'IMBRETIL' AS A RELAXANT IN ANAESTHESIA

J. W. MOSTERT, M.B., F.F.A.R.C.S., D.A.

Johannesburg Hospital and the University of the Witwatersrand

Discussion of a series of 108 cases, in which hexamethylene-1,6-bis-carbaminoylcholine bromide (hexabiscarbacholine, 'imbretil') was used as a curarizing agent in conjunction with all currently used anaesthetics, may prove of value to those who desire a more potent skeletal-muscle relaxant.

Imbretil contains a pair of secondary amino nitrogen atoms, with 16 atom interquaternary distance comprising six $-CH_2-$ groups. Hexafluorenium ('mylaxen') is another diquaternary skeletal muscle relaxant with six $-CH_2-$ radicals separating the ammonium ions, its full name being: hexamethylene-1,6-bis (9-fluorenyldimethylammonium) dibromide. Because the interquaternary distance has been related to the distance between the anionic sites on the receptor,[1] I examined the interaction of imbretil and hexafluorenium in the human being; they were found to be perfect antagonists.[2]

Hexafluorenium is a potent inhibitor of plasma cholinesterase, and it has been claimed that it prolongs suxamethonium-block as a result.[3] However, the antagonism between imbretil and hexafluorenium militates against such a mode of action of hexafluorenium. It has been decisively demonstrated that imbretil-blockade is characterized by an early depolarization phase at the neuromuscular junctions, and that this is only followed after approximately 3 - 25 minutes by a competition, tubocurarine-like block. The latter is more or less reversible with neostigmine, a drug which would, in striking contrast to hexafluorenium, potentiate the early depolarizing phase. After repeated doses of imbretil there is a very definite cumulative action at the neuromuscular junction, and this fact definitely accounts for the early American reports on imbretil[4-6] which cast some doubt on the constancy with which its reversibility by neostigmine could be guaranteed, as compared to that of tubocurarine. During these early trials the cardinal feature of imbretil paralysis was not sufficiently appreciated, namely, the hitherto unknown potency of imbretil. If imbretil is re-injected after the first dose appears to be wearing off, during clinical anaesthetic practice, where operations lasting more than 3 hours are

quite exceptional, then trouble is courted and encountered in almost every case, regardless of the dosage employed. The potency of imbretil is simply such that a second injection will inevitably lead to severe respiratory depression for some 3 to 4 hours, during most of which time the neuromuscular block will not be amenable to neostigmine therapy. If, however, the cardinal law is obeyed, according to which 0·05 mg./kg. or 2·5 - 4·75 mg. are injected only once, then it will be found that neostigmine

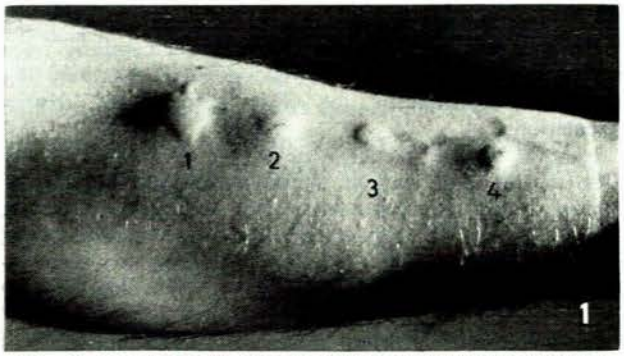

Fig. 1. Reactions 10 minutes after the intradermal injection of (1) tubocurarine (10 mg./ml.), (2) normal saline, (3) imbretil (2 mg./ml.), and (4) MY 301 (50 mg./ml.).
At the corresponding sites 0·2 ml. of the undiluted drugs were injected. Note the absence of histamine release by imbretil in striking contrast to tubocurarine.

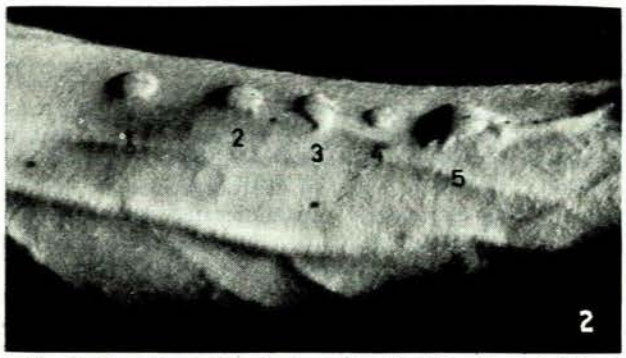

Fig. 2. Reactions 10 minutes after the intradermal injection of (1) gallamine (40 mg./ml.), (2) succinylcholine (50 mg./ml.), (3) hexafluorenium (20 mg./ml.), (4) toxiferine (0·5 mg./ml.), and (5) tubocurarine (10 mg./ml.).
The drugs were all undiluted and given intradermally in a dose of 0·2 ml. Note the histamine release after tubocurarine.

resistance is evanescent, not usually exceeding 5 - 15 minutes. The muscular relaxation lasts much longer, of course, and can be reinforced by either *small doses of suxamethonium* (10 - 20 mg.), or by larger doses of general anaesthetics such as halothane, diethyl ether, chloroform or thiopentone.

The absence of histamine release by imbretil and the marked histamine release by tubocurarine are illustrated in Figs. 1 and 2.

CLINICAL SERIES

In all the 108 patients, with the exception of those in whom caesarean section was performed (2 cases) and two infants under the age of 5, premedication was with pethidine and atropine in appropriate dosage, and perphenazine ('trilafon') in the patients who underwent cardiac surgery, or who were unduly apprehensive. Anaesthesia was induced with methohexitone ('brietal') in doses varying from 10 to 100 mg. The ages of the patients ranged from 3 months to 83 years. The following are the operations for which imbretil was used:

Operation	*No.*
Oesophagoscopy	3
Bronchoscopy	4
Tonsillectomy	4
Thyroidectomy	3
Orthopaedic (unclassified)	7
Anal and rectal operations	6
Inguinal herniorrhaphy	8
Hiatus herniorrhaphy	3
Laparotomy (appendicectomy, colostomy, hysterectomy)	24
Laparotomy (gastrectomy, cholecystectomy)	17
Mitral valvotomy	11
Surgery of the lungs	13
Caesarean section	2
Operations on the aorta and ductus arteriosus	3

ADMINISTRATION AND RESULTS

Imbretil was always preceded or followed, within 30 minutes, by hexafluorenium in a dose of 20 - 40 mg., intravenously, in all the patients under the first 7 categories above, that is, in all the 35 minor cases which lasted not longer than about 1 - 2 hours. In 14 of these the action of imbretil was completely blocked, and in the remaining 21 the administration of hexafluorenium restored the minute volume of respiration to normal levels of 5½ litres per minute or more in every case. This was frequently verified by using a Parkinson Cowan dry gas meter, a basal metabolism meter of the Sanborn variety, and a one-way Ruben valve (when the minute volume could be read from the rotameter dials as soon as the reservoir bag remained persistently about two-thirds full).

In all the major cases listed in the last 7 categories above, hexafluorenium was omitted, but in two instances neostigmine, 1½ mg., and atropine, 0·65 mg., failed to block the action of imbretil, and in 3 cases the same medication failed to restore spontaneous respiration after 3 - 5 minutes, (unlike the cases in which hexafluorenium was given). In 10 of these cases a second dose of imbretil (0·5 - 1 mg.) was injected after 40 - 55 minutes, when the initial dose of 4·0 - 4·5 mg. was beginning to wear off, as manifested by the return of spontaneous respirations. *Eight of these patients had marked respiratory depression at the end of the operation,* refractory to the administration of 3·5 - 5·0 mg. of neostigmine. In all the other cases neostigmine completely reversed any residual respiratory depression at the conclusion of the operations in a dose that never exceeded 1½ mg., with the exception of 2 patients who both received 50 - 100 mg. of suxamethonium for closure of the peritoneum. In 17 patients 10 - 20 mg. of suxamethonium ('lysthenon') were injected for peritoneal closure, and although the resulting apnoea lasted 10 - 15 minutes, there was no respiratory depression at the termination of the surgical procedure.

Side-effects. No deleterious side-effects were noted in any of these patients. One death occurred one week after a cholecystectomy during which there was an episode of hypotension lasting about 15 minutes. The latter had no connection with imbretil administration; it followed a relative overdose of the myanesin-like drug, guaiacol glycerol ether, 12 G., given to supplement the central action of imbretil; but the patient also had a haemorrhage postoperatively which required massive blood transfusion.

The bowels were of the same appearance and state of contraction, with active peristaltic movements in evidence, as is the case after a spinal subarachnoid or epidural block. During thoracotomy with a diathermy knife hardly any muscular twitching was discernible.

Of the 73 patients who underwent major surgery, 15 received only nitrous oxide 50% in oxygen by hyperventilation, without any supplement of the nitrous oxide anaesthesia. No difficulty at all was encountered clinically, and there were no instances of patients who remembered becoming aware of their surroundings during their operations, with one notable exception: The patient was a 18-year-old girl, about 7 months pregnant, who had a previous mitral valvotomy 8 years before. She received seconal, gr. 1½ (100 mg.), and methaminodiazepoxide ('librium'), 10 mg., the night before the repeat-valvotomy, and seconal, 100 mg., 2 hours before the operation. One hour before the induction of anaesthesia she had pethidine, 100 mg., perphenazine (trilafon) 5 mg., and atropine, 0·65 mg., intramuscularly. After methohexitone (brietal), 90 mg., she received 4·0 mg. of imbretil, and, after the usual 4-minute interval, she was intubated uneventfully. The only other anaesthetic agent she received during the first 30 minutes of anaesthesia, and 20 minutes of thoracotomy up to the opening of the pleura, was 50% nitrous oxide with which she was hyperventilated. After her operation she gave a detailed account of the appearance of an assistant at the operation whom she had never seen before, as well as the exact sequence of surgical events up to the opening of the pleura, a story she could not have made up. During this early phase of the operation the anaesthetist encountered difficulty in keeping the eyes of the patient closed, and when the pleura was opened some grimacing was apparent; from that time 0·5 - 1·0% halothane was added to the nitrous oxide mixture, and there was no further recollection.

Imbretil was very unwisely given to 2 women undergoing caesarean section. The infants were both depressed and cried only 12 and 17 minutes after delivery, respectively, with Apgar scores of 5 and 6.

The most striking overall result was the delayed recovery in consciousness. Very early during this trial it became apparent that the need for anaesthetics was much less than that to which one is accustomed when other muscle relaxants are employed. Its use in thoracic surgery was actually discontinued at the conclusion of this trial because the early awakening on the operating table, desirable in this category of surgical patients, was simply not possible in my hands when imbretil had been used for muscle relaxation. It was remarkable that even this central action appeared to be dispelled by the early administration of hexafluorenium.

DISCUSSION AND CONCLUSIONS

Imbretil is not only a most potent drug in the sense that it is very long-acting; it also exerts a unique central action. This action must not be interpreted as a central *anaesthetic* effect, because it does not protect the patient against awareness during the surgical procedure. On the other hand, imbretil allows an impressive saving in the amounts of general anaesthetics otherwise required. This clinical finding fits in well with the finding of a centrally respiratory depressant effect in cross-over experiments in dogs who received imbretil only *via* their isolated cerebral circulations.[7]

Imbretil should certainly never be given as a second dose in the same patient. It is entirely excreted by the kidneys in an unchanged form after 48 hours,[1] it accumulates at the neuromuscular endplates,[8] and it is so potent, in any case, as never to justify the administration a second time, unless the operation is of quite extraordinary length. Ideal operating conditions can invariably be preserved by means of relatively small doses of curaremimetics such as ether, halothane and chloroform, or drugs such as guaiacol glyceryl ether and suxamethonium in a diluted form, e.g. lysthenon (10 - 15 mg). In this way the relaxation can be rendered entirely flexible and therefore safe, because there is then very rarely any need at the conclusion of the operation for the administration of potentially harmful drugs such as neostigmine.

SUMMARY

My experience with imbretil (hexabiscarbacholine) as a skeletal-muscle relaxant in 108 patients suggests that its administration should never be repeated during the same operation, that it is relatively contraindicated in thoracic surgery and absolutely contraindicated in obstetrical practice, and that its action can be completely prevented and blocked early on by hexafluorenium, and afterwards, less predictably perhaps, by neostigmine. I have not found antidotes essential during the eminently satisfactory employment of imbretil in a single-dose technique, involving the use of very small doses of suxamethonium to render the muscle relaxation flexible.

The central action of imbretil is not an anaesthetic action, but it does allow an impressive sparing in the amounts of anaesthetic required. The slight but significant delayed recovery of consciousness which imbretil causes clinically is an outstanding feature of its action.

The hexabiscarbacholine (imbretil) used in this trial was kindly supplied by Continental Ethicals, and the hexafluorenium (mylaxen) by M.L. Laboratories, Johannesburg.

REFERENCES

1. Loewe, S. and Harvey, S. C. (1952): Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak., **214**, 214.
2. Mostert, J. W. (1963): Canad. Anaesth. Soc. J. (in press).
3. Foldes, F. F., Molloy, R. E., Zsigmond, E. K. and Zwartz, J. A. (1958): Fed. Proc., **17**, 367.
4. Foldes, F. F., Wolfson, B., Torres-Kay, M. and Monte, A. (1959): Anesthesiology, **20**, 767.
5. Dripps, R. D., Hanks, E. C., Ngai, S. H., Oech, S. R., Papper, E. M. and Sechzer, P. H. (1959): *Ibid.*, **20**, 646.
6. Ngai, S. H., Hanks, E. C., Fink, B. R., Holiday, D. A. and Papper, E. M. (1959): *Ibid.*, **20**, 653.
7. Hersey, L. W., Gowdrey, C. W. and Spoerel, W. E. (1961): Canad. Anaesth. Soc. J., **8**, 335.
8. Leong, W., Given, J. B. and Little, D. M. (1962): *Ibid.*, **9**, 312.