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Etidocaine Toxicity in the Adult, Newborn, and Fetal Sheep

Hisayo O. Morishima, M.D., Ph.D., Hilda Pedersen, M.D.,† Mieczyslaw Finster, M.D.,‡*
Hal S. Feldman, B.Sc.,§ Benjamin G. Covino, Ph.D., M.D.¶

The systemic toxicity of etidocaine was compared in adult, newborn, and fetal sheep during continuous infusion of the drug into the jugular vein at the rate of 0.5 mg·kg^{-1}·min^{-1}. All recipients exhibited symptoms of toxicity in the following order: convulsions, hypotension, respiratory arrest, and circulatory collapse. The dose of etidocaine required to produce CNS and cardiovascular toxicity was significantly different among the three age groups, being the highest in the fetus and the lowest in the adult. In contrast, no significant difference in etidocaine blood concentrations at the onset of each toxic symptom was observed among the groups except that convulsions and hypotension occurred at lower blood levels in the fetus as compared with the newborn and adult. Comparisons of etidocaine blood concentrations associated with the onset of convulsions and circulatory collapse (CC/CNS ratio) with those of lidocaine reported previously indicate that a narrower margin exists in adults and newborn following administration of etidocaine. (Key words: Anesthesia: obstetric. Anesthetics, local: etidocaine. Toxicity: cardiac; convulsions.)

THE CARDIOVASCULAR SYSTEM generally is believed to be more resistant to the toxic effects of local anesthetics than is the central nervous system (CNS). For example, cardiovascular manifestations of toxicity to lidocaine occur at significantly higher doses and blood concentrations than do CNS symptoms in adult sheep as well as newborn and fetal lambs.[1] Similar findings have been reported for other local anesthetics in cats.[2] However, it recently has been suggested that the cardiovascular system may be less resistant to the toxic effects of the more lipid soluble and highly protein-bound agents, such as etidocaine and bupivacaine.[3] No difference in the relative cardiovascular toxicity of the various ester and amide agents was observed in anesthetized, ventilated dogs.[4,5] However, Moore and his associates have reported that convulsive activity due to local anesthetic intoxication is associated with the rapid development of hypoxia and acidosis.[6] Therefore, in the absence of controlled ventilation, a difference in the potential cardiovascular toxicity of the various local anesthetics may exist. The present study was initiated to determine the dose and blood level of the highly lipid soluble agent, etidocaine, required for CNS and cardiovascular toxicity in adult sheep, newborn lambs, and fetal lambs. In addition, the results could be compared directly with those previously obtained with lidocaine, a significantly less lipid soluble agent.[1]

Materials and Methods

Nine nonpregnant adult sheep, weighing 50.9 ± 4.1 kg (mean ± SE), and nine newborn lambs (3.5 ± 0.3 kg), as well as nine pregnant ewes (54.5 ± 5.0 kg) and their fetuses were used. The lambs, born vaginally at term, were 4 h to 6 days old (average, 3 days). The fetal age at the time of the study ranged from 125 to 135 days (average, 130 days; term, 148 days); the mean weight was 2.8 ± 0.2 kg. Surgical procedures for the preparation of animals and the recording of arterial blood pressure, heart rate, respiratory movements, and electrocortical activity have been described elsewhere.[1] In addition, an ultrasonic pulsed Doppler flow transducer was placed around the carotid artery in four newborns and two fetuses to measure blood velocity.[7] In the adult and newborn, experiments were performed one to three days after surgery, and in fetuses and their mothers from 3 to 14 days (average, 7 days) after operation, by which time all animals had normal vital signs and acid-base values (table 1).

Etidocaine hydrochloride, 0.5 mg·kg^{-1}·min^{-1}, was infused continuously into the jugular vein of the nonpregnant adult, the newborn, or the fetus until circulatory collapse was evidenced by the disappearance of arterial pressure wave and absence of heart rate tracings. 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.[8,9] Subsequent weighing after delivery confirmed the fetal infusion rates of the drug to have been 0.5 ± 0.1 mg·kg^{-1}·min^{-1}. Arterial blood samples (0.5 ml) were withdrawn

* Associate Professor of Anesthesiology, College of Physicians and Surgeons of Columbia University.

† Associate Professor of Clinical Anesthesiology, College of Physicians and Surgeons of Columbia University.

‡ Professor of Anesthesiology, Obstetrics and Gynecology, College of Physicians and Surgeons of Columbia University.

§ Senior Research Associate, Harvard Medical School, Brigham and Women's Hospital.

¶ Professor of Anaesthesia, Harvard Medical School, and Chairman, Department of Anesthesiology, Brigham and Women's Hospital.

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Address reprint requests to Dr. Morishima: Department of Anesthesiology, College of Physicians and Surgeons, Columbia University, 630 W. 168th Street, New York, New York 10032.

TABLE 1. Mean (±SE) Preinfusion Values for Heart Rate, Mean Arterial Pressure, pH_a, Pa_{CO_2}, and Pa_{O_2} in the Nonpregnant Adult, Newborn, Fetus, and Mother

	Nonpregnant Adult (n = 9)	Newborn (n = 9)	Fetus (n = 9)	Mother (n = 9)
Heart rate (beats/min)	115 ± 10	216 ± 12	172 ± 14	105 ± 3
Mean arterial pressure (mmHg)	111 ± 9	68 ± 8	51 ± 2	103 ± 7
pH_a	7.47 ± 0.02	7.39 ± 0.03	7.37 ± 0.02	7.51 ± 0.01
Pa_{CO_2} (mmHg)	33 ± 2	43 ± 3	44 ± 1	32 ± 2
Pa_{O_2} (mmHg)	90 ± 5	68 ± 6	19 ± 1	89 ± 4

prior to the experiment and at the onset of the following major signs of intoxication: convulsions, hypotension (decrease in systolic arterial pressure of 20% compared to preinfusion values), respiratory arrest, and circulatory collapse, which were seen in that sequence in all infused animals. No respiratory or cardiovascular support was given. Arterial blood samples also were obtained simultaneously from the mother when etidocaine was infused to the fetus. All samples were analyzed for pH, P_{CO_2}, and P_{O_2} using Radiometer® microelectrodes and a Radiometer gas analyzer; whole blood etidocaine concentrations were determined by a gas chromatographic technique described previously.[10]

Eight analyses of variance were carried out to compare the mean doses and mean concentrations of etidocaine 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 prior to the experiment (table 1). During the continuous infusion of etidocaine, symptoms of intoxication occurred in all animals in the sequence already described in the Materials and Methods section. In the adult and newborn, shivering, fasciculations, and twitching were followed by tonic-clonic convulsions. In the fetus, seizure-like activity was manifested by the abrupt appearance of an irregular EEG wave pattern of large amplitude and low frequency. In all three groups, seizures were accompanied by an increase in arterial pressure and heart rate (fig. 1). As etidocaine infusion was maintained, convulsions continued intermittently to be followed by other signs of toxicity. Hypotension and bradycardia were next to develop, followed by the abrupt onset of shallow tachypnea, then respiratory arrest. In the fetus, respiratory arrest was defined as the cessation of breathing-like movements manifested by changes in tracheal pressure. Finally, circulatory collapse and cardiac asystole were the terminal manifestations of etidocaine intoxication. While arterial pressure and heart rate changed significantly, carotid blood flow measured in the newborn and the fetus remained relatively stable until the onset of circulatory collapse (table 2).

The mean dose and blood concentration of etidocaine at the onset of each toxic manifestation are summarized in tables 3 and 4. The adult sheep demonstrated convulsive activity at a mean dose of 2.21 ± 0.23 mg/kg of etidocaine. Significantly higher doses of the drug were required to produce convulsions in the newborn (5.71 ± 0.46 mg/kg) and the fetus (15.56 ± 5.36 mg/kg) ($P < 0.01$). Differences between the three age groups in doses needed for other toxic manifestations were also significant ($P < 0.01$). In contrast, blood con-

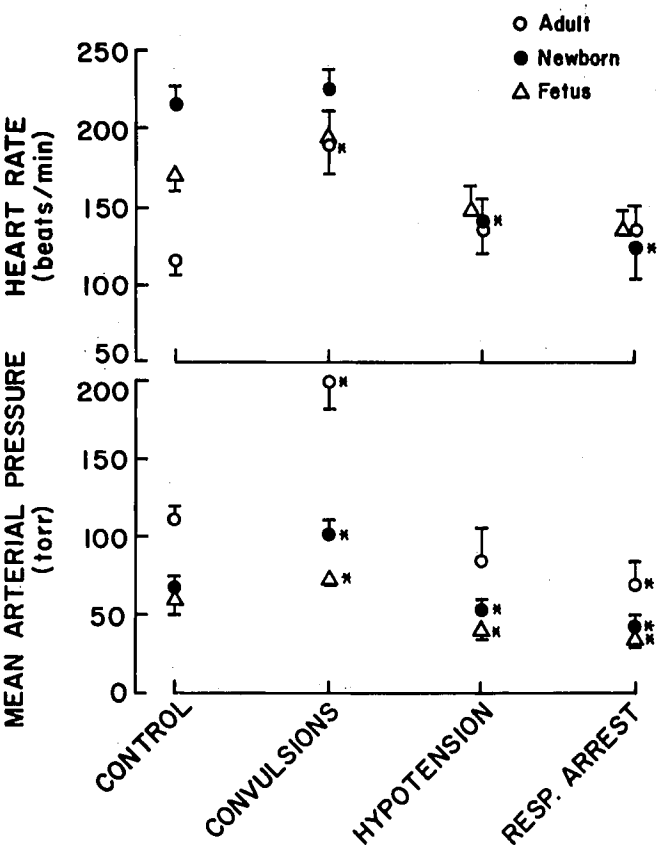

FIG. 1. Mean (±SE) heart rate and mean arterial pressure in the adult, newborn, and fetus before the infusion of etidocaine and during toxic manifestations. *Significantly different from preinfusion values.

TABLE 2. Carotid Blood Flow (CBF), Mean Arterial Pressure (MBP), and Heart Rate (HR) before and during Etidocaine Infusion

Experiment	Wt (kg)	Preinfusion			Convulsions			Hypotension			Respiratory Arrest		
		CBF (%)	MBP (mmHg)	HR (bpm)	CBF (%)	MBP (mmHg)	HR (bpm)	CBF (%)	MBP (mmHg)	HR (bpm)	CBF (%)	MBP (mmHg)	HR (bpm)
Fetus #7	3.0	100	54	200	89	90	230	94	49	140	89	34	160
Fetus #51	3.7	100	48	190	76	63	220	90	40	130	80	21	66
Newborn #13	4.4	100	63	210	64	93	240	85	47	130	75	31	120
Newborn #50	3.9	100	60	170	85	83	200	105	40	160	95	23	160
Newborn #52	4.0	100	56	165	75	106	250	100	33	170	50	26	100
Newborn #53	3.8	100	68	200	91	90	270	110	53	140	90	40	100

centrations of etidocaine at the time of each symptom were not significantly different with two exceptions: in the fetus, convulsions began at an average blood concentration of 1.41 ± 0.31 μg/ml, which was significantly lower ($\dot{P} < 0.05$) than that noted in the adult (3.92 ± 0.46 μg/ml) and newborn (3.21 ± 0.27 μg/ml). Hypotension occurred in the fetus at 3.89 ± 0.64 μg/ml which was significantly lower than that in the newborn (5.90 ± 0.56 μg/ml). During the infusion of etidocaine into the fetus, the drug also was detected in maternal blood, increasing from a level of 0.56 ± 0.23 μg/ml at the onset of fetal convulsions to a maximum of 1.53 ± 0.41 μg/ml at the time of fetal circulatory collapse. However, no toxic symptoms were noted in the mother.

Changes in arterial blood *p*H, P_{CO_2}, and P_{O_2} are depicted in figure 2. Acid-base state and oxygenation remained essentially unchanged until the onset of hypotension in all animals. As intoxication became more prolonged and severe, hypoxemia and respiratory acidosis were noted in the adult and the newborn. In the fetus, acidosis was the most prominent feature, while Pa_{O_2} and Pa_{CO_2} were relatively well-maintained until the onset of circulatory collapse. Maternal acid-base state and oxygenation did not change throughout the fetal infusion.

Discussion

The present results are in agreement with those previously reported for lidocaine.[1] The dose of etidocaine required to produce toxic manifestations was greatest in the fetus and least in the adult sheep. In contrast, the mean blood level of etidocaine in the fetus at the onset of CNS toxicity and hypotension was less than that in the newborn and the adult. This marked difference between dose and blood level in the fetus probably reflects the placental transfer of drug to the mother. The lower blood level of etidocaine associated with the onset of convulsions in the fetus may not necessarily be indicative of increased fetal susceptibility to local anesthetic toxicity. Protein binding of local anesthetics is significantly less in the fetus.[11] For example, etidocaine is presumably 90% plasma protein bound in the adult which would indicate an average free drug level of 0.39 μg/ml at the onset of convulsions. In the fetus in which the drug is believed to be 50% bound to plasma proteins, a free etidocaine level of 0.70 μg/ml would be present when convulsions occurred.

The differences between the newborn and the adult in etidocaine dosage necessary to produce toxic manifestations can be attributed to the larger volume of dis-

TABLE 3. Mean Doses (±SE) of Etidocaine (mg/kg) Associated with the Onset of Toxic Manifestations

	Convulsions	Hypotension	Respiratory Arrest	Circulatory Collapse
Adult (n = 9)	2.2 ± 0.2	7.7 ± 1.1	8.3 ± 1.4	9.4 ± 1.4
Newborn (n = 9)	5.7 ± 0.5	12.1 ± 1.4	12.7 ± 1.4	13.5 ± 1.3
Fetus (n = 9)	15.6 ± 5.4	66.5 ± 18.7	73.5 ± 20.1	82.7 ± 24.1

Values for each age group were statistically different from the other two groups.

TABLE 4. Mean (±SE) Blood Concentration (μg/ml) of Etidocaine Determined at the Onset of Each Toxic Manifestation

	Convulsions	Hypotension	Respiratory Arrest	Circulatory Collapse
Adult (n = 9)	3.0 ± 0.4	5.3 ± 0.6	6.1 ± 0.9	6.6 ± 0.9
Newborn (n = 9)	3.2 ± 0.3	5.9 ± 0.6	7.0 ± 0.9	8.1 ± 0.9
Fetus (n = 9)	1.4 ± 0.3*	3.9 ± 0.6†	6.1 ± 1.3	11.0 ± 2.1

* Significantly different from the adult and newborn values.

† Significantly different from the newborn value.

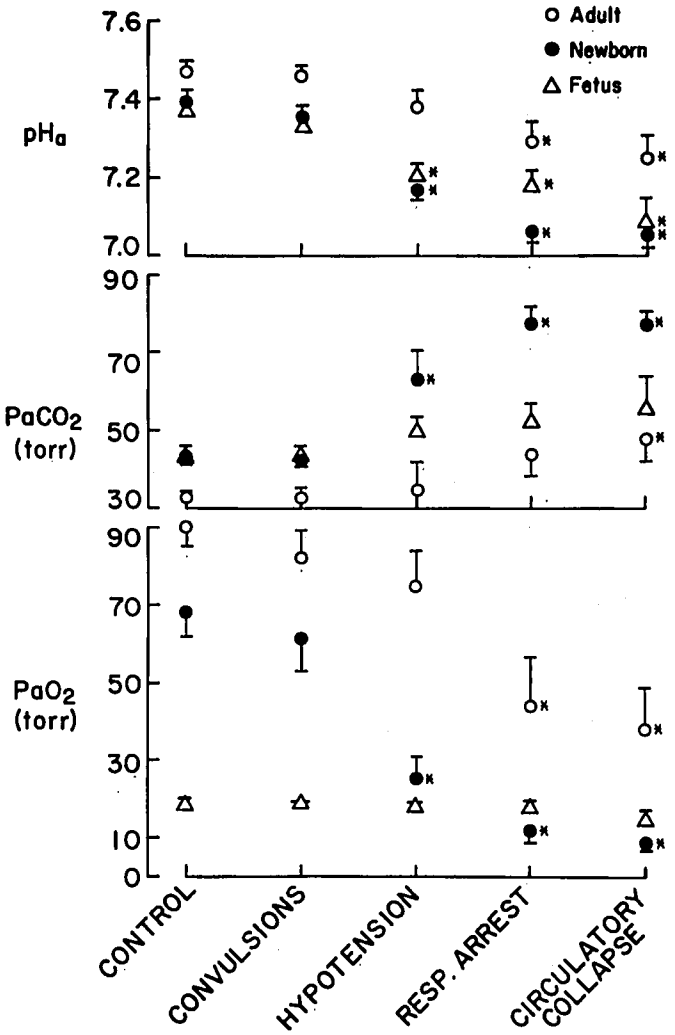

FIG. 2. Mean (±SE) pH_a, Pa_{CO_2}, and Pa_{O_2} in the adult, newborn, and fetus before the infusion of etidocaine and during toxic manifestations. *Statistically significant.

tribution in the newborn which has been demonstrated both in sheep and humans.[12,13] The results of this study pertaining to blood levels are also similar to those previously reported with lidocaine.[1] Data from these investigations would indicate that the newborn is no more sensitive to the potential toxic effect of local anesthetic than is the adult. Furthermore, development of a more severe degree of acidosis in the newborn lamb probably resulted in relatively higher concentrations of etidocaine in neonatal tissues through "ionic trapping".[14,15] In fact, these results may indicate greater drug tolerance in the newborn than in the adult. Based on lower threshold blood levels for convulsions and hypotension in the fetus, one also could conclude greater drug tolerance in the newborn than in the fetus. Causes for the latter differences are not apparent at the present time.

In this protocol, just as in the lidocaine study, no attempt was made to support ventilation and circulation. Thus, adult and newborn animals were permitted to become progressively more hypoxic, hypercarbic, and acidotic. In contrast, fetuses, being independent of "breathing" for the maintenance of normal blood gases, kept their Pa_{O_2} and Pa_{CO_2} essentially unchanged until the onset of circulatory collapse. The progressively increasing acidosis in fetal lambs probably was related to the infusion of the acidic local anesthetic solution and/or the release of acidic metabolites from hyperactive skeletal muscle. Interestingly, in all age groups, significant hypoxia and acidosis did not occur shortly after the onset of convulsions, as has been noted in humans.[6]

Recent clinical reports of cardiac arrests following inadvertent intravascular injections of large doses of etidocaine or bupivacaine raised the question of these agents being potentially more cardiotoxic than older drugs, such as lidocaine.[3] Studies in paralyzed, ventilated cats indicate the development of cardiac arrhythmias following infusion of high doses of bupivacaine, but not lidocaine.[2] In contrast, no arrhythmias were observed and no differences in the relative cardiovascular toxicity to lidocaine, bupivacaine, and etidocaine were noted in anesthetized, ventilated dogs.[5] It is conceivable that differences in toxicity between various agents may become apparent in the presence of hypoxia and acidosis. In order to evaluate this possibility, dosages and blood levels of etidocaine associated with convulsions (CNS) and circulatory collapse (CC) expressed as CC/CNS toxicity ratios, were compared with those for lidocaine, calculated from previously reported values (table 5). Although the CC/CNS dose ratio for

TABLE 5. Convulsive (CNS) and Circulatory Collapse (CC) Dosage and Blood Concentration Ratios of Etidocaine and Lidocaine

	Dosage CC/CNS Ratio		Blood Concentration CC/CNS Ratio	
	Etidocaine	Lidocaine*	Etidocaine	Lidocaine*
Adult	4.44 ± 0.85	7.13 ± 1.13	1.72 ± 0.23†	3.52 ± 0.26
Newborn	2.36 ± 0.16†	3.82 ± 0.26	2.48 ± 0.10†	3.59 ± 0.32
Fetus	6.06 ± 1.24	11.40 ± 3.30	9.08 ± 1.44	5.61 ± 1.79

* Calculated from previously reported data.[1]
Values of CC/CNS ratios of both drug dosage and blood concentration of etidocaine for each age group are significantly different from the other two groups.
† Significantly different from lidocaine.

etidocaine was significantly lower than for lidocaine in the newborn only, the trend was similar in the other age groups. The CC/CNS blood concentration ratios for etidocaine were significantly lower in the adult and in the newborn, but not in the fetus. These results may suggest that etidocaine is potentially more cardiotoxic than lidocaine when hypoxia and acidosis are allowed to develop in the adult and newborn, due presumably to a greater uptake by cardiac tissue. On the other hand, etidocaine has been shown to have a greater volume of distribution than lidocaine, due probably to a greater uptake in peripheral fat depots as a result of its high lipid solubility. Thus, the lower blood etidocaine level relative to lidocaine in the adult and newborn at the time of circulatory collapse may not necessarily reflect a significantly greater concentration in the myocardium. Tissue level studies similar to those performed with lidocaine in normal and asphyxiated baboons are required to resolve this question.[15] Similar data should also be obtained for bupivacaine.

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