STUDIES CONCERNING THE PROLONGATION OF ACTIVITY OF SUCCINYLCHOLINE* †‡

L. JENNINGS HAMPTON, M.D., DAVID M. LITTLE, JR., M.D., GALON S. RODABAUGH, M.D., AND WILLIAM R. CHAPPEE, M.D.

New Haven, Connecticut

Succinylcholine, or diacetylcholine, is one of many synthetic compounds possessing the ability to produce neuromuscular blockade, and therefore muscular relaxation (1, 2). In the twelve years since Griffith's classic demonstration of the utility of d-tubocurarine for the production of muscular relaxation during surgical anesthesia (3), a number of these compounds have been employed for this purpose during operative interventions with varying degrees of success (4–10). Succinylcholine, because of its extremely brief action, has proved to be the most versatile of all these muscle relaxant drugs. Its extremely rapid hydrolysis permits administration by an infusion technique, with complete controllability of both the degree and the duration of relaxation on a minute-to-minute basis. This method provides continuous, spinal-like relaxation in operations lasting for several hours or longer, and such deliberate prolongation of succinylcholine's neuromuscular blockade is now an accepted clinical technique (11).

A second means of deliberately prolonging the blocking activity of succinylcholine has been made possible by the concurrent administration of what may be termed, pharmacologically, an "extender" of succinylcholine activity. It was previously reported by Castillo and de Beer (1949) (12) and de Beer et al. (1951) (13) that the amide analogues of succinylcholine were capable of prolonging that drug's neuromuscular blocking action. The study of these amides has been extended to include many types with variations in chain lengths and with various substitutions on the terminal nitrogen atoms. Of particular interest has been an amide in which the terminal nitrogen atoms are incorporated in piperidino groups (fig. 1), or N,N'-bis-(B-piperidino-ethyl) glutaramide (14). This compound is a white crystalline solid which has a molecular weight of 352.3, a melting point of 134 C., and is extremely soluble in water or alcohol. Aqueous solutions are very stable even when exposed to light and air, or when autoclaved at 15 pounds pressure for twenty minutes. Laboratory experiments on cats,

* From the Department of Anesthesiology, Grace-New Haven Community Hospital, and the Section on Anesthesiology, Yale University School of Medicine, New Haven, Connecticut.
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dogs and rabbits have shown that this "extender" compound markedly intensifies and prolongs the neuromuscular blocking action of succinylcholine. In addition, an antagonism to the curariform action of d-tubocurarine has also been demonstrated. Studies of both acute toxicity and chronic toxicity revealed the drug to be extremely safe in the experimental animal. The response of the cat to parasympathetic and sympathetic nerve stimulation was studied, and it was concluded that there was no evidence that autonomic block was produced by the drug. Dose levels required to potentiate succinylcholine-induced paralysis did not produce noticeable neuromuscular blockade in the anesthetized animal.

\[
\text{CH}_2\text{COOCH}_2\text{CH}_2\text{N(CH}_3\text{)}_3 \\
\text{CH}_2\text{COOCH}_2\text{CH}_2\text{N(CH}_3\text{)}_3
\]

**SUCCINYLCHOLINE**

\[
\text{CONHCH}_2\text{CH}_2\text{N(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{})}_3 \\
\text{CONHCH}_2\text{CH}_2\text{N(\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{})}_3
\]

"EXTENDER"

50-354

**Fig. 1.**

This "extender" compound § has been studied in human patients during surgical anesthesia, and has been found to prolong and also to intensify succinylcholine's blockade at the neuromuscular junction. In the beginning of this study, resort was had to measurement of the duration of apnea, and of duration or degree, or both, of muscular relaxation based on clinical observation. Succinylcholine, in doses of 10 to 40 mg. (that is, sufficient to produce apnea) was administered to

§ Supplied as Compound 50-354 by Burroughs Wellcome & Co., Tuckahoe, N. Y.
patients undergoing superficial operations in light planes of general anesthesia, and the duration of the apnea and also the apparent total duration of relaxant effect was measured. Following a twenty to thirty minute rest period, an intravenous dose of 20 to 60 mg. of "extender" compound was administered, and the original dosage of succinylcholine was repeated. Again, the duration of apnea was measured, as well as the apparent total duration of relaxant effect. The results of these studies may be summarized by stating that the duration of apnea from a given dosage of succinylcholine (average two to four minutes) could be doubled by the concurrent use of the "extender" compound (average three to eleven minutes), and the apparent total duration of relaxant activity also was increased. Intensification of succinylcholine's neuromuscular blocking activity was demonstrated under similar clinical conditions by the administration of a small intravenous dose of succinylcholine insufficient to produce apnea and the occurrence of apnea upon subsequent injection of a dose of 40 to 60 mg. of the "extender" compound. The intensifying and prolonging activity of this compound was evident whether it was injected simultaneously with, before, or after, the administration of succinylcholine.
Side effects, such as pulse and blood pressure change, salivation, or bronchospasm were not encountered.

Because of the many obvious pitfalls encountered in attempting to define an end point of neuromuscular blockade by duration of apnea or apparent muscular relaxation, other criteria were sought after observations had been carried out on 25 patients. The method finally employed consisted of the application of a tetanizing current (fig. 2) to a motor point of the tibialis anterior muscle and determining the degree of response both by palpation and observation of muscle contraction. Maximal stimulation, sufficient to produce marked dorsiflexion of the foot, was not used because onset of neuromuscular blockade and return of function could be noted more accurately with weaker currents. During the test period, stimuli were applied every ten seconds. Although this method also allowed for the possibility of introduction of personal error, it seemed sufficiently accurate for clinical testing of succinylcholine and its "extender" compound. With a little practice, disappearance of muscle response indicating onset of neuromuscular blockade could be determined quite accurately; return of function was a more gradual phenomenon and, when resumption of normal response was used as an end point, it was believed this could be determined within a limit of ± thirty seconds.

ILLUSTRATIVE CASE (See figs. 3 and 4)

The patient aged 52 years, weighed 63 kg. Esophagotomy was performed. Duration of paralysis of the left tibialis anterior following intravenous administration of 40 mg. of succinylcholine was found to be eight minutes and forty seconds. Ten minutes after return of normal response, a second dose of 40 mg. of succinylcholine produced paralysis of seven minutes' duration. This indicated there was no summation of effect of any succinylcholine remaining from the first dose. After another waiting period of ten minutes, 40 mg. of "extender" compound and 40 mg. of succinylcholine were administered, resulting in paralysis for thirteen and a half minutes. Administration of another test dose of 40 mg. of succinylcholine forty-eight minutes after the "extender" resulted in six minutes of paralysis. This indicated there was no residual effect of the "extender." Finally, 80 mg. of "extender" compound was administered, followed by 40 mg. of succinylcholine, and this produced a paralysis of seventeen and a half minutes. Subsequent 40 mg. test doses of succinylcholine administered forty-nine minutes and ninety-two minutes after the "extender" resulted in paralysis of nine and a half and eight minutes respectively. Because the operation involved thoracotomy, no attempt was made to correlate tibialis anterior response with respiratory activity.

It is possible that the clinical applications of this "extender" compound will be somewhat limited in scope. It has been administered in conjunction with succinylcholine to prolong slightly the period of

‖ Suggested by Dr. T. F. Hines, Ass't Prof. Medicine (Physical Medicine), Yale University School of Medicine. The apparatus used was the "Medeclator," sold by Medco Products Company, Tulsa, Oklahoma.
RELAXATION NECESSARY TO FACILITATE TRACHEAL INTUBATION, AND ALSO TO PROLONG AND INTENSIFY MUSCULAR RELAXATION FOR THE CLOSURE OF ABDOMINAL WOUNDS. BOTH THESE SITUATIONS CAN BE MANAGED ADEQUATELY BY THE USE OF THE INFUSION TECHNIQUE OF SUCCINYLCHOLINE ADMINISTRATION, BUT FOR ANESTHESIOLOGISTS WHO PREFER THE SINGLE INJECTION TECHNIQUE THE "EXTENDER" COMPOUND MAY BE A VALUABLE ADJUVANT.

PHARMACOLOGICALLY, THE "EXTENDER" COMPOUND IS A FASCINATING DRUG, AND ITS MODE OF ACTION IS NOT AS YET ENTIRELY UNDERSTOOD. THE MOST OBVIOUS EXPLANATION FOR THE DRUG'S ABILITY TO PROLONG EFFECTIVELY THE
neuromuscular blocking action of succinylcholine and at the same time act as an effective antagonist to the curariform action of d-tubocurarine would be that the compound is an anticholinesterase drug. Anticholinesterase drugs are known to produce all the effects described for the "extender" compound. One discrepancy in this explanation, however, is the failure to find potentiation of the muscarinic actions of acetylcholine in either the laboratory animal or man.

**Summary**

Intentional prolongation of the neuromuscular blocking action of succinylcholine may be accomplished either by the administration of the drug by a continuous infusion technique, or by the concurrent administration of an "extender" compound in conjunction with single intravenous doses of succinylcholine.

A simple, but reasonably accurate, method of measuring neuromuscular blockade is described.

**REFERENCES**