ON THE ACTION OF IMBRETIL ON ISOLATED HUMAN INTERCOSTAL MUSCLE

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THE CHOLINE ESTER, carbaminoylcholine, possesses muscle paralyzing properties of the two-phase "depolarization" type in a dose range similar to that of acetylcholine itself.[1] In such doses, however, it also possesses powerful parasympathomimetic effects.[2] In order to suppress these "muscarinic" properties, many synthetic derivatives of carbaminoylcholine have been prepared and studied by Cheymol *et al.*,[3] and by Klupp *et al.*[4]

The most promising of these derivatives appears to be hexamethylene-1,6-bis-carbaminoylcholine bromide (Imbretil) on which numerous clinical reports have been published (for references see Foldes and associates[5]). The pharmacology of this subject has been well reviewed by Brucke.[6] In clinical studies it has been shown to have a slightly slower onset, but more prolonged action than equipotent doses of decamethonium bromide (C-10).[5] The present work was undertaken to study the similarity in action between Imbretil and C-10 on isolated human muscle preparations, since C-10 had enjoyed a certain degree of popularity until it was largely replaced by the shorter acting succinylcholine.

METHODS

The pharmacologic use of the human intercostal muscle has previously been described in detail.[7] The preparation was suspended on a plastic holder in a bath containing modified Krebs' saline which was maintained at 37 C. and continuously gassed with 95 per cent O_2 and 5 per cent CO_2. Electrical stimuli were delivered to the muscle once every 10 seconds. Selective stimulation of the nerve fibers lying within the muscle tissue was achieved by pulses of very short duration (2.5 μsec). This indirect stimulation was alternated with pulses of longer duration (150 μsec) which stimulated the muscle directly. Resulting contractions were picked up by a Statham strain gauge and recorded on an ink-writing dynograph. In all records the smaller response is that evoked by indirect (nerve) stimulation.

Drugs were administered to the bathing saline at the times and in the amounts mentioned under "Results." Three experiments were performed using a completely closed chamber[8] to study the effect of a combination of ether and Imbretil, since in clinical studies it has been found that the action of depolarizing relaxants is not potentiated by general anesthetic agents in common use.[5]

RESULTS

A series of preliminary experiments were performed to arrive at the dose of Imbretil which would invariably produce a well-marked, two-phase neuromuscular block. This was done by administering different amounts of the drug to the saline solution bathing a number of preparations. Three records obtained from one such experiment are shown in figure 1. The optimum dose (15 μg Imbretil/50 ml. Krebs) determined from the above experiments (fig. 1*B*) is the same as that for C-10,[7] although in this concentration, C-10 produces more profound first-phase effects. Six experiments were then performed to elucidate the effect of neostigmine (Prostigmin) on the two-phase paralysis produced by an optimum dose of Imbretil. If neostigmine is administered early in the first phase, the result is a marked potentiation of this phase of paralysis (fig. 2*A*), but if administered long after the muscle has passed into a second phase paralysis, neostigmine possesses a marked antagonistic action (fig. 2*B*). These results are similar to those for other depolarizing relaxants,[7] and explain the clinical observation that neostigmine is an unreliable antagonist.[9]

Figure 3 shows records from two experi-

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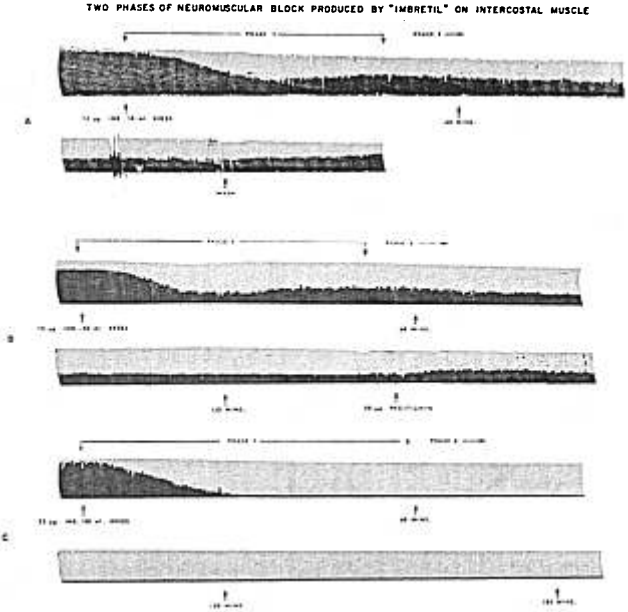

FIG. 1. Paralyzing action of Imbretil on isolated human intercostal muscle. All preparations from same patient. Concentration of Imbretil as follows: *A*. 0.24 μg./ml.; *B*. 0.3 μg./ml; *C*. 0.5 μg./ml. Well-marked, two-phase blocks in *A* and *B*, with good recovery between phases. Phase 1 slightly longer and more profound in *B* than in *A*. In *C* the dose of Imbretil is sufficiently high to suppress the recovery between phases, so that phase 1 block has passed imperceptibly into a phase 2 block.

ments performed at the same time on two specimens of intercostal muscle removed from the same patient. Each record has been shown as strips, approximately one hour long, so that a comparison can be made as the neuromuscular block passes from a first to a second phase paralysis. Figure 3A shows a typical two-phase paralysis obtained by the

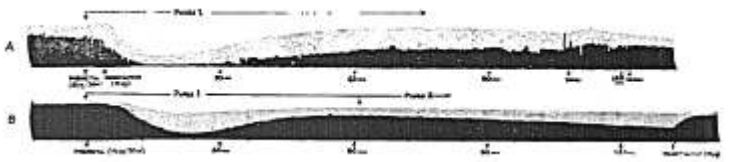

FIG. 2. *A*. Potentiation of first phase block by the addition of neostigmine early in first phase. Some antagonism to second phase block evident. *B*. Two-phase block produced by same dose Imbretil as in *A*. Note antagonistic action of neostigmine when administered late in the second phase. Dose of neostigmine same as in *A*.

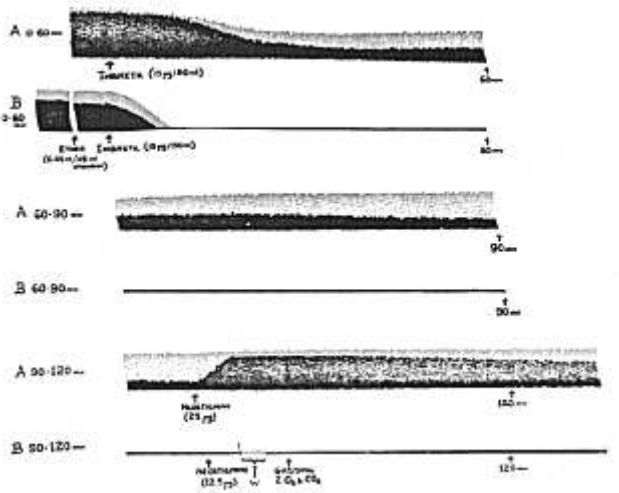

FIG. 3. Two-phase action of Imbretil to serve as control for figure 3B which shows the action of Imbretil in the presence of 6.25 per cent ether. Result suggests that ether potentiates both phases of a "depolarizing" neuromuscular block, or that first phase is extremely prolonged. Note good recovery with neostigmine added at about 100 minutes in A, but no recovery in B.

addition of 15 μg. Imbretil to 50 ml. of physiologic saline, the pattern of paralysis being similar to that shown in figures 1B and 2B. Figure 3B shows the record of a "closed-bath" experiment[8] showing the effect of administering Imbretil (same concentration as in fig. 1A) in the presence of 6.25 per cent ether vapor. This concentration of ether produces no neuromuscular block of its own. One hour was allowed for equilibrium to be established between the amount of ether vapor above the level of the physiologic saline and the amount in solution. If Imbretil is introduced to the muscle under these circumstances, a profound paralysis is the result. In the experiment recorded, both indirect and direct responses disappeared within ten minutes of the addition of Imbretil. This total block could not be reversed by neostigmine which was added 100 minutes later. The muscle recovered from the paralysis only after repeated washing and the resumption of gassing with O_2 and CO_2.

DISCUSSION

The present study shows that, like any other "depolarizing relaxant," a suitable dose of Imbretil always produces a two-phase paralysis in the isolated human intercostal muscle. Early studies[10, 11] using intact animals also described such a two-phase paralysis, perhaps because Imbretil possesses a slower but more prolonged action than C-10,[5] and as has been shown in this study, Imbretil produces lesser first phase (depolarization) effects, but greater second phase (curariform) effects than equal doses of C-10. The latter fact also explains the numerous reports indicating that neostigmine antagonizes an Imbretil paralysis.[10, 11] However, it has been shown in this study that if neostigmine is given too early, it will potentiate the neuromuscular block. This is also true for other depolarizing relaxants.[7] Since it is quite impossible to distinguish clinically a first-phase from a second-phase paralysis, the most

important factor controlling the response to neostigmine administered in the presence of a paralysis induced by a depolarizing relaxant is time. It is better to be patient and allow the effects of the relaxant to wear off than to rush the administration of neostigmine and end up with a profoundly paralyzed patient.[5, 9] In an effort to obtain the maximum advantage from Imbretil, elaborate dose schedules have been employed[5, 9, 12] and the long-acting Imbretil has been replaced by succinylcholine for procedures requiring maximum relaxation for short periods, such as endotracheal intubation and closure of the peritoneum.[12] If multiple doses of any depolarizer are administered, the response to each succeeding dose depends upon the intervals between them. Phase one effect is always less than if two (or more) doses are given together as a single large dose, while the ultimate phase-two block depends upon the total dose given and is quite independent of the number of doses or the intervals between them.[1] Therefore, if the anesthetist is looking for a depolarizing block in his patient, he would describe the action of Imbretil as being tachyphylactic,[5] forgetting that the end-result is always cumulative. It has been said that the muscle-paralyzing effect of Imbretil, like that of other depolarizing relaxants, is not potentiated by commonly used general anesthetic agents.[5] This clinical observation is not supported by our experimental findings on the isolated nerve muscle preparation, perhaps due to the fact that the concentration of drugs in our study remains unchanged over long periods of time. This condition cannot be duplicated in the intact animal or in the operating room.

Summary

A number of experiments are described to demonstrate the action of the muscle relaxant Imbretil on isolated human muscle. This drug is shown to possess a two-phase action similar to that of other "depolarizing" relaxants such as decamethonium and succinylcholine.

It has been shown that neostigmine antagonizes the second phase of this paralysis, but potentiates the first phase. Diethyl ether greatly accentuates the paralysis resulting from the addition of a suitable dose of Imbretil.

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