Anesthesiology
68:367–372, 1988

Does Gestational Age Affect the Pharmacokinetics and Pharmacodynamics of Lidocaine in Mother and Fetus?

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The pharmacokinetics and pharmacodynamics of lidocaine were studied in nine chronically prepared pregnant ewes and their fetuses at a mean (±SE) gestation of 119 ± 1.0 days, and the results were compared to the data previously published for ten animals at 138 ± 1.2 days of gestation (term 148 days). Lidocaine was infused intravenously to the mother at a constant rate of 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$ over a period of 180 min, in order to reach a steady-state maternal plasma lidocaine concentration of approximately 2 μg/ml. Maternal and fetal blood samples and maternal urine were collected at intervals throughout the infusion for determination of *p*H, blood gases, and lidocaine concentrations. Maternal and fetal heart rate, blood pressure, and intraamniotic pressure were continuously recorded. Fetal cardiac output and organ blood flow were determined before and at the end of lidocaine infusion using radionuclide-labeled microspheres. Lidocaine tissue concentrations were determined in several maternal and fetal organs excised at the end of infusion. In both groups, the steady-state plasma concentrations of lidocaine were similar; namely, 2.3 ± 0.17 and 2.1 ± 0.21 μg/ml in preterm and term ewes, respectively. There were also no significant differences in steady-state plasma drug concentrations in preterm and term fetuses (1.3 ± 0.11 and 1.2 ± 0.15 μg/ml). The mean fetal maternal concentration ratios (F/M) were the same; namely, 0.6. Maternal urinary excretion of lidocaine correlated with urine *p*H, being greater in the more acid urine. Tissue uptake of drug tended to be higher in the preterm than term mothers, but only significantly so in the brain and adrenals. In the fetuses, tissue uptake was similar in both groups except in the lungs and liver, where it was higher at term. Liver uptake was significantly higher in the fetuses than in the corresponding ewes. Maternal and fetal vital signs and blood gases, as well as the fetal cardiac output and organ blood flow, were not altered by lidocaine infusion. It is concluded that the pharmacokinetics and dynamics of lidocaine in the mother and fetus are not affected by maturation between 80% and 95% of gestation. (Key words: Anesthesia: obstetric. Anesthetics, local: lidocaine. Gestation: preterm, term. Pharmacokinetics. Pharmacodynamics.)

IN THE PAST 20 yr, the incidence of cesarean delivery in the management of premature labor has almost tripled in the United States.‡‡ This change in obstetric practice is thought to have contributed to an improvement in perinatal outcome.[1] However, it has also resulted in more frequent administration of a major anesthetic to the parturient, and exposure of more premature fetuses to drugs commonly used in obstetric anesthesia. All of these drugs readily cross the placenta, but there is a lack of data regarding the pharmacokinetics and pharmacodynamics of these drugs at different stages of gestation.

This study was designed to test whether the kinetics of lidocaine change during the last weeks of pregnancy, and whether the drug distribution and effects in the fetus vary with gestational maturation. For this purpose, data obtained from preterm sheep were compared with those previously obtained from a term group.[2]

Materials and Methods

A total of nine chronically prepared ewes and their fetuses were studied at a mean (±SE) gestation of 119 ± 1.0 days, and the results were compared to the data previously published for ten animals at 138 ± 1.2 days of gestation (term 148 days). The two studies were completed during the same 2-yr period. Surgical preparation and study protocol were identical, except for an additional group of 16 animals, contained in the published study, in which fetal asphyxia was induced.

All ewes, deprived of food for 48 h preceding surgery, had spinal anesthesia induced with tetracaine hydrochloride (8–10 mg) supplemented with thiopental infusion 0.05%, as necessary. The total dose of barbiturate varied between 0.3 and 1.0 g, over the period of surgery lasting approximately 2 h. Catheters were in-

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Received from the Departments of Anesthesiology and Obstetrics and Gynecology, College of Physicians and Surgeons of Columbia University, New York, New York; and the Department of Anaesthesia, Brigham and Women's Hospital, Boston, Massachusetts. Accepted for publication October 6, 1987. Supported in part by NIH Grant R01 GM29571.

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‡‡ Cesarean Childbirth: U. S. Department of Health and Human Services. NIH Publ No. 82-2067, 1981, p 167

serted into the maternal femoral artery and vein. An intravenous infusion of 1000 ml of lactated Ringer's solution was begun and completed by the end of surgery. The uterus was exposed through a midline abdominal incision, and, *via* a small hysterotomy, the fetal head and neck were delivered. Polyethylene catheters were introduced into the fetal thoracic aorta through a carotid artery, and superior vena cava through the jugular vein. The fetus was returned and the uterine wall was closed, after a polyethylene catheter had been placed in the amniotic cavity. A second uterine incision was made to insert catheters into the fetal abdominal aorta and inferior vena cava through the femoral vessels. The estimated loss of amniotic fluid was replaced with an equal volume of warmed normal saline after the uterine and abdominal walls had been closed. All catheters were tunneled subcutaneously and secured in a pouch attached to the flank area of the ewe. The intravascular catheters were flushed daily. Postoperatively, antibiotics were injected intramuscularly to the ewe, and into the amniotic cavity *via* the implanted catheter.

Experiments were conducted, at the earliest, 4 days after the surgery, the minimum required for fetal recovery.[3] The urinary bladder of the ewe was catheterized on the morning of the study, and the animal was kept in a cart with freedom to stand or sit; water and food were supplied *ad libitum*. Collection of urine began at least 2 h before the study. Prior to the administration of lidocaine, control samples of maternal and fetal arterial blood were obtained.

Lidocaine was infused intravenously to the mother, at a constant rate of 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$ over a period of 180 min. The rate of infusion was calculated as the product of the desired plasma concentration (C_{ss}) × clearance (Cl). The 180 min, corresponding to five elimination half-lives, was chosen for the duration of infusion, to assure that the steady-state concentration of the drug would be established. The pharmacokinetic parameters were determined previously from single bolus injections to pregnant ewes.[4] A target plasma lidocaine concentration of 2 μg/ml was chosen to be similar to the concentration in maternal arterial blood in human subjects following epidural administration.[5]

Maternal and fetal heart rate and arterial pressure, as well as intra-amniotic pressure, were measured throughout the experiment, and recorded on a Beckman polygraph.

Maternal and fetal blood samples were withdrawn and maternal urine collected and volume measured at intervals, at 15, 30, 60, 90, 120, 150, and 180 min from the onset of infusion, for determination of acid-base values, as well as for lidocaine concentrations using a gas chromatographic technique.[6] After separation of plasma, all samples for drug analysis were stored at −20° C. To avoid fetal anemia and/or hypovolemia, the volume of each fetal sample was limited to 1.5 ml.

For the determination of fetal cardiac output and organ blood flow, one or two of the following 15-μm radionuclide-labeled microspheres, ^{57}Co, ^{113}Sn, ^{103}Ru, ^{96}Nb, and ^{46}Sc, were injected into the fetal jugular vein and/or inferior vena cava prior to and at the end of lidocaine infusion. Reference blood samples from the carotid artery and abdominal aorta were taken at a constant rate of 1.35 ml/min using Harvard withdrawal pumps, starting 30 s prior to microsphere injection, and continuing for 60 s after the end of injection. Fetal blood loss was replaced with an equal volume of stored maternal blood.

At the end of lidocaine infusion, the mother and fetus were killed by intravenous injection of an overdose of pentobarbital (1–2 g). The fetus was delivered and weighed, and the maternal and fetal brain, heart, lungs, liver, kidneys, and adrenals, as well as the placenta, were removed, blotted, and weighed for later determination of drug concentrations. Thereafter, small samples of the fetal organs were dissected, weighed again, and placed in counting vials for determination of radioactivity with an auto-gamma scintillation spectrometer connected to a multichannel analyzer. A computer program, using the stripping method, was used to resolve the radioactivity of each isotope, as well as to calculate the radioactivity per 100 g tissue sample, the flow rate per 100 g of tissue sample per min, and the cardiac output.[7]

Total body clearance of lidocaine at steady state was calculated by dividing the infusion rate by the steady-state blood concentration. The tissue/plasma concentration ratio was calculated by dividing the concentration of lidocaine in the organ (μg/g) by the steady state plasma concentration (μg/ml).

Data pertaining to maternal and fetal vital signs, acid-base balance, fetal cardiac output, and organ blood flow, before and at the end of lidocaine infusion, were compared within each gestational group using a paired *t* test. Plasma and tissue lidocaine concentrations, as well as tissue/plasma concentration ratios, were analyzed using an unpaired *t* test. $P < 0.05$ was considered to be significant.

Results

The results of this study obtained in nine preterm pregnant ewes are compared with those previously obtained in ten term animals.[2] The maternal plasma lidocaine concentrations in the preterm animals approached a steady state after approximately 120 min of

infusion. At 180 min, maternal concentrations were similar; 2.3 ± 0.17 and 2.1 ± 0.21 μg/ml, respectively (fig. 1). The calculated total clearance of lidocaine at steady state (table 1) was 42.7 ± 3.3 ml·kg^{-1}·min^{-1} *versus* 56.0 ± 8.2 ml·kg^{-1}·min^{-1}. The difference did not reach statistical significance ($P < 0.1$). The preterm and term fetuses weighed 2.5 ± 1.3 kg and 3.6 ± 0.4 kg, respectively. In both groups of fetuses, the mean plasma lidocaine concentrations also approached a steady state after approximately 120 min, amounting to 1.2 ± 0.15 μg/ml in the preterm, and 1.0 ± 0.10 μg/ml in the term. At 180 min, these were 1.3 ± 0.11 and 1.2 ± 0.15 μg/ml. The mean feto/maternal (F/M) concentration ratio in both groups at 180 min was the same; namely, 0.6.

Unchanged lidocaine was detectable in the maternal urine as early as 15 min into the infusion (fig 1). However, over a period of 180 min, the total amount of unchanged lidocaine excreted was only 4.27 ± 2.39 mg, or 0.4 ± 0.3% of the administered dose in the preterm ewes, and 6.90 ± 2.02 mg, or 0.7 ± 0.2% in the term ewes (table 1). Excretion of lidocaine was significantly related to urinary *p*H. Therefore, groupings were made according to the value of urinary *p*H regardless of gestation. In the acid urine (*p*H 5.6–7.0), lidocaine excretion increased steadily from 17.3 ± 6.7 μg/min at 15 min to 68.6 ± 33.8 μg/min within 60 min, and reached a plateau of approximately 120 μg/min towards 120 min. In contrast, lidocaine did not appear in alkaline urine (*p*H 7.2–8.1) until after 15 min of infusion, and remained low within the range between 5.1 ± 1.6 and 5.6 ± 4.1 μg/min for the first 45 min. The total amount of drug excreted by the end of infusion was 1.2 ± 0.2% and 0.2 ± 0.1% ($P < 0.001$) of the administered dose, respectively, in the two *p*H groups.

With the exception of the liver, tissue concentrations of lidocaine in the preterm ewes tended to be higher than in the ewes at term (table 2). The difference was significant in the brain and adrenals, where the concentrations were 9.71 ± 0.61 and 18.15 ± 2.74 μg/g, respectively, in the preterm ewe; and 6.45 ± 0.87 and 10.03 ± 2.63 μg/g, respectively, in the term ewe. Tissue concentrations of lidocaine were similar in both groups of fetuses. In general, the drug concentrations in the fetal organs were lower than in the corresponding maternal organs. The only exception was the liver, in which lidocaine concentrations, in both preterm and term groups, were significantly higher in the fetus.

When data were expressed as the tissue-to-blood concentration ratios, the only gestation-related differences were found in the maternal brain and adrenals (lower in the term group) and in the fetal lungs and liver (higher at term) (table 3). Within each gestational group, the mean liver/blood ratio was higher in the fetus than in the ewe.

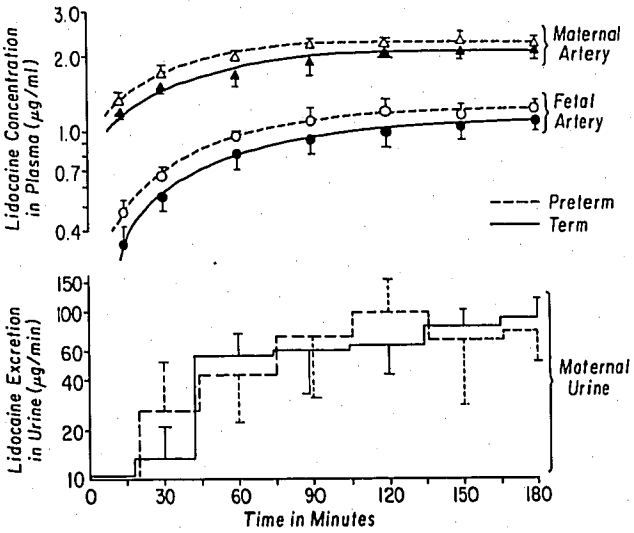

FIG. 1. Mean (±SE) lidocaine concentration in maternal and fetal arterial blood, and maternal urine, during constant rate intravenous infusion to preterm (N = 9) and term (N = 10) ewes.

The mean arterial *p*H and blood gases, blood pressure and heart rate and fetal cardiac output prior to and at the end of lidocaine infusion are summarized in table 4. There was no significant difference in control values or response to lidocaine infusion between the preterm and term ewes. The control fetal values were also similar in both gestational groups, and remained essentially unchanged during lidocaine infusion. The mean cardiac output prior to the lidocaine infusion was 432 ± 65 ml·min^{-1}·kg^{-1} in the preterm fetuses; and 459 ± 44 ml·min^{-1}·kg^{-1} in those at term. Similar values were obtained at 180 min: 469 ± 45 in the preterm and 502 ± 40 ml·min^{-1}·kg^{-1} in the term fetuses. The distribution of blood flow to the placenta and various fetal organs was not significantly different between preterm and term fetuses, and the measurements made at 180

TABLE 1. Lidocaine Values in the Ewe (Mean ± SE)

	Preterm (N = 9)	Term (N = 10)*
Infusion rate (mg·kg^{-1}·min^{-1})	0.095 ± 0.001	0.104 ± 0.006
Plasma concentration at 180 min (μg/ml)	2.31 ± 0.17	2.13 ± 0.21
Total clearance (ml·kg^{-1}·min^{-1})	42.7 ± 3.3	56.0 ± 8.2
Dose recovered in urine		
mg	4.27 ± 2.39	6.90 ± 2.02
%	0.4 ± 0.3	0.7 ± 0.2

* Data from published study.[2]

TABLE 2. Mean (±SE) Lidocaine Concentrations (μg/g) in Maternal and Fetal Organs

	Ewe		Fetus	
	Preterm (N = 9)	Term (N = 10)	Preterm (N = 9)	Term (N = 10)
Brain	9.71 ± 0.61	6.45 ± 0.87*	4.83 ± 0.44	3.76 ± 0.30
Heart	9.12 ± 0.69	7.49 ± 1.01	3.65 ± 0.24	3.08 ± 0.40
Lungs	15.01 ± 2.59	8.50 ± 2.21	5.00 ± 0.65	6.72 ± 1.53
Liver	1.87 ± 0.64	2.18 ± 0.41	3.73 ± 0.92†	3.80 ± 0.57†
Kidneys	17.90 ± 1.76	12.67 ± 1.99	6.48 ± 0.62	5.05 ± 1.20
Adrenals	18.15 ± 2.74	10.03 ± 2.63*	6.34 ± 1.62	5.55 ± 0.84

* Significantly lower than in preterm ewes.

† Significantly higher than in the liver of the corresponding group of ewes.

TABLE 3. Mean (±SE) Tissue/plasma Lidocaine Concentration Ratios

	Ewe		Fetus	
	Preterm (N = 9)	Term (N = 10)	Preterm (N = 9)	Term (N = 10)
Brain	4.82 ± 0.44	3.35 ± 0.35*	3.37 ± 0.53	4.22 ± 0.48
Heart	4.53 ± 0.54	3.93 ± 0.39	2.52 ± 0.33	3.30 ± 0.29
Lungs	7.47 ± 1.30	4.36 ± 1.07	3.52 ± 0.76	6.63 ± 0.65†
Liver	0.95 ± 0.33	1.23 ± 0.29	2.58 ± 0.53‡	3.96 ± 0.27†‡
Kidneys	9.15 ± 1.22	6.45 ± 0.88	4.41 ± 0.49	5.05 ± 0.60
Adrenals	9.61 ± 1.64	5.64 ± 0.94*	4.43 ± 1.38	5.97 ± 0.97

* Significantly lower than in preterm ewe.
† Significantly higher than in preterm fetus.

‡ Significantly higher than in corresponding group of ewes.

min did not show any significant change from the pre-infusion values (table 5).

Discussion

The results of this study indicate that the pharmacokinetics and pharmacodynamics of lidocaine in pregnant ewes and their fetuses change very little between 80% and 95% of gestation. This could be due, in part, to large intragroup variability. The desired steady-state maternal plasma lidocaine concentration of approximately 2 μg/ml was achieved in both gestational groups with an infusion rate of approximately 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$, derived from pharmacokinetic data obtained previously.[4] Steady-state fetal plasma concentrations of lidocaine were also similar in both groups,

TABLE 4. Mean (±SE) Maternal and Fetal Arterial *p*H and Blood Gases, Mean Blood Pressure, Heart Rate, and Fetal Cardiac Output, Prior to and at the End of Lidocaine Infusion to the Ewe

Gestational group	Preterm (N = 9)		Term (N = 10)	
Infusion (min)	0	180	0	180
Ewe				
*p*Ha	7.47 ± 0.01	7.49 ± 0.01	7.46 ± 0.02	7.48 ± 0.02
Pa_{CO_2} (mmHg)	33 ± 2	30 ± 1	33 ± 2	31 ± 1
Pa_{O_2} (mmHg)	100 ± 4	101 ± 4	97 ± 5	96 ± 2
Mean arterial pressure (mmHg)	90 ± 5	90 ± 8	90 ± 3	92 ± 6
Heart rate (beats/min)	104 ± 8	99 ± 5	112 ± 5	116 ± 4
Fetus				
*p*Ha	7.40 ± 0.01	7.42 ± 0.01	7.40 ± 0.02	7.39 ± 0.02
Pa_{CO_2} (mmHg)	43 ± 1	43 ± 2	43 ± 1	43 ± 2
Pa_{O_2} (mmHg)	24 ± 2	24 ± 2	22 ± 2	22 ± 1
Mean arterial pressure (mmHg)	49 ± 3	48 ± 3	48 ± 3	49 ± 2
Heart rate (beats/min)	173 ± 9	173 ± 9	171 ± 9	168 ± 8
Cardiac output ($ml \cdot min^{-1} \cdot kg^{-1}$)	432 ± 65	469 ± 45	459 ± 44	502 ± 40

while the F/M ratios were the same. This is surprising, since the F/M ratio of local anesthetics has been shown to depend on the differential protein binding in the maternal and fetal plasma.[8] In humans, as pregnancy progresses, there is an increase in α_1-acid glycoprotein (the principal protein which binds local anesthetics) concentrations in the fetus, leading to an increase in the ratio between the fetal and maternal serum concentrations of α_1-acid glycoprotein, which reaches a value of 0.4 at term.[9] If similar changes occur in the ovine species, one would expect that, with similar plasma lidocaine concentrations in both groups of ewes, the fetal total plasma drug concentrations would be higher at term. However, this effect of enhanced protein binding may be offset by the maturation of fetal hepatic and renal function, resulting in increased capability of drug clearance as gestation progresses. Investigations in newborn lambs and human infants have demonstrated that the total lidocaine clearance is higher than, and the metabolic clearance equal to, that in the adult.[10,11] Urinary excretion of unchanged lidocaine was similar in both groups of pregnant ewes, and represented less than 1% of the administered dose. There was a negative correlation between the urine *p*H and lidocaine excretion, more drug being eliminated in acid urine. This is probably due to decreased tubular reabsorption of lidocaine, which is more ionized at lower *p*H. A similar observation was made in nonpregnant humans.[12] Tissue lidocaine concentrations and tissue/plasma concentration ratios of the drug tended to be higher in preterm ewes, the difference being significant in the brain and adrenals. The reason for this is unclear. No ewes in either group exhibited any signs of CNS toxicity. In general, drug uptake in fetal tissues was also unaffected by the duration of gestation. Only in the lungs and liver was the tissue/plasma concentration ratio higher at term. At steady state, the tissue/plasma partition of a drug depends on lipid solubility and the protein binding in the two compartments. As already stated, fetal plasma protein binding of local anesthetics increases with gestational maturation, but no information is available about tissue protein binding. Comparing fetal to maternal tissue uptake of lidocaine, the only significant differences were found in the liver, where the tissue concentrations and tissue/plasma concentration ratios were higher in the fetuses than in the corresponding mothers. This is probably due to a more rapid hepatic metabolism of the drug in the mother and higher lipid content of the fetal liver. Substantial uptake by the fetal liver has been documented for a variety of drugs, including thiopental[13] and halothane.[14]

In both gestational groups, throughout the maternal infusion of lidocaine, during which maternal plasma drug concentrations did not exceed 2.5 μg/ml, maternal cardiovascular, as well as acid-base status, remained stable. Fetal plasma lidocaine concentrations did not exceed 1.5 μg/ml, at which even preterm fetuses showed no significant changes in the parameters measured. It is not known whether the threshold plasma concentration of lidocaine required to elicit toxicity in the preterm fetal lamb is different from that in the term fetus, which has been shown to be approximately 16 μg/ml.[15]

TABLE 5. Mean (±SE) Blood Flow in Fetal Organs and Placenta ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)

Infusion (min)	Preterm (N = 9)		Term (N = 10)	
	0	180	0	180
Brain	111 ± 12	126 ± 16	151 ± 29	139 ± 18
Heart	185 ± 22	169 ± 21	160 ± 26	149 ± 20
Lungs	89 ± 10	72 ± 5	99 ± 30	91 ± 21
Kidneys	193 ± 15	179 ± 10	178 ± 19	152 ± 20
Adrenals	254 ± 33	237 ± 43	307 ± 35	282 ± 62
Placenta	168 ± 28	122 ± 10	180 ± 36	158 ± 26

As already stated, the fetuses included in this report were in good general condition prior to maternal lidocaine infusion. In another study of ours, preterm fetal lambs were asphyxiated by partial cord occlusion prior to the onset of maternal lidocaine infusion.[16] Fetal plasma drug concentrations of approximately 1.5 μg/ml resulted in significant decreases in cardiac output, mean arterial pressure, and arterial *p*H. No such deterioration occurred in term asphyxiated fetuses exposed to lidocaine.[2]

In summary, our data indicate that, in a healthy preterm fetal lamb, the cardiovascular and acid-base status are not adversely affected by transplacentally obtained lidocaine, when the fetal plasma concentrations do not exceed 1.5 μg/ml. This is not the case in the asphyxiated preterm fetal lamb. It is not known whether these results are applicable to preterm human fetuses.

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