Transmission of Mepivacaine Hydrochloride (Carbocaine) Across the Human Placenta

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Transmission of mepivacaine hydrochloride (Carbocaine) across the placenta was studied in 56 healthy women at term who received epidural analgesia during labor and delivery. All infants were delivered vaginally. Concentrations of mepivacaine were determined in maternal and umbilical cord blood by the methyl orange method. Mepivacaine administered into the maternal epidural space passed rapidly into the blood stream and crossed the placenta. Five mothers who received repeated injections, developed toxic symptoms; concentrations of the drug in blood were significantly higher than those in patients without complications. Twelve infants were depressed at birth; in 5, blood levels of the drug were significantly higher than those found in vigorous babies.

IT IS widely believed that little of the local anesthetic agent administered into the epidural space of the mother reaches the fetus. The infant is usually vigorous at birth provided that there have been no maternal complications.[1-8]

A number of local anesthetic agents including procaine, chlorprocaine (Nesacaine), and tetracaine (Pontocaine) contain ester bonds, and are rapidly inactivated by plasma esterase. Thus absorption of these drugs from the epidural space is not accompanied by a significant rise in blood concentration. On the other hand, drugs with an amide linkage such as lidocaine (Xylocaine) and mepivacaine (Carbocaine) are relatively stable in blood and are likely to remain in the maternal vascular space in detectable amounts after absorption from the epidural space. If the mother receives a large dose of one of these substances during prolonged labor, it is possible that a sufficient quantity could cross the placenta into the fetal circulation.

Since mepivacaine hydrochloride is widely used for regional analgesia during labor, the present study was undertaken to determine the rate of absorption of this drug from the epidural space, to discover whether it reaches the fetus and if so, whether it results in depression.

Material and Methods

Fifty-six healthy pregnant women at term and their newborn infants were studied. All deliveries were per vaginam, 23 infants being born spontaneously and 33 with the assistance of outlet forceps. Caudal anesthesia was administered to 37 mothers and lumbar epidural anesthesia to the remainder. Fourteen of these mothers were given sedative or tranquilizing drugs prior to administration of regional anesthesia; 12 received secobarbital sodium (Seconal) 100 mg. or chlordiazepoxide hydrochloride (Librium) 100 mg. intramuscularly, and 2, 200 mg. of each drug. The remaining 42 received no preanesthetic drugs.

Mepivacaine hydrochloride (Carbocaine) (1.5%) was used without epinephrine. The drug was administered into the caudal or lumbar epidural space either as a single injection (32 cases) or intermittently through an indwelling catheter (24 cases). Mean total dose for those receiving a single injection was 5.2 mg./kg. (range 3.5–7.2) and for those receiving intermittent injections, 6.6 mg./kg. (range 4.4–9.4). Maternal responses, blood pressure and the fetal heart rate were observed frequently. The infants were clinically

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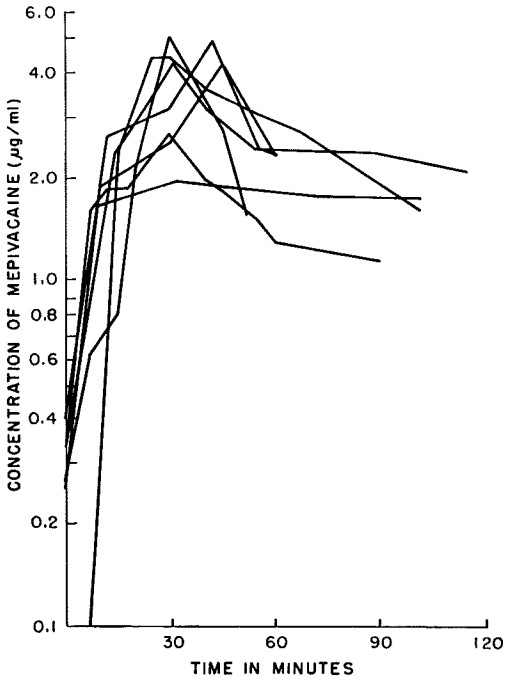

FIG. 1. Relationship between blood concentration of mepivacaine and time lapse following single injection of 300 to 375 mg. of the drug in 7 mothers.

evaluated by the Apgar scoring system, one minute after birth.[9] Blood samples were withdrawn from the maternal antecubital vein and the umbilical artery and vein at the time of delivery. In 7 patients additional venous samples were taken between 7 and 114 minutes after a single injection of mepivacaine.

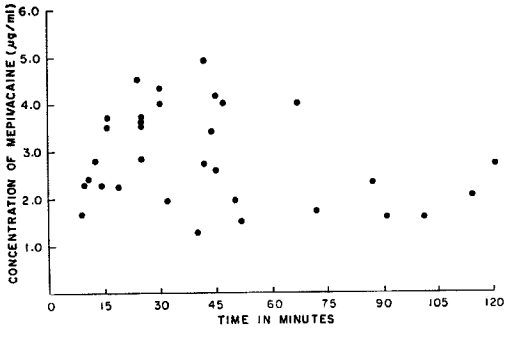

FIG. 2. Concentration of mepivacaine in maternal blood following single injection. Duration of analgesia, prior to delivery, ranged from 9 to 120 minutes.

Mepivacaine concentration was determined as the methyl orange salt by a micromodification of Sung and Truant's methyl orange method for lidocaine.[10] Details of the analytic method will be published elsewhere.[11] Calibration curves were obtained by addition of known amounts of mepivacaine to blood or water. From these curves, it was ascertained that 95 per cent of the drug could be recovered from blood. Both curves were found to be linear up to a concentration of 9 μg./ml. Because the concentration of mepivacaine in the ampules supplied could vary, a new standard was determined for each batch.

Values for plasma blank were determined in maternal venous blood prior to administration of mepivacaine and in cord blood of 5 infants whose mothers had received no mepivacaine. They were 0.23 ± 0.038 (S.E.) μg./ml. for maternal blood and 0.20 ± 0.004 (S.E.) for both umbilical arterial and venous blood.

The *p*H, P_{CO_2} and base deficit of umbilical arterial and venous blood were determined within 30 minutes by the method of Siggaard-Andersen and associates.[12] The oxygen saturation of blood was measured spectrophotometrically[13] and the hematocrit by a micro technique.

Results

Concentration of Mepivacaine in Blood. Mepivacaine was present in maternal plasma as early as seven minutes following a single injection (fig. 1), and peak concentrations were reached in 25–40 minutes. The drug was also consistently present at birth in both maternal and fetal blood (figs. 2 and 3). Maternal concentrations averaged 2.91 μg./ml. ± 0.280 (S.E.) and were significantly higher than in either of the umbilical cord vessels ($P < 0.01$). Levels in umbilical venous blood (UV) averaged 1.90 ± 0.158 μg./ml., and in umbilical arterial blood (UA), 1.42 ± 0.131 μg./ml.; the concentrations in UV were significantly higher than in UA ($P < 0.05$). Peak concentrations in fetal blood appeared to be reached in 30 to 45 minutes after the administration of the drug to the mother. After this time levels in both mother and fetus fell gradually.

Following intermittent administration, con-

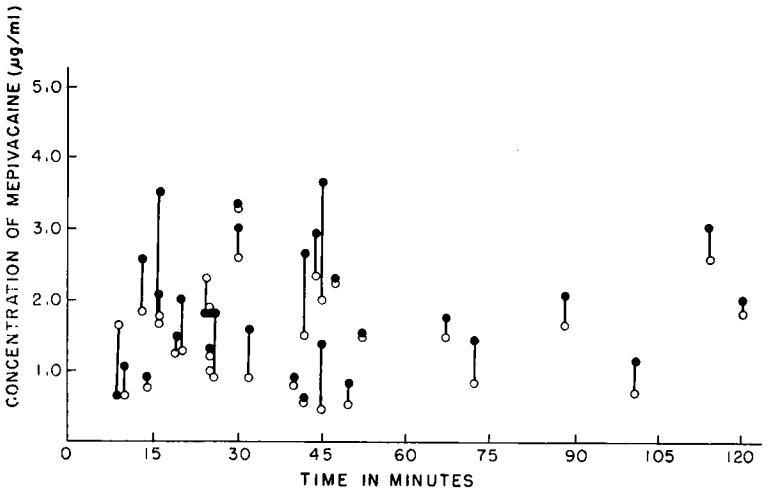

FIG. 3. Concentration of mepivacaine in umbilical artery (○) and umbilical vein (●) following single injection of the drug to the mother.

centrations of mepivacaine in both maternal and fetal blood were significantly higher ($P < 0.01$) than when the drug was given as a single injection (figs. 4 and 5). Individual variations were considerable; maternal levels averaged 3.90 ± 0.394 μg./ml., and fetal levels 2.68 ± 0.221 μg./ml. (UV) and 2.47 ± 0.205 μg./ml. (UA). Maternal concentrations in blood did not correlate significantly with duration of anesthesia nor was there any tendency to decline during the 250-minute period of investigation. The ratio of drug concentration in umbilical vein and maternal vein was 0.71 ± 0.042 and appeared to be relatively constant after 60 minutes (fig. 6).

Reaction of the Mother to Mepivacaine. No

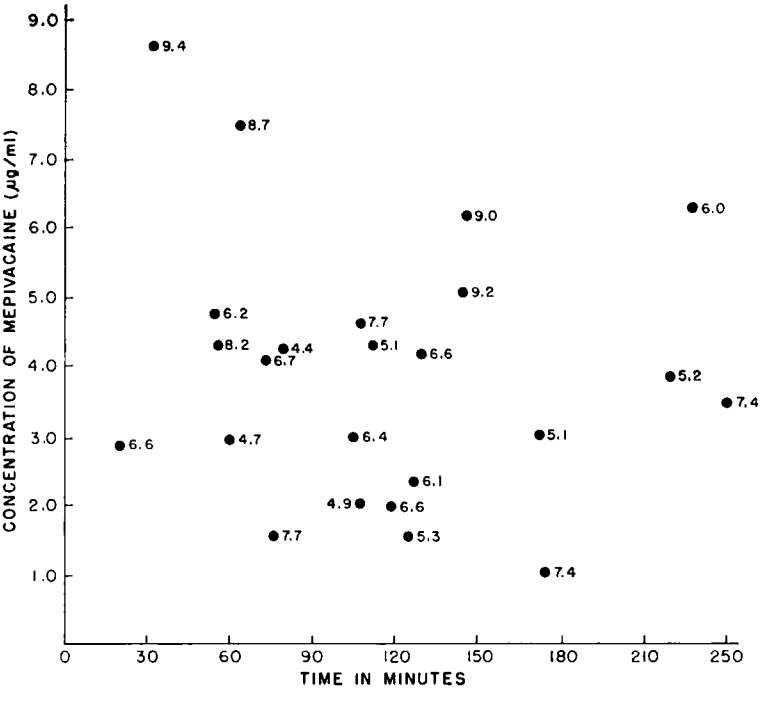

FIG. 4. Mepivacaine concentration in maternal blood at time of delivery following repeated injections. Duration of analgesia from the time a test dose was given to the time of delivery was 20 to 251 minutes. Numbers indicate total dose of drug (mg./kg.).

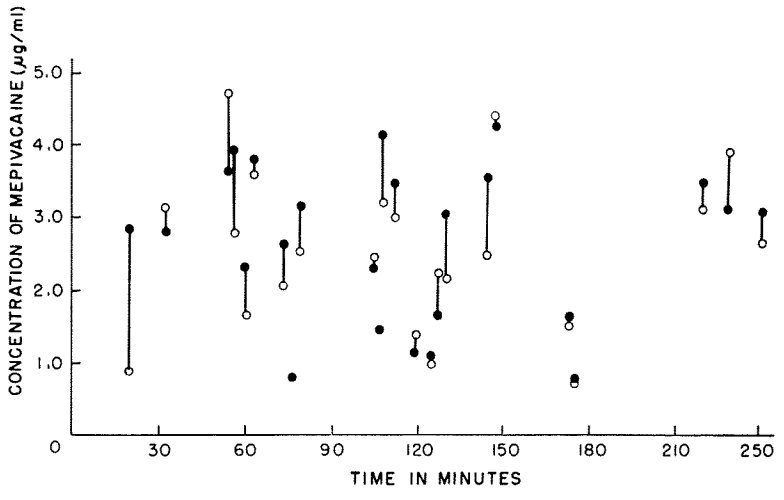

FIG. 5. Mepivacaine concentration in umbilical artery (○) and umbilical vein (●) following repeated administration to the mother.

major maternal complications such as convulsions, loss of consciousness or circulatory collapse occurred in this series. However 7 patients had transient hypotension between 3 and 17 minutes after administration of mepivacaine with systolic pressures below 90 mm. of mercury (table 1). All responded satisfactorily to displacement of the uterus to the left (L.U.D.) and administration of ephedrine, the blood pressure returning promptly to normal. The hypotension did not appear to be related either to the dose administered or to the blood concentration at the time of birth.

Five other patients developed mild cerebral symptoms including apprehension, confusion, shivering, muscular twitching, nausea and vomiting (table 1). All had received an average dose of 8.9 mg./kg. by intermittent administration. The concentrations in blood of mepivacaine averaged 6.27 μg./ml. and were significantly higher than those in patients without complications or with hypotension alone.

Reaction of the Infants to Mepivacaine. Twelve of the 56 infants were depressed at birth with Apgar scores of 6 or less (table 2). The mothers of 8 had received mepivacaine by multiple injection. In 5 of the 12, blood levels were significantly higher than the mean for all infants, and the concentration gradient between umbilical vein and artery was small or reversed. Mothers of these 5 infants all experienced various untoward effects of anesthesia. In the remaining 7 infants, concentrations of mepivacaine in blood were not different from those in the vigorous group. In all but one, depression could have been related to fetal distress (irregular fetal heart rate and meconium), tight nuchal cord (4 cases) or excessive maternal premedication (2 cases); these showed significantly more acidosis than infants scoring 7 or higher (table 3).

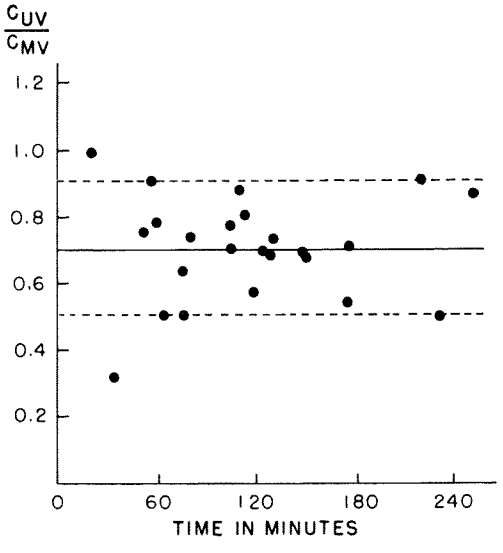

FIG. 6. Ratio of mepivacaine concentration in umbilical vein (CUV) and maternal vein (CMV) following administration of the drug. Solid line indicates the mean value (0.71) and broken lines signifying two standard deviations (0.203) from the mean.

TABLE 1. Summary of Reaction to Mepivacaine-Analgesia in Twelve Mothers

Patient	Method of Analgesia	Total Dose of Mepivacaine (mg.)	Total Dose of Mepivacaine (mg./kg.)	Time from First Injection to Delivery (min.)	Blood Concent. of Mepivacaine at Birth (μg./ml.)	Signs and Symptoms
1	Single caud.	375	6.1	42	2.72	Hypotension
2	Single caud.	375	5.5	25	3.72	Hypotension
3	Single caud.	360	5.6	30	4.37	Hypotension, nausea, vomiting
4	Single caud.	375	7.2	42	4.95	Hypotension
5	Cont. caud.	375	6.2	54	4.77	Hypotension, nausea, vomiting
6	Cont. caud.	390	6.5	105	5.40	Hypotension
7	Cont. epi.	390	6.0	229	6.30	Hypotension, nausea, vomiting
8	Cont. caud.	620	8.2	56	4.35	Confusion
9	Cont. epi.	675	9.2	145	5.08	Shivering, nausea, muscular twitching
10	Cont. caud.	600	9.0	147	6.20	Shivering, muscular twitching
11	Cont. epi.	600	8.7	63	7.47	Apprehension, vomiting, sweating
12	Cont. caud.	750	9.4	32	8.62	Apprehension

Caud. = caudal; epi. = epidural; cont. = continuous.

Discussion

The findings of this study indicate that the mepivacaine, administered into the maternal epidural space, passes rapidly into the maternal blood stream, and crosses the placenta. Within 10 minutes of injection, the drug can be detected in fetal blood. The rate of absorption from the epidural space was not quite as rapid as that for lidocaine, as reported by Bromage and Robson,[14] although the difference was not striking.

It seems that the drug traverses the placenta by simple diffusion, probably because of its low molecular weight (282.8).[15] Peak levels were found in both maternal and fetal blood approximately 30 minutes after injection. The ratio of concentrations of drug in umbilical vessels and maternal vein suggests that equilibrium between mother and fetus is reached in 60 minutes.

In the group receiving multiple injections, there was a decrease in the concentration gradient across the placenta and between the cord vessels 45 minutes after the initial dose, suggesting that the drug was accumulating in the fetus.

The high incidence of depression in the study group is probably related to the small number of patients involved since in a larger series of 1,900 infants only 13.5 per cent were depressed.[17] It is probable that more than one factor was responsible for the neonatal depression observed in this study. The drug might have acted directly on the central nervous system of the fetus. Depression might also have been secondary to the effect of the drug on maternal circulation since epidural anesthesia can interfere with vasomotor reflexes; the lower *p*H and greater degree of metabolic acidosis in the depressed group indicate more severe degrees of intrauterine asphyxia.

A toxic threshold for mepivacaine has not been reported, but in patients anesthetized with thiopental and nitrous oxide it is about 10 μg./ml. of blood for lidocaine.[14] In the conscious patient it appears to be considerably lower, in the region of 5.29 ± 0.55 μg./ml.[18] More severe maternal complications in the present series were generally accompanied by high blood concentrations of mepivacaine, the average level being 6.27 μg./ml.

No maternal convulsions were seen in the present series but the mother in whom the blood level reached 8.62 μg./ml. was markedly apprehensive. Two others with blood levels of 5.08 and 6.20 μg./ml., respectively, had several episodes of muscular twitching. Hypotension with relatively low blood levels might have been postural since it was relieved by L.U.D.[19]

It has recently been reported that general-

TABLE 2. Data on Twelve Depressed Infants

Infant	Apgar Score	Fetal Complications	Blood Concentration of Mepivacaine (μg./ml.)			Acid-base in Cord Blood	Method of Analgesia	Total Dose (mg./kg.)	Maternal Complications
			Maternal Vein	Umbilical Vein	Umbilical Artery				
1	1	Irregular HR	7.47	3.81	3.60	Mild acidosis, low O_2 Sat.	Cont. epi.	8.7	Apprehensive, nausea, vomiting
2	1	Irregular HR	6.20	4.28	4.40	Mild acidosis	Cont. caud.	9.0	Shivering
3	3	Irregular HR, meconium	6.30	3.15	3.90	Severe metabolic acidosis	Cont. epi.	6.0	Hypotension, nausea, vomiting
4	3	Meconium	4.37	3.37	3.35	Moderate metabolic acidosis	Single caud.	5.6	Hypotension, nausea, vomiting
5	6	Irregular HR, meconium	4.77	3.72	4.70	Severe metabolic acidosis	Cont. caud.	6.2	Hypotension, nausea, vomiting
6	1	Nuchal cord	3.00	2.32	2.45	Severe acidosis, large A-V difference	Cont. caud.	6.4	None
7	2	Cord around neck × 2, meconium	4.12	2.63	2.06	Moderate metabolic acidosis	Cont. epi.	6.7	None
8	4	Cord around neck, tight, meconium, ↓HR	1.23	0.89	0.80	Severe metabolic acidosis	Single epi.	3.8	None
9	6	None	2.37	2.22	1.63	Normal	Cont. epi.	6.1	None
10	6	Meconium, sleepy newborn	3.02	1.65	1.52	Normal	Cont. epi.	5.1	Drowsy by 200 mg. Seconal and 200 mg. Librium
11	6	Irregular ECG, tight nuchal cord, meconium	3.42	2.95	2.35	Mild metabolic acidosis	Single caud.	5.9	None
12	6	Irregular HR, sleepy newborn	4.04	1.73	1.47	Normal	Single caud.	4.4	Depressed by 200 mg. Seconal and 200 mg. Librium

Caud. = caudal; epi. = epidural; cont. = continuous; HR = heart rate.

ized convulsions were observed in 4 infants into whom mepivacaine was accidentally injected during attempted caudal anesthesia.[20] Initial blood levels of the drug in 2 of these infants were 31.3 and 75.0 μg./ml., respectively. Following exchange transfusions when the concentrations of mepivacaine had decreased to 8.17 and 8.70 μg./ml., respectively, no further seizures were observed.

Therapeutic Implications. Untoward reactions were unexpectedly high in 5 patients receiving over 600 mg. of mepivacaine in 2½ hours or less; all showed some toxic effects. However in one patient who received as much as 700 mg. no toxic reactions were observed, but the drug was administered over a period of 4 hours.

From the data obtained by single injection

TABLE 3. Biochemical Analysis of Umbilical Cord Blood at Time of Delivery

Score		pH		P_{CO_2} (mm.Hg)		Base deficit (mEq./liter)	
		Umbilical vein	Umbilical artery	Umbilical vein	Umbilical artery	Umbilical vein	Umbilical artery
7–10	Mean	7.30	7.23	45.5	61.9	6.2	8.0
	SE	0.009	0.013	1.12	2.63	0.41	0.53
	N	41	31	41	29	41	29
Below 6	Mean	7.24*	7.15*	50.7†	72.0†	8.5*	11.4*
	SE	0.025	0.032	2.30	7.90	1.11	1.67
	N	12	12	12	9	12	9

* $P < 0.01$.
† $P < 0.05$.

(fig. 1) the blood level of mepivacaine appears to decrease very slowly. This low rate of disappearance should be kept in mind, since elevated concentrations of mepivacaine can occur even when consecutive injections of the drug are administered at hourly intervals. These data indicate that large doses of mepivacaine, particularly if given over a short period, are potentially dangerous.

Because the fetal blood levels of the drug also tend to remain elevated they may be sufficient to cause depression of the central nervous system of the infant at birth. Any untoward effects related to the drug are likely to continue for some time, since detoxification by the liver is slow in the fetus and newborn.[21, 22, 23]

When hypotension occurred, it took place within the first 17 minutes of injection. This observation re-emphasizes the importance of careful blood pressure monitoring particularly during the first 20 minutes after administering the drug.

Summary

Mepivacaine hydrochloride (Carbocaine) is rapidly absorbed from the epidural space into the maternal blood stream and readily crosses the placenta.

Following intermittent administration of the drug, maternal blood levels may become sufficiently high to cause toxic effects in the mother, elevation of fetal blood levels and depression of the infant at birth.

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IMBRETIL When 1 mg. of Imbretil, given intravenously to an anesthetized adult patient, was followed within a few minutes by 0.5 to 1 mg. of neostigmine, return to normal was no faster than in the controls. However, when neostigmine was given 45 minutes and longer following larger doses of Imbretil (2.5 to 11 mg.), the muscular relaxation was promptly reversed. Imbretil causes a dual block; the initial depolarization changes gradually into a competitive block, which can be promptly antagonized by neostigmine. (*Schmidt, A., Scholler, K. L., and Wiemers, K.: Investigations on the Antagonism of Prostgmine against the Muscle Relaxant Imbretil in Man, De Anaesthesist 14: 177 (June) 1965.*)

SPLANCHNIC REFLEX In lightly anesthetized cats, activation of splanchnic nerve gamma-delta fibers evoked reflex responses in the vagi of both side irrespective of the side of peripheral stimulation. Somatic nerve stimulation had little effect except when in a state of systemic strychninization. The reflex discharges were conducted mainly to the recurrent laryngeal branch. The reflex was inhibited by inactivating the somatic nerves by means of sensory block at the spinal level. Post-tetanic potentiation could be elicited by applying threshold stimulation. Among the various central nervous structures, the brain-stem reticular formation and the hypothalamus exerted an inhibitory effect on the reflex, while reflex facilitation was obtained from some restricted points of the brain-stem and the cortical surface. The limbic system showed no apparent effects upon the reflex. (*Ohsaki, K., and Iwama, K.: Splanchnic-to-Vagal Reflex in Cats (Japanese), Tohoku J. Exp. Med. 83: 353, 1964.*)