CONTROLLED PARALYSIS OF SKELETAL MUSCLE*†

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"THE advent of curare and curare-like agents into clinical anesthesia introduced a new era in anesthetic management, for it provided muscular relaxation by means of a peripherally acting drug rather than by the effects of profound central narcosis" (1). The use of myoneural blocking agents in conjunction with lighter planes of anesthesia has thus afforded the anesthesiologist a means for providing profound muscular relaxation without disturbing to any great extent the compensatory reflex mechanisms of the body.

For short procedures such as endotracheal intubation or convulsive shock therapy, short-lasting complete relaxation is desirable. Prolonged surgical procedures, on the other hand, may require controlled relaxation for several hours.

Control over duration of action should be achievable by several methods. The most obvious method would be to regulate the size of dose administered. With the usual relaxants, however, a dose which will give complete relaxation is fairly long lasting, and repeated doses evidence varying degrees of cumulative action. Small doses of decamethonium or *d*-tubocurarine are only partially effective for short-lasting procedures because relaxation is not complete. With a dose of *d*-tubocurarine sufficient to produce just complete paralysis of the gastrocnemius-sciatic preparation of a cat, a period of twenty to forty-five minutes is required for restoration of functional myoneural transmission. The same recovery period is required in the cat and dog after a just completely paralyzing dose of decamethonium. Larger doses can produce undesirable side effects such as apnea of central origin (2, 3).

Decamethonium and flaxedil®, like *d*-tubocurarine, sometimes show cumulative effects (4–7) and because of this characteristic, doses of the compounds should be repeated only with caution.

It is conceivable that a long-lasting relaxant could be used for short periods of intense relaxation by administration of a sufficiently large dose of the paralyzant followed at the appropriate time by a dose of

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an antagonist. For instance, the myoneural blockade produced by *d*-tubocurarine is quickly and dramatically abolished by an appropriate dose of prostigmine (8), that from flaxedil® by tensilon® (9), and more recently the 2-substituted stilbazoline, No. 49–204, has been reported to be an antagonist to decamethonium (10).

Unfortunately, although the specificity and effectiveness of these antagonists have been clearly established in experimental studies, their use clinically has not been too satisfactory. With *d*-tubocurarine, the anticurare activity of prostigmine has been found to be limited (11). Moreover, the side effects from prostigmine such as violent peristaltic movements of the gut, dyspnea due to bronchoconstriction, and with large doses a fall in blood pressure and pulse rate (12) and even added curarelike action with very large doses (13) are undesirable. With decamethonium, the efficacy of No. 49–204 has not yet been fully determined.

A drug which will produce intense relaxation the duration of which can be carefully controlled must possess certain specific properties such as quick onset, short duration without cumulative effects, intense action and freedom from side effects (14). The repeated injection or continuous infusion of a short-lasting relaxant drug of intense action might be expected to afford sufficient control of the myoneural blockade to provide the desired intensity and duration of relaxation, control being obtained by proper continuous or repeated dosages.

These requirements are most nearly met by the recently introduced ultra short-acting myoneural blocking agent, succinylcholine. Pharmacologic studies on this compound have been reported by Castillo and de Beer (15), Bovet and his co-workers (16, 17, 18) and de Beer *et al.* (19) and the agent has been clinically investigated by Foldes (14) and used by others (19–25).

In order to study the problem of controlled paralysis, therefore, it was thought advisable to examine *d*-tubocurarine, decamethonium and succinylcholine with respect to the methods of control just mentioned.

METHODS

The relaxant effects of *d*-tubocurarine (tubarine® chloride), decamethonium (syncurine®), and succinylcholine‡ diiodide have been studied on the gastrocnemius-sciatic nerve preparation in lightly anesthetized cats and dogs. Single pulses from a thyratron stimulator were applied to the nerve at six second intervals, and the isometric contractions of the gastrocnemius muscle were recorded on a smoked drum. A clearly objective measure of both intensity of relaxation and duration of myoneural blockade thus was obtained. Respiration was recorded by means of a tambour placed in the partially occluded airway. When

‡ Investigations in our laboratories have shown that responses to equivalent doses of the chloride and iodide salts of succinylcholine are quantitatively similar when dosage is compared on a molecular basis. Succinylcholine chloride is now available as anectine® chloride.

necessary, positive pressure artificial respiration was given. Blood pressure, when measured, was recorded by using a mercury manometer.

Pentobarbital sodium was used intraperitoneally to produce anesthesia. Injection of the myoneural blocking agents was made into an inlying cannula in a femoral vein and, by providing a short length of polyethylene tubing between the cannula and syringe, multiple injections could be made with a minimum of disturbance to the animal. When repeated injections of the same solution were anticipated, a Cornwall pipet unit was used.

RESULTS

Duration of Action of Doses which Produce Just-Complete Myoneural Blockade. In cats the approximate doses required to just abolish the twitch response of the gastrocnemius to indirect stimulation have been found to be 0.1 mg. per kilogram of *d*-tubocurarine chloride, 0.015 mg. per kilogram of decamethonium bromide, and 0.075 to 0.10 mg. per kilogram of succinylcholine diiodide. The paralysis after these doses of both *d*-tubocurarine and decamethonium is long lasting (about twenty to forty-five minutes) in comparison with the ultra short-lasting blockade produced by succinylcholine, recovery from which requires only three to seven minutes.

Intimately related to the duration of action is the presence of cumulative effect. Figure 1 shows quite clearly that a dose of 0.02 mg. per kilogram of *d*-tubocurarine had no action the first time it was given, but when repeated at intervals of twenty minutes, the successive injections resulted in increasingly greater degrees of relaxation, greater duration of relaxation, and increasingly severe respiratory difficulty. With succinylcholine, however, successive doses sufficient to produce complete myoneural blockade (0.1 mg. per kilogram) showed little cumulative action (fig. 2). As can be seen from table 1, the period of complete paralysis (over 95 per cent) gradually increased in duration, and after 12 doses had lengthened only from 7.1 to 10.6 minutes.

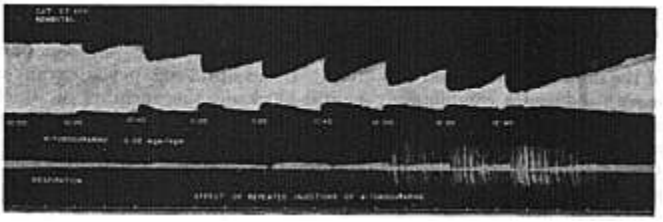

FIG. 1. Effect of repeated intravenous injections of *d*-tubocurarine chloride in doses of 0.02 mg. per kilogram on the response of the gastrocnemius muscle of the cat to electrical stimulation of the sciatic nerve. Single pulses were given at six second intervals. A rest period of twenty minutes was allowed between doses. Time, ten minutes.

Recovery was complete within the twenty minute interval after each of the first nine doses. Thereafter cumulative effects prevented recovery to the initial contraction height. The time over which these injections were made was two hours forty minutes.

Dose-response Relationships for Succinylcholine. Two discrete factors are involved in the dose response characteristics of succinylcholine. From the level of no effect whatsoever to induction of complete paralysis there is a graded response which can be studied in terms of *intensity* of blockade. On the other hand, with doses larger than the minimal one which just produces complete paralysis, the dose response curve can still be followed by measuring the *duration* of the failure of the muscular response to indirect stimulation.

TABLE 1

DURATION OF 95% PARALYSIS OF CAT GASTROCNEMIUS-SCIATIC PREPARATION FOLLOWING ADMINISTRATION OF SUCCINYLCHOLINE DIIODIDE (IN DOSES OF 0.1 MG. PER KILOGRAM) AT TWENTY MINUTE INTERVALS

Time of Injection	Onset, min.	Duration, min.	Recovery, min.	Total, min.	Recovery Height, % Initial
10:00	0.6	4.5	7.1	12.2	100
10:20	1.0	4.6	6.5	12.1	100
10:40	0.6	4.7	7.7	13.0	104
11:00	0.5	6.2	9.2	15.9	104
11:20	0.5	6.9	8.8	16.2	100
11:40	0.5	7.1	9.0	16.6	100
12:00	0.5	7.7	9.2	17.4	100
12:20	0.6	8.4	10.0	19.0	100
12:40	0.6	9.0	10.4	20.0	96
1:00	0.5	9.4	—*	—	90
1:20	0.5	10.6	—*	—	85
1:40	0.5	10.6	—*	—	79

* Recovery incomplete at end of twenty minute interval.

Intensity. Effect of doses producing partial paralysis. Study of the dose response relationships of succinylcholine in cats has shown that the range of dosage which results in partial paralysis is quite narrow, the calculated ED–50 (50 per cent paralysis) dose being 0.08 mg. per kilogram. The slope of the regression line for the logarithm of the dose was calculated ($b = 137$). Doses of 0.1 mg. per kilogram or more produced a complete myoneural blockade, the duration of which was related to dosage. Analysis of variance of a latin square experiment on 4 cats showed that the effect of the dose was highly significant ($P = <0.01$). The order of dosage and variation between animals were not significant ($P = >0.05$).

Duration. Relationship of duration of paralysis to dose. The dose response regression line for duration of blockade from the onset of 50 per cent paralysis to return to the 50 per cent recovery of the gastrocnemius twitch was calculated from the data obtained in a latin

square experiment involving 4 cats and four dose levels. The duration increased in a straight line with reference to the logarithm of the dose. Analysis of variance showed that the effect of the dose was highly significant ($P = <0.01$), whereas the order of dosage and variation between animals were not significant ($P = >0.05$).

Rate of Onset of Paralysis. The establishment of myoneural blockade by succinylcholine is very prompt. As can be seen in table 1, for instance, the onset time from injection of the drug to the level of a 95 per cent blockade was about one half minute.

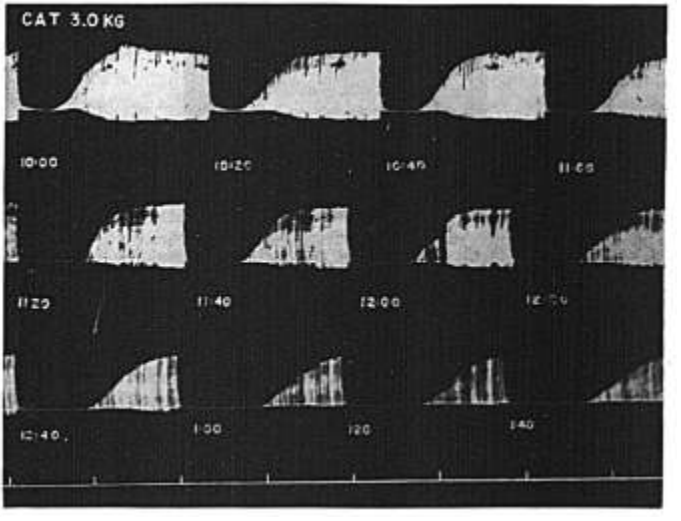

FIG. 2. Effect of repeated intravenous injections of succinylcholine diiodide in doses of 0.10 mg. per kilogram on the response of the gastrocnemius muscle of the cat to electrical stimulation of the sciatic nerve. Single pulses were given at six second intervals. A rest period of twenty minutes was allowed between doses. Time, ten minutes.

Effect of Repeated Doses at Intervals which Do Not Permit Full Recovery. Figure 3 illustrates an experiment on a dog in which 0.01 mg. per kilogram doses of succinylcholine were given at two minute intervals. It can be seen that recovery had begun before the next subsequent dose was injected, but upon injection of the new dose a deepening of the blockade took place, giving the scalloped appearance to the record. Doubling the interval between injections permitted complete recovery between doses to occur; increasing the dosage resulted in progressively more complete myoneural blockade.

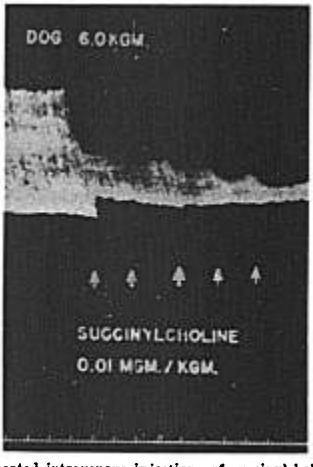

FIG. 3. Effect of repeated intravenous injections of succinylcholine diiodide in doses of 0.01 mg. per kilogram on the response of the gastrocnemius muscle of the dog to indirect stimulation when insufficient time was given between doses for recovery to be complete. Time, ten seconds and one minute.

Continuous Intravenous Infusion of Succinylcholine. Using a Cornwall pipet unit adjusted to deliver 0.25 cc. portions, injections could be made at desired intervals ranging from five seconds to two minutes. After producing a total blockade in a cat by injecting 0.1 mg. per kilogram in a single dose, 0.25 cc. portions of a succinylcholine solution containing 1 mg. per kilogram of body weight in 100 cc. were given as often as was required to maintain complete paralysis of the gastrocnemius-sciatic preparation for two hours (fig. 4). At the end of the two hour period the animal was allowed to recover. Recovery was almost immediate in onset and complete restoration of the twitch was

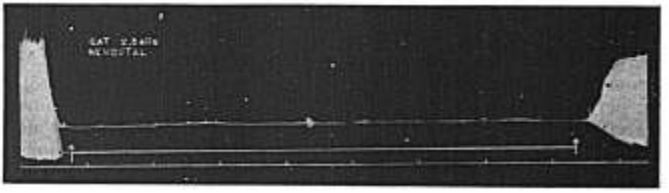

FIG. 4. Maintenance of complete blockade of the gastrocnemius-sciatic preparation of the cat by repeated injections of succinylcholine diiodide at a rate of 0.01 mg. per kilogram per minute. Time, fifteen minutes.

FIG. 5. Controlled relaxation in gastrocnemius-sciatic preparation of the cat by repeated injections of succinylcholine diiodide. The lines indicating the desired level of relaxation were drawn before the infusion was begun. Time, fifteen minutes.

observed within five to seven minutes. At no time during the experiment was respiration impaired, nor were other side reactions noted.

Controlled relaxation involving both intensity and duration was obtained in a similar manner. After the normal response of the muscle to electrical stimulation of the sciatic nerve had been established, the lever was removed from contact with the drum and lines were arbitrarily drawn in according to a predetermined pattern suggested by a disinterested person. The lever was then returned to its recording position. Using the lines as indexes of the desired levels of myoneural blockade, the height of the contractions was controlled by injecting 0.25 cc. portions of the succinylcholine solution at appropriate intervals to match the levels of the previously selected plan. Two such experiments are shown in figures 5 and 6. Respiration was slightly depressed during the periods of complete paralysis, but in neither of these experiments was artificial respiration needed. In all, about a dozen experiments have been done using dogs and cats, showing the remarkable ease with which predetermined degrees of relaxation can be obtained with succinylcholine. Complete paralysis has been maintained for over two hours with quick recovery upon stopping the infusion, and graded partial paralyses have been established and maintained for periods up to

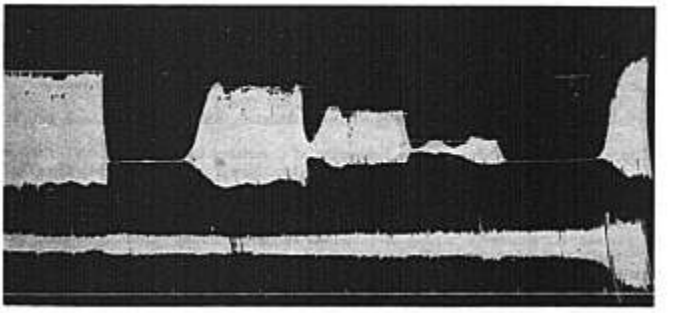

FIG. 6. Same as figure 5.

forty-five minutes at each level totaling as much as two and two thirds hours.

DISCUSSION

In view of the sudden onset of intense myoneural depression by succinylcholine and the short duration of its action, repeated small doses should be expected to maintain a controlled level of relaxation. In animal experiments this has been clearly shown, but it must be emphasized that in the laboratory the exact state of myoneural transmission can be followed by measurement of the gastrocnemius twitch. In the operating room, however, changes in degree of relaxation are less easily evaluated. Preliminary clinical investigation of succinylcholine using a continuous infusion technic has been reported by Foldes (14).

The short duration of action of succinylcholine, at one time considered undesirable, should be rated as an asset since it makes possible controlled paralysis of skeletal muscle.

SUMMARY

Succinylcholine is an ultra short-acting myoneural blocking agent. Its action is of quick onset and the intensity of the paralysis is marked.

There is only slight evidence of cumulative effects when subsequent doses of succinylcholine are given at rather short intervals.

The absence of cumulative action, the rapid recovery time and the intense action of quick onset, together with the very short period of action, make administration of succinylcholine by infusion technic a suitable procedure for production and maintenance of controlled muscular relaxation.

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AMERICAN BOARD OF ANESTHESIOLOGY

Written examinations of the American Board of Anesthesiology will be held in various locations, July 17, 1953. The oral examination will be held in St. Paul, Minnesota, September 27–October 1, 1953.