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The Effect of Depolarizing Relaxants on the Neuromuscular Refractory Period of Anesthetized Man

Ralph A. Epstein, M.D., and Stephen H. Jackson, M.D.†*

In anesthetized man decamethonium and succinylcholine, in subparalytic doses, increased the neuromuscular refractory period, as determined by observation of both the tension and the compound action potential of the indirectly stimulated adductor pollicis muscle. This is opposite to the effect previously reported for the nondepolarizing relaxants, curare and gallamine, which decrease the refractory period. Determination of changes in the refractory period allows detection of the presence of relaxant drugs in doses which fail to cause blockade. (Key words: Depolarizing relaxants; Neuromuscular refractory period; Halothane.)

THE NEUROMUSCULAR refractory period in anesthetized man has been shown to be a sensitive index of the actions of various relaxant and anesthetic drugs in subparalytic doses.[1-3] We report here the effect of the depolarizing relaxants, succinylcholine chloride and decamethonium bromide.

Methods

Eleven healthy patients were studied during surgical anesthesia. After premedication with atropine (0.007 mg/kg, im), anesthesia was induced and maintained with halothane in 60 per cent N_2O in a nonrebreathing system. During and for at least one hour prior to the study period the inspired halothane concentration was held constant at 1.0 per cent. The tracheas of all patients were intubated without the use of relaxant drugs, and a constant minute volume 50 per cent greater than that predicted from the Radford nomogram was maintained with a volume-limited ventilator. No other drugs were administered except the drugs studied.

* Assistant Professor, Columbia University.
† Assistant Professor, Stanford University.
Received from the Department of Anesthesiology, Columbia University, New York, New York 10032, and the Department of Anesthesiology, Stanford University, Palo Alto, California. Accepted for publication September 18, 1972.

The methods used to study the neuromuscular refractory period have been described.[1] In brief, using bare needle electrodes, the adductor pollicis EMG and the antidromic ulnar nerve compound action potential at the elbow (seven subjects only), along with the thumb tension, were simultaneously photographed from a dual-beam oscilloscope and recorded on a polygraph, respectively. The ulnar nerve was stimulated at the wrist at 5-second intervals with supramaximal stimuli of 0.1-msec duration. Single stimuli and paired stimuli with 0.5–10.0-msec pair intervals were used. Evoked tension was plotted on linear graph paper as a function of pair intervals in order to determine the "average neuromuscular refractory period" (ARP). The ARP is defined as that pair interval which determines that tension which is the average of the tension evoked by a single stimulus and the maximal tension which can be evoked by a paired stimulus.[1] Subjects in whom repetitive muscle depolarization was evoked by a single nerve stimulus were excluded from this study.[4]

For the decamethonium studies control data were obtained from five subjects anesthetized with halothane in N_2O. Decamethonium (0.5 mg, iv) was then administered and ARP was restudied 5 minutes later and followed at intervals until recovery. For the succinylcholine studies similar control data were obtained in another four subjects. Succinylcholine (3.0 mg, iv) was then administered and ARP was redetermined 90 seconds later and followed until recovery. Because of the extremely brief action of succinylcholine, we also studied an additional two subjects from whom control data were obtained 10 minutes after administration of hexafluorenium bromide (0.4 mg/kg, iv). Succinylcholine (2.0 mg, iv) was administered and ARP redetermined five minutes later and followed until recovery. Preliminary studies had indicated that no paralysis would

TABLE 1. Neuromuscular Refractory Period: Effects of Decamethonium

	Sex	Age (Years)	Weight (kg)	Dose (mg)	ARP (msec)		
					Control	Experimental	Recovery
Patient 1	F	64	54	0.5	1.65	2.00	1.65
Patient 2	F	32	62	0.5	1.75	1.90	1.75
Patient 3†	M	57	86	0.5	1.05	1.55	1.05
Patient 4	M	40	69	0.5	2.00	2.30	2.20
Patient 5†	M	43	80	0.5	1.85	2.80	1.80
Mean					1.66	2.11*	1.69
±SE					0.16	0.21	0.19

* $P < 0.05$.
† Nerve action potential recorded.

TABLE 2. Neuromuscular Refractory Period: Effects of Succinylcholine

	Sex	Age (Years)	Weight (kg)	Dose (mg)	ARP (msec)		
					Control	Experimental	Recovery
No previous hexafluorenium							
Patient 6†	M	23	83	3	1.75	2.30	1.65
Patient 7†	M	53	67	3	1.60	1.95	1.45
Patient 8	M	45	61	3	2.30	3.60	2.25
Patient 9†	M	43	88	3	1.85	3.00	1.90
Mean					1.88	2.71*	1.81
±SE					0.15	0.37	0.17
After 0.4 mg/kg hexafluorenium							
Patient 10†	M	44	54	2	1.30	2.40	1.35
Patient 11†	M	27	76	2	1.80	2.75	1.70
Mean					1.55	2.58*	1.53
±SE					0.25	0.18	0.18

* $P < 0.05$.
† Nerve action potential recorded.

result from these doses and that the maximal effects would be seen at the times chosen. The significance of any changes in ARP was tested by Student's t test for differences between paired samples.

Results

DECAMETHONIUM

In each of the five subjects a subparalytic dose of decamethonium caused the tension curve to move to the right. The mean increase in ARP was 0.45 msec ($P < 0.05$) (table 1). There was generally a return to control within 20 to 30 minutes. The electromyogram invariably reflected the increase in ARP. The EMG evoked by the single stimulus was unchanged. However, decamethonium increased the pair interval needed to evoke a double muscle response. The antidromic nerve response was unaffected. Figures 1 and 2 show the results of a typical study.

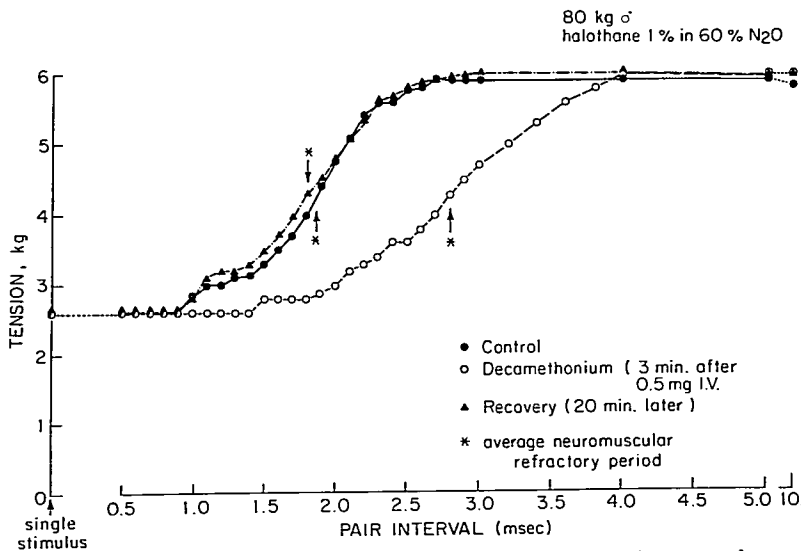

FIG. 1. The effect of decamethonium on the average neuromuscular refractory period. Tension is plotted as a function of the pair interval. Decamethonium caused the curve to shift to the right and the ARP to increase from 1.85 to 2.80 msec. The ARP returned to control 20 min later. The evoked twitch response to the single stimulus was not affected by this dose of decamethonium.

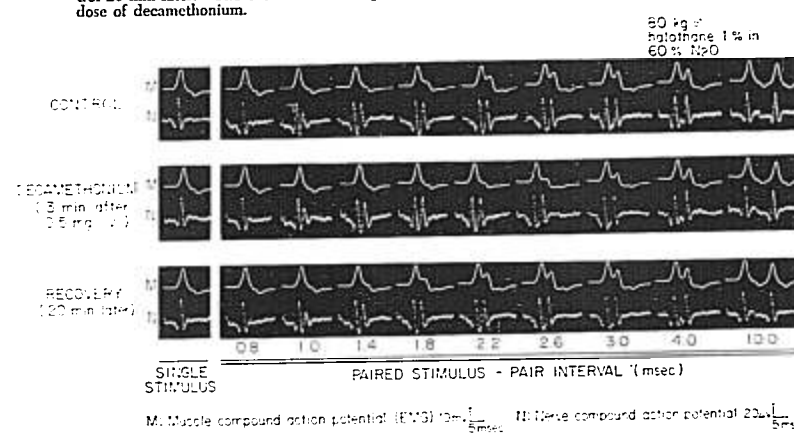

FIG. 2. Muscle and nerve compound action potentials obtained from the subject in figure 1. Decamethonium increased the least pair interval at which there was a second electromyographic deflection 1.4 to 2.2 msec. Decamethonium did not affect the electromyographic response to the single stimulus, nor did it affect the nerve compound action potentials evoked by single or paired stimuli.

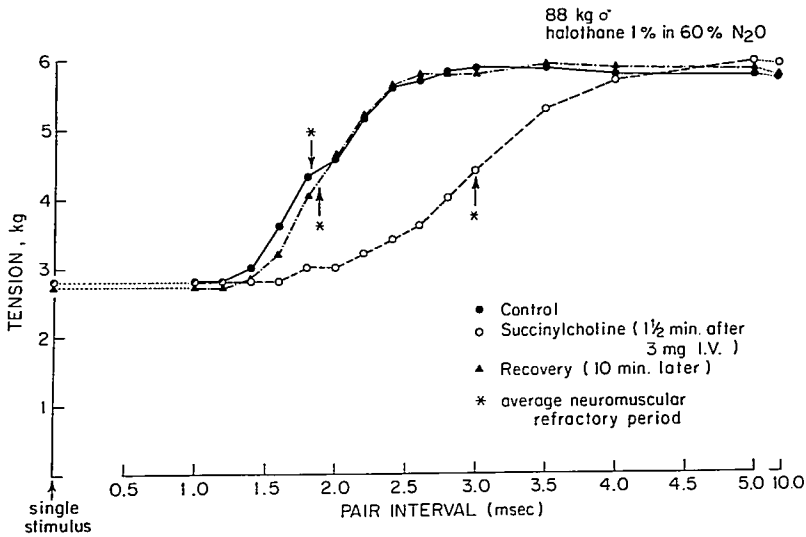

FIG. 3. The effect of succinylcholine on the average neuromuscular refractory period. Succinylcholine caused the tension curve to shift to the right and the ARP to increase from 1.85 to 3.00 msec, with return to control within 3 minutes. Fewer paired stimuli were used to determine this curve than the curves in figures 1 and 6 because of the brief time available during the transient effect.

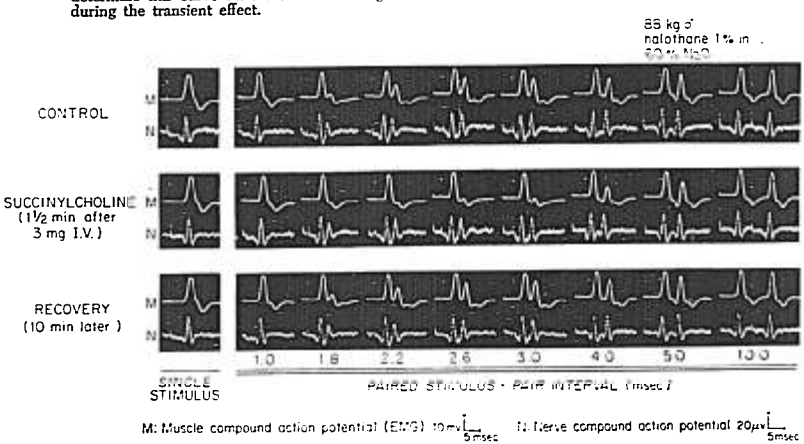

FIG. 4. Muscle and nerve compound action potentials obtained from the subject in figure 3. Succinylcholine increased the least pair interval at which there was a second electromyographic deflection from 1.8 to 2.6 msec. Succinylcholine did not affect the electromyographic response to the single stimulus, nor did it affect the nerve compound action potentials evoked by single or paired stimuli.

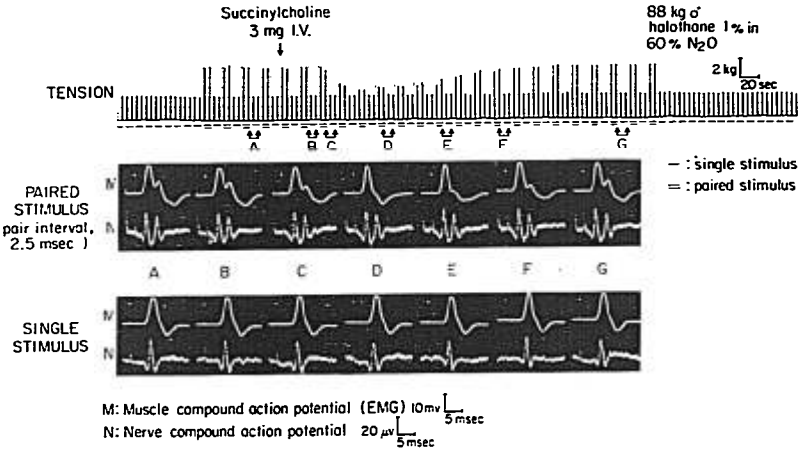

FIG. 5. The time course of the increase in ARP caused by succinylcholine. *Top panel:* Polygraph record of tension evoked by single stimuli and paired stimuli with 2.5-msec pair interval before and after administration of succinylcholine. *Middle and bottom panels:* Muscle (EMG) and nerve compound action potentials from paired and single stimuli at the times indicated in the top panel. Succinylcholine decreased the tension evoked by the paired but not the single stimulus, and only the muscle compound action potential evoked by the second member of the stimulus pair. The effect was maximal at 90 seconds and there was return to control within 3 minutes. Figures 3, 4 and 5 are from the same patient. The study shown in figure 5 was done half an hour after the study in figures 3 and 4.

SUCCINYLCHOLINE

In each of the four subjects a subparalytic dose of succinylcholine increased the refractory period, as reflected by the tension curves and EMG (table 2, figs. 3 and 4). The increase was transient, generally peaking at 90 seconds with recovery within 3 to 4 minutes. Thus, the ARP was returning towards control during the time (one minute) necessary for its determination. The ARP increase observed (table 2) therefore underestimates the actual increase. In one subject the time course of the change in ARP was determined by observing the effect of succinylcholine on single stimuli and paired stimuli with a 2.5-msec pair interval (fig. 5). Succinylcholine selectively abolished the response to the second member of the stimulus pair, with return to control within 3 minutes. Succinylcholine had no effect on the nerve action potentials.

To facilitate the study of succinylcholine, hexafluorenium was administered to two subjects. Hexafluorenium invariably decreased ARP, as previously reported.[3] Succinylcholine administered 10 minutes after hexafluorenium increased the refractory periods in both subjects, as judged by the tension curves and EMG's (table 2, figs. 6 and 7). The increase was sustained and returned to control within 30 minutes.

Discussion

The ARP has proven to be an exquisitely sensitive indicator of the presence of many drugs in subparalytic doses. These include *d*-tubocurarine chloride and gallamine triethiodide,[1] neostigmine methylsulfate and edrophonium chloride,[2] hexafluorenium,[3] potent anesthetics,[2] and now succinylcholine and decamethonium. These observations are consistent with the

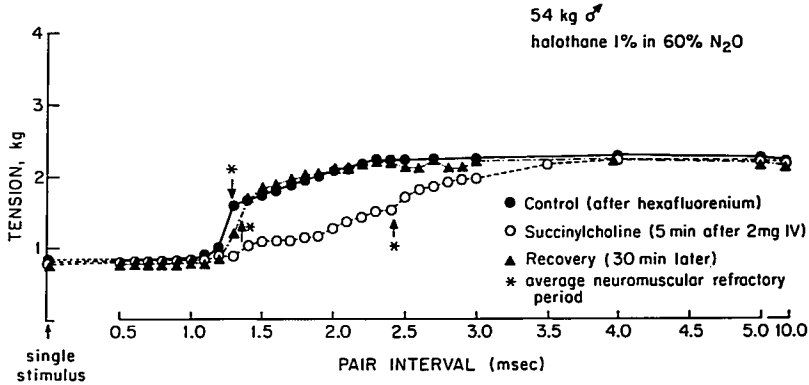

FIG. 6. The effect of succinylcholine on the average neuromuscular refractory period in a subject previously given hexafluorenium. Succinylcholine caused the tension curve to shift to the right and the ARP to increase from 1.30 to 2.40 msec, with recovery in 30 minutes.

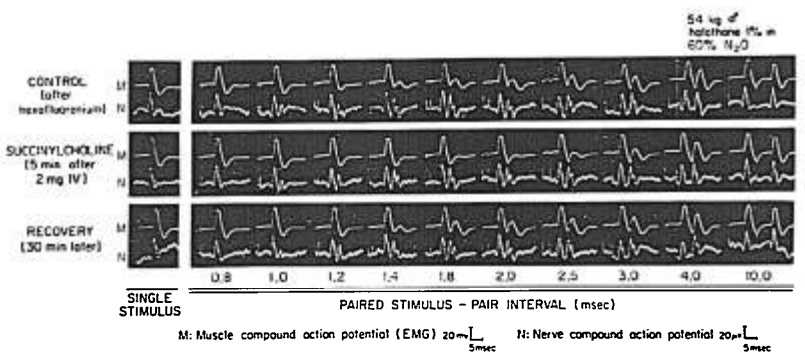

FIG. 7. Muscle and nerve compound action potentials obtained from the subject in figure 6. Succinylcholine increased the least pair interval at which there was a second electromyographic response from 1.2 to 1.8 msec.

general view that a relaxant drug may occupy many receptor sites without causing overt blockade: that is, there is a "margin of safety" of neuromuscular transmission.[5] That such a drug indeed occupies receptor sites may be revealed when the "margin of safety" is reduced by other means. For example, a dose of a nondepolarizing relaxant which alone is subparalytic may produce blockade in the presence of certain potent anesthetics.[6] Also, blockade may be uncovered during tetanic stimulation where depletion of readily releas-

able acetylcholine causes a decreased number of quanta of acetylcholine to be available for release per nerve stimulus.[7] This tetanic fade may be difficult to detect in man without use of extremely high-frequency stimulation [8] unless electromyography is used.[9] In contrast to the many reports demonstrating such receptor occupancy in anesthetized man by subparalytic doses of nondepolarizing relaxants, detection of an effect of subparalytic doses of depolarizing relaxants has not been reported previously. Determination of ARP is equally useful in demonstrating the presence of depolarizing and nondepolarizing relaxants in subparalytic doses.

The mechanisms involving drug-induced refractory-period changes are unknown. In general, however, drugs or techniques which mimic the effect of acetylcholine, for example, depolarizing relaxants, anticholinesterases,[1] and tetanic stimulation (unpublished), increase ARP, whereas drugs which compete with acetylcholine, for example, nondepolarizing relaxants,[1] decrease the refractory period. It is of interest that depolarizing and nondepolarizing relaxants have opposite effects on ARP despite the fact that de Jong and Freund,[10] using tetanic fade and posttetanic potentiation as indicators, could not demonstrate a difference between curare- and succinylcholine-induced blocks in man. It would be of interest to determine whether, after recovery from prolonged infusion of succinylcholine, additional succinylcholine increases or decreases ARP.

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