THE DOSE RESPONSE RELATIONSHIP AND DURATION OF ACTION OF SUCCINYLCHOLINE IN ANESTHETIZED MAN * †

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THE chemical structure and action at the neuromuscular junction of many synthetic drugs have been investigated following the elucidation of the chemical structure of *d*-tubocurarine by King in London in 1935 (1). These investigations were given great impetus by the successful use of a standardized curare extract in anesthetized man by Griffith in Montreal in 1942 (2). Great credit goes to Bovet, working in Paris and Rome, for his synthesis of a whole host of synthetic compounds with neuromuscular blocking properties (3, 4, 5). These studies, reported in 1946, mark the first preparation of these synthetic compounds.

The studies of Patan, Zaimis, Unna, True, Barlow, Riker and Wescoe (6–13) have added to the fundamental pharmacology and physiology of curarelike compounds in more recent years.

Succinylcholine was synthesized in 1906 by Hunt and Traveaux (14) while studying the pharmacological properties of a series of acetylcholine derivatives. The neuromuscular blocking properties, however, were overlooked by these investigators. In 1941, Glick (15) described the complete synthesis of this drug and demonstrated that it was readily hydrolysed by pseudocholine esterase of horse serum. In 1949 Bovet (16) first described the effects of succinylcholine at the neuromuscular junction.

In 1950, Patan, Zaimis and Walker in England and Phillips, Castillo and de Beer (17–20) in this country confirmed and elaborated upon Bovet's studies. Succinylcholine has had extensive clinical use in Europe beginning in 1950 and in 1952 the drug was clinically introduced in this country.

At present, *d*-tubocurarine and the synthetic muscle relaxing drugs, flaxedil®, decamethonium and mytolon®, are in wide clinical use. These agents have been satisfactory adjuvants to clinical anesthesia when used properly, but owing to their relatively long duration of action, histamine release, autonomic ganglion blockade and summation at the

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junctional region, they fall short of the ideal muscle relaxant. Because succinylcholine, the most recently introduced synthetic drug, is reported to have fewer of the undesirable side actions and to spare the respiratory musculature, we believed it mandatory to determine the dose response relationship and duration of action of this compound as a comparison study to our investigations of *d*-tubocurarine and flaxedil (21, 22).

METHOD

The experiments were performed on 50 surgical patients. Of these, 28 were female and 22 were male. All patients studied had liver function tests within normal limits. Thirty-eight of the operative pro-

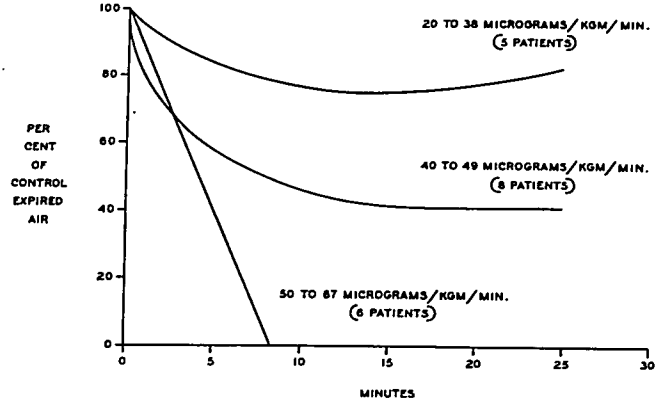

FIG. 1. Neuromuscular blocking action of succinylcholine in patients anesthetized with cyclopropane and ether.

cedures were intra-abdominal and 12 were extra-abdominal. The average duration of anesthesia was ninety-seven minutes. Thirty-seven patients received cyclopropane as the anesthetic agent and 13 patients received ether.

Multiple dose vials of succinylcholine hydrochloride (anectine®, 20 mg. per milliliter) were used in these studies. The drug was kept under refrigeration and solutions were prepared daily. All observations were made using a continuous infusion of a 0.1 per cent solution of succinylcholine hydrochloride in 5 per cent dextrose in water. The solution was suspended by means of a calibrated spring from an infusion stand. The surface of the fluid was placed at a predetermined height of 31 cm. above the level of the heart. As the solution decreased

in volume and weight, the spring maintained the surface of the fluid at a constant height above the venous pressure. A calibrated flowmeter ‡ was placed in the system to provide a constant size drop. A 15 gauge needle was inserted in the antecubital vein for injection of the drug. Expired air was measured during these investigations using a wet test gas meter according to the method described by Artusio *et al.* 1950 (23). Blood pressure readings (sphygmomanometric) and cardiac rates and rhythms were observed and recorded simultaneously with expired air.

RESULTS

The dose response relationship was determined for doses ranging from 20 to 67 micrograms per kilogram per minute.

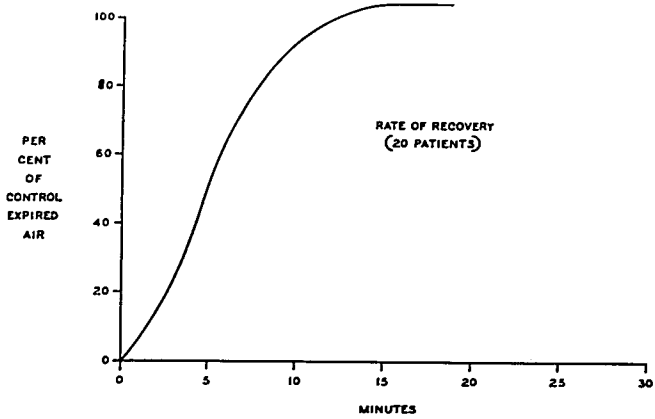

FIG. 2. Recovery curve from succinylcholine in patients anesthetized with cyclopropane and ether.

In figure 1 the first curve indicates the effect of a dose of 20 to 40 micrograms per kilogram per minute of succinylcholine. This dose range produced an average respiratory depression of approximately 20 per cent of control and was maintained as long as the injection rate was constant at this dose level. The second curve shows the effect of neuromuscular blockade produced by a dose of 40 to 49 micrograms per kilogram per minute. This dose results in a 50 per cent respiratory depression from control values, which again was maintained without accumulation at the neuromuscular junction. The third indicates that

‡ The calibrated flowmeter was provided for these studies by the American Optical Company.

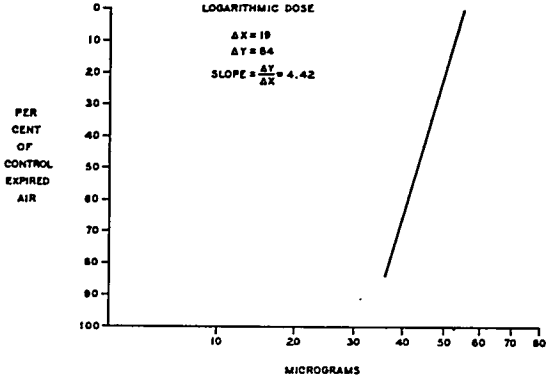

FIG. 3. The dose response relationship of succinylcholine in patients anesthetized with cyclopropane and ether.

SUCCINYLCHOLINE

500mgm. SUCCINYLCHOLINE (ANECTINE) IN 500cc 5% DEXTROSE IN WATER = 0.1% SOLUTION.
1 mg. PER cc 25 DROPS PER cc 1 DROP = 0.04 mgm.
18 GAGE NEEDLE. 31 IN. HEIGHT ABOVE HEART. CALIBRATED SPRING AND FLOWMETER USED.

KILOGRAMS OF BODY WEIGHT	DROPS PER MINUTE	20	30	40	50	60
		MICROGRAMS PER KILOGRAMS PER MINUTE				
20		10	15	20	25	30
25		12	19	25	31	37
30		15	22	30	37	45
35		17	26	35	44	52
40		20	30	40	50	60
45		22	34	45	56	67
50		25	37	50	62	75
55		27	41	55	69	82
60		30	45	60	75	90
65		32	49	65	81	97
70		35	52	70	87	105
75		37	56	75	94	112
80		40	60	80	100	120
85		42	64	85	106	127
90		45	67	90	112	135
95		47	71	95	119	142
100		50	75	100	125	150

CHART 1. Dose in drops per minute to produce a desired neuromuscular blockade with succinylcholine in patients anesthetized with cyclopropane or ether.

a dose of 50 to 67 micrograms per kilogram per minute produced respiratory arrest in all cases in an average period of eight minutes.

The rate of recovery is represented in figure 2. Immediately upon cessation of respiratory movements, the drug was discontinued and the patient allowed to recover. Respiratory movements reappeared within two minutes. At the end of five minutes, recovery was 50 per cent complete, at ten minutes, 92 per cent complete and at the end of fifteen minutes recovery had returned to control levels.

Figure 3 shows the dose response for succinylcholine in anesthetized man. When the percentage depression of expired air is plotted against the logarithmic dose, a straight line relationship is seen. It is evident that the critical dose lies at 50 micrograms per kilogram per minute. Doses exceeding this level are most likely to produce respiratory arrest.

Chart 1 presents the dose response relationship using the technique outlined for rapid calculation of the number of drops per minute necessary to produce a continuous infusion of the desired number of micrograms per kilogram per minute. The effect and duration of action will remain the same in the presence of ether or cyclopropane.

DISCUSSION

From an analysis of these studies in the anesthetized patient, it is believed that the effect of succinylcholine is predictable on a milligram per kilogram body weight basis. The onset of action is immediate and reaches its maximal effect at all dose levels studied within ten minutes. These maximal effects are sustained as long as the rate of infusion is constant at a given dose level and a constant level of anesthesia is maintained.

The duration of action is exceedingly brief. The average recovery, from the point of respiratory paralysis, is 80 per cent complete within ten minutes.

The duration of action of this compound is approximately 25 per cent less than that of *d*-tubocurarine or flaxedil. This provides the singular advantage of producing neuromuscular blockade in situations in which relaxation of skeletal musculature is needed for brief periods of time. This briefness of action decreases considerably the need for an antagonist, which is available for the longer acting agents, *d*-tubocurarine or flaxedil.

Succinylcholine hydrochloride does not spare the respiratory musculature. Respiration is progressively paralyzed as the degree of neuromuscular blockade becomes more complete. We doubt whether any muscle relaxant drugs will spare respiration and simultaneously produce adequate muscular relaxation.

The critical dose lies approximately at 50 micrograms per kilogram per minute. When this dose is exceeded, profound respiratory depression occurs. Therefore, the dose recommended for clinical use

averages 40 to 50 micrograms per kilogram per minute. This dose will produce adequate muscular relaxation, but at the same time considerable respiratory depression. Assisted respiration is recommended, therefore, at this dose level.

Blood pressure and pulse rate were not directly affected by the drug. Cumulation or tachyphylaxis was not observed with this compound.

The rapid onset of action and recovery of succinylcholine as well as the absence of cumulative, tachyphylactic and other undesirable side effects indicates that this compound approaches the ideal neuromuscular blocking agent in clinical use today.

SUMMARY

The action of succinylcholine in patients who have normal liver function is predictable on a milligram per kilogram body weight basis.

The onset of action, maximal effect and recovery occur within ten minutes.

Respiratory depression is commensurate with the degree of neuromusclar blockade.

Direct effects on blood pressure have not been observed.

Accumulation or tachyphylaxis was not observed at the dose levels studied.

The dose response relationship is identical when the drug is administered in the presence of ether or cyclopropane.

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