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Placental Transfer of Lidocaine:

Effects of Fetal Acidosis

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To investigate whether fetal acidosis increases the placental transfer of lidocaine, resulting in higher fetal blood levels of the drug, lidocaine was infused intravenously into ten pregnant ewes to maintain plasma levels of 2–4 μg/ml. After maternal–fetal equilibrium was reached, the fetus was made acidotic by infusing lactic acid intravenously. Fetal blood *p*H decreased from 7.35 to 7.10. With fetal acidemia, fetal blood lidocaine levels increased significantly from 1.60 ± 0.11 μg/ml to 2.72 ± 0.26 μg/ml. The fetal–maternal lidocaine ratio increased from 0.76 to 1.21. Correction of the acidosis by bicarbonate infusion returned the fetal–maternal ratios to control values. It is concluded that acidosis in the fetus may result in trapping of ionized lidocaine in the fetal circulation and increase the transfer of lidocaine across the placenta. (Key words: Anesthesia, obstetric; Anesthetics, local, lidocaine; Acid–base equilibrium, fetal; Toxicity, fetal.)

LIDOCAINE is a weak base (*p*K 7.86) and rapidly crosses the placenta in its unionized state.[1,2] The ratio of ionized to unionized drug increases with a decrease in *p*H. Brown *et al.*[3] recently described four newborns with increased blood levels of anesthetic at birth who were also acidotic. They postulated that these increased blood levels of local anesthetic resulted from increased conversion (trapping) of lidocaine to the ionized form. To determine the extent of accumulation of lidocaine in the acidotic fetus, the animal studies described below were undertaken.

Method

Studies were performed on ten pregnant ewes near term (mean gestational age 132 days; range 130–135 days). Each ewe carried a single fetus. All animals underwent preparatory surgical procedures while anesthetized with halothane in oxygen. Polyvinyl catheters (#8 French, 0.105 inch O.D.) were placed via a groin incision into a maternal femoral artery and vein. The arterial catheter was used for recording of maternal blood pressure (Statham P23 Ob) and heart rate, and blood sampling. A precalibrated, electromagnetic flow probe (Statham SP2022) was secured to a branch of a uterine artery via a midline abdominal incision. Through a small hysterotomy incision, a polyvinyl catheter (#4 French, 0.053 inch O.D.) was inserted into a fetal femoral artery for arterial sampling and measurement of blood pressure and heart rate, and into a fetal femoral vein for subsequent acid and bicarbonate infusion. An additional polyvinyl catheter (#8 French, 0.105 inch O.D.) was placed in the amniotic fluid cavity for continuous pressure measurements, using a Statham P23 Db strain gauge. The uterus was closed in a manner that prevented leakage of amniotic fluid.

At least 24 hours elapsed between the above preparations and the conduct of a study. Maternal and fetal blood pressure and pulse rate values and uterine blood flow were recorded continuously using a Grass polygraph recorder. Fetal blood pressure was corrected by subtracting intra-amniotic fluid pressure from fetal arterial pressure. Maternal and fetal arterial blood-gas and *p*H values were sampled at 15-min intervals. These variables were measured immediately after sampling, using an Instrumentation Laboratories 313 Blood Gas Analyzer, and corrected to maternal temperature, which was measured with a Yellow Springs rectal probe. Maternal and fetal base excess values were calculated using the Severinghaus slide rule.[4]

Studies were performed with the animal awake and standing quietly in her cage. Following a control interval of 30 min during which time maternal and fetal cardiovascular and acid–base values were stable, each study consisted of three sequential periods: a maternal lidocaine-infusion period, a maternal lidocaine-infusion and fetal acid-infusion period, and a maternal lidocaine-infusion and fetal bicarbonate-infusion period. The first period lasted 135 min. Lidocaine was infused into the mother at a rate of 0.25 mg/kg/min. Arterial blood was drawn at 15-min intervals from both mother and fetus for measurement of lidocaine using a modification of our gas chromatographic method.[5] This infusion period

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TABLE 1. Maternal and Fetal Cardiovascular Changes during Control and Lidocaine-infusion Periods with Percentage Change from Control during Acid and Bicarbonate Infusions to the Fetus (n = 10) (Mean ± SE)

	Control*	135 Min Lidocaine Infusion*	Acid Infusion to Fetus, Per Cent Change from Control				Bicarbonate Infusion to Fetus, Per Cent Change from Control			
			15 Min	30 Min	45 Min	60 Min	15 Min	30 Min	45 Min	60 Min
Mean arterial blood pressure (torr)										
Maternal	78.1 ± 3.2	80.5 ± 0.6	5.3 ± 1.4	7.7 ± 2.3	4.2 ± 2.0	5.3 ± 2.2	4.3 ± 2.6	3.6 ± 2.7	4.3 ± 2.7	7.4 ± 2.4
Fetal	41.9 ± 2.3	42.6 ± 0.3	27.1 ± 5.5†	25.8 ± 5.7†	23.9 ± 6.6†	28.8 ± 7.7†	35.7 ± 6.3†	27.7 ± 7.7†	22.4 ± 10.9†	16.1 ± 7.7
Heart rate (beats/min)										
Maternal	108 ± 3.9	105 ± 1.2	−3.2 ± 2.8	−2.5 ± 3.0	1.7 ± 3.4	1.4 ± 3.9	1.4 ± 3.9	0.1 ± 3.9	−2.7 ± 4.7	5.8 ± 6.0
Fetal	162 ± 4.9	158 ± 1.2	−5.9 ± 5.6	3.4 ± 5.5	1.3 ± 4.4	−3.6 ± 5.6	3.1 ± 5.9	0.8 ± 5.1	−7.1 ± 7.1	−11.4 ± 5.6
Uterine Blood flow (ml/min)	656 ± 74.8	582 ± 12.4	−12.9 ± 7.1	−12.9 ± 6.1	−11.2 ± 7.2	−12.9 ± 7.3	−11.9 ± 6.1	−13.8 ± 8.9	−4.0 ± 9.3	−9.5 ± 7.7

* Mean of values obtained at 5-minute intervals.
† $P < 0.05$ compared with 135-minute lidocaine-infusion period.

allowed maternal and fetal lidocaine levels to come into equilibrium. The infusion rate was continued unchanged during the second and third periods.

The second period lasted 60 min. We infused 2.5 M lactic acid in physiologic saline solution into the fetus to decrease fetal arterial blood *p*H from a mean of 7.31 ± 0.02 SE to 7.10 ± 0.02 (range 6.98–7.18). The total volume of lactic acid was approximately 10 ml, and the infusion rate was adjusted by measuring fetal blood *p*H at 3–5-min intervals. Maternal

TABLE 2. Maternal and Fetal Blood-Gas and Acid–Base Values during Control Period, Lidocaine-infusion Period, and during Periods of Acid Infusion and Bicarbonate Infusion to the Fetus (n = 10) (Mean ± SE)

	Control	135 Min Lidocaine Infusion*	Acid Infusion to Fetus				Bicarbonate Infusion to Fetus			
			15 Min	30 Min	45 Min	60 Min	15 Min	30 Min	45 Min	60 Min
*p*H										
Maternal	7.51 ± 0.01	7.51 ± 0.01	7.49 ± 0.01	7.50 ± 0.01	7.49 ± 0.01	7.48 ± 0.01	7.50 ± 0.01	7.51 ± 0.01	7.50 ± 0.01	7.49 ± 0.01
Fetal	7.34 ± 0.04	7.31 ± 0.02	7.12 ± 0.02†	7.10 ± 0.02†	7.07 ± 0.02†	7.08 ± 0.01†	7.27 ± 0.02	7.29 ± 0.02	7.29 ± 0.02	7.27 ± 0.02
Pa_{CO_2} (torr)										
Maternal	29.9 ± 1.0	29.5 ± 0.2	30.4 ± 1.0	29.8 ± 1.0	29.8 ± 0.8	32.1 ± 1.2	30.2 ± 0.6	29.0 ± 1.3	29.6 ± 1.2	28.9 ± 0.5
Fetal	41.3 ± 0.8	39.8 ± 0.4	49.0 ± 1.6†	47.2 ± 1.2†	47.1 ± 0.8†	45.2 ± 1.1†	46.7 ± 2.1†	46.1 ± 1.7†	47.5 ± 1.5†	45.4 ± 3.3†
Pa_{O_2} (torr)										
Maternal	106 ± 4.8	104 ± 0.4	104 ± 5.2	105 ± 4.4	103 ± 4.6	104 ± 5.6	102 ± 5.8	104 ± 5.1	102 ± 5.0	104 ± 6.8
Fetal	19.3 ± 1.8	20.1 ± 0.5	18.7 ± 1.6	18.4 ± 3.0	18.1 ± 1.9	18.3 ± 1.9	15.1 ± 2.2	16.2 ± 2.0	14.8 ± 1.8	12.8 ± 1.9
Base excess (mEq/l)										
Maternal	1.3 ± 1.0	0.3 ± 0.1	0.3 ± 1.0	0.1 ± 1.1	−0.2 ± 0.9	0.2 ± 1.1	0.3 ± 1.0	−0.4 ± 1.2	0.8 ± 0.4	0.4 ± 0.6
Fetal	−3.9 ± 0.6	−6.2 ± 0.3†	−16.0 ± 0.3†	−15.5 ± 1.1†	−17.0 ± 1.1†	−17.5 ± 1.0†	−5.6 ± 1.3	−4.2 ± 1.4	−5.0 ± 0.8	−6.5 ± 1.8

* Mean of values obtained at 15-minute intervals.
† $P < 0.05$ compared with 135-minute lidocaine-infusion period.

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and fetal arterial blood lidocaine concentrations, blood-gas and acid–base variables were measured at 15-min intervals.

The final experimental period lasted 60 min. Sodium bicarbonate, 0.1 M, was infused into the fetus to return fetal blood *p*H to the control value and maintain the *p*H in a range of 7.28–7.35. The total volume of bicarbonate infused was approximately 20 ml. The infusion rate was adjusted by measuring fetal blood *p*H at 3–5 min intervals. Maternal and fetal arterial lidocaine concentrations and blood gas and acid–base values were measured at 15-min intervals. The volume of blood required for sampling from the mother and fetus was 1 ml at each 15-min interval. Total blood volume removed from the fetus during the experiment was 25 ml or less, thus representing less than 5 per cent of the estimated fetal blood volume.[6]

All cardiovascular values (table 1) during the fetal acid- and bicarbonate-infusion periods are given as percentage changes from the values obtained during the initial maternal lidocaine-infusion period. One-way analysis of variance was used to examine the cardiovascular and blood-gas data for statistical significance. Fetal–maternal lidocaine ratios were compared using Student's t test for paired data. $P < 0.05$ was considered significant.

Results

Control maternal and fetal blood pressure, pulse rate, uterine blood flow and acid–base values remained stable during the initial 135-min lidocaine infusion (tables 1 and 2). The mean maternal blood lidocaine level was 2.25 ± 0.13 (SE) μg/ml (range 0.81–4.60 μg/ml) (table 3). The mean fetal blood lidocaine level was 1.60 ± 0.11 μg/ml (range 0.65–4.0 μg/ml), giving a mean fetal–maternal lidocaine ratio of 0.76 ± 0.05. Acid infusion decreased fetal base excess 10 mEq/l and increased fetal Pa_{CO_2} 5–10 torr, giving an average *p*H of 7.10 (table 2). Fetal blood pressure increased almost 30 per cent (table 1). Maternal blood pressure, pulse rate, uterine blood flow and acid–base status were unchanged. Lactic acid infusion into the fetus significantly increased fetal arterial blood lidocaine concentration by 30 min (table 3). Maternal blood lidocaine levels did not change, and thus, the mean fetal–maternal ratio for lidocaine increased significantly from 0.76 ± 0.05 to 1.10 ± 0.08 (fig. 1).

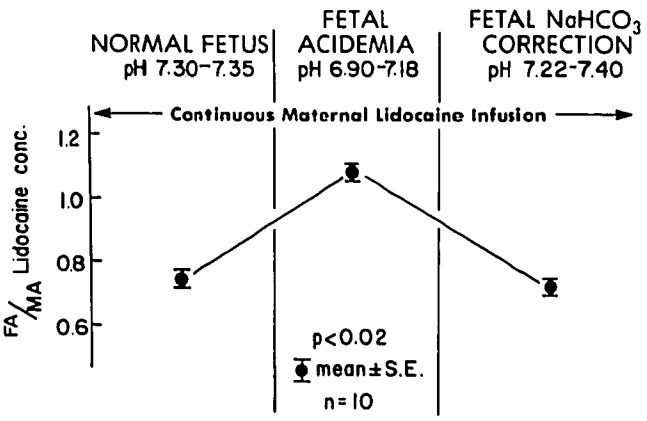

FIG. 1. Fetal–maternal arterial (FA/MA) lidocaine ratios were significantly higher ($P < 0.02$) during fetal acidemia than during control or during *p*H correction with bicarbonate.

Bicarbonate infusion returned fetal base excess and *p*H to control values. Fetal Pa_{CO_2} and blood pressure remained above normal. Maternal hemodynamic and acid–base status were unchanged. The fetal–maternal lidocaine concentration ratios rapidly decreased to control values, producing a mean fetal–maternal ratio of 0.75 ± 0.03, a value equalling that found in the control period (fig. 1).

Discussion

In the pregnant ewe, fetal acidemia increased fetal arterial blood levels of lidocaine and the fetal–maternal lidocaine concentration ratio. This phenomenon may be explained by the preferential

TABLE 3. Mean Maternal and Fetal Arterial Lidocaine Concentrations and Fetal/Maternal Concentration Ratios during Lidocaine Infusion and Acid and Bicarbonate Infusion to the Fetus (n = 10) (Mean ± SE)

	135 Min Lidocaine Infusion*	Acid Infusion to Fetus				Bicarbonate Infusion to Fetus			
		15 Min	30 Min	45 Min	60 Min	15 Min	30 Min	45 Min	60 Min
Maternal arterial level (μg/ml)	2.25 ± 0.13	2.50 ± 0.18	2.64 ± 0.25	2.42 ± 0.26	2.28 ± 0.18	2.58 ± 0.20	2.35 ± 0.10	2.44 ± 0.15	2.25 ± 0.25
Fetal arterial level (μg/ml)	1.60 ± 0.11	2.26 ± 0.26	2.72 ± 0.26	2.52 ± 0.28	2.60 ± 0.35	1.85 ± 0.22	1.76 ± 0.16	1.74 ± 0.15	1.67 ± 0.25
FA/MA ratio (mean)	0.76 ± 0.05	0.90 ± 0.03	1.05 ± 0.05†	1.21 ± 0.04†	1.14 ± 0.04†	0.73 ± 0.06	0.74 ± 0.05	0.72 ± 0.04	0.76 ± 0.05

* Mean of values taken at 15-minute intervals.
† $P < 0.05$ compared with 135-minute lidocaine-infusion period.

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distribution of weak bases from a region of high *p*H to a region of low *p*H.[1,7] This effect of *p*H on weak bases certainly plays a significant role in determining the distribution and excretion of local anesthetics in other tissues.[6,7] For instance, gastric lavage decreases the blood levels of local anesthetic in newborns with toxic levels of these drugs.[8–10] The acidic *p*H of the gastric aspirate traps the local anesthetic in the ionized form. Alterations of urinary *p*H may be used to hasten excretion of drugs in their ionized form.[7]

Morishima *et al.* observed increased blood lidocaine levels in fetal lambs that had inadvertently become asphyxiated.[11] The acidotic fetuses had blood levels of lidocaine significantly higher than those in non-asphyxiated fetuses. The work of this group, as well as our own, supports the thesis that acidotic fetuses will accumulate lidocaine. The phenomenon of ion-trapping of weak bases in an acidic medium is a logical explanation for these findings. Furthermore, acidemia decreases local anesthetic protein binding by blood, thereby increasing the proportion of free drug available for entry into vital tissues, such as the brain and heart. Such an effect of acidosis on bilirubin protein binding[12–14] has been observed. On the other hand, blood levels of local anesthetic with induced acidemia may not accurately reflect tissue levels. The increased fetal blood lidocaine concentration may, in fact, represent a decreased fetal tissue concentration during the period of fetal blood acidification.

The study reported by Brown[3] would suggest that clinically the ion-trapping phenomenon may occur during prolonged labor with fetal distress. The increased blood levels of local anesthetic in this study were still less than what are considered toxic to the newborn. However, it does seem prudent to consider that this trapping mechanism may be important in some clinical situations. Prolonged labor with evidence of fetal distress may create profound fetal acidosis and significant trapping by the fetus of local anesthetics. In such situations, regional anesthesia with ester-type local anesthetics, which are rapidly metabolized in maternal blood and not transferred to the fetus, may be preferable.

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