Uptake and Distribution of Lidocaine in Fetal Lambs

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The fetal uptake of lidocaine was measured continually and quantitatively during and after a constant rate intravenous (iv) maternal infusion into five chronically prepared pregnant ewes. Lidocaine, 6 mg/kg (base), was infused at a constant rate for 1 h and measurements continued to 5 h. Rate of fetal uptake was determined from the product of the umbilical venous (UV) and fetal aortic (FA) concentration difference and umbilical blood flow ($\dot{Q}u$). Total fetal uptake was determined by integrating fetal uptake rate with respect to time. Maternal and fetal protein binding was determined, and its effect on fetal blood concentrations was evaluated. Mean total fetal uptake as it related to time and infused dose increased linearly ($r = 0.998$, $P < 0.001$) with a constant, weight-normalized fetal–maternal dose fraction of 0.45 during the infusion. Despite rapidly declining blood concentrations after the infusion, uptake increased an additional 17%. The sevenfold variation in uptake appeared to be inversely related to the biodegradation rate of lidocaine. Fetal–maternal concentration ratios (F/M) increased during declining blood concentrations. Protein binding determinations for maternal and fetal blood were $43.6 \pm 2.48\%$ and $26.9 \pm 1.59\%$, respectively. These values were used to calculate the F/M in conjunction with the maternal and fetal pH. At maternal–fetal equilibrium the calculated F/M, 1.0 ± 0.05, closely approximated the observed, 1.0 ± 0.03. Variations in lidocaine concentrations among the vital organs 4 h after the infusion were small, but high concentrations of metabolites were found in the lungs and kidneys. The results challenge the validity of placental transfer estimates commonly based on the F/M and umbilical cord blood concentrations. (Key words: Anesthesia, obstetric. Anesthetic techniques, regional: epidural. Anesthetics, local: lidocaine. Measurement techniques: high-pressure liquid chromatography. Placenta. Protein: binding; ovine.)

ALTHOUGH lidocaine has been extensively used in obstetrics and its presence in umbilical cord blood has been readily detected, the rate and amount of fetal uptake after maternal administration have proved difficult to deter-

mine. Speculation regarding fetal uptake and placental transfer has been related to blood concentrations, with conflicting opinions regarding the role of lipid solubility,[1] degree of ionization, and amount of protein binding. Because fetal uptake could not be quantitated, it could not be clearly understood. Intermittent blood sampling from the umbilical vein (UV) and fetal descending aorta or iliac artery (FA) blood and continuous measurement of the umbilical blood flow ($\dot{Q}u$) permit a continual estimation of maternal–fetal exchange, which we recently reported for bupivacaine.[2] Furthermore, this method provides a better understanding of currently available data in humans as they relate to uptake and blood concentration.

In this study we determined the fetal uptake of lidocaine following a constant rate infusion into the mother. From the determination of maternal and fetal protein binding, we evaluated the role that free lidocaine and its pK$_a$ play in determining the fetal–maternal blood concentration ratio (F/M). These results were then compared with the protein binding, pK$_a$, lipid solubility, and total fetal uptake of bupivacaine reported previously.[2]

Methods

ANIMAL PREPARATION

We studied five pregnant ewes (58 ± 4.5 kg), the gestations of which were known to be 118–125 days (0.81–0.86 gestation) and confirmed by radiograph to be single. The surgical preparation for quantitative evaluation in fetal uptake was reported previously.[2] Briefly, using sterile technique and general anesthesia, an electromagnetic flow transducer was placed on the common umbilical artery[3] to determine umbilical blood flow ($\dot{Q}u$), and sampling catheters were positioned in the common UV,[4] FA *via* the femoral artery, fetal bladder, and a maternal femoral artery (MA). All flow transducers were previously calibrated *in vitro* according to the Gould Blood Flowmeter Manual.

EXPERIMENTAL PROTOCOL

On the third postoperative day the ewe was brought to the laboratory in a cart designed to allow limited but unrestrained movement. After an observation period

during which fetal and maternal blood pressure, heart rate, blood gases, and maternal temperature were found to be normal, 7 mg/kg (6 mg base) lidocaine hydrochloride was infused into a jugular vein by syringe pump at a constant rate over 60 min. The total dose was comparable to a maximum dose in humans. From the MA, UV, and FA, simultaneous blood samples, 0.5 ml, were withdrawn and mixed with borate buffer (pH 9.5). The alkalinity was enough to render the lidocaine lipid-soluble for the extraction without precipitating the protein. Sampling times were at 5-min intervals for 45 min, 15-min intervals for 75 min, and then 30-min intervals until the end of the 5-h observation period. At hourly intervals pH and blood gases from the MA, UV, and FA were determined, and fetal urine was collected. The $\dot{Q}u$, maternal and fetal blood pressure, and fetal heart rate were recorded continuously on a Grass polygraph.

At the end of the 5-h observation period, the fetus was killed by an injection of saturated potassium chloride through the UV, the ewe was killed with a commercial concentrated pentobarbital solution, and the fetus was delivered. The fetal weight was 3.49 ± 0.43 kg and ranged from 2.50 to 4.96 kg. Fetal brain, heart, liver, kidneys, and lungs were removed, the wet weight of each was obtained, and they were frozen for later analysis.

Sample Preparation and Analysis

After collection all blood samples, fetal urine, and fetal tissues were frozen for later analysis by high-pressure liquid chromatography (HPLC) as previously described for bupivacaine[2] with modifications for lidocaine. Etidocaine, 80 ng, was added to each specimen as an internal standard. The mobile phase consisted of acetonitrile (HPLC grade) in 0.05 M sodium phosphate di-basic buffer (20/80 v/v), pH 3.50. The blood samples were analyzed for lidocaine. Tissues and urine were analyzed when we were able to simultaneously determine lidocaine and its primary and secondary N-deethylated metabolites, monoethylglycinexylidide (MEGX), and glycinexylidide (GX), respectively. The coefficients of variation are shown in table 1. The standard curves were linear within the ranges of 20–2,000 ng/ml for lidocaine and 20–500 ng/ml for GX and MEGX. The extraction recovered approximately 97%, 99%, and 80% of lidocaine, MEGX, and GX, respectively.

Protein Binding

Blood samples were refrigerated immediately and dialyzed within 24 h. Protein binding of lidocaine by maternal and fetal blood was determined by equilibrium dialysis as previously described.[2] Briefly, lidocaine was added to maternal and fetal blood to yield concentrations of 1,875 and 1,250 ng/ml, respectively. Dialysis proceeded at ovine body temperature (39° C) and pH (maternal 7.5, and fetal 7.4) against 0.134 M sodium phosphate buffer.

TABLE 1. Coefficient of Variation (%)

Concentration (ng/ml)	Intraday Variation			Interday Variation Days 1–3
	Day 1	Day 2	Day 3	
Lidocaine				
62.5	7.79	5.69	9.05	7.19
125	5.13	4.16	9.73	6.86
250	4.27	2.01	3.42	3.45
1,000	0.67	0.09	0.10	0.37
MEGX				
62.5	5.18	3.02	4.45	4.40
125	1.83	2.87	3.70	2.94
250	2.88	2.12	1.03	2.61
500	0.58	0.40	0.09	0.50
GX				
62.5	17.90	11.80	14.63	13.69
125	8.57	6.15	5.70	6.61
250	5.49	2.54	3.58	4.28
625	0.70	0.37	0.52	0.54

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

CALCULATIONS

Fetal uptake rate was determined from the product of the $\dot{Q}u$ and the difference between UV blood concentration (C_{uv}) and FA blood concentration (C_{fa}). Total fetal uptake or accumulation at any time from the start of maternal drug infusion was determined by integrating uptake rate from time zero to time t as shown in equation 1.[2]

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

The calculated F/M was based on the maternal (pH$_m$) and fetal (pH$_f$) arterial blood pH at ovine body temperature, 39° C, and unbound (free) maternal (FF$_m$) and fetal (FF$_f$) drug fractions (1-bound fraction) as shown in equation 2.[5] Because the reported pK_a values for local anesthetics were determined at a standard temperature of 25° C, the pK_a for lidocaine at 39° C was calculated to be 7.65.[6] Blood samples from the MA and FA were used in the calculation.

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

The fetal accumulated dose was compared with the maternal infused dose by linear regression. Changes in $\dot{Q}u$ were evaluated by the runs test.[7] Unless otherwise indicated, all data are reported as means and, for graphing purposes, ±SEM.

Results

The fetal condition remained satisfactory throughout the observation period. Initial and 5-h mean pH values (39° C) were as follows: MA, 7.44 ± 0.04 and 7.47 ± 0.04; FA, 7.35 ± 0.02 and 7.31 ± 0.04; and UV, 7.36 ± 0.03

FIG. 1. Plots (n = 5) of the mean (±SE) lidocaine concentrations (ng/ml) versus time (h) for the maternal artery, umbilical vein, and fetal artery. Lidocaine was infused during the first hour.
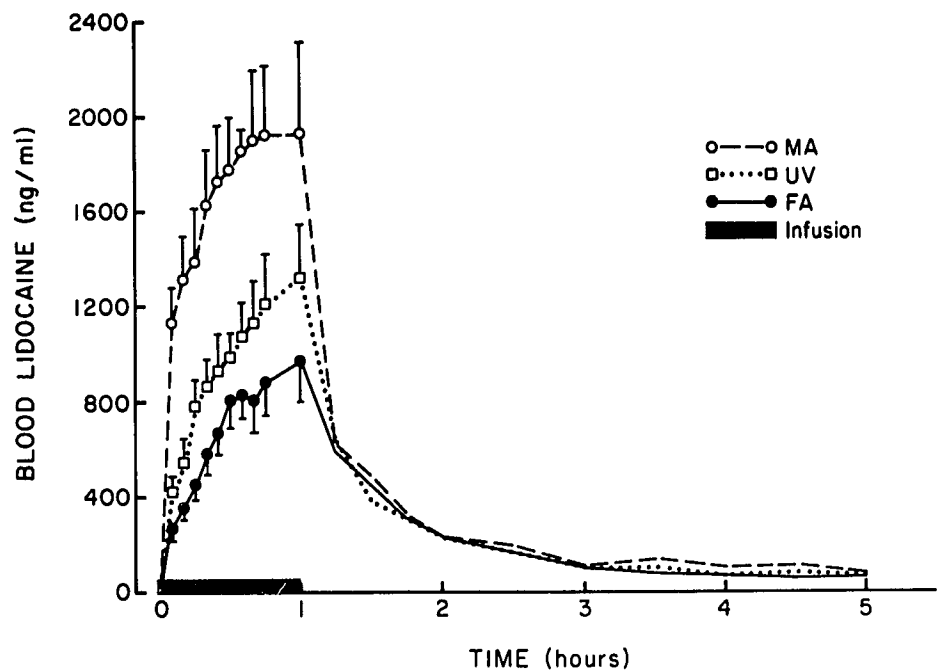
and 7.39 ± 0.03. P_{O_2}, P_{CO_2}, and base excess remained within normal limits.

Plots of mean lidocaine concentrations (n = 5) in the MA, UV, and FA versus time are shown in figure 1. The difference between the UV and FA concentrations is readily apparent and represents uptake by the fetus. Although the lidocaine concentration from the three sampling sites dropped precipitously after the infusion was terminated, a positive UV–FA concentration difference continued for another 20 min as indicated by the intersection of the UV and FA concentration lines. Thereafter concentrations approached equality.

The mean (±SD) percentages of lidocaine bound to protein were $43.56 \pm 2.48\%$ (n = 8) for maternal and $26.91 \pm 1.59\%$ (n = 29) for fetal whole blood. Concentrations of lidocaine were within the range of those observed in this study.

Mean F/M (n = 5), both UV/MA and FA/MA (fig. 2), reflect the changes observed in figure 1. The lower ratios during maternal-to-fetal transfer result from the higher maternal concentrations.

The mean $\dot{Q}u$ [n = 5 (fig. 3)] decreased ($P < 0.02$) from 164 ± 42 $ml \cdot kg^{-1} \cdot min^{-1}$ to 123 ± 25 $ml \cdot kg^{-1} \cdot min^{-1}$ at 3 h.

Mean fetal uptake rate [n = 5 (fig. 4)] rapidly increased to a maximum of 53 ± 21 $\mu g \cdot kg^{-1} \cdot min^{-1}$ where it remained with little change for the duration of the infusion. Although fetal uptake rate rapidly declined after termination of the infusion, mean uptake rate continued for another 20 min as indicated by the time intercept.

Mean total fetal uptake (accumulation) increased linearly during the infusion to 2.56 ± 0.92 mg/kg (fig. 5). Because the maternal dose (6 mg/kg) was infused at a constant rate, at any time during the infusion it was di-

FIG. 2. Mean (±SE) fetal/maternal blood lidocaine concentration ratios (n = 5) expressed as UV/MA (umbilical vein/maternal artery) and FA/MA (fetal artery/maternal artery) during the 1-h infusion and for the following 4 h.
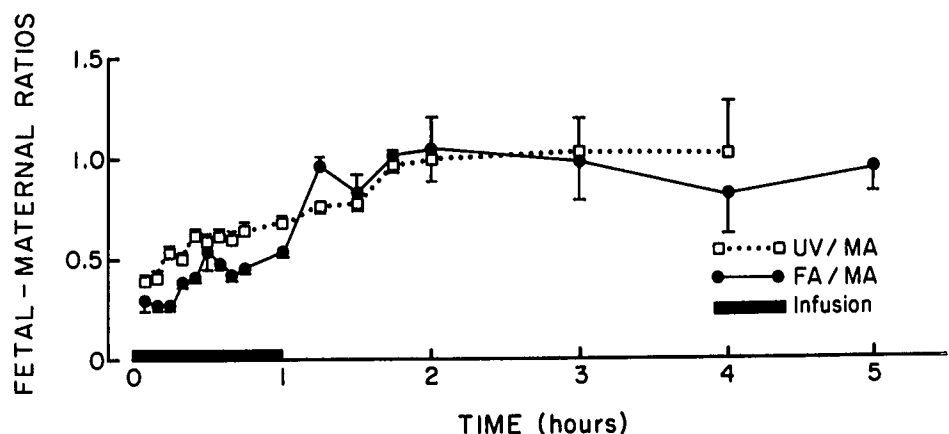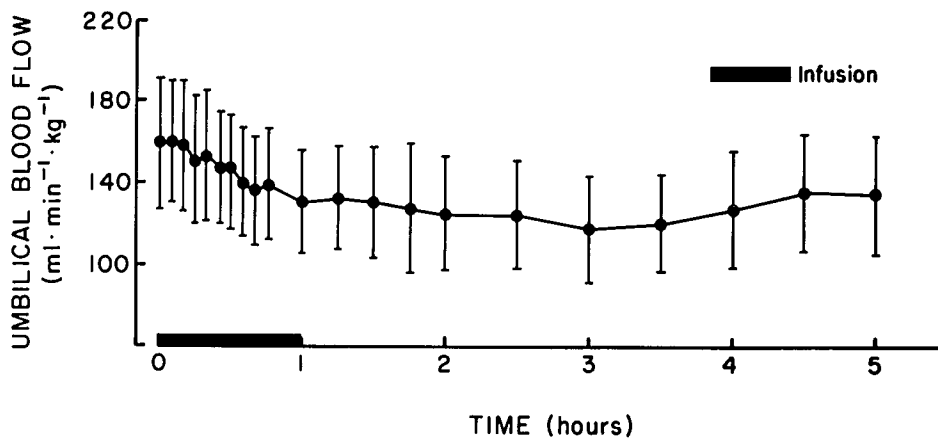
FIG. 3. Mean (±SE) umbilical blood flow (ml·min⁻¹·kg⁻¹) (n = 5) during the 1-h lidocaine infusion and the following 4 h.

rectly proportional to the elapsed fraction of the first hour. The cumulative maternal dose (X) and the cumulative fetal uptake (Y) were correlated during the infusion period $(r = 0.998, P < 0.001)$. The equation $Y = 0.45X - 213$ describes this relationship.

The slope indicates that mean uptake was a constant fraction of the maternal-infused dose. Individual uptake fractions varied from 0.15 to 1.09, and all individual correlation coefficients exceeded 0.996. Although the UV and FA concentrations declined after the infusion terminated, the difference remained positive, accounting for an increase in uptake over the next 20 min from 2.56 to 3.00 ± 0.10 mg/kg, equal to a fetal–maternal fraction of 0.5. Except in the fetus with the highest uptake fraction, which returned 18% to the mother by 3 h, the general pattern was similar. Little maternal–fetal lidocaine exchange occurred once the maximum uptake was attained.

Urine was collected from three fetuses. The hourly excretion of lidocaine and its metabolites is shown in figure 6.

Figure 7 shows the mean tissue concentrations of lidocaine and metabolites in vital organs (n = 5) and, for comparison, the 5-h mean concentration of lidocaine in

FA blood (n = 4). Concentrations of MEGX and GX were highest in kidney and lung. The two concentrations were similar in all tissues.

Discussion

The dose of lidocaine used in this study produced mean maternal and fetal blood concentrations similar to those reported after epidural anesthesia in pregnant women.[8,9] There were, however, considerable individual variations in MA, UV, and FA concentration at the end of the infusion, when the variation in MA concentration was threefold. At the same time there was a sevenfold individual difference in fetal uptake.

Variations in total fetal lidocaine uptake were much higher than that of bupivacaine,[2] and we speculate that this was caused by variations in degradation. For example, we observed that the preparation with the highest uptake produced the lowest metabolite concentration (MEGX) in the fetal lung. The converse was true for the fetus with the greatest lung MEGX concentration. This fetus had the lowest fetal lidocaine uptake. The least urinary metabolite excretion of the three fetuses from which urine
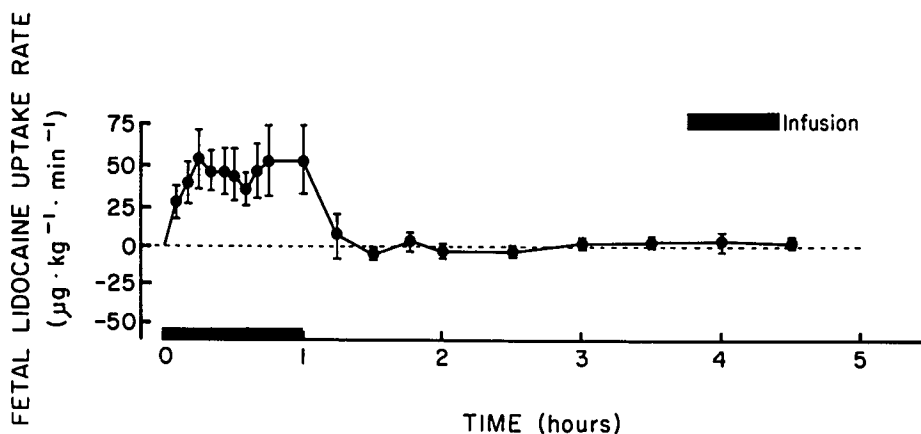

FIG. 4. Mean (±SE) fetal lidocaine uptake rate (μg·kg⁻¹·min⁻¹) (n = 5) during the 1-h lidocaine infusion and the following 4 h.

LIDOCAINE

FIG. 5. Plot of mean (n = 5) fetal lidocaine uptake *versus* cumulative maternal dose during a 1-h constant rate infusion. The equation for the regression line is $Y = 0.45X - 213$, $P < 0.001$. The time equivalent of the abscissa in minutes = 0.01 μg so that the calculated X-intercept in minutes is 4.73 min. Therefore, the equation indicates that the fetal accumulation is 45% of the maternal dose offset by a 4.73-min time lag.
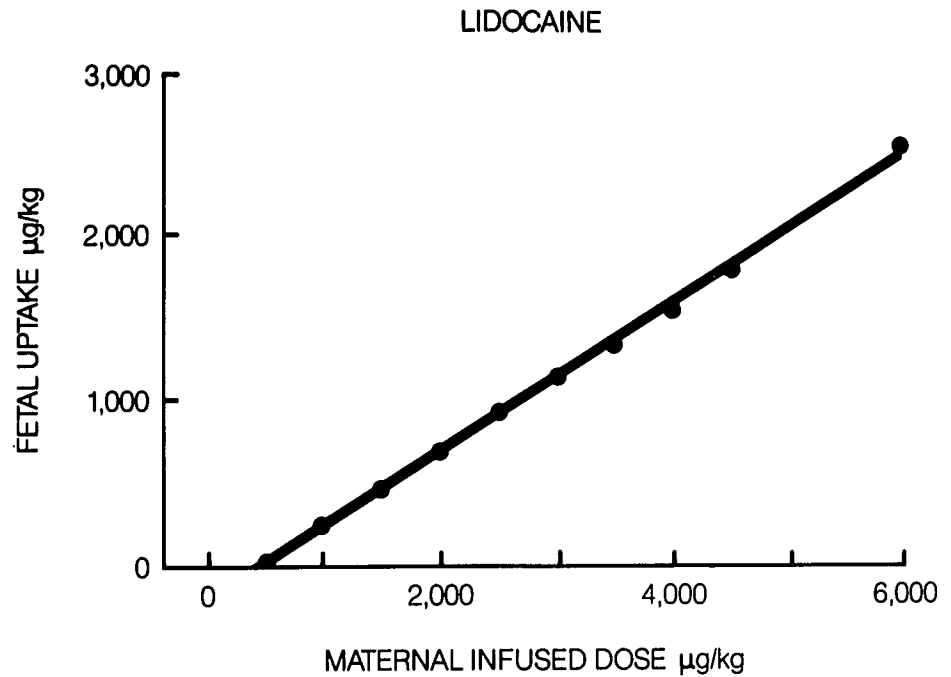
was collected was also from the fetus with the highest uptake.

Variation of uptake appears to affect back transfer of lidocaine from fetus to mother. The only fetus that exhibited back transfer of lidocaine from fetus to mother was the one with the highest uptake. By 3 h 18% of the fetal uptake had returned. The occurrence of back transfer with minimal metabolite concentration appears similar to the findings in our study of bupivacaine: the drug was not degraded and back transfer occurred in all preparations.[2] The lack of back transfer of lidocaine suggests that fetal liver must also participate in the lidocaine degra-

dation for the decline of the fetal blood concentration to keep pace with that of the mother. Otherwise the decline of the fetal concentration would lag behind the maternal concentration and create a higher fetal than maternal concentration gradient that would favor back transfer.

Unfortunately, when the blood was analyzed for lidocaine, we were unable to determine GX and MEGX levels from the same sample simultaneously with lidocaine and had not previously considered it necessary to do so.

The decrease in Qu at 3 h (fig. 3) was associated with a simultaneous decrease in fetal blood pressure. Because no other variations, such as changes in pH or blood gases,

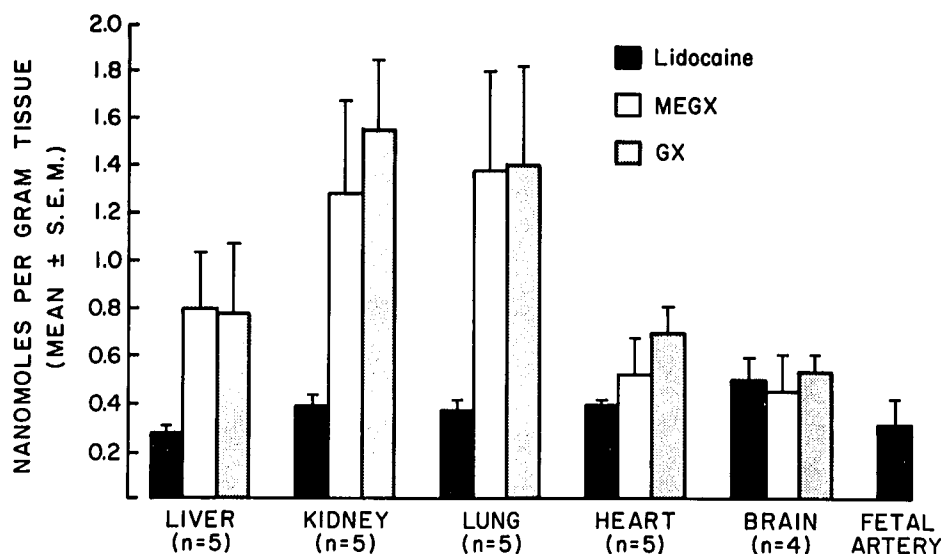FIG. 6. Hourly fetal mean excretion (n = 3) of lidocaine, MEGX, and GX.
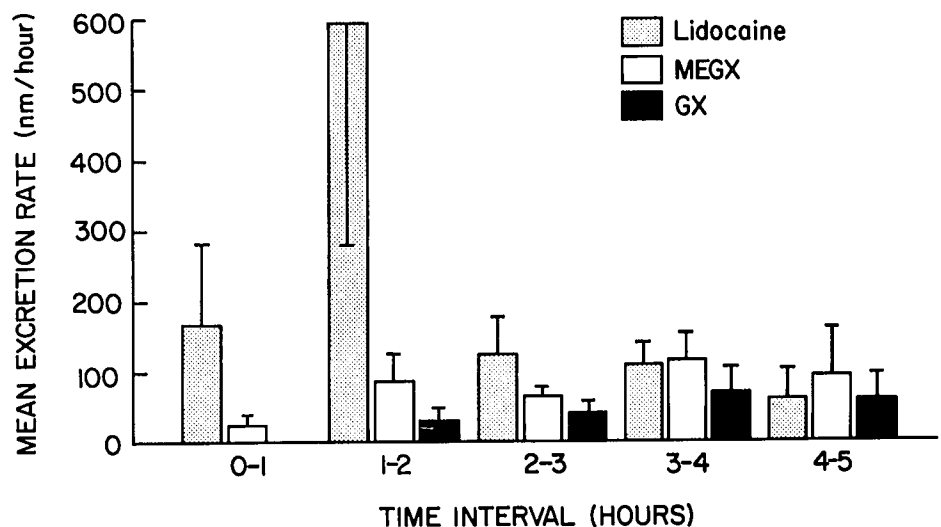
FIG. 7. Mean concentrations (±SE) of lidocaine, MEGX, and GX and, for comparison, FA blood lidocaine concentration in the vital organs.

were evident, we concluded that the changes in $\dot{Q}u$ and blood pressure were due to lidocaine and possibly its metabolites. Considering that the total dose was infused in 1 h and that over the same time absorption of a similar dose from the epidural space would have equaled 50% of the total dose,[10] the decreased blood pressure and $\dot{Q}u$ may have resulted from a relative overdose of lidocaine.

Despite varying $\dot{Q}u$ and blood concentrations, the relation of total fetal uptake to the maternally infused dose was linear during the course of the infusion (fig. 5). The slope of the mean regression line ($Y = 0.45X - 213$) interpreted as a constant indicates the weight-normalized fetal accumulation at any time during the infusion. At 30 min, when the cumulative maternal dose was 3,000 $\mu g/$ kg (a dose that will occur clinically), the fetal accumulation was 1,137 $\mu g/kg$, which in a 3-kg fetus would equal 3.4 mg. Because the maternal infusion of lidocaine proceeded at a constant rate, the abscissa has a time equivalent (fig. 5). The mean X-intercept for time, calculated from the formula in figure 5, was 4.73 min. This delay was considered to be the time lag for fetal accumulation to begin. The required maternal and fetal circulation times from the injection site to the fetal vessels and the time for placental transfer are offered to explain the time lag. Individual lag times varied from 1.21 to 6.12 min.

Because fetal lidocaine uptake is a product of $\dot{Q}u$ and concentration difference of UV and FA, the increasing UV–FA difference noted in figure 1 implies that there should have been an increase in fetal uptake rate. However, a rate increase did not occur after 5 min (fig. 4). Thus, for fetal uptake rate to have remained constant during an increase in the concentration difference required a reduction in $\dot{Q}u$, which indeed occurred (fig. 3). A similar inverse relation of $\dot{Q}u$ and UV–FA concentration difference occurs with fetal oxygen uptake, which

may be unaffected by reductions in $\dot{Q}u$ of more than 25%.[11,12] We observed the same $\dot{Q}u$ UV–FA relationship to be true of fetal uptake of bupivacaine as well.[2]

Mean lidocaine concentrations varied little among the vital organs, and all were close to the FA concentration (fig. 7). Except in the brain, MEGX and GX concentrations exceeded lidocaine concentration. Higher liver concentrations of lidocaine have been reported previously, but the liver was obtained when the animal was killed soon after a maternal lidocaine injection.[13] Approximately 50% of the umbilical venous blood perfuses the liver, so that during infusion of lidocaine, higher liver concentrations would have been observed.[14] In our study tissues were examined 4 h after lidocaine infusion ended; thus, our findings would be expected to differ. Twenty minutes after the infusion FA concentrations, representing arterial blood below the ductus arteriosus, approximately equaled UV concentrations, so that the liver would not have been perfused with two different blood concentrations. The highest accumulations of MEGX and GX were in the lung and kidney, suggesting that fetal accumulation was similar to that reported in adult laboratory animals.

Lidocaine appeared rapidly in the fetal urine, with maximum excretion occurring during the second hour (fig. 6). The time lag in the excretion of GX in relation to MEGX appears to be consistent with a longer time for complete deethylation when compared with the monodeethylation of lidocaine to MEGX. Variation in degradation was noted in the total 5-h excretion ratios of metabolites over lidocaine, which were 0.48, 0.32, and 0.16. As noted, the lowest ratio, 0.16, occurred in the fetus with the highest uptake.

The progressive increases in each F/M, UV/MA, and FA/MA ratio during the infusion period reached their maximum levels during the second hour. A transplacental

equilibrium occurred when UV concentrations equaled FA, indicating that lidocaine was neither entering nor leaving the fetus. At this time (1 h 45 min) the mean observed ratio was 1.0 ± 0.03. The observed ratio was compared with the calculated ratio obtained by using the previously reported formula to calculate the F/M (equation 2).[5] This formula is based on the transplacental equilibration of unbound nonionized drug and is derived from maternal and fetal protein binding and pH at 39° C. The average calculated ratio for the five preparations at maternal–fetal equilibrium was 1.00 ± 0.05. The close approximation of calculated and observed F/M substantiates the values we determined for ovine protein binding. The difference from human values for maternal and fetal protein binding of lidocaine explains the lower human F/M, 0.44 to 0.58.[15] The similarity between predicted and observed F/M supports the concept that the F/M results from a transplacental equilibration of free nonionized drug.[5] Variations above or below this ratio may be explained by drug transfer to or from the fetus.

In conclusion, these results, along with those from our bupivacaine study, fail to support two often-quoted concepts. The first states that lipid solubility, not protein binding, produces lower fetal blood concentrations by promoting rapid tissue uptake.[1] It follows, however, that fetal uptake of bupivacaine should exceed that of lidocaine because bupivacaine's lipid solubility is ten times that of lidocaine (n-heptane solubility coefficient, 27.5 vs. 2.9). The opposite occurred: the uptake fraction of lidocaine was approximately three times that of bupivacaine (0.16).[2] Thus, maternal and fetal protein binding and pH appear to be the fundamental components controlling the fetal concentration.

The second concept states that if a maternal overdose occurred, fetal toxicity would less likely occur because fetal concentrations are lower.[16] Fetal local anesthetic concentration is established by the maternal free drug concentration, a situation that may be compared with a dialysis membrane with one side (maternal) containing protein and the other side (fetal) containing only buffer. After equilibration the protein binding is determined from the free drug concentration in the buffer. If protein with binding capacity is added to the buffer, then the total concentration increases but the free drug concentration remains constant. Therefore, maternal free drug concentration determines the fetal free drug concentration regardless of the degree of fetal protein binding. Fetal protein binding can provide little additional protection to prevent fetal toxicity.

The amount of drug carried by the fetus into the neonatal period is important because, lacking maternal placental clearance, the neonate is totally responsible for drug elimination. Evaluation of the time course of blood concentrations and the F/M, on which estimation of placental transfer is often based, casts doubt upon the validity of using these values to estimate placental transfer. Fetal lidocaine blood concentrations may decline as fetal uptake progresses, so that relating umbilical artery and vein concentrations at delivery to neonatal pharmacologic effects may give spurious conclusions. In distinction to bupivacaine, lidocaine exhibits little back transfer. Thus, should a large intravascular dose of lidocaine occur accidentally during an attempted epidural injection, there would be no benefit in delaying delivery to reduce the fetal dose.

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