Plasma Levels of Lidocaine (Xylocaine®) in Mother and Newborn Following Obstetrical Conduction Anesthesia:

Clinical Applications

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Fifty-seven randomly-selected obstetrical patients who received lidocaine for caudal, epidural, paracervical or pudendal block anesthesia were studied. The local anesthetic was absorbed from the sites of injection into the maternal arterial circulation within three to five minutes, and was transmitted across the placenta to the fetus. The umbilical venous concentration of lidocaine at birth was 52 ± 23 per cent (S.D.) of that found simultaneously in the maternal artery. Of five infants which were mildly depressed at birth, three had lidocaine levels greater than 3.0 μg./ml. in the umbilical venous blood. In the large majority of cases, however, the umbilical venous blood levels were below 2.5 μg./ml. and no depression was apparent in the newborn.

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LOCAL ANESTHETICS are the most widely used agents in obstetrics. Their popularity can be attributed in part to the widespread belief that local anesthetics have few depressant effects on the fetus or newborn. In a previous report[1] we demonstrated that lidocaine crosses the placenta rapidly, appearing in fetal blood within three minutes after intravenous administration to the mother. The present paper demonstrates that lidocaine used for obstetrical anesthesia is rapidly absorbed from the sites of injection into the maternal circulation, crosses the placenta and, very rarely, achieves relatively high fetal blood levels which are associated with neonatal depression.

Method

Fifty-seven randomly-selected women in labor, and their infants, were studied. The regional block employed, the local anesthetic solution, total dose used and the number of patients in each group are given in table 1.

Before the local anesthetic was administered, a sample of venous blood was drawn for

TABLE 1. Regional Blocks Employed, Solutions, Dosage Used and Number of Patients in Each Group

Block	Solution	Dosage		Number of Patients
		Mean	Range	
Caudal or lumbar epidural, single dose	Lidocaine 1½ per cent with 1:200,000 epinephrine	4.8 mg./kg.	2.9 to 10.1 mg./kg.	7
Continuous caudal or lumbar epidural, multiple dose	Lidocaine 1½ per cent with 1:200,000 epinephrine	8.2 mg./kg.	3.0 to 14.2 mg./kg.	27
Paracervical and pudendal blocks, multiple dose	Lidocaine 1 per cent without epinephrine	5.6 mg./kg.	1.8 to 10.2 mg./kg.	23

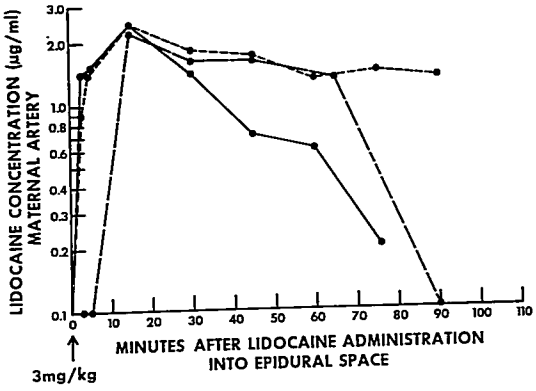

FIG. 1. Concentrations of lidocaine in maternal artery (three patients) following epidural injection of 3 mg./kg. lidocaine with 1:200,000 epinephrine.

"blank" determination. Following the block, maternal arterial blood pressure, pulse, respiration, and fetal heart rate were observed every two minutes for ten minutes, then every five minutes until delivery of the infant. In three patients who received 3 mg./kg. of 1½ per cent lidocaine with 1:200,000 epinephrine in the epidural space, samples of blood were drawn from an indwelling catheter in a maternal artery 3, 5, 15, 30, 45, 60, 75 and 90 minutes following injection of the drug. Immediately following delivery in all patients, samples of blood were drawn simultaneously from the maternal artery and from the umbilical vein and umbilical artery in a doubly-clamped segment of umbilical cord. In 13

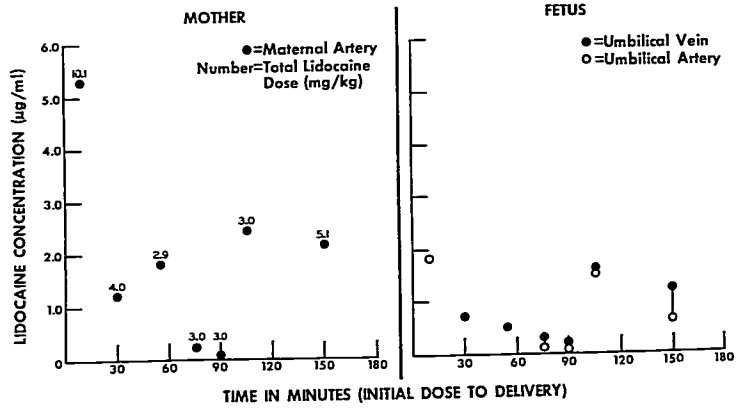

FIG. 2. Concentrations of lidocaine in maternal arterial and fetal blood following a single-dose caudal or lumbar epidural injection. Durations of analgesia from time a test dose was given to time of delivery were 10 to 150 minutes.

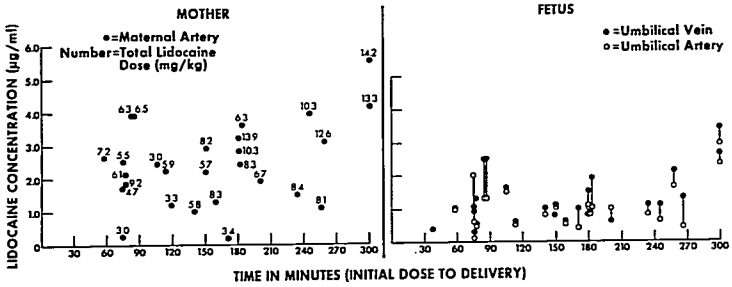

FIG. 3. Concentrations of lidocaine in maternal arterial and fetal blood at time of delivery following multiple doses of caudal or lumbar epidural injections. Durations of analgesia from the time the test dose was given to time of delivery were 55 to 300 minutes.

patients who received continuous caudal or lumbar epidural anesthesia, a maternal venous sample was also drawn at the time of birth. All samples were analyzed for plasma lidocaine concentration according to the method of Sung and Truant,[2] modified as previously reported to yield a high degree of specificity for lidocaine.[1] All infants were evaluated clinically by means of the Apgar score at one and five minutes after birth, and maternal anesthetic complications were noted.

Results

Maternal Anesthetic Complications

Convulsions, coma or cardiovascular collapse were not seen. Decreases in maternal blood pressure greater than 30 per cent of control values or to below 100 mg. Hg were found in six of the 34 patients undergoing epidural anesthesia. Treatment with left uterine displacement was effective in immediately restoring the blood pressure to normal.

Blood Levels of Lidocaine

Single-dose Epidural Block Serial Determination—Three Mothers: 3 mg./kg. (each). In two of the three mothers, lidocaine was detectable in arterial blood as early as three minutes after injection. At 15 minutes, the blood levels of all three had exceeded 2 μg./ml. (fig. 1). In two patients the levels declined fairly rapidly, and little or no lidocaine was detected at 75 and 90 minutes. In the other the fall in plasma lidocaine was much slower; a relatively high blood level was still present at 90 minutes.

Single-dose Caudal or Epidural Block—Seven Mothers: 4.8 mg./kg. (mean). Following administration of lidocaine 9 to 150 minutes before delivery appreciable levels were found in the systemic circulation of mother and fetus. The mean maternal arterial concentration of lidocaine at birth was 2.2 μg./ml. (range < 0.2 to 5.3) (fig. 2). These concentrations were significantly higher than those in either of the umbilical cord vessels ($P = <$ 0.05). Umbilical venous levels averaged 0.9 μg./ml. (range < 0.2 to 1.6); umbilical arterial levels averaged 0.8 μg./ml. (range < 0.2 to 1.5).

Continuous Caudal and Lumbar Epidural Block—27 Mothers: 8.15 mg./kg. (mean). Following intermittent epidural administration, lidocaine concentrations in maternal arterial blood at birth varied greatly between 0.2 and 5.5 μg./ml., with a mean concentration of 2.7 μg./ml. (fig. 3). The maternal arterial concentrations were significantly higher than those in the umbilical cord vessels ($P = <$ 0.01). Levels in the umbilical vein averaged 1.3 μg./ml. (range 0.4 to 3.4) and in the umbilical artery, 1.1 μg./ml. (range 0.4 to 2.9). The concentrations in the umbilical vein were significantly higher than those in the umbilical artery ($P = < 0.01$ by paired analyses Student's t test).

TABLE 2. Comparison of Lidocaine Concentration in Blood Simultaneously Sampled from Maternal Brachial Artery and Antecubital Vein at Delivery Following Epidural Anesthesia

Patient	Lidocaine Dose		Duration (min)		Lidocaine Concentration μg./ml.		Ratio Concentration Maternal Vein/Maternal Artery (per cent)
	Total (mg.)	mg./kg.	First Dose to Delivery	Last Dose to Delivery	Maternal Artery	Maternal Vein	
1	405	7.0	77	39	2.1	1.1	52
2	450	7.2	58	38	2.6	2.0	77
3	560	9.2	77	37	1.8	1.6	89
4	495	8.3	159	14	1.3	0.6	46
5	630	10.3	245	20	3.9	2.4	62
6	600	8.1	256	26	1.1	1.1	100
7	375	5.5	75	10	2.5	2.2	88
8	245	3.3	118	53	1.2	1.2	100
9	345	5.7	149	24	2.2	1.3	59
10	405	6.7	200	20	1.9	1.6	84
11	940	13.9	180	3	3.2	2.1	66
12	970	14.2	301	26	5.5	4.9	89
13	375	5.9	113	98	2.2	1.8	82
Mean					2.42	1.84	76

At time of delivery lidocaine concentrations in maternal venous blood were generally lower than those in simultaneously-sampled maternal arterial blood (table 2); the mean maternal vein/maternal artery ratio was 76 ± 17.8 (S.D.) per cent.

Paracervical and Pudendal Blocks—23 Mothers: 5.6 mg./kg. (mean). Following administration of lidocaine first as a paracervical block and later as a pudendal block, the mean maternal arterial concentration of lidocaine at birth was 3.5 μg./ml. (range 0.7 to 6.0) (fig. 4). The mean umbilical venous concentration was 1.3 μg./ml. (range < 0.2 to 3.4), and mean umbilical arterial concentration was 1.1 μg./ml. (range < 0.2 to 1.9). Maternal arterial concentrations of lidocaine were significantly higher than those in either umbilical vein or umbilical artery ($P = < 0.01$). The lidocaine concentrations in the umbilical vein were also significantly higher than those in the umbilical artery ($P = < 0.01$).

Figure 5 summarizes the data by illustrating the gradient in concentration between maternal arterial and umbilical venous blood following the use of lidocaine for epidural, paracervical or pudendal blocks. The ratio of drug concentrations in umbilical vein and maternal artery was 0.52 ± 0.23 (S.D.).

EFFECT OF LIDOCAINE ON THE NEWBORN

To determine the effect of lidocaine upon the clinical condition of the infant, 50 of the 57 mothers, in whom all other factors known or suspected to cause neonatal depression had been eliminated, were selected. The factors eliminated included prolonged or precipitous labor, maternal diseases such as pre-eclampsia, diabetes, heart disease, or infection, and operative obstetrics. The series included no breech or premature births or twin deliveries. Thus, only healthy mothers who were delivered of full-term infants, vaginally, in vertex presentation, and who received no other analgesics or hypnotics within six hours of delivery were considered. Figure 6 gives the Apgar scores at one minute and lidocaine concentrations in the umbilical veins in this group of 50 patients. Ninety per cent of the infants were vigorous, with Apgar scores of 7 to 10; of the 42 infants with lidocaine levels of 2.5 μg./ml. or less, only one had a low Apgar score. On the other hand, at lidocaine levels higher than 2.5 μg./ml., four of eight infants had low Apgar scores, and three of these depressed infants had lidocaine levels greater than 3.0 μg./ml. Following resuscitation with tactile stimulation and administration of oxygen, all infants were vigorous (score 8–10) at five minutes. All postnatal courses were uneventful.

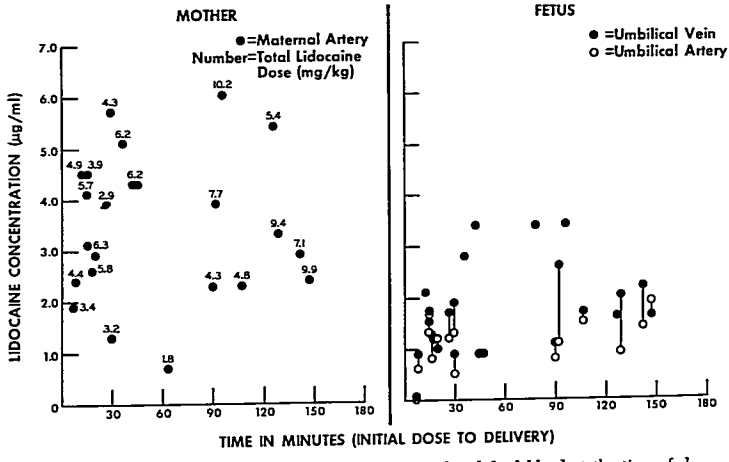

FIG. 4. Concentrations of lidocaine in maternal arterial and fetal blood at the time of delivery following multiple doses of paracervical and pudendal injections. Durations of analgesia from the time of initial injection to the time of delivery were 5 to 150 minutes.

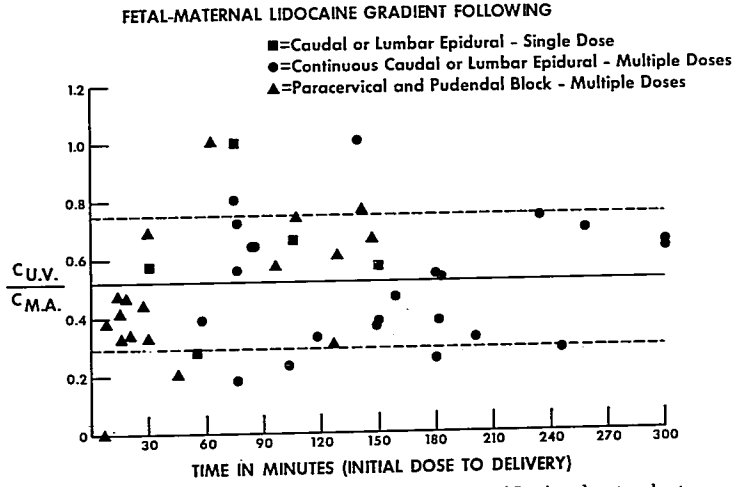

FIG. 5. Ratios of lidocaine concentrations in umbilical vein ($C_{U.V.}$) and maternal artery ($C_{M.A.}$) following administration of the drug to provide caudal, lumbar epidural, paracervical or pudendal block anesthesia.

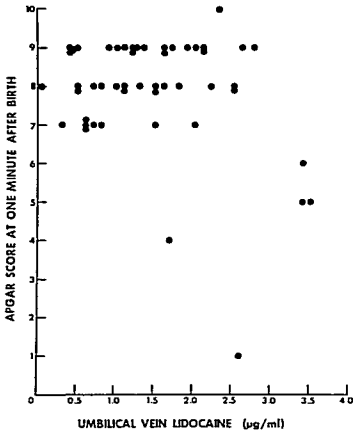

FIG. 6. Relation of lidocaine concentration in the umbilical vein at birth to condition of infant as measured by the Apgar score at one minute.

Discussion

MATERNAL LIDOCAINE BLOOD LEVELS AND TOXICITY

The results clearly indicate that when lidocaine is used to produce lumbar epidural, caudal, paracervical or pudendal anesthesia, the drug is rapidly absorbed from sites of injection into the maternal circulation and transmitted across the placenta to the fetus. Following a single epidural injection, lidocaine was detected in maternal arterial blood within two to three minutes, and reached a maximum level of approximately 2 μg./ml. in 15 minutes (fig. 1).

The blood level of local anesthetic at birth appeared to depend on various factors, including total dose, interval between final dose and delivery, and presence of epinephrine in the local anesthetic. Thus, maternal blood levels of lidocaine tended to be higher following paracervical and pudendal blocks (3.5 μg./ml.) than following epidural block (2.7 μg./ml.), despite the fact that the mean total dose used in the latter procedure was greater (paracervical and pudendal 5.6 mg./kg.; epidural 8.2 mg./kg.). Likely reasons for the higher levels in the paracervical–pudendal blocks are that epinephrine was not used and the final injection was invariably closer to delivery than in the epidural series. Moreover, the paracervical region is highly vascular, which would favor rapid absorption of lidocaine.

With the exception of minimal hypotension, which immediately responded to left uterine displacement, no abnormal signs or symptoms were found in the mothers during regional anesthesia. It appears, therefore, that the toxic threshold for lidocaine in maternal arterial blood is more than 6 μg./ml. Unfortunately, the only data available relate venous rather than arterial blood levels to drug toxicity. This is regrettable because the arterial plasma level (together with blood flow) determines the level of the drug in the brain and heart. Our studies following epidural anesthesia indicated that venous levels were usually lower than arterial levels, but varied greatly.

Foldes [3] reported that with slow intravenous infusion of lidocaine, 5 mg./kg./min., into ten conscious volunteers, after 13 minutes all patients showed signs of cortical irritation, such as visible muscular fasciculations and, occasionally, convulsions. The venous blood level at this time was 5.29 ± 0.55 μg./ml. Even earlier (after three minutes or after receiving approximately 100 mg. of lidocaine I.V.) subjective symptoms such as euphoria, disorientation, numbness and sleepiness were noted. The toxic threshold apparently is increased under light general anesthesia. Bromage [4] reported that in patients anesthetized with thiopental and nitrous oxide, cardiovascular signs were not observed until the lidocaine level in venous blood was approximately 10 μg./ml. Results of our previous studies [1] suggested that an arterial blood level even as high as 30 μg./ml. may not be associated with toxic signs, provided this level is transient and declining (for example, 30 seconds following a rapid I.V. injection of lidocaine).

FETAL LIDOCAINE BLOOD LEVELS AND TOXICITY

The use of lidocaine to produce obstetrical anesthesia presumably is based on the assumption that the fetus will rarely be harmed. Any adverse effects are thought to result from maternal anesthetic complications such as con-

vulsions, apnea or hypotension, which result in fetal hypoxia. However, on rare occasions the fetus can be subjected to toxic quantities of a local anesthetic when large quantities are accidentally injected into the fetal scalp during caudal anesthesia.[5] In this catastrophe, fetal blood levels would obviously be far higher than those found during maternal administration.

Our results indicate that when lidocaine is used to provide a variety of types of obstetrical anesthesia, the fetal umbilical venous blood levels at birth are approximately 50 per cent of the maternal arterial levels. However, the variation is such (fig. 5) that predictions of fetal blood levels of lidocaine based on maternal levels yield only a rough approximation.

Our results further suggest that occasionally relatively high levels of lidocaine may be achieved transplacentally, and these levels may be associated with depression of the infant at birth. In the large majority of our 50 cases (90 per cent) the infants born following epidural, caudal, paracervical, or pudendal blocks were vigorous, with Apgar scores of 7 to 10. With one exception these infants had umbilical venous blood levels of lidocaine of less than 2.5 μg./ml. On the other hand, three of the five depressed infants had lidocaine levels greater than 3.0 μg./ml.

Morishima and her associates [6] studied the transmission of mepivacaine across the placenta in 56 healthy women at term who received epidural analgesia during labor and delivery. Twelve infants were depressed at birth; in five, umbilical venous blood levels of the drug were significantly higher (3.15 to 4.28 μg./ml.) than those found in vigorous babies. Comparison of their data with ours suggests that at drug concentrations and doses which produce equivalent continuous epidural anesthesia in the mother, the mean fetal blood levels following mepivacaine are higher than those following lidocaine (mepivacaine, umbilical vein = 2.68 ± 0.22 μg./ml.; lidocaine, umbilical vein = 1.3 ± 0.16 μg./ml.). This may be due to inherent differences in uptake, metabolism and excretion of the two drugs, or to our routine use of 1:200,000 epinephrine, which decreases absorption of lidocaine from the epidural space into the maternal circulation.[7]

The ability of local anesthetics to exert depressant effects in the newborn is not unexpected. Usubiaga [8] has demonstrated that lidocaine administered systemically to human adults can depress ventilation and diminish or abolish cutaneous reflexes. What is of interest is the relatively lower blood levels in the newborn at which these effects can be noted (newborn > 2.5 μg./ml.; adult > 5.0 μg./ml.). Possible explanations are additive effects of birth asphyxia and drug depression and/or a lower blood–brain barrier to the drug in the infant. Wagman and associates [9] and Englesson [10] have demonstrated in experimental animals that the higher the Pa_{CO_2} the lower the threshold dose of lidocaine needed to produce toxic effects. Since all infants have some degree of asphyxia with elevated Pa_{CO_2},[11] this might result in a high cerebral blood flow, with lidocaine reaching the brain more rapidly. Experimental findings [12] indicate also that the enhanced sensitivity of the newborn rat to morphine in comparison with the adult is attributable to the fact that a partial blood barrier to morphine develops with increasing age. However, a more definitive explanation can be obtained only by further experimentation.

Summary

When lidocaine was used in obstetrical patients to produce lumbar epidural, caudal, paracervical or pudendal block anesthesia, the drug was rapidly absorbed from sites of injection into the maternal circulation. Umbilical venous lidocaine concentration at birth was 52 ± 23 (S.D.) per cent of that found simultaneously in the maternal artery. Very rarely, the infant was slightly depressed at birth, and this depression appeared to be associated in part with high lidocaine levels in the umbilical venous blood.

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Silver wire sculpture on a black background by Mrs. Narendrakumar Shah, Bronx, N. Y., first prize winner in the special awards category at the 1967 Physicians' Art Exhibit at the 1967 Annual Meeting in Las Vegas.