

Clinical Studies of the Interaction of Hexafluorenium and Succinylcholine in Man

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Sixty patients anesthetized with halothane were given either succinylcholine alone or succinylcholine after hexafluorenium. The authors determined the degree of prolongation of relaxation induced by hexafluorenium, as well as the rapidity of recovery following multiple injections of the combination of drugs. Neuromuscular block was evaluated by recording muscle twitch tension response to nerve stimulation. The duration of action of a single dose of succinylcholine, 0.2 mg/kg, was increased sixfold to eightfold when preceded by hexafluorenium, 0.4 mg/kg. After multiple doses of the two drugs, rapidity of recovery from the final dose of succinylcholine was dependent upon the period of time over which the drugs had been administered. Four of 20 patients so treated did not recover for nearly an hour. Since the purported advantage of using hexafluorenium with succinylcholine is to avoid the delayed recovery sometimes seen when succinylcholine is used alone, the authors question the continued use of this technique. (Key words: Hexafluorenium; Succinylcholine; Delayed recovery; Phase II block; Surgical relaxation.)

HEXAFLUORENIUM (Mylaxen) is a nondepolarizing neuromuscular blocking drug which, as a side-effect, can inhibit plasma cholinesterase.¹ Previous clinical trials of the primary effect of hexafluorenium revealed it to be less useful than *d*-tubocurarine and gallamine (Flaxedil) in providing relaxation.² The drug has gained usage, however, for its side-effect. Hexafluorenium is now used as a pharmacologic extender of the duration of action of succinylcholine.³⁻⁵

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Studies of this side-effect of hexafluorenium have shown that it produces a tenfold prolongation in the duration of apnea and respiratory depression produced by succinylcholine.⁶ In one clinical study, the authors found five- to sevenfold reductions in the doses of succinylcholine required to maintain adequate surgical relaxation.⁷ They reported no post-operative apnea or prolonged respiratory depression with the combination of drugs. Since some patients have delayed recovery from succinylcholine alone, the combination of drugs was said to offer an advantage.

The purpose of our study was to re-examine the effect of hexafluorenium on the duration of action of succinylcholine, using a nerve stimulator technique. Our objectives were to determine the degree of prolongation of the action of a single dose of succinylcholine provided by hexafluorenium and the rapidity of complete recovery from the last dose following multiple doses of succinylcholine and hexafluorenium.

Material and Methods

Sixty adult surgical patients of both sexes were studied. The operations varied in type and duration. Excluded were patients undergoing cardiac operations, patients who developed hemorrhage and shock, those with diseases of neuromuscular transmission, and those taking medications known to affect neuromuscular transmission. Premedication varied, but it generally included morphine sulfate, 8-12 mg, or meperidine hydrochloride (Demerol), 75-150 mg. Occasionally, pentobarbital (Nembutal), 100 mg, hydroxyzine (Atarax, Vistaril), 25-50 mg, or Innovar, 2 ml, was substituted for the above medications. All patients were given either atropine or scopolamine, 0.3-0.4 mg. Anesthesia was induced with a thiobarbiturate and maintained with nitrous oxide, 2

TABLE 1. Results in Patients Receiving Single Injections of Succinylcholine Alone or After Hexafluorenum*

	Age (Years)	Hexa-fluorenum (mg)	Succinylcholine (mg)	Latency (min)	Recovery Times (min)		
					10 Per Cent	50 Per Cent	90 Per Cent
Group I (20 patients)	42 ± 18 (15-80)	—	13.0 ± 2.0 (9.5-17)	0.9 ± 0.4 (0.3-1.7)	2.3 ± 0.63 (1.3-3.7)	3.1 ± 0.57 (2.0-4.3)	4.0 ± 1.1 (2.7-6.7)
Group II (20 patients)	37 ± 15 (15-58)	25.6 ± 6.1 (18-44)	12.8 ± 3.0 (9-22)	3.5 ± 1.7 (1.0-10.7)	18.5 ± 6.0 (6-31.3)	21.0 ± 6.4 (9.3-34.3)	26.0 ± 7.2 (10-38.7)

* Values are averages ± SD. Numbers in parentheses are ranges.

liters, oxygen, 2 liters, and halothane (Fluothane), 0.5-1 per cent. When tracheal intubation was desirable, it was facilitated with the relaxants used in the study.

The patients were arbitrarily placed in three groups of 20 each. During anesthesia, Group I was given succinylcholine, 0.2 mg/kg, intravenously. The latency to fully developed block was determined, as well as the times to 10, 50 and 90 per cent recovery. Group II patients were given hexafluorenum, 0.4 mg/kg, followed in three minutes by succinylcholine, 0.2 mg/kg. Observations following the succinylcholine were similar to those in Group I. Group III patients were treated like those in Group II but succinylcholine was repeated each time the patient had 10 per cent recovery from the preceding dose. If the intervals between succinylcholine injections became shorter than 10 minutes, we repeated the hexafluorenum. Following the last dose of succinylcholine, times to 10, 50 and 90 per cent recovery were determined.

Latency and duration of action were evaluated by recording thumb adductor twitch tension in response to supramaximal ulnar nerve stimulation, a technique previously described.⁷ The nerve was stimulated at a rate of one shock/3.5-4 sec with the Block-Aid Stimulator.

Results

Patients in Group I received an average of 13 mg of succinylcholine (table 1). The latency period averaged slightly less than a minute. Mean recovery times were 2.3, 3.1, and 4.0 minutes to 10, 50, and 90 per cent of maxi-

mum twitch tension. Group II patients were given a similar dose of succinylcholine. The average dose of hexafluorenum was approximately 26 mg. The mean latency period was longer in this group than in Group I, averaging 3.5 minutes. Recovery times averaged 18.5, 21, and 26 minutes to 10, 50, and 90 per cent of maximum twitch tension.

The weights of Group III patients (table 2) were similar to the weights of the other groups. The total time over which succinylcholine was administered for relaxation averaged 113 minutes. These patients were given one to three doses of hexafluorenum and three to 22 doses of succinylcholine. Recovery from neuromuscular weakness was prompt following the last injection of succinylcholine in 14 patients. Average times to 10, 50, and 90 per cent twitch tension recovery were 12.2, 18.0 and 24.4 minutes. Mean recovery time was similar to that of patients in Group II, who had only single injections of succinylcholine. Six patients, however, had delayed recoveries. Four of these patients had residual muscle weakness lasting nearly an hour (table 3). In two other patients we antagonized the blocks with edrophonium (Tensilon) prior to 50 per cent recovery. In one patient the antagonism was accomplished after 40 minutes, in another after 68 minutes.

There was a significant correlation between the period over which the succinylcholine was given and the time to 90 per cent recovery from the last dose of succinylcholine ($r = 0.7$, $P < 0.005$). The regression equation can be expressed as follows: recovery time = $0.33 \times$ (duration of block)^{1.005}, or approximately: re-

covery time = $0.33 \times (\text{duration of block})$. The relative standard deviation was 54 per cent. §

The delayed recovery caused by the neuromuscular blockers is illustrated in figure 1.

Discussion

These studies reconfirm the observation that hexafluorenum significantly prolongs the duration of action of succinylcholine. Following a single injection of succinylcholine, prolongation can be thought of as sixfold or eightfold, depending on whether the endpoint of the drug's action is taken as 10, 50 or 90 per cent of twitch tension recovery.

The results in Group III patients verified that hexafluorenum reduces the absolute doses of succinylcholine needed to maintain continuous relaxation for operation. The average dose of succinylcholine given was 0.82 mg/min. Katz, in a study of intravenous infusion of succinylcholine alone, found that the dose requirement for 90 per cent twitch tension depression averaged 5.8 mg/min.⁸ Considering that he maintained twitch tension at 10 per cent of control and we were producing intermittent total paralysis, we believe that hexafluorenum causes at least a sevenfold sparing of succinylcholine.

The study of Group III patients also revealed that recovery from the final dose of succinylcholine in some patients is not prompt. The delay in recovery from succinylcholine has been ascribed to several possible causes. The possibility that our six patients had atypical plasma cholinesterases can be ruled out, however, since early recovery from the initial dose of succinylcholine was not delayed.

A more likely explanation for the prolongation of the time to twitch tension recovery following the last dose of succinylcholine is the development of a phase II block. As evidence in support of this mechanism's being responsible, we submit:

1) We were able to demonstrate fatigue from tetanic stimulation at 30 cycles/sec, as

§ The equation is based on 17 cases. Two studies were omitted because the blocks were antagonized prior to 90 per cent recovery. One case lasting 430 minutes was omitted because the duration was unusual.

TABLE 2. Results in Patients Receiving Multiple Doses of Succinylcholine and Hexafluorenum*

	Number Patients	Age (Years)	Hexafluorenum		Succinylcholine		Recovery Times after Last Dose of Succinylcholine (min)			
			Number of Doses	Total Dose (mg)	Number of Doses	Total Dose (mg)	10 Per Cent	50 Per Cent	90 Per Cent	
Rapid-recovery group	14	34 ± 5.3 (15-64)	1-4 (1-4)	37.7 ± 18.0 (10-81)	7.5 (3-22)	102 ± 70.7 (40-310)	103 ± 98† (42-430)	12.2 ± 5.7 (6.3-27.7)	18.0 ± 8.0 (8.7-30.0)	24.4 ± 11.3 (12-47.3)
Slow-recovery group	6	57 ± 25.2 (10-70)	1.7 (1-2)	38.0 ± 13.5 (20-62)	8.7 (6-14)	100 ± 45.1 (60-182)	141 ± 51 (102-240)	24.7 ± 8.7 (10.7-33.0)	(See table 3)	(See table 3)

* Values are averages ± SD. Numbers in parentheses are ranges.
† Excluding one case which lasted more than seven hours, the value is 81 ± 13.

TABLE 3. Individual Recovery Times in the Slow-recovery Group

	Time to 50 Per Cent Recovery (min)	Time to 90 Per Cent Recovery (min)
Patient 1	28.0	59.3
Patient 2	>40	—
Patient 3	49.0	61.3
Patient 4	56.7	76.3
Patient 5	>68	—
Patient 6	35.7	64.3

well as marked posttetanic potentiation, in the patients with delayed recovery (fig. 1).

2) The neuromuscular block was successfully antagonized with edrophonium in two of the patients with delayed recovery. Such antagonism would not have been possible had

free succinylcholine molecules been present in plasma.⁹

3) Following each injection of succinylcholine during the later stages of the block, a rapid increase in twitch tension was noted (fig. 2). This momentary antagonism to the previous block has been noted when succinylcholine was given after *d*-tubocurarine.¹⁰ The phenomenon can be ascribed to depolarization of the partially desensitized postjunctional membrane.

4) After the second injection of hexafluorenum, twitch tension decreased, indicating synergism between the hexafluorenum and the established block. Katz reported that hexafluorenum alone in doses up to 1 mg/kg had no effect on twitch height.¹¹

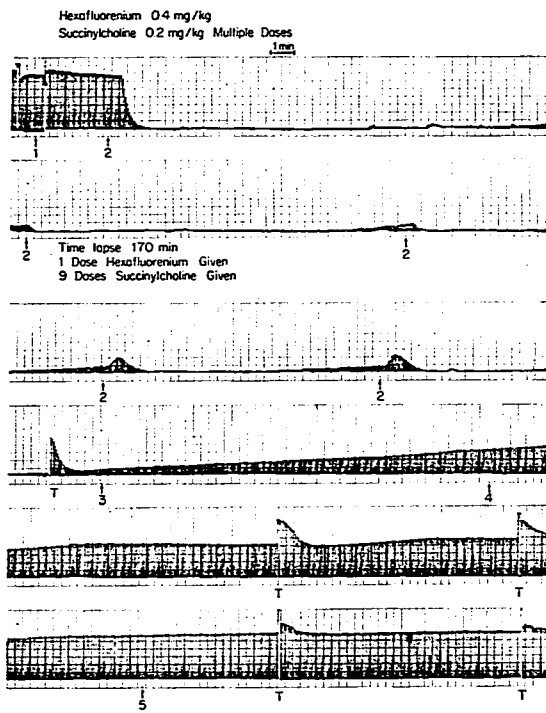


FIG. 1. Delayed recovery following hexafluorenum-succinylcholine. The patient was given two doses of hexafluorenum (total, 52 mg) and 14 doses of succinylcholine (total, 182 mg). The succinylcholine was given over 152 minutes. Note the time lapse of 170 minutes between the second and third strips. Following the last injection, 90 per cent twitch tension recovery required 59 minutes. 1, injection of hexafluorenum; 2, injection of succinylcholine; 3, 10 per cent recovery; 4, 50 per cent recovery; 5, 90 per cent recovery. T, tetanic stimulation.

These findings raise serious question about the use of hexafluorenum-succinylcholine for maintenance of relaxation. The supposed advantage of the technique is the avoidance of delayed recovery. Our studies reveal that delayed recovery is not avoided by the use of hexafluorenum. Its occurrence is primarily a function of the duration of block.

Although we demonstrated antagonism to the neuromuscular block with edrophonium, we do not propose this as a routine clinical technique. We did not give edrophonium to our two patients until 40 minutes and 68 minutes after the last doses of succinylcholine. That we were able to antagonize the block indicated that significant amounts of free succinylcholine were no longer circulating in the plasma. Had the antagonism been attempted earlier, it might not have been successful.

We conclude that hexafluorenum can extend the duration of succinylcholine paralysis and reduce the amount of succinylcholine given during an operation. However, the rapidity of recovery from the neuromuscular block produced by these agents is related to the length of time that the relaxation is maintained. Muscle weakness can last an hour or longer after the last dose of succinylcholine.

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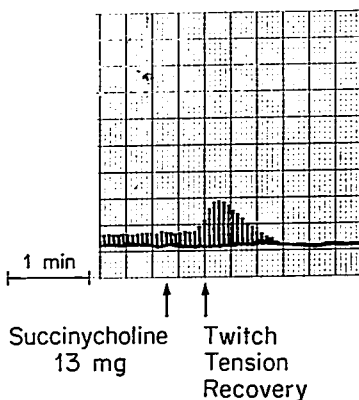


FIG. 2. An illustration of the increasing twitch tension after injection of succinylcholine and prior to paralysis.

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Drugs

BETA BLOCKERS Alpha-methyl substitution in the side-chain of *N*-isopropyl-p-nitrophenylethanolamine (INPEA) alters the beta-adrenergic blocking properties of INPEA so that it antagonizes the vasodilatory effects of isoproterenol but not the inotropic or chronotropic effects in intact cats and in isolated perfused turtle hearts. (Somani, P.: *Study of Some Selective Beta-adrenoreceptor Blocking Effects of Alpha-methyl INPEA*, *Brit. J. Pharmacol.* 37: 609 (Nov.) 1969.)