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Effect of Lidocaine on the Asphyxial Responses in the Mature Fetal Lamb

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The effects of lidocaine on the fetal circulatory responses to asphyxia were evaluated in chronically instrumented pregnant sheep. Twenty-six preparations were studied. Animals were assigned to one of three groups. The animals in group I (N = 10) did not have umbilical cord occluders placed. Lidocaine at 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$ was infused to the mother for 180 min. The animals in group II (N = 11) had an umbilical cord occluder, which was inflated to induce fetal asphyxia (Pa_{O_2} 15 mmHg) for 90 min. Occlusion was then maintained for an additional 180 min while lidocaine at 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$ was infused. The animals in group III (N = 5) also had an umbilical cord occluder inflated for 90 min. While occlusion was maintained for an additional 180 min, saline was infused, in place of lidocaine. The infusion rate of lidocaine of 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$ over 180 min resulted in a steady-state arterial lidocaine blood concentration in the mother of approximately 2.15 μg/ml. Fetal circulatory responses to asphyxia were evaluated before and after maternal infusion of lidocaine or normal saline. Measurements included heart rate, blood pressure, arterial pH, and blood gases. Cardiac output and organ blood flow were determined using the radio-labelled microsphere technique. In general, arterial and tissue lidocaine concentrations in asphyxiated fetuses were higher than those in the nonasphyxiated ones, the differences being significant in the brain, heart, liver, and adrenal glands. Ninety minutes of asphyxia resulted in a decrease in fetal heart rate, while the blood pressure and cardiac output did not change significantly. At the same time, there was a significant increase in blood flow to the fetal brain, heart, and adrenals. These fetal responses were not altered after a further 180 min of asphyxia during which either lidocaine or normal saline was infused to the mother. It is concluded that lidocaine, in moderate concentrations, does not alter fetal responses to asphyxia, although placental transfer of the drug is enhanced by fetal acidosis. (Key words: Anesthesia: obstetric. Anesthetics, local: lidocaine. Complications: asphyxia. Pharmacodynamics.)

FETAL ASPHYXIA results in circulatory adaptations that increase oxygen delivery to the vital organs, such as brain and heart.[1-6] Fetal acidosis, by altering the pharmacokinetics of drugs transferred from the mother,[7-9] could have an adverse effect on these fetal responses to asphyxia. In this study, using chronically prepared pregnant sheep, lidocaine was infused into the mother, while asphyxia, induced by partial occlusion of the umbilical cord, was maintained in the fetus. The aim was to determine the effects of lidocaine on the physiological responses to asphyxia in the fetus, while maintaining a steady-state drug concentration in the maternal arterial blood similar to that found in human subjects following epidural administration.

Materials and Methods

Twenty-six chronically prepared ewes and their near-term fetuses were studied, having been assigned to three groups. Fetuses in group I (N = 10) were not asphyxiated, whereas those in groups II (N = 11) and III (N = 5) were asphyxiated by partial cord occlusion. The mean (±SE) gestational age was 137 ± 2 days (term 148 days). All ewes, deprived of food but not water for 48 h preceding surgery, had spinal anesthesia induced with tetracaine hydrochloride (8-10 mg). Catheters were introduced into the maternal descending aorta and inferior vena cava *via* the femoral vessels. An intravenous infusion of a balanced salt solution was begun, and maintained at approximately 10 ml/min during surgery. A dilute thiopental drip was administered, as required. The uterus was exposed through a midline abdominal incision, and, *via* a small hysterotomy, the fetal head and neck were delivered. A polyethylene catheter was introduced into the fetal thoracic aorta through the carotid artery, and superior vena cava through the jugular vein. The fetus was returned into the uterine cavity and the uterus closed, after a polyethylene catheter had been placed in the amniotic cavity.

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A second uterine incision was made to insert catheters into the fetal abdominal aorta and inferior vena cava through the femoral vessels. In 16 preparations (groups II and III) an inflatable occluder was placed around the umbilical cord and secured onto the fetal abdominal wall.[9,10,11] The estimated loss of amniotic fluid was replaced with an equal volume of warmed normal saline after the uterine and abdominal walls had been closed. All catheters were tunneled subcutaneously and secured in a pouch attached to the flank area of the ewe. Postoperatively, catheters were flushed daily with a heparin-containing solution.

Experiments were carried out, at the earliest, 4 days after surgery, the minimum time required for fetal recovery.[12] The urinary bladder of the ewe was catheterized the morning of the study, and the animal was kept in a cart with freedom to stand or sit; water and food were supplied ad libitum. Collection of urine began at least 2 h before the study. Prior to the administration of lidocaine, control samples of maternal and fetal arterial blood were obtained for determination of acid-base values, as was 20–30 ml of maternal blood, to be used for replacement of fetal blood loss due to sampling for blood flow determinations.

To induce fetal asphyxia, the cuff of the umbilical cord occluder was inflated until the fetal Pa_{O_2} was reduced to approximately 15 mmHg. Fetal arterial *p*H and gases were determined at 15 min intervals, and occlusion adjusted to maintain this level of Pa_{O_2} for at least 90 min prior to the infusion of either lidocaine (group II) or saline (group III), in 11 and 5 experiments, respectively. The Pa_{O_2} of 15 mmHg was chosen, since prolonged hypoxemia below 10 mmHg led to a high incidence of fetal mortality in a preliminary study.

Lidocaine was infused intravenously to mothers in groups I and II at a constant rate of 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$ for 180 min. The group III mothers received normal saline over a period of 180 min. The rate of lidocaine infusion was calculated as the product of the desired blood concentration (C_{ss}) × volume of central compartment (V_1) × elimination constant (k_{10}). The duration of infusion was for five half-lives to assure steady-state drug concentrations in maternal and fetal plasma. A target lidocaine concentration of 2 μg/ml was chosen to be similar to the arterial blood concentration occurring in human subjects following epidural administration. Values for V_1 (1.1 ± 0.3 l/kg) and k_{10} (0.06 ± 0.01 $\cdot min^{-1}$) were obtained in earlier experiments.[13]

Maternal and fetal arterial blood, and maternal urine samples were obtained at 15, 30, 60, 90, 120, 150, and 180 min following the onset of lidocaine or saline infusion for analysis of acid-base values and lidocaine concentrations, where appropriate. The *p*H, Pa_{CO_2}, and Pa_{O_2} were determined using microelectrodes and a Radiometer gas analyzer at 39.0° C (normal sheep temperature 38.5–39.5° C). The volume and *p*H of maternal urine samples was measured. The hematocrit was also determined at frequent intervals. All samples for drug determinations (separated plasma and urine) were stored at −20° C until analyzed by means of a gas chromatographic technique[14] (lower limit of sensitivity 0.02 μg/ml, coefficient of variation 5–10% over the range of the assay).

Maternal and fetal arterial pressure were measured with Statham transducers, the heart rate with a cardiotachometer, and recorded on a Beckman polygraph.

For the determination of fetal cardiac output and organ blood flow, 15 μm diameter microspheres, labeled with ^{57}Co, ^{113}Sn, ^{103}Ru, ^{96}Nb, and ^{46}Sc, were injected into the fetal inferior vena cava. In approximately 1/3 of the fetuses, microspherse were injected simultaneously into the inferior vena cava and jugular vein. Fetuses in group I received microsphere injections prior to, and at the end of, lidocaine infusion. Fetuses in groups II and III were injected prior to, and after 90 min of, asphyxia, and again at the conclusion of 180 min infusion of lidocaine or saline. Reference blood samples were obtained from the abdominal aorta (and carotid artery in 1/3 of fetuses) at a constant rate of 1.35 ml/min using Harvard withdrawal pumps, starting 30 s prior to microsphere injection, and continuing for 60 s after the end of the injection. Fetal blood loss was immediately replaced with an equal volume of stored maternal blood. At the end of the experiment, the ewe and the fetus were killed by the intravenous injection of pentobarbital, and the uterus and its contents were removed, and weighed. Fetal brain, heart, lungs, liver, kidneys, and adrenals were dissected, weighed, and stored for later determination of drug concentrations.[14] Before storage, small samples of the fetal organs were dissected, weighed again, and placed in counting vials for determination of radioactivity with an auto-gamma scintillation spectrometer connected to a multichannel analyzer. The radioactivity and weight of each tissue sample were entered into a PDP-11/10 microcomputer. A computer program was used to resolve the radioactivity of each isotope and to calculate the radioactivity per 100 g of tissue sample, the flow rate per 100 g of tissue sample per min, and the cardiac output.[15]

The total clearance of lidocaine at steady state was calculated as the infusion rate divided by the steady-state lidocaine concentration in plasma.

Analysis of variance tests were performed using the null hypothesis that there were no significant differences in the mean responses among the three groups of mothers and among the three groups of fetuses. Tukey's multiple comparison procedure was used where appropriate.

Tissue concentrations of lidocaine and tissue/plasma concentration ratios were compared between asphyxiated and nonasphyxiated fetuses using an unpaired *t* test. $P <$

TABLE 1. Mean (±SE) Maternal *p*Ha, Pa_{CO_2}, Pa_{O_2}, Heart Rate, and Mean Arterial Pressure

	*p*Ha	Pa_{CO_2} (mmHg)	Pa_{O_2} (mmHg)	Heart Rate (Beats/Min)	Mean Arterial Pressure (mmHg)
Group I (N = 10)					
Control	7.46 ± 0.02	33 ± 2	97 ± 5	112 ± 5	90 ± 3
Lidocaine	7.48 ± 0.02	31 ± 1	96 ± 2	116 ± 4	92 ± 6
Group II (N = 11)					
Control	7.49 ± 0.01	32 ± 1	95 ± 4	117 ± 8	94 ± 4
Fetal asphyxia	7.51 ± 0.02	29 ± 3	92 ± 3	119 ± 7	98 ± 7
Asphyxia + Lidocaine	7.52 ± 0.02	31 ± 2	94 ± 2	118 ± 9	97 ± 5
Group III (N = 5)					
Control	7.47 ± 0.01	31 ± 1	96 ± 2	116 ± 6	98 ± 4
Fetal asphyxia	7.52 ± 0.02	30 ± 1	96 ± 4	115 ± 7	97 ± 6
Asphyxia + Saline	7.50 ± 0.02	30 ± 2	95 ± 2	117 ± 5	99 ± 5

0.05 was considered to be significant. Values are presented as the mean ± S.E.

Results

MOTHERS

The mean weights of the ewes were as follows: group I, 57.8 ± 2.5 kg; group II, 54.6 ± 2.0 kg; group III, 55.5 ± 3.4 kg. There were no signficant differences in acid-base and cardiovascular state between all mothers prior to infusion. All values were within the normal range, indicating adequate recovery from surgery. The infusion of either lidocaine or saline did not alter these parameters (table 1).

Mean lidocaine concentrations in the arterial blood were similar in mothers of nonasphyxiated and asphyxiated fetuses at all points measured. They approached a steady state by 120 min of infusion; at the end of infusion the concentrations were 2.13 ± 0.21 and 2.18 ± 0.24 μg/ml, respectively. Calculated total clearances of lidocaine were 55.9 ± 8.2 and 51.6 ± 3.1 $ml \cdot kg^{-1} \cdot min^{-1}$. Unchanged lidocaine was present in maternal urine after 15 min (fig. 1). Over a period of 180 min, the total amount of lidocaine excreted was related to urinary *p*H and did not exceed 2% of the administered dose. Animals having urine *p*H of 5.3–7.0 (N = 9) excreted 17.26 ± 5.26 mg (1.73 ± 0.49% of dose), whereas those having a urine *p*H of 7.2–8.8 (N = 12) excreted only 3.73 ± 0.61 mg (0.33 ± 0.07 % of dose) ($P < 0.05$).

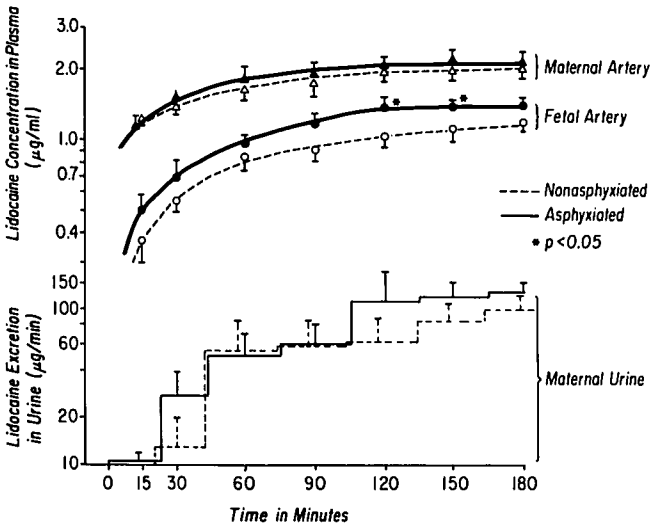

FIG. 1. Mean (±SE) lidocaine concentrations in maternal and fetal arterial blood, and maternal urine, during constant rate intravenous infusion to the mother (N = 21).

FETUSES

The mean weights of the fetuses were 3.6 ± 0.4 kg in the nonasphyxiated group, 3.4 ± 0.4 kg in the asphyxia-lidocaine group, and 3.5 ± 0.2 kg in the asphyxia-saline group. Control values for fetal arterial *p*H, blood gases, mean arterial pressure, heart rate, and cardiac output were similar in all three groups and normal for our laboratory (table 2, fig. 2). No statistically significant changes in fetal *p*H, blood gases, blood pressure, heart rate, or cardiac output were observed after 180 min of maternal lidocaine infusion in the nonasphyxiated fetuses. There were also no significant changes in blood flow to fetal organs and the placenta (table 3). Following inflation of the cord occluders in the 16 preparations in which they were inserted, there was an abrupt fall in fetal heart rate, accompanied by a decrease in Pa_{O_2} (fig. 2). The degree of occlusion was adjusted to maintain the fetal Pa_{O_2} at about 15 mmHg for 90 min. Beginning at 90 min after partial cord compression, the fetal *p*Ha was significantly different from the preocclusion value ($P < 0.01$). The fetal heart rate fluctuated between 10 and 20% below the pre-occlusion rate, and in most fetuses a slight rise ($P < 0.2$) in mean arterial pressure was noted. Thereafter, maternal infusion of either lidocaine or saline resulted in no further significant changes in any of the above parameters.

TABLE 2. Mean (±SE) Fetal *p*Ha, Pa_{O_2}, Heart Rate, Mean Arterial Pressure, and Cardiac Output

	*p*Ha	Pa_{O_2} (mmHg)	Heart Rate (Beats/Min)	Mean Arterial Pressure (mmHg)	Cardiac Output ($ml \cdot min^{-1} \cdot kg^{-1}$)
Group I (N = 10)					
Control	7.40 ± 0.02	22 ± 2	171 ± 9	48 ± 3	459 ± 44
Lidocaine	7.39 ± 0.02	22 ± 1	168 ± 8	49 ± 2	502 ± 40
Group II (N = 11)					
Control	7.39 ± 0.01	23 ± 1	172 ± 8	47 ± 3	537 ± 42
Asphyxia	7.30 ± 0.02*	15 ± 2*	147 ± 4*	54 ± 6	406 ± 86
Asphyxia + Lidocaine	7.24 ± 0.03*	13 ± 1*	140 ± 7*	55 ± 6	401 ± 89
Group III (N = 5)					
Control	7.38 ± 0.02	22 ± 2	179 ± 8	50 ± 2	464 ± 36
Asphyxia	7.30 ± 0.03*	15 ± 1*	146 ± 9*	54 ± 3	427 ± 66
Asphyxia + Saline	7.20 ± 0.07*	14 ± 2*	138 ± 11*	57 ± 5	410 ± 92

* Significantly different from control.

A steady-state plasma concentration of lidocaine in the fetus was approached at about 120 min. Values were 1.02 ± 0.10 μg/ml in the nonasphyxiated, and 1.37 ± 0.13 μg/ml in the asphyxiated group ($P < 0.05$) (fig. 1). At the end of infusion, the fetal values were 1.18 ± 0.15 and 1.41 ± 0.21 μg/ml, respectively, which represented 55% and 66% of the corresponding maternal concentrations. In all fetuses, induction of asphyxia resulted in a significant increase in blood flow to the brain, heart, and adrenals (table 3). The subsequent infusion of lidocaine or saline did not alter these changes. The mean concentrations of lidocaine in the fetal organs are depicted in figure 3. In general, arterial and tissue drug concentrations in asphyxiated fetuses were higher than those in the nonasphyxiated fetuses. The differences were significant in the brain ($P < 0.01$), heart ($P < 0.01$), liver ($P < 0.02$), and adrenal glands ($P < 0.05$). In the asphyxiated group, the mean lidocaine concentrations in the brain and heart were 6.83 ± 0.71 and 8.78 ± 1.60 μg/g, compared with 3.76 ± 0.30 μg/g and 3.08 ± 0.40 μg/g in the nonasphyxiated group. However, the differences between the tissue to plasma concentration ratios were significant only in the heart (fig. 4). This ratio in the nonasphyxiated fetuses was 3.30 ± 0.29, while in the asphyxiated group it was 6.98 ± 1.72.

Discussion

The cardiovascular responses to hypoxemia and acidemia in the fetal lamb and monkey have been extensively studied.[1-6] In many instances, hypoxemia was induced by administering low concentrations of oxygen to the mother, resulting in alterations in maternal hemodynamics and biochemical state. Increased catecholamine release, associated with maternal hyperventilation and agitation, may lead to hypertension and vasoconstriction, which, in turn, may cause a reduction in uterine blood flow, rendering fetal hypoxemia uncontrollable over a prolonged period of time.

In the present study, fetal hypoxemia and acidosis were induced by applying partial cord compression using an implanted inflatable occluder. This more nearly approaches the situation during labor, where maternal hypoxemia is rare, but where intermittent cord compression is frequent, resulting in alterations of fetal heart rate patterns, and occasionally in fetal asphyxia.[3,10,11] This method of producing fetal asphyxia also permits the fetus to be maintained in a controllable degree of asphyxia, while the mother is undisturbed. In the two published studies involving cord compression in fetal lambs, the degree of induced fetal asphyxia was more severe than in our study.

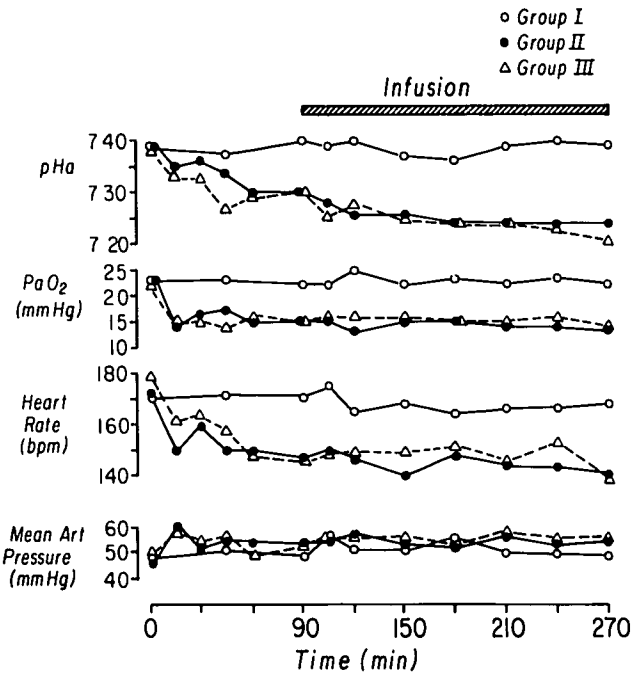

FIG. 2. Mean fetal *p*Ha, Pa_{O_2}, heart rate, and mean arterial pressure during the 90-min control period (group I) or 90 min of asphyxia (groups II and III), and during 180 min of infusion of lidocaine (groups I and II) or normal saline (group III).

TABLE 3. Mean Values (±SE) for Blood Flows in Various Fetal Organs and Placenta (ml · min^{-1} · 100g^{-1})

	Brain	Heart	Lung	Kidney	Adrenals	Placenta
Group I (N = 10)						
Control	151 ± 29	160 ± 26	99 ± 30	178 ± 19	307 ± 35	180 ± 36
Lidocaine	139 ± 18	149 ± 20	91 ± 21	152 ± 20	282 ± 62	158 ± 26
Group II (N = 11)						
Control	113 ± 12	153 ± 21	89 ± 29	181 ± 30	249 ± 61	192 ± 54
Asphyxia	222 ± 60*	673 ± 232*	48 ± 19	200 ± 43	594 ± 103*	156 ± 34
Asphyxia + Lidocaine	242 ± 42*	590 ± 186*	45 ± 23	172 ± 36	662 ± 170*	129 ± 29
Group III (N = 5)						
Control	110 ± 21	145 ± 27	78 ± 13	188 ± 22	276 ± 33	162 ± 27
Asphyxia	236 ± 58*	555 ± 201*	53 ± 20	201 ± 41	598 ± 113*	139 ± 42
Asphyxia + Saline	221 ± 42*	504 ± 108*	66 ± 31	180 ± 30	763 ± 208*	138 ± 36

* Significantly different from control.

In one of them,[3] the fetal *p*H was reduced from 7.40 to 7.04, and oxygen saturation from 50% to 19%. These changes were accompanied by an increase in mean fetal arterial blood pressure from 58–71 mmHg, while the heart rate did not change significantly. There was also a significant increase in cerebral blood flow, varying from 65% in the cerebral cortex to 102% in the brain stem. In the other study,[11] the umbilical blood flow (UBF) was gradually reduced by 25%, 50%, and 75% of control. Fetal Pa_{O_2} dropped significantly from 21 to 18 mmHg at 25% UBF reduction, and to 15 mmHg at 75% UBF reduction. The fetal arterial *p*H declined, and the Pa_{CO_2} rose, only after 50 and 75% reductions in UBF had been achieved. Similarly, the fetal heart rate declined from 182 bpm to 156 bpm and 108 bpm, at 50% and 75% UBF reduction, respectively, while the mean aortic pressure did not change, even at 75% UBF reduction.

The near-term fetus has well-developed cardiovascular reflexes, involving sympathetic responses and baro- and chemo-receptor mechanisms.[16] During asphyxia, these reflexes are activated to allow for redistribution of cardiac output to vital organs. Partial cord occlusion, as applied in this study, resulted in a controllable fetal hypoxemia associated with a mild degree of acidemia. Fetal responses consisted of a moderate reduction in heart rate without significant changes in blood pressure and cardiac output. There was also a significant increase in blood flow to fetal brain, heart, and adrenals. These changes were not altered by an additional 180 min of cord occlusion, during saline infusion. Neither were they altered by maternal lidocaine infusion (also over 180 min) resulting in fetal blood concentrations not exceeding 1.6 μg/ml. Therefore, a suitably controlled model was produced in which to compare the distribution of lidocaine between asphyxiated and nonasphyxiated fetuses during maternal lidocaine infusion, as well as to evaluate the effects of the drug on fetal circulatory responses to asphyxia.

Constant rate intravenous infusion of lidocaine produced steady-state blood concentrations in the mother, as well as in the normal and asphyxiated fetus, after ap-

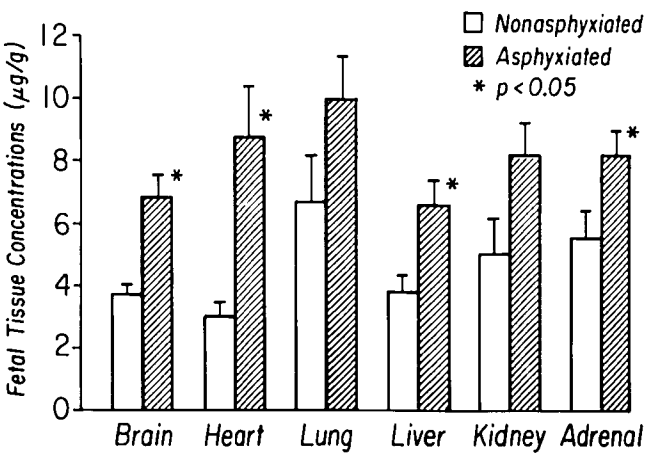

FIG. 3. Mean (±SE) tissue concentrations of lidocaine in nonasphyxiated (N = 10) and asphyxiated fetuses (N = 11).

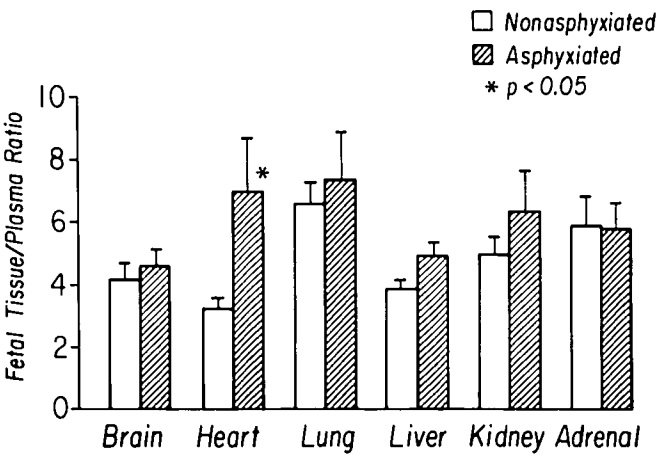

FIG. 4. Mean (±SE) tissue/plasma concentration ratios of lidocaine in nonasphyxiated (N = 10) and asphyxiated fetuses (N = 11).

proximately 120 min. Concentrations in the mother were approximately 2 μg/ml, which is similar to that reported in human subjects during epidural anesthesia. Fetal arterial concentrations of the drug tended to be higher, and tissue uptake was markedly higher in the asphyxiated group. This was probably due to several factors, such as increased blood flow and delivery of lidocaine to vital organs, particularly the brain, heart, and adrenals; decrease in blood *p*H resulting in reduced plasma protein binding; and tissue acidosis leading to ion trapping. Elevated blood concentrations of local anesthetics in the acidotic and/or hypoxemic fetus have been previously reported in animals and humans.[7-9,17]

In conclusion, the use of lidocaine resulting in moderate maternal concentrations does not appear to alter the fetal responses to mild to moderate asphyxia, although placental transfer of the drug is enhanced by fetal acidosis.

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