

Gestational Differences in Lidocaine Toxicity in the Fetal Lamb

K. Teramo, M.D.,* N. Benowitz, M.D.,† M. A. Heymann, M.D.,‡ A. M. Rudolph, M.D.§

Effects of lidocaine on arterial pressure, heart rate and electrocortical activity were studied in nine fetal lambs at 0.77 to 0.92 gestation (116 to 138 days of gestation; term in sheep is 150 days). Lidocaine was administered into a fetal femoral vein either as a continuous infusion or as a bolus injection. Epileptiform activity was observed in all fetuses both after continuous infusion and after bolus injection of lidocaine. Fetal arterial concentrations of lidocaine at the time of the first epileptiform discharge during continuous infusion ranged from 6.9 to 40.0 $\mu\text{g/ml}$, and correlated negatively with gestational age ($\bar{Y} = -1.727 \times +242.7$; $r = -0.94$). The increases in fetal mean arterial pressure during epileptiform bursts correlated directly with the gestational age ($\bar{Y} = 1.27 \times -150.0$; $r = 0.91$). The convulsive doses of lidocaine in-

jected as a bolus ranged from 8.0 to 34.1 mg/kg, and correlated negatively with gestational age ($\bar{Y} = -0.991 \times +144.9$; $r = -0.88$). The increased sensitivity to lidocaine of the fetal central nervous system with advancing gestation probably reflects differences in fetal brain development. The increase in cardiovascular responses to epileptiform activity with advancing gestation could be related to differences either in the strength of epileptiform discharges or in permeability of the blood-brain barrier to lidocaine, or to immaturity of the autonomic nervous supply to the cardiovascular system in young fetuses. (Key words: Brain, fetal convulsions, lidocaine; Anesthetics, local; lidocaine; Toxicity, fetal, convulsions; Anesthesia, obstetric, fetal convulsions.)

* Recipient of research fellowship of Bay Area Heart Research Committee, San Francisco. Present address: Department of Obstetrics and Gynecology, University of Helsinki, 00290 Helsinki 29, Finland.

† Research Fellow, Division of Clinical Pharmacology, University of California, San Francisco. Present address: Acute Detoxification Study Unit, San Francisco General Hospital, San Francisco, California 94110.

‡ Associate Professor of Pediatrics and Obstetrics and Gynecology. Associate Staff Member, Cardiovascular Research Institute. Recipient of United States Public Health Service Research Career Development Award (HD-35398) from the National Institute of Child Health and Human Development.

§ Professor of Pediatrics, Physiology and Obstetrics and Gynecology. Senior Staff Member, Cardiovascular Research Institute.

Received from the Cardiovascular Research Institute and the Departments of Pediatrics and Physiology, and the Division of Clinical Pharmacology, Department of Medicine, University of California, San Francisco Medical Center, San Francisco, California 94143. Accepted for publication October 13, 1975. Supported by United States Public Health Service Grants HL-06285 and GM-01791. Presented in part before the Scandinavian Society of Gynecology and Obstetrics, Uppsala, Sweden, June 6, 1974; and before the European Society of Perinatal Medicine, Prague, Czechoslovakia, August 29, 1974.

Address reprint requests to: Kari Teramo, M.D., Department of Obstetrics and Gynecology, University of Helsinki, 00290 Helsinki 29, Finland.

WE HAVE RECENTLY demonstrated that intravenous administration of lidocaine to fetal lambs produces fetal epileptiform cortical activity.¹ This epileptiform activity is closely associated with marked changes in fetal arterial blood pressure and heart rate in lambs at 0.83 gestation (124 days; term in sheep is 150 days) or more. Here we present evidence that the responses of the central nervous system to lidocaine in the fetal sheep are related to gestational age; advancing gestation is associated with increasing sensitivity to lidocaine.

Materials and Methods

Nine time-dated pregnant sheep at 0.77–0.92 gestation (116–138 days) were prepared for chronic observations of the fetuses. Using techniques we have described previously, we inserted polyvinyl catheters into a fetal femoral vein and artery and, in some instances, a carotid artery.¹ A catheter was also implanted in the amniotic cavity for recording of amniotic pressure and into the fetal trachea for recording of tracheal pressure. In all fetuses two electrodes were fixed with screws through the parietal skull bone for recording of fetal electrocortical activity. The screws

TABLE 1. Data on Seven Fetal Lambs That Received Lidocaine by Continuous Infusion

Fetus	Gestational Age (Days)	Weight (g)	Continuous Infusion of Lidocaine		
			Rate of Infusion (mg·min ⁻¹ ·kg ⁻¹)	Duration of Infusion (Min)	Fetal Arterial Concentration of Lidocaine at Onset of Epileptiform Activity (μg/ml)
1	118	2,500	3.28 6.4	60 9	40.0
2	120	2,050	1.34 2.53 3.05	73 54 37	30.0
3	124	2,250	2.33 4.85	65 11	35.0
4	130	3,000	1.36 2.04	100 94	16.9
5	133	5,030	0.74 1.64	70 92	12.5
6	134		0.96 2.04	65 48	6.9
	135	4,000	1.98	96	13.0
7	138	3,300	1.25	33	Not recorded

were placed 1.5 cm apart in the sagittal plane, 1 cm from the mid-line, and covered with dental cement. The catheters and electrodes were led through the maternal abdominal wall to the flank and protected with a Teflon cloth pocket. At least three days were allowed for recovery from the operation before the studies were performed. Only fetuses in

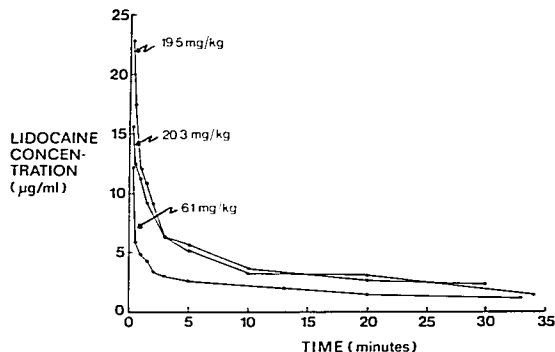
which pH of blood was 7.30 or higher at the time of study are included in this report.

Seven fetuses received lidocaine (Xylocaine, Astra) by continuous intravenous infusion into a femoral vein, until epileptiform activity was evident on the electrocortical recording; one fetus received two infusions on separate days (Table 1). We have

TABLE 2. Data on Eight Fetal Lambs That Received Lidocaine as a Bolus Injection

Fetus	Gestational Age (Days)	Weight (g)	Bolus Injection of Lidocaine	
			Range of Dose (mg/kg)	Convulsive Dose (mg/kg)
1	117 120	2,500	12.0-32.0 8.0-20.0	32.0 20.0
2	118	2,050	4.9-34.1	34.1
3	123	2,250	8.9-22.2	22.2
4	131	3,000	10.0-20.0	20.0
5	135	5,030	4.0-8.0	8.0
7	136 138	3,300	3.3-12.1 6.6-9.1	12.1 9.1
8	116	1,970	5.1-30.5	30.5
9	124	2,850	3.5-14.0	14.0

FIG. 1. Arterial lidocaine concentrations 15 sec to 35 min after bolus injections of lidocaine into the femoral vein in three fetal lambs (fetuses 1, 8, and 9). The dose of lidocaine (mg/kg fetal weight) is indicated in each case.



previously shown that continuous lidocaine infusion at a rate of $1 \text{ mg} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ into a fetal femoral vein for 50 minutes produces a lidocaine concentration of approximately $10 \text{ } \mu\text{g/ml}$ in fetal arterial blood.¹ Concentrations of $10 \text{ } \mu\text{g/ml}$ or more produce epileptiform cortical activity in most fetal lambs older than 124 days of gestation.¹ The amounts of lidocaine infused in the present series ranged from 0.74 to $6.4 \text{ mg} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$. The rate of infusion was approximately doubled after 48 to 100 minutes, if no epileptiform cortical activity was observed (table 1).

Single bolus injections of 1 to 2 per cent lidocaine were injected within 5 seconds into the femoral vein in eight fetuses (table 2). In six of these fetuses in which continuous infusions were also given, the studies were performed on different days. The initial doses ranged from 10 to 30 mg lidocaine, 30 to 60 min after which the dose was increased by 10-mg increments until epileptiform activity was observed on the fetal electrocortical recording; this was considered the convulsive dose for the fetus. Because arterial lidocaine levels decrease rapidly, probably in part because lidocaine is rapidly transferred from the fetus to the mother after fetal intravenous injection (fig. 1), it is possible to repeat the bolus injection after 30 to 60 minutes. During the interval between injections, arterial pressure, heart rate, and acid-base values returned to control levels.

Serial samples of fetal arterial blood were

obtained for measurement of lidocaine, pH, P_{O_2} , and P_{CO_2} . Lidocaine concentrations in whole blood were determined with a gas chromatograph after ether extraction; 2-diethylamino-3'-bromo-acetanilide was used as the internal standard.² pH and blood-gas measurements were made on fetal arterial blood at 39 C using a Radiometer blood-gas analyzer with appropriate electrodes. Fetal arterial blood pressure and tracheal and amniotic pressures were measured with Statham P₂₃D pressure transducers, and heart rate was recorded from the arterial pulse wave using a cardiograph. Mean arterial pressure was calculated from the systolic and diastolic pressures with the formula: mean arterial pressure = diastolic pressure + $\frac{1}{3}(\text{systolic pressure} - \text{diastolic pressure})$. Pressures, heart rate and fetal electrocortical activity were continuously recorded with a Beckman Dynograph multichannel direct-writing oscillograph.

Results

Data for fetuses 4-9 have been published in part previously.¹ These fetuses are included in this report because it became clear after further studies that there were differences between immature and mature fetal lambs in both the concentration of lidocaine at which epileptiform activity occurred and the cardiovascular responses associated with the epileptiform activity.

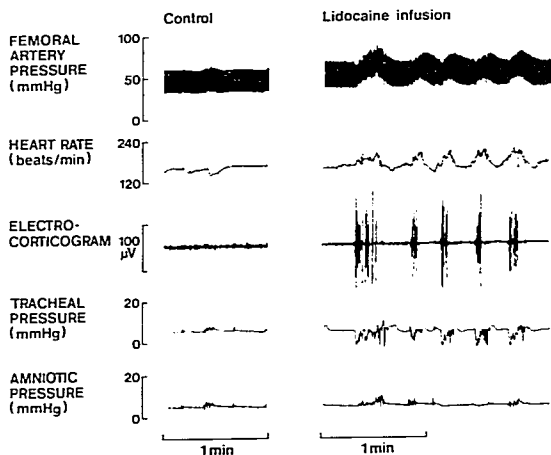


FIG. 2. Recordings from a fetal lamb of 0.87 (130 days) gestation (fetus 4) before and during lidocaine-induced epileptiform activity. Note deep fetal respiratory movements in association with each epileptiform discharge (compare with figure 3).

CONTINUOUS LIDOCAINE INFUSION

Epileptiform activity was produced in all seven fetuses during lidocaine infusion. The epileptiform discharges occurred in short bursts lasting 5 to 45 seconds. They consisted of clusters of polyspikes of high

amplitude with a mean frequency of 3 to 4 cycles per second. After each epileptiform discharge the fetal electrocortical tracing became isoelectric. We have described the fetal epileptiform activity during lidocaine infusion in detail elsewhere.¹

In five of the seven fetuses arterial blood

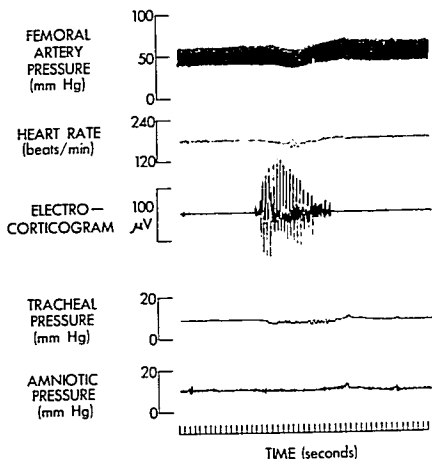


FIG. 3. Recordings from a fetal lamb of 0.78 (117 days) gestation (fetus 1) during lidocaine-induced epileptiform activity. Note only minimal respiratory movements in association with the epileptiform discharge (compare with figure 2).

pressure increased acutely with each epileptiform burst (fig. 2). In the two youngest fetuses (118 and 120 days of gestation) only minimal changes in arterial blood pressure occurred during the epileptiform activity (fig. 3). The respiratory movements associated with each epileptiform burst were considerably stronger in the older (fig. 2) than in the younger fetuses (fig. 3). There was a significant correlation between gestational age and the magnitude of the increase in fetal mean arterial blood pressure during the phasic hypertensive episodes associated with lidocaine-induced epileptiform activity (fig. 4).

Concentrations of lidocaine in fetal arterial blood ranged from 6.9 to 40.0 $\mu\text{g/ml}$ at the time of the first epileptiform discharge during lidocaine infusion. The younger the fetus, the higher the lidocaine concentration in arterial blood at which epileptiform discharges were first induced (fig. 5).

BOLUS INJECTION OF LIDOCAINE

With bolus injections of lidocaine the doses required to produce epileptiform activity ranged from 8.0 to 34.1 mg/kg fetal weight. There was a highly significant negative correlation between the convulsive dose of lidocaine and gestational age (fig. 6). One fetus died acutely without epileptiform discharge after a bolus injection of 25.4 mg/kg given during a second study three days after the first experiment.

Discussion

Very little is known about the epileptogenic properties of the fetal brain. Bernhard *et al.*³ observed that electrical stimulation caused epileptiform cortical activity in exteriorized sheep fetuses older than 90 days of gestation (0.6 term). However, pentylentetrazol (Metrazol) caused epileptiform cortical activity in fetal lambs as young as 65 days of gestation (0.43 term). Mann *et al.*⁴ recorded cortical activity in sheep fetuses after 120 to 143 days of gestation during fetal intravenous administration of lidocaine as a bolus injection in doses of as much as 36.8 mg/kg fetal weight. They observed transient inhibition of fetal cortical activity but no epileptiform activity. We have previously reported on the induction of epileptiform activity by lidocaine in fetal lambs.¹ The difference between our findings

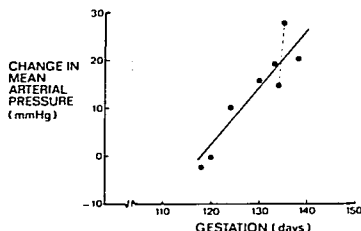


FIG. 4. Relationship between change in fetal mean arterial pressure during lidocaine-induced fetal epileptiform activity and gestational age. Each point represents the mean change during the first six epileptiform bursts ($\bar{Y} = 1.27 \times -150.0$; $r = 0.91$). Points connected with a line represent data from the same fetus.

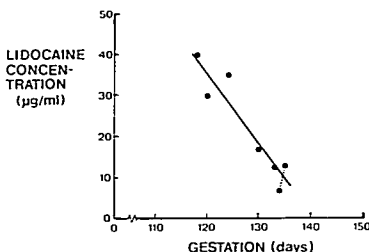


FIG. 5. Correlation between the concentration of lidocaine in fetal arterial blood at the time of the first epileptiform activity and gestational age ($\bar{Y} = -1.727 \times +242.7$; $r = -0.94$). Points connected with a line represent data from the same fetus.

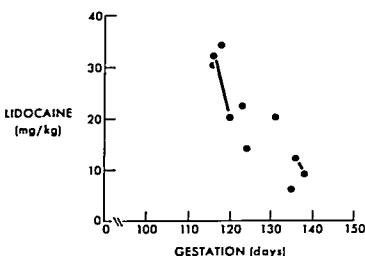


FIG. 6. Correlation between the convulsive dose of lidocaine (mg/kg fetal weight) and gestational age ($\bar{Y} = -0.991 \times +144.9$; $r = -0.88$). Points connected with a line represent data from the same fetus.

and those of Mann *et al.*⁴ may be explained by the fact that the ewes were anesthetized in their studies. This could have prevented the fetal epileptiform discharge since volatile anesthetics increase the seizure threshold to local anesthetics in adult animals.^{5,6} We delayed our experimental observations for three days after the surgical procedure because it has been shown that the spontaneous electrocortical activity of fetal sheep after an operation for catheter insertion returns to normal within two days.⁷

Although epileptiform activity occurred in all fetuses studied, there was more than a fivefold difference in the fetal arterial blood concentrations of lidocaine at which epileptiform activity first occurred during continuous lidocaine infusion, and more than a fourfold difference in the convulsive doses of lidocaine injected as a bolus, between the youngest and the oldest fetuses. These observations raise questions regarding the toxic effects of lidocaine and the maturation of the central nervous system. The greater toxicity in the older fetuses could be related to an increased rate of entry of lidocaine into the neural tissues. It would thus be helpful to know the relationship between tissue concentration of lidocaine in the brain as compared with blood concentration in younger and older fetuses. Another possible explanation for the increasing sensitivity of the brain to lidocaine with advancing gestation is that there is either an increase in the number of individual neurons, or an increase in the sensitivity of individual neurons.

The fetal epileptiform bursts induced by lidocaine precede acute increases in fetal blood pressure and heart rate by approximately 1 to 2 seconds.¹ The acute increases in blood pressure and heart rate associated with epileptiform activity occur similarly in fetuses paralyzed with succinylcholine.¹ This suggests that the cardiovascular changes in the oldest fetuses resulted from

central stimulation of the autonomic nervous system. The lack of response of blood pressure and heart rate during epileptiform activity in the youngest fetuses could possibly be explained on the basis of a weaker epileptiform stimulation. The weak gasping movements in the younger fetuses during epileptiform discharges support this hypothesis. However, it could well be related to lack of maturity of the autonomic nervous supply to the cardiovascular system. Sympathetic innervation of the heart in the fetal lamb begins to appear at about 0.6 gestation.⁸ It is not known at what age sympathetic innervation of systemic resistance vessels develops in the lamb. Differences in cardiovascular responses to epileptiform bursts in fetal lambs of different gestational ages could reflect differences in the development of autonomic innervation.

References

1. Teramo K, Benowitz N, Heymann MA, et al: Effects of lidocaine on heart rate, blood pressure and electrocorticogram in the fetal sheep. *Am J Obstet Gynecol* 118:935-949, 1974
2. Benowitz N, Rowland M: Determination of lidocaine in blood and tissues. *ANESTHESIOLOGY* 39:639-641, 1973
3. Bernhard CG, Kaiser IH, Kolmodin GM: On the epileptogenic properties of the fetal brain. *Acta Paediatr* 51:81-87, 1962
4. Mann LI, Bailey C, Carmichael A, et al: Effect of lidocaine on fetal heart rate and fetal brain metabolism and function. *Am J Obstet Gynecol* 112:789-795, 1972
5. de Jong RH, Heavner JE, de Oliveira LF: Nitrous oxide elevates local anesthetic seizure threshold. *Exp Neurol* 35:558-564, 1972
6. Stanivski JA, Aldrete JA: The effects of inhalation agents on convulsant (LD-50) doses of local anesthetics in the rat. *Can Anesth Soc J* 17:602-606, 1970
7. Scibetta JJ, Fox HE, Chik L, et al: On correlating the fetal heart and brain in the sheep. *Am J Obstet Gynecol* 115:946-952, 1973
8. Lebowitz EA, Novick JS, Rudolph AM: Development of myocardial sympathetic innervation in the fetal lamb. *Pediatr Res* 6:887-893, 1972