INVESTIGATION OF PLACENTAL THRESHOLDS TO SUCCINYLCHOLINE

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METHODS for the bioassay analysis of succinylcholine levels in urine [1] and blood [2] have been described recently. Determinations in maternal and cord blood samples simultaneously drawn at delivery showed that no succinylcholine could be found in cord blood when usual clinical doses of the relaxant were employed.[3] The low lipid solubility of the drug was suggested as a probable explanation for the apparent "barrier" that was observed. Since the rate of entry of any substance, regardless of its physical nature, is at least partially dependent upon the concentration gradient driving it through the cell, it seemed pertinent to study the effect of a progressive increase in this gradient.

The experimental results of Thesleff,[4] Leone [5] and Pittinger and Morris [6] have been summarized elsewhere in this issue of the Journal.[3] However, there are no reports available concerning the investigation of minimal threshold dose levels. This report presents the results of progressively increasing the doses of succinylcholine on the serum levels in maternal and cord blood as well as the clinical response of the newborn. Thereby the minimum dose necessary to transmit pharmacologically detectable and clinically significant quantities may be estimated.

MATERIAL AND METHOD

These studies were conducted in both full term pregnant women and rabbits. Thirteen patients about to undergo vaginal delivery were given either meperidine (50–100 mg.) or secobarbital (50 mg.) from one to three hours before delivery. At the time of delivery, with the patient in position on the table, high flows of oxygen were administered for at least 3 minutes in order to secure effective alveolar denitrogenation. Nitrous oxide-oxygen (12:3 liters) was used for induction of anesthesia and a single dose of succinylcholine was administered from 45 to 60 seconds after induction. The doses varied from 200 to 500 mg. injected rapidly intravenously. Delivery took place from one to five and one-quarter minutes after administration of the relaxant. At the exact time of delivery blood was drawn from the opposite antecubital vein of the mother and from the umbilical vein of the infant. The two samples were usually drawn simultaneously. Forty micrograms of physostigmine were added immediately for each 10 ml. of blood to secure inhibition of the plasma cholinesterase. The samples were analyzed for succinylcholine as soon as possible. Prior to delivery a control sample of blood was drawn from each patient. Every resuscitative precaution was taken if the babies had failed to breathe at birth.

The threshold dose necessary to transmit clinically significant quantities of succinylcholine to the fetus, *i.e.*, paralysis of all muscular activity, was studied in eight New Zealand white rabbits at term. This animal was chosen because the anatomy of its placenta is similar to that of the human counterpart in that both have basically three layers of tissue interposed between maternal and fetal blood (hemochorial placenta).[7] The sensitivity of the rabbit to succinylcholine is sufficiently similar to man so that this animal is a valid and practical experimental model. Thesleff [4] reported that the mg./kg. dose which caused loss of the ability to right themselves in 50 per cent of the trials were: rabbit–0.25, man–0.15, horse–0.15, cat–0.08 and dog–0.06. In our study we found that a dose of 0.5 mg./kg. was necessary to completely paralyze the rabbit. Under local anesthesia, a tracheostomy followed by cesarean section was performed. From one to 3 control fetuses were extracted from the uterus immediately after the abdomen was opened. Single doses of succinylcholine (from 0.25 to 570 mg./kg.) were injected

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TABLE 1

BLOOD LEVELS AND CONDITION OF INFANTS FOLLOWING VAGINAL DELIVERY WITH A SINGLE, LARGE DOSE OF SUCCINYLCHOLINE

Dose		Minutes from Injection to Sample	Blood Levels at Birth, μg./ml. Serum		Infant	
mg.	mg./kg.		Maternal	Infant	Apgar score	T.S.R.* sec.
200	3.28	4	1.4	0	9	10
200	3.30	1¼	10.4	0	7	60
200	3.30	2¾	3.9	0	9	30
200	3.17	4¼	0	0	7	70†
200	2.86	4¾	3.5	0	9	45
300	4.28	1	5.5	0	7	70
300	5.08	2	11.6	1.5	6	30
300	3.94	5	1.9	0	8	60
300	3.70	3	1.7	1	8	40
300	6.00	3¼	1.8	1.9	9	20
300	4.68	3¾	6.2	1.5	7	30
500	7.70	5¼	1.2	1.1	8	50
500	6.58	5	2.4	2.0	8	20

* Time to sustained respiration.

† Tight nuchal cord.

0 = less than one microgram succinylcholine per milliter serum.

through a vein in the ear and the rabbits' lungs were artificially ventilated with air through the tracheostomy. The remaining intrauterine fetuses were extracted from 3 to 6 minutes after injection of succinylcholine and their appearance compared to that of the controls regarding vigor, ability to move and spontaneous respiration, or gasps on stimulation.

RESULTS

Table 1 summarizes the results obtained in women. Doses of 300 and 500 mg. of succinylcholine were necessary before small (1.0 to 2.0 μg./ml. of serum) but detectable amounts appeared in the umbilical vein blood. No determinations were performed on umbilical artery samples. The corresponding maternal peripheral venous concentrations were found to range from 1.2 to 11.6 μg./ml. of serum. The most rapidly achieved equilibrium between maternal and fetal blood was noted three and one-half minutes following a 300 mg. dose. None of the infants appeared to be affected by the relaxant irrespective of the dose and time interval between injection and delivery. The majority were vigorous at birth with Apgar scores[9] of seven to nine. All mothers were apneic at the time of delivery and remained so for a maximum of 16 minutes.

Eighteen control fetuses were extracted from the 8 rabbits. Of these, 4 were partially macerated stillborn and the remaining were alive and vigorous. Forty-five fetuses were delivered after injection of succinylcholine into the rabbits. Three were stillborn and the other 42 were alive and most behaved in a manner similar to the controls even when subjected to hypoxia during the delivery. A difference in vigor of the neonates was observed only when the doe had received an intravenous dose of 1,500 mg. of succinylcholine (340 mg./kg.). These fetuses appeared distinctly different from the controls, moving only when stimulated. Finally, at a dose level of 2,000 mg. of succinylcholine (570 mg./kg.) all fetuses were extracted flaccid and paralyzed, yet alive. In order to verify the susceptibility of the newborn to succinylcholine, single 0.25 to 1.0 mg. doses were administered into the umbilical vein of 4 of the young animals. This dose consistently produced total muscular paralysis.

Discussion

The apparent placental "barrier" which seems to exist when ordinary clinical doses of succinylcholine are used appears, in view of the present results, to be a relative one. When sufficiently large doses are injected into the maternal circulation small amounts appear in the fetal circulation. In women the minimal or threshold dose necessary to permit the passage of barely detectable quantities into the fetal blood is in the region of 300 mg. *i.e.*, five to six times the usual clinical dose. This threshold represents the dose at which a sufficient concentration gradient is present to overcome the main limiting factor of low lipid solubility.

The rabbit experiments revealed that a dose approximately 1,000 times the minimal paralyzing dose was necessary to transmit quantities of succinylcholine that will produce demonstrable effects in the newborn. Since the sensitivity of the rabbit to succinylcholine and the placental morphology are similar to that found in man, these results may be of value in estimating the dose necessary to obtain the same effect in humans. There is, however, one important difference that must be considered. Rabbits, unlike man, have a predominance of the specific acetylcholinesterase present in the plasma, and there is some evidence to suggest that the nonspecific cholinesterase is primarily localized in the liver.[9] Therefore, in these animals succinylcholine may be destroyed by this organ.

The data presented in this report can be interpreted as providing additional indirect evidence for a lipoid theory of placental permeability. If succinylcholine were freely diffusable across the placenta with the concentration gradient the prime limiting factor in its transmission, any of the 200 to 500 mg. doses could be expected to produce detectable levels in the cord blood of the babies. Moreover, the levels found ought to be at their peak within the first few minutes, corresponding to the maximal concentration gradient. Instead, the drug was first detectable two minutes following a 300-mg. dose, and the quantity present was 1.5 μg./ml. of serum whereas the maternal serum had 11.5 μg./ml.

None of the human babies in this series appeared to have muscular paralysis even when the drug was demonstrated in small amounts in the cord blood. In rabbits, massive single doses were necessary to affect the fetus. This "resistance" to succinylcholine appears consistent with Stead's[10] suggestion that the newborn is somewhat resistant to succinylcholine, requiring a milligram per kilogram dose more than double that of the adult. The validity of Stead's conclusions has been questioned by Foldes[11] on the ground that the observations were made on infants with intestinal obstruction and possible fluid and electrolyte disturbances. This is supported by the recent work of Salanitre and Rackow,[12] who reviewed their experience with the use of succinylcholine in the newborn and found no evidence of an increased resistance to the drug.

The liver may be an important factor in the apparent resistance of the newborn to the succinylcholine found in umbilical vein blood. It is estimated that approximately ¾ of the blood carried by the umbilical vein from the placenta to the fetus passes through the liver.[12] This organ is considered to be the source of the enzyme pseudocholinesterase. In addition, experiments by Frumin[14] indicate that the liver is the primary site of inactivation of succinylcholine in the dog. It is possible, therefore, that ⅞ of the drug may never reach the systemic circulation of the fetus because of destruction in transit through this organ. However, little is known of the role played by the liver in this process in humans and there is increasing evidence that the fetal liver may be unable to detoxify foreign substances.[15,16] A study of the succinylcholine levels in the umbilical artery should clarify this point.

Little information is available concerning the ability of fetal blood to metabolize succinylcholine. The *in vitro* rate of destruction in infants' blood appears to be slower than in maternal plasma.[17] Navratil[18] has shown that the pseudocholinesterase level of the newborn is approximately 40 per cent of the maternal level. However, Foldes[11] cautions against the use of quantitative changes in this enzyme alone in interpreting altered sensitivity to succinylcholine. He noted that the duration of succinylcholine-induced apnea was

not excessively prolonged in patients in whom pseudocholinesterase activity was reduced by severe liver disease.

Any conclusions on why these infants appeared vigorous and with good muscle tone despite detectable quantities of succinylcholine in umbilical vein blood must be tentative. More data are required for a complete understanding of the problem.

Summary

The placental transmission of large doses of succinylcholine was studied in 13 healthy pregnant women undergoing vaginal delivery and in 8 pregnant rabbits delivered by cesarean section.

In the women, single doses of 300 to 500 mg. of succinylcholine were necessary before small but definitely detectable quantities were found in the umbilical vein blood of the babies. None of the infants appeared to be affected by the relaxant, irrespective of the dose and the presence of the drug in cord blood.

In the rabbits, single injections approximately 1,000 times the minimum paralyzing dose were necessary before all fetuses were delivered flaccid and unresponsive to stimulation.

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