

THE NEUROMUSCULAR ACTIVITY OF HEXAMETHYLENE-1, 6-BIS-CARBAMINOYLCHOLINE BROMIDE (IMBRETIL) IN MAN

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HEXAMETHYLENE-1,6-bis-carbaminoylcholine bromide (Imbretil, BC-16) is one of the many polymethylene-bis-carbaminoylcholine compounds studied pharmacologically by Klupp and coworkers.¹ It has been widely used in Europe for the production of muscular relaxation in surgery²⁻⁷ and also employed in the treatment of tetanus.⁸ It has been reported that in man^{5,6,7} and most other mammals studied^{9,10,11} it has a biphasic¹² effect and after an initial depolarization block, it produces a nondepolarization block that can be antagonized by neostigmine. The reports regarding its optimal mode of administration and duration of action have been contradictory.

The purpose of the present investigation was to study, under controlled conditions, the neuromuscular effects of Imbretil in anesthetized human subjects with special reference to onset and duration of action, reversibility by anticholinesterases and side effects. In a small number of patients, observations were also made on the effects of Imbretil used alone, or after a single dose of succinylcholine for the production of muscular relaxation for intra-abdominal surgery.

MATERIAL AND METHODS

Experimental Studies. Imbretil was administered intravenously at two dose levels to 60 human subjects, lightly anesthetized with thiopental sodium and nitrous oxide-oxygen undergoing surgery on the lower part of the body under regional anesthesia, not extending above the tenth dorsal dermatome. Details of the anesthetic technique used have been published elsewhere.¹³ Thirty subjects (group 1), after stabilization of the level of anesthesia and recording of minute volume of respiration (measured by a Bennett or Draeger ventilation meter

included in the anesthetic circuit), respiratory and pulse rates and blood pressure, received intravenously (at zero time) 0.03 mg./kg. Imbretil in 30 seconds. Thirty other subjects (group 2) were given 0.05 mg./kg. Imbretil. Ten subjects each in both group 1 (group 1a) and group 2 (group 2a) received no other medication. Ten subjects of group 1 received intravenously, 7 minutes after the injection of Imbretil, 0.02 mg./kg. neostigmine bromide together with 0.4 mg. atropine sulphate (group 1b) and 10 subjects of group 2 the same medication at the return of spontaneous respiration (group 2b). Ten subjects each of group 1 and 2 (group 1c and group 2c) received under identical circumstances, instead of neostigmine, 0.30 mg./kg. edrophonium chloride (table 1). The observations made before the administration of Imbretil were repeated at 3, 6 and 10 minutes and every 5 minutes thereafter until the termination of the experiment. The time of onset and duration of apnea or respiratory depression (measure from maximal depression to the return of tidal volume to control values)

TABLE 1
THE DOSE AND MODE OF ADMINISTRATION OF THE DRUGS USED IN THE GROUPS OF SUBJECTS STUDIED

Group	Imbretil (mg./kg.)	Other Drugs and Their Time of Administration
1a	0.03	None used
1b	0.03	Neostigmine, 0.02 mg./kg., 7 minutes after Imbretil; atropine 0.4 mg.
1c	0.03	Edrophonium, 0.30 mg./kg., 7 minutes after Imbretil
2a	0.05	None used
2b	0.05	Neostigmine, 0.02 mg./kg., atropine 0.4 mg., at the return of spontaneous respiration
2c	0.05	Edrophonium, 0.30 mg./kg., at the return of spontaneous respiration

Received from the Department of Anesthesiology, Mercy Hospital, and Section on Anesthesiology, Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, and accepted for publication May 27, 1959.

and in group 2, the time from the termination of apnea to the return of tidal volume to control values were also noted. The circulatory and other side effects of the drugs used were also observed. In a few other subjects, 0.02 or 0.025 mg./kg. Imbretil was administered in conjunction with edrophonium or neostigmine. Respiratory tracings were made of these subjects by substituting a Sanborn basal metabolism apparatus in place of the breathing bag in the anesthetic circuit.¹⁴

Clinical observations were made on 14 patients anesthetized with thiopental nitrous oxide-oxygen and alphaprodine¹⁵ for intra-abdominal surgery. All patients' tracheas were intubated. Five patients received 0.05 mg./kg. Imbretil before tracheal intubation. Nine others were given 0.6 mg./kg. succinylcholine chloride intravenously, followed by tracheal intubation and then 0.03 mg./kg. Imbretil at the end of the succinylcholine induced apnea. Fractional doses of 0.015 to 0.025 mg./kg. Imbretil were administered whenever necessary for the maintenance of surgical relaxation. The onset and duration of apnea, the relationship between the presence or absence of apnea and relaxation of the abdominal muscles, the time necessary for the return of tidal volumes to control values after the last dose of Imbretil and the antagonistic effects of 0.3 mg./kg. edrophonium or 0.02 mg./kg. neostigmine on the residual neuromuscular block at the end of surgery were noted.

RESULTS

Experimental Studies. Of the 30 subjects who received 0.03 mg./kg. Imbretil, apnea occurred in 15. The average time necessary for the development of apnea or maximal respiratory depression varied in the 3 subgroups of group 1 from 4.5 to 5.0 minutes (table 2) with a range of from 2.5 to 7.0 minutes. At 6 minutes after the injection of Imbretil, the average tidal volume, including the apneic subjects, was depressed to 8.8, 12.9 and 25.5 per cent of control values in groups 1a, 1b and 1c, respectively. Unfortunately, the average respiratory depression in group 1c was significantly less than in group 1a (t value between groups 1a and 1c = 2.1) indicating that at the 0.03 mg./kg. level the dose response was variable. At 10 and 15 minutes after Imbretil there was no significant difference between the average tidal volumes in group 1a, where no medication was used, and group 1b where 0.03 mg./kg. neostigmine with 0.4 mg. atropine was given at 7 minutes. The difference between the average tidal volumes of group 1a and 1c are statistically significant at both 10 and 15 minutes (t equals 2.3 and 2.7, respectively). In view of the fact that the Imbretil induced depression of tidal volume at 6 minutes, before edrophonium, was less in group 1c than in the groups 1a and 1b, the importance of this difference is doubtful. The duration of respiratory depression was not significantly different in groups 1a, 1b and 1c.

TABLE 2

THE EFFECTS OF 0.03 MG./KG. HEXAMETHYLENE-1,6-BIS-CARBAMOYLCHOLINE-BROMIDE (IMBRETIL) ALONE OR FOLLOWED BY NEOSTIGMINE OR EDROPHONIUM ON TIDAL VOLUME OF ANESTHETIZED SUBJECTS

Agents Used	Time to Maximal Respiratory Depression* (minutes)	Tidal Volume Expressed as Per Cent of Control at Times Indicated After Injection of Imbretil			Duration of Respiratory Depression
		6 Minutes	10 Minutes	15 Minutes	
Imbretil	4.8 \pm 0.33	8.8 \pm 3.0	16.6 \pm 6.0	42.6 \pm 11.2	20.1 \pm 1.36
Imbretil followed by neostigmine*	4.5 \pm 0.59	12.9 \pm 4.9	23.7 \pm 8.9	51.9 \pm 13.5	19.2 \pm 1.76
Imbretil followed by edrophonium*	5.0 \pm 0.26	25.5 \pm 7.75†	42.8 \pm 11.4†	80.1 \pm 8.0†	16.9 \pm 1.8

* Neostigmine (0.02 mg./kg.) or edrophonium (0.30 mg./kg.) was given intravenously 7 minutes after the administration of Imbretil.

† Statistically significant.

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TABLE 3

THE EFFECTS OF 0.05 MG./KG. HEXAMETHYLENE-1,6-BIS-CARBAMINOYLCHOLINE-BROMIDE (IMBRETIL) ALONE OR FOLLOWED BY NEOSTIGMINE OR EDROPHONIUM ON TIDAL VOLUME OF ANESTHETIZED SUBJECTS

Agents Used	Onset of Apnea* (minutes)	Duration of Apnea (minutes)	Duration of Respiratory Depression (minutes)	Time from End of Apnea to Return to Control Value (minutes)
Imbretil	2.5 ± 0.39	18.9 ± 1.4	30.0 ± 1.53	7.4 ± 0.71
Imbretil followed by neostigmine*	2.4 ± 0.25	16.2 ± 1.3	23.6 ± 1.04†	4.7 ± 0.46†
Imbretil followed by edrophonium*	2.7 ± 0.23	17.8 ± 1.4	26.6 ± 0.60†	6.4 ± 0.76

* Neostigmine (0.02 mg./kg.) or edrophonium (0.30 mg./kg.) was given intravenously at the return of spontaneous respiration.

† Statistically significant.

The results obtained after the intravenous administration of 0.05 mg./kg. Imbretil (group 2) are summarized in table 3. The response at this dose level was more uniform and of all the subjects studied, apnea failed to develop in only 3 subjects who were not included in the statistical analysis. Apnea in this group developed about two times faster than in group 1, and lasted an average of 16.2 to 18.9 minutes in the 3 subgroups. The administration of 0.02 mg./kg. neostigmine with 0.4 mg. atropine or 0.3 mg./kg. edrophonium at the start of spontaneous respiration decreased the duration of respiratory depression. The effect of neostigmine, probably because of its longer duration of action, was more marked than that of edrophonium. The *t* values between groups 2a and 2b, and 2a and 2c were 3.5 and 2.1, respectively. The time from the end of apnea to return of tidal volumes to control values was shortened by neostigmine, but not by edrophonium.

The observations made with 0.02 and 0.025 mg./kg. Imbretil are presented in figures 1, 2, 3 and 4. Comparison of figures 1 and 2 again points to the marked variation in the effects of small doses of Imbretil on respiratory muscles. In the subject whose respiratory tracing is presented in figure 1, 0.02 mg./kg. Imbretil caused a 60 per cent reduction of tidal volume; in another subject (fig. 2), the same dose had no discernable effect. In neither subject did 0.02 mg./kg. neostigmine with 0.4 mg. atropine influence the intensity or duration of the

Imbretil induced neuromuscular block. In a third subject (fig. 3) who received 0.025 mg./kg. Imbretil, 0.02 mg./kg. neostigmine with 0.4 mg. atropine prolonged the Imbretil induced depression of tidal volume. Similarly, in a fourth subject (fig. 4), the administration of 0.3 mg./kg. edrophonium 7 minutes after 0.02 mg./kg. Imbretil intensified the neuro-

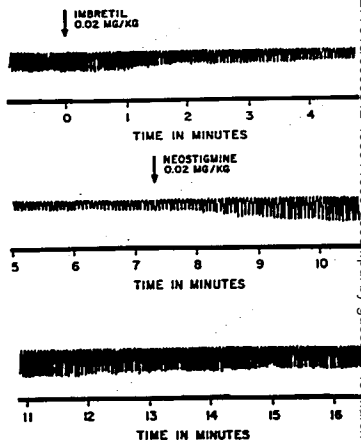


FIG. 1. The effects of 0.02 mg./kg. Imbretil followed by 0.02 mg./kg. neostigmine on tidal volume. Note the absence of the antagonistic effect of neostigmine.

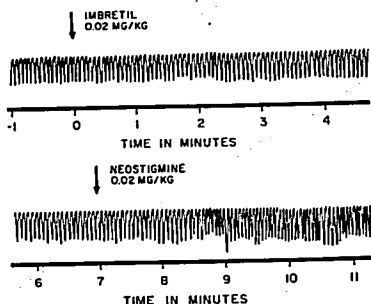


FIG. 2. Experimental circumstances as in figure 1. Note the absence of any discernable effect of Imbretil or neostigmine.

muscular block. In yet another subject whose respiratory tracing is not presented, the same dose of edrophonium after 0.02 mg./kg. Imbretil caused apnea of 4 minutes duration. It is evident from figures 1, 2, 3 and 4 that development of the maximal effect of small doses of Imbretil requires 5 to 7 minutes.

Figure 5 indicates that 0.3 mg./kg. edrophonium at the start of spontaneous respiration following apnea caused by 0.05 mg./kg. Imbretil had no marked antagonistic effect on the paralysis of respiratory muscles.

Imbretil, in the dose range used in these studies, had no significant effect on pulse rate or blood pressure. Similarly no clinical manifestations of histamine release could be observed.

Clinical Observations. In the 5 patients who received 0.05 mg./kg. Imbretil after induction of anesthesia, apnea developed in 1.7 to 2.5 minutes. The tracheas of all were intubated within 1 minute after the development of apnea. The relaxation of the jaw was adequate in 4, poor in 1 patient. In 4 of the 5 patients, the vocal cords reacted to tactile stimulation and despite the use of topical anesthesia, 3 of the patients coughed after intubation. In none of the 5 patients were the conditions for tracheal intubation as favorable as those commonly seen after intravenous succinylcholine. The duration of adequate surgical relaxation varied from 23 to 30 minutes, and it outlasted apnea by only 1 to 3 minutes.

Increments of 0.015 to 0.025 mg./kg. doses of Imbretil were needed 9 to 40 minutes apart to maintain satisfactory relaxation of the abdominal muscles. In 2 of the 5 patients, the surgeons, accustomed to relaxation from succinylcholine, complained of tightness of the abdominal muscles at times when the patients were apneic. The time between the administration of the last dose of Imbretil and the return of tidal volume to control values varied from 26 to 125 minutes. In one patient weighing 54 kg., who received 8 mg. Imbretil for an ileocolostomy lasting 130 minutes, spontaneous respiratory effort returned 16 minutes after the last dose of Imbretil but the patient required assisted respiration for 90 minutes after termination of surgery. The repeated administration of 0.3 mg./kg. edrophonium failed to antagonize the residual neuromuscular block and only after the administration of 40 mEq. of potassium chloride in 1,000 ml. of 5 percent dextrose in water did respiration become satisfactory.

The tracheas of other patients were intubated following the intravenous administration of 0.6 mg./kg. succinylcholine chloride. At the return of spontaneous respiration, they

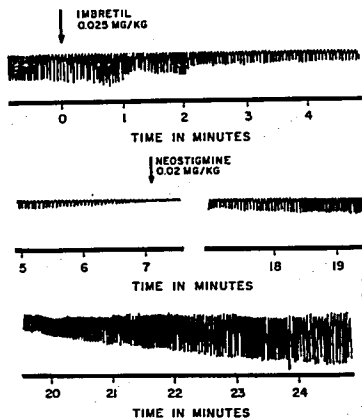


FIG. 3. The effects of 0.025 mg./kg. Imbretil followed by 0.02 mg./kg. neostigmine on tidal volume. Note the prolongation of the depressant effect of Imbretil by neostigmine.

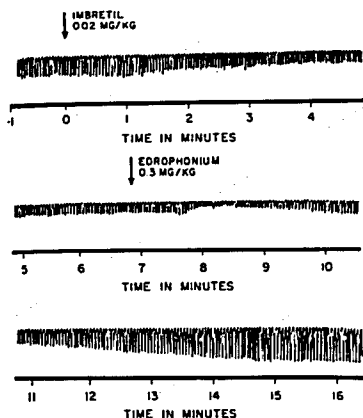


FIG. 4. The effects of 0.02 mg./kg. Imbretil followed by 0.30 mg./kg. edrophonium on tidal volume. Note the intensification of the effect of Imbretil by edrophonium.

received 0.03 mg./kg. Imbretil which caused apnea in 7 of 9 cases. In the 2 patients in whom apnea did not develop, a second 0.015 mg./kg. dose was necessary for adequate surgical relaxation. These two patients needed a third 0.015 mg./kg. dose of Imbretil at 6 and 11 minutes, respectively, to maintain relaxation. The other 7 patients required fractional doses of 0.015 mg./kg. 12 to 46 minutes apart. With one exception, where adequate relaxation was present for 36 minutes after termination of apnea, the relaxation only lasted 1 to 8 minutes after the return of spontaneous respiration. The time between the last dose of Imbretil and the return of tidal volumes to control values varied from 20 to 74 minutes. In the patient in whom 74 minutes were required for the return of the tidal volume to control value, the breathing was so labored that it had to be assisted for an additional 25 minutes. In another patient weighing 64 kg., who received 6.4 mg. Imbretil for an exploratory laparotomy lasting 70 minutes, the tidal volume reached control value 25 minutes after the last dose of Imbretil; a few minutes later respiration became gasping and depressed. Spontaneous respirations only became adequate after the

intravenous administration of 40 mEq. of potassium chloride in 1,000 ml. of 5 per cent dextrose. Neither 0.3 mg./kg. edrophonium or 0.02 mg./kg. neostigmine with 0.4 mg. atropine seemed to be beneficial in any case of prolonged postoperative respiratory depression observed after Imbretil.

DISCUSSION

For the objective evaluation of the usefulness of a neuromuscular blocking agent, several aspects of its activity have to be considered, and compared with those of other relaxants already in use. The properties to be evaluated include: rapidity of onset; presence or absence of initial stimulation; dose response; stability of the characteristics of the block; cumulation or tachyphylaxis on repeated administration; rate and completeness of recovery; reversibility; relative effect on respiratory and other muscles; suitability for use for endotracheal intubation; the effect of commonly encountered factors on its activity; compatibility with other drugs used in anesthesiology; and side effects and safety.

The onset of action of Imbretil is relatively slow both in animals and in man and is influenced by the dose. In cats and dogs after intravenous doses which caused 60 to 70 per cent depression of the gastrocnemius twitch, maximum effect developed in 6 to 8 minutes, and after fully paralyzing doses in 4 to 6 min-

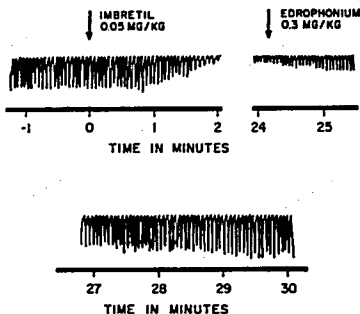


FIG. 5. The effects of 0.05 mg./kg. Imbretil followed by 0.30 mg./kg. edrophonium administered at the start of spontaneous respiration. Note the absence of the antagonistic effect of edrophonium.

utes.¹⁰ In the present study, maximal effect developed after 0.02, 0.03 and 0.05 mg./kg. doses in 5 to 7, 4 to 6 and 2 to 3 minutes, respectively.

Imbretil, similarly to other depolarizing neuromuscular blocking agents, produces contracture in avians and amphibians⁹ and in subparalytic doses, potentiates the twitch response of the gastrocnemius in cats and dogs.¹⁰ Despite this no signs of initial stimulation were observed after the slow intravenous injection of Imbretil in the present study.

On a mg./kg. basis, Imbretil is more potent than decamethonium in dogs.¹⁰ In cat and also in man, Imbretil and decamethonium have the same order of potency. According to Reis,⁴ its effect in man is less variable than that of succinylcholine. In contrast to this, we found that 0.02 mg./kg. Imbretil which causes 50 to 70 per cent decrease in tidal volume in some patients had no effect in others (figs. 1 and 2). The 0.03 mg./kg. dose caused apnea in half of the subjects and 36 to 94 per cent depression of tidal volume in the other half. The 0.05 mg./kg. dose caused apnea, with 3 exceptions, in 33 subjects studied. The species variation in the effects of depolarizing relaxants is well known.¹⁷ In a recent study¹⁸ unanesthetized human subjects showed greater individual variation to the neuromuscular effects of depolarizing than to those of nondepolarizing relaxants. Following the intravenous administration of a single 0.03 or 0.05 mg./kg. dose of Imbretil, the duration of respiratory depression was fairly uniform and averaged 20 and 30 minutes, respectively. When, however, more than one dose of Imbretil was administered for the maintenance of surgical relaxation, the time necessary for the return of tidal volume to control values was variable.

Like other depolarizing neuromuscular blocking agents,^{12, 14} Imbretil produces a biphasic block in rats and dogs⁹ and also in man.⁵ In man the duration of exposure necessary to produce the change from a depolarization block to a nondepolarization block, reversible by neostigmine or edrophonium, is variable and is not complete in every individual. In the course of transition from depolarization to nondepolarization block, tachyphylaxis to the effects of Imbretil may develop. This explains

why in some subjects the repeated administration of Imbretil causes tachyphylaxis while in others there is a cumulative effect.

After repeated administration of Imbretil especially if the total dose exceed 0.1 mg./kg. prolonged apnea may develop.⁴ In cats and dogs, cumulative effect develops if the doses of Imbretil are placed close and tachyphylaxis can be seen if they are given further apart.¹⁴ In our limited clinical experience, we encountered tachyphylaxis in two patients who received a single dose of succinylcholine for tracheal intubation and signs of accumulation in others.

After a single 0.02 to 0.05 mg./kg. dose of Imbretil, recovery is fairly uniform and predictable. Following 0.05 mg./kg. Imbretil the time from the end of apnea to the return of tidal volume to control value is a little less than half of the duration of apnea. Reis⁴ who used somewhat larger doses found that the recovery time from the end of apnea was about the same as the duration of apnea. The recovery time after repeated doses of Imbretil, however, was unreliable and the return of tidal volumes to control values after the last fractional dose of Imbretil required 20 to 125 minutes. Respiration in 5 of 14 patients had to be assisted for variable lengths of time post-operatively. In one patient whose tidal volume was adequate at the termination of surgery, "recurarization" occurred which lasted over 120 minutes and seemed to be terminated only after the intravenous infusion of potassium chloride. The seemingly beneficial effects of potassium chloride, also seen with other relaxants,^{19, 20} are in line with the finding that Imbretil liberates potassium from the skeletal muscles of the cat and other mammals.²

Most reports indicate that neostigmine is capable of antagonizing the neuromuscular effects of Imbretil in several mammalian species¹ and also in man.^{5, 6, 7} In contrast to this, it was found by other workers¹⁶ that in cats and dogs, 0.1 to 0.3 mg./kg. neostigmine administered at the start of recovery of the Imbretil induced block of the sciatic-gastrocnemius preparation did not antagonize the induced block and intensified the respiratory depression. One half to 1.0 mg./kg. doses of neostigmine not only produced apnea, but also caused a three-fold increase in the duration

of neuromuscular block in the sciatic-gastrocnemius preparation. One-half to 1.5 mg./kg. edrophonium antagonized the Imbretil induced neuromuscular block for a short period, but higher doses caused potentiation. In the present study, the administration of 0.02 mg./kg. neostigmine or 0.30 mg./kg. edrophonium at the height of the neuromuscular block induced by 0.02 to 0.025 mg./kg. Imbretil, in some cases, intensified and prolonged (figs. 3 and 4) while in others (figs. 1 and 2) had no discernible effect on the tidal volume of anesthetized subjects. As already discussed, the moderate antagonism of 0.3 mg./kg. edrophonium given 7 minutes after 0.03 mg./kg. Imbretil on the tidal volume of anesthetized subjects (table 2) might be coincidental or due to a direct effect of edrophonium on the endplate.²¹ Neostigmine in 0.02 mg./kg. doses had no effect under these circumstances (table 2). The same doses of neostigmine and edrophonium given at the start of recovery after 0.05 mg./kg. Imbretil had a moderate, but definite antagonistic effect and reduced the average duration of respiratory depression (table 3). It is evident from figure 5, however, that this antagonism is not universal. This was borne out by the observations made on patients in whom surgical relaxation was maintained by repeated doses of Imbretil. In the 5 of 14 patients in whom postoperative depression of tidal volume was present, neither edrophonium or neostigmine had an antagonistic effect. It is difficult to correlate the uniform effectiveness of neostigmine against Imbretil induced respiratory depression reported by others^{5,6,7} with our findings. Even if one considers that higher or repeated doses of neostigmine were used by some^{5,6} than those considered safe²² and used in the present study, it would have to be assumed from the uniform effectiveness of neostigmine that the Imbretil induced neuromuscular block undergoes a consistent and complete change from depolarization to nondepolarization block in human subjects. Should this be the case, it would mean that the characteristics of the Imbretil induced neuromuscular block differ from those produced by decamethonium or succinylcholine. The results of pharmacological studies in other mammals^{8,16} and the findings in man in this study

indicate that there is no justification for this assumption.

Reis⁴ reported that Imbretil had a sparing effect on respiration and adequate muscular relaxation could be maintained with it while the patients maintained spontaneous respiration. This sparing effect on respiratory musculature was not experienced in the study. In only one of the 14 patients, was it feasible to maintain satisfactory relaxation without apnea and in two patients the surgeons complained of inadequate relaxation despite the presence of apnea. Since all of our patients were anesthetized with thiopental, nitrous oxide-oxygen and alphaprodine, it is conceivable that the discrepancy between our findings and those of Reis⁴ might be due to the different general anesthetics employed.

Because of its relatively slow onset of activity, the occasionally incomplete relaxation of the jaw muscles and coughing after tracheal intubation, Imbretil is not the agent of choice for tracheal intubation. Reis⁴ stated that the dose of Imbretil necessary for good tracheal intubation is 0.06 mg./kg. which may cause apnea lasting 30 to 45 minutes. She suggested the use of 40 to 60 mg. succinylcholine for tracheal intubation and then maintenance of relaxation by Imbretil.

The prior administration of ganglionic blocking agents double and hypothermia causes 3 to 4 fold increase in the duration of the Imbretil induced neuromuscular block.⁴ It seems that the administration of single 0.6 mg./kg. dose of succinylcholine may also intensify and prolong the neuromuscular effects of Imbretil. However, on occasion, the prior administration of a single dose of succinylcholine may increase the sensitivity to nondepolarizing and decrease it to depolarizing relaxants.

Similarly to other depolarizing relaxants, the neuromuscular effects of Imbretil are not potentiated by commonly used general anesthetic agents.

No prolonged apnea or other difficulty was encountered in this study when a single apneic dose of Imbretil was administered intravenously to anesthetized human subjects. On the other hand, when repeated doses of Imbretil were used for the maintenance of surgical relaxation, prolonged postoperative respiratory

depression was encountered in 5 of 14 patients. Reis⁴ encountered apnea of 5 hours duration under similar circumstances. It seems that Imbretil used alone is not a suitable agent for the maintenance of muscular relaxation for prolonged surgical procedures. As suggested by Reis⁴ and Bergman,⁷ succinylcholine should be used for tracheal intubation, Imbretil either in a single dose adjusted to the patient and the expected duration of surgery⁴ or in fractional doses⁷ for maintenance, and succinylcholine again for peritoneal closure.

SUMMARY

Imbretil in a single 0.03 or 0.05 mg./kg. dose has been administered intravenously to two groups of 30 anesthetized human subjects. Ten patients in the 0.03 mg./kg. group received, 7 minutes after Imbretil, 0.02 mg./kg. neostigmine and 0.4 mg. atropine and 10 other 0.30 mg./kg. edrophonium. In the 0.05 mg./kg. group, 10 patients each received the same dose of neostigmine or edrophonium at the start of spontaneous breathing.

When administered 7 minutes after Imbretil, neostigmine had no, and edrophonium questionable, antagonistic effect. When administered at the start of recovery from the effects of Imbretil, both neostigmine and edrophonium showed a moderate antagonistic effect. This antagonism, however, was not consistent.

Respiratory tracings made after the intravenous administration of subparalytic (0.02 to 0.025 mg./kg.) doses of Imbretil revealed that edrophonium and neostigmine, instead of antagonizing, may also intensify and prolong the neuromuscular block.

In 14 patients anesthetized with thiopental, nitrous oxide-oxygen, alphaprodine muscular relaxation was maintained with fractional doses of Imbretil. Postoperative apnea or respiratory depression was encountered in 5 of these patients. The respiratory depression could not be antagonized with the above doses of neostigmine or edrophonium.

Imbretil had no effect on pulse rate or blood pressure and there was no evidence of histamine release after its use.

Except for a somewhat slower onset and more prolonged duration of action, Imbretil induced neuromuscular block is similar to that produced by decamethonium.

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STERIOD THERAPY There are three situations in which steroid therapy is indicated:

(1) In acute severe injury or illness in which adrenal insufficiency is suspected because of a significant fall in blood pressure not explained by blood loss or coronary disease. (2) In patients who have been receiving steroid medication for arthritis or colitis for weeks or months. (3) In the chronically ill, malnourished patient who has no desire for food. Contraindications to the routine use of steroid therapy for surgical patients include tuberculosis, malignant hypertension, uremia, psychoses, and the presence of active ulceration in the gastro-intestinal tract. As a rule, these problems are not encountered during short-term administration of the steroids, but become manifest when large doses are administered for periods exceeding seven days. (Schncewind, J. H., and Cole, W. H.: *Steroid Therapy in Surgical Patients*, J. A. M. A. 170: 1411 (July 18) 1959.)

RADIOPAQUE MEDIA Contrast media were injected through a carotid catheter positioned near the coronary ostia of dogs. Minor

and fleeting electrocardiographic changes were noted, the dominant one being depression of the T wave. More prolonged affects were hypotension and bradycardia. (Moe, R. A., and Craver, B. N.: *Evaluation of Physiological Responses to Intra-Arterial Administrations of Various Contrast Media*, *Ann. New York Acad. Sc.* 78: 894 (July 2) 1959.)

FOCAL SEIZURES The use of general anesthesia in patients too young to cooperate for cortical excision for focal seizures has presented a problem previously, since anesthesia would distort the electrocortigram. The suggested technique is to use a small amount of thiarnylal followed by succinylcholine 0.2 per cent, intubation and vigorous ventilation, thus achieving lower carbon dioxide tension. This allowed the use of electroencephalogram without introducing changes from anesthesia. There is no hazard from the occurrence of convulsions during the anesthetic since ventilation could continue even during the convulsions. (Rumble, L., Jr., and Wickers, D. S.: *Anesthesia for Cortical Excision and Focal Seizures*, *South. M. J.* 52: 832 (July) 1959.)