THE CHANGING PATTERN OF NEUROMUSCULAR BLOCK*

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THE MUSCLE RELAXANTS have now been in general clinical use for just over fifteen years and it is therefore worthwhile to pause for a moment and take stock of the present position. If a popularity poll were to be conducted for the favourite relaxant drug in the world today, the winner would almost certainly be either d-tubocurarine or succinyldicholine.

At first glance, succinyldicholine appears to possess all the necessary attributes of the "perfect muscle relaxant," since it is extremely short-acting, it produces profound relaxation, and recovery from it is complete. A closer look at this drug, however, reveals certain disadvantages, and it is with these that this paper is principally concerned.

MUSCLE PAINS

It is now well known that following the use of succinyldicholine pains may arise the next day in many muscles throughout the body. These pains occur whether the succinyldicholine is given by single or repeated injection, and even when an infusion technique is used. On some occasions these pains are extremely severe and incapacitating. There is no doubt that their occurrence is clearly related to the amount of movement the patient undertakes in the first few hours after receiving the drug (see Table I).

TABLE I

INCIDENCE OF MUSCLE PAINS

Resting (in bed)	12 per cent
Ambulant	66 per cent

From time to time various claims have been made for methods used to reduce the incidence of these muscle pains. For example, it has been suggested that the bromide salt is free from an incidence of muscle pains, or, alternatively, that a small intramuscular dose of neostigmine given after the succinyldicholine paralysis prevents the onset of these distressing *sequelae*. Foster (1960) has made a study of some of these claims and his results are summarized in Table II.

It will be seen that the only satisfactory method of reducing the incidence of these pains in clinical practice is to give a small dose of a non-depolarizing drug before the injection of the succinyldicholine: the greater this dose, the less likely are muscle pains to occur, but at the same time there is a much greater

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TABLE II

ATTEMPTS TO PREVENT MUSCLE PAINS

	Incidence
Succinyldicholine chloride v. bromide salt	no change
Neostigmine (1.0 mg. i.m. after S.C.)	no change
Gallamine (20 mg. before S.C.)	halved

risk of producing a prolonged response. Needless to say, such a practice of mixing relaxants cannot be recommended for routine clinical use.

EFFECT OF SUCCINYLDICHOLINE UPON THE HEART RATE

Another aspect of this drug that deserves brief mention is its effect upon the heart rate in man.

Martin of Heidelberg[8] first drew attention to the bradycardia, and even temporary cardiac arrest, that may follow the second and third injection of succinyldicholine, and Bullough[1] confirmed this finding.

Lupprian and Churchill-Davidson[7] have taken the matter one stage further and have attempted to analyse the changes and relate the incidence to the actual dose used. The main findings were as follows.

1. A slowing of the heart rate almost always occurs on subsequent doses of succinyldicholine.
2. In some cases, an actual arrhythmia may be observed and this may take almost any form.
3. Arrhythmias are related to the size of the dose administered and are very rarely seen when the dose is less than 50 mg. at a time.
4. These effects are probably due to vagal stimulation since they can be prevented by the previous intravenous injection of 1 mg. atropine.

INCIDENCE OF APNOEA DUE TO LOW PLASMA CHOLINESTERASE

The short action of succinyldicholine is owing to its being rapidly hydrolysed by the enzyme cholinesterase in the plasma. Occasionally a patient is encountered who either has a low titre of this enzyme or has inherited an abnormal form of this substance.

The incidence of this condition at our hospital over the past two years has been approximately one in every 2,000 cases to whom succinyldicholine has been administered. Although it is inconvenient when the apnoea is prolonged, such cases, if properly handled, should never give rise to alarm. The introduction of a new test paper from Austria has certainly simplified the measurement of plasma cholinesterase levels, and the anaesthetist can now use this method himself in the operating theatre to determine the enzyme level in a partieular patient. Once a sample of plasma or serum has been obtained, it takes no more than twenty minutes to determine whether the patient has a normal value of plasma

cholinesterase. Very much more complex techniques are required to detect the extremely rare case of an abnormal type of enzyme.

In a study based upon this colour-paper (Churchill-Davidson and Griffiths)[3] it has been found that the new method corresponds closely with the values found by the alternative and somewhat complex technique of Michel.[9]

Dual Block

Our main investigations in the field of the muscle relaxants have centred upon the possible occurrence of a dual type of neuromuscular block; that is to say, whether—after repeated doses of a depolarizing drug—the nature of the block gradually changes from that of depolarization to that of non-depolarization.

This subject has great clinical significance because a non-depolarizing block can be reversed by an anticholinesterase drug, whereas a depolarizing block is only made worse.

The results can best be illustrated by actual examples of the effect of the various relaxant drugs on neuromuscular transmission. In the cases that follow, the ulnar nerve is stimulated electrically and the resultant contraction of the hand muscles is recorded electromyographically.

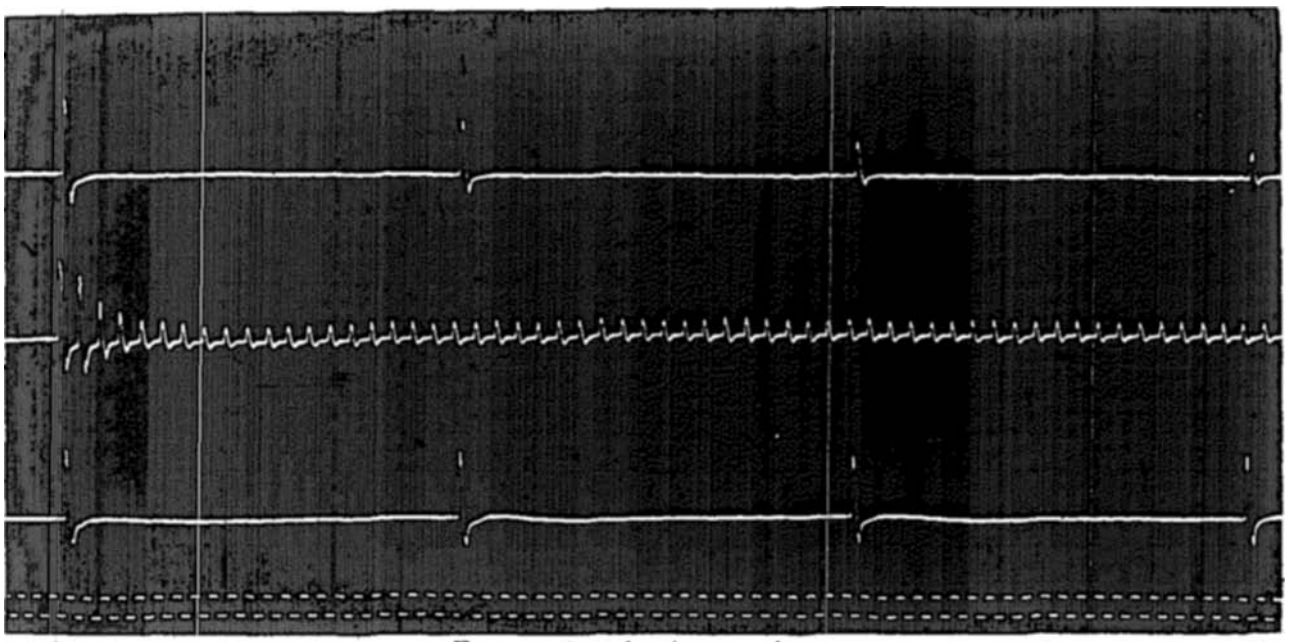

FIGURE 1. d-tubocurarine.

In Figure 1 note the characteristic way in which successive responses "fade" with both slow and fast rates of stimulation. Observe also the way in which neuromuscular transmission is briefly improved by a burst of fast or tetanic stimulation—the so-called post-tetanic facilitation.

These changes are diagnostic of a non-depolarizing block such as d-tubocurarine produces.

In direct contrast with the previous figure, Figure 2 indicates the way in which both slow and fast rates of stimulation are well maintained and the com-

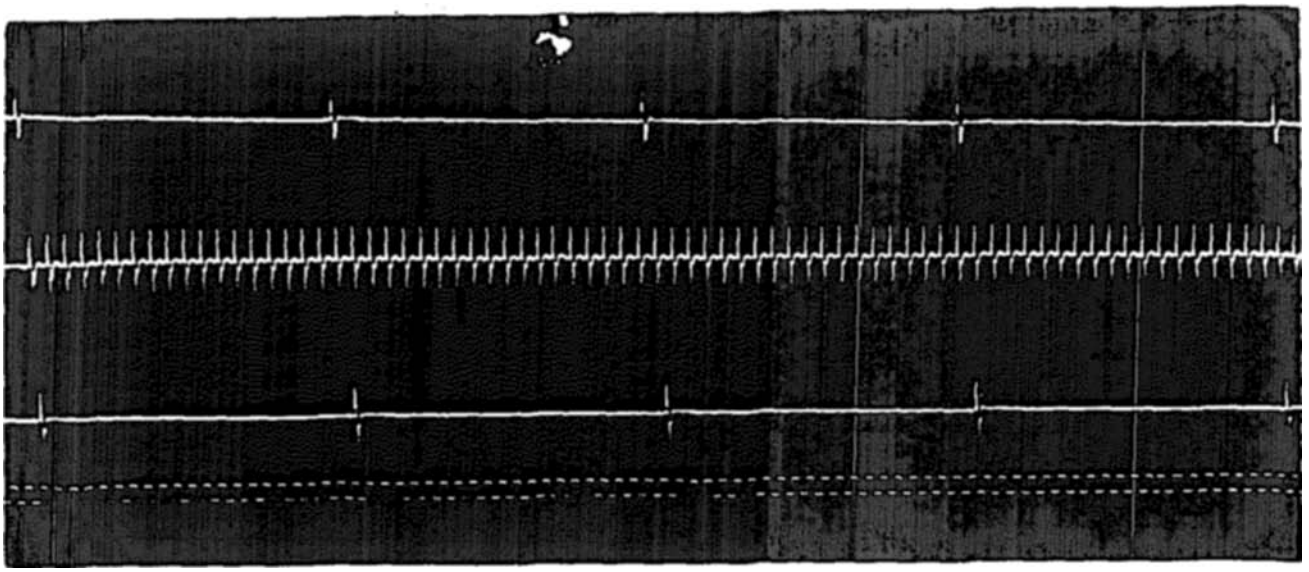

FIGURE 2. Effect after small dose of depolarizing drug, for example, succinyldicholine.

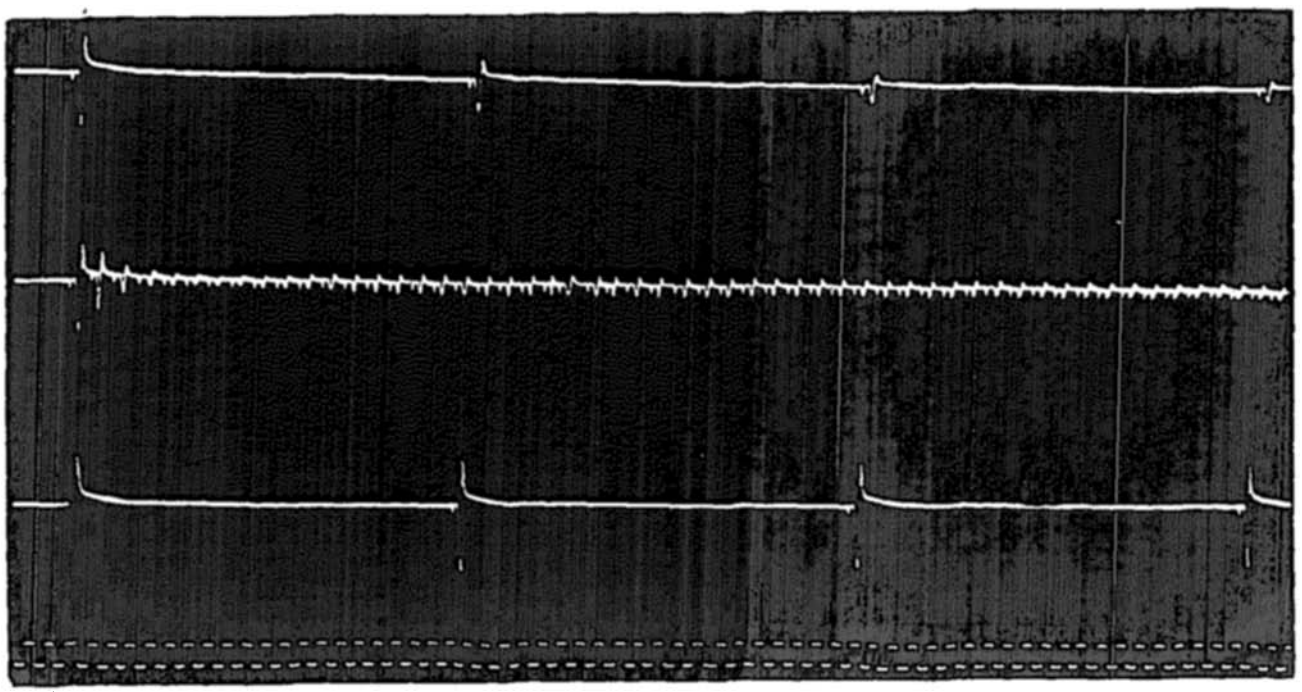

FIGURE 3. Effect of large dose of a depolarizing drug.

plete absence of post-tetanic facilitation. Exactly the same changes are seen after a small dose of decamethonium and for research purposes these changes are easier to study with this drug because it is not destroyed, as is succinyldicholine, by plasma cholinesterase.

Figure 3 illustrates the effect of a large total dose of a depolarizing drug, that is, in all 18 mg. decamethonium. Observe how repeated doses of the depolarizing drug have led to a gradual change in the pattern of the neuromuscular block until it finally closely resembles that seen after d-tubocurarine.

The effect of neostigmine upon the final pattern in Figure 3 is equally dramatic (Fig. 4), showing that a dual block had been produced which was reversed by neostigmine.

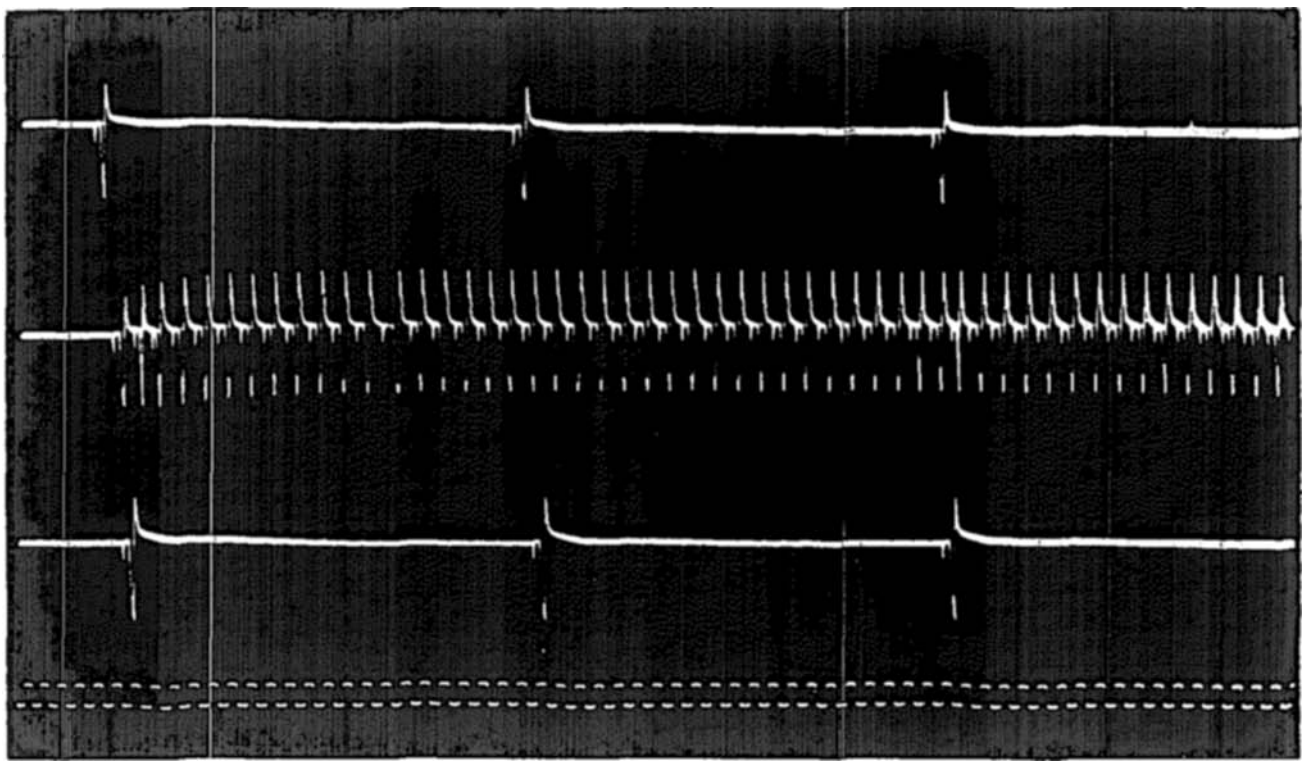

FIGURE 4. Effect of neostigmine upon the final pattern of Figure 3.

Some twenty patients were studied using both decamethonium and succinyldicholine.[2] The first signs of a dual block could be recognized in this series after 500–1500 mg. succinyldicholine and after 6–20 mg. decamethonium. These results imply that if one continues giving a depolarizing drug by infusion or intermittent injection the point will be always reached in every patient when a full dual type of neuromuscular block is present. In one most unusual case outside this series, the signs of dual block have been observed after a single dose of only 100 mg. succinyldicholine.

It must be emphasized, however, that in this study a deliberate attempt was made to produce the signs of a full dual block. Occasionally, to our bitter disappointment, the surgeon finished the operation before this goal could be achieved! From the clinical aspect such cases can present a real problem, since, without the help of diagnostic instruments, the anaesthetist cannot tell whether the neuromuscular block at the end of operation is predominantly a depolarizing or a non-depolarizing one.

A dual block should always be suspected after an infusion of succinyldicholine if the patient recovers his muscle tone only slowly and also has a persistently poor volume of ventilation. The use of the accessory muscles of respiration and "tracheal tug" are also suggestive signs.

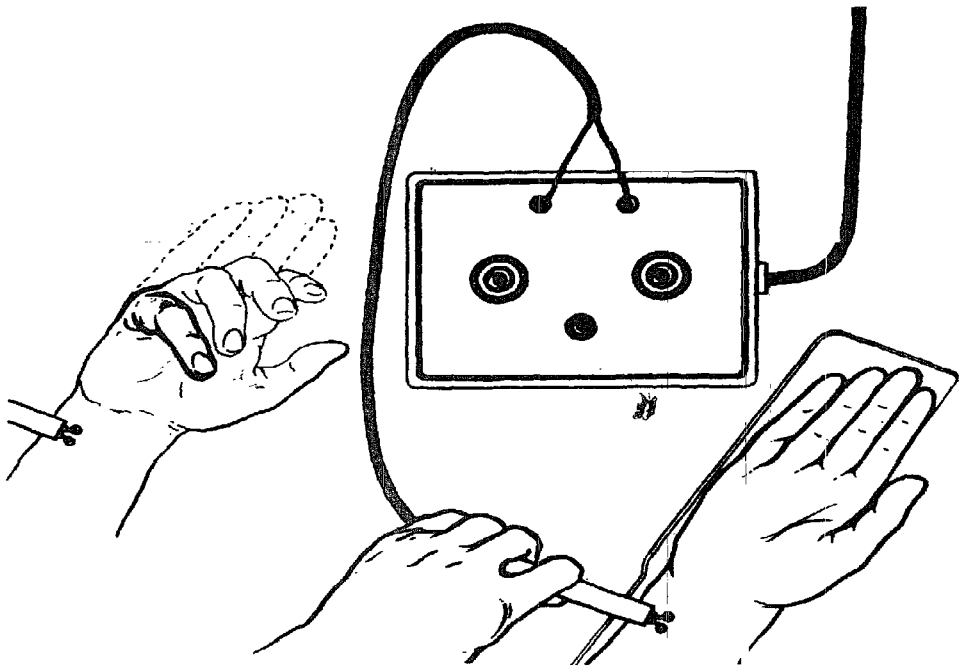

FIGURE 5. Peripheral nerve-stimulator.

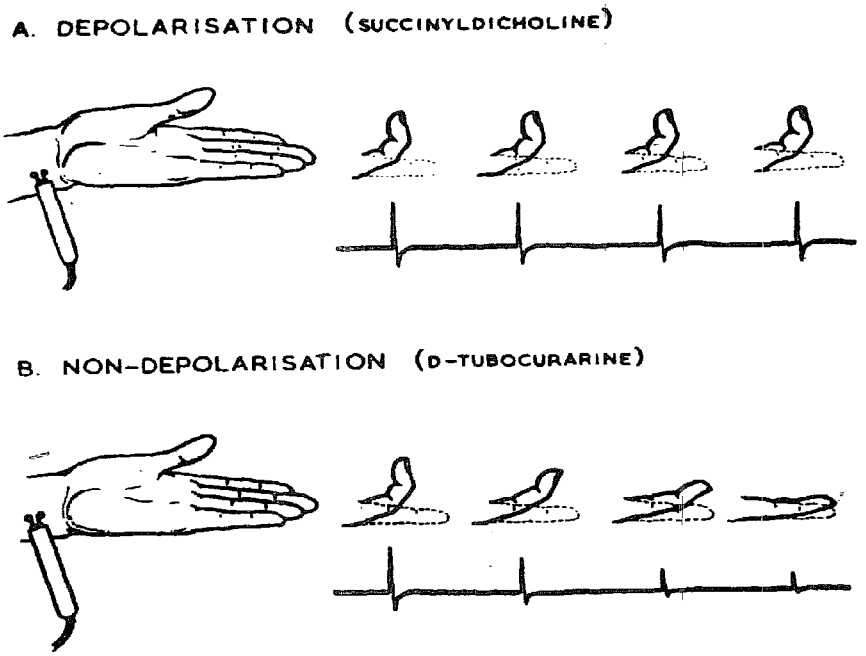

FIGURE 6

Identification of the exact type of block that is present in the peripheral muscles can be made at any time with a peripheral nerve-stimulator (Fig. 5). If the ulnar nerve at the wrist is stimulated electrically, the mechanical movement of the fingers will reveal which type of block is present in exactly the same way as will the electromyographic responses (Fig. 6).

If the fingers move rhythmically and the contraction is sustained, a depolarization block is present. On the other hand, if the response rapidly fades away and post-tetanic facilitation is present, the block is of the non-depolarizing type and will be improved by an injection of neostigmine.

A simple peripheral nerve-stimulator is an essential piece of apparatus for any anaesthetic department. It is not needed very often, but it can at any time tell the anaesthetist firstly whether a neuromuscular block is actually present and, secondly, what type of block prevails.

Conclusion

These studies on the disadvantages of succinyldicholine are not intended to detract from what is a most useful clinical relaxant. Nevertheless, they indicate the urgent necessity to find a short-acting non-depolarizing drug. At the meeting in Venice on muscle relaxants in 1958, just such a compound (namely "Compound 41") was described, which appeared from animal experiments to be highly promising.[4] Alas! the investigations in man showed that it produced profound histamine release with severe hypotension and tachycardia, and was quite unsuitable for clinical use. Haining[5,6] has stimulated our interest in a series of tropine derivatives. By a careful pharmacological analysis he has produced several most interesting compounds. Some have had a shorter action than succinyldicholine, while others have proved much longer-acting. All have been found to act like d-tubocurarine.

One compound, "DF 752" is of particular interest (Fig. 7).

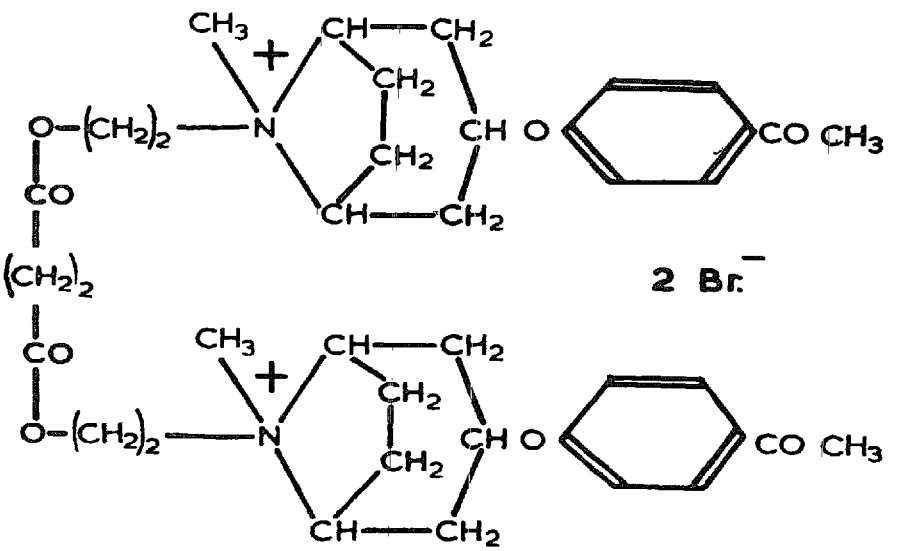

Figure 7

Unfortunately, this is not the very short-acting drug we were seeking. Nevertheless, in a limited clinical trial it has shown certain advantages over gallamine triethiodide. It has a shorter duration of action (10–15 min.) and the degree of tachycardia is lower. Paralysis of the laryngeal muscles is rapidly achieved.

The ideal short-acting non-depolarizing drug with minimal side-effects, that will replace succinyldicholine, still eludes us; but the search goes on.

ACKNOWLEDGMENTS

Figures 1, 2, 3, and 4 previously appeared in *Anesthesiology* and Figures 5 and 6 in the *British Journal of Anaesthesia*. I should like to thank the editors of these journals for kindly permitting me to reproduce them here.

RÉSUMÉ

Il existe une gamme étendue de relaxants musculaires à action dépolarisante utilisables en clinique, mais le succinyldicholine est le seul qui jouisse d'une popularité qui ne s'est jamais démentie. Toutefois cette substance présente deux inconvénients principaux. D'une part, elle entraîne des douleurs musculaires au cours de la période post-opératoire; diverses tentatives pour réduire la fréquence de cette complication sont discutées. D'autre part, toutes les substances à action dépolarisante sont susceptibles de modifier progressivement le blocage sousjacent jusqu'à ce qu'apparaisse un blocage du type non dépolarisant. En bref, on se trouve en présence d'un double blocage. L'auteur expose l'incidence et les conditions nécessaires à l'apparition de ce dernier type de blocage (blocage double).

Aussi, le désir de surmonter les principaux inconvénients du succinyldicholine a-t-il conduit à rechercher intensivement un type de relaxant musculaire à action brève et non dépolarisante. Les résultats de ces recherches sont exposés.

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