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Adverse Effects of Maternally Administered Lidocaine on the Asphyxiated Preterm Fetal Lamb

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Lidocaine was infused at a constant rate of 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$ for 180 min into 12 chronically prepared pregnant sheep while asphyxia, induced by partial umbilical cord occlusion, was maintained in the premature fetus (80% of gestation). In five similar preparations saline instead of lidocaine was infused into the mother for 180 min. Maternal and fetal arterial blood pressure, heart rate, *p*Ha, Pa_{CO_2}, and Pa_{O_2} were monitored, and fetal cardiac output and the distribution of blood flow to fetal organs were measured, using labeled microspheres, before and after asphyxia and again after maternal infusion of lidocaine or saline. Maternal and fetal arterial blood and maternal urine were obtained at intervals for determination of lidocaine concentrations and urinary drug clearance. At the end of infusion, these animals were killed and tissues dissected for determination of lidocaine concentrations and organ blood flow. Maternal and fetal lidocaine plasma concentrations at steady state were 2.32 ± 0.12 and 1.23 ± 0.17 μg/ml, respectively, similar to those seen during human epidural anesthesia. Asphyxia resulted in a significant drop in fetal heart rate and increased blood flow to the brain, heart, and adrenals. Asphyxia and saline did not produce additional deterioration of the fetus, but asphyxia and lidocaine led to a significant increase in Pa_{CO_2} and decreases in *p*Ha, mean arterial pressure, and blood flows to the brain, heart, and adrenals. It is concluded that the immature fetus loses its cardiovascular adaptation to asphyxia when exposed to clinically acceptable plasma concentrations of lidocaine obtained transplacentally from the mother. (Key words: Anesthetics, local: lidocaine. Asphyxia: fetal responses. Prematurity.)

THE INCREASED USE of cesarean section for delivery of the preterm fetus is thought to have contributed to improved perinatal outcome. However, it has also resulted in a more frequent administration of major anesthesia to the parturient. Because all agents used in obstetric anesthesia cross the placenta readily, fetal exposure to these drugs is almost immediate, and greater numbers of immature fetuses, which are vulnerable to asphyxia, are exposed to these drugs.

Fetal circulatory adaptations to asphyxia are believed to be of great importance because they result in increased oxygen delivery to vital organs, such as the brain and heart.[1–4] We have shown in near-term pregnant ewes that moderate concentrations of lidocaine delivered transplacentally do not alter fetal responses to asphyxia, although placental transfer of the drug is enhanced by fetal acidosis.[5]

The reported study was extended to include immature fetuses, which are frequently exposed to local anesthetics, because epidural anesthesia is considered particularly beneficial in preterm labor. It avoids using drugs that may depress the CNS of the fetus, and it facilitates an atraumatic, controlled vaginal delivery. The protocol was the same, *i.e.*, using chronically prepared pregnant sheep, lidocaine was infused into the mother to obtain steady state arterial blood concentrations of the drug, while asphyxia, induced by partial umbilical cord occlusion, was maintained in the fetus.

Materials and Methods

A total of 17 mixed breed pregnant sheep and their fetuses were studied at a mean (±SE) gestational age of 119 ± 2 days (80% of pregnancy, term being 148 days). The protocol was approved by the institutional Animal Care and Use Committee. All animals were obtained at least 7 days before surgery to become acclimatized, and were deprived of food, but not water, for 24 h preceding the operation. Surgery was performed during spinal anesthesia with tetracaine hydrochloride (8–12 mg), supplemented with intermittent iv administration of 0.5% thiopental. An iv infusion of Ringer's lactate and glucose solution (1,000 ml) was given throughout the operative procedure. Under sterile conditions polyvinyl catheters were inserted into the descending aorta and inferior vena cava via the femoral vessels. Following a midline laparotomy and hysterotomy catheters were inserted into the fetal carotid artery, jugular vein, and abdominal aorta and inferior vena cava (through the femoral vessels). In all preparations an inflatable occluder was placed around

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the base of the umbilical cord and secured to the fetal abdominal wall. The fetus was then returned into the uterine cavity, and the uterine incision was closed after insertion of an intraamniotic catheter. Catheters were tunneled subcutaneously into a pouch attached to the ewe's flank. After surgery animals were placed in the recovery room for 24 h; then they were transferred to individual pens in the animal facility. Postoperatively, antibiotics were administered to the ewe by iv injection and into the amniotic cavity; the intravascular catheters were flushed daily with a heparin-containing solution.

Experiments were conducted at the earliest 3–4 days after the surgery to assure fetal recovery. On the day of the study, the ewe was weighed and transferred to the research laboratory where the urinary bladder was catheterized. Collection of urine began at least 2 h before the experiment. During this stabilization period maternal and fetal arterial blood pressure and heart rate were monitored continuously, and arterial blood samples were obtained at least twice to ascertain the acid–base state and oxygenation in both mother and fetus. In addition, 20–30 ml of maternal blood was obtained to be used for replacement of fetal blood loss due to sampling for blood flow determinations. Animals were divided into two groups: group I fetuses (n = 12) were asphyxiated by partial cord occlusion and their mothers received a constant rate iv infusion of lidocaine, and group II fetuses (n = 5) were also asphyxiated as in group I, but their mothers were given normal saline instead of lidocaine.

To induce a moderate degree of fetal asphyxia, the cuff of the umbilical cord occluder was inflated with normal saline to produce partial cord occlusion. Fetal arterial *p*H and gases were determined at 10–15 min intervals, and occlusion adjusted to maintain a Pa_{O_2} of approximately 15 mmHg for at least 90 min prior to infusion of either lidocaine (group I) or saline (group II) to the mother.

Lidocaine was infused intravenously to mothers in group I at a constant rate of 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$ for 180 min. The group II mothers were given the same volume of normal saline over the 180-min infusion period. The rate and duration of lidocaine infusion were the same as in the previous study.[5] The target steady state arterial plasma concentration (Css) of 2 μg/ml was chosen to be similar to that measured in human parturients following epidural administration. The total clearance of lidocaine at steady state in the mother was calculated as the infusion rate divided by the Css.

Maternal and fetal arterial blood and maternal urine samples were obtained at 15, 30, 60, 90, 120, 150, and 180 min following the start of lidocaine or saline infusion for determination of drug concentrations where appropriate and *p*H and blood gases.

Two fetuses in group I died before completion of lidocaine infusion. Therefore, they were excluded from data analysis and are presented separately.

Maternal and fetal arterial pressure and intraamniotic pressure were measured with Statham pressure transducers, and maternal and fetal heart rate monitored with a Beckman cardiotachometer triggered by the arterial pulse pressure. They were recorded on a Beckman polygraph throughout the study.

The *p*Ha, Pa_{CO_2}, and Pa_{O_2} were determined with the use of an IL 1303 blood gas analyzer (Instrument Laboratories, Lexington, MA) at 39° C (normal sheep temperature is 38.5–39.5° C). The volume and *p*H of maternal urine samples were measured. Hematocrit was determined repeatedly.

To measure fetal cardiac output and organ blood flow, 15 μm diameter microspheres labeled with ^{46}Sc, ^{57}Co, ^{103}Ru, ^{113}Sn, or ^{96}Nb were used. One or two of the above microspheres were injected into the fetal jugular vein and/or inferior vena cava before the study to obtain the baseline values. Fetuses were injected again after 90 min of asphyxia and at the completion of 180 min of lidocaine or saline infusion. Reference blood samples were withdrawn for 90 s from the carotid artery and/or the abdominal aorta at a constant rate of 1.3 ml/min using Harvard withdrawal pumps. Fetal blood loss was immediately replaced with an equal volume of stored maternal blood.

At the conclusion of the study, the ewe and the fetus were killed by iv injection of an overdose of pentobarbital, and the uterus and its contents were immediately removed and weighed. In group I fetal brain, heart, lungs, liver, kidneys, and adrenals were dissected and stored for subsequent measurement of lidocaine concentrations. For the calculation of organ blood flow in both groups, small pieces from several areas of the above organs, as well as placenta, were taken, weighed, and placed in counting tubes for later determination of radioactivity using an auto-gamma scintillation spectrometer connected to a multichannel analyzer. A computer program, employing the stripping method, was used to resolve the radioactivity of each isotope and to calculate the radioactivity per 100 g tissue sample, the flow rate per 100 g of tissue sample per min and the cardiac output.[6] All samples for lidocaine determinations, (separated plasma, urine, and tissues) were stored at −20° C until analyzed, using a gas chromatographic technique similar to that previously described by Tucker[7] (lower limit of sensitivity 0.02 μg/ml, coefficient of variation 5–10% over the range of the assay).

Analysis of variance tests were performed using the null hypothesis that there were no significant differences in the mean responses within and between the two groups of mothers and within and between the two groups of fetuses. Tukey's multiple comparison procedure was used where appropriate. A $P < 0.05$ was considered to be significant. Values are presented as the mean ± SE.

TABLE 1. Mean Values (±SE) for Maternal *p*Ha, $PaCO_2$, PaO_2, Heart Rate, and MAP during the Control Period and at the End of Infusion of Lidocaine (Group I) or Saline (Group II)

	*p*Ha	$PaCO_2$ (mmHg)	PaO_2 (mmHg)	Heart Rate (beats/min)	MAP (mmHg)
Group I (n = 12)					
Control	7.53 ± 0.02	31 ± 2	98 ± 6	113 ± 8	96 ± 4
End of infusion	7.55 ± 0.01	30 ± 2	94 ± 5	117 ± 10	100 ± 7
Group II (n = 5)					
Control	7.50 ± 0.02	29 ± 1	97 ± 5	103 ± 10	103 ± 6
End of infusion	7.54 ± 0.01	28 ± 2	95 ± 4	107 ± 7	102 ± 10

Results

The mean weights of the ewes were similar: group I, 53.7 ± 2.5 kg; group II, 54.1 ± 3.5 kg. Mean values for maternal *p*Ha, Pa_{CO_2}, Pa_{O_2}, heart rate, and mean arterial pressure during the control period and at the end of lidocaine or saline infusion are summarized in table 1. These vital signs were within the normal range, and remained so throughout the study.

Lidocaine in maternal plasma (group I) approached a steady state concentration after about 150 min of infusion (fig. 1). At 180 min it was 2.32 ± 0.12 μg/ml. The drug was detectable in maternal urine as early as 15 min after the start of infusion, but the total amount of the unchanged lidocaine recovered during 180 min was only approximately 1.0% of the administered dose (10.8 ± 6.2 mg). Calculated total clearance was 45.4 ± 2.1 $ml \cdot kg^{-1} \cdot min^{-1}$ (table 2).

The mean weights of fetuses were 2.4 ± 0.6 kg in group I (asphyxia and lidocaine) and 2.5 ± 1.5 kg in group II (asphyxia and saline).

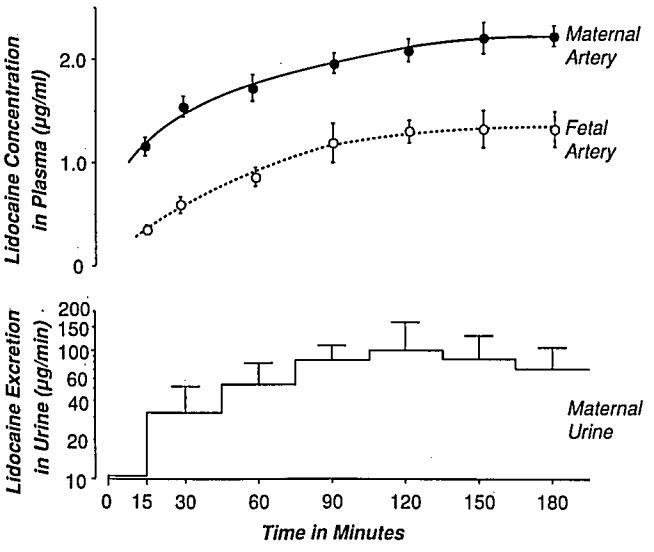

FIG. 1. Lidocaine concentrations (μg/ml) in maternal and fetal plasma during 180 min maternal infusion at a rate of 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$ and lidocaine excretion in maternal urine (μg/min) (n = 12).

Tables 3 and 4 summarize data pertaining to fetal *p*Ha, Pa_{O_2}, Pa_{CO_2}, heart rate, mean arterial pressure, cardiac output, and blood flow to various fetal organs and the placenta. These were obtained prior to and after 90 min of asphyxia and after a further 180 min of asphyxia plus lidocaine or saline infusion to the mother. Control values were normal for our laboratory and similar in both groups. After 90 min of asphyxia, there was a significant decline in *p*Ha, Pa_{O_2}, and heart rate. There was also a significant increase in Pa_{CO_2} in group I. In both groups of fetuses 90 min of asphyxia also resulted in a significant increase in blood flow to the brain, heart, and adrenals. Maternal infusion of saline produced no changes in fetal cardiovascular or acid–base state, whereas infusion of lidocaine resulted in an additional decline in *p*Ha from 7.30 ± 0.04 to 7.14 ± 0.04 and a rise in Pa_{CO_2} from 50 ± 3 to 62 ± 5 mmHg. Mean arterial pressure declined from 52 ± 8 to 30 ± 6 mmHg. The fall in Pa_{O_2} and cardiac output following lidocaine infusion did not reach statistical significance. Lidocaine abolished the increases in blood flows to the brain, heart, and adrenals induced by asphyxia, while reducing placental perfusion by the fetus.

A steady state concentration of lidocaine in the fetal plasma was reached after approximately 150 min of maternal infusion (fig. 1). At 180 min the concentration was 1.23 ± 0.17 μg/ml and the fetal/maternal concentration ratio was 0.55 ± 0.10. Lidocaine concentrations in the fetal organs and tissue/plasma concentration ratios are presented in table 5 and figure 2, which also include previously published data from premature nonasphyxiated fetuses.[8] In the asphyxiated group, the mean values for tissue/plasma concentration ratios were significantly higher in the brain, heart, lung, and liver. For example,

TABLE 2. Lidocaine Data in the Mother

Steady state plasma concentration (μg/ml)	2.32 ± 0.12
Total clearance ($ml \cdot kg^{-1} \cdot min^{-1}$)	45.4 ± 2.1
Amount recovered in urine	
mg	10.78 ± 6.24
% of dose	1.11 ± 0.61

Values are mean ± SE; group I (n = 12).

TABLE 3. Mean Values (±SE) for Fetal *p*Ha, PaO_2, $PaCO_2$, Heart Rate, MAP, and Cardiac Output

	*p*Ha	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	Heart Rate (beats/min)	MAP (mmHg)	Cardiac Output (ml/min/kg)
Group I (n = 10)						
Control	7.39 ± 0.02	23 ± 1	41 ± 2	179 ± 4	48 ± 6	438 ± 42
Asphyxia	7.30 ± 0.04*	15 ± 1*	50 ± 3*	150 ± 10*	52 ± 8	406 ± 56
Asphyxia + lidocaine	7.14 ± 0.04*†	11 ± 3*	62 ± 5*†	124 ± 11*	30 ± 6*†	270 ± 52*
Group II (n = 5)						
Control	7.40 ± 0.01	24 ± 1	42 ± 1	180 ± 4	47 ± 5	432 ± 47
Asphyxia	7.31 ± 0.04*	15 ± 2*	49 ± 4	148 ± 9*	49 ± 7	400 ± 48
Asphyxia + saline	7.28 ± 0.04*‡	14 ± 2*‡	53 ± 4*‡	152 ± 5*‡	50 ± 6‡	418 ± 39‡

* Significantly different from control.
† Significantly different from asphyxia alone.
‡ Significantly different from asphyxia + lidocaine in group I.

the mean brain/plasma concentration ratios in the asphyxiated and nonasphyxiated fetuses were 5.0 ± 0.5 and 3.4 ± 0.5, respectively, and the mean heart/plasma ratios were 3.8 ± 0.5 and 2.5 ± 0.3, respectively.

The two fetuses that died during maternal infusion of lidocaine had gestational ages of 120 and 118 days, respectively. As in all fetuses, a moderate degree of asphyxia was maintained for 90 min prior to maternal infusion (table 6). At 40 and 60 min of infusion, the fetal heart rate began to fall, reaching 110 and 98 beats/min, respectively. This was accompanied by decreases in Pa_{O_2} from 14 to 11 mmHg, and from 15 to 10 mmHg (sample 1). The fetal deterioration became more pronounced after 90 min of lidocaine administration. Marked bradycardia and hypotension were associated with Pa_{O_2} values of 6 and 7 mmHg, respectively (sample 2). Concomitantly, Pa_{CO_2} increased and *p*Ha decreased to 6.67 and 6.49, respectively. Lidocaine concentrations in plasma obtained at 90 min were 0.92 and 0.85 μg/ml, respectively.

Discussion

The present study demonstrates that in the sheep the immature fetus loses its cardiovascular adaptation to asphyxia when exposed to clinically acceptable plasma concentrations of lidocaine obtained transplacentally from the mother.

Hemodynamic effects of lidocaine administered to the mother have been studied in the healthy immature and mature lamb (at 80% and 95% of gestation), as well as in the mature asphyxiated fetus.[5,8] It should be emphasised that in all our studies in this series, maternal and fetal plasma concentrations were well below those known to elicit toxicity. Also, the work of others involving pregnant sheep showed no decrease in uteroplacental blood flow during prolonged maternal infusion of lidocaine, resulting in maternal plasma drug concentrations seen clinically in the human (2–4 μg/ml).[9] A constant rate lidocaine infusion (180 min) to pregnant ewes failed to show any differences, either kinetic or dynamic, between the drug effects on healthy premature compared with mature fetuses.[8]

When a controlled degree of hypoxemia and acidemia was induced by partial cord compression in the mature fetal lamb, there was a moderate reduction in heart rate without significant changes in blood pressure and cardiac output, whereas blood flow to the brain, heart, and adrenals increased significantly.[5] Addition of a lidocaine infusion to the mother, resulting in fetal concentrations of

TABLE 4. Mean Values (±SE) for Blood Flows in Various Fetal Organs and Placenta ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)

	Brain	Heart	Lung	Kidney	Adrenal	Placenta
Group I (n = 10)						
Control	102 ± 21	171 ± 23	79 ± 32	176 ± 22	258 ± 23	164 ± 16
Asphyxia	215 ± 47*	516 ± 109*	88 ± 43	207 ± 38	655 ± 102*	154 ± 37
Asphyxia + lidocaine	92 ± 30†	150 ± 53†	32 ± 21	121 ± 30	190 ± 38†	98 ± 22*
Group II (n = 5)						
Control	105 ± 20	150 ± 17	77 ± 20	158 ± 25	240 ± 38	156 ± 22
Asphyxia	208 ± 44*	485 ± 98*	85 ± 42	181 ± 38	556 ± 108*	162 ± 31
Asphyxia + saline	197 ± 32*‡	498 ± 52*‡	57 ± 28	167 ± 33	573 ± 134*‡	168 ± 34

* Significantly different from control.
† Significantly different from asphyxia alone.
‡ Significantly different from asphyxia + lidocaine in group I.

TABLE 5. Mean (±SE) Lidocaine Concentrations (μg/g) in Fetal Organs in Asphyxiated and Nonasphyxiated Premature Fetuses

	Asphyxiated	Nonasphyxiated*
Brain	5.9 ± 0.8	4.8 ± 0.4
Heart	4.4 ± 0.6	3.7 ± 0.2
Lung	6.9 ± 1.4	5.0 ± 0.7
Liver	5.5 ± 1.0	3.7 ± 0.9
Kidney	7.2 ± 1.9	6.5 ± 0.6
Adrenal	5.7 ± 1.2	6.3 ± 1.6

* Data from Pedersen *et al.*[8]

TABLE 6. Individual Data from 2 Fetuses That Died during Maternal Lidocaine Infusion

	*p*Ha	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	Heart Rate (beats/min)	MAP (mmHg)
Experiment 27					
Control	7.40	21	43	180	45
Asphyxia	7.28	14	54	152	48
Asphyxia + lidocaine					
Sample 1	7.06	11	68	110	32
Sample 2	6.67	6	78	72	20
Experiment 35					
Control	7.42	24	42	178	43
Asphyxia	7.29	15	51	140	49
Asphyxia + lidocaine					
Sample 1	7.08	10	66	98	28
Sample 2	6.49	7	99	68	18

the drug not exceeding 1.6 μg/ml, did not lead to additional deterioration of the fetus. Fetal tissue uptake of drug was higher in asphyxiated than in nonasphyxiated fetuses, presumably related to altered blood flow, protein binding, and ion trapping.

The mature near-term sheep fetus has well-developed cardiovascular reflexes, involving sympathetic responses and baroreceptor and chemoreceptor mechanisms, but this may not be equally so in the premature fetus.[10] It was therefore decided to use the same experimental preparation to examine the effects of lidocaine in the asphyxiated preterm fetus, in which these reflex responses might be expected to be absent, or less well developed. The rationale for this exploration was that preterm delivery has become much more common, whereas little is known about the effects of local anesthetics, popularly administered by the epidural route to the mother, on the premature fetus and newborn, which are vulnerable to birth asphyxia.

In the present study, 90 min of induced asphyxia in the premature fetus indeed produced responses similar to those in the mature asphyxiated fetus,[5,8] *i.e.*, a reduction in heart rate, without significant change in mean arterial pressure or cardiac output, and significant increases in blood flow to the brain, heart, and adrenals. This would seem to suggest that even at a gestational age of 120 days (or 80% of pregnancy) the fetal lamb at least has a fairly sophisticated cardiovascular response mechanism. However, marked changes were observed during the subsequent lidocaine infusion to the mother. The prolongation (180 min) of asphyxia alone (saline infusion) did not produce additional deterioration in the fetus; but superimposition of lidocaine (for a similar period) resulted in a significant reduction in cardiac output and placental blood flow, as well as in the perfusion of vital organs, such as the brain, heart, and adrenals. There was also an increase in Pa_{CO_2} and a decrease in *p*H and mean blood pressure. This is in sharp contrast to the responses to lidocaine in the mature asphyxiated fetus, which were unaffected by the drug.

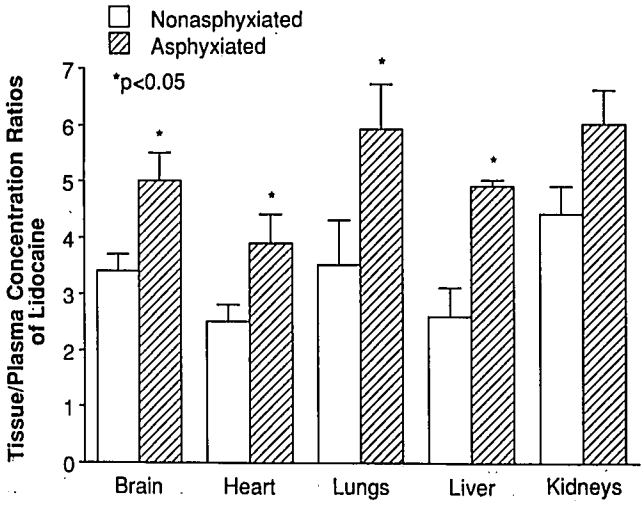

FIG. 2. Tissue/plasma concentration ratios of lidocaine in nonasphyxiated[8] and asphyxiated premature fetuses.

Of particular interest is the fact that this deterioration after lidocaine occurred at only moderate degrees of fetal asphyxia. Thus, immaturity may be the major factor contributing to the adverse effects of lidocaine. It has been suggested that the parasympathetic innervation of the heart precedes the development of sympathetic fibers.[11] It could be that the beta-adrenergic response to asphyxia, while functioning, is not sufficiently established in the premature fetus, so that there is a greater vulnerability to reduction in fetal heart rate.[12] It is also known that lidocaine produces a direct effect on cardiac conduction, not mediated through the autonomic nervous system. Recent studies have suggested that for lidocaine and procainamide drug effects at the cellular level change with maturation.[13,‡‡] Another possibility might be that the lidocaine modifications of the surface charge of cell mem-

‡‡ Ezrin AM, Nilsson K, Bassett AL, Myerburg RJ, Gelband H: Electrophysiologic effects of procaine amide on newborn canine cardiac tissue (abstract). Fed Proc 37:573, 1978.

branes may differ in the premature and mature fetus.[14] Whatever the mechanism, it seems that the protective responses to asphyxia, which the sheep fetus can usually command, are compromised in some way in the presence of lidocaine at plasma levels commonly seen in the human clinical situation.

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