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THE URINARY EXCRETION OF SUCCINYLDICHOLINE AND SUCCINYLMONOCHOLINE IN MAN*

BY

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Reports on the urinary excretion of the muscle relaxants used clinically indicate that 20 to 50% of (+)-tubocurarine and dimethyl tubocurarine (Mahfouz, 1949; Guarino, 1949; Marsh, 1952; Kalow, 1953) and 70 to 90% of decamethonium (Paton and Zaimis, 1952), gallamine triethiodide (Mushin, Wien, Mason, and Langston, 1949) and benzoquinonium chloride (Hoppe, 1950) are eliminated unchanged through the kidneys.

It has been reported that the plasma of various animals (Glick, 1941; Bovet-Nitti, 1949; Castillo and de Beer, 1950) and of man (Evans, Gray, Lehmann, and Silk, 1952; Tsuji and Foldes, 1953) is capable of hydrolysing succinylcholine (succinyldicholine; SDC) *in vitro*. It has been shown that the hydrolysis of SDC occurs in two steps (Whittaker and Wijesundera, 1952). SDC is first hydrolysed to succinylmonocholine (SMC) and choline and then SMC is hydrolysed considerably more slowly to succinic acid and choline. The hydrolysis of SDC in plasma is enzymatic because heating, or the addition of plasma cholinesterase inhibitors, markedly reduces the rate of hydrolysis of SDC (Tsuji and Foldes, 1953). SDC is also hydrolysed by acetylcholine esterase, although more slowly than by plasma cholinesterase (Bovet-Nitti, 1949). SDC inhibits the enzymatic hydrolysis of acetylcholine (Evans *et al.*, 1952). SMC, which is weakly active at the neuromuscular junction (Bovet, 1951; Foldes and Tsuji, 1953; Lehmann and Silk, 1953; Foldes, 1953; Ellis, Wnuck, Fanelli, and de Beer, 1953), is hydrolysed by both plasma cholinesterase (Whittaker and Wijesundera, 1952; Foldes, 1953) and acetylcholine esterase (Lehmann and Silk, 1953).

On the basis of *in vitro* hydrolysis studies, it has been assumed that the brief action of SDC in various laboratory animals, and especially in man, is due to its rapid enzymatic hydrolysis *in vivo* (Bovet, Bovet-Nitti, Guarino, Longo, and Marotta, 1949; Thesleff, 1952; Foldes, McNall, and Borrego-Hinojosa, 1952). To test this assumption, it seemed necessary to investigate how much SDC is excreted unchanged in the urine of patients after its intravenous administration. Similar studies in animals have been reported (Norton and de Beer, 1954). Since in the course of the enzymatic hydrolysis of SDC a considerable amount of SMC can accumulate in the body (Foldes, McNall, and Birch, 1954), the urinary excretion of SMC was also studied.

MATERIAL AND METHODS

The observations were made on 14 female and 9 male patients anaesthetized for various surgical procedures. Nine patients received a single 1 mg./kg. dose of succinyldicholine chloride (SDC–Cl_2). To 6 other patients SDC–Cl_2 was administered by slow intravenous injection of 30 to 56 μg./kg./min. for the production of muscular relaxation for intra-abdominal procedures. Succinylmonocholine iodide (SMC–I) was administered to 8 patients—as a single dose of 0.8 mg. to each of 3, as a continuous intravenous injection at the rate of 29 to 48 μg./kg./min. to 3 others, and in fractional doses, for the production of muscular relaxation, at the rate of 558 and 472 μg./kg./min. to the remaining 3. The first 2 dose levels of SMC–I were chosen so that on a molar basis they corresponded to the quantities of SMC formed by the enzymatic hydrolysis of SDC–Cl_2 in the preceding series. All patients were lightly anaesthetized with thiopentone sodium and N_2O–O_2. Besides the urinary excretion of SDC and SMC, the plasma cholinesterase activity of all patients, and the duration of apnoea produced by a 1 mg./kg. dose of SDC in 9 patients, were also investigated.

Plasma Cholinesterase Activity.—Heparinized plasma, obtained before the induction of anaesthesia, was used to determine the plasma cholinesterase activity. Since Kalow's investigations indicate that plasma "procaine" esterase and plasma cholinesterase are identical (Kalow, 1952), procaine was used as a substrate. The hydrolysis of procaine in plasma was estimated by a method previously described (Foldes and Aven, 1952). The plasma cholinesterase activity was measured by the number of μg. of procaine hydrolysed by 0.8 ml. of plasma in 10 min. It has been shown that with this

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method the normal range of "procaine" esterase activity is 57.9±1.5 (S.E.) for males and 44.5±1.5 for females (Davis, Borrego, and Foldes, 1953).

Neuromuscular Blocking Activity.—The duration of apnoea after a single dose of 1 mg./kg. of SDC–Cl_2 was used as a measure of neuromuscular paralysis.

Urinary Excretion of SDC.—Urine was collected by an indwelling catheter for 30 to 69 min. after the administration of the single 1 mg./kg. dose and during, and 10 to 25 min. after, the continuous administration of SDC–Cl_2. Urine was collected for 55 to 100 min. after the single 0.8 mg./kg. dose of SMC–I and during, and 10 to 25 min. after, the continuous or fractional administration of SMC–I. A control urine sample was obtained from each patient before the administration of SMC or SDC. After collection the urines were quick-frozen in a dry ice-acetone mixture and kept frozen until the SMC and SDC were determined.

Estimation of SDC and SMC in urine was carried out according to the method of Norton and de Beer (1954). This method is based on the property of acetylcholine (Riesser and Neuschloss, 1921) and similar depolarizing substances (Paton and Zaimis, 1949; Bovet *et al.*, 1949) of causing contraction of amphibian muscle. The sensitivity of this method for SDC–Cl_2 is 0.1 μg./ml. of bath fluid. Rectus abdominis muscles of *Rana pipiens* were dissected and suspended in a bath containing 10 ml. of Ringer's solution (NaCl 0.6%, KCl 0.042%, $CaCl_2.2H_2O$ 0.032%, $NaHCO_3$ 0.05%, dextrose 0.05%). Control urine samples were added to the bath 10 min. before solutions containing SDC or SMC, which were added to the bath in quantities not exceeding 1 ml. The quantities of urine were chosen to give contractions similar to those caused by 0.25 to 0.50 μg./ml. of SDC–Cl_2 (Fig. 1) or 10 μg./ml. of SMC–I (Fig. 2). All urine samples and solutions of SDC–Cl_2 and SMC–I were allowed to remain in contact with the muscle preparation for 15 min. Each urine sample was tested on four preparations and the SDC and SMC concentrations were estimated by comparing the contraction with those produced by known concentrations of SDC–Cl_2 or SMC–I. A one-hour recovery period was allowed between two tests on the same muscle.

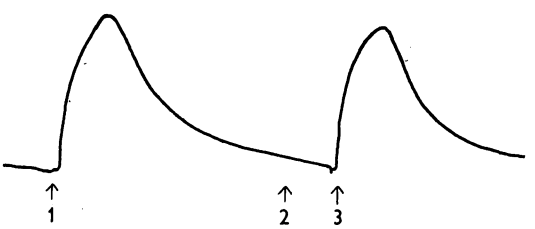

FIG. 1.—Contractions of the frog rectus in 10 ml. bath. At 1, 0.05 ml. of the urine collected over 86 min. following a slow intravenous injection of 280 mg. SDC (Expt. F–12 of Table II). At 2, 0.05 ml. normal urine. At 3, SDC 4.0 μg.

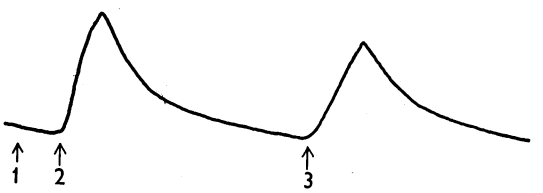

FIG. 2.—Contractions of the frog rectus in 10 ml. bath. At 1, 0.25 ml. normal urine. At 2, SMC 100 μg. At 3, 0.3 ml. of the urine collected over 57 min. following slow intravenous injection of SMC(Expt. M–7, Table III).

RESULTS

The results are summarized in Tables I, II, and III. Table I shows that the plasma cholinesterase activity, measured by the hydrolysis rate of procaine, varied from 15.0 to 83.0 units. There seemed to be an inverse relationship between the hydrolysis rate of procaine and the duration of apnoea after a single 1 mg./kg. dose of SDC–Cl_2. This relationship, however, did not show the close correlation observed by Evans *et al.* (1952) between the hydrolysis rate of acetylcholine in plasma and the sensitivity of patients to SDC. No correlation was found between the hydrolysis rate of procaine and the percentage of the administered SDC–Cl_2 excreted in the urine.

TABLE I

SUMMARY OF OBSERVATIONS AFTER THE INTRAVENOUS ADMINISTRATION OF 1 MG./KG. OF SUCCINYLDICHOLINE CHLORIDE (SDC–Cl_2)

Sample No.	Total Dose (mg.)	Urine Excreted		SDC–Cl_2 Excreted			Duration of Apnoea (sec.)	Procaine Esterase Activity
		(ml.)	Time (min.)	μg./ml. of Urine	Total in mg.	% of Total Administered		
F–1	60	25	30	13·0	0·33	0·54	547	48·5
F–3	89	50	50	1·0	0·05	0·06	410	39·9
F–4	54	25	40	120·0	3·00	5·55	1,065	40·0
F–5	62	27	64	82·5	2·23	3·59	585	40·3
F–6	56	54	30	1·0	0·05	0·10	245	42·1
M–1	113	75	30	6·5	0·49	0·43	780	15·0
M–2	83	66	30	37·5	2·48	2·98	390	49·0
M–3	77	167	69	14·0	2·34	3·04	297	41·6
M–4	95	60	39	53·0	3·18	3·35	194	83·0

TABLE II

SUMMARY OF OBSERVATIONS AFTER THE CONTINUOUS INTRAVENOUS ADMINISTRATION OF SUCCINYLDICHOLINE CHLORIDE (SDC–Cl_2)

Sample No.	SDC–Cl_2 Administered		Urine Excreted		SDC Excreted			Procaine Esterase Activity
	μg./kg./min.	Total Dose in mg.	ml.	Time (min.)	μg./ml. of Urine	Total in mg.	% of Total Administered	
F–2	56	220	20	82	213·0	4·36	1·94	47·5
F–7	30	160	47	95	288·0	12·38	7·74	48·0
F–8	38	120	47	75	88·0	4·14	3·45	57·0
F–12	49	280	18	86	120·0	2·16	0·77	34·0
F–13	35	40	190	26	2·5	0·48	1·19	37·0
M–8	49	157	51	33	50·0	2·55	1·60	48·0

TABLE III

SUMMARY OF OBSERVATIONS AFTER THE INTRAVENOUS ADMINISTRATION OF SUCCINYLMONOCHOLINE IODIDE (SMC–I)

Sample No.	SMC–I Administered	Urine Excreted		SMC–I Excreted			Procaine Esterase Activity
		ml.	Time (min.)	μg./ml. of Urine	Total in mg.	% of Total Administered	
F–9	0·8 mg./kg.	23	100	100·0	2·3	3·8	47·0
F–10	0·8 „	275	77	40·0	11·0	22·9	34·0
M–5	0·8 „	36	55	133·0	4·8	9·2	30·0
F–11	42 μg./kg./min. continuous injection	18	82	1,000·0	18·0	5·5	54·0
M–6	29 „ „	53	65	280·0	14·9	8·1	28·0
M–7	48 „ „	42	54	400·0	16·8	7·3	63·0
F–15	558 μg./kg./min. fractional doses	59	66	2,400·0	141·6	11·8	48·0
M–9	472 „ „	41	93	1,800·0	325·8	14·5	43·0

After the administration of 1 mg./kg. SDC–Cl_2 apnoea of 194 to 1,065 sec. duration developed in all the patients (Table I). There was no correlation between the duration of apnoea and the percentage of the administered SDC–Cl_2 excreted in the urine. No apnoea developed with the continuous infusion of SDC–Cl_2 at the rates of 30 to 56 μg./kg./min. (Table II) or after the administration of SMC–I in doses as high as 472 to 558 μg./kg./min. (Table III).

The ability of SDC–Cl_2 to produce contracture of the frog's rectus was, on a molar basis, about the same as that of acetylcholine (Norton and de Beer, 1954) and about 30 to 40 times greater than that of SMC–I (Fig. 3).

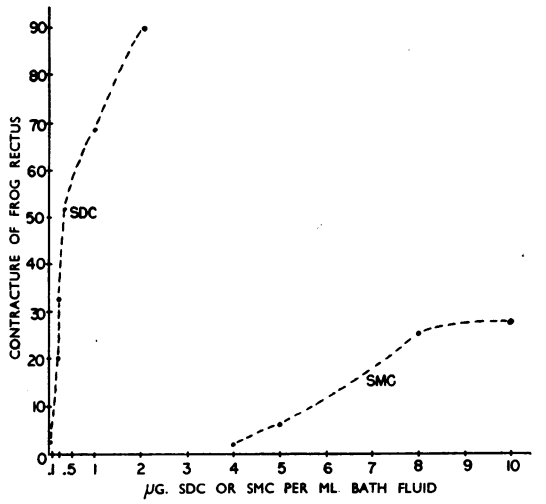

FIG. 3.—Contracture of the frog rectus abdominis in response to varying doses of succinyldicholine chloride and succinylmonocholine iodide.

The percentage of SDC execreted 30 to 69 min. after the administration of a single dose of 1 mg./kg. varied from 0.06% to 5.55% (average 2.2%). Increasing the time taken to collect the urine beyond 30 min. did not seem to affect the amount of SDC excreted, indicating that a 30 min. collection period, after the administration of a single dose of 1 mg./kg., is adequate. The percentage of SDC–Cl_2 excreted after its continuous intravenous injection in doses producing adequate surgical relaxation varied, with one exception (7.74%), between 0.77 and 3.45% of the total dose injected, averaging 2.8%.

The percentage of SMC recovered in the urine was considerably greater. Following a single 0.8 mg./kg. dose of SMC–I, it ranged from 3.8 to 22.9%. With the continuous infusion of SMC–I at the rate of 29 to 48 μg./kg./min. it was 5.5 to 8.1%. These doses of SMC–I had no discernible neuromuscular blocking effect. Following the administration of SMC–I in doses that produced adequate muscular relaxation, the excretion was 11.8 and 14.5% of the total.

DISCUSSION

The results indicate that, following the intravenous injection of single large doses of SDC–Cl_2, or the continuous intravenous administration of doses producing adequate relaxation for abdominal surgery, an average of less than 3.0% of the amount administered is excreted unchanged in the urine.

As both SDC and its hydrolysis product, SMC, cause the frog's rectus to contract, the contraction produced by urine samples is the sum of the effects of SDC excreted unchanged and of SMC. To estimate the error introduced by SMC in the determination of SDC, SMC–I was administered to patients in doses corresponding, on a molar basis, to those of SDC–Cl_2. The SMC excreted in the urine was calculated in terms of SDC, the activity of SMC being regarded as about 1/40 of that of SDC. On the assumption that the same percentage of SMC would be excreted whether it was injected or formed by the breakdown of SDC, the values of excreted SDC may be too high by about 0.25%. Correction for this decreases the average SDC–Cl_2 excretion, after a single 1 mg./kg. dose, from 2.2% to less than 2.0%, and after its continuous intravenous administration to less than 2.6%. Where very low values are found in the urine (for example, F–1, F–3, F–6 and M–1), conversion of SDC to SMC and excretion of almost all of this SMC could account for the contracture produced. However, this may be considered unlikely since only from 3.8 to 22.9% of injected SMC is excreted.

The findings that there was no close correlation between the hydrolysis rate of procaine and the duration of apnoea, and none at all between the plasma procaine esterase activity and the percentage of the total SDC excreted unchanged in the urine, suggest several possibilities. It is conceivable that the esterase present in human plasma has different characteristics in different individuals, and that the ability of this enzyme to hydrolyse procaine, SDC, acetylcholine and other substrates does not change in parallel in different persons. Another possibility is that there may be, in human plasma, several esterases capable of hydrolysing acetylcholine and that these may vary in relative amount and activity. Furthermore, it is also possible that similar, but even more pronounced, differences may exist between the plasma cholinesterases of various species. These assumptions are indirectly favoured by the finding that, whereas there is no marked sex variation in the hydrolysis rate of acetylcholine in human plasma (Levine and Hoyt, 1949 ; Callaway, Davies, and Rutland, 1951), a statistically significant difference is found in the hydrolysis rate of procaine in normal male and female plasmas (Davis *et al.*, 1953). Similarly, whereas the hydrolysis rates of acetylcholine in horse serum (Glick, 1941 ; Ginzel, Klupp, and Werner, 1951) and of succinylcholine in dog plasma (Hall, Lehmann, and Silk, 1953) were as fast or faster than that in human plasma (Evans *et al.*, 1952 ; Tsuji and Foldes, 1953), the hydrolysis rate of procaine in the plasma of these species, and of other mammals, is many times slower than in human plasma (Aven, Light, and Foldes, 1953). To clarify these problems it will be necessary to study the hydrolysis rate of various substrates (acetylcholine, SDC, procaine, etc.) in human plasma and in plasma from various mammalian species.

Summary

1. By using a biological method, based on the contraction of the frog rectus, the urinary excretion of SDC and SMC was estimated in anaesthetized patients after the intravenous administration of SDC–Cl_2 and SMC–I.

2. The "procaine esterase" activity of the plasma of these patients and the duration of apnoea following a single intravenous dose of 1 mg./kg. of SDC–Cl_2 were also observed.

3. The average amount of SDC excreted after the intravenous administration of a single 1-mg./kg. dose was 2.2%. After its continuous intravenous administration, in doses providing adequate surgical relaxation, the value was 2.8%.

4. The amount of SMC excreted after the administration of equimolar doses of SMC–I, which had no discernible neuromuscular effect, averaged 9.2%. After the administration of SMC–I in doses producing muscular relaxation the excretion was 11.8 to 14.5% of the total.

5. In some patients there was some correlation between the duration of apnoea and the "procaine esterase" activity of the plasma, but no such correlation was observed between the latter and the urinary excretion of SDC and SMC.

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