PLACENTAL TRANSMISSION OF D-TUBOCURARINE CHLORIDE FROM MATERNAL TO FETAL CIRCULATION IN DOGS *

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PLACENTAL transmission of *d*-tubocurarine chloride from maternal to fetal circulation has not been demonstrated previously. In the field of human obstetrics, Whitacre and Fisher (1) and others (2–9) detected no clinical evidence of curarization of infants delivered either spontaneously or by cesarean section of curarized mothers.

Laboratory studies pertinent to the problem of placental transmission of curare have been made. Harroun, Beckert and Fisher (10) and Harroun and Fisher (11), working with pregnant bitches, reported no evidence of clinical curarization of pups delivered of curarized mothers. Buller and Young (12) curarized rabbits 28 to 31 days pregnant and likewise detected no apparent effect on the offspring; however, they did report placental transmission of *d*-tubocurarine chloride from *fetal to maternal circulation* in rabbits.

The feasibility of neuromuscular blocking in fetuses by curare has been demonstrated in dogs near term (10, 11), 28 to 31 day fetal rabbits (12), 50 to 60 day fetal guinea pigs (12), and 20 to 22 week human fetuses (12). Thus, in these species at least, clinical effects should be produced by adequate plasma levels of the drugs.

In view of the known permeability of the placenta to water-soluble drugs in general, we were interested in determining whether a "placental barrier" to *d*-tubocurarine chloride actually exists or whether the absence of demonstrable curarization in fetuses after intravenous injection into mothers is due to the paucity of the drug in the plasma reaching the uterus.

In planning the following experimental work on dogs, the prime consideration was provision of an adequate plasma level of *d*-tubocurarine chloride to the placental tissue. Therefore, the decision was made to inject the drug into the uterine artery. In order to confirm any clinical manifestations of curarization which might occur in the pups, it was decided to make determinations of the *d*-tubocurarine chloride content in their plasma.

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EXPERIMENTAL DATA

Four pregnant bitches near term were prepared and draped for a cesarean section. The midline of the lower abdominal wall was infiltrated with procaine hydrochloride solution. An incision was made which extended from the pubis to the umbilicus. The peritoneal cavity was opened and both horns of the uterus were exposed upon the abdomen. Manipulations were gentle in order to prevent injury to the vessels and fetuses. The uterine artery supplying one of the horns was isolated and a short number 25 gauge needle attached to a syringe containing 20 cc. of *d*-tubocurarine chloride (Squibb, 3 mg. per cubic centimeter) was inserted into it. With 2 of the bitches, A and B, the fetuses were delivered through multiple incisions in the horns and their activity was noted. The cords of some of the fetuses were then clamped and the drug was injected over a period of two to three minutes. With bitches C and D, intra-uterine activity of the fetuses was observed, but delivery was delayed until the uterine and ovarian vessels on the right side and the junction of the right horn with the body of the uterus had been securely clamped and the drug injected. Thus, by either procedure, some of the fetuses were exposed to the placental blood supply of the bitch, whereas others were effectively isolated. The bitches had to be maintained by artificial ventilation after curarization occurred. This was accomplished by means of endotracheal intubation and attachment of the tube to an Emerson resuscitator activated by oxygen under pressure.

In order to obtain chemical as well as visual evidence of curarization, determinations were made of the *d*-tubocurarine chloride contents of plasma from curarized pups of bitches A, C and D. Blank determinations were made on plasma from noncurarized littermates. Because of the small blood volume of a pup, a composite sample was obtained from two or three of them by intracardiac puncture. The technics used in this study for the collection and processing of the blood samples were those described by Pittinger *et al.* (13).

Motion picture records and other photographs were prepared to show some aspects of the operative procedure and visual evidences of curarization in the pups.

RESULTS

The observations noted during these experiments are shown in table 1. Each pup is designated by a combination of a capital and a small letter.

In the litters of bitches A, C and D, curarization was evident in all pups whose maternal-fetal circulation was intact. Evidences of curarization included diminished intercostal activity, decreased motility, limpness, quietness and onset of cyanosis when cord pulsations had ceased before the impaired ventilation had improved. Various degrees of

TABLE 1

EVIDENCES OF CURARIZATION IN PUPS DELIVERED OF CURARIZED BITCHES

Bitch	*D*-tubocurarine Chloride Dose	Pups	Observations
A (12 kg.)	45 mg. into left uterine artery	Rb*—	Active and noisy; not depressed.
		Ra —	Developed weakness and moderate respiratory depression which lasted about 10 min.; quite active and noisy again after 20 min.
		La —	Developed apnea and extreme limpness lasting for 5–10 min.; fairly active again after 20 min.
		Lb*—	Active and noisy; not depressed.
B (13.5 kg.)	60 mg. into right uterine artery	Rc — Rb — Ra — La*— Lb*— Lc*—	All pups active and noisy upon delivery and remained so throughout the experiment without evidence of depression. Injection of the drug was delayed 10 min. after delivery of the pups owing to difficulties during attempted insertions of the needle into artery; cord pulsations had ceased before completion of the injection, and the efficiency of the cord circulations during it was in doubt.
C (12.2 kg.)	60 mg. into left uterine artery	Rc*— Rb*— Ra*—	All active prior to delivery; remained active and were noisy after delivery; no signs of depression evident.
		La — Lb — Lc — Ld — Le —	Decreased activity noted during injection; labored respiratory efforts, muscular weakness and quietness noted after delivery. —Killed after 5 min.; —Active after 20–30 min.; —Killed after 5 min.; —Active after 20–30 min.; —Killed after 5 min.
D (18 kg.)	60 mg. into left uterine artery	Rc*— Rd*— Rc*— Rb*— Ra*—	All active within horn prior to interruption of blood supply; suggestion of mild depression lasting about one min. after delivery; very active and noisy thereafter.
		La — Lb —	Marked depression of intercostal activity and muscle tonus when killed 5 min. after delivery.
		Lc —	Moderate respiratory depression and weakness; much improved after 30 min.
		Ld —	Runt of the litter; only minimal depression at any time; quite active after 20 min.

* Denotes interrupted circulation between mother and fetus.

The capital letters R and L refer to the location of the pup in the right or left horn, respectively; the small letters were assigned successively according to the alphabet, beginning with the fetus in each horn nearest the body of the uterus.

curarization were noted in the different pups, but in all of them the onset followed the introduction of the drug into the uterine artery of the bitch, and diminution of the effects was observed within fifteen minutes after the injection. Return of full activity was observed within the thirty to sixty minute period after the injection in those pups which had not been killed earlier during the obtaining of blood specimens.

TABLE 2

D-TUBOCURARINE CHLORIDE CONCENTRATIONS IN PLASMA OF PUPS CURARIZED BY PLACENTAL TRANSMISSION OF THE DRUG

Bitch	Pups Used for Analysis	Time of Sampling after Injection	*d*-Tubocurarine in Plasma (gamma/cc.)
A	Ra and La	20–25 min.	1.3
C	La, Lc and Le	5–10 min.	2.5
D	La and Lb	5–10 min.	2.5

Curarization was not evident in any of the offspring of bitch B. After delivery of her pups, a delay of ten minutes occurred before the injection of *d*-tubocurarine chloride was made. The difficulty was associated with the introduction of the hypodermic needle into the artery. When the injection had been completed, it was observed that the attached cords were no longer pulsating and it is probable that these circulatory pathways had ceased to function effectively before or during the administration of the drug.

Pup Ra of bitch A was curarized even though its placental attachment was to the horn opposite the side of injection.

The results of chemical analyses of plasma from the curarized pups are shown in table 2. A concentration of 2.5 gamma of *d*-tubocurarine chloride per cubic centimeter of plasma was found in composite samples of blood drawn during the five to ten minute period after injection of the drug in animals C and D; 1.3 gamma per cubic centimeter of plasma

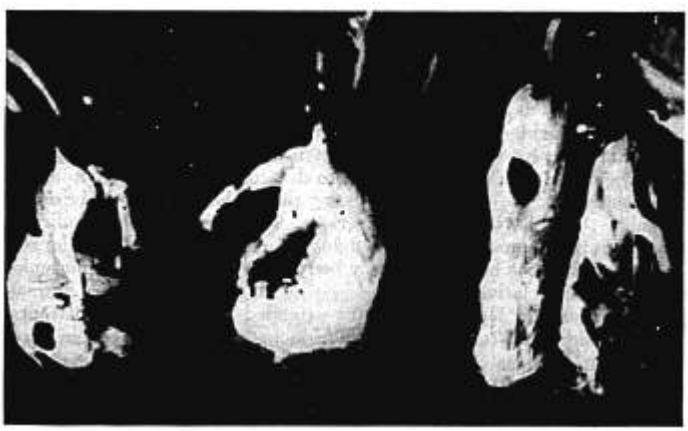

FIG. 1. Comparison between pairs of curarized (right) and noncurarized (left) pups from bitch D; the curarized pups were La and Lb just before they were sacrificed for blood samples.

was present in a composite sample of blood drawn during the twenty to twenty-five minute period after injection in animal A.

Figure 1 illustrates the difference between suspended pairs of curarized and noncurarized pups.

COMMENT

The demonstration of curarization in pups delivered of bitches in which *d*-tubocurarine chloride was injected into the uterine artery is evidence of placental transmission of the drug. The failure of earlier investigators to demonstrate this phenomenon after intravenous injection of the drug is believed due to the fact that plasma levels sufficient to produce visual curarization of the offspring were not attained. Quinn and Woislawski (14) demonstrated that a critical and constant plasma level was present when "head drop" occurred in rabbits.

The discrepancy of results obtained by intra-arterial (uterine) versus intravenous administration of *d*-tubocurarine chloride may be reconciled by a consideration of the differences in distribution occurring during and immediately following injection. In this study, the situation was created in which a high plasma concentration of the drug reached the endometrial tissue in contact with the placenta. On the contrary, intravenous administration allows for great dilution of the injected drug and a relatively low plasma level in the uterine tissues. Orth (15), who has opposed the contention that curare does not pass the placental barrier, offered an explanation of the facts observed after intravenous injection in terms of usage by the mother through processes of combination, fixation or neutralization at the myoneural junctions. Pittinger *et al.* (13) and Marsh (16) have shown the rapid rate of decline in the plasma concentration of *d*-tubocurarine chloride immediately after intravenous injection. The relatively slower rate of urinary excretion (16) as compared with the rapid rate of clearance of *d*-tubocurarine chloride from the blood stream and the short duration of clinical effects is explainable on the basis of distribution to tissues. In this regard, Marsh (16) was unable to determine any specific uptake of radioactive curare derivatives by any particular tissue and is of the opinion that distribution is universal. Thus, the evidence indicates that an intravenously administered dose of a curare derivative is largely removed from the blood stream by body tissues, of which the muscular component is relatively large.

Pittinger and Morris (17) have extended their study of placental transmission of *d*-tubocurarine chloride to include chemical analyses of human cord blood from infants delivered of completely curarized mothers. Under the conditions of that study none of the drug which had been given by intravenous injection to the mothers was detectable in the infants. Two factors are believed responsible for the failure to do so: (a) insensitivity of the chemical method employed in the presence

of a high blank which is encountered with fetal blood, and (b) the fact that the small amount of the drug transmitted probably does not reach significant plasma levels due to removal by the tissues of the infant. A better approach to the detection of minute quantities of *d*-tubocurarine chloride would be through the use of radioactive isotopes provided they could be incorporated within the molecule in a position from which they would not easily be dislodged. With this technic, fetal muscle tissue rather than plasma would be the logical substance to analyze.

The suggestion of mild depression observed in the pups from the right horn of bitch D at the time of delivery is interesting. In view of its disappearance almost immediately after the pups began to breathe, a plausible explanation is the hypoxia due to interference with the blood supply for approximately five minutes before delivery.

This demonstration of placental transmission of *d*-tubocurarine chloride in dogs has been accomplished by use of large intra-arterial doses which, when compared on a weight basis, are approximately ten times the amount which will ordinarily provide apnea in either the dog or human being. Any criticism of the large doses of drug used in this study may be answered by saying that no attempt was made to determine the minimal quantity of *d*-tubocurarine chloride required to produce fetal curarization. A more important consideration to the investigators was the simultaneous collection of chemical as well as visual evidence of placental transmission. As already stated, evidence of decreased fetal activity was usually apparent before the entire dose had been injected. Continued injection after incipient curarization was evident was considered necessary in view of the anticipated drop in fetal plasma levels of the drug before blood samples could be drawn.

CONCLUSIONS

Placental transmission of *d*-tubocurarine chloride has been demonstrated in dogs by the injection of large doses of the drug into the uterine artery.

Since the smaller amounts of *d*-tubocurarine chloride ordinarily employed are without significant effects on human infants, the obstetrical use of the drug by experienced personnel does not seem to be contraindicated.

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