

The Nondepolarizing Neuromuscular Blocking Action of Succinylcholine in Man

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THE NEUROMUSCULAR blocking action of succinylcholine was originally believed to be due to depolarization of the motor-end plate.^{1, 2} It has been demonstrated, however, that in certain species succinylcholine produces a nondepolarizing as well as depolarizing block.^{3, 4} Studies in man have suggested that prolonged administration of large amounts of succinylcholine may in some patients produce a nondepolarizing type of block.⁵⁻⁸ The present study was undertaken to answer the following questions: How often does succinylcholine produce a nondepolarizing block in man? Is the development of such a block time dependent or dose dependent? Is the mode of administration of succinylcholine a factor in producing a nondepolarizing block? What is the relationship between the development of tachyphylaxis and a nondepolarizing block? Does the anesthetic agent used or depth of anesthesia affect the development of a nondepolarizing block?

Method

Fifty-three patients undergoing plastic or urologic surgery were studied. Most of the patients were premedicated with a belladonna drug (atropine or scopolamine), a barbiturate and or a narcotic. Anesthesia was usually induced with thiamylal sodium and maintained with halothane, trichlorethylene, methoxyflurane, halopropane, nitrous oxide or cyclopropane. The trachea was intubated in 37 patients. In the 12 patients who received 20-40 mg. of succinylcholine to facilitate intubation this dose is included in the total

cumulative dose. Ventilation was measured with a Wright ventilometer or a Wedge spirometer. Respiration was assisted or controlled as required. The patient's hand was carefully fixed in place on a specially constructed arm board. A supramaximal stimulus from a Grass stimulator (model SC 4) was applied to the ulnar nerve at the wrist by means of surface electrodes. Twitch responses were elicited with square pulse stimuli of 0.3 msec. duration delivered at a rate of 18/minute. Tetanus was obtained by stimulation at 50 cycles/second and was maintained for two to three seconds. The resulting adduction of the thumb was measured by a force displacement transducer (Grass FT-03) and recorded on a polygraph. Succinylcholine was administered by intermittent injection of 2 per cent or by continuous infusion of 0.1, 0.2, and 0.4 per cent solutions. Intermittent injection of 0.15 mg./kg. was made at five-minute intervals, 0.3 mg./kg. every ten minutes, 0.75 mg./kg. every five or ten minutes and 1.5 mg./kg. every fifteen minutes. The rate of continuous infusion varied from 0.1 mg./kg. per minute to 1 mg./kg. per minute. All patients received a minimum cumulative dose of 3 mg./kg. The maximum cumulative dose was 10 mg./kg. The twitch response was measured throughout the experiment to determine the degree and duration of action of each dose of succinylcholine. Tetanic stimuli were applied at appropriate intervals to determine whether the tetanus was well maintained, and for the presence or absence of post-tetanic facilitation. Edrophonium 0.15 mg./kg. was injected following the cumulative injection of 0.5 to 10 mg./kg. of succinylcholine. When edrophonium was administered more than once in any given patient at least one-half hour was allowed to elapse between injections.

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TABLE 1. Effect of Cumulative Dose of Succinylcholine Upon Development of Wedensky Inhibition, Post-tetanic Facilitation and Edrophonium Antagonism

	Wedensky Inhibition	Post-tetanic Facilitation	Edrophonium Antagonism
Smallest cumulative dose at which seen	0.4 mg./kg.	1.0 mg./kg.	2.2 mg./kg.
Cumulative dose at which regularly seen, number of patients ()	1.5 mg./kg. (53)	2.0 mg./kg. (53)	3.0 mg./kg. (16)

Results

Tetanic Stimulation and Post-Tetanic Facilitation. At a cumulative dose of succinylcholine of less than 0.4 mg./kg. tetanus was well sustained and PTF (post-tetanic facilitation) was not observed. As the dose of succinylcholine increased, tetanus was poorly sustained (Wedensky inhibition) but PTF was not seen. With further increases in the dose of succinylcholine both Wedensky inhibition and PTF were observed. The cumulative dose of succinylcholine required to produce Wedensky inhibition was usually less than that

required to produce PTF. The minimum dose required for the former was 0.4 mg./kg. and for the latter 1.0 mg./kg. After 1.5 mg./kg., Wedensky inhibition was regularly observed while after 2 mg./kg. PTF was regularly observed (table 1). Although some degree of PTF was seen in all patients after 2 mg./kg., there was a gradual increase in the degree of facilitation as the cumulative dose of succinylcholine increased (fig. 1). All 53 patients who received at least 3 mg./kg. of succinylcholine exhibited Wedensky inhibition and PTF. The magnitude of PTF after 3 mg./

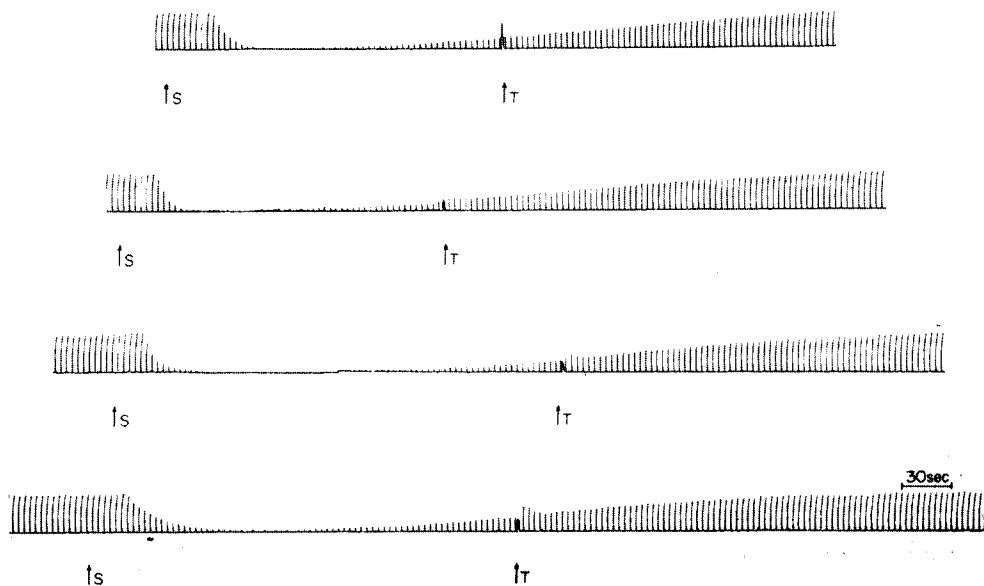


FIG. 1. Development of post-tetanic facilitation with intermittent injections of 0.3 mg./kg. succinylcholine every 10 minutes. $\uparrow S$ = succinylcholine, $\uparrow T$ = tetanus. Cumulative dose of succinylcholine: Upper panel—1.2 mg./kg. Note Wedensky inhibition but absence of post-tetanic facilitation. Second panel—1.8 mg./kg. Earliest suggestions of post-tetanic facilitation. Third panel—2.7 mg./kg. Fourth panel—3.3 mg./kg. Note increase in magnitude of post-tetanic facilitation.



FIG. 2. Response to edrophonium after 0.6 mg./kg. cumulative dose of succinylcholine. $\uparrow T$ = tetanus. $\uparrow E$ = 0.15 mg./kg. edrophonium. Note absence of post-tetanic facilitation in left panel and decrease in twitch response (potentiation of succinylcholine) after edrophonium in right panel. Before edrophonium respiratory rate, 22/minute, and tidal volume, 210 ml. After edrophonium rate, 21/minute, and tidal volume, 160 ml.

kg. was such that the first twitch following tetanus was two or more times greater than the twitch immediately preceding the tetanus.

Edrophonium. In the absence of succinylcholine, edrophonium 0.15 mg./kg. did not significantly affect the twitch response. With a cumulative dose of succinylcholine of less than 1.0 mg./kg. the response to 0.15 mg./kg. of edrophonium was a potentiation of the succinylcholine block in 8 patients studied (fig. 2, table 2). Associated with a potentiation of the neuromuscular block, there was a fall in tidal volume. In the range of 1.0 to 3.0 mg./kg. of succinylcholine, edrophonium produced a potentiation of the block in 4 patients, no significant effect in 9 patients, and antagonism of the block in 7 patients (tables 1 and 2). Once again changes in tidal volume paralleled the twitch response. When greater than 3.0 mg. kg. of succinylcholine had been infused, edrophonium antagonized the block and increased tidal volume in the 16 patients

studied (fig. 3, tables 1 and 2). In 8 patients who received more than one dose of 0.15 mg./kg. of edrophonium a potentiation of succinylcholine was seen when less than 1.0 mg./kg. of succinylcholine had been infused, but antagonism was observed in the same patient when greater than 3.0 mg./kg. of succinylcholine had been infused. In the range of 1.0 to 3.0 mg./kg. of succinylcholine, edrophonium antagonism could be predicted accurately from the degree and nature of PTF. When the first twitch following the tetanus was two or more times greater than the twitch immediately preceding the tetanus, edrophonium antagonized the block (figs. 3 and 4). The greater the PTF, the greater the edrophonium antagonism. At lesser degrees of PTF, edrophonium either potentiated the block or had no effect.

Tachyphylaxis. Significant tachyphylaxis (a consistent decrease in degree or duration of action of greater than 20 per cent) was observed in 6 of 20 patients who received 0.3 mg. kg. of succinylcholine every 10 minutes until PTF or edrophonium antagonism was observed. The word consistent is important here since in 5 of the remaining 14 patients a decreased response to succinylcholine was observed at one time, but on a subsequent injection a response similar to or greater than the first injection was observed. It was noted that in many patients the response from dose to dose varied so that neither tachyphylaxis nor a cumulative effect was regularly observed. The one consistent observation was that the presence or absence of tachyphylaxis did not affect the development of Wedensky inhibition, PTF, or edrophonium antagonism.

TABLE 2. Response to Edrophonium (0.15 mg./kg.) After Various Cumulative Doses of Succinylcholine

Cumulative Dose of Succinylcholine	Twitch Height	Tidal Volume
<1 mg./kg.	Decreased (potentiation of block)	Decreased
1-3 mg./kg.	Decreased, no change, increased	Decreased, no change, increased
>3 mg./kg.	Increased (antagonism of block)	Increased

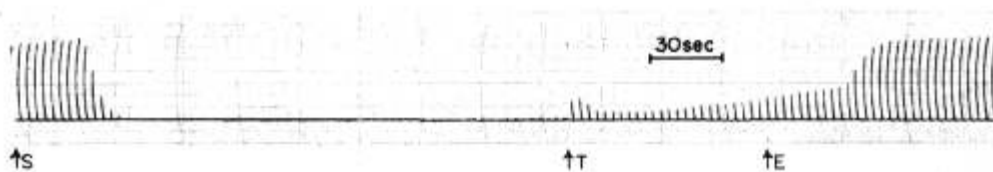


FIG. 3. Response to edrophonium after 3 mg./kg. cumulative dose of succinylcholine. \uparrow S = 0.3 mg./kg. succinylcholine. \uparrow T = tetanus. \uparrow E = edrophonium 0.15 mg./kg. Note post-tetanic facilitation and edrophonium antagonism. Before edrophonium respiratory rate, 15/minute and tidal volume, 300 ml. After edrophonium rate of 16/minute and tidal volume, 470 ml.

Other Observations. The mode of administration of succinylcholine did not alter the results. When succinylcholine was infused by continuous drip or intermittently in doses ranging from 0.15 to 1.5 mg./kg., Wedensky inhibition, PTF and edrophonium antagonism were regularly observed after 1.5 mg./kg., 2 mg./kg. and 3 mg./kg. respectively (table 1). The use of 20–40 mg. of succinylcholine to facilitate intubation in 12 patients did not alter the results. In figure 3 intermittent injection of 0.3 mg./kg. was used. In figure 4 a continuous infusion was used.

The development of Wedensky inhibition, PTF and edrophonium antagonism was not time-dependent. The time required for their development depended only upon the time it took to reach the appropriate cumulative dose. Three patients demonstrated Wedensky inhibition after an initial dose of 0.75 mg./kg. and two patients demonstrated both Wedensky inhibition and PTF after an initial dose of 1.5 mg./kg.

The anesthetic agent (of those listed), the depth of anesthesia and the presence or absence of surgical manipulation did not affect the results.

Discussion

Although neuromuscular blocking agents were originally classified as depolarizing or nondepolarizing in their action at the neuromuscular junction, it soon became apparent that the classification was an over-simplification. It was demonstrated in a variety of species that succinylcholine and decamethonium produced first a depolarizing block and later a nondepolarizing block.^{3, 4, 9, 10, 11} Thesleff¹² showed that the end-plate depolarization produced by succinylcholine and decamethonium in the frog muscle did not correlate well with the presence of a neuromuscular block. In relatively few controlled studies in man, it has been suggested that succinylcholine may under certain circumstances produce a nondepolarizing block.^{5, 8} The criteria and tech-

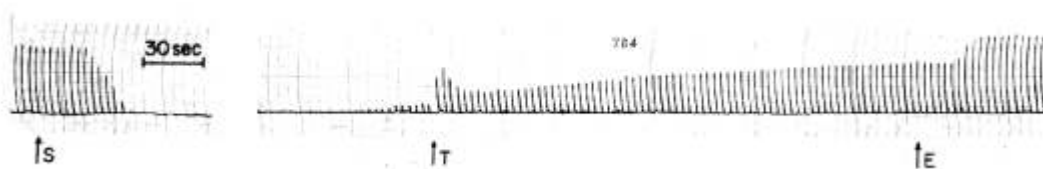


FIG. 4. Response to tetanus and edrophonium after continuous infusion of succinylcholine. \uparrow T = tetanus. \uparrow E = edrophonium 0.15 mg./kg. At \uparrow S in left panel continuous infusion of 0.4 per cent succinylcholine started. In the 27 minutes between panels 4.0 mg./kg. succinylcholine were infused and infusion discontinued. In right panel note marked post-tetanic facilitation and edrophonium antagonism of the succinylcholine block. Before edrophonium respiratory rate, 22/minute and tidal volume, 200 ml. After edrophonium rate, 24/minute and tidal volume, 330 ml.

niques used in these studies must be carefully scrutinized in order to interpret the different results obtained in the present and previous studies. Some of the techniques used include the measurement of tidal volume as an index of neuromuscular blockade, interaction of neuromuscular blocking agents, muscle response to nerve stimulation, or the effect of anticholinesterases.

In preliminary studies we observed that changes in tidal volume provided a poor index of neuromuscular blockade. This is not surprising since ventilation can be modified by the anesthetic agent used, depth of anesthesia, development of acidosis or alkalosis, and surgical manipulation. After a small (0.15 mg./kg.) dose of succinylcholine in 4 patients, it was possible to demonstrate a decrease in twitch height without a change in ventilation. A decrease in ventilation without a change in twitch height could regularly be produced by increasing the depth of anesthesia.

The interpretation of experiments on interaction of neuromuscular blocking agents is difficult. In one study,⁶ following the administration of a dose of *d*-tubocurarine which minimally affected respiration, succinylcholine was infused. After ventilation returned to control levels the initial dose of *d*-tubocurarine was repeated. The greater effect of the second dose of *d*-tubocurarine given one to two hours after the first dose was attributed to a nondepolarizing effect of succinylcholine. We repeated this experiment but omitted the succinylcholine between doses of *d*-tubocurarine. The first dose of *d*-tubocurarine did not affect the twitch height. The same dose repeated after one to two hours markedly decreased the twitch height and was clearly a cumulative effect. The conclusion that a mixed or dual block results from the alternate administration of depolarizing and nondepolarizing neuromuscular blocking agents, even if justified, offers little useful information.

The response of a muscle (electrical or mechanical) to nerve stimulation appears to be an acceptable index of neuromuscular transmission. The time course of the block can easily be determined. By measuring muscle response to twitch and tetanic rates of stimulation the nature of the block can be deter-

mined. With a nondepolarizing block the response to tetanic stimulation interpolated into a series of single nerve stimuli (twitch) is a twofold one. Initially tetanus is poorly sustained. This is followed by PTF upon return to a twitch rate of stimulation. With a depolarizing block, tetanus is well sustained and PTF is not observed.

The effect of anticholinesterases on the neuromuscular block has frequently been used as a means of distinguishing depolarizing from nondepolarizing blocks. A depolarizing block is potentiated and nondepolarizing block antagonized by edrophonium and neostigmine.

We chose in this study to use the muscle response to twitch and tetanic stimulation and edrophonium as the criteria for characterizing a neuromuscular block as depolarizing or nondepolarizing. Using these criteria succinylcholine appeared to produce in man first a depolarizing and then a nondepolarizing block. The progression of the nondepolarizing block to the point of being antagonized by edrophonium was seen after 2.2 mg./kg. of succinylcholine in some patients, and in all patients after 3 mg./kg. The nondepolarizing block did not appear to be time dependent in that the development of such a block depended only upon the time required to achieve the above-mentioned cumulative dose of succinylcholine. Although tachyphylaxis was observed in some patients, this was not necessary for the development of a nondepolarizing block. The mode of administration, *i.e.*, intermittent or continuous, did not influence the course of development of the nondepolarizing block. The anesthetic agent used and the depth of anesthesia did not affect these results.

The block produced by succinylcholine should not be considered either depolarizing or nondepolarizing or as abruptly changing from one to the other with increasing dosage. The progressive development of Wedensky inhibition, PTF, and edrophonium antagonism appears to represent different phases of a continuum. Elements of both kinds of block are frequently seen simultaneously and may represent the balance of many units in different phases of block. With the clinically used doses of succinylcholine (0.75 and 1.5 mg./kg.) the first dose can produce a block with

both depolarizing and nondepolarizing characteristics.

These results are different from those of Foldes *et al.*,⁶ Brennan,⁵ and Churchill-Davidson *et al.*^{7, 8} in terms of frequency of development of nondepolarizing block, role of tachyphylaxis and time-dose requirement. Although we observed a nondepolarizing block in all 53 patients studied, Foldes⁶ stated that in some persons, but by no means in all, the change in sensitivity of the end-plate can progress so far that a nondepolarizing block is seen. However, no case was reported in which a nondepolarizing block could not be elicited. Churchill-Davidson^{7, 8} believed that tachyphylaxis was the first change seen in the development of a nondepolarizing block. In this study, tachyphylaxis was not related to the development of a nondepolarizing block.

Brennan,⁵ Foldes,⁶ and Churchill-Davidson^{7, 8} suggested that a nondepolarizing block was observed only after prolonged administration of large amounts of depolarizing agents. In the eight patients studied by Churchill-Davidson⁸ the average dose of succinylcholine used to produce a "complete nondepolarizing block" was 944 mg. (range from 500 to 1,600 mg.) and the time required was 140 minutes (85 to 196 minutes). The experimental design and techniques used were such that the demonstration of a nondepolarizing block with smaller doses of succinylcholine might not have been possible. If a nondepolarizing block followed only the prolonged administration of a large amount of succinylcholine it would be an interesting but presumably rare occurrence. The rapid onset of a nondepolarizing block following relatively small doses of succinylcholine seen in this study makes it an effect to be considered whenever succinylcholine is used. Whether the nondepolarizing block produced by succinylcholine is exactly the same as that of *d*-tubocurarine is not yet known.

Summary

The nature of the neuromuscular block produced by succinylcholine was studied in 53 patients by measuring the response to twitch,

tetanus and edrophonium administration. First a depolarizing and then a nondepolarizing block were observed in all the patients studied. The nondepolarizing block was dose but not time dependent, and was unrelated to the mode of administration of succinylcholine. The presence of tachyphylaxis was not necessary for the development of a nondepolarizing block. The anesthetic agents used and depth of anesthesia did not affect the results.

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