

# Placental Clearance of Mepivacaine Following Administration to the Guinea Pig Fetus

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The efficacy of placenta in removing mepivacaine (Carbocaine) from the fetus has been studied in the pregnant guinea pig and comparison made between the tolerance of the fetus and that of the newborn to the systemic effects of the anesthetic. Mepivacaine injected into the brain in doses without sequelae to the fetus were invariably lethal to the newborn. Direct relationship was encountered between the condition of the newborn and the interval between administration of the drug and delivery.

We conclude that the high tolerance of the fetus to administration of mepivacaine is due to the rapid transfer of the agent across the placenta, and to the independence of the fetus on the state of activity of its respiratory center. Inference has been made that following inadvertent administration of a local anesthetic to the human fetus, it is advantageous not to expedite delivery and to rely on the placenta for drug clearance.

MOST SUBSTANCES used in human therapeutics cross the placenta. Nevertheless, only a small fraction of the drug administered to the mother reaches fetal tissues, except when concentration in maternal blood is maintained for prolonged periods. This is chiefly due to the epicyclic arrangement of the fetal circulation in relationship to the maternal one, and to the fact that blood returning from the placenta is partly cleared by the fetal liver before reaching systemic circulation. Thus, preferential intoxication of the fetus following administra-

tion of a drug to the mother can only result when fetal susceptibility greatly exceeds that of the mother.

On rare occasions, a local anesthetic has been administered inadvertently to the human fetus during attempted caudal analgesia of the mother.<sup>1</sup> Exchange transfusions combined with gastric lavage have been employed in the treatment of the affected newborn infant.<sup>2</sup> It has not been established, however, whether this represents optimal management. There is circumstantial evidence that the placenta possesses a high diffusion capacity for local anesthetics and could, therefore, clear them more rapidly from fetal circulation than other organs. Thus immediate delivery following administration of the agent to the fetus might remove an important route of elimination and impose the burden of detoxification of the drug on the fetal liver, which possesses a low activity of oxidative enzymes.

The present study was designed to investigate whether mepivacaine (Carbocaine) crosses the placenta when administered directly to the fetus, and to compare placental clearance of the drug with the rate of its metabolism by the newborn.

## Methods

Observations were made on Hartley strain pregnant guinea pigs and their fetuses and newborns. Sixty pregnant guinea pigs thought to be near term were lightly anesthetized by intravenous administration of sodium pentobarbital (10 mg./kg.). A catheter was placed into the carotid artery for sampling of blood and monitoring of blood pressure. Animals were allowed to breathe spontaneously throughout the experiment to avoid acute changes in maternal acid-base state which could effect the fetus.<sup>3, 4</sup> After an initial blood

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sample was obtained, a small incision was made in the abdominal wall and the size of the fetus estimated by palpation. The head was secured through the intact uterine wall and mepivacaine hydrochloride (1.5 per cent) was injected directly into the fetal brain at a depth of approximately 3 mm. using a 26 gauge needle. The region between sagittal suture and supraorbital margin was chosen because it has represented the site of accidental injections of local anesthetics in the human fetus.<sup>2</sup> The drug was given only to one fetus of each litter, other fetuses serving as controls.

After 5 to 64 minutes, amniotic fluid was withdrawn from each uterine horn. The fetuses were then delivered by hysterectomy and umbilical venous samples obtained. The condition of the newborn was evaluated 1 minute after birth using a scoring system for newborn guinea pigs<sup>2</sup> which is similar to the Apgar score. Simultaneously, arterial blood samples were taken from the mother via the carotid catheter and from the newborn by puncture of the left ventricle for determination of mepivacaine concentration, pH,  $P_{CO_2}$  and base deficit. After obtaining the final blood samples, the newborn piglet was killed and the location of the injection ascertained by examination of the brain.

In a preliminary experiment varying amounts

of mepivacaine (10.3 to 690 mg./kg. of fetal body weight) were used to determine the dose required to depress the fetus without arresting placental circulation. These experiments disclosed that a dose between 10.3 to 21.8 mg./kg. had no detectable effect whereas a dose exceeding 65 mg./kg. stopped fetal circulation immediately; an intermediate dose of  $50 \pm 5$  mg./kg. depressed the fetus without seriously impairing placental circulation. For this reason the latter dose was chosen to examine the role of placenta in clearance of mepivacaine from fetal circulation.

Thirty-six spontaneously delivered newborns were used as control for the fetuses receiving mepivacaine, *in utero*. They were well developed and vigorous. Experiments were carried out at a postnatal age of 0.5 to 24 hours. Twenty-nine newborns received 50 mg./kg. body weight of 1.5 per cent mepivacaine into the brain and 7 received 0.9 per cent sodium chloride in a volume calculated to match the volume of mepivacaine diluent. Blood samples were obtained by puncture of the left ventricle through a thoracotomy immediately after the last heart beat.

Mepivacaine concentration in blood was determined by a micro-modification of the method of Sung and Truant for lidocaine.<sup>6</sup> Details of the analytic method will be published.<sup>7</sup> The maternal pH of whole blood was

TABLE 1. Mepivacaine Concentrations in Fetal and Maternal Blood and Clinical Condition of Newborn Piglets at Birth Following Injection of Small Dose (10.3 to 21.8 mg./kg. of Fetal Body Weight) of the Drug Into Fetal Brain

Experiment	Time from Injection to Delivery (minutes)	Injected Fetus			Control Fetus		Mother
		Dose (mg./kg.)	Score	Mepivacaine Concentration in Cardiac Blood ( $\mu\text{g.}/\text{kg.}$ )	Score	Mepivacaine Concentration in Cardiac Blood ( $\mu\text{g.}/\text{kg.}$ )	Mepivacaine Concentration in Arterial Blood ( $\mu\text{g.}/\text{kg.}$ )
1	5	14.6	6	3.95	10	0.55	1.20
2	5	21.8	6	8.50	10	0.11	0.34
3	5	16.6	7	5.01	9	0.11	1.12
4	45	15.5	8	4.60	9	0.19	0.83
5	46	16.3	9	2.65	9	—	—
6	46	20.0	9	4.05	9	0.41	0.91
7	48	17.7	10	3.54	10	0.62	1.06
8	48	19.4	7	3.01	8	2.01	2.17
9	49	10.3	10	4.50	10	—	—
10	57	17.3	9	2.30	9	1.59	2.05
11	57	21.8	7	7.90	9	1.49	2.65

determined at 38° C. using a microglass electrode.  $P_{CO_2}$  and base deficit values were calculated by the method of Siggaard Andersen, Engle, Jørgensen and Astrup.<sup>2</sup>

### Results

**Effects of Low Doses of Mepivacaine.** A dose of 10.3 to 21.8 mg./kg. of fetal body weight was employed in 11 experiments. The fetuses were delivered 5 to 57 minutes after injection of the drug. Nine were vigorous and scored 7 to 10 at 1 minute after birth, and 2 newborns delivered at 5 minutes were moderately depressed but recovered rapidly. The concentration of the drug obtained by cardiac puncture from 11 fetuses was less than 10  $\mu\text{g./kg.}$  (table 1) and the level in umbilical venous blood ranged from 1.68 to 2.64  $\mu\text{g./ml.}$  (mean 1.97). Mepivacaine was also detected in cardiac blood of the litter mates, in amniotic fluid and in maternal blood. The concentrations, however, were much lower averaging 0.79, 0.98 and 1.37  $\mu\text{g./ml.}$  in the respective compartments.

**Effects of Intermediate Doses of Mepivacaine.** Thirty fetuses received  $50 \pm 5$  mg./kg. of fetal body weight of mepivacaine and delivered 5 to 64 minutes following injection. A direct relation was encountered between the condition of the newborn and the time of delivery (fig. 1). All delivered 45 minutes or more following injection were vigorous and had low concentrations of the drug in blood. Those delivered within 20 minutes following

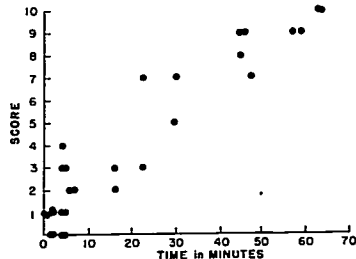


FIG. 1. Clinical condition of newborn at birth and time from injection of mepivacaine ( $50 \pm 5$  mg./kg. of fetal body weight) into fetal brain to delivery.

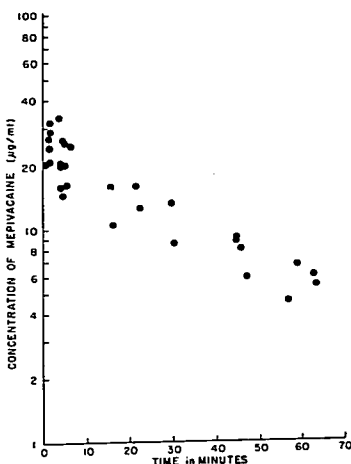


FIG. 2. Concentration of mepivacaine in fetal blood and time from injection of the drug ( $50 \pm 5$  mg./kg. of fetal body weight) into fetal brain to delivery.

injection were severely depressed, scoring 0 to 4. They were limp and unresponsive and had bradycardia; none recovered. Convulsive movements were not observed in either the vigorous or the depressed newborns.

A correlation between blood concentration of mepivacaine in the fetus and the time of delivery following the intracerebral injection is shown in figure 2. It can be seen that the drug appears in blood rapidly and reaches highest concentration in about 4 minutes. After 30 minutes the levels were below 10  $\mu\text{g./ml.}$  The concentration within 7 minutes averaged  $23.23 \mu\text{g./ml.} \pm 1.405$  (SE) and beyond 45 minutes averaged  $6.90 \mu\text{g./ml.} \pm 0.443$  (SE).

Mepivacaine was also detected in maternal blood within 2 minutes; the level remained constant over 65 minutes and averaged  $2.75 \mu\text{g./ml.} \pm 0.221$  (SE). Concentration of the drug in the noninjected litter mates was even lower than that in maternal blood, ranging between 0 to 6.9  $\mu\text{g./ml.}$  with a mean of 1.47 depending on time of delivery; concentration

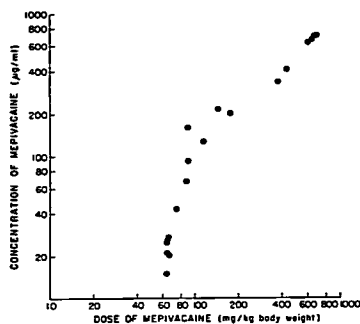


FIG. 3. Concentration of mepivacaine in fetal blood at 35 to 64 minutes and the amount of drug (65 to 690 mg./kg. of fetal body weight) into fetal brain.

was low when the fetus was delivered within 7 minutes after administration of the drug. Mepivacaine in the litter mates delivered 7 minutes after the injection of the drug averaged 0.74  $\mu\text{g./ml.}$ , in contrast to 3.01  $\mu\text{g./ml.}$  in those delivered after 45 minutes. The concentration in the amniotic fluid of litter mates ranged from 0 to 1.92  $\mu\text{g./ml.}$  and followed a similar pattern to that of blood of the corresponding fetus.

**Effects of Large Doses of Mepivacaine.** Nineteen fetuses were kept *in utero* for 35 to 64 minutes (mean 56 minutes) after injection of the drug, since it had been established that administration of a smaller dose was lethal when the fetus was delivered promptly. Twelve of 19 were stillborn, the others were severely depressed. Five scored 1, and 2 scored 3; all died shortly after birth. Their litter mates were in good condition at birth, scoring 7 to 9. The relationship between the dose of mepivacaine and concentration in blood is given in figure 3.

Despite the high levels of drug in the injected fetus concentration in umbilical venous blood was considerably lower than that following administration of the small dose. The same observation applied also to the concentration of drug in maternal blood, in litter mates and their amniotic fluids, indicating that

only small amounts of mepivacaine had crossed the placenta.

**Effects of Mepivacaine Administered to the Newborn.** None of the 29 newborns survived after intracerebral injection of the intermediate dose ( $50 \pm 5$  mg. per kg. of mepivacaine). Apnea occurred immediately following administration of the drug with the exception of 9 who made a few gasps before apnea ensued. Heart beat, however, persisted for a period of 2 to 19 minutes. Bilateral clonic seizures lasting a few seconds occurred in 17 newborns. The relation between mepivacaine concentration in blood of the newborn and the time from administration to sampling is given in figure 4. Highest levels were detected at 3 to 4 minutes following which the values declined rapidly. The mean concentration of the drug at 2 to 7 minutes was 32  $\mu\text{g./ml.}$  which significantly exceeds that encountered in the fetuses receiving the same dose of mepivacaine *in utero*.

No untoward effects were noted in the newborn in the control series receiving intracere-

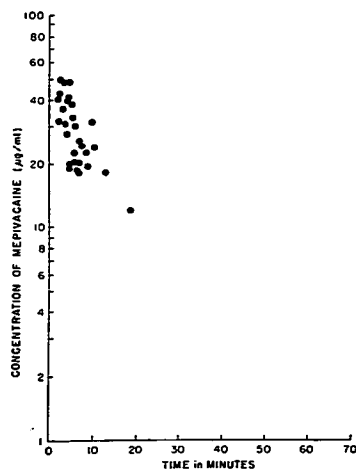


FIG. 4. Concentration of mepivacaine in the blood of the newborn and time from injection of drug ( $50 \pm 5$  mg./kg. of body weight) into the brain of newborn.

bral injection of saline. Their growth curve up to 6 weeks was normal.

### Discussion

The present investigation has demonstrated that mepivacaine is rapidly transferred across the guinea pig placenta after intracerebral injection of the drug into the fetus. As a result of this a large gradient exists between the concentrations of the local anesthetic in the blood of the systemic circulation of the fetus and that of the umbilical vein. Having entered the maternal compartment, mepivacaine also reaches the litter mates and their amniotic fluid; the concentrations in these compartments, however, remain lower than that in maternal blood and peak values are reached after a delay of several minutes.

Upon injection of a large dose into the fetus the drug could not be detected in the mother, in litter mates or in the amniotic fluid indicating that transmission to the mother had not occurred. The critical dose that impaired fetal circulation appears to be about 50 mg. per kg. The low concentration of mepivacaine observed in the litter mates following administration of a large dose to the fetus makes it unlikely that a significant quantity of the drug is transferred directly from one fetus to the other without entering the systemic circulation of the mother.

Previous work has shown that mepivacaine administered into the maternal epidural space crosses the placenta rapidly.<sup>9</sup> Within minutes after injection of the drug, mepivacaine can be detected in fetal blood. On the basis of a few studies concerning the passage of substances across the placenta from fetus to mother, it has been inferred that substances which are able to pass from mother to fetus must also be able to move in the opposite direction. Our findings support this contention.

The higher tolerance of the fetus to local anesthetics compared to that of the newborn is chiefly related to the rapid transfer of drug across the placenta. If the rate of placental elimination of mepivacaine is similar to that of the absorption from the site of administration, increase in dosage will lead to only a

small increment in the concentration of the agent in systemic blood. Another factor that contributes to the high tolerance of the fetus is its independence upon the state of activity of the respiratory center. Depression of the respiratory center as documented by apnea occurred in the newborn piglet immediately following injection of mepivacaine; this has also been a constant feature in the cases of inadvertent administration of mepivacaine to the human fetus.<sup>1,2</sup> Since the exchange of respiratory gases by the placenta does not depend upon the integrity of the respiratory center, this side effect should be of no consequence to the fetus. Ventilation of the apneic asphyxiated newborn by positive pressure on the other hand may not succeed in establishing adequate oxygenation because of the high pulmonary vascular resistances and the unfavorable hemodynamic effects of increased intrathoracic pressure on the failing circulation. Unfavorable sequelae of positive pressure ventilation have been demonstrated in the adult guinea pig.<sup>4,5</sup>

Immediate recognition of accidental injection of the fetus with local anesthetic agents may at times be difficult in the human. In the reported cases of such an incident, fetal bradycardia occurred shortly after the initial dose of drug had been injected during the attempted caudal analgesia.<sup>1,2</sup> Bradycardia was also the cardinal sign of intoxication in guinea pigs. Thus, suspicion should be raised when analgesia is not observed in the mother and when sudden bradycardia occurs in the fetus. Upon verification of inadvertent administration of the drug to the fetus, it may be prudent to take advantage of placental clearance of the drug and exchange of respiratory gases through the placenta instead of relying on artificial ventilation and drug clearance by exchange transfusion and gastric lavage following prompt delivery of the affected fetus. Immediate delivery does not seem warranted even in cases in which circulation of the fetus is significantly impaired because less work is expected to be required to perfuse the placenta than the lung, which in the presence of hypoxia and acidosis has a high vascular resistance.

### Summary

Comparison was made between the tolerance of the fetus and that of the newborn to intracerebral injection of a local anesthetic agent (mepivacaine). Doses which were without sequelae to the fetus were invariably lethal to the newborn. There was a direct correlation between the clinical condition of the newborn and the time between administration of the drug and delivery. Mepivacaine was rapidly transferred across the placenta to the mother and was present, although in lower concentrations, in control litter mates.

It is concluded that the rate of disappearance of mepivacaine resulting from degradation of the drug in the newborn does not compare favorably with the rate of elimination of the drug by the placenta. The inference is made that following inadvertent administration of a local anesthetic agent to the human fetus it is advantageous to defer delivery and to rely on the placenta for drug clearance and exchange of respiratory gases.

### References

1. Finster, M., Poppers, P. J., Sinclair, J. C., Morishima, H. O., and Daniel, S. S.: Accidental intoxication of the fetus with local anesthetic drug during caudal anesthesia, *Amer. J. Obstet. Gynec.* 92: 922, 1965.
2. Sinclair, J. C., Fox, H. A., Lentz, J. F., Fuld, C. L., and Murphy, J.: Intoxication of the fetus by a local anesthetic; a newly recognized complication of maternal caudal anesthesia, *New Eng. J. Med.* 273: 1173, 1965.
3. Morishima, H. O., Moya, F., Bossers, A. C., and Daniel, S. S.: Adverse effects of maternal hypoxapnea on the newborn guinea pig, *Amer. J. Obstet. Gynec.* 88: 524, 1964.
4. Morishima, H. O., Daniel, S. S., Adamsons, K., Jr., and James, L. S.: Effects of positive pressure ventilation of the mother upon the acid-base state of the fetus, *Amer. J. Obstet. Gynec.* 93: 269, 1965.
5. Morishima, H. O., and Daniel, S. S.: Evaluation of the newborn guinea pig, In preparation.
6. Sung, C., and Truant, A. P.: The physiological disposition of lidocaine and its comparison in some respects with procaine, *J. Pharmacol. Exp. Therap.* 112: 432, 1954.
7. Daniel, S. S., and Morishima, H. O.: Determination of mepivacaine in biological fluids, In preparation.
8. Siggaard Andersen, O., Engel, K., Jørgensen, K., and Astrup, P.: A micro method for determination of pH, carbon dioxide tension, base excess and standard bicarbonate in capillary blood, *Scand. J. Clin. Lab. Invest.* 12: 172, 1960.
9. Morishima, H. O., Daniel, S. S., Finster, M., Poppers, P. J., and James, L. S.: Transmission of mepivacaine hydrochloride (Carboaine) across the human placenta, *ANESTHESIOLOGY* 27: 147, 1966.

### Surgery

**HEARING LOSS** The effect of increased ambient air pressure on hearing function in 26 experienced divers was investigated. Audiograms were done at 1, 4, 7, 10 and 11 atm. An elevation of threshold of hearing was demonstrated from air conducted sound which increases with increased ambient air pressure. Bone conduction remains normal. (*Fluur, E., and Adolfsen, J.: Hearing in Hyperbaric Air, Aerospace Med.* 37: 783 (Aug.) 1966.)

**ABSTRACTOR'S NOTE:** This fact should be borne in mind during communication in a hyperbaric chamber.