also to a high fetal tissue uptake of bupivacaine due to its high lipophilicity.[2] Alternatively, we believe that the low fetal concentrations result from maternal and fetal differences in protein binding and *p*H because concentrations resulting from a transplacental equilibrium are dependent on the concentration of free, nonionized drug.[3]

Studies of placental drug transfer have used fetal blood concentrations and fetal–maternal concentration ratios (f/m) to evaluate the transfer. Because the rate and extent of drug crossing the placenta cannot be determined by a single time-point determination, the results of such studies can only be considered qualitative. Studies in small animals in which whole fetuses are extracted to yield the amount of drug absorbed may be considered semiquantitative. However, only a single determination can be obtained following maternal administration.

Rather than indirectly determining an index of placental transfer, we now are able directly to evaluate placental transfer in fetal lambs quantitatively and continually. The development of maternal and fetal blood concentrations and f/m as they relate to total fetal uptake (accumulation) may be simultaneously observed. Using chronically prepared pregnant ewes, we determined the uptake of bupivacaine in fetal lambs during and following a constant rate infusion into the mother, and obtained the time-related fetal and maternal blood concentrations with their ratios. The distribution to the vital fetal organs was determined at the end of this observation period.

Methods

Animal Preparation

Five pregnant ewes were used whose times of gestation were known to be 118–125 days and whose pregnancies were confirmed by x-ray to be single. Food, but not water, was withheld for 24 h. Anesthesia was induced with thiopental, 500 mg, through a jugular vein catheter; endotracheal anesthesia was maintained with inspired concentration of 60% nitrous oxide, 1% halothane; and respiration was mechanically controlled. Sterile surgical technique was used throughout. After hysterotomy, the lower half of the fetus was removed sufficiently to expose the umbilicus. An incision from the umbilical skin margin, approximately 8 mm long, was made over an umbilical vein (UV) and fascia was dissected away. An 18-gauge needle was used to puncture the vein and, as it was being removed, polyethylene tubing (OD 0.50 in) was imme-

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TABLE 1. Assay Reproducibility

Concentration (ng/ml)	Coefficient of Variation (%)*			
	Intraday Variation			Interday Variation
	Day 1	Day 2	Day 3	Days 1–3
Bupivacaine				
25	4.96	4.56	2.40	13.24
100	1.05	2.66	7.77	8.58
375	1.96	2.53	1.43	2.92
1,000	2.24	2.31	9.30	2.35
PPX				
25	9.19	9.30	7.82	12.95
100	1.83	0.87	1.55	6.73
375	1.43	0.42	1.03	2.25
1,000	3.58	6.61	2.07	4.72

* Each value represents the coefficient of variation for four individual samples for intraday variation and all 12 samples at each concentration for interday variation.

diately inserted to a depth of approximately 1 in into the common UV.[4,5] The tubing was secured to fascia and skin, thus eliminating the need for occlusive ligatures that would compromise umbilical circulation. Tubing of the same size was inserted into the fetal distal aorta (FA) *via* a femoral artery. Through a left flank incision the common umbilical artery was exposed by a retroperitoneal dissection. An electromagnetic flow transducer was then positioned around the artery.[6] All transducers were previously calibrated *in vitro* according to the *Gould Blood Flowmeter Manual.* When possible, the bladder was catheterized through the urachus. The fetus was replaced along with warmed amniotic fluid to which ampicillin, 1 g, had been added. The uterine incision was closed around each tube and the cable. Following abdominal closure, a maternal femoral artery (MA) was cannulated with polyethylene tubing, OD 0.50 in. All catheters and the transducer cable were exteriorized through a single flank incision and retained in a plastic bag secured over the incision. Ampicillin, 1 g, was injected intramuscularly at the termination of the surgical procedure and again at 24 h. The ewe was observed daily and the fetal condition was determined by monitoring blood *p*H and blood gases. All vascular catheters, including that in the jugular vein, were flushed daily with heparinized saline, 10 IU · ml^{-1}.

After 72 h the ewes were weighed (49.1 ± 1.2 kg) and brought from the animal quarters to the laboratory in a specially designed cart. After each mother and her fetus were found to be normal as demonstrated by blood gases, blood pressure, fetal heart rate, $\dot{Q}_u$, and maternal temperature, bupivacaine, 3 mg · kg^{-1} (2.7 mg · kg^{-1} base), representing a maximum human dose, was infused into a jugular vein at a constant rate over 1 h. Blood was sampled simultaneously from the MA, UV, and FA every 5 min for 45 min, every 15 min for 75 min and, thereafter, every 60 min to 5 h. At hourly intervals blood gases were determined from the MA, UV, and FA. Initial and 5-h mean *p*H values at 39.5° C were: MA, 7.51 ± 0.03 and 7.53 ± 0.03; FA, 7.36 ± 0.02 and 7.34 ± 0.02; and UV, 7.39 ± 0.01, and 7.39 ± 0.01, respectively. Fetal urine was collected from only the two fetuses that could be successfully catheterized through the urachus. Observation continued for a total of 5 h when the fetuses were killed by injection of saturated potassium chloride into the UV. They were then removed after the ewe was killed with a commercial concentrated pentobarbital solution. Each fetus was weighed (2.44 kg ± 0.20), and vital organs were dissected free, weighed, and frozen.

Sample Preparation and Analysis

Blood samples were drawn into heparinized syringes and immediately placed into ice. A 0.5-ml portion of the sample was placed into 1.0 ml 0.5 M borate buffer, *p*H 9.5, and this sample was frozen until time of analysis for bupivacaine in whole blood. Fetal urine was collected every hour and frozen until analysis, at which time a 0.5-ml sample diluted with high-pressure liquid chromatography (HPLC) grade water was added to 1.0 ml 0.5 M borate buffer, *p*H 9.5. Fetal tissue was homogenized in an appropriate volume of distilled water using a Polytron® homogenizer (Brinkmann Instruments, Westbury, NY) and a 1.0-ml portion of the homogenate was added to 1.0 ml 0.5 M borate buffer.

All specimens were analyzed for bupivacaine and pipecololxylidide (PPX) by HPLC. Following addition of the internal standard, an aqueous solution of etidocaine, 150 ng/10 μl, samples in borate buffer were extracted with a methylene chloride:n-heptane mixture (30:70 v/v), followed by extraction of the organic phase using 0.01 N hydrochloric acid. The HCl extract was injected by a Waters WISP® model 710A programmable automatic injector onto the HPLC system consisting of a Waters Model 6000 A pump that delivered a mobile phase of acetonitrile:0.05 M sodium phosphate buffer, *p*H 3.5 (33:67 v/v), to a Waters micro-Bondapak® C-18 reversed phase column at ambient temperature. The eluate was analyzed by a Schoeffel UV detector (Model SF 770) at a wavelength of 210 nm. The extraction method yielded a recovery of approximately 99% for bupivacaine and approximately 85% for PPX. Standard curves for parent drug were linear from 20 ng · ml^{-1} to 2,000 ng · ml^{-1} for parent drug and from 25 ng · ml^{-1} to 1,000 ng · ml^{-1} for PPX. Intraday and interday assay reproducibility (table 1) was determined using blood samples to which bupivacaine and PPX had been added to yield concentrations of 25, 100, 375, and 1,000 ng · ml^{-1}. The coefficient of variation (CV) was determined from the means and stan-

dard deviations of the peak area ratios for four individual samples of each concentration analyzed on each of three consecutive days. Interday variability for each concentration was determined as the CV for all 12 samples.

Protein Binding

Protein binding of lidocaine by maternal and fetal ovine blood was determined by equilibrium dialysis. The dialysis system consisted of acrylic dialysis cells divided into two 0.5-ml–capacity compartments by a Spectrapor® dialysis membrane 2 (Spectrum, Medical Industries, Inc., Los Angeles, CA) and rotated within a water bath maintained at 39° C. Maternal and fetal blood samples to which drug had been added to yield concentrations of 1,250 ng · ml^{-1} or 625 ng · ml^{-1}, respectively, were dialyzed for 4 h against 0.134 M sodium phosphate buffer at a *p*H of 7.5 (maternal) or 7.4 (fetal). Preliminary studies showed that equilibrium conditions were established within 4 h. Blood samples were drawn by venipuncture (maternal) or *via* the umbilical venous catheter (fetal) into heparinized syringes and refrigerated until use within 24 h of withdrawal. The protein content in all samples was determined by Paragon electrophoresis.

Fetal Uptake Calculations

The rate of fetal uptake was calculated as the product of the umbilical blood flow rate ($\dot{Q}_u$) and the difference between UV blood concentration (C_{uv}) and FA blood concentration (C_{fa}). Total fetal uptake at any time after initiating the maternal drug infusion was determined by integration of uptake rate from time zero to time t as shown in equation 1.

$$\text{total uptake} = \int_0^t (C_{uv} - C_{fa}) \times \dot{Q}_u \times d_t \qquad (1)$$

This equation represents the area under the uptake rate curve *versus* time and was calculated using the trapezoidal rule.

F/M Ratio Calculation

Equation 2 was employed as described previously[3] to calculate the predicted f/m ratio at transplacental equilibrium, based on the observed maternal (pH_m) and fetal (pH_f) arterial blood *p*H, maternal (FF_m) and fetal (FF_f) free fraction in blood (not protein bound), and the pK_a of bupivacaine at 39.5° C. Because the pK_a reported for bupivacaine was determined at a standard temperature of 25° C, the method described by Kamaya was used to calculate a pK_a of 7.88 for a temperature of 39.5° C.[7]

$$\frac{f}{m} = \frac{C_f}{C_m} = \frac{1 + 10^{pK - pH_f}}{1 + 10^{pK - pH_m}} \times \frac{FF_m}{FF_f} \qquad (2)$$

Equation 3 also was derived from the Henderson-Hasselbach equation to calculate the concentration of free, unionized drug (D) from the total concentration (C) in either fetal or maternal blood.

$$D = \frac{C}{10^{pK - pH} + 1} \times FF \qquad (3)$$

Fetal uptake curves during the infusions were evaluated by linear regression. Analysis of variance for repeated measures (ANOVA) was used to evaluate the $\dot{Q}_u$ and both UV and FA concentration curves. Magnitude of reversal of UV and FA concentrations indicating back-transfer of bupivacaine from fetus to mother was substantiated by tetrad differences.[8] $P < 0.05$ was considered significant. Unless otherwise indicated and for graphing purposes, values are expressed as means ± SEM.

Results

Mean concentration–time plots for bupivacaine in MA, UV, and FA blood samples are shown in figure 1. Although the infusion continued for 60 min, the MA concentration reached a maximum at 40 min, where it remained with little change until the infusion ended. All three concentrations, MA, UV, and FA, decreased precipitously after the infusion was terminated. UV and FA were significantly different from 60 to 105 min ($P < 0.0001$). The UV became less than the FA (tetrad differences significant at 75 to 105 min, $P < 0.05$), indicating passage of bupivacaine from the fetus back to the mother (equation 1). This reversal continued for the duration of observation, though to a lesser extent after 3 h. Because the MA concentration was higher than either the UV or FA concentration, the fetal to maternal passage of bupivacaine occurred against an apparent concentration gradient. At 5 h, fetal blood concentrations were nondetectable in two sheep.

The mean (±SD) percentages of bupivacaine bound to protein as determined from *in vitro* binding studies were 85.49 ± 2.61 for maternal (n = 20) and 40.43 ± 9.60 for fetal samples (n = 14). Mean protein concentrations in g · dl^{-1} (SD) for albumin and total protein in blood samples from three sheep were 2.92 (0.35) and 6.60 (0.92) for maternal samples, 2.10 (0.53) and 3.29 (0.76) for fetal samples.

Mean f/m (n = 4), both UV/MA and FA/MA (fig. 2), reflects variations seen in figure 1 in both the fetal blood levels (numerator) and the maternal blood levels (denominator). During maternal to fetal passage, ratios were low, reflecting the higher maternal and lower fetal concentrations. The ratios increased following cessation of the infusion because the MA concentration declined more rapidly than either UV or FA concentration.

Equal UV and FA concentrations suggest a maternal–fetal equilibrium, because equal amounts of drug are entering and leaving the fetus. The mean of the f/m ratios observed at the time of this equilibrium condition in each

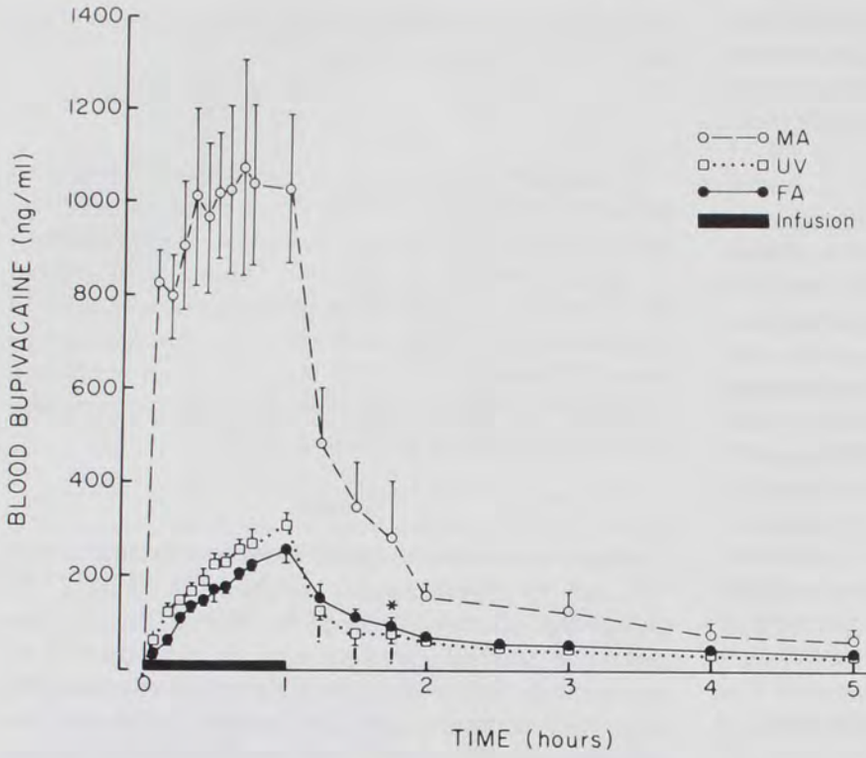

FIG. 1. Plots of the mean (±SE) bupivacaine blood concentration ($ng \cdot ml^{-1}$) *vs.* time (h) for the maternal artery (n = 4), umbilical vein (n = 5) and fetal artery (n = 5). Bupivacaine (2.7 mg/kg) was infused during the first hour. * denotes significant ($P < 0.0001$) changes from 60 min concentrations, and ! denotes significant differences ($P < 0.05$) between UV and UA concentrations.

sheep was 0.35 ± 0.02. A predicted f/m ratio for such equilibrium conditions was calculated (equation 2) using the *in vitro* binding data, the actual fetal and maternal blood *p*H values, and the pK_a adjusted for a temperature of 39.5° C. This mean predicted ratio of 0.36 ± 0.02 was in close agreement with the observed value.

The mean $\dot{Q}_u$ (fig. 3) increased from 152 ± 18.2 to 169.0 ± 30.0 $ml \cdot min^{-1}$ at 24 min and then decreased to a low of 132.5 ± 15.2 at 3 h. These changes were not significant.

The mean uptake rate (fig. 4) increased to 8.31 ± 2.29 $\mu g \cdot min^{-1} \cdot kg^{-1}$ at 10 min, then fluctuated between 6.06 ± 1.68 and 9.72 ± 1.89 $\mu g \cdot min^{-1} \cdot kg^{-1}$ until the infusion was terminated. Therefore, during the period in which bupivacaine blood concentrations were increasing, the uptake rate did not. The UV–FA concentration difference from 10 to 60 min varied from 48 to 58 $ng \cdot ml^{-1}$, except for low variations of 31 and 27 $ng \cdot ml^{-1}$ at 20 and 25 min, respectively. The negative rate, which persisted during the remainder of the observation period, represented fetal to maternal diffusion, which at 2 h was considerable. The lowest mean uptake rate was −3.76 ± 1.39 $\mu g \cdot min^{-1} \cdot kg^{-1}$ at 75 min.

Mean total fetal uptake (fig. 5) in all animals increased in a linear manner during the infusion. A mean uptake of 415 ± −28 $\mu g \cdot kg^{-1}$ was attained at 60 min when the infusion was ended. Because bupivacaine was infused at a constant rate, the fraction of the cumulative maternal dose delivered (2.7 $mg \cdot kg^{-1}$) was directly proportional to the time from the beginning of the infusion. The cumulative maternal dose (X) and cumulative mean fetal uptake (Y) during the infusion period were correlated (r

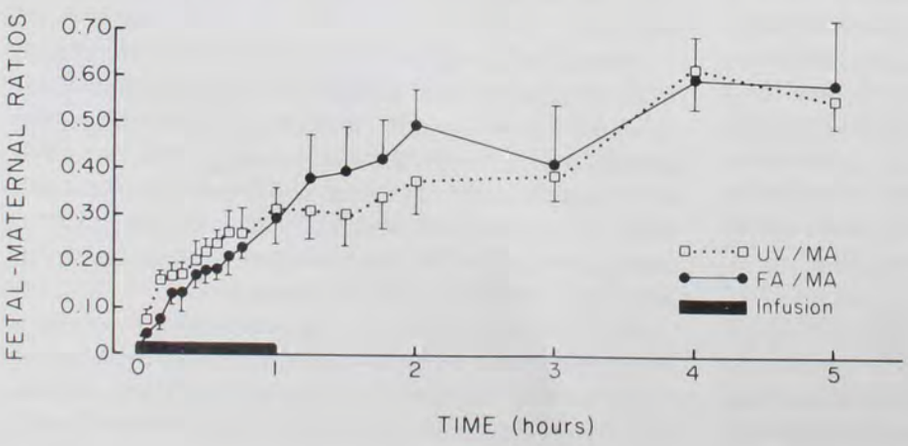

FIG. 2. Mean (±SE) fetal/maternal total blood bupivacaine concentration ratios (n = 4), expressed as UV/MA (umbilical vein/maternal artery) and FA/MA (fetal artery/maternal artery) during a 1-h infusion and for the following 4 h.

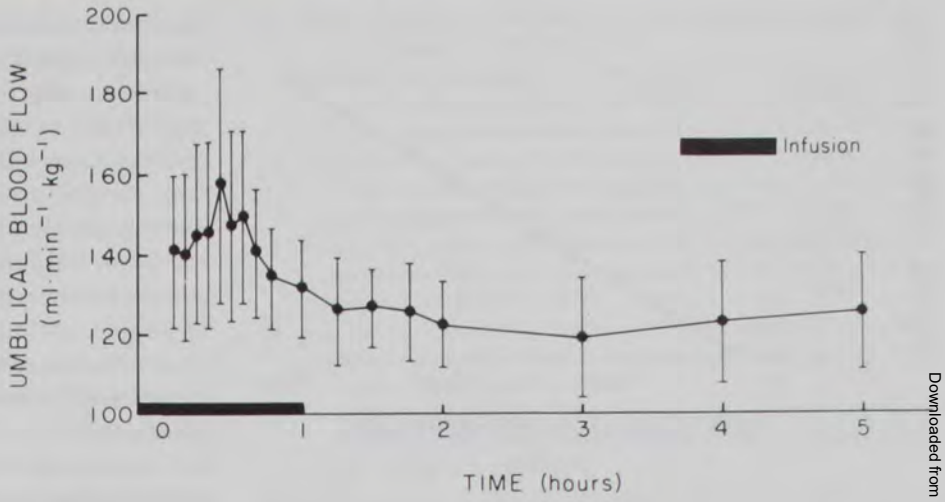

FIG. 3. Mean (±SE) umbilical blood flow ($ml \cdot min^{-1} \cdot kg^{-1}$) (n = 5) during the bupivacaine infusion for 1 h and the following 4 h.

= 0.992, $P < 0.001$). The equation describing this linear relationship (fig. 5) is as follows.

$$Y = 0.16X - 25.0$$

The slope of the regression line is a constant, representing the fetal fraction of the maternal dose at any time during the infusion. Individual slopes varied from 0.12 to 0.20 and the lowest correlation coefficient was 0.983.

As indicated in figures 1 and 4 after the infusion, fetal uptake decreased, representing the loss of bupivacaine back to the mother. Considerable variations occurred in the fetal to maternal return of bupivacaine, which at 3 h ranged from 44% to 93% of the total uptake.

Mean tissue concentrations (fig. 6) were similar in brain, heart, and liver, with higher concentrations in lung and kidney. PPX was not detected in the tissues from any of the fetuses.

Urine was collected in two fetuses. The amount of bupivacaine excreted, in μg, was: hour 1, 21.5 and 54.2; hour 2, 19.1 and 78.4; hour 3, 1.6 and 23.6; hour 4, 1.4 and 4.0; hour 5, 0.7 and 1.6; and totals, 44.3 and 161.8, respectively. Again, no PPX was detected.

Discussion

The dose of bupivacaine employed for this study produced maternal and fetal blood concentrations similar to those reported after epidural anesthesia in pregnant women.[9,10] Also in agreement with previous studies, fetal blood concentrations were less than maternal concentrations throughout the experimental period, resulting in f/m ratios less than unity (fig. 2). The absence of PPX in tissue and urine samples suggests that, in these sheep, neither mother nor fetus metabolizes bupivacaine to PPX. Thus, this animal model may differ from the human, in which maternal and fetal metabolism of bupivacaine has been reported.[11] Analysis of fetal urine from two fetuses indicated that renal excretion is an important pathway for fetal bupivacaine elimination.

The reversal of bupivacaine diffusion back to the mother, where the total concentration is higher, is related to the difference in protein binding of bupivacaine in mother and fetus. Tucker *et al.*[12] recognized the importance of considering conditions on both sides of the placenta when assessing the f/m ratio. The results of the

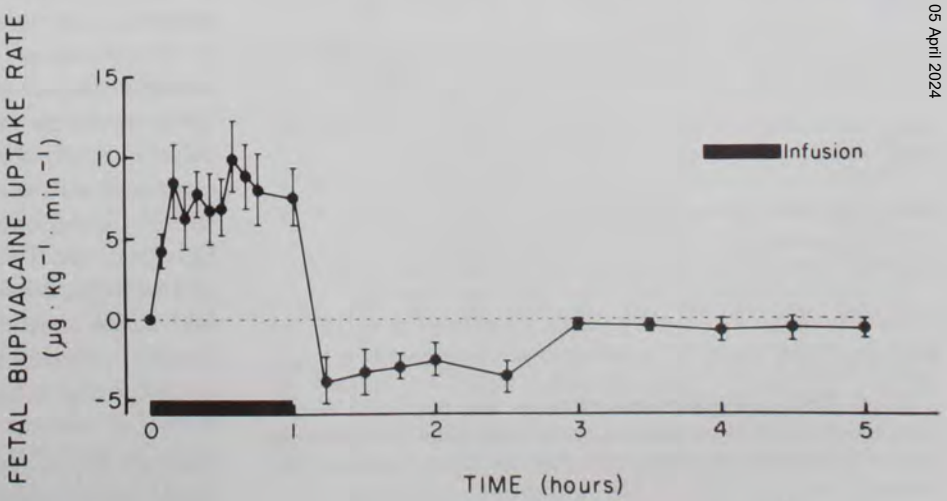

FIG. 4. Mean (±SE) fetal bupivacaine uptake rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$) (n = 5) during the bupivacaine infusion and the following 4 h.

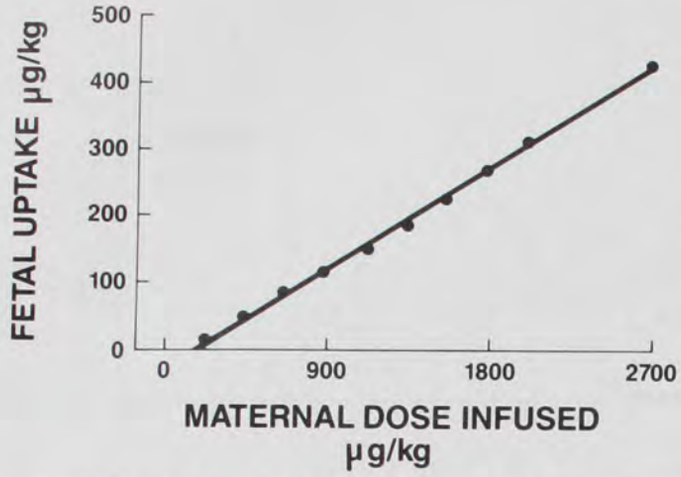

FIG. 5. Plot of mean (n = 5) fetal bupivacaine uptake *vs.* cumulative maternal dose during a 1-h constant-rate infusion. The line represents the regression line having the equation $Y = 0.16X - 25$ ($r = 0.997$, $P < 0.0001$). The slope represents the fetal fraction of the maternal dose at any time during the infusion.

present study lead to the conclusion that the principal factor responsible for the low f/m is the difference in fetal and maternal protein binding, rather than maternal binding alone.[13] This difference establishes a fetal to maternal concentration gradient of free, unionized drug for which the ratio is greater than unity, and results in a net passage of drug back to the mother after the infusion has ended. Such a concentration gradient was indicated when the concentrations of transferrable species of drug were calculated using equation 3. Mean concentrations at 75 min in ng · ml^{-1} were MA, 14.5; UV, 16.3; and FA, 20.1. These free-drug concentrations indicated an important contribution of the maternal–fetal differences in protein binding and, to a lesser extent, *p*H. Furthermore, the

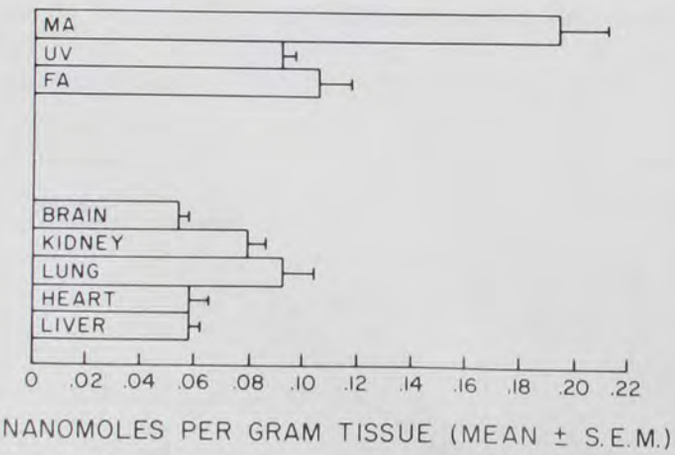

FIG. 6. Mean bupivacaine concentrations (nM · gm^{-1}) in fetal vital organs (n = 5) and for comparison, mean total blood concentrations (nM · ml^{-1}) in the umbilical vein (n = 3), fetal artery (n = 3), and maternal artery (n = 4).

agreement of actual f/m at equilibrium to those predicted using equation 2 demonstrates the role of protein binding in determining fetal blood concentrations and does not support the premise that a low f/m results from a high tissue uptake related to lipid solubility and subsequent fetal metabolism.[2,11] Tucker *et al.*[12] predicted that the observed fetal–maternal gradients may result largely from the lower binding of the drugs in the fetal plasma compared with the maternal plasma rather than from an effect of plasma binding on the rate of placental transfer. Additionally, we are in agreement with the conclusion of Hamshaw-Thomas *et al.*[14] that tissue uptake cannot explain the low UV concentrations. Finally, that the f/m is not a good index of the placental transfer is shown by the increasing ratio following the infusion when fetal accumulation is actually decreasing by fetal to maternal passage. This increase occurs because the denominator, MA concentration, decreases more rapidly. It is apparent that the UV follows the MA more closely while the FA lags, hence the back-transfer.

The linear increase in fetal uptake during the course of the infusion suggests a direct relationship of fetal uptake to the cumulative maternal infused dose. Indeed, plots of fetal uptake *versus* the cumulative maternal dose indicate a high correlation (fig. 6). In this relationship, the slope of the regression line can be interpreted as the fraction of the maternal dose representing fetal uptake at any time during the infusion. This value, normalized for both maternal and fetal weight, was 0.16 (range 0.12–0.20); therefore, at 30 min, a 3,000 g fetus would accumulate approximately 16% of 1,350 $\mu g \cdot kg^{-1}$ to equal 216 $\mu g \cdot kg^{-1}$, or a total of 0.648 mg. A similar linear relationship was also noted in a previous report regarding fetal uptake of etidocaine.[15] Etidocaine uptake displayed more variation in the individual uptake slopes, which was significantly and inversely related to drug biotransformation. The comparison to bupivacaine, not degraded in this study, suggests that the smaller variation in slope of the uptake patterns noted for bupivacaine could be explained by the lack of detectable degradation.

$\dot{Q}_u$ variations (fig. 3) may have been related to the method of administration. Absorption from the epidural space would be more gradual than by the constant rate infusion where the total dose was injected in 1 h. When compared with epidural absorption, the total dose infused within 1 h was excessive and may have accounted for the $\dot{Q}_u$ variations. The changes were not significant.

The high correlation of the mean fetal bupivacaine uptake to the maternal dose, despite considerable interindividual variation in $\dot{Q}_u$, suggests a flow-independent fetal uptake. Fetal oxygen uptake bears a similar relationship in that it remains constant, despite reductions in $\dot{Q}_u$ as much as 25%.[16] The $\dot{Q}_u$ is therefore inversely related to the UV-FA oxygen concentration difference.[17] Moll re-

ferred to this phenomenon as a "trick of nature," where chemical binding in blood (oxygen with hemoglobin and drugs with plasma protein) has the same effect as an increase in blood flow ($\dot{Q}_u$) equal to the total concentration change divided by the concentration change of the free substance.[18] The concentration changes along the placental barrier are buffered, which then tends to minimize changes in the uptake rate. Hence, fetal uptake independent of $\dot{Q}_u$ within limits is reasonable depending on the degree of binding.

Flow-dependent placental transfer of bupivacaine was observed by Hamshaw-Thomas, who artificially perfused rabbit placentas with local anesthetics.[14] The perfusate was a buffered low-molecular-weight dextran solution. Had there been protein binding in the perfusate, he may have observed a flow-independent uptake within the upper ranges of $\dot{Q}_u$.

Tissue concentrations in the fetal vital organs demonstrate the known affinity of the lung for local anesthetics.[19] Although approximately 50% of the umbilical venous blood perfuses the liver,[20] higher hepatic concentrations noted soon after a drug administration[21] would no longer be apparent after 4 h because there was little difference in UV and FA concentrations. Although the mean fetal blood concentrations exceeded those of the vital organs (fig. 6), complete comparisons were prevented by only trace blood concentrations detectable in two fetuses at 5 h.

Using bupivacaine, this study has demonstrated a more complete evaluation of placental transfer than is available from previous studies. Most important, continual quantitation allowed evaluation during changes in blood concentrations and $\dot{Q}_u$. The constant-rate infusion and its termination produced an abrupt change in maternal and fetal blood concentrations that would not have occurred during epidural anesthesia. This abrupt concentration decrease resulted in back-transfer to the mother and permitted the observation of increasing f/m as fetal accumulation decreased and a critical evaluation of the free-drug concentrations that resulted in the back-transfer. An obvious clinical implication would be the benefit of delaying the delivery following the unintentional intravascular injection of bupivacaine, providing maternal and fetal circulation remain adequate. Under the conditions of this study, fetal uptake appeared low as demonstrated by the linear relation to the infused dose. This small fraction should be reassuring to those using a much smaller dose of bupivacaine for intrapartum anesthesia, knowing that the neonate's responsibility for bupivacaine elimination is small.

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