

Toxicity and Distribution of Lidocaine in Nonasphyxiated and Asphyxiated Baboon Fetuses

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The dosage and blood concentration of lidocaine required to produce central nervous and cardiovascular system toxicity in both nonasphyxiated and asphyxiated fetuses were determined in ten pregnant baboons with fetuses of average gestation of 158 days (term, 185 days). Lidocaine was infused into the fetal jugular vein until cardiac arrest occurred, following which fetal brain, heart, lungs, liver and kidneys were obtained. Mean dosage and blood concentration of lidocaine associated with seizures were 9.4 mg/kg and 15.2 μ g/ml, respectively, in the nonasphyxiated fetuses, and 3.9 mg/kg and 5.6 μ g/ml, respectively, in the asphyxiated ones. The dosage and blood concentration of the drug required to produce cardiac arrest were significantly higher in the nonasphyxiated group (35 mg/kg and 269 μ g/ml, respectively) compared to the sphyxiated group (9 mg/kg and 40 μ g/ml, respectively). Tissue-plasma ratios of lidocaine were significantly higher ($P < 0.05$) in the brain, heart, and liver of the asphyxiated fetuses as compared with the nonasphyxiated ones. The relative proportion of the injected dose found in the organs was also higher ($P < 0.05$) in the asphyxiated group. These results indicate that the increased sensitivity of the asphyxiated fetus to lidocaine may be related in part to a greater uptake of local anesthetics by the fetal organs. (Key words: Anesthesia: obstetrics. Anesthetics, local: lidocaine. Pregnancy. Toxicity: fetal; tissue uptake.)

THE POTENTIAL toxicity of local anesthetic agents to the fetus *in utero* is related to the rate of placental transfer of drug and the degree of fetal acidosis and hypoxemia.¹⁻³ A smaller dose and lower blood concentration of lidocaine will produce cardiovascular toxicity in the acidotic fetal lamb as compared with the nonacidotic fetus when the drug is injected directly into the fetus.³ It has also been shown that the blood concentration of lidocaine and mepivacaine is higher in acidotic fetuses following administration of the drug to the mother.^{4,5} We have recently reported that the nonasphyxiated fetus or newborn lamb requires a much greater dosage and blood concentration of lidocaine or etidocaine than the adult to produce symptoms of toxicity in the central nervous system

(CNS) or cardiovascular system.[‡] The etiology of the increased sensitivity of the acidotic or hypoxic fetus to local anesthetic agents has not been determined. The results of this study suggest that the greater toxicity of lidocaine in the asphyxiated fetal baboon is related in part to an increased uptake of local anesthetic by tissues such as the brain and heart.

Materials and Methods

Ten pregnant baboons (*Papio* hybrid) with fetuses of 147 to 168 days' (term, 185 days) gestation were operated upon under nitrous oxide and halothane anesthesia. Details of the technique used for the administration of anesthesia and postoperative management have been reported elsewhere.⁶ Polyethylene catheters were placed in a maternal femoral artery and vein and, following hysterotomy, in a fetal carotid artery, jugular vein, and the trachea. In three instances, an intravascular PaO₂ electrode catheter⁷ was used instead of polyethylene catheters for the fetal carotid artery cannulation. Maternal and fetal ECG electrodes and fetal biparietal superficial scalp EEG electrodes were implanted, and thermistor probes were placed in the fetal esophagus and maternal colon. A catheter was also inserted in the amniotic cavity.

Postoperatively, the mother was placed in the semi-lateral position and lightly restrained. She was sedated with nitrous oxide-oxygen mixture and ventilated mechanically in order to maintain maternal arterial pH and blood gas values within the normal range.⁸ This was continued until the end of the experiment. Throughout the experiment, the maternal core temperature was kept at approximately 38° C by means of a heating pad and an overhead source of infrared radiation. Maternal and fetal arterial blood pressure and heart rate, fetal intratracheal pressure, and intra-amniotic pressure were recorded continuously. Fetal intravascular PaO₂ was also monitored in three experiments. The heart rate was measured using either a cardi tachometer from the arterial pulse pressure, or the R wave of the ECG. Fetal electrocortical activity

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TABLE 1. Gestational Age, Weight, Acid-base and Hemodynamic Variables Measured Prior to Lidocaine Infusion in Nonasphyxiated and Asphyxiated Fetuses

Animal Number	Animal Sex	Gestational Age (days)	Weight (g)	pH _a	Pa _{CO₂} (torr)	Base Deficit (mEq/L)	Sa _{O₂} (per cent)	Hematocrit (per cent)	Heart Rate (beats/min)	Mean Arterial Pressure (torr)
<i>Nonasphyxiated</i>										
1	♂	150	780	7.30	31	10.7	52	37	170	40
2	♂	154	800	7.35	40	3.2	70	42	195	43
3	♀	157	743	7.31	35	11.0	62	45	180	50
4	♂	158	680	7.27	56	4.1	52	37	150	40
5	♀	168	725	7.26	50	6.8	37	47	210	35
Mean		157	746	7.30	42	7.2	55	42	181	42
SE		3	21	0.02	5	1.6	6	2	10	3
<i>Asphyxiated</i>										
6	♀	147	590	7.02	56	18.5	11	44	155	47
7	♂	155	840	6.87	94	19.5	7	47	120	60
8	♀	162	850	6.93	62	23.0	5	48	180	39
9	♀	163	610	7.05	64	16.8	10	47	200	47
10	♀	165	780	7.20	48	10.4	14	42	200	53
Mean		158	734	7.01*	65	17.6†	9*	46	171	49
SE		3	56	0.06	8	2.1	2	1	15	4

* = $P < 0.01$; † = $P < 0.02$ significantly different from nonasphyxiated group.

was recorded continuously from biparietal superficial scalp electrodes. In the period three to five hours after the hysterotomy but before the experiment was begun, baseline measurements were made of fetal breathing movements and temperature gradient between mother and fetus, and continuous measurement was made of intravascular Pa_{O₂} in the fetus. The results of these observations have been published elsewhere.⁹

For the purpose of this experiment, the fetuses were divided into two groups according to their arterial pH and oxygenation prior to the study. Five fetuses were relatively well oxygenated with a mean pH_a of 7.30 ± 0.02 (SE) and Sa_{O₂} of 55 ± 5.6 per cent (non-asphyxiated group). In the remaining five experiments, despite identical management, the fetuses were severely acidotic and hypoxemic, with a mean pH_a of 7.01 ± 0.06 and Sa_{O₂} of 9 ± 1.6 per cent (asphyxiated group) due to prolonged strong uterine contractions. Lidocaine, 0.2 per cent solution, was infused at a constant rate (approximately 4 mg/kg/min) into the fetal jugular vein until cardiac arrest was evident on the fetal ECG. The infusion rate was calculated by estimating the fetal weight at surgery. The actual weight was obtained prior to the removal of fetal organs after delivery. Blood samples were obtained simultaneously from the maternal and fetal artery prior to the infusion of lidocaine, at the onset of seizure activity, and at the time of cardiac arrest. Immediately following

cardiac arrest, the fetus was delivered, and brain, heart, lungs, liver, and kidneys were removed. They were blotted dry, weighed (wet weight) and frozen. All blood samples were analyzed for pH, P_{CO₂} and P_{O₂}, using radiometer microelectrodes and a radiometer gas analyzer. Plasma was then separated by centrifugation and stored at -15° C. The base deficit was calculated using the Siggaard-Andersen nomogram. The oxygen saturation was estimated using nomograms for the adult and fetal baboons.¹⁰ Blood and tissue samples were analyzed for lidocaine concentrations using a gas chromatographic technique.¹¹ For determination of the concentration of lidocaine in tissues, each entire organ was transferred to a homogenizer cup, to which a measured quantity of internal standard solution of methyl-ethyl lidocaine in distilled water was added. The mixture was homogenized. The subsequent extraction procedure and gas chromatographic assay for lidocaine were carried out as described previously for blood.¹¹ This procedure was specific for unchanged lidocaine, since the retention time for the drug was 15 min, whereas the retention times of the two most likely metabolites, monoethyl glycinexylidide and glycinexylidide, were 11 and 14 min, respectively. The results were expressed as micrograms of lidocaine per gram of tissue (wet weight). Comparisons between the means of the two groups were made using the unpaired *t* test, and $P < 0.05$ was considered to be as significant difference.

TABLE 2. Dose and Blood Concentration of Lidocaine at Time of Seizures

	Nonasphyxiated Fetuses (n = 5)	Asphyxiated Fetuses (n = 2)
Dose (mg/kg)	9.4 ± 2.4*	3.6, 4.1
Concentration in blood (μg/ml)	15.2 ± 2.5*	4.7, 6.4

* Values are mean ± SE.

Results

Gestational age, weight, acid-base values, hematocrit, heart rate, and mean arterial pressure in the nonasphyxiated and the asphyxiated fetuses prior to administration of lidocaine are listed in table 1. Gestational age and fetal weight were comparable in both groups. The degree of fetal acidosis and hypoxemia was related to the degree of uterine activity, which in turn affected the adequacy of uteroplacental perfusion. It is generally accepted that strong and prolonged uterine contractions may reduce the intervillous space perfusion and cause oxygen deprivation to the fetus. During the course of baseline measurement, five mothers commenced a progressive increase in intra-amniotic pressure and frequency of uterine contractions, leading to abnormally elevated uterine activity and severe fetal asphyxia. Under the hypoxic state, anaerobic glycolysis is increased, and this results in a further rise in base deficit. The remaining five mothers had only mild uterine activity throughout the experiment. Expressed in Montevideo units,¹² uterine activity prior to the infusion averaged 142 ± 26.0 in the asphyxiated group compared with 71 ± 14.4 units in the nonasphyxiated one. Although one fetus (number 5) in the nonasphyxiated group had relatively low pH_a and Sa_{O_2} values, most fetuses classed as asphyxiated showed significantly greater degrees of metabolic acidosis and hypoxemia as judged by lower mean pH_a and Sa_{O_2} values ($P < 0.01$), and higher base deficit ($P < 0.02$) in comparison with the nonasphyxiated group.

During infusion of lidocaine, EEG changes characteristic of seizure activity, *i.e.*, irregular pattern of large amplitude and slow wave of electrical activity, occurred in all nonasphyxiated and in two asphyxiated fetuses. This was accompanied by a significant increase in mean systolic blood pressure (48 ± 8 per cent above control) and heart rate (32 ± 8 per cent above control). These changes occurred intermittently and were subsequently followed by hypotension and bradycardia, leading to irreversible circulatory collapse. The remaining three severely asphyxiated fetuses (numbers 6, 7, and 8) showed no sign of

seizure activity. Arterial pressure and heart rate decreased steadily until cardiac arrest occurred.

Mean dosage and blood concentration of lidocaine required to produce seizure activity are summarized in table 2. These doses were expressed in terms of mg/kg of fetal body weight measured at the end of the study. The dosage and blood concentration of the drug associated with seizures in the nonasphyxiated fetuses were much higher than in the asphyxiated ones. The dosage of lidocaine necessary to produce cardiac arrest was also significantly higher in the nonasphyxiated group (35 ± 3 mg/kg) compared to the asphyxiated group (9 ± 2 mg/kg) ($P < 0.01$). Details of the infusion rates of lidocaine and the concentration of the drug in blood and tissues obtained at the time of cardiac arrest are listed in table 3. The mean concentration of lidocaine in brain and myocardium was 14 ± 3 μg/g and 111 ± 16 μg/g, respectively, in the nonasphyxiated fetuses, and 11 ± 3 μg/g and 80 ± 28 μg/g, respectively, in the asphyxiated animals at the time of cardiac arrest. Although the blood lidocaine concentration was significantly higher in the nonasphyxiated group, no statistically significant difference existed in the tissue levels of the two groups except for the kidney. The lidocaine level in renal tissue was significantly higher in the nonasphyxiated fetuses ($P < 0.02$). However, the tissue-plasma ratios of lidocaine were significantly higher in the brain, heart, and liver of the asphyxiated group as

TABLE 3. Rate of Infusion and Concentration of Lidocaine in Blood (μg/ml) and Tissue (μg/g wet weight) in Nonasphyxiated and Asphyxiated Fetuses at Time of Cardiac Arrest

Animal Number	Infusion Rate (mg/kg/min)	Blood	Brain	Myocardium	Lungs	Liver	Kidney
<i>Nonasphyxiated</i>							
1	3.8	183.0	16.3	117.0	—	79.0	54.9
2	4.2	290.0	8.8	83.3	56.7	66.9	52.3
3	5.2	303.9	10.9	146.2	37.9	46.7	79.9
4	4.3	186.0	8.9	66.3	13.9	26.3	35.3
5	6.1	382.1	25.6	141.7	34.7	49.9	63.2
Mean	4.7	269.0	14.1	110.9	35.8	53.8	57.1
SE	0.4	37.9	3.2	15.8	8.8	9.0	7.3
<i>Asphyxiated</i>							
6	4.2	26.7	8.1	36.7	9.8	24.6	15.1
7	3.7	27.3	12.3	180.6	—	56.8	20.9
8	2.2	7.4	1.2	29.5	6.5	11.7	—
9	3.8	110.6	12.8	53.1	32.8	19.0	24.8
10	3.6	27.2	18.7	99.4	23.5	27.9	35.2
Mean	3.5	40.0*	10.6	79.9	18.2	28.0	24.0†
SE	0.3	18.1	2.9	28.0	6.1	7.7	4.2

* = $P < 0.01$; † = $P < 0.02$ significantly different from nonasphyxiated group.

compared with those in the nonasphyxiated group (fig. 1). The relative proportion of the injected dose found in these organs was also higher in the asphyxiated group (fig. 2). The tissue uptake of lidocaine has probably been underestimated in this study since residual blood was not washed out from organs prior to homogenization.

Maternal cardiovascular and acid-base status prior to the infusion of lidocaine into the fetal vein were normal for our laboratory.⁸ Average values for the mean arterial pressure and heart rate were 114 ± 3 torr and 137 ± 4 beats/min, respectively; mean pH_a , 7.48 ± 0.05 ; P_{aCO_2} , 35 ± 2 torr; P_{aO_2} , 126 ± 17 torr, and base deficit, 4.5 ± 0.8 mEq/L. These values remained essentially unchanged throughout the experiment. The maternal blood concentration of lidocaine at the time of fetal seizures was less than $0.01 \mu\text{g/ml}$. At the time of fetal cardiac arrest, the maternal blood concentration of lidocaine was $0.5 \pm 0.09 \mu\text{g/ml}$ in the nonasphyxiated group and $0.4 \pm 0.12 \mu\text{g/ml}$ in the asphyxiated group.

Discussion

The results of this study demonstrate the enhancement of local anesthetic toxicity in the subhuman primate fetus by hypoxemia and acidosis. They confirm our previous observations in human and sheep fetuses that the nonasphyxiated fetus and neonate can tolerate a high blood concentration of local anesthetic before exhibiting signs of CNS and cardio-

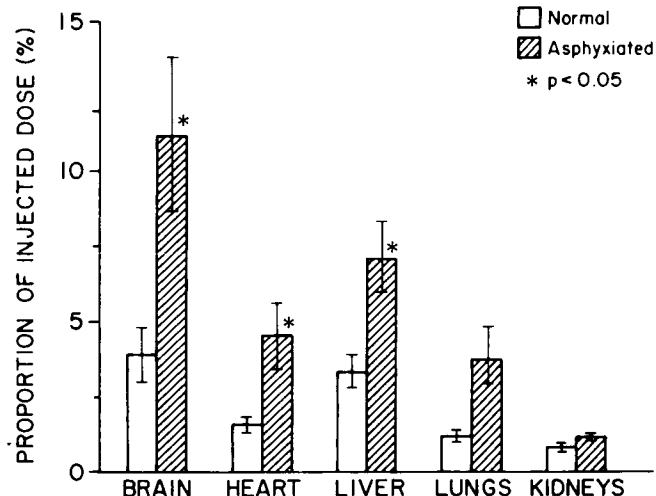


Fig. 2. Mean (\pm SE) values for the proportions of injected lidocaine dose found in the brain, heart, liver, lungs and kidneys in nonasphyxiated and asphyxiated fetuses. $N = 5$ in each group. *Significantly different from the nonasphyxiated group.

vascular toxicity.^{3,13} The higher dosage of lidocaine required to achieve toxic levels in the fetal blood may be related in part to the rapid placental clearance of the drug into the maternal compartment. Indeed, in this and in previous experiments, local anesthetics injected directly into the fetus were quickly detected in maternal blood.^{14,15} The decreased tolerance of the hypoxic and acidotic baboon fetus to the toxic actions of lidocaine is consistent with previous studies in adult animals, fetal sheep, and newborn lambs.^{3,16,17} Three baboon fetuses with profound asphyxia exhibited no seizure pattern on the EEG during infusion of lidocaine. This was probably related to preexisting severe CNS depression. In human infants accidentally injected with local anesthetic during attempted maternal caudal anesthesia,¹³ there was prolonged hypotonia in the newborns; convulsions appeared only after the newborns were resuscitated and well oxygenated.

The present study also indicates that the increased susceptibility of the asphyxiated fetus is due to a greater tendency of local anesthetics to accumulate in fetal organs, particularly the brain and heart. This is probably due in part to the pH effect on ionic trapping of the local anesthetic agent. The ratio of ionized to nonionized form of the drug is of pharmacologic importance since free base more readily penetrates the tissue diffusion barriers. All amide-type

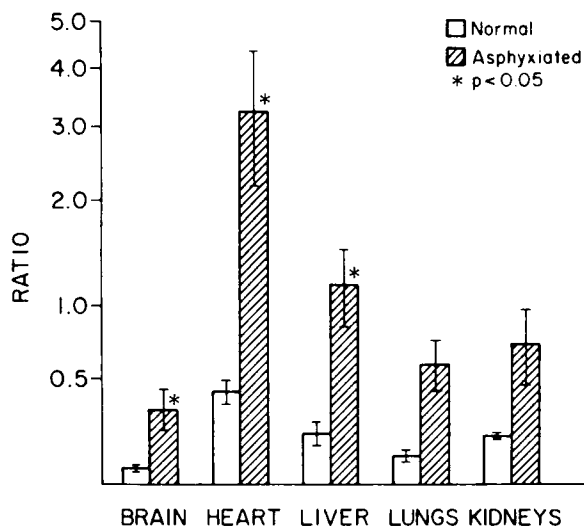


Fig. 1. Mean (\pm SE) for tissue-plasma ratios of lidocaine concentrations in the brain, heart, liver, lungs and kidneys in the nonasphyxiated (open bars) and asphyxiated (shaded columns) fetuses. $N = 5$ in each group. *Significantly different from the nonasphyxiated group.

§ Morishima HO, Pedersen H, Sakuma K, et al: Toxicity of lidocaine and etidocaine in the fetal newborn and adult sheep. Abstracts of Scientific Papers, Annual Meeting, American Society of Anesthesiologists, 1978, pp 343-344.

local anesthetics are weak bases with pK_a values ranging from 7.7 to 8.1.¹⁸ A decrease in extra- and intracellular pH causes conversion of the local anesthetic agent from the base to the cationic form. Therefore, when the fetus is acidotic, the drug will be trapped intracellularly, leading to an accumulation in tissues as demonstrated in this study. An additional factor may be the degree of protein binding of local anesthetics, which is influenced by pH ¹⁸; acidosis causes decreased binding of local anesthetic to serum albumin.

Circulatory changes may also affect tissue uptake of drugs. Cohn *et al.*¹⁹ studied the percentage distribution of cardiac output to various organs during both hypoxemic and hypoxemic-acidemic conditions in the fetal lamb. The proportion of cardiac output distributed to the placenta, brain, heart, and adrenals increased significantly, whereas that to the lungs, gut, kidney, spleen, and carcass was decreased. Similar results have also been obtained in the rhesus monkey.²⁰ An increased placental, cerebral, and coronary blood flow should increase the percentage of local anesthetic drug delivered to the liver, brain, and heart per unit time, which will again result in an enhanced uptake of the drug by these organs. Indeed, our study shows that the fetal liver, brain, and heart were the three organs in which the tissue-blood ratio of lidocaine was significantly higher in asphyxiated fetuses. The combination of increased delivery of local anesthetics to the brain and heart, decreased plasma protein binding, and intracellular ionic trapping probably account for the enhanced tissue uptake and the marked increase in the toxicity of lidocaine observed in the asphyxiated primate fetus in this study.

Finally, one might consider the "blood-brain barrier" as another possible factor altering uptake of the drug in the asphyxiated fetus. It has been shown that during experimental asphyxia there is a breakdown of the blood-brain barrier to such a compound as the albumin tracer, Evans blue.²¹

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References

- Morishima HO, Daniel SS, Finster M, et al: Transmission of mepivacaine hydrochloride (Carbocaine®) across the human placenta. *ANESTHESIOLOGY* 27:147-154, 1966
- Morishima HO, Heymann MA, Rudolph AM, et al: Transfer of lidocaine across the sheep placenta to the fetus: Hemodynamic and acid-base responses of the fetal lamb. *Am J Obstet Gynecol* 122:581-588, 1975
- Morishima HO, Heymann MA, Rudolph AM, et al: Toxicity of lidocaine in the fetal and newborn lamb and its relationship to asphyxia. *Am J Obstet Gynecol* 112:72-79, 1972
- Brown WU, Bell GC, Alper M: Acidosis, local anesthetics, and newborns. *Obstet Gynecol* 48:27-30, 1976
- Biehl D, Shnider SM, Levinson G, et al: Placental transfer of lidocaine: Effects of fetal acidosis. *ANESTHESIOLOGY* 48:409-412, 1978
- Morishima HO, Hyman AI, Adamsons K, et al: Anesthetic management for fetal operation in the subhuman primate. *Am J Obstet Gynecol* 110:926-933, 1971
- Soutter LP, Conway M, Parker D: A system for monitoring arterial oxygen tension in sick newborn babies. *Biomed Eng* 10:257-260, 1975
- Morishima HO, Daniel SS, Richards RT, et al: The effect of increased maternal Pa_{O_2} upon the fetus during labor. *Am J Obstet Gynecol* 123:257-264, 1975
- Morishima HO, Yeh M-N, James LS: Temperature gradient between fetus and mother as an index for assessing intra-uterine condition. *Am J Obstet Gynecol* 129:443-448, 1977
- Paton JB, Peterson E, Fisher DE, et al: Oxygen dissociation curves of fetal and adult baboons. *Respir Physiol* 12:283-290, 1971
- Keenaghan JB: The determination of lidocaine and prilocaine in whole blood by gas chromatography. *ANESTHESIOLOGY* 29:110-112, 1968
- Cardyro-Barica R, Sica-Blanco Y, Poseiro JJ, et al: A quantitative study of the action of synthetic oxytocin on the pregnant human uterus. *J Pharmacol Exp Ther* 121:18-31, 1957
- Finster M, Poppers PJ, Sinclair JC, et al: Accidental intoxication of the fetus with local anesthetic drug during caudal anesthesia. *Am J Obstet Gynecol* 92:922-924, 1965
- Morishima HO, Finster M, Pedersen H, et al: Pharmacokinetics of lidocaine in fetal and neonatal lambs and adult sheep. *ANESTHESIOLOGY* 50:431-436, 1979
- Morishima HO, Adamsons K: Placental clearance of mepivacaine following its administration to the fetus. *ANESTHESIOLOGY* 28:343-348, 1967
- Engleson S: The influence of acid-base changes on central nervous system toxicity of local anaesthetic agents. *Acta Anaesthesiol Scand* 18:79-87, 1974
- de Jong RH, Wagman IH, Prince DA: Effect of carbon dioxide on the cortical seizure threshold to lidocaine. *Exp Neurol* 17:221-232, 1967
- Burney RG, DiFazio CA, Foster JA: Effects of pH on protein binding of lidocaine. *Anesth Analg (Cleve)* 57:478-480, 1978
- Cohn HE, Sacks EF, Heymann MA, et al: Cardiovascular responses to hypoxemia and acidemia in fetal lambs. *Am J Obstet Gynecol* 120:817-824, 1974
- Behrman RE, Lees MH, Peterson EN, et al: Distribution of the circulation in the normal and asphyxiated fetal primate. *Am J Obstet Gynecol* 108:956-969, 1970
- Lou HC, Lassen NA, Tweed WA, et al: Pressure passive cerebral blood flow and breakdown of the blood-brain barrier in experimental fetal asphyxia. *Acta Paediatr Scand* 68:57-63, 1979