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Neurobehavioral Responses and Drug Concentrations in Newborns after Maternal Epidural Anesthesia with Bupivacaine

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The neurobehavioral status of 20 newborn infants was evaluated after two to four hours of life following maternal epidural anesthesia with bupivacaine for labor and vaginal delivery. All infants were normal products of uncomplicated full-term gestations. The 20 infants, whose mothers had received continuous lumbar epidural anesthesia with bupivacaine, demonstrated no measurable difference from control infants and did not have the decrease in muscle tone and strength observed in infants whose mothers had received continuous lumbar epidural anesthesia with lidocaine or mepivacaine in a previous study. (Key words: Anesthetic techniques, peridural: Anesthesia, obstetric: Anesthetics, local, bupivacaine: Psychologic responses, neonatal.)

IN 1974, we reported significant neurobehavioral effects in newborn infants following maternal epidural anesthesia for relief of pain during labor and delivery.[1] In that study, in which the techniques for the neurobehavioral examination of the newborn were detailed, significant differences were observed in a group of infants whose mothers had received either lidocaine or mepivacaine compared with a similar group where epidural block had not been employed. Subsequently,[2] we compared the blood levels of lidocaine or mepivacaine and the time courses of drug disappearance from the blood of 94 newborn infants whose mothers had received these local anesthetics for epidural anesthesia during labor and delivery.

Since these two earlier studies, bupivacaine has been introduced and has achieved widespread use in obstetric patients. The present report is an extension of the earlier ones and presents, for comparison, bupivacaine blood levels and neurobehavioral responses in 20 infants following maternal epidural anesthesia with bupivacaine.

Methods

The subjects for this study were randomly selected from a group of healthy parturients with uncomplicated full-term pregnancies who were admitted in labor for normal vaginal deliveries. Any abnormality of either this or a previous pregnancy, any problem during labor or delivery, or with the fetus or newborn, excluded potential subjects from the study. Written informed consent was obtained from the mother. The characteristics of the study population (table 1) did not differ significantly from those in our earlier studies.[1,2]

At an appropriate time during labor, a

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catheter was inserted into the maternal lumbar epidural space and anesthesia established with 0.5 per cent bupivacaine without epinephrine. At suitable intervals thereafter, anesthesia was reinforced with further injections of bupivacaine. Maternal vital signs and fetal heart rate were monitored throughout labor.

Utilizing a doubly-clamped segment of umbilical cord, blood samples were taken from the umbilical artery and umbilical vein at delivery, along with a sample from a maternal vein, for measurement of bupivacaine concentration and *p*H. When the infants were 2, 4, 8, and 24 hours old, arterialized blood samples were obtained from a heel as previously described.[2] The content of bupivacaine in these blood samples was analyzed by a previously described method[3-5] that requires 0.2 ml of blood. Results were reproducible within ± 10 per cent at concentrations as low as 0.02 μg/ml.

Each infant was examined once between the ages of 2 and 4 hours using the neurobehavioral examination described earlier.[1] The examiner was unaware of the type of anesthesia that had been given to the mother.

Results

Table 2 presents the results with bupivacaine in these 20 deliveries. For comparison, our earlier data[2] with lidocaine and mepivacaine without epinephrine are recapitulated.

The total dose of bupivacaine averaged 112 mg. This is 26 to 30 per cent of the doses of lidocaine and mepivacaine, respectively, in the earlier series of patients, despite the similar total durations of anesthesia in the three groups.

TABLE 1. Study Population*

Number	20
Maternal age (years)	26 (19–30)
Parity	2 (1–3)
Duration of labor (hours)	7.5 (5–10.5)
Birth weight (g)	3,300 (2,538–3,632)
Gestational age (weeks)	40 (37–41)
Apgar score (5 min)	9 (8–10)
*p*H at delivery	
Umbilical vein	7.37 ± 0.02
Umbilical artery	7.26 ± 0.03

* The figures are averages and ranges except that medians are given for parity and Apgar score; *p*H at delivery is mean ± SE.

The average concentration of bupivacaine in maternal venous blood at the time of delivery was 0.41 ± 0.05 μg/ml (1.42 nM/l). Concentrations in umbilical-vein blood averaged 0.11 ± 0.02 μg/ml (0.38 nM/l) and those in umbilical-artery blood, 0.10 ± 0.01 μg/ml (0.35 nM/l). The average fetal/maternal concentration ratio at delivery was 0.27.

In all infants bupivacaine was present in the umbilical vessels at the time of delivery, but in only one infant was the drug detectable thereafter. In this case, the mother had received the largest total dose of bupivacaine in this series (170 mg) and the maternal

TABLE 2. Characteristics of Epidural Anesthesias and Blood Levels of Local Anesthetics

	Bupivacaine* (n = 20)	Lidocaine* (n = 11)	Mepivacaine* (n = 42)
Total maternal dose (mg)	112 ± 7†	423 ± 40	374 ± 21
Number of doses (median)	2	4	3
Time from initial dose to delivery (min)	177 ± 22	183 ± 10	136 ± 10
Time from last dose to delivery (min)	71 ± 10	22 ± 10	27 ± 2
Concentration of local anesthetic at delivery (μg/ml)			
Maternal venous blood	0.41 ± 0.05	2.30 ± 0.29	2.89 ± 0.16
Umbilical vein blood	0.11 ± 0.02	1.17 ± 0.14	1.84 ± 0.12
Umbilical artery blood	0.10 ± 0.01	0.94 ± 0.10	1.56 ± 0.56
Fetal/maternal ratio (UV/MV)‡	0.27 ± 0.01	0.52 ± 0.02	0.64 ± 0.02

* Reference 2.
† Mean ± SE.
‡ UV/MV = umbilical vein concentration/maternal vein concentration at delivery.

TABLE 3. Results of Neurobehavioral Tests*

	Median Score	Comments
1. Predominant state	A_2	(10 in A_2; 6 in A_1; 4 in S_1)
2. Response to pin prick	2	
a. Habituation	7	
3. Muscle tone scores		
a. Pull to sitting	2	
b. Arm recoil	2	
c. Trunk tone	2	
d. General body tone	2	
4. Rooting	2	
5. Sucking	2	
6. Moro response	2	
a. Habituation	6	(Absent in one infant)
7. Habituation to light	6	
8. Response to sound	2	
a. Habituation	6	
9. Placing	2	
10. Alertness	2	
11. General assessment	Normal	(15 normal; 5 superior)

In the classification of state, A is awake and S is sleeping; A_1 is drowsy but easily arousable, A_2 is alert with a high level of spontaneous activity, S_1 is light sleep with a low spontaneous activity level.

The numbers represent the median scores of the infants in each test category. In each instance where the score is 2, this represents a normal or high score. The results for the four tests of habituation reflect the median number of times that the stimulus was applied before the infant altered his response (response decrement or habituation behavior).

* Further details of the testing and scoring procedures are found in reference 1.

venous blood concentration of bupivacaine at delivery was 0.33 μg/ml. In the infant, the concentration of bupivacaine in the venous blood was 0.10 μg/ml and that in umbilical-artery blood, 0.10 μg/ml. The heel blood sample at 2 hours of age contained 0.04 μg/ml, and at 4 hours 0.03 μg/ml. Bupivacaine was not found in this baby's 8- and 24-hour samples; therefore, its concentration was assumed to be less than 0.02 μg/ml which is the lower limit of the analytic method.

All 20 babies were either normal or superior in the single neurobehavioral examination carried out on these infants between 2 and 4 hours of age (table 3). The predominant state in each newborn was awake, and the median responses to all stimuli were prompt and brisk. Muscle tone was normal, as was the infants' ability to alter their responses to repeated stimulation (response decrement behavior or habituation). The latter phenomenon was recorded as absent in only one infant and in response to only one of the battery of stimuli, specifically the test for the Moro reflex.

Discussion

The experimental group of 20 mothers and their infants clinically did not differ significantly from those previously studied with lidocaine and mepivacaine[1,2] except that in the present group, 0.5 per cent bupivacaine was used for the epidural anesthesia during labor and delivery. In all instances, excellent relief of pain was obtained. Since no epinephrine was used in the bupivacaine group, comparisons are limited to the lidocaine and mepivacaine subjects who received epinephrine-free solutions.

A number of differences are apparent when comparing the clinical data and the blood levels among the three groups of patients. Because of the greater potency and duration of action of bupivacaine, a much lower total dose was needed to provide adequate block than is the case with lidocaine or mepivacaine. The average patient needed only one supplemental dose of bupivacaine, and the times between last dose and delivery averaged about three times longer than with either lidocaine or mepivacaine. It is not surprising, then, that the concentration of bupivacaine in maternal blood at the time of delivery was significantly lower than with the other two drugs (table 2).

In the distributions of the three drugs between mother and fetus at the time of delivery, a comparison of the fetal/maternal concentration ratios reveals the highest value (0.64) for mepivacaine; next, lidocaine (0.52); last, bupivacaine (0.27). These differences are statistically significant ($P < 0.01$).

The low fetal/maternal concentration ratio for bupivacaine in our series confirms the findings of others.[6,7] Tucker and associates found that the differences in the fetal/maternal concentration ratios for bupivacaine and lidocaine can be largely accounted for by the differences in the binding to maternal and

TABLE 4. Physiochemical Characteristics of the Amide Local Anesthetics*

	Molecular Weight (Base)	pK, (25°C)	Per Cent Ionized at pH 7.4	Plasma Protein Binding		Partition Coefficients	
				Maternal	Fetal	N-Heptane	Oleyl Alcohol
Mepivacaine	246	7.7	61	65 per cent	—	0.8	16.7
Lidocaine	234	7.9	75	56 per cent (1 μg/ml)	24 per cent	2.9	25
Bupivacaine	288	8.1	83	95 per cent (1 μg/ml)	66 per cent	27.5	314
Etidocaine	276	7.7	61	94 per cent	—	142.0	—

* Adapted from references 7, 9, 11 and 16.

fetal plasma proteins. Bupivacaine has a high affinity for maternal plasma proteins and a somewhat lower affinity for fetal plasma proteins. At a concentration of 1 μg/ml, 95 per cent of bupivacaine is bound to maternal plasma protein, whereas only 66 per cent is bound to fetal protein. The corresponding figures for lidocaine are 56 and 24 per cent, respectively (table 4).

It is important to recognize, however, that the fetal/maternal concentration ratio is only an index of the relative concentrations of a drug in maternal blood and fetal blood at the time of delivery. By itself, this ratio does not allow inferences to be drawn regarding the magnitude of transfer of a drug from mother to fetus, nor does it permit speculation about the distribution of a drug within the mother or fetus.

Preliminary experimental data that shed light on the latter issues were obtained by Morishima *et al.*** in a comparison of lidocaine and etidocaine in pregnant guinea pigs. They found that the same proportions of maternally administered etidocaine and lidocaine were found in the fetus, despite greatly differing fetal/maternal concentration ratios (lidocaine ratio = 0.8; etidocaine ratio = 0.2). In addition, they presented evidence that uptake of etidocaine by fetal tissues (heart, brain and liver) was significantly greater than in their earlier studies with lidocaine.[9] They argue that the lower blood concentration of etidocaine and the lower fetal/maternal concentration ratio do not result from lessened net transfer from mother to fetus, but rather from greater uptake by fetal tissues and more rapid disappearance of etidocaine from the fetal blood stream, presumably because of the higher lipid solubility of etidocaine and its larger volume of distribution.

Our data comparing the disappearances of lidocaine, mepivacaine and bupivacaine from neonatal blood in the early hours of life might also be interpreted in this way. If a major element in the clearance of a local anesthetic from the blood is its uptake into tissues, and if the latter is primarily a function of lipid solubility, then one would expect that the three local anesthetics would behave as we have found.

As detailed by Tucker *et al.*,[9] the three local anesthetics we studied differ among themselves not only in binding to plasma proteins but also in lipid solubilities (table 4). Measured with n-heptane and measured with oleyl alcohol, the rank orders of lipid solubility of the three local anesthetics are the same, mepivacaine < lidocaine ≪ bupivacaine. Bupivacaine is by far the most lipid-soluble of the three. Etidocaine is even more lipid-soluble than bupivacaine (table 4) and binds to plasma proteins to about the same extent.[10,11]

Our experimental data show that mepivacaine persists longest in blood of the newborn, with a half-life of approximately nine hours. Lidocaine occupies an intermediate position, with a half-life of three hours. The half-life of bupivacaine could not be determined from our experiments since it was detectable after birth in the blood of only one

** Morishima HO, Finster M, Pederson H, et al: Placental transfer and tissue distribution of etidocaine and lidocaine in guinea pigs. Abstracts of Scientific Papers, Annual Meeting of the American Society of Anesthesiologists, 1975, pp 83–84.

infant. The correlation with lipid solubility is apparent, and suggests that the rapidity of drug exit from the blood stream of a neonate may be directly related to the lipid solubility of that drug. The higher the lipid solubility, the more rapid is the distribution of the anesthetic into and, perhaps, the more firm its retention by, tissues.

It is likely, then, that both binding and lipid solubility play important roles in distribution of a local anesthetic within the mother, in its transplacental transfer, and in its distribution within the fetus and neonate. Other possible explanations include developmental differences in metabolism and excretion. More work must be done before these speculations can be converted into explanations.

Turning to the neurobehavioral data, one is struck by the absence of appreciable effect in the bupivacaine group of infants compared with those exposed to either lidocaine or mepivacaine. Since the publication of our earlier report in 1974,[1] the possible significance of these observations has been commented on in editorials and reviews.[12–14] Only two further comments need be made here.

First, it continues to be unclear whether the decrease in muscle tone and strength observed in the neonates following lidocaine or mepivacaine has any clinical significance for early growth and development. Nevertheless, the data from the present group of 20 infants whose mothers received bupivacaine and who were free of the effects associated with the other local anesthetics can be taken *a priori* as at least a theoretical advantage for bupivacaine in obstetrics. Brazelton and co-workers[15] have shown that the effects of lidocaine and mepivacaine largely disappear by the second day of life, suggesting that these transient effects, limited to very early neonatal life, are of limited clinical significance in the healthy, full-term neonate delivered after a totally uncomplicated labor.

The second point relates to the possible mechanism of the differences in the neurobehavioral effects of bupivacaine versus lidocaine and mepivacaine. As described above, bupivacaine disappears very rapidly from neonatal blood, perhaps owing to its higher lipid solubility. It would also be expected to disappear from extracellular fluid more rapidly than lidocaine and mepivacaine. One may speculate that, as discussed in our previous paper,[1] lidocaine and mepivacaine produce neonatal hypotonia by an effect at the neuromuscular junction. The lack of such an effect with bupivacaine may be the result of its rapid disappearance from blood and extracellular fluid, and hence from the pre- and postsynaptic membranes at the neuromuscular junction. Better understanding of the implications of these observations must await further explanation of both the distribution and the mechanism of action of local anesthetics in the newborn.

Pending such clarification, and in view of our findings with bupivacaine, lidocaine and mepivacaine, it is our opinion that bupivacaine offers important advantages for the obstetric patient. Injections are needed less frequently because of its long duration of action, and tachyphylaxis has not been a problem. Bupivacaine can be used without epinephrine, thus eliminating concern about the latter's potential depressant effect on uterine contractility. Finally, the absence of detectable neurobehavioral effects in the newborn may be a significant advantage.

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Thoracic Anesthesia

FIBEROPTIC BRONCHOSCOPY The fiberoptic bronchoscope is especially valuable for evaluation of peripheral lung densities, in elucidating hemorrhage of obscure cause, and in examination of patients on respirators or those who have cervical or cranial disease. The rigid bronchoscope retains certain advantages: it is preferred for removal of a foreign body or broncholith, for pediatric bronchoscopy, for aspiration of massive hemorrhage or retained thick secretions, and for use in patients with narrowed tracheal diameters. The fiberoptic scope permits visualization of the larynx and nasopharynx. (*Krock CJ: Fiberoptic bronchoscopy, Carle Selected Papers 28: 26, 1975, Urbana, Ill.*) ABSTRACTER'S COMMENT: The fiberoptic bronchoscope can serve as a guide over which an endotracheal tube can be passed in a patient whose anatomy prevents visualization of the larynx with a conventional laryngoscope.