EFFECT OF *D*-TUBOCURARINE ON BLOOD COAGULATION TIME * †

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Received for publication April 24, 1952

CURARE has been employed in clinical anesthesia for about ten years. Recently it has been suggested that increased bleeding occurs during the use of cyclopropane and curare (1). This was not observed by others (2). No mention was made of coagulation during these discussions. A review of the literature revealed that as early as 1856 Claude Bernard observed that blood of a curarized animal coagulated satisfactorily (3). The same year Kölliker (4) also noticed that blood clotting was not hindered by curare. Unfortunately, their descriptions were not accompanied by conclusive data. The present experiment, therefore, was planned to study quantitatively the blood coagulation time before and after *d*-tubocurarine chloride (dTC) was injected into dogs.

METHOD

Dogs of both sexes, ranging in weight from 7.7 to 21.9 kg., were employed. The dog was placed in the supine position on an animal operating table. The skin areas over both groins and legs were shaved and cleansed. A dose of 0.17 mg. per kilogram of 0.05 per cent solution of *d*-tubocurarine in saline solution was injected intravenously through a 22 gauge needle in a period of thirty seconds. Two blood samples were taken, the first approximately five minutes before and the second five minutes after the injection. Blood samples were withdrawn from either the femoral artery or the femoral vein. The determination of whole blood clotting time was performed according to Allen's technic (5). This is essentially a five-tube modification of the one-tube Lee-White procedure (6). Blood flowed under its own pressure into a metal tipped B-D syringe that had previously been coated with mineral oil. Eighteen gauge needles were used for blood sampling. This blood was immediately placed in a test tube (11 by 100 mm.) from which 5 ml. of blood was aspirated into a graduated pipet. One milliliter was then placed in each of five soft glass test tubes (10 by 75 mm). All tubes and

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† Aided by a grant from the Office of Naval Research N6-ori-20, task order 11.

pipets were dry, chemically clean, and unscratched. The time from the onset of paralysis after *d*-tubocurarine was injected until the dog stood up on his hind legs was recorded as duration of paralysis of hind legs.

RESULTS

The results are summarized in table 1. In the 8 female and 17 male dogs employed, the average coagulation time before *d*-tubocurarine was

TABLE I

EFFECT OF INTRAVENOUS ADMINISTRATION OF 0.17 MG. PER KILOGRAM *d*-TUBOCURARINE CHLORINE (dTC) ON BLOOD CLOTTING TIME IN DOGS

No.	Dog Weight (kg.)	Sex	Room Temp. (°F.)	Clotting Time Before dTC (min.)	*	Time Interval After dTC (min.)	Clotting Time After dTC (min.)	*	Duration of Paralysis of Hind Legs (min.)	Miscellaneous Observations After dTC
1	17.0	F	72	28	A	6	35	A	15	
2	13.8	M	72	63	A	3½	70	A	46	
3	17.2	M	72	30	A	5	27	A	17	
4	13.3	M	72	38	A	5	41	A	15	
5	16.2	M	68	62	A	5	69	A	10	Blood slightly dark.
6	20.0	M	68	50	A	5	56	A	17	Dog uncooperative.
7	19.0	M	77	31	A	5	18	A	42	Blood dark.
8	20.2	F	77	18	V	5	17	V	38	
9	17.8	M	83	30	A	5	26	A	26	
10	17.7	M	73	29	A	6	28	A	16	
11	18.0	M	73	32	A	5	20	A	23	
12	20.2	F	74	31	A	4½	31	A	20	
13	17.4	M	76	35	A	5	28	A	28	
14	20.5	M	71	35	A	4½	42	A		Blood very dark. Dog died 8 min. after dTC.
15	17.5	M	73	45	V	5½	35	A	16	
16	9.0	M	76	25	A	4½	26	A	9	
17	21.2	F	77	19	V	5	30	V	22	
18	12.3	F	77	19	V	5	21	V	21	Dog frightened, but quiet.
19	10.6	M	83	17	V	5	18	V	14	
20	21.9	F	87	14	V	5	13	V	23	
21	9.1	M	76	28	A	5	36	A	24	
22	7.7	F	76	20	A	8½	20	A	12	
23	9.5	M	79	29	V	13	26	A	16	
24	10.4	F	76	32	V	13	21	A	17	
25	10.4	M	86	13	V	5	13	V	12	
			Average	31.3			30.7		20.8	

* A: femoral artery. V: femoral vein.

31.7 minutes, while that after *d*-tubocurarine was 30.8 minutes. By "individual comparison" (7) this difference in coagulation time was statistically not significant (t is 0.6, df is 24, 5 per cent level is 2.06, 1 per cent level is 2.80). The average duration of paralysis of the hind legs was 20.8 minutes with a standard deviation of 9.6 minutes.

The normal range of blood clotting time in dogs usually is from twenty to thirty-five minutes. Possibly the initial prolonged clotting time in a few of these animals was the result of some otherwise unsuspected pathologic condition. The effect of increased room temperature on blood clotting time must be considered in interpreting these results.

COMMENT

The dose of *d*-tubocurarine employed, 0.17 mg. per kilogram, was considered satisfactory for this experiment after a preliminary test with doses varying from 0.10 to 0.20 mg. per kilogram. This dose was similar to doses employed by others (8, 9, 10). After this dose of 0.17 mg. per kilogram the average duration of paralysis of the hind legs was 20.8 minutes which agrees with Guyton and Reeder (11) who stated that, after a dose sufficient to paralyze the gastrocnemii completely, all evidence of curarization usually disappeared in approximately twenty-five minutes. Among the 25 dogs used in this study, one dog (No. 14) died of respiratory failure eight minutes after the intravenous injection of *d*-tubocurarine.

Because Unna *et al.* (12) reported that the maximal total curarizing effect occurred four to six minutes after intravenous injection, the second blood sample from each of these animals was withdrawn five minutes after the intravenous administration of *d*-tubocurarine. Mahfouz (13) stated that tubocurarine disappeared from the plasma exponentially with a half-time of about thirteen minutes in man and rabbit, whereas Marsh (14), by using radioactive isotopes, recently demonstrated that the biologic half-time for a single head-drop dose was approximately seven minutes.

After the intravenous injection of *d*-tubocurarine there are many physiologic changes which might directly or indirectly influence the blood coagulation mechanism. Li *et al.* (15) observed early respiratory depression from curare which was interpreted as caused by a peripheral action of the drug on the intercostal muscles. This respiratory depression produced hypoxemia and hypercapnia in varying degrees. Gillies (16) stated that McIntyre considered that curarization can occur with little or no cardiovascular disturbances. Robson and Keele (17) reported that curare produced very little effect on the circulation, apart from the secondary effects due to asphyxia. Although *d*-tubocurarine has been said to have no cerebral effect (18), asphyxia causes free discharge of epinephrine (19), as do emotional disturbances which may shorten the blood clotting time (20). However, curare in a paralyzing dose markedly depressed the output of epinephrine from the adrenal glands (21) and complete curarization abolished the action of epinephrine (22). In addition to these intricate effects, curare is believed to liberate histamine (23, 24, 25). Delcourt (26) reported that *d*-tubocurarine did not change the concentration of cholinesterase in

blood, while McIntyre *et al.* (27, 28) demonstrated that *d*-tubocurarine had essentially no effect on serum cholinesterase and 14 other enzymes. All these complex factors must be taken into consideration before the mechanism of the influence of *d*-tubocurarine on blood coagulation can be elucidated.

SUMMARY

An experimental study has been made of the effect on the blood coagulation time of 0.17 mg. per kilogram of 0.05 per cent solution of *d*-tubocurarine injected intravenously in 25 dogs. Under the conditions of these experiments it appears that in dogs the whole blood clotting time before and after the intravenous injection of *d*-tubocurarine was not significantly altered.

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