

## Toxicity of Lidocaine in Adult, Newborn, and Fetal Sheep

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The relative central nervous system and cardiovascular toxicity of lidocaine was compared in adult, newborn, and fetal sheep during continuous infusion of lidocaine into the jugular vein at the rate of  $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . An identical sequence of toxic manifestations occurred in the adult, newborn, and fetus: convulsions, hypotension, respiratory arrest, and circulatory collapse. Doses necessary to produce these manifestations were highest in fetuses and lowest in adults. For example, in order to elicit convulsions,  $5.8 \pm 1.8 \text{ mg/kg}$  of lidocaine was required in the adults,  $18.4 \pm 2.2$  in the newborns, and  $41.9 \pm 6.0$  in the fetuses. Measurements of lidocaine concentrations in blood demonstrated that these toxic symptoms occurred at levels which were not significantly different among the three groups. The results indicate that fetal and newborn lambs are no more sensitive to lidocaine toxicity than are adult sheep. The fact that the highest doses were required in the fetuses is probably related to the placental clearance of the drug into mothers and better fetal maintenance of arterial  $\text{P}_{\text{O}_2}$  despite convulsions and respiratory arrest (cessation of breathing-like movements). (Key words: Anesthetics, local; lidocaine. Brain: convulsions. Toxicity: cardiac; convulsions, fetal; neurotoxicity.)

LOCAL ANESTHETIC DRUGS are probably the most commonly used agents in obstetric anesthesia today. Since these agents are easily transferred across the placenta, their concentrations in newborn are sometimes sufficiently high to cause depression.<sup>1,2</sup> Accidental in-

jection and severe intoxication of the fetus also has been reported during an attempted induction of caudal, paracervical, or pudendal block in the mother. Nonetheless, most of the affected infants survived and thrived.<sup>3,4</sup> It has been generally assumed that the fetus and neonate are more vulnerable to intoxication with amide local anesthetics than adults because of the immaturity of their liver and kidney.<sup>5</sup> This study was undertaken in order to determine if differences in susceptibility to local anesthetic intoxication do exist between the ovine adult, newborn, and fetus. In addition, the comparative sensitivity of the central nervous and cardiovascular systems to local anesthetics was evaluated. Recently, it has been suggested that the cardiovascular system may be more vulnerable to the toxic effects of certain local anesthetic drugs than previously suspected.<sup>6</sup>

### Materials and Methods

Ten nonpregnant adult sheep, weighing  $52 \pm 2.1 \text{ kg}$  (mean  $\pm$  SE), and ten newborn lambs, as well as nine pregnant ewes and their fetuses ( $58 \pm 3.2 \text{ kg}$ ) were used. The newborn lambs, born vaginally at term, were 1-5 days old (average 2.8 days), and weighed  $4.3 \pm 0.5 \text{ kg}$ . The fetal age at the time of the experiment ranged from 126 to 145 days (average 132 days, term 148 days), and the mean weight was  $3.5 \pm 0.3 \text{ kg}$ . For preparation of the adult and newborn, polyethylene catheters were placed in a carotid artery and jugular vein, and also into the intrapleural space for monitoring of respiratory movements. These procedures were carried out following local infiltration with 2-chloroprocaine. For the fetal preparations, the pregnant ewes underwent hysterotomy under spinal anesthesia with tetracaine hydrochloride, supplemented as necessary with an intravenous infusion of thiopental. Catheters were placed in a carotid artery, jugular vein, and the trachea of each fetus. In addition, two EEG electrodes were implanted in the fetal scalp overlying both parietal lobes in order to identify seizure activity. Prior to uterine closure, a catheter was inserted into the amniotic cavity for monitoring and recording of amniotic fluid pressure. A femoral artery and vein of each mother were also catheterized. All catheters were kept in a pouch. They were flushed and filled with heparinized saline solution daily. In the adults and newborns, experiments were performed 1-10 days after surgery; fetuses were

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TABLE 1. Mean  $\pm$  SE Preinfusion Values for Heart Rate, Mean Arterial Pressure,  $pH_a$ ,  $P_{aCO_2}$  and  $P_{aO_2}$  in Nonpregnant Adults, Newborns, Fetuses, and Mothers

	Nonpregnant Adult (n = 10)	Newborn (n = 10)	Fetus (n = 9)	Mother (n = 9)
Heart rate (beats/min)	101 $\pm$ 9	200 $\pm$ 11	176 $\pm$ 7	120 $\pm$ 9
Mean arterial pressure (torr)	96 $\pm$ 6	82 $\pm$ 7	49 $\pm$ 5	115 $\pm$ 5
$pH_a$	7.48 $\pm$ 0.01	7.40 $\pm$ 0.02	7.40 $\pm$ 0.01	7.52 $\pm$ 0.02
$P_{aCO_2}$ (torr)	36 $\pm$ 1	41 $\pm$ 2	42 $\pm$ 3	33 $\pm$ 2
$P_{aO_2}$ (torr)	86 $\pm$ 1	77 $\pm$ 6	19 $\pm$ 2	93 $\pm$ 3

studied from 3–25 days (average 9 days) after operation.

During the experiment, the animals were restrained in a cart. All catheters were connected to Statham® pressure transducers. Maternal and fetal arterial blood pressure and heart rate, and in the fetus, respiratory movements, as well as electrocortical activity, were monitored and recorded continuously. The arterial pulse waves served as input for the cardiometer. In the newborns, colonic temperature was maintained at 39–40° C with a radiant heater in order to avoid metabolic acidosis due to hypothermia.<sup>7</sup>

Lidocaine hydrochloride, 2 mg·kg<sup>-1</sup>·min<sup>-1</sup>, was infused continuously into the jugular vein until circulatory collapse was evident on the arterial pressure and

heart rate recordings. To determine fetal infusion rates, the fetal weight was estimated on the basis of a composite curve of average weights of fetal lambs in relation to gestational age, obtained from two reported studies.<sup>8,9</sup> Subsequent weighing after delivery confirmed the fetal infusion rates of the drug to have been 2  $\pm$  0.3 mg·kg<sup>-1</sup>·min<sup>-1</sup>.

Arterial blood samples (1.5 ml) were withdrawn prior to the experiment and at the onset of the following major signs of intoxication: convulsions, hypotension, respiratory arrest, and circulatory collapse, which were generally seen in that sequence in all animals. No respiratory support was given. Arterial blood samples were also obtained simultaneously from each mother when lidocaine was infused to the fetus. All samples were analyzed for lidocaine concentrations using a gas chromatographic technique<sup>10</sup> as well as for  $pH$ ,  $P_{CO_2}$  and  $P_{O_2}$  using Radiometer microelectrodes and a Radiometer gas analyzer.

Eight analyses of variance were carried out to compare the mean doses and mean concentrations of lidocaine associated with each manifestation of toxicity between all three age groups.  $P < 0.05$  was considered significant. Where the overall analysis of variance showed significance, Tukey's method of multiple comparisons was used to identify pair-wise differences between individual age groups.

## Results

All animals were in a normal cardiovascular and acid-base state<sup>11</sup> prior to the infusion of lidocaine (table 1). A virtually identical sequence of symptoms of local anesthetic intoxication occurred in all animals during the continuous infusion of lidocaine, namely: convulsions, hypotension, respiratory arrest, and finally, circulatory collapse. Hypotension was defined as decrease of systolic blood pressure of 20 per cent or greater from the preinfusion value. Circulatory collapse was diagnosed at the disappearance of the arterial pressure wave. In adults and newborns, shivering, fasciculations and twitching were followed by tonic-clonic convulsions which were associated with hypertension and tachycardia (fig. 1). In the fetuses,

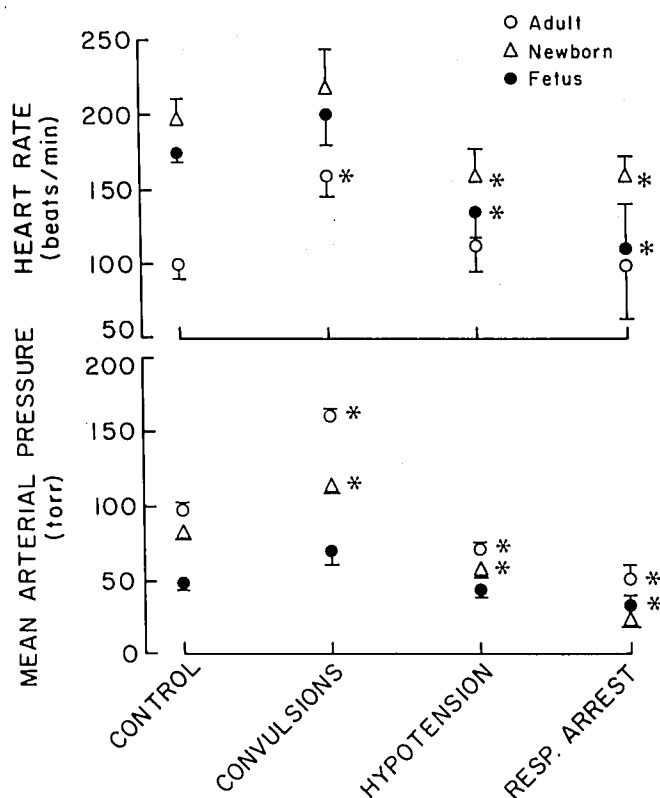


FIG. 1. Mean  $\pm$  SE heart rate and mean arterial pressure in adult, newborn and fetal sheep before and during toxic manifestations. \*Significantly different from preinfusion values.

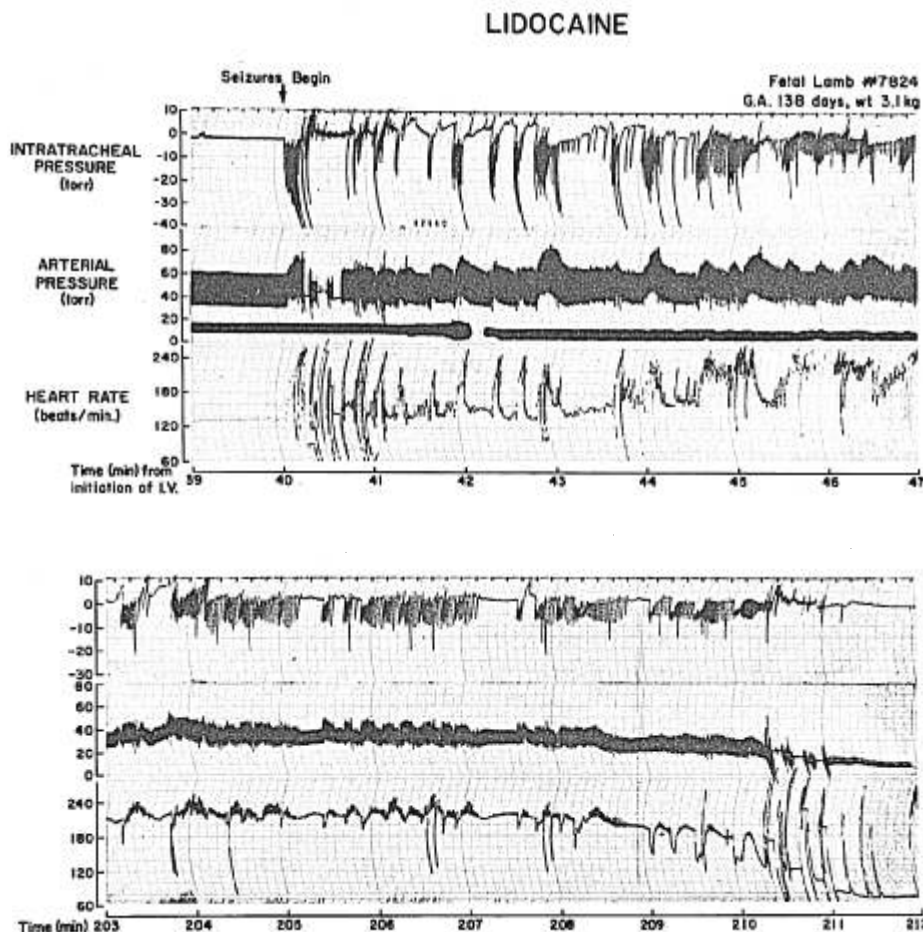


FIG. 2. Record of intratracheal pressure, arterial pressure and heart rate in the fetal lamb during continuous infusion of lidocaine ( $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) into the jugular vein. Note an abrupt onset of gasping accompanied by an increase in arterial pressure and heart rate which were seen shortly after the onset of seizure activity. Gasping continued with infusion until cardiovascular collapse began at 210 min.

seizure-like activity was manifested by the abrupt appearance of an irregular EEG wave pattern of large amplitude and low frequency. This was accompanied by an increase in arterial pressure and heart rate. Figure 2 displays a typical record of vital signs and breathing-like movements in the fetuses. Gasping patterns occurred when lidocaine concentrations reached toxic levels. As lidocaine infusion was maintained, convulsions continued intermittently in all animals followed by other signs of toxicity. Progressive hypotension and bradycardia developed, followed by respiratory depression and arrest. Finally, circulatory collapse and cardiac asystole were the terminal manifestations of lethal lidocaine intoxication. No attempt was made

to resuscitate the animals or to provide respiratory or circulatory support.

The mean dosages and blood levels of lidocaine necessary to produce each toxic manifestation are summarized in tables 2 and 3. The mean toxic dose varied between the different age groups. The adult sheep demonstrated convulsive activity at a mean dose of  $5.8 \pm 1.8 \text{ mg/kg}$  of lidocaine. Significantly higher doses of lidocaine were required to produce convulsions in the newborns ( $18.4 \pm 2.2 \text{ mg/kg}$ ) and the fetuses ( $41.9 \pm 6.0 \text{ mg/kg}$ ) ( $P < 0.01$ ). Similar differences in relative doses needed for cardiovascular depression were seen between the three groups (table 2).

TABLE 2. Mean Doses ( $\pm$ SE) of Lidocaine (mg/kg) Necessary to Produce Toxic Manifestations

	Convulsions	Hypotension	Respiratory Arrest	Circulatory Collapse
Adult (n = 10)	$5.8 \pm 1.8$	$31.2 \pm 2.6$	$32.4 \pm 2.8$	$36.7 \pm 3.3$
Newborn (n = 10)	$18.4 \pm 2.2$	$57.0 \pm 6.3$	$64.8 \pm 6.4$	$66.9 \pm 5.9$
Fetus (n = 9)	$41.9 \pm 6.0$	$320.5 \pm 69.1$	$325.4 \pm 64.2$	$376.6 \pm 78.0$

Values for each age group were statistically different from the other two groups ( $P < 0.01$ ).

TABLE 3. Mean  $\pm$  SE Blood Concentration ( $\mu\text{g/ml}$ ) of Lidocaine Measured at the Onset of Each Toxic Manifestation

	Convulsions	Hypotension	Respiratory Arrest	Circulatory Collapse
Adult (n = 10)	11.7 $\pm$ 2.0	27.6 $\pm$ 2.1	34.2 $\pm$ 5.2	41.2 $\pm$ 6.7
Newborn (n = 10)	16.6 $\pm$ 1.2	35.6 $\pm$ 2.2	40.9 $\pm$ 2.1	53.4 $\pm$ 6.9
Fetus (n = 9)	16.4 $\pm$ 3.4	42.2 $\pm$ 5.0*	43.8 $\pm$ 5.9	68.7 $\pm$ 9.1*

\* Significantly different from the adult and the newborn values ( $P < 0.05$ ).

In terms of lidocaine blood levels at the time of toxic symptoms, convulsions and respiratory arrest occurred in all three age groups in association with values which were not significantly different (table 3). The convulsive threshold in the adult sheep was of the same order of magnitude as that reported in adult humans. Hypotension began in the fetuses at blood concentrations of lidocaine which were significantly higher than those noted in the adults and newborns, and remained higher than those in the other two age groups at circulatory collapse.

The relative sensitivity of the central nervous system and the cardiovascular system in the three groups is also demonstrated in tables 2 and 3. Significantly higher doses and blood levels of lidocaine were required to produce hypotension and circulatory collapse as compared to the doses and blood levels determined at the onset of convulsive activity ( $P < 0.01$ ). During the infusion of the drug to the fetuses, lidocaine was also detected in maternal blood, rising from  $1.9 \pm 0.3 \mu\text{g/ml}$  at the onset of fetal convulsions up to a maximum of  $3.7 \pm 0.8 \mu\text{g/ml}$  at the time of fetal circulatory collapse. However, no toxic symptoms were noted in the mothers.

Changes in blood  $p\text{H}$ ,  $P_{\text{CO}_2}$  and  $P_{\text{O}_2}$  are depicted in figure 3. Acid-base state and oxygenation remained essentially unchanged at the onset of convulsions in all animals. As intoxication became progressively more severe, hypoxemia and respiratory acidosis were noted in the adults, while the newborns were also hypoxemic and developed acidemia of mixed origin. In the fetuses, acidosis was the most prominent feature, while  $P_{\text{aO}_2}$  was relatively well-maintained for two to three hours until the onset of respiratory arrest (cessation of breathing-like activity). Maternal acid-base state and oxygenation did not change throughout the fetal infusion.

### Discussion

In contrast to common belief, these data indicate that fetal and newborn lambs are no more sensitive to lidocaine than adult sheep. The blood levels asso-

ciated with toxic manifestations were not significantly different among the three age groups, except for higher levels in the fetuses than in the adults and newborns at the onset of hypotension and circulatory collapse. Considering that plasma protein binding of local anesthetics is much lower in the fetus and neonate,<sup>12</sup> so that differences in free drug concentrations were presumably higher, one can infer even greater tolerance in the newborn. Since the newborns developed a more severe degree of acidosis than the adults, one can also assume that "ionic trapping"<sup>13</sup> resulted in relatively higher concentrations of lidocaine in such vital organs of the newborns as the brain and myocardium.

The significantly higher dosages of lidocaine necessary to produce symptoms of toxicity in newborns probably can be explained on the basis of the larger volume of distribution in the newborn which we have demonstrated in sheep<sup>11</sup> and others have shown in humans.<sup>14</sup> The greater volume of distribution in neonates is consistent with the fact that, in this age group, a larger percentage of total body mass is con-

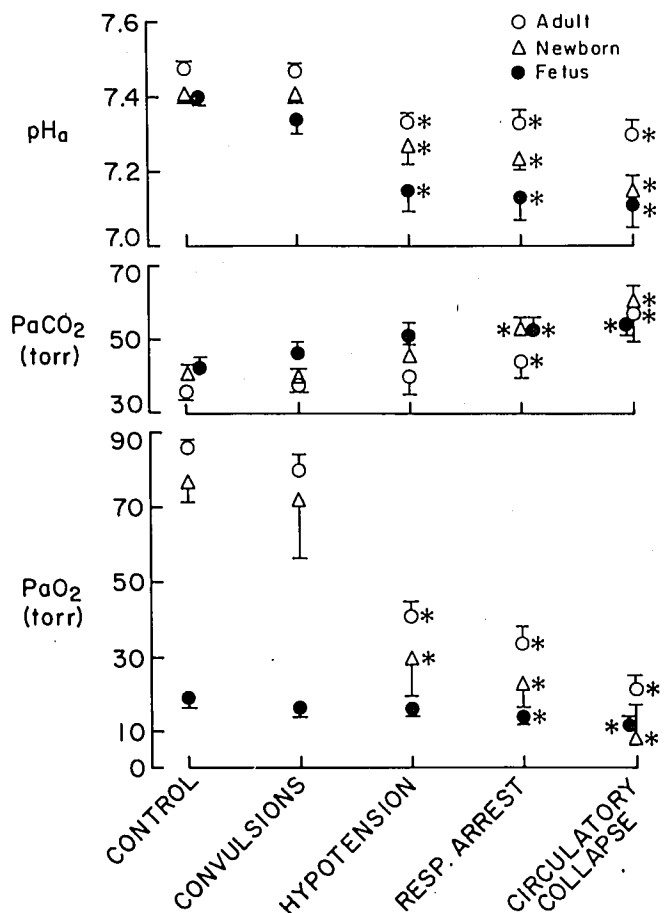


FIG. 3. Mean  $\pm$  SE  $p\text{H}_a$ ,  $P_{\text{aCO}_2}$ , and  $P_{\text{aO}_2}$  in adult, newborn, and fetal sheep during toxic manifestations. \*Statistically significant.

stituted of highly perfused organs.<sup>15</sup> More restricted neonatal ability to metabolize and excrete local anesthetics has been assumed primarily from studies indicating more prolonged half-lives of lidocaine and mepivacaine in the newborn.<sup>4,16</sup> However, recent reports<sup>11,14</sup> attribute these differences to a greater volume of distribution in the newborn since the neonate's renal clearance of lidocaine was greater and hepatic clearance the same as in the adult. Other studies also substantiated the ability of human newborns to metabolize and excrete lidocaine.<sup>17,18</sup>

The ability of the newborn to recover even from a severe local anesthetic intoxication has been demonstrated by Hillman and co-workers.<sup>4</sup> They have shown that with the proper treatment, infants inadvertently injected *in utero* with large doses of mepivacaine not only survive, but apparently develop normally.

The highest dose requirement for toxic manifestation was seen in the fetuses. This is undoubtedly due to the rapid drug transfer across the placenta into the maternal compartment. Indeed, lidocaine was detectable in the mothers' blood within minutes of starting fetal infusion, and its concentration increased progressively. This finding is in accordance with a previous study in which guinea pig fetuses injected with mepivacaine died if delivered immediately, but survived if delivery was delayed to allow placental clearance of the drug.<sup>19</sup> Compared with adults and newborns, the fetuses have the advantage of not depending on ventilation for the maintenance of normal blood gases. In this study, fetal Pa<sub>O<sub>2</sub></sub> changed little prior to circulatory collapse.

In the present protocol, ventilation was not supported during convulsions and animals were permitted to become progressively more hypoxic and acidotic. Nonetheless, cardiovascular manifestations of lidocaine toxicity occurred at significantly higher doses and blood levels of lidocaine than did CNS symptoms. Blood concentrations of lidocaine at the onset of hypotension were approximately twice as high as those at the onset of convulsions. These findings substantiate a higher threshold for lidocaine toxicity in the cardiovascular system as compared to the CNS.<sup>20</sup>

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