POTENTIATION OF THE NEUROMUSCULAR EFFECT OF SUCCINYLCHOLINE BY HEXAFLUORENIUM

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HEXAFLUORENIUM BROMIDE (Mylaxen), a bis-quaternary ammonium compound, was synthesized by Cavallito *et al.*[1] Macri [2] found that administered intravenously its neuromuscular effect was equal to that of *d*-tubocurarine in dogs and was twice as great in rabbits; in mice, however, it was but one-twentieth as potent as *d*-tubocurarine. On subcutaneous administration to mice, it was 1,000 times less potent than *d*-tubocurarine. Cordaro and Arrowood,[3] who first investigated hexafluorenium in anesthetized man, reported that 6 to 9 mg. (about 0.1 to 0.15 mg./kg.) produced adequate muscular relaxation in plane 2, stage III cyclopropane anesthesia. Studies in unanesthetized human subjects [4] revealed that hexafluorenium in up to 1 mg./kg. doses had no discernible neuromuscular effect. Induction of anesthesia with thiopental did not relax the abdominal muscles or decrease the respiratory tidal volume after the administration of as much as 1.0 mg./kg. hexafluorenium. Only in deep ether anesthesia was it possible to demonstrate a 30 to 40 per cent decrease of respiratory tidal volume after the intravenous injection of 0.5 to 1.0 mg./kg. hexafluorenium. However, the intravenous administration of 0.6 mg./kg. succinylcholine (suxamethonium) after 0.66 mg./kg. hexafluorenium caused 40 minutes apnea in an anesthetized patient. The potentiating effect of hexafluorenium on the suxamethonium-induced neuromuscular block was subsequently and independently reported by Arrowood and Kaplan [5] and Rizzi [6] and Rizzi and Galeotto.[7]

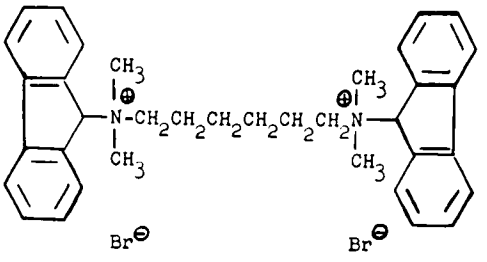

FIG. 1. The structural formula of hexafluorenium (Mylaxen) bromide.

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Investigation of the mechanism whereby hexofluorenium potentiates and prolongs the neuromuscular effect of suxamethonium and its bis-ethyldimethyl analog, suxethonium, revealed that hexafluorenium is a potent, selective inhibitor of human plasma cholinesterase (causes 50 per cent inhibition of activity in 1.5×10^{-7} *M* concentration). Thus it inhibits the enzymatic breakdown of suxamethonium and suxethonium both *in vitro* and *in vivo*.[8, 9] In premedicated patients, in contrast to other anticholinesterases (*e.g.*, neostigmine), the slow intravenous administration of hexafluorenium caused little muscarinic effect (*e.g.*, salivation and bradycardia).

The present investigation was undertaken to determine if the combined administration of hexafluorenium with suxamethonium or suxethonium is suitable for the production of surgical relaxation in lightly anesthetized patients.

MATERIAL AND METHODS

In preliminary studies, 20 patients operated on the lower part of the body under regional anesthesia, the level of which did not extend above the tenth thoracic dermatome, were lightly anesthetized with thiopental–N_2O-O_2.[10] After stabilization of the depth of anesthesia, respiratory tidal volume was determined with a Bennett ventilation meter included in the anesthetic circuit. Respiratory rate, pulse rate and blood pressure were also recorded. Following this (at 0 minutes), 10 patients received, intravenously, in 30 seconds, 0.2 mg./kg. suxamethonium and 10 others 0.4 mg./kg. suxethonium. The onset and duration of apnea or maximal decrease of tidal volume,

and the duration of respiratory depression (defined as the time interval from the start of injection to the return of tidal volume to control values) were observed. At 6 minutes, 0.5 mg./kg. hexafluorenium was injected rapidly, and at 9 minutes, the same respiratory and circulatory parameters measured before the start of the experiment were again recorded. At 10 minutes, 0.2 mg./kg. suxamethonium or 0.4 mg./kg. suxethonium was administered once more, and the onset and duration of apnea and duration of respiratory depression were measured.

Observations were made in 266 patients. Seventy-eight received a continuous intravenous infusion of 0.04 per cent suxamethonium or 0.10 per cent suxethonium. In 188 patients, suxamethonium was administered in fractional doses. All patients were anesthetized with a combination of thiopental–N_2O-O_2 and alphaprodine according to a previously described technique [11] for various intraperitoneal operations.

The group of patients who received suxamethonium or suxethonium infusions were each further divided into two subgroups. Members of the first subgroups received after induction of anesthesia, 0.6 mg./kg. suxamethonium or 1.2 mg./kg. suxethonium and their tracheas were intubated. On return of spontaneous respiration, 0.5 mg./kg. hexafluorenium was injected intravenously and the infusion of the 0.04 per cent suxamethonium or 0.1 per cent suxethonium was started 5 minutes later.

Members of the second subgroups received 0.5 mg./kg. hexafluorenium 5 minutes prior to induction of anesthesia. Immediately after induction the continuous infusion of suxamethonium or suxethonium was started at about 40 drops per minute, and when conditions became suitable, endotracheal intubation was performed.

We attempted to use assisted instead of controlled respiration in the patients who received suxamethonium or suxethonium by continuous infusion. Controlled respiration was used only when an overdose of the relaxant or the narcotic caused temporary apnea.

The patients in whom suxamethonium was used in fractional doses were also divided into two subgroups. In the first subgroup (113 patients), 0.5 mg./kg. hexafluorenium was administered immediately prior to the start of anesthesia, and 4 to 7 minutes later after induction with thiopental, 0.2 mg./kg. suxamethonium was injected. In the second subgroup (75 patients) the same quantities of hexafluorenium and suxamethonium were administered simultaneously after induction of anesthesia. Repeated 0.10 and 0.15 mg./kg. doses of suxamethonium were administered as required (15 to 35 minutes apart) to maintain muscular relaxation. Additional 0.15 to 0.25 mg./kg. hexafluorenium doses were administered when the effect of a fractional dose of suxamethonium lasted less than 15 minutes and the expected duration of operation was more than 30 minutes. The fractional dose of hexafluorenium was chosen according to the expected length of operation. If this was less than 30 minutes, then instead of giving more hexafluorenium, somewhat larger (0.2 to 0.3 mg./kg.) doses of suxamethonium were given as often as required. If the patients were apneic or the respiratory rate was below 12 per minute at the end of operation, they received 0.02 mg./kg. levallorphan tartrate (Lorfan) intravenously.

The following observations were made in all patients: (1) respiratory tidal volume, respiratory rate, pulse rate and blood pressure; (2) the approximate time required for the development of the maximal effect of suxamethonium and suxethonium administered after hexafluorenium; (3) the presence or absence of muscular fasciculations; (4) the relaxation of the jaw, pharyngeal and laryngeal muscles at the time of tracheal intubation; (5) the duration of action of the first dose of hexafluorenium; (6) the mg./minute doses of thiopental, alphaprodine, suxamethonium or suxethonium and hexafluorenium used; and (7) state of consciousness at end of operation.

In the patients where suxamethonium or suxethonium was given in continuous infusion, the time required for the respiratory tidal volume to return from a minimum of 50 ml. to control values after termination of the infusion was also observed. In the patients who received suxamethonium in fractional doses, the time necessary for the return of respiratory tidal volume to control values after the last fractional dose of suxamethonium was recorded.

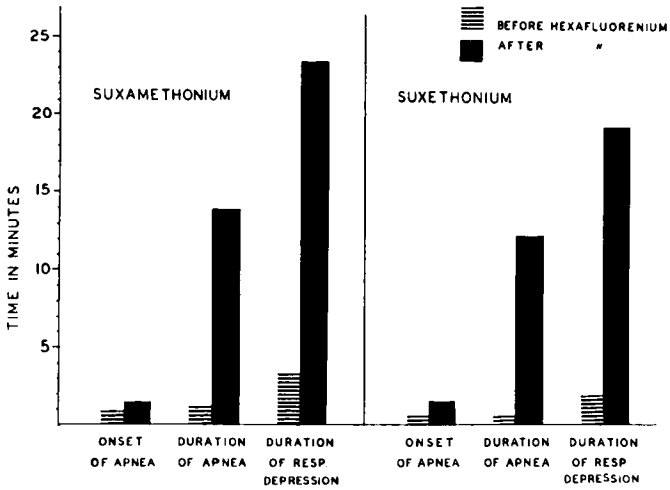

FIG. 2. Comparison of the onset and duration of apnea and the duration of respiratory depression following the intravenous injection of 0.2 mg./kg. suxamethonium or 0.4 mg./kg. suxethonium before and after 0.5 mg./kg. hexafluorenium. The data presented are the averages of observations made on 10 subjects.

RESULTS

Experimental Studies. The findings of the experimental studies on the 20 subjects who received 0.2 mg./kg. suxamethonium or 0.4 mg./kg. suxethonium are summarized in figure 2. It is evident that the administration of 0.5 mg./kg. hexafluorenium delayed the onset and prolonged the duration of the suxamethonium or suxethonium-induced apnea and respiratory depression. The differences between the figures obtained before and after hexafluorenium were highly significant.[9] No significant changes in pulse rate and blood pressure were observed after suxamethonium, suxethonium or hexafluorenium.

Clinical Observations. The maximal effect of suxamethonium and suxethonium was delayed by the previous administration of hexafluorenium from about 60 seconds to 180 to 300 seconds.

When suxamethonium or suxethonium was administered after hexafluorenium, the muscular fibrillation and twitching, usually observed after the intravenous administration of these agents, were absent. When suxamethonium and hexafluorenium were administered simultaneously, the incidence of fibrillation and twitching was usually about the same with the 0.2 mg./kg. dose used as that encountered after an 0.6 mg./kg. dose, but its intensity was usually less.

Conditions for endotracheal intubation were

TABLE 1

RELATIONSHIP BETWEEN THE RETURN OF TIDAL VOLUMES TO CONTROL VALUES AND THE TERMINATION OF OPERATION

Tidal Volumes At or Above Control Values	Hexafluorenium Administered Before Suxamethonium		Hexafluorenium and Suxamethonium Administered Together	
	Number of Patients	Per Cent	Number of Patients	Per Cent
At or before end of operation	86	76.1	56	74.6
1 to 5 minutes after operation	15	13.4	14	18.7
6 to 10 minutes after operation	4	3.5	3	4.0
11 to 30 minutes after operation	8	7.0	2	2.7

TABLE 2

DRUG REQUIREMENTS WITH THE ADMINISTRATION OF SUXAMETHONIUM IN CONTINUOUS INFUSION

Mode of Administration	Dose—Mg./Minute			
	Suxamethonium	Hexafluorenium	Thiopental	Alphaprodine
Hexofluorenium before intubation	0.61 ± 0.07*	0.43 ± 0.04	3.00 ± 0.28	1.25 ± 0.11
Hexafluorenium after intubation	0.58 ± 0.06	0.37 ± 0.03	2.85 ± 0.33	1.10 ± 0.05

* Standard error.

unsatisfactory after the 1.2 mg./kg. suxethonium. After 0.6 mg./kg. suxamethonium alone, or when 0.2 mg./kg. suxamethonium or 0.4 mg./kg. suxethonium was administered after hexafluorenium, endotracheal intubation could be performed easily provided that enough time was allowed for the development of their maximal effect. The administration of 0.6 mg./kg. suxamethonium alone, or that of 0.2 mg./kg. suxamethonium or 0.4 mg./kg. suxethonium after hexafluorenium, invariably produced apnea. However, whereas the duration of apnea after 0.6 mg./kg. suxamethonium is usually 2 to 4 minutes,[10] the duration of apnea after the 0.2 mg./kg. suxamethonium or 0.4 mg./kg. suxethonium administered after hexafluorenium was 12 to 25 minutes. After 1.2 mg./kg. suxethonium used alone, apnea developed in only about two-thirds of the patients and lasted 40 seconds to 2 minutes.

The first 0.5 mg./kg. dose of hexafluorenium markedly potentiated and prolonged the neuromuscular effects of suxamethonium or suxethonium for 65 and 50 minutes, respectively, when they were used in continuous infusion and for 75 to 80 minutes when suxamethonium was administered in fractional doses. When suxamethonium and hexafluorenium were administered simultaneously, the duration of effect of the first 0.2 mg./kg. dose of suxamethonium was shorter than when it was administered 3 to 5 minutes after hexafluorenium. This was undoubtedly due to the fact that some of the suxamethonium was hydrolyzed by plasma cholinesterase before the inhibitory effect of hexafluorenium had fully developed. When the potentiating effect of hexafluorenium started to wear off, the injection of 0.15 to 0.25 mg./kg. doses re-established this effect for about the same length of time as the duration of the effect of the first 0.5 mg./kg. dose.

Respiratory tidal volumes returned to control values in an average of 14 and 12 minutes respectively after the discontinuation of the continuous infusion of suxamethonium or suxethonium. When suxamethonium was administered in fractional doses, an average of 34 minutes elapsed between the injection of the last dose and the return of tidal volume to control values. The relationship between the return of tidal volumes to control values and the end of surgery after the combined use of hexafluorenium and suxamethonium in fractional doses is summarized in table 1. It is evident from this table that tidal volumes were at or above control values at the end of operation in 75 per cent of the patients. In only 2 to 7 per cent of the cases did respiratory depression persist for more than 10 minutes after

TABLE 3

DRUG REQUIREMENTS WITH THE ADMINISTRATION OF SUXETHONIUM IN CONTINUOUS INFUSION

Mode of Administration	Dose—Mg./Minute			
	Suxethonium	Hexafluorenium	Thiopental	Alphaprodine
Hexafluorenium before intubation	1.56 ± 0.12*	0.43 ± 0.03	2.33 ± 0.15	0.92 ± 0.06
Hexafluorenium after intubation	1.43 ± 0.17	0.43 ± 0.04	3.70 ± 0.45	1.15 ± 0.08

* Standard error.

TABLE 4

DRUG REQUIREMENTS WITH THE ADMINISTRATION OF SUXAMETHONIUM IN FRACTIONAL DOSES

Mode of Administration	Dose—Mg./Minute			
	Suxamethonium	Hexafluorenium	Thiopental	Alphaprodine
Hexafluorenium administered before Suxamethonium	0.48 ± 0.02*	0.35 ± 0.01	5.91 ± 0.24	0.53 ± 0.03
Hexafluorenium and Suxamethonium administered together	0.44 ± 0.02	0.32 ± 0.02	5.00 ± 0.21	0.54 ± 0.02

* Standard error.

termination of surgery and never beyond 30 minutes. None of the patients were apneic at the end of operation.

The mg./minute drug requirements after the administration of hexafluorenium together with suxamethonium or suxethonium in continuous infusion or suxamethonium in fractional doses are summarized in tables 2, 3 and 4.

Comparison of the figures of tables 2, 3 and 4 revealed that: (1) In the series where suxamethonium or suxethonium was administered by continuous infusion, the mg./minute suxamethonium, suxethonium and hexafluorenium requirements were not influenced by the sequence of the hexafluorenium and relaxant administration (see Methods). (2) Similarly, when suxamethonium was administered in fractional doses, the relaxant and hexafluorenium requirements were the same whether hexafluorenium was administered before or together with suxamethonium. (3) In contrast, significantly greater mg./minute doses of suxamethonium and hexafluorenium ($p < 0.05$) were required in the patients where suxamethonium was administered in continuous infusion, and respiration was assisted (see table 2) than in those who received suxamethonium in fractional doses and whose respiration was controlled (see table 4). (4) The mg./minute suxethonium requirements were more than twice greater than those of suxamethonium (see tables 2 and 3). (5) Considerably more thiopental and less alphaprodine ($p < 0.05$) was used when suxamethonium was administered in fractional doses and respiration was controlled than when continuous infusion of suxamethonium was used and respiration was assisted (see tables 2 and 4).

Patients who received suxamethonium and suxethonium in continuous infusion and where relatively more relaxant, hexafluorenium and alphaprodine and less thiopental was used, were more awake at the end of operation than those who received fractional doses of suxamethonium, and where relatively smaller doses of suxamethonium, hexafluorenium and alphaprodine, but larger amounts of thiopental were used (table 5). No significant changes in pulse rate or blood pressure attributable to the use of hexafluorenium were observed. As already mentioned, no prolonged postoperative apnea was encountered in the series reported.

TABLE 5

STATE OF CONSCIOUSNESS WITHIN 5 MINUTES AFTER TERMINATION OF ANESTHESIA

Relaxant and Its Mode of Administration	Answers Questions		Obeys Commands		Responds to Stimulation		Did Not React	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Suxamethonium in continuous infusion	26	65	3	8	8	20	3	8
Suxethonium in continuous infusion	23	61	2	5	13	34	0	0
Hexafluorenium before Suxamethonium in fractional doses	37	33	28	25	42	37	6	5
Hexafluorenium together with Suxamethonium in fractional doses	32	43	15	20	24	32	4	5

Discussion

The modifying effects of hexafluorenium on the suxamethonium and suxethonium induced neuromuscular block are due primarily to its selective inhibitory effect on plasma cholinesterase and secondarily to the mild, but definite nondepolarizing blocking action at the neuromuscular junction.* Its anticholinesterase effect causes the marked intensification and prolongation of the neuromuscular effect of the short acting suxamethonium and suxethonium. Its mild curare-like effect is responsible for the prevention of the initial muscular fasciculation and twitching commonly seen after the intravenous injection of suxamethonium.

Other anticholinesterases, *e.g.*, neostigmine, are also capable of prolonging and intensifying the effects of suxamethonium. Thesleff reported,[12] however, that an 0.03 mg./kg. dose of neostigmine, which not quite doubled the duration and did not potentiate the effect of suxamethonium, had severe muscarinic side effects that made it unsuitable for clinical application. The use of much larger doses of neostigmine than those which would be required to produce comparable prolongation and potentiation of the action of suxamethonium to that observed after the use of hexafluorenium in this series would undoubtedly be too dangerous. It is fortunate that the low permeability of biological membranes to hexafluorenium [9] makes possible the selective inhibition of plasma cholinesterase with little or no signs of cholinesterase inhibition at other sites.

In experimental studies [9] identical doses of suxamethonium or suxethonium caused a more than ten-fold prolongation of the duration of apnea and respiratory depression after hexafluorenium. In the clinical series here reported, the administration of hexafluorenium caused a 5 to 7 fold reduction in the mg./minute dose of suxamethonium that was required for the maintenance of adequate surgical relaxation in an otherwise comparable series where hexafluorenium was not used.

Despite the fact that hexafluorenium markedly prolonged the action of suxamethonium, the depth of respiration at the end of operation was as good as or better than after the use of *d*-tubocurarine or gallamine in another series.[13]

Because of the inhibition of its enzymatic breakdown, suxamethonium, which until now has been used primarily for tracheal intubation and the modification of convulsions in electroshock therapy, used with hexafluorenium proved to be a suitable agent for the production of muscular relaxation for prolonged surgical procedures.

There was a definite difference in the mg./minute-drug requirements between the series where suxamethonium was administered by continuous infusion and assisted respiration was used and the other where fractional doses of suxamethonium were given to patients whose respiration was controlled. The greater mg./minute dose of suxamethonium required with the continuous infusion technique is probably due to the fact that in the presence of hexafluorenium suxamethonium was primarily decomposed by alkaline hydrolysis. Since the alkaline hydrolysis of suxamethonium is a second order reaction, which is proportional to the square of its concentration in plasma, the hydrolysis probably proceeds at a more rapid rate when its concentration is kept relatively constant by continuous infusion than when its plasma level fluctuates with the administration of fractional doses. Another factor which should tend to reduce the suxamethonium requirements when administered in fractional doses is that because of the temporarily higher plasma levels reached immediately after the injection of a fractional dose, higher concentrations of suxamethonium will accumulate at the end-plate.[14]

The higher alphaprodine and lower thiopental requirements used in the series with assisted respiration were probably due to the circumstance that in the presence of spontaneous breathing it was easier to assess the depth of anesthesia.[15] Thus it could be determined whether more thiopental or more alphaprodine was required.[16] In contrast to this, when controlled respiration was used, thiopental was administered without the guidance

* Since the completion of this study, 0.3 mg./kg. hexafluorenium was administered intravenously to 10 healthy, young adult volunteers. In some of these, increased peristalsis and slight abdominal cramps developed. Measurement of the vital capacity and grip strength revealed in some, but not all, a moderate (less than 10 per cent) decrease of neuromuscular activity which was not detectable by the less sensitive methods used earlier.

of respiratory signs resulting in a higher mg./minute dose of this compound and a reduction of the alphaprodine requirements. In agreement with the smaller thiopental doses used with assisted respiration, the level of consciousness was high in a larger percentage of those patients (65 per cent were capable of answering questions) at the end of operation than in those whose respiration was controlled (33 to 43 per cent answered questions).

The question arises: does the combined use of hexafluorenium and suxamethonium offer any advantages over other means already in use for the production of muscular relaxation? It is evident that hexafluorenium eliminates one of the greatest advantages of suxamethonium, namely, its controllability, and makes the duration of its neuromuscular blocking effect similar to that obtained with the long acting agents. On the other hand, despite the usually rapid return of the depth of respiration to control values after the use of suxamethonium in continuous infusion, many instances have been reported [17] in which prolonged apnea was irreversible and resulted in the patient's death. Irreversible curarization is occasionally also encountered with the long acting neuromuscular blocking agents.[18]

Of the numerous causes of prolonged apnea, at least three can conceivably be modified by the concomitant use of hexafluorenium. It has been pointed out elsewhere [14, 19] that intravenously injected quaternary-ammonium-type muscle relaxants are taken up very rapidly by the end-plates. Up to the point of complete saturation of these structures, the concentration reached at the end-plate will depend on the maximal plasma level of the relaxant reached at the end of injection. Because of the rapid enzymatic breakdown of suxamethonium, its plasma level and also its concentration at the end-plate dependent on it drops rapidly under normal circumstances. Therefore, in order to obtain relaxation of sufficient duration initially, relatively high suxamethonium concentrations must be reached at the end-plate. Since the initial mg./kg. dose of suxamethonium and therefore, also its plasma level necessary for the production of neuromuscular block is at least 3 times lower if used after hexafluorenium than when it is used alone, its concentration at the end-plate will also be lower with this method of administration. Consequently if there is any tendency for the pathological fixation of suxamethonium to the end-plate receptors, which has been suggested as one of the possible causes of prolonged apnea, the quantity of suxamethonium fixed at the end-plate will be smaller, and the duration of postoperative apnea will be shorter.

Occasionally, because of the gradually increasing resistance of the end-plate to depolarization, unusually high mg./minute doses of suxamethonium are required for the maintenance of muscular relaxation. Because of this, its breakdown product, succinylmonocholine, may accumulate and cause prolonged postoperative apnea. Preventing the hydrolysis of suxamethonium by hexafluorenium will bring about a 5 to 7 fold decrease of the suxamethonium requirement and thereby prevent the accumulation of paralytic concentrations of succinylmonocholine.

Kalow and Gunn have shown [21] that in subjects whose plasma cholinesterase is atypical, the enzymatic hydrolysis of suxamethonium is extremely slow with the plasma levels encountered with its clinical use. In such individuals termination of the suxamethonium-induced neuromuscular block will depend partly on its alkaline hydrolysis, which is also very slow with the substrate concentrations present in the plasma under clinical circumstances, and partly on urinary excretion. It stands to reason that if the initial dose of suxamethonium is markedly reduced by the simultaneous use of hexafluorenium then the duration of the neuromuscular block will be markedly reduced even in the presence of atypical plasma cholinesterase.

In agreement with these considerations, no postoperative apnea or prolonged respiratory depression was encountered so far after the combined use of hexafluorenium and suxamethonium.

Besides the prevention of postoperative apnea and the reduction of the duration and incidence of postoperative respiratory depression, hexafluorenium when administered before suxamethonium prevented the development of muscular fasciculations and twitching. The muscle pain described [12, 20, 21] in ambulatory patients after the use of suxamethonium has

been attributed to the initial tetanic contraction of the muscle fibers seen with this agent. Since hexafluorenium prevents the visible muscular twitching caused by suxamethonium, it should also decrease the incidence and severity of muscle pain seen after the use of this agent.

Another question still has to be answered: Does this method of the production of muscular relaxation have any advantages over the use of other long acting neuromuscular blocking agents? Disposition of the clinically used, long acting muscle relaxants depends wholly (*e.g.*, gallamine) or primarily (*e.g.*, *d*-tubocurarine) on redistribution to inactive sites and urinary excretion. In contrast to this, suxamethonium, even in the presence of hexafluorenium, is broken down by alkaline hydrolysis. Irreversible curarization encountered after the use of long acting relaxants [18] has so far not been seen after the combined use of hexafluorenium and suxamethonium. If this serious complication will not occur in considerably larger series of patients, this would be a valid argument in favor of the combined use of hexafluorenium and suxamethonium. Besides the apparently decreased danger of prolonged postoperative apnea or irreversible curarization, the absence of side effects like tachycardia or hypotension and bronchospasm (occasionally seen after the use of gallamine and *d*-tubocurarine respectively) should also tilt the balance in favor of the combined use of hexafluorenium and suxamethonium.

Of the several methods of the combined administration of hexafluorenium and suxamethonium investigated, the use of small fractional doses of suxamethonium after an 0.5 mg./kg. dose of hexafluorenium seem to offer the most advantages. With this method of administration, the concentration of suxamethonium at the end-plate is never excessively high; there is no initial muscular fasciculation or twitching; conditions for endotracheal intubation are favorable; and by adapting the dose of suxamethonium or hexafluorenium to expected duration of surgery, postanesthetic respiratory depression can be prevented.

Summary

The potentiating effect of 0.5 mg./kg. hexafluorenium on the neuromuscular effect of 0.2 mg./kg. succinylcholine (suxamethonium) or 0.4 mg./kg. suxethonium was investigated in 20 lightly anesthetized subjects. Hexafluorenium delayed the onset and markedly prolonged the duration of neuromuscular effects of suxamethonium or suxethonium.

Hexafluorenium and suxamethonium or suxethonium were used together for the production of muscular relaxation in 266 patients for various intraperitoneal operations. For all patients the initial dose of hexafluorenium was 0.5 mg./kg. In 78 patients, continuous infusions of 0.04 per cent suxamethonium or 0.10 per cent suxethonium were used. One hundred and thirteen patients received, after hexafluorenium, an initial 0.2 mg./kg. dose of suxamethonium. In 75 others, the same dose of suxamethonium was administered simultaneously with hexafluorenium. In the clinical studies, hexafluorenium caused a 5 to 7 fold reduction of the mg./minute suxamethonium requirements. When administered before suxamethonium, hexafluorenium prevented the development of muscular fasciculation and twitching. No postoperative apnea or prolonged respiratory depression was encountered after the combined use of hexafluorenium and suxamethonium.

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MEDICOLEGAL ASPECTS Plaintiff's complaints in suits against anesthesiologists are: (1) too much anesthesia, (2) death from anesthesia, (3) injury to eyes or skin, (4) injury from mask, (5) injury from mouth gag, (6) injury from improper position on the table, (7) injury from struggling, (8) pneumonia caused by fluid ether in lungs, (9) spinal anesthesia administered without consent or against wishes, (10) injury from spinal anesthesia, (11) responsibility in recovery room, (12) injury to teeth, and (13) fire and explosion. Among the methods of preventing malpractice claims are listed the following suggestions: (1) Criticism of the work of other physicians must be avoided. (2) Good medical records must be kept. (3) Physicians should avoid promising the patient too much or guaranteeing results. (4) The physician should frequently check the condition of his equipment and make use of every available safety installation. (5) The physician should have sufficient and proper medical malpractice insurance coverage to prevent financial ruin if professional liability charges are brought against him. (6) Consultation by the anesthesiologist with the patient regarding the anesthesia prior to premedication and surgery will help to avoid misunderstandings regarding the anesthesia given. (*Ochsner, A. J., II: Medicolegal Aspects of Anesthesiology, South. M. J. 52: 958 (Aug.) 1959.*)