Clinical Studies of the Interaction between d-Tubocurarine and Succinylcholine

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Succinylcholine and *d*-tubocurarine were given to patients during the administration of general anesthesia in order to test their interaction. *d*-Tubocurarine given prior to full recovery from succinylcholine showed no significant change in mean duration of action, but did show a significant decrease in intensity of block. Succinylcholine given after a small dose of *d*-tubocurarine had a significantly diminished duration and a significantly decreased intensity of block. Succinylcholine after a prolonged block with *d*-tubocurarine generally reversed the block, while the succinylcholine had a diminished action. One patient developed a prolonged desensitization block after receiving succinylcholine, 52 mg, during a partial *d*-tubocurarine block.

PATON AND ZAIMIS, in 1949, described an antagonism between the neuromuscular blocks produced by depolarizing and nondepolarizing relaxants.[1] They found that pretreating an animal with *d*-tubocurarine or gallamine reduced or prevented decamethonium-induced weakness. Hutter and Pascoe observed that the reverse situation also was true.[2] They were able to antagonize an established *d*-tubocurarine block with a small dose of decamethonium. Similar antagonistic behavior between succinylcholine and gallamine was demonstrated by Brennan in 1956.[3]

In spite of the knowledge that nondepolarizing and depolarizing relaxants may have antagonistic actions, anesthesiologists often use succinylcholine and *d*-tubocurarine concurrently. Among the techniques frequently used in clinical anesthesia is one in which succinylcholine is given to facilitate tracheal intubation, following which *d*-tubocurarine is given for prolonged muscle relaxation. Another common practice is to give a small dose of *d*-tubocurarine prior to succinylcholine to avoid fasciculations and postoperative muscle pain. In a third technique, anesthesiologists use *d*-tubocurarine to produce relaxation during an operation, then, near termination, give a single injection of succinylcholine to facilitate peritoneal closure.

The purpose of this study was to determine how the effects of these relaxants are modified by their concurrent use. We also sought to determine whether the effects of mixing these drugs were sufficiently predictable to insure safe usage.

Methods and Results

Studies were carried out on 230 randomly selected adult patients receiving general anesthesia for operation. No patient was taking medication or had an illness known to affect neuromuscular transmission. Hyperthermic patients were omitted from the study. Hypothermia was avoided. Although blood was given to some patients, no patient was in hemorrhagic shock during the study. The patients were premedicated with moderate doses of narcotics, barbiturates and tranquilizing drugs, together with atropine or scopolamine. Anesthesia was maintained with nitrous oxide, 2 l/min, oxygen, 2 l/min, and halothane, approximately 1.0 per cent. Neuromuscular transmission was evaluated with the Block-Aid stimulator and suitable recording apparatus, using a technique described elsewhere.[4]

Studies were designed to test the effects of the interactions between *d*-tubocurarine and succinylcholine in the three situations cited above.

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In all studies, each patient received only one injection of *d*-tubocurarine and/or one injection of succinylcholine. In studies 1 and 2, the results found after the concurrent use of relaxants were compared with the results found when similar doses of relaxants were used alone. Means and standard deviations were calculated, and the statistical significances of the findings determined using Student's *t* test. The values of *t* were converted to *P* values from standard tables. Study 3 reports our observation of the interaction without statistical analysis.

Study 1a: modification of the action of *d*-tubocurarine by the previous use of succinylcholine—duration studies. The time to 10 per cent recovery from *d*-tubocurarine, 8 mg/m² (absolute dose approximated 14 mg) was determined in 100 patients. Thirty of the patients received no succinylcholine prior to the *d*-tubocurarine. To a second group of 30 patients, succinylcholine was given for tracheal intubation but recovery from succinylcholine was complete prior to the use of *d*-tubocurarine. In another group of 20 patients *d*-tubocurarine was given when we could still demonstrate a 90 per cent reduction in twitch force from succinylcholine, 40 mg/m² (absolute dose approximated 68 mg). In a final group of 20 patients *d*-tubocurarine was given together with succinylcholine, 40 mg/m².

Study 1b: modification of the action of *d*-tubocurarine by the previous use of succinylcholine—twitch-depression studies. We gave *d*-tubocurarine, 4 mg/m² (absolute dose approximated 7 mg), to 40 patients and determined the mean percentage depression in twitch force. A similar study was carried out in another group of 20 patients who previously had received succinylcholine, 40 mg/m², for tracheal intubation. The *d*-tubocurarine was given to the latter group when we could still demonstrate 90 per cent reduction in twitch force due to the succinylcholine.

Results

Study 1a. We found the mean duration of *d*-tubocurarine to 10 per cent twitch recovery in the control group to be 21.5 minutes. The mean time to 10 per cent twitch recovery in the group to whom *d*-tubocurarine was given after recovery from succinylcholine was 22.6 minutes. If the *d*-tubocurarine was given in the presence of a 90 per cent block from succinylcholine the mean duration to 10 per cent recovery was extended to 25.6 minutes. When the drugs were given together the mean time to 10 per cent twitch recovery from *d*-tubocurarine was 25.4 minutes (table 1).

Although there was nearly a 20 per cent increase in mean duration between groups 1 and 3, the difference was not statistically significant (*P* 0.15). Combining the results from patients given *d*-tubocurarine with no evidence of succinylcholine block (groups 1 and 2), and those given *d*-tubocurarine during a succinylcholine block (groups 3 and 4) and again comparing durations, we were still unable to demonstrate a statistically significant difference (*P* 0.07).

Study 1b. We found the control group given *d*-tubocurarine, 4 mg/m², had a mean twitch depression of 65 per cent. When the same dose of *d*-tubocurarine was given after only partial recovery from succinylcholine, the mean twitch depression was 39 per cent. These differences were statistically significant (*P* 0.002) (table 2). Thus, succinylcholine did not significantly increase the mean duration of *d*-tubocurarine, but significantly decreased the percentage depression in twitch force.

Study 2a: modification of the action of succinylcholine by the previous use of a small dose of *d*-tubocurarine—duration studies. The mean durations of succinylcholine, 40 mg/m², to 10, 50 and 90 per cent recovery in twitch force were determined in 20 patients. We repeated the study in a second group of 20 patients who three minutes earlier had been given *d*-tubocurarine, 2 mg/m² (absolute dose approximated 3.3 mg).

Study 2b: modification of the action of succinylcholine by the previous use of a small dose of *d*-tubocurarine—twitch-depression studies. Twenty patients were given succinylcholine, 3 mg/m² (absolute dose approximated 4.9 mg), and mean percentage twitch depression was determined. A similar dose of succinylcholine was given to each of ten other patients who, three minutes previously, had been given *d*-tubocurarine, 2 mg/m², and twitch depression was again determined.

TABLE 1. *d*-tubocurarine Duration

	No. of Studies	Mean Age (years)	Mean Dose (mg)		Mean 10 Per Cent Recovery Time (min)
			SCh	*d*-tubocurarine	
d-tubocurarine only	30	39	0	14.0	21.5 ± 9.6
Succinylcholine and *d*-tubocurarine					
Full recovery, SCh	30	43	64	13.7	22.6 ± 8.7
Partial recovery, SCh	20	42	67	13.4	25.6 ± 9.5
No recovery, SCh	20	33	69	13.7	25.4 ± 12.0

TABLE 2. *d*-tubocurarine Twitch Depression

	No. of Studies	Mean Age (years)	Mean Dose (mg)		Mean Per Cent Twitch Depression
			SCh	*d*-tubocurarine	
d-tubocurarine only	40	42	0	7.0	65 ± 31
Succinylcholine and *d*-tubocurarine	20	43	66.3	6.6	39 ± 28

TABLE 3. Duration of Effect of Succinylcholine

	No. of Studies	Mean Age (years)	Mean Dose (mg)		Mean Recovery Times (min)		
			d-tubocurarine	SCh	10 per cent	50 per cent	90 per cent
Succinylcholine only	20	40	0	68	7.2 ± 1.3	8.4 ± 1.7	10.4 ± 2.4
d-tubocurarine and succinylcholine	20	36	3.3	65.3	5.6 ± 1.7	6.7 ± 1.9	8.0 ± 2.3

TABLE 4. Twitch Depression by Succinylcholine

	No. of Studies	Mean Age (years)	Mean Dose (mg)		Mean Per Cent Twitch Depression
			d-tubocurarine	SCh	
Succinylcholine only	20	37	0	4.9	66
d-tubocurarine and succinylcholine	10	39	3.15	4.7	0

RESULTS

Study 2a. In control studies we found succinylcholine, 40 mg/m², had mean durations of 7.2, 8.4 and 10.4 minutes to 10, 50 and 90 per cent recovery. When the same dose was given after *d*-tubocurarine, 2 mg/m², the durations to the same end points were 5.6, 6.7 and 8.0 minutes. These differences are statistically significant (P 0.002–0.004) (table 3).

Study 2b. The small dose of succinylcholine, 3 mg/m², produced a mean twitch depression of 66 per cent. The same dose following *d*-tubocurarine, 2 mg/m², produced no twitch depression (table 4). Thus, preceding succinylcholine by *d*-tubocurarine significantly decreased both the duration and the degree of block of succinylcholine.

Study 3: modification of the action of suc-

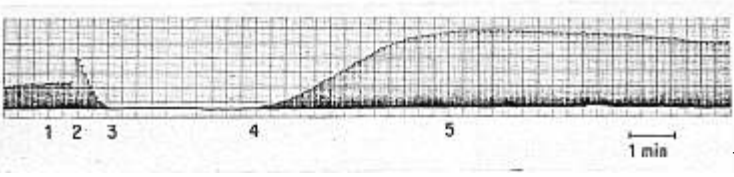

FIG. 1. Succinylcholine given after a maintenance dose of *d*-tubocurarine. 1, Succinylcholine, 68 mg iv—twitch recovery 23 per cent of control. 2, Primary twitch reversal. 3, Total paralysis. 4, Onset of recovery from succinylcholine. 5, Secondary twitch reversal to 82 per cent of control.

cinylcholine by the previous use of a large dose of *d*-tubocurarine. Succinylcholine, 40 mg/m², was given to 20 patients who previously had been given *d*-tubocurarine, 8 mg/m². The succinylcholine was given to half of the patients when we could still demonstrate a 75 to 90 per cent block from *d*-tubocurarine. In the others, we allowed recovery to proceed to 50 per cent of control before giving the succinylcholine.

RESULTS (Figure 1)

In 19 of the 20 patients the responses to succinylcholine followed a similar pattern. We first noted a sudden increase in slope of twitch recovery—primary reversal. This effect lasted 10 to 20 seconds, and occurred during the time we would have expected to see fasciculation from succinylcholine (no fasciculations occurred). The initial response was followed in nearly all of the patients by total twitch paralysis. Twitch recovery in these patients began in about five minutes and progressed beyond the degree of recovery from *d*-tubocurarine noted before the succinylcholine was given—secondary reversal.

It was not possible to estimate accurately the times to 10, 50 and 90 per cent recoveries from succinylcholine since we had no fixed baseline of 100 per cent recovery. We did determine that the time to onset of twitch recovery averaged five minutes. This corresponded closely with the onset of twitch recovery seen in patients given 40 mg succinylcholine after 2 mg *d*-tubocurarine (4.9 min).

The amount of secondary twitch reversal of the *d*-tubocurarine block averaged 30 per cent of control. More reversal was noted when the succinylcholine was given earlier in the course of recovery from *d*-tubocurarine. In nine of the 19 patients who had secondary twitch reversal, we noted slight declines in twitch tension over the next five minutes. Usually these declines amounted to only 1 to 2 per cent of the maximum twitch tensions. The most exaggerated decline is illustrated in figure 1.

One patient had an atypical response after succinylcholine (fig. 2). Initially, the patient had a brief period of primary reversal. This was followed by total paralysis for 6.6 minutes. Twitch force then recovered slowly with an evidence of secondary twitch reversal. Recovery to 50 per cent of control force following succinylcholine took an hour; during this time tetanic stimulation revealed muscle fatigue and posttetanic facilitation. At the end of an hour the block was reversed with 1.5 mg neostigmine.

Analysis of this patient's plasma cholinesterase disclosed a dibucaine number of 80; activity, 17 units (low-normal).

Discussion

Waud, in a recent review of the nature of depolarizing block, suggested a mechanism by which nondepolarizing and depolarizing muscle relaxants could be mutually antagonistic.[5] *d*-tubocurarine blocks the action of succinylcholine by occluding a fraction of the receptor sites. On administration of succinylcholine, membrane permeability to potassium and sodium is diminished and the depolarization cannot reach the threshold for muscle action potential. Succinylcholine reverses the competitive block of *d*-tubocurarine by producing partial depolarization. This allows the small end-

FIG. 2. Succinylcholine given after a maintenance dose of *d*-tubocurarine. 1, Succinylcholine 32 mg IV—twitch recovery 50 per cent of control. 2, Primary (with) reversal. 3, Total paralysis. 4, Onset of recovery from succinylcholine. 5, Tetanic stimulation. 6, Tetanic stimulation. 7, Reversal with neostigmine. 8, Partial recovery.

plate potential to reach the threshold for muscle action potential. Whether or not the muscle cell develops an action potential following stimulation of its nerve will depend on which of the relaxants exerts a predominant effect at receptor sites. The force of contraction of an entire muscle group will, in turn, depend on the number of cells developing action potentials when the motor nerve is stimulated.

We found nearly a 20 per cent increase in the mean duration of action of *d*-tubocurarine given prior to full recovery from succinylcholine. In spite of the lack of usually-accepted limits for significance, some comment about the difference is in order. Foldes has shown that the prolonged use of succinylcholine will potentiate a *d*-tubocurarine block.[7] In his studies he found potentiation of not only duration but also twitch depression. He attributed the synergistic effects of these relaxants to a change in the nature of the succinylcholine block from depolarizing to desensitizing. deJong has demonstrated evidence of desensitization when even small doses of succinylcholine are given.[8] The trend toward an increase in mean *d*-tubocurarine duration which we found could have been an early manifestation of desensitization block by succinylcholine.

With the exception of the one unusual case, the results of study 3 could have been predicted from the findings in studies 1 and 2. In study 3 we found that succinylcholine given during a partial *d*-tubocurarine block had a decreased duration of action, as evidenced by the short time to onset of twitch recovery. Succinylcholine also had decreased intensity of effect as demonstrated in two patients who, when given succinylcholine, failed to show complete abolition of muscle twitch. The residual *d*-tubocurarine block, on the other hand, was reversed by succinylcholine.

It has been suggested that succinylcholine not be given near the end of anesthesia that includes nondepolarizing relaxants.[9] Foldes reasoned that the depolarizer would be less effective in its action; this would necessitate the use of larger doses of drug, and this, in turn, could predispose to prolonged apnea. In our study we found that a single dose of succinylcholine given after *d*-tubocurarine occasionally can result in desensitization block.

Yet to be determined are the frequency with which this complication occurs and whether it will follow administration of a small dose of *d*-tubocurarine.

Conclusion

Giving *d*-tubocurarine prior to full recovery from succinylcholine decreased the maximum intensity of *d*-tubocurarine block. A small dose given prior to succinylcholine, caused significant reductions in both duration and intensity of the succinylcholine block. Succinylcholine given after a maintenance dose of *d*-tubocurarine (approximately 14 mg) had a reduced block intensity and duration, while the *d*-tubocurarine block was partially reversed. Although these effects, in general, were predictable, one patient developed prolonged desensitization block when given 52 mg succinylcholine while he still had a 50 per cent block from *d*-tubocurarine. Because of this occasional abnormal response to the concurrent use of relaxants, we suggest that a nerve stimulator be used to test for residual weakness at the termination of an anesthetic regimen in which both relaxants have been used.

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