A CLINICAL STUDY OF THE MUSCLE RELAXANT–IMBRETIL

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Imbretil is a long acting muscle relaxant synthetized in Austria. It was first tested pharmacologically by Klupp *et al.*[1] in 1953 and clinically by Brücke and Reis[2, 3] in 1954. During the past four years it has been used in over four thousand surgical patients in Europe.[4–7] In this paper we shall describe our findings following administration of the drug to 573 anesthetized individuals.

Chemistry and Pharmacology

Imbretil is 1, 6-hexamethylene-bis-carbaminoylcholine-bromide.

$$NH \cdot CO \cdot O \cdot CH_2 \cdot CH_2 \cdot N \cdot (CH_3)_3 \cdot BR$$
$$\vdots$$
$$(CH_2)_6$$
$$\vdots$$
$$NH \cdot CO \cdot O \cdot CH_2 \cdot CH_2 \cdot N \cdot (CH_3)_3 \cdot BR$$

It is a white, slightly hydroscopic, crystalline powder, soluble in water and alcohol, and almost insoluble in ether, chloroform and benzene. The aqueous solution is clear, colorless and has a *p*H of 7.45. The micro melting point ranges from 172–176 C. The molecular weight is 536.34.

The mechanism of action of Imbretil has been described as that of a "dual block" similar to that described by Zaimis for decamethonium.[5–9] The initial phase, or depolarizing block is said to last a few minutes and is followed by a persistent paralysis of the curare type. Antagonism or reversal of the effects of Imbretil have been reported with neostigmine and other anticholinesterase drugs.

Quantities resulting in complete muscular relaxation do not show any nicotinic or muscarinic side effects.[8] Cardiac activity, blood pressure and intestinal function are said not to be influenced by therapeutic doses. Twenty to thirty times the muscle relaxing dose causes a slight and transient rise in blood pressure in animals.[1, 2, 3, 7] Tachyphylaxis does not occur with repeated injections but the drug action is cumulative. Imbretil is probably excreted in the urine in an unaltered condition. In dogs, approximately 50 per cent of the drug is eliminated within two hours after a single intravenous dose and 75 per cent within six to eight hours. After 48 hours, excretion is almost entirely completed.[10] The intraocular pressure in man is alleged to increase temporarily with Imbretil.[10]

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Material and Methods

During the past eight months Imbretil has been given to 573 anesthetized patients undergoing major surgical procedures at The Presbyterian Hospital, New York, and at The Hospital of the University of Pennsylvania. Three hundred and seventy-two were females. The age distribution (9–85 years), and physical status of the patients is shown in tables 1 and 2.

Preanesthetic medication consisted of secobarbital, meperidine or morphine and scopolamine or atropine in average therapeutic doses. Cyclopropane, following induction with thiopental, and thiopental, nitrous oxide, and oxygen were the main anesthetic agents (table 3). Imbretil was administered in single dose in 321 cases and by multiple injection in 252 cases. The total dose ranged from 0.5 to 9.0 mg. Data on dosage are summarized in table

TABLE 1

Age Range (9–85 years)

0– 9	1
10–19	18
20–29	44
30–39	103
40–49	151
50–59	130
60–69	86
70–79	37
80–89	3

TABLE 2

PHYSICAL STATUS *

One	307
Two	196
Three	45
Four	4
Five	1
Not recorded	20
	573

* 1 = Excellent, no systemic disease.
2 = Slight to moderate systemic disease.
3 = Moderate to severe systemic disease.
4 = Desperately ill.
5 = Moribund.

TABLE 3

ANESTHETIC AGENTS

Cyclopropane	105
Cyclopropane-thiopental-N_2O	202
Cyclopropane-thiopental and/or ether	59
Thipental-N_2O	119
Thiopental-N_2O-meperidine	40
Thiopental-N_2O-ether	26
Other combinations	22

TABLE 4

DOSAGE

Total Absolute Dose		Total Dose Mg./Kg.	
Mg.	No. Patients	Mg./Kg.	No. Patients
		0.00–0.019	19
1.0 or less	14	0.02–0.029	20
1.5	7	0.03–0.039	39
2–2.5	54	0.04–0.049	51
3–3.5	85	0.05–0.059	144
4–4.5	277	0.06–0.069	103
5–5.5	54	0.07–0.079	85
6–7	66	0.08–0.089	40
		0.09–0.099	23
8–9	16	0.10–0.109	14
		0.11–0.119	15
		0.12–0.159	14
			567*

* 6 patients not recorded because of lack of data on weight.

4. When Imbretil was used together with another muscle relaxant, succinylcholine was usually selected (table 5). The indications for the use of Imbretil were the production of muscular relaxation for tracheal intubation and surgical operation (table 6).

TABLE 5

COMBINATION WITH OTHER RELAXANTS

Imbretil only	248
Succinylcholine followed by Imbretil	158
Imbretil followed by Succinylcholine	92
Succinylcholine followed by Imbretil-Succinylcholine	72
Other Combinations	3

TABLE 6

SURGICAL OPERATIONS

Intra-abdominal	
Upper	178
Lower	219
Thoraco-abdominal	7
Intrathoracic	32
Others	137

RESULTS

Onset, duration and intensity of action. It was easiest to observe the onset of respiratory depression. This began within 40–60 seconds of an intravenous injection, and if the dose was sufficient, apnea occurred by 45–180 seconds. Abdominal relaxation appeared to develop within one to three minutes. These time relationships resemble those of decamethonium, and represent a longer onset than is seen after the intravenous administration of succinylcholine.

The duration of respiratory depression following initial, non-apneic, doses of Imbretil varied from 9–20 minutes. If apnea was produced, it persisted for 9–35 minutes. In addition to the action of Imbretil, depth of anesthesia and the degree of ventilation, to cite two of many factors, also have important influences on the duration of apnea. With controlled conditions if the end-tidal P_{CO_2} is kept constant in the normal range during controlled respiration, the duration of apnea following the administration of 0.032–0.083 mg./kg. of Imbretil was 14–33 minutes.[12] Abdominal relaxation appeared to continue for 45–90 minutes.

The degree of abdominal relaxation produced by Imbretil was profound. The drug produced a "putty-like" abdomen. The intestines appeared to be contracted. Imbretil was injected after the abdomen was opened in seven patients. Within 45 seconds the dilated intestines contracted and occupied less space. In these instances dilation returned about 40 minutes later. An additional 1 mg. dose of Imbretil was given and the intestines again contracted.

TABLE 7

RESPIRATORY DEPRESSION OR APNEA AT END OF OPERATION

	No. of Cases
Mild depression	5
Moderate depression	10
Severe depression	10
Apnea	4
	29 (of 573)

Jaw relaxation was inadequate for direct laryngoscopy in 15 of 291 cases, partially because laryngoscopy was attempted too early. The vocal cords were still moving in 32 and were closed in 10 patients. Coughing and bucking after tracheal intubation was noted in 23 patients.

Fasciculation. Fine muscular fasciculations involving mostly the neck and shoulder muscles were noted in 84 of 337 patients receiving Imbretil as the initial relaxant. These fibrillary tremors were of lesser degree and duration than those seen after succinylcholine.

Postoperative Respiratory Depression or Apnea. Twenty-nine of the 573 patients were apneic or clinically had an inadequate respiratory exchange at the end of operation (table 7). In 11 of these cases the total dose of Imbretil was 0.10 mg./kg. or greater. These relatively large doses represented either errors in judgment or efforts to determine dose-response curves. Two of the 29 patients had impaired renal function judged by elevated blood urea nitrogen values. One patient was "cachectic" and dehydrated. The duration of the postanesthetic respiratory depression ranged from 30 minutes to six hours.

Antagonists. In 25 of the 29 patients with apnea or hypopnea at the end of operation, one or more of various "antagonists" were administered intravenously and the respiratory tidal volume monitored with a spirometer or Dräger Volumeter (table 8).

Neostigmine methylsulfate and edrophonium hydrochloride, when given under these circumstances, affected respiration in an unpredictable manner. Antagonism was not observed consistently. An antagonist specific for decamethonium [12] was tried in one case and increased the depression of respiration. In the two cases where thiamine was found to be an effective antagonist, the tidal volume first became depressed for two to three minutes and then showed a steady increase to values deemed adequate for these patients. This secondary respiratory stimulant effect was not observed in all cases where thiamine was administered. In fact, it produced further respiratory depression in three patients.

Since tetraethylammonium chloride given intravenously in doses of 2 mg./kg. has been reported to antagonize the respiratory depression caused by *d*-tubocurarine,[13] the drug was tested against similar depression from Imbretil. Hypotension and tachycardia lasting for 5–15 minutes developed, but no improvement in ventilation could be shown.

A controlled study of this problem in which the depth of anesthesia and end tidal P_{CO_2} were kept constant, is reported in the following paper. This study showed that after a relatively short duration (25–35 minutes) of forearm muscle paralysis with 2–4 mg. of Imbretil, edrophonium and neostigmine ap-

TABLE 8

EFFECTS OF "ANTAGONISTS" ADMINISTERED INTRAVENOUSLY FOR TREATMENT OF APNEA OR HYPOVENTILATION.

Drug and Dose	Marked Improvement	Slight Improvement	No Improvement	Increased Respiratory Depression
Edrophonium Cl (5–90 mg.)	5	6	4	—
Neostigmine methylsulfate (0.5–2.5 mg.)	7	10	3	—
B.W. Drug No. 49-204 (2 mg./kg.)	—	—	—	1
Thiamine Cl (5.5-12.5 mg./kg.)	2*	1	1	3

(Number of injections exceeds number of cases because of repeated injections.)

* Tidal volume first became depressed for two to three minutes and then showed steady increase to values deemed adequate for these patients.

parently did not influence the rate of recovery of these muscles. However, neostigmine appeared to antagonize the larger doses of Imbretil only when the duration of paralysis was prolonged (more than 1 hour). B.W. Drug No. 49–204 [12] potentiated the Imbretil in 2 trials. Thiamine Cl in doses of 5–10 mg./kg. body weight caused definite acceleration of recovery in 5 instances but in 2 patients thiamine caused a transient reparalysis.

It is possible that with larger or multiple doses of Imbretil and longer duration of paralysis the nature of the neuromuscular blockade or the sensitivity of the end-plate region to acetylcholine may be altered so that an anticholinesterase can become effective in overcoming the neuromuscular block. Further study in this area is necessary. Furthermore, since thiamine in large doses may produce neuromuscular blockade in a manner similar to that of *d*-tubocurarine,[13] the circumstances under which thiamine may antagonize or potentiate Imbretil need definition.

The possibility that edrophonium, neostigmine or atropine caused respiratory stimulation through direct actions, rather than via antagonism of the neuromyal junction block produced by Imbretil was investigated. In nine anesthetized patients who had received no muscle relaxant, the intravenous administration of therapeutic doses of these drugs individually produced no increase in respiratory rate or tidal volume.

Cumulation. Repeated injection of Imbretil was followed by an increasingly prolonged action of successive doses. Repeated doses appeared to be approximately four times as effective as the initial dose.

Circulation. Hypertension occurred in 16 patients 45–60 seconds after administration of the drug and lasted three to five minutes. The usual increase in systolic pressure was 20–30 mm. of mercury; however, there was a 40–80 mm. of mercury rise in four cases. In three patients (one debilitated) there was a marked hypotension. In one case the systolic blood pressure decreased 40 mm. and in the other 70 mm. of mercury. Both of these patients responded immediately to ephedrine (25 mg. intravenously and 25 mg. intramuscularly).

TABLE 9

INTRACUTANEOUS TEST FOR HISTAMINE LIBERATION

Subject	*d*-Tubocurarine 0.05 ml.		Imbretil 0.05 ml.		Saline 0.05 ml.	
	Wheal	Flare	Wheal	Flare	Wheal	Flare
D	1 cm.	3 cm.	0.5 cm.	None	—	—
J	1 cm.	3 cm.	1 cm.	None	None	None
O	0.7 cm.	3 cm.	0.7 cm.	None	0.4 cm.	1.7 cm.
G	2 cm.	3 cm.	1 cm.	None	None	None
F	0.3 cm.	1 cm.	0.3 cm.	None	None	None

Synergism. Succinylcholine in doses of 20–30 mg. intravenously acted with greater intensity and two to four times longer when injected after Imbretil had been given. Single doses of succinylcholine produced muscular relaxation persisting for as long as 15–20 minutes under these circumstances.

There was also a suggestion of material reinforcement between Imbretil and ethyl ether or cyclopropane.

Pupillary Dilation. Pupillary dilation occurred within 60 seconds of injection in 13 of 46 patients in whom the pupil was observed.

Histamine Liberation. Intracutaneous injection in the volar surface of the forearm of five subjects was carried out with 0.05 ml. each of *d*-tubocurarine, Imbretil and saline. The solutions used were injected without dilution as taken from commercial ampules. Results shown in table 9 indicated that Imbretil liberated less histamine than *d*-tubocurarine. Bronchospasm was not recorded after the administration of Imbretil in any of the anesthetized patients.

Miscellaneous Observations. Hiccough or diaphragmatic flipping was present and annoying in 25 cases.

When the lightest levels of anesthesia were maintained various movements occurred, consisting of wrinkling of the forehead, movement of the head from side to side, slight elevation of the lower extremities, bucking on the endotracheal tube, and motion of the jaw. Curiously enough, these movements seemed to take place in the presence of adequate abdominal relaxation. Both the hiccoughs and the

muscular activity could be abolished by increasing the depth of anesthesia.

No deaths attributable to anesthesia occurred in this series, but it must be pointed out that the majority of patients were in good physical condition prior to operation.

Discussion

The ultimate place of Imbretil among the muscle relaxants is difficult to predict. Its greatest advantage is its ability to produce profound abdominal relaxation, almost equivalent to that obtained with spinal anesthesia. Its outstanding disadvantage is the lack of a reliable antagonist, and perhaps, as a consequence of this, the increased likelihood of inadequacy of respiration in the immediate postoperative period. An important aim therefore is a dosage regimen to avoid postoperative respiratory depression. A single dose of Imbretil of 0.04–0.055 mg./kg. (3–4 mg. for a 160 lb. patient) will provide conditions adequate for tracheal intubation during first plane surgical anesthesia, provided two to three minutes are allowed to elapse after intravenous injection. Since the total dose of Imbretil should rarely exceed 0.10–0.12 mg./kg. at least within a three hour period if postoperative respiratory depression is to be prevented, it is wise to use succinylcholine to assist with tracheal intubation in patients scheduled for prolonged procedures. This reduces the total amount of Imbretil required. To accomplish this succinylcholine (40–100 mg.) is administered after induction of anesthesia and three minutes of oxygenation. Imbretil (3–4 mg. as a rule, 5–6 mg. occasionally) is injected intravenously immediately prior to the need for muscular relaxation for the surgical procedure. For operations lasting approximately one hour 0.050–0.060 mg./kg. of Imbretil will be adequate. Usually 0.060–0.080 mg./kg. will provide adequate relaxation for one and one half to three hours of surgery; and 0.080–0.100 mg./kg., three hours or longer. As the operation nears completion, and if additional muscular relaxation is required, succinylcholine in small doses may again be preferable, particularly because of the prolonged and more intense action previously mentioned.

Imbretil may be compared to other relaxants of the depolarizing group. Its action is obviously slower in onset and much more prolonged in duration than that of succinylcholine. It seems to be a more reliable drug than decamethonium in that abdominal muscular relaxation is dependable, profound and prolonged. The tachyphylaxis attributed to decamethonium was not seen with Imbretil. Imbretil is therefore a muscle relaxant somewhat slow in onset of action, powerful in its effect and acts for a longer period than any of the depolarizing relaxants in common use.

European clinicians have indicated that neostigmine will reverse the respiratory depression caused by Imbretil. Two aspects of this relationship deserve comment. When neostigmine was injected intravenously after a single dose of Imbretil, we noted either further depression of respiration or no change at all. Under these circumstances antagonism was obviously lacking. If large or multiple doses of Imbretil had been given and 45–90 minutes or more had elapsed, both edrophonium and neostigmine appeared to stimulate breathing in about 80 per cent of the trials. This suggested the development of a curare-type blockade, but the antagonism was not sufficiently reliable to offer solace to the anesthesiologist relying on a chemical reversal. Tetraethylammonium proved completely ineffective as an antagonist. Results with thiamine chloride were difficult to interpret, some patients showing reversal, others becoming more paralyzed. B.W. Drug No. 49–204 apparently potentiated the action of Imbretil.

The results obtained with these drugs in man are different from those obtained in cats. In a peroneal nerve-tibialis muscle preparation in the cat the action of Imbretil was potentiated by edrophonium and neostigmine and antagonized by B.W. Drug No. 49–204.[11]

The possibility that the effects noted following the use of edrophonium, neostigmine or atropine were related not to reversal of a neuromyal junction blockade but to a direct action of these drugs proved unlikely, for no respiratory stimulation was observed when these substances were injected intravenously

to anesthetized subjects who had not received muscle relaxants.

We are of the opinion that the apparent effectiveness of edrophonium and neostigmine in some instances might be attributable to spontaneous recovery from Imbretil paralysis.

The chief problem with Imbretil in this series was the relatively high incidence of respiratory inadequacy seen at the conclusion of operation and persisting into the immediate postoperative period. This could be explained in part by early exploration of dose-response relations, for some patients were given large doses deliberately. Because of the tendency toward accumulation and because of the prolonged duration of action, it seems best to provide muscular relaxation toward the end of long operations with a deeper plane of anesthesia or with succinylcholine, acting as it does after Imbretil in a more intense and more prolonged fashion. Similarly, since total dosage was, not unexpectedly, related to the incidence of postoperative hypoventilation, there is merit in not using Imbretil to assist in tracheal intubation. This spares 2–4 mg. of the drug for the provision of relaxation during operation.

It is not yet possible to define those conditions under which Imbretil's action will be even further prolonged. If the major route of elimination is shown to be the kidney, impairment of renal function may cause increased intensity and duration of action of the drug. The possible synergy between diethyl ether, cyclopropane and Imbretil deserves study. Our data on this question are too fragmentary for opinion. The relation of Imbretil to relaxants other than succinylcholine has also not been explored by us.

The circulatory effects of Imbretil seem minimal. The histamine-liberating property of the drug appears of little importance. Its alleged ability to raise intraocular tension briefly is probably of little moment although measurements of this response should be made.

Summary

A clinical study in 573 patients of a new potent muscle relaxant, Imbretil, is presented.

The drug provided an excellent surgical field if muscular relaxation was required. Repeated doses were approximately four times as effective as the initial dose. Imbretil caused apnea or hypopnea in 29 of the 573 patients in the immediate postoperative period. Various antagonists were used in 25 of these patients with inconsistent and inconclusive results. Recommended dose schedules for the use of Imbretil are proposed.

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