Brit. J. Pharmacol. (1952), 7, 601.

ANTAGONISTIC ACTIONS AT THE NEURO-MUSCULAR JUNCTION

BY

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(Received May 20, 1952)

Paton and Zaimis (1949) observed that decamethonium iodide blocks the neuromuscular junction with the same results, so far as the mechanical myogram is concerned, as tubocurarine. Each of these substances, however, is able to modify the action of the other; for instance, the injection of a small dose of tubocurarine reduces the effect of a later administration of decamethonium iodide. This observation has been confirmed by Macfarland *et al.* (1950) in man: previous "curarization" almost completely abolishes the response to decamethonium.

According to Paton and Zaimis (1949), decamethonium itself does not greatly modify the blocking properties of tubocurarine, and no real reciprocal antagonism between the two drugs exists. However, Depierre (1951) has observed an unmistakable reciprocal antagonism between flaxedil, a curare-like substance, and decamethonium. Moreover, Hutter and Pascoe (1951) have shown that suitable doses of decamethonium iodide are able to restore neuromuscular transmission after it has been blocked by tubocurarine. All these authors used cats.

The purpose of this paper is to describe our findings on the reverse phenomenon, namely the action of tubocurarine on neuromuscular block produced by decamethonium iodide. In some experiments we have used amyltrimethylammonium, the properties of which are quite similar to those of decamethonium.

Our results can be summarized as follows: tubocurarine has proved to be an excellent "deblocking agent" when administered to cats previously injected with decamethonium iodide or amyltrimethylammonium.

METHOD

The experiments were performed on cats anaesthetized with chloralose, sometimes with dial. A detailed procedure has been described elsewhere (Philippot and Dallemagne, 1951).

The tibialis anterior and soleus muscles were stimulated through the sciatic nerve every 6 sec. (supramaximal condenser discharges released by an electronic timer). The muscle twitches were recorded by means of an isometric lever coupled with Marey's drum. The movements were transmitted by a length of rubber tubing to a second drum-lever assembly equipped with a writing stylus.

The arterial pressure was recorded by means of an ordinary mercury manometer. Animals were treated with heparin.

RESULTS

Fig. 1 shows the effect of 25 μg./kg. of decamethonium iodide, injected intravenously. The injection produced a deep and long-lasting block of the neuromuscular transmission. Subsequent injection of 100 μg./kg. of tubocurarine (after

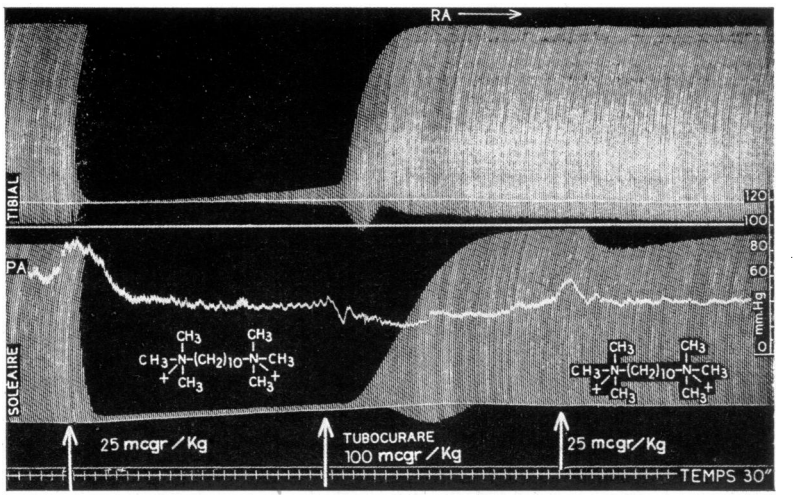

FIG. 1.—Cat (chloralose). Simultaneous records of arterial pressure, contractions of tibialis anterior and soleus. The muscles were excited with single maximal shocks at 10/sec. to the sciatic nerve. From left to right, at arrows, successively, 25 μg./kg. decamethonium iodide, 100 μg./kg. tubocurarine, and 25 μg./kg. decamethonium iodide. (On the figure, μg. is represented by mcgr.)

12 minutes) was soon followed by recovery of the junctional system. Complete restoration occurred in less than 3 min. for the tibialis anterior and in less than 9 min. for the soleus.

A fresh injection of 25 μg./kg. of decamethonium iodide did not reduce the twitches of the tibialis anterior and had only a small effect on the soleus.

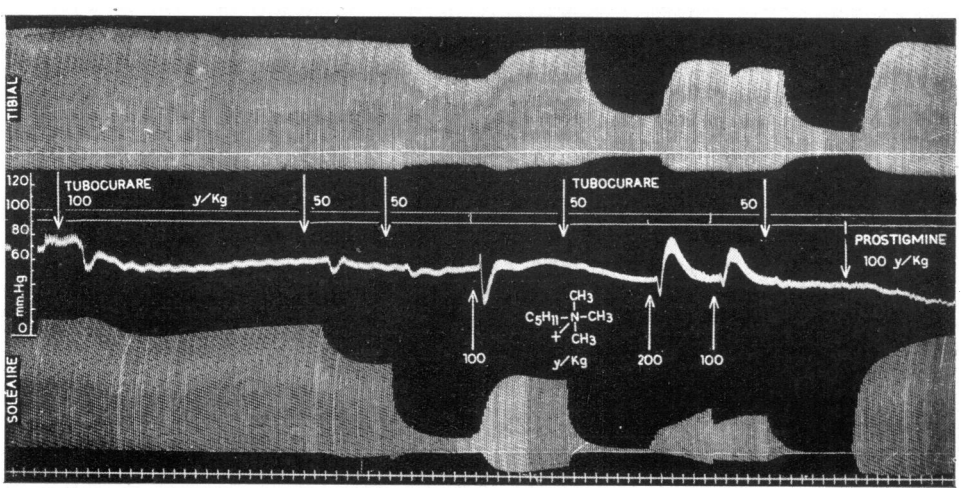

FIG. 2.—Similar preparation to that in Fig. 1. From left to right, at arrows, successively, tubocurarine, 100 μg./kg., 50 μg./kg., and 50 μg./kg.; amyltrimethylammonium iodide, 100 μg./kg.; tubocurarine, 50 μg./kg.; amyltrimethylammonium, 200 μg./kg., 100 μg./kg.; tubocurarine, 50 μg./kg.; and prostigmine, 100 μg./kg. (On the figure, μg. is represented by γ.)

After the first injection of decamethonium iodide, the respiratory movements (not recorded in Fig. 1) were not significantly depressed in spite of the marked paralysis of the hind limbs. After the injection of tubocurarine, the amplitude of the respiratory movements decreased, while normal neuromuscular transmission was being restored in the limb. Before long, spontaneous respiration stopped altogether.

Amyltrimethylammonium, like butyltrimethylammonium (Philippot and Dallemagne, 1951), is antagonistic to curare. Fig. 2 shows the effect of repeated injections of tubocurarine: it is well known (Paton and Zaimis, 1949) that the soleus is more sensitive to the paralysing action of tubocurarine than is the tibialis anterior.

When amyltrimethylammonium was injected during this period of decreased twitch tension, there was a complete restoration of the neuromuscular transmission in the tibialis anterior and a partial recovery of the soleus.

A further injection of tubocurarine was more efficient, and the decurarizing action of amyltrimethylammonium was now smaller. A third injection of this drug no longer increased the twitch tension, but reduced it transiently. The junctional system was still sensitive to tubocurarine. Neostigmine was able to restore neuromuscular transmission completely.

The successive deblocking and blocking actions of tubocurarine are clearly shown in Fig. 3. In this experiment, neuromuscular block had been produced by the

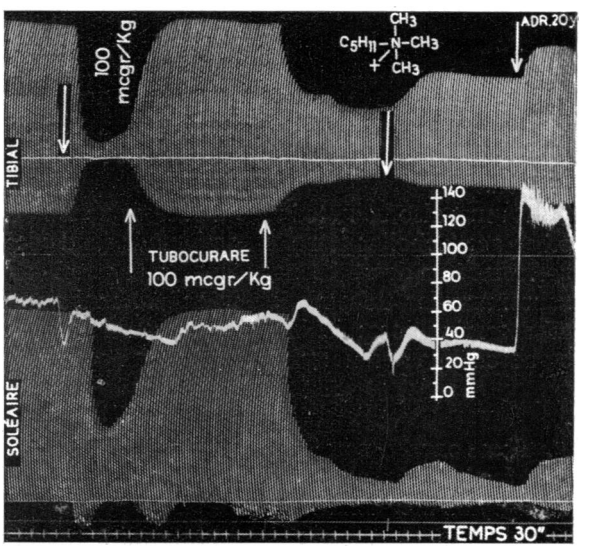

FIG. 3.—Similar preparation to that in Fig. 1. From left to right, at arrows, successively, amyltrimethylammonium, 100 μg./kg.; tubocurarine, 100 μg./kg., 100 μg./kg.; amyltrimethylammonium, 100 μg./kg.; and adrenaline, 20 μg./kg. (On the figure μg. is represented by mcgr or γ.)

injection of amyltrimethylammonium. There was a definite tendency to spontaneous recovery; but the first injection of tubocurarine undoubtedly accelerated the increase of twitch tension. The second injection had an opposite effect, i.e. true curarization. Subsequent injection of amyltrimethylammonium was able partly to restore neuromuscular transmission in the tibialis anterior. There was only a small effect on the soleus. Adrenaline had the same action.

Discussion

In a previous report (Philippot and Dallemagne, 1951) we described the reciprocal antagonism between tubocurarine and butyltrimethylammonium. Our present findings show a similar antagonism between tubocurarine and amyltrimethylammonium or decamethonium. This suggests that decamethonium iodide and the lower homologues of alkyltrimethylammonium salts exert their paralysing effects through a somewhat similar mechanism.

The most spectacular phenomenon was the deblocking action of tubocurarine when paralysis had been induced by the so-called acetylcholinomimetic compounds, such as decamethonium iodide and amyltrimethylammonium. The optimal doses required to reveal this antagonism are equi-active: in other words, they exhibit the same blocking activity when used alone.

After injection of tubocurarine and decamethonium iodide (or amyltrimethylammonium), it is possible to obtain a state of functional disequilibrium at the neuromuscular junction; either true curarization may occur or a paralysis of the acetylcholinomimetic type.

The " deblocking " action of tubocurarine is very strong, while the " decurarizing " properties of decamethonium iodide are definitely weaker and more irregular. This difference may be due to the fact that decamethonium does not act only on the motor endplate itself, but also produces a depolarization of the adjacent muscle fibres.

All muscles are not equally sensitive to the drugs mentioned. The soleus is more sensitive than the tibialis anterior to the action of tubocurarine; the reverse holds for decamethonium iodide (Paton and Zaimis, 1949) and amyltrimethylammonium.

These reasons (choice of the optimal dose and unequal sensitivity of the muscles) explain why repeated injections in the same animal generally result in the disappearance of the antagonism described, at least at the level of one of the two muscles studied.

It must also be noted that tubocurarine is not antagonized by decamethonium or other acetylcholinomimetic compounds (and vice versa) when the experiments are performed on dogs. Decamethonium is poorly active in the latter species and blocks neuromuscular transmission in this animal apparently by the same mechanism as tubocurarine does: its blocking effects are enhanced by tubocurarine and alleviated by adrenaline and neostigmine (Dallemagne and Philippot, 1952).

Summary

These experiments have disclosed the powerful deblocking effects exerted by tubocurarine on neuromuscular block produced by decamethonium iodide or amyltrimethylammonium in the cat.

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