Clinical Studies on Succinylcholine Chloride

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Following single intravenous injections of succinylcholine chloride in doses of 0.5 to 4.0 mg./kg., the duration of muscle paralysis to 50 per cent recovery lasted from 5.9 to 17.1 minutes; duration was dose dependent. Following intramuscular injection of succinylcholine chloride, 1.0 to 4.0 mg./kg., the latent period was between 1.8 and 2.7 minutes, and dependent on both dose and the addition of hyaluronidase. The duration of weakness was quite variable, with 50 per cent recovery requiring between 20 and 27 minutes.

There was a strong suggestion that the formation of Phase II nondepolarizing block is not only dependent on the dose of succinylcholine chloride, but upon the duration of depolarization of the myoneural junction.

Much of the information regarding latency and duration of action of succinylcholine chloride in the anesthetized patient has been obtained by observing the effects of this drug on respiration.[1, 2] Since changes in respiration can result from factors other than the action of the muscle relaxant, information obtained by this method may be misleading.

With the use of the nerve stimulator in anesthesia, a new technique for studying muscle relaxants became available.[3] One need observe only the contraction of a muscle in response to stimulation of its motor nerve, in order to determine how soon after injection a muscle relaxant exerts its effect, and how long the effect lasts. By observing the response to tetanic stimulation, it is possible to determine the formation of Phase II nonpolarizing block. The muscular response to stimulation has been shown to be independent of depth of anesthesia, extent of pulmonary ventilation within the physiologic range, and external stimulation.[4, 6]

In the following investigation a nerve stimulator was used to gain information about: (1) the duration of action of succinylcholine chloride following a single intravenous injection; (2) the latency and duration of action of succinylcholine chloride following intramuscular administration; and, (3) the incidence of formation of Phase II nondepolarizing block following both methods of administration.

Materials and Methods

One hundred twenty patients who were having operations under general anesthesia were included in this study. Premedication, given intramuscularly approximately 90 minutes before the operation, included 75–100 mg. pentobarbital and/or 75–100 mg. meperidine with 0.3–0.4 mg. atropine or scopolamine. Anesthesia was induced with a thiobarbiturate, 150–400 mg., and maintained with general anesthetic agents. Although several kinds of nonexplosive agent were used (nitrous oxide-oxygen supplemented with meperidine, nitrous oxide-oxygen supplemented with methoxyflurane), in the majority, anesthesia was maintained with nitrous oxide, oxygen and halothane. Respiration was assisted or controlled as necessary for the duration of the study.

Following induction of anesthesia, needle electrodes of a Blockaid • nerve stimulator were inserted subcutaneously over the ulnar nerve at the wrist. The stimulator provided supramaximal stimuli of 6 milliseconds duration at a rate of approximately 36 per minute. A force displacement transducer was secured to the hand, and the signal resulting from thumb adduction was recorded on a Sanborn recorder. The latency and duration of response were measured from the tracing.

The latent period was estimated as the time from injection of drug to: a) first evidence of twitch suppression; and, b) complete twitch

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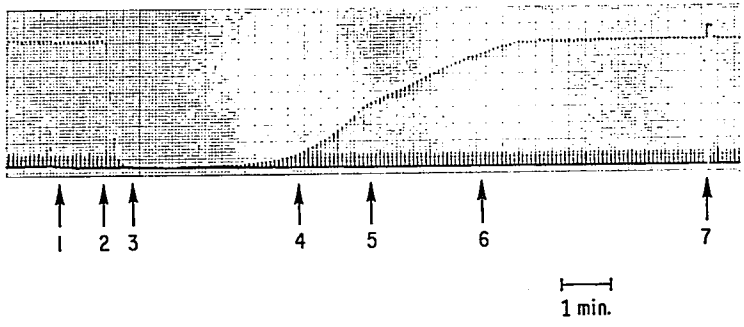

FIG. 1. Record of change in force of muscle contraction following an intravenous injection of succinylcholine chloride, 0.5 mg./kg. 1—Time of injection; 2—Onset of twitch suppression; 3—Complete twitch suppression; 4—Twitch recovery 10 per cent (T10); 5—Twitch recovery 50 per cent (T50); 6—Twitch recovery 90 per cent (T90); 7—Tetanic stimulation.

suppression. For duration, the time was taken from the first evidence of twitch suppression to recovery of twitch to 10 per cent (T10), 50 per cent (T50), and 90 per cent (T90) of maximum twitch height (fig. 1). Time to recovery to 50 per cent twitch height was used for comparison of duration between groups, since least variance was found at this end point. Although no measurements of ventilation were made, we noted whether onset of respiration occurred prior to the first evidence of twitch return.

When the twitch height reached a relative plateau, a burst of tetanic stimulation was given to determine the ability to sustain contraction and the presence or absence of post-tetanic facilitation. If, (a) the muscle could not sustain a contraction well, (b) the ability to sustain contraction improved with time, and (c) post-tetanic facilitation was present, it was assumed that some degree of Phase II nondepolarizing block was present.[3] Since recovery from Phase II block seemed to occur by a different mechanism than recovery from Phase I block, those patients exhibiting Phase II block were not included in determination of duration.

Patients were arbitrarily divided into groups of 15 in order to study the response to differing doses and routes of administration of the drug. Four groups of patients were given intravenous succinylcholine chloride (20 mg./ml.) in doses of 0.5 mg./kg., 1.0 mg./kg., 2.0 mg./kg., and 4.0 mg./kg., respectively. Since the rate of intravenous injection of the drug was not controlled, only data regarding duration of action and incidence of development of Phase II nondepolarizing block were utilized.

Four groups of patients received intramuscular succinylcholine chloride in doses of 1.0 mg./kg., 2.0 mg./kg., 2.0 mg./kg. with hyaluronidase 30 units/ml. of muscle relaxant, and 4.0 mg./kg. The concentration of succinylcholine chloride in the first group was 20 mg./ml.; in the latter three groups the concentration was 100 mg./ml. Intramuscular injections were made into the deltoid muscle. In these patients the latent period, duration of action, and incidence of Phase II block were determined.

The solvent for the succinylcholine chloride used in this study was saline. The drug was given as a single injection and was the first dose of muscle relaxant to be used on the patients in all groups except those receiving doses of 4.0 mg./kg. In these two groups, a 5.0 mg. test dose was given prior to the larger dose.

Results

The results are summarized in tables 1 through 4.

Following intravenous injection of succinylcholine chloride 0.5 mg./kg., recovery time of twitch to 50 per cent of final twitch height averaged 5.9 minutes. When the dose of succinylcholine chloride was increased to 1.0 mg./kg., 50 per cent recovery averaged 10.1 minutes. Following the injection of 2.0 mg./kg., recovery to 50 per cent averaged 12.7 minutes. After the largest intravenous dose of succinylcholine chloride, 4.0 mg./kg., recovery to 50 per cent averaged 17.1 minutes. The return of respiration was found to bear no constant relationship to the return of muscle twitch. Although in most cases respiration had begun prior to any demonstrable activity at the thumb, in some cases the reverse was true. These results, as well as 10 and 90 per cent recovery times, are summarized in table 1.

TABLE 1. Results Found in Patients Receiving Intravenous Succinylcholine Chloride

Dose (mg./kg.)	Mean Age (years)	Mean Recovery Time (minutes)			
		T10	T50	T90	ΔT10–T90
0.5	37.3±17	(13) 4.6±1.4	(13) 5.9±1.6	(13) 7.4±2.1	(13) 2.7±1.4
1.0	39.0±17	(14) 8.1±3.0	(15) 10.1±3.0	(15) 12.1±3.4	(14) 4.0±1.6
2.0	39.0±15	(14) 10.7±3.0	(14) 12.7±3.7	(14) 14.8±4.6	(14) 4.1±1.8
4.0	38.2±12	(14) 14.8±3.1	(15) 17.1±3.2	(15) 19.6±3.6	(14) 4.7±1.2

Number in parentheses indicates number of cases included in sample.

Significant differences in 50 per cent recovery time were found among all groups except between those receiving 1.0 and 2.0 mg./kg. succinylcholine chloride (table 2). The duration of twitch inhibition was dose dependent, according to the regression equation $T50 = 9.68 + 3.62 \log_2 (\text{dose})$, where time is in minutes and dose is in mg./kg. The variation about the regression line had an estimated standard deviation of approximately 3 minutes. No correlation between the patients' ages and duration of block could be demonstrated (table 1). The time for return of muscle contraction from 10 to 90 per cent took approximately 4.5 minutes and was not significantly different in groups receiving 1.0, 2.0, and 4.0 mg./kg. There was no evidence of development of Phase II block in any patient in the groups receiving intravenous succinylcholine chloride.†

TABLE 2. Comparison (P) of Results Found in Groups Receiving Intravenous Succinylcholine Chloride

Groups Compared	T10	T50	T90	ΔT10–T90
0.5 mg./kg. vs. 1.0 mg./kg.	0.001	<0.001	<0.001	0.030
0.5 mg./kg. vs. 2.0 mg./kg.	<0.001	<0.001	<0.001	0.040
0.5 mg./kg. vs. 4.0 mg./kg.	<0.001	<0.001	<0.001	<0.001
1.0 mg./kg. vs. 2.0 mg./kg.	0.011	0.060	0.108	0.84
1.0 mg./kg. vs. 4.0 mg./kg.	<0.001	<0.001	<0.001	0.19
2.0 mg./kg. vs. 4.0 mg./kg.	0.002	0.004	0.008	0.36

† It had been previously reported, erroneously, that Phase II nondepolarizing block was seen after

TABLE 3. Results Found in Patients Receiving Intramuscular Succinylcholine Chloride

Dose (mg./kg.)	Mean Age (years)	Latency (minutes)		Mean Recovery Time (minutes)			Patients with Phase II Block
		Onset of Suppression	Complete Suppression	T10	T50	T90	
1.0	35.8±15	(15) 1.3±0.51	(7) 2.7±1.1	(7) 10.6±5.2	(7) 20.6± 9.0	(7) 24.3± 8.9	0
2.0	42.2±13	(15) 1.2±0.38	(14) 2.4±0.77	(9) 24.3±9.4	(9) 26.6±10.5	(9) 30.0±11.9	5
2.0 with hyaluronidase 30 μ per ml.	32.0±15	(15) 1.2±0.36	(15) 1.8±0.44	(12) 20.0±3.7	(12) 23.9± 3.9	(12) 28.0± 4.4	3
4.0	41.0±16	(15) 1.1±0.28	(15) 1.8±0.50	—	—	—	11

Number in parentheses indicates number of cases included in measurement of sample.

TABLE 4. Comparison (P) of Results Found in Patients Receiving Intramuscular Succinylcholine Chloride

Groups Compared	Onset of Suppression	Complete Suppression	Recovery T50
1.0 mg./kg. vs. 2 mg./kg.	0.43	0.57	0.24
1.0 mg./kg. vs. 2 mg./kg. with hyal.	0.45	0.09	0.40
1.0 mg./kg. vs. 4 mg./kg.	0.098	0.08	
2.0 mg./kg. vs. 2 mg./kg. with hyal.	0.96	0.025	0.51
2.0 mg./kg. vs. 4 mg./kg.	0.30	0.018	
2.0 mg./kg. with hyal. vs. 4.0 mg./kg.	0.27	0.76	

Following the intramuscular injection of succinylcholine chloride 1.0 mg./kg., only 7 patients developed complete twitch inhibition. The mean time to onset of twitch suppression was 1.3 minutes, while the time to complete suppression was 2.7 minutes. Recovery of twitch to 50 per cent maximum twitch height took 20.6 minutes. When the dose was increased to 2.0 mg./kg., total twitch suppression was seen in 14 of 15 patients. The time to onset of suppression was 1.2 minutes, and time to complete suppression, 2.4 minutes. Fifty per cent twitch recovery took 26.6 minutes.

When hyaluronidase was added to succinylcholine chloride 2.0 mg./kg., all patients developed total inhibition of twitch. The time to onset of inhibition was 1.2 minutes, and time to total suppression was 1.8 minutes. Mean recovery time was shortened by the addition of hyaluronidase, with recovery to 50 per cent requiring 23.9 minutes.

Patients receiving 4.0 mg./kg. succinylcholine chloride showed evidence of initial twitch suppression in 1.1 minutes, and total twitch suppression in 1.8 minutes. Only 4 patients recovered without Phase II nondepolarizing block. Because of the small number of cases, assessment of the duration of the block at this dose was not made. These results, as well as 10 and 90 per cent recovery times, are summarized in table 3.

A significant difference in time to onset of suppression and time to 50 per cent recovery was not present in these groups. There was, however, a significant shortening of time to complete suppression when the groups of patients receiving 4.0 mg./kg. or 2.0 mg./kg. with hyaluronidase were compared to the group of patients who received 2.0 mg./kg. succinylcholine chloride without hyaluronidase (table 4).

Discussion

Using the nerve stimulator as a measuring device, we found the average duration of action of 1 mg./kg. intravenous succinylcholine to be 12.1 minutes. The duration became greater as the intravenous dose was increased, and was markedly prolonged, 20 to 30 minutes, when the drug was given intramuscularly.

Intravenous succinylcholine produced neuromuscular inhibition in two distinct phases. In the first there was total inhibition (estimated by T10), and in the second, recovery of twitch (estimated by T10-T90). Mean twitch recovery time (T10-T90) was not significantly different among groups in the 1.0 to 4.0 mg. dose range. We can ascribe the difference in duration, then, to the difference in length of total twitch suppression.

There is no evidence extant that the succinylcholine molecule undergoes changes at the myoneural junction. True cholinesterase does not hydrolyze succinylcholine,[7] and there is little or no plasma cholinesterase at that site. Foldes has suggested that the neuromuscular block is terminated by redistribution of succinylcholine to other tissues, presumably away from the end plate.[8] Redistribution is facilitated by hydrolysis of the drug in the blood stream. In our study the duration to T10 may represent the time necessary to reduce the concentration at the end plate to the threshold for myoneural conduction. Since this duration is dependent upon the initial concentration of

single intravenous injections of succinylcholine chloride in doses of 2.0 and 4.0 mg./kg.[5] At the time, the author did not appreciate the fact that post-tetanic facilitation, in itself, is not an indication of Phase II block, and that it may be seen in the absence of the use of a muscle relaxant.

drug, it is variable. The time T10-T90 begins when the concentration has already been reduced to threshold for conduction, and continues to recovery. This period would be expected to be constant in patients with normal enzymatic hydrolysis of succinylcholine.

The incidence of development of Phase II nondepolarizing block seemed to be related to the duration of depolarization of the myoneural junction. Patients given a single intravenous injection of drug in doses of 4.0 mg./kg., had a prompt recovery and no measurable evidence of Phase II block. Patients given a similar dose intramuscularly had a longer duration of depolarization and showed a 73 per cent incidence of Phase II block. Katz has shown that succinylcholine 3.0 mg./kg. given by slow intravenous drip, causes a 100 per cent incidence of Phase II block.[9] We concluded that the formation of Phase II nondepolarizing block is not only dose dependent but time dependent as well.

The response to tetanic stimulation served as a guide to the duration of Phase II nondepolarizing block. Recovery was prompt in patients who could sustain a tetanic contraction fairly well and had post-tetanic facilitation of 50 per cent or less. Muscle weakness and evidence of Phase II block lasted for many hours in patients who had a poor ability to sustain tetanus and facilitation of several hundred per cent.

The addition of hyaluronidase to intramuscular succinylcholine shortened the time to complete twitch inhibition and decreased the variance of duration. Hyaluronidase did not decrease the duration of the block significantly, nor did it eliminate the formation of Phase II nondepolarizing block.

Summary

The effects of succinylcholine were studied by observing the force of thenar adduction, in response to ulnar nerve stimulation. After succinylcholine 0.5 to 4.0 mg./kg., injected intravenously, twitch inhibition to 50 per cent recovery took from 5.9 to 17.1 minutes. Duration of inhibition was found to be dose dependent.

After succinylcholine 1.0 to 4.0 mg./kg. injected intramuscularly, the latent period was found to be between 1.8 and 2.7 minutes, and was dependent upon both dose and the addition of hyaluronidase. Duration of action was variable and no significant difference among groups was observed.

Formation of Phase II nondepolarizing block was seen only in patients receiving the neuromuscular blocker intramuscularly. We suggest that the formation of Phase II block is not only related to dose of the neuromuscular blocker, but also to the length of time that the myoneural junction remains depolarized.

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