THE CLINICAL USE OF IMBRETIL*

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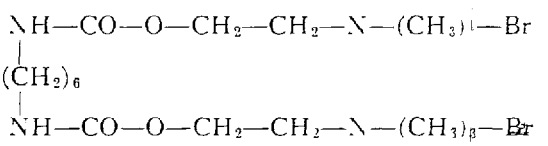
HEXAMETHYLENE-1,6-BIS-CARBAMINOYLCHOLINE BROMIDE (Imbretil) is one of a number of polymethylene-bis-carbaminoylcholine compounds first studied pharmacologically by Cheymol and co-workers[1–3] and independently by Klupp and associates.[4,5] It is a long-acting muscle-relaxant drug that has been used extensively in Europe[6–12] in surgical anaesthesia, but has had considerably less clinical usage on this side of the ocean.[13–15] The present report is based on clinical observations made in patients in whom Imbretil has been employed as the chief muscle-relaxant drug during surgical anaesthesia.

CHEMISTRY AND PHARMACOLOGY

Imbretil is a white, slightly hydroscopic, crystalline powder with the following chemical formula:



The molecular weight is 536.34. The substance is soluble in water and alcohol, but is almost insoluble in ether, chloroform, and benzene. The aqueous solution has a pH of 7.45.

There is no precise agreement concerning the mode of action of Imbretil at the myoneural junction. Several workers have described the mechanism as similar to the "dual block" described by Zaimis for decamethonium.[16] Certainly there is an initial depolarizing phase, and all workers agree to this; but whether a biphasic effect exists (i.e., initial depolarization block, followed by a non-depolarization block that can be antagonized by neostigmine) is less certain. Sabawala and Dillon, using their technique of isolated human intercostal muscle strip, demonstrated a definite two-phase action similar to other "dual block" muscle relaxants.[17] Bowmann and colleagues,[18] on the other hand, have shown that there is a difference in the type of block produced in different muscles of the same animal species. Imbretil produced a "depolarizing" type block in the tibialis anterior of the cat, but a "dual" type block, which could be antagonized by neostigmine, in the soleus muscle of that animal species. A pharmacological feature of great clinical importance is the fact that there is a very definite cumulative action at the myoneural junction with repeated doses of Imbretil.

Therapeutic doses of the drug do not appear to influence the cardiovascular

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system, cardiac activity, or blood pressure, although large doses (in the order of twenty to thirty times the muscle-relaxing dose) do cause slight and transient increases in blood pressure in laboratory animals.[4,6,8,11] Active contraction of the intestines occurs within 45 seconds following the administration of Imbretil in man, and persists for some 40 minutes thereafter. This obviously contributes significantly to the profound degree of abdominal relaxation noted clinically.[13] The intraocular tension in man is increased temporarily following the administration of Imbretil.[19] The drug appears to be excreted in the urine in an unaltered condition. Approximately 50 per cent of the drug is eliminated within two hours of a single intravenous injection in the dog, 75 per cent within six to eight hours, and excretion is almost complete at the end of forty-eight hours.[19]

Material and Methods

Imbretil has been employed clinically to produce muscular relaxation in 225 patients during general anaesthesia. The vast majority of these patients were undergoing abdominal hysterectomy, but the series also included some exploratory laparotomies, colectomies, gastrectomies, and cholecystectomies. In almost all instances, the physical condition and general health of the patients were excellent (physical status 1–2), and the nutrition and hydration were good. The patients ranged in age from 21 to 82 years, the average age being 41.8 years. In general, therefore, these were healthy middle-aged females undergoing uncomplicated, major pelvic surgery.

Premedication consisted of an oral barbiturate (secobarbital 100 mg. or pentobarbital 100 mg.) two hours preoperatively, and a narcotic (meperidine 100 mg. or morphine sulphate 10 mg.) and a Belladonna derivative (atropine sulphate 0.4 mg. or scopolamine hydrobromide 0.4 mg.) intramuscularly one hour prior to anaesthesia. Anaesthesia was induced with a hypnotic dose of $2\frac{1}{2}$ per cent thiopental (5–12 cc.) and generally maintained with cyclopropane administered by the closed circle, carbon dioxide absorption technique, although in some instances nitrous oxide–oxygen–Fluothane or nitrous oxide–oxygen–Fluether were employed for maintenance.

Imbretil was employed in two separate ways in this series. In the first group of 100 patients, Imbretil was the initial muscle-relaxant drug that was administered and provided the necessary relaxation for endotracheal intubation as well as for the intra-abdominal surgical manipulations. If the effects of the Imbretil waned prior to the completion of the operation and further muscle-relaxant drug was needed, small (10–20 mg.), intermittent doses of succinylcholine were employed for this purpose. In the second group of 125 patients, succinylcholine (generally in a dosage of 40 mg.) was employed first to facilitate endotracheal intubation, and then Imbretil was administered for abdominal relaxation after the resumption of normal spontaneous respirations following intubation. Again, if the effects of Imbretil waned prior to the completion of operation and further muscle-relaxant drug was needed, small (10–20 mg.), intermittent doses of succinylcholine were employed for this purpose.

The administration of Imbretil was followed by the onset of apnoea in all but one patient (*vide infra*), and controlled respirations were then immediately

instituted and maintained for the duration of the period of apnoea. Approximately half the patients were ventilated by hand, and the other half by the use of a mechanical ventilator. It is important to point out that in a number of instances actual hyperventilation was achieved, as measured by arterial blood gas analyses.

Results

The doses of Imbretil employed in this series were calculated on a weight basis, the fundamental dosage being 0.050 mg./kg. The doses ranged from 2.50 to 4.75 mg., the average dose being 3.2 mg. Apnoea occurred within 1–5 minutes following the administration of the drug, the average time of onset being 3 minutes and 16 seconds. The duration of apnoea following the administration of Imbretil ranged from 18 to 240 minutes, the average duration being 56 minutes and 48 seconds. No apnoea was produced with the dosage employed in one patient in this series. The duration of muscular relaxation, judged purely subjectively on the basis of the need for further administration of a muscle-relaxant drug in order to produce adequate conditions for the completion of the surgical procedure, ranged from 35 to 270 minutes, the average duration being 85 minutes and 18 seconds. These results are summarized in Table I.

TABLE I
Summary of Results

Dose (0.050 mg./kg.)	
Range	2.50–4.75 mg.
Average	3.2 mg.
Onset of apnoea	
Range	1–5 minutes
Average	3 minutes and 16 seconds
Duration of apnoea	
Range	18–240 minutes
Average	56 minutes and 48 seconds
Duration of muscular relaxation	
Range	32–270 minutes
Average	85 minutes and 18 seconds

In the group of 100 patients in whom Imbretil was the initial muscle-relaxant drug administered, fibrillary twitchings, generally involving the muscles of the head, neck, and arms, occurred in seven patients. Fibrillary twitchings were not seen following the administration of Imbretil in the other group of patients, who had first received succinylcholine to facilitate endotracheal intubation. The conditions for endotracheal intubation produced by Imbretil alone in this first group of 100 patients were graded and recorded, and are presented in Table II. It can be seen that relaxation of the jaw was considered excellent in 83 of 100 patients, abduction of the vocal cords was considered excellent in 82 patients, and reaction on the endotracheal tube (or "bucking") immediately following its insertion was totally absent in 81 patients. Lesser degrees of relaxation and abduction were present in the other patients, and slight to moderate "bucking" occurred immediately following intubation.

TABLE II
CONDITIONS FOR ENDOTRACHEAL INTUBATION
(100 patients)

Relaxation of jaw	
Excellent	83
Good	11
Fair	5
Poor	1
None	0
Abduction of vocal cords	
Excellent	82
Good	9
Fair	8
Poor	1
None	0
Reaction on endotracheal tube ("bucking")	
Absent	81
Slight	10
Moderate	9
Marked	0
Extreme	0

DISCUSSION

This series was undertaken specifically to evaluate the clinical utility of a single dose of Imbretil for the production of muscular relaxation during a standard surgical procedure. The cumulative effect of Imbretil is well established, and the unpredictability of even a small, second dose is such as to prohibit any technique based on repeated administrations. In one patient, during the preliminary clinical trial that preceded the present study, a second dose of only 1.0 mg. of Imbretil produced an apnoea of almost 3 hours' duration.

A single dose of Imbretil, however, employed in conjunction with controlled respirations, will provide excellent muscular relaxation for pelvic surgery of up to 1½–2 hours' duration. Imbretil itself can produce profound relaxation with contracted intestines and what has been called a "putty-like" abdomen[13]; but there is no doubt that in the present series two other factors of importance played a role. The first of these was the fact that the vast majority of the operations in this series consisted of abdominal hysterectomies, and there is little question that adequate muscular relaxation is considerably easier to provide for lower abdominal than for upper abdominal surgery. The second factor of importance was that many of these patients were intentionally hyperventilated to the point that the arterial pH was in the range 7.50–7.60 and the arterial pCO_2 was in the range 20–30 mm. Hg—this extent of hyperventilation will increase, of course, both the degree and the duration of muscular relaxation produced by a muscle-relaxant drug. Any conclusions, therefore, must be tempered to state that a single dose of Imbretil, supplemented when necessary with small doses of succinylcholine, will produce adequate—even superb—muscular relaxation during controlled respirations for lower abdominal surgery of up to 1½–2 hours' duration.

The anaesthetic regimen, which consists of the administration of a single dose of succinylcholine to facilitate endotracheal intubation, then a single dose of Imbretil for abdominal relaxation, and then further small doses of succinylcholine as necessary if the effects of the Imbretil are inadequate prior to the completion

of the operative procedure, is perhaps the most useful clinical technique in that it spares the duration of Imbretil activity for relaxation during actual operation. However, Imbretil was employed as the initial muscle-relaxant drug in the first 100 patients in this series in order to evaluate the conditions that the drug produced for endotracheal intubation, since there has been a tendency to regard Imbretil as an unsatisfactory drug for this purpose.[20] The results clearly indicate that this is not so if sufficient time (up to 5 minutes) is allowed to elapse for the production of apnoea and complete muscular relaxation. It is true, however, that the conditions for intubation produced by Imbretil are not as satisfactory as those produced by succinylcholine.[21]

Summary

The long-lasting muscle-relaxant hexamethylene-1,6-bis-carbaminoylcholine bromide (Imbretil) has been employed as the chief muscle-relaxant drug in 225 patients, most of whom were healthy, middle-aged females undergoing uncomplicated, major pelvic surgery. General anaesthesia usually was maintained with cyclopropane, and the dosage of Imbretil employed was 0.050 mg./kg.

The duration of apnoea following the administration of Imbretil averaged 56 minutes and 48 seconds, and the duration of clinically adequate muscular relaxation averaged 85 minutes and 18 seconds. When Imbretil was employed as the initial muscle-relaxant drug it produced very satisfactory conditions for endotracheal intubation. The most useful clinical technique, however, since it spared the duration of Imbretil activity for relaxation during actual operation, was the administration of a single dose of succinylcholine first to facilitate endotracheal intubation, then a single dose of Imbretil for abdominal relaxation, and then further small doses of succinylcholine as necessary if the effects of the Imbretil waned prior to the completion of the operative procedure.

Since Imbretil is a cumulative drug, repeated administrations should be avoided. However, a single dose of Imbretil, supplemented as necessary with small doses of succinylcholine, will produce adequate—even superb—relaxation during controlled respirations for lower abdominal surgery of up to $1\frac{1}{2}$–2 hours' duration.

Résumé

Nous avons employé le myorésolutif à action prolongée hexamethylene-1,6-bis-carbaminoylcholine bromure (Imbretil) comme principal curarisant chez 225 malades, la plupart en santé, des femmes d'âge moyen, soumises à de la chirurgie pelvienne, majeure, sans complications. Le maintien de l'anesthésie générale s'est fait d'habitude avec le cyclopropane et la quantité d'Imbretil donnée a été de 0.050 mg./kg.

La durée de l'apnée à la suite de l'administration d'Imbretil a été en moyenne, de 56 minutes et 48 secondes et la durée du relâchement musculaire clinique adéquat a été d'environ 85 minutes et 18 secondes. Lorsque nous avons employé l'Imbretil comme myorésolutif initial, il a produit des conditions très satisfaisantes pour l'intubation endotrachéale. Toutefois, la technique clinique la plus utile, puisqu'elle conserve les effets de l'Imbretil pour le relâchement durant le temps

principal de l'opération, a consisté en l'administration d'une seule dose de succinylcholine, d'abord pour faciliter l'intubation endotrachéale, ensuite une seule dose d'Imbretil pour le replâchement abdominal et alors plusieurs petites doses de succinylcholine selon qu'il est nécessaire si les effets de l'Imbretil disparaissent avant la fin de l'opération. Puisque l'Imbretil a des effets cumulatifs, il faut éviter les doses répétées. Cependant, une seule dose d'Imbretil complétée s'il le faut par de petites doses de succinylcholine, va produire un relâchement adéquat—même superbe—durant la respiration controlée, pour la chirurgie abdominale basse, durant $1\frac{1}{2}$ à 2 heures.

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