The Use of Trimethylammoniumcaproylcholine for the Maintenance of Surgical Relaxation

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Trimethylammoniumcaproylcholine (TACCh) is a hydrolyzable, depolarizing muscle relaxant. Its neuromuscular effects are similar to those of succinylcholine. TACCh was used for the maintenance of surgical relaxation in two groups of anesthetized patients. The first group of 12 patients received TACCh in continuous intravenous infusion; in the second group intermittent doses of TACCh were used in conjunction with hexafluorenium. Respiratory rate, tidal volume, onset and duration of apnea, blood pressure, and pulse rate were recorded. Satisfactory surgical relaxation was achieved in all cases. No bradycardia, unexplained hypotension, arrhythmia, urticaria, bronchospasm, prolonged postoperative apnea, or tachyphylaxis was observed in this short series. In contrast to succinylcholine, the breakdown products of TACCh have no significant neuromuscular blocking effect. Consequently, further studies are indicated to determine whether or not it has any clinical advantages over the well-established succinylcholine.

THE NEUROMUSCULAR effect of choline esters of the methylamino, dimethylamino and trimethylammonium omega substituted lower homologues of the fatty acid series was investigated in laboratory animals [1] and in man.[2] The general formula of the compounds tested is: $R\text{-}N\text{-}(CH_2)_n\text{-}CO\text{-}O\text{-}(CH_2)_2\text{-}N(CH_3)_3$. R can be H, CH_3; $(CH_3)_2$; or $(CH_3)_3$. All 17 homologues tested were hydrolyzed, at variable rates, by human plasma, but not by human red cell cholinesterase.[3] Their enzymatic breakdown in cat plasma was insignificant.[4] In cats, three of the compounds tested, namely 6-dimethylaminocaproylcholine iodide hydroiodide ($n = 5$, $R = (CH_3)_2$), 6-trimethylammoniumcaproylcholine diiodide ($n = 5$, $R = (CH_3)_3$), and 7-aminoheptanoylcholine chloride hydrochloride ($n = 6$, $R = H, CH_3$) exhibited almost identical neuromuscular activity. (For the sake of brevity the salts of the various compounds will only be indicated when first mentioned.) The myoneural block produced by these compounds was qualitatively and quantitatively similar to that observed after comparable doses of succinylcholine (Anectine) chloride. In man, however, the duration and intensity of the neuromuscular effects of the three compounds were found to be dependent on their enzymatic hydrolysis rate by human plasma cholinesterase.[2] The neuromuscular effect of the rapidly hydrolyzable 7-aminoheptanoylcholine or 6-dimethylaminocaproylcholine was insignificant [2] and could only be demonstrated after the inhibition of plasma cholinesterase activity by hexafluorenium (Mylaxen) dibromide.[5] However, the neuromuscular effect of 6-trimethylammoniumcaproylcholine (TACCh) which was hydrolyzed by plasma cholinesterase at about the same rate as succinylcholine,[6] was qualitatively and quantitatively similar to that of the latter compound.

This compound was synthesized by Fusco and associates [7] and its pharmacological effects in animals were investigated by Bovet *et al.*[8] It has also been used for the production of surgical relaxation by Rizzi.[9] The present study was undertaken to determine the suitability of TACCh, alone, and in combination with hexafluorenium, for the production of surgical relaxation.

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Material and Methods

Because of the scarcity of the available material,* TACCh was used for the maintenance of surgical relaxation in only 50 patients. To 12 patients (group I) TACCh dichloride was administered in continuous intravenous infusion. In 38 others (group II) TACCh diiodide was administered in conjunction with hexafluorenium in fractional doses. There were 3 male and 9 female patients in group I. Their ages ranged from 32 to 70 years. In group II there were 10 men and 28 women; their ages ranged from 25 to 76 years. All underwent various intraperitoneal operations, *e.g.*, gastrectomy, cholecystectomy or hysterectomy, requiring good muscular relaxation.

These patients received 50 to 100 mg. pentobarbital (Nembutal) sodium or secobarbital (Seconal) sodium 90 to 120 minutes, and 50 to 100 mg. meperidine (Demerol) hydrochloride and 0.3 to 0.4 mg. scopolamine hydrobromide 35 to 60 minutes before the anticipated start of anesthesia. All drugs were administered intramuscularly. In a few elderly patients, scopolamine was replaced by atropine hydrochloride.

Patients were lightly anesthetized with thiopental (Pentothal) sodium and nitrous oxide-oxygen, supplemented with alphaprodine (Nisentil) hydrochloride or meperidine administered before skin incision and, as required, during surgery. Details of the technique used have been described elsewhere.[10] After the induction of light thiopental, nitrous oxide-oxygen anesthesia the patients in group I received 0.6 mg./kg. TACCh during a 30-second period. They were hyperventilated with oxygen and the tracheas intubated 30 seconds later. Following intubation the administration of nitrous oxide-oxygen was resumed in a semiclosed circuit. To decrease the likelihood of narcotic-induced respiratory depression all patients in group I and most in group II received levallorphan (Lorfan) tartrate 0.5 to 1.0 mg. intravenously after intubation. After the return of spontaneous respiration anesthesia was deepened by the intravenous administration of fractional doses of alphaprodine or meperidine and occasionally thiopental, to the level necessary for the patient to tolerate a skin incision. In group I a continuous infusion of 0.2 per cent TACCh was started about 5 minutes before the anticipated entry into the peritoneal cavity. The TACCh solution was administered at the rate of 80 to 100 drops per minute until tidal volume became markedly depressed or apnea developed. At this time the infusion was stopped until the patient's spontaneous respiration returned or became deeper. Subsequently, depending on the patient's weight, age, physical condition, and the observed effects of the initial infusion, the drip rate was empirically set between 40 and 60 drops per minute. After entering the peritoneal cavity, the drip rate was further adjusted to produce optimal relaxation, whenever possible without complete paralysis of all respiratory muscles. Except when apnea developed ventilation was assisted in this group. In general, the mode of administration of the TACCh infusion was similar to that previously described for succinylcholine.[11] The infusion was discontinued after the peritoneum was closed and the fascial layers had been approximated. Additional doses of alphaprodine or meperidine and thiopental were administered throughout anesthesia as required.

The anesthetic technique used in the 38 patients of group II was similar to that used in group I except that after induction of thiopental, nitrous oxide-oxygen anesthesia the patient received 0.4 mg./kg. hexafluorenium intravenously. Three minutes later, 0.2 mg./kg. TACCh was injected intravenously and another three minutes later endotracheal intubation was performed. From then on muscular relaxation was maintained by the intravenous administration of TACCh in fractional doses, amounting to about 80 per cent of the initial dose. The time interval between the initial dose and the first fractional dose varied from 7 to 45 and averaged 25.9 ± 1.3 minutes. The interval between subsequent fractional doses became progressively smaller as the inhibitory effect of hexafluorenium on plasma cholinesterase gradually wore off. When the interval between two fractional

* The trimethylammoniumcaproylcholine, first as its diiodide and later as its dichloride, was supplied by Dr. Georg E. Cronheim of Riker Laboratories, Inc.

doses of TACCh became less than 10 minutes, 0.15 to 0.2 mg./kg. hexafluorenium was administered two to three minutes before the next dose of TACCh. No TACCh was administered after the peritoneum had been closed. Controlled respiration was necessary most of the time in this group. Control values of pulse rate, blood pressure, respiratory rate and tidal volume were determined after induction of light thiopental, nitrous oxide-oxygen anesthesia. In group I tidal volumes were determined by dividing the minute volume (measured with a ventilation meter inserted into the anesthetic circuit) by the respiratory rate. In group II tidal volume was determined by taking the averages of several readings made on the ventilation meter. In group I all measurements were repeated before skin incision and in ten patients before, in two immediately after, and in six both before and after extubation; and in group II, after hexafluorenium, two minutes after the administration of each fractional dose of TACCh, and after extubation. In addition pulse rate, blood pressure and respiratory rate were observed regularly at 5- to 10-minute intervals throughout anesthesia. The time of onset of fasciculations and apnea measured from the start of the TACCh injection, the duration of the apnea and respiratory depression, and the state of relaxation of the vocal cords at the time of intubation were also observed in both groups. In addition, in group II the onset and duration of apnea after each fractional dose of TACCh were also recorded. The time elapsed between the discontinuation of the infusion in group I or the administration of the last fractional dose in group II and the return of the tidal volume to control values was also noted. The μg./kg./min. doses of TACCh used during the intravenous infusion in group I, and from the time of administration of the first dose to the end of anesthesia in group II were calculated.

The cholinesterase activity of samples of heparinized plasma from the patients of group I was determined by a null-point potentiometric titration procedure using a *p*H-Stat (Radiometer, Copenhagen). The determinations were made at 37° C. and *p*H 7.4, using 0.2 ml. plasma in a final volume of 4.0 ml. The substrate was acetylcholine chloride ($1 \times 10^{-2}M$) and 1.10*N* sodium hydroxide was used for titration.

TABLE 1. Comparison of the Effects of the Initial Dose of TACCh Administered Alone* or After Hexafluorenium†

	Group I (12 Cases)	Group II (38 Cases)
Fasciculation	12	1
Onset of fasciculation	34.2 ±2.3‡ Seconds	—
Onset of apnea	<50 Seconds	2 to 3 Minutes
Duration of apnea	4.7 ±0.5 Minutes	18.2 ±1.4 Minutes
Cords paralyzed at intubation	11	32
Satisfactory conditions for intubation	12	38

* Dose of TACCh 0.6 mg./kg.
† Dose of Hexafluorenium 0.4 mg./kg., that of TACCh 0.2 mg./kg.
‡ Standard Error.

The state of consciousness of the patients of both groups was evaluated 5 minutes after the discontinuation of the administration of nitrous oxide-oxygen by determining whether the patient answered questions, obeyed commands, responded to stimuli or was nonresponsive.

Results

Muscular fasciculations could be observed in group I in 34.2 ± 2.3 (range 20 to 50) seconds after the start of the intravenous administration of TACCh (table 1). Of the 38 patients in group II who received TACCh, three minutes after the intravenous administration of hexafluorenium, fasciculation developed in only one subject in 180 seconds. Apnea occurred in 11 of the 12 patients of group I within 50 seconds after the start of the TACCh injection and in 37 out of the 38 patients of group II within 180 seconds. At the time of intubation the cords were paralyzed in 11 out of 12 and in 32 out of 38 patients of groups I and II respectively. Conditions for intubation, however, were satisfactory in all patients of both groups. The duration of apnea measured from the start of injection of TACCh, after the initial dose, was 4.7 ± 0.5 (range 3 to 10) minutes and 18.2 ± 1.4 (range 5 to 38) minutes in groups I and II respectively. In group I tidal volumes returned to control values in 6.6 ± 0.5 (range 4 to 11) minutes. With normal enzyme levels there was no correlation between the plasma cholinesterase activity and the duration of the

TABLE 2. Plasma Cholinesterase Activity, Duration of Apnea, and Duration of Respiratory Depression After TACCh* in Group I

Patient and Sex	Plasma Cholinesterase Activity†	Duration of Apnea (Seconds)	Duration of Respiratory Depression (Seconds)
1 F	110	265	360
2 F	154.9	265	320
3 F	132	260	320
4 F	86.3	195	300
5 F	87.3	180	480
6 M	119.7	180	360
7 F	97.5	None	240
8 F	55.7	360	480
9 F	70.5	360	480
10 M	113.9	210	300
11 M	68.6	600	660
12 F	136.6	240	420

* Dose of TACCH 0.6 mg./kg.

† Mean plasma cholinesterase values with acetylcholine substrate: μmoles/ml. plasma/30 minutes. Normal values: for men, 145.5 (range 83–198); for women, 123.8 (range 85–180).

apnea or respiratory depression. With low plasma cholinesterase activity, however, both the duration of apnea and respiratory depression were prolonged (table 2). The incidence and duration of apnea after fractional doses of TACCh in group II is summarized in table 3. It is evident from this table that the duration of apnea after identical doses of TACCh becomes progressively shorter the longer the time elapsed after the administration of hexafluorenium. This is due to the diminishing inhibitory effect of hexafluorenium on plasma cholinesterase.[5]

Muscular relaxation was excellent throughout operation in all patients of group I. In group II the relaxation was also satisfactory except that occasionally it tended to wear off abruptly if the administration of a fractional dose was delayed. At the end of surgery tidal volumes returned to their control value in 5.9 ± 0.75 (range 2 to 11) minutes after the discontinuation of the TACCh infusion in group I and in 26.0 ± 2.3 (range 11 to 59) minutes in group II after the administration of the last fractional dose of TACCh. All patients in both groups were breathing spontaneously at the time of extubation. The tidal volume was 130.2 ± 16.3 per cent of control after extubation in group I and varied from 210 to 500 ml. In group II the tidal volume after extubation was 190 ± 23.7 per cent of control and ranged from 300 to 1,000 ml. No muscarinic side effect, *e.g.*, salivation or bradycardia could be observed in any patients of group I or group II either during or after anesthesia. The state of consciousness of the patients in both groups is presented in table 4. It is evident from this table that the level of consciousness was lower in group I where assisted respiration was used than in group II where the patient's respiration was usually controlled. None of the patients of either group complained of muscle pain postoperatively.

The dose of TACCh in group I was 78.4 ± 4.9 μg./kg./minute (range 54.6 to

TABLE 3. The Incidence and Duration of Apnea After All Fractional Doses of TACCh in Group II

Hexafluorenium	TACCh	Number of Cases	Number of Apneas	Duration of Apnea (Minutes)		
				Mean	Standard Error	Range
First administration	1st	38	37	18.2	±1.4	5–38
	2nd	38	35	12.8	±1.2	3–28
	3rd	32	24	11.1	±1.5	2–26
0.4 mg./kg.	4th	14	8	11.1	±2.3	2–24
	5th	7	5	8.6	±2.3	6–10
Second administration	1st	22	22	19.2	±2.0	7–39
	2nd	16	14	13.7	±1.5	7–26
0.15–0.2 mg./kg.	3rd	8	8	16.4	±3.7	4–26

121.3), and in group II it was 6.68 ± 0.39 μg./kg./minute (range 2.73 to 12.92). In group II the dose of hexafluorenium was 4.63 ± 0.22 μg./kg./minute (range 2.04 to 7.75). The first dose of hexafluorenium was effective for 85 ± 5.7 minutes (range 35 to 180).

Discussion

Because of the scarcity of the available material, TACCh was used in relatively few cases. Despite this limitation, the uniformity of the results permits the drawing of certain conclusions.

The consistent fasciculation observed in group I after the intravenous administration of 0.6 mg./kg. TACCh indicates that, as in the cat,[1] this compound produces a typical depolarization block in man. In this, and in many other respects, *e.g.*, the onset, duration and intensity of the neuromuscular block, the effects of TACCh and succinylcholine are very similar. When used alone for the maintenance of surgical relaxation the mg./min. doses of TACCh (5.14) and succinylcholine (4.0)[11] were of the same order. Similarly, after inhibition of plasma cholinesterase by hexafluorenium, the mg./min. doses of TACCh (0.79) and succinylcholine (0.48)[5] were comparable. This also applies to the mg./min. dose of hexafluorenium used with TACCh (0.53) and succinylcholine (0.35)[5], respectively.

Satisfactory surgical relaxation could be maintained both by the continuous infusion of 0.2 per cent TACCh alone, and by the combined use of hexafluorenium and small fractional doses of TACCh. The maintenance of muscular relaxation, however, was easier and the anesthetic course smoother, when TACCh was used in continuous intravenous infusion. With the latter method, adequate surgical relaxation and respiratory exchange could be achieved with assisted respiration without complete paralysis of all respiratory muscles. In contrast when small doses of TACCh were administered in conjunction with hexafluorenium controlled respiration had to be used almost continuously. With the return of spontaneous respiration, muscular relaxation had a tendency to wear off abruptly.

TABLE 4. State of Consciousness of Patients Five Minutes After Discontinuation of Anesthesia

State of Consciousness	Group I (12 Cases)	Group II (38 Cases)
Nonresponsive	4	1
Responds to painful stimuli	3	12
Obeys commands	4	11
Answers questions	1	14

In the 50 patients studied, the clinical course was satisfactory. There were no signs of histamine release, *e.g.*, unexplained hypotension, urticaria or bronchospasm. Not only was there no postoperative apnea but the respiratory tidal volume in both groups studied was significantly higher after extubation at the end of anesthesia than before intubation. None of the patients complained of postoperative msucle pain.

The question to be answered is whether TACCh has enough advantages over the well-established succinylcholine to warrant its introduction into clinical practice. The possible disadvantages ascribed to succinylcholine include: (1) Occasional tendency to the development of tachyphylaxis both under experimental[12,13] conditions and during clinical use.[14] (2) Accumulation of its breakdown product, succinylmonocholine,[15] which also has considerable neuromuscular activity,[16] that may lead to prolonged postoperative apnea. (3) Stimulation of the sympathetic or parasympathetic nervous system.[17-22] Sympathetic stimulation may cause hypertension.[17, 24] Vagal effects may be responsible for bradycardia, block of cardiac conduction, arrhythmias, ventricular fibrillation, asystole and cardiac arrest.[28, 30, 37] (4) Excessively prolonged apnea in patients with atypical plasma cholinesterase activity.[31, 32]

No increase in the milligrams per minute TACCh requirements was observed as anesthesia progressed indicating that tachyphylaxis to its neuromuscular effect did not develop in this series. In contrast to succinylcholine, the enzymatic breakdown products of TACCh, choline and trimethylammoniumcaproic acid, have insignificant neuromuscular blocking effects.[33] None of the cardiovascular complica-

tions reported after the use of succinylcholine were encountered in this small series with TACCh. The *in vitro* enzymatic hydrolysis rate of TACCh by atypical plasma cholinesterase, however, was found to be as markedly reduced as that of succinylcholine.[34]

On the basis of this limited study, no definite conclusions can be drawn as to the advantages or disadvantages of TACCh as a clinically suitable muscle relaxant. Additional studies on both anesthetized and unanesthetized subjects are needed to establish whether tachyphylaxis develops after the repeated or prolonged administration of TACCh. It will also have to be determined if the prolonged administration of TACCh will sensitize human subjects to subsequent doses of non-depolarizing agents, as in the case with decamethonium and succinylcholine.[35, 36] The effect of TACCh on patients with atypical plasma cholinesterase will also have to be observed.

The encouraging results of this study, however, warrant further experimental study and clinical investigation of TACCh. If prolonged postoperative apnea or serious cardiovascular disturbances are not associated with its use in large clinical series, if experimental evidence and clinical experience indicate that the incidence and extent of tachyphylaxis with TACCh is negligible, and if its use in patients with atypical plasma cholinesterase is not followed by excessively prolonged apnea, then the introduction of TACCh would represent a significant advance in the clinical application of neuromuscular blocking agents.

Summary

Trimethylammoniumcaproylcholine (TACCh), a hydrolyzable depolarizing relaxant, has been used for the maintenance of muscular relaxation for intraperitoneal operations in 50 patients. Twelve of these (group I) received an initial dose of 0.6 mg./kg. TACCh before intubation; subsequently muscular relaxation was maintained by continuous intravenous infusion of a 0.2 per cent solution. To 38 other patients (group II) TACCh was administered in divided doses, after inhibition of their plasma cholinesterase activity with 0.4 mg./kg. hexafluorenium. The initial dose of TACCh in group II was 0.2 mg./kg. followed by somewhat smaller fractional doses. Fasciculation preceded the development of apnea in all patients of group I but only in one patient of group II. Apnea of 4.7 ± 0.5 minutes duration developed in group I within 50 seconds from the start of injection. In group II apnea lasting 18.2 ± 1.4 minutes developed in two to three minutes after the first dose of TACCh and in most instances after the administration of fractional doses. The time interval between the administration of the initial dose of TACCh and the first fractional dose averaged 25.9 ± 1.3 minutes. As the inhibitory effect of hexafluorenium gradually wore off the interval between subsequent fractional doses became progressively smaller. Relaxation for endotracheal intubation and surgery was satisfactory in all patients of both groups. The anesthetic course, however, was smoother in group I than in group II. Tidal volumes returned to control values in 5.8 ± 0.75 minutes after discontinuation of TACCh infusion in group I and in 26.0 ± 2.3 minutes in group II after the administration of the last fractional dose of TACCh. At the time of extubation all patients of both groups had adequate spontaneous respiration. No tachyphylaxis or disturbing side effects were observed in this series. The encouraging results obtained in this small number of patients warrant further investigation of TACCh.

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