Brit. J. Pharmacol. (1951), **6**, 691.

DECURARIZATION BY DECAMETHONIUM

BY

O. F. HUTTER* AND J. E. PASCOE

From the Department of Physiology, University College, London

(Received August 1, 1951)

Paton and Zaimis (1949) have drawn attention to the curious relationship between decamethonium and *d*-tubocurarine. They found that previous administration of a small dose of tubocurarine rendered decamethonium less effective as a neuromuscular blocking agent; on the other hand, decamethonium given before tubocurarine did not protect against block by the alkaloid. From these observations it has been inferred that decamethonium does not antagonize the action of *d*-tubocurarine (Castillo, Phillips, and de Beer, 1949; Macfarlane, Unna, Pelikan, Cazort, Sandove, and Nelson, 1950; Winter and Lehman, 1950). The experiments here reported show that this is only partly true, for in suitable doses decamethonium restores neuromuscular transmission after block by tubocurarine.

METHODS

Cats, decerebrate or anaesthetized with chloralose, were used. Tension was recorded from tibialis anterior excited through its nerve by supramaximal shocks once every 10 seconds. For close arterial injection the muscle was prepared as described by Brown (1938). End-plate potentials were recorded from the gracilis muscle (Brown and Burns, 1949) by means of fine platinum electrodes about 5 mm. apart and a condenser coupled amplifier whose time constant was 0.41 second. The infusion apparatus described by Burn and Dale (1924) proved suitable for intravenous administration of *d*-tubocurarine chloride. It consists of a burette whose delivery is controlled by the flow of oil through a capillary tube. For initial curarization a positive pressure was created in the oil reservoir until the desired degree of neuromuscular block was attained. Curarization was then maintained by suitably adjusting the height of the reservoir. The rate of infusion necessary to maintain block varied greatly between preparations, and the range, in our experience, extended from 0.25 to 1.1 mg./kg./hr.

RESULTS

The experiment illustrated in Fig. 1 shows the effect of close arterial injection of decamethonium into a preparation which had received enough tubocurarine to reduce the twitch tension to 10 per cent of its initial value. As little as 0.8 μg. decamethonium iodide produced a distinct decurarization which lasted 20 minutes. With twice this amount restoration of transmission was more complete, and the twitch tension reached 80 per cent of its initial value. With doses in this range the first few twitches after the injection grew, their peaks forming an upward concave curve. When 3.2 μg. decamethonium was given a new phenomenon made its appearance. The response to the first stimulus after the injection was the largest; after this the twitch tension decreased for three minutes, but then waxed and waned again. With

* Sharpey Scholar.

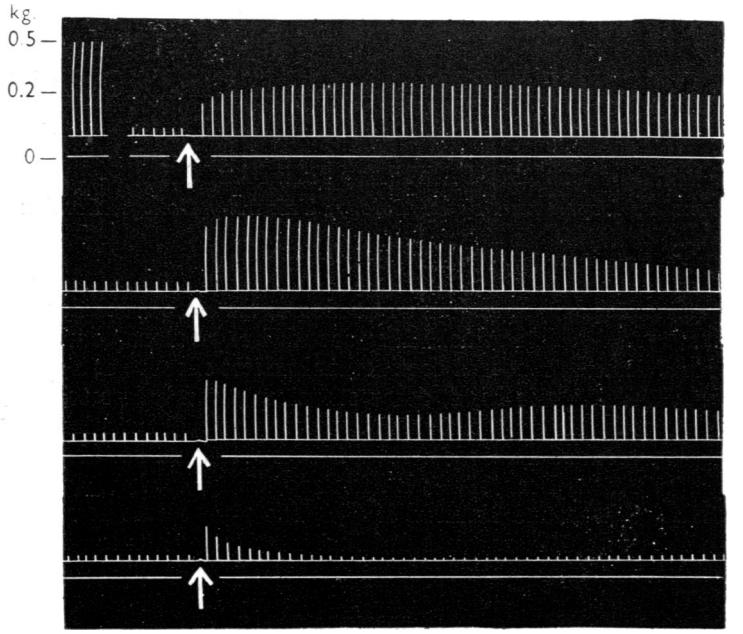

FIG. 1.—Cat, 2.5 kg. Chloralose. Contractions of tibialis anterior in response to maximal stimuli to nerve every ten seconds. Preparation partly curarized. At arrows, from above downwards, close arterial injection of 0.8, 1.6, 3.2, 6.4 μg. decamethonium iodide. Top left: twitches of untreated muscle.

yet larger doses of decamethonium restoration of transmission was slight and transient, and rapidly gave way to a renewed block.

Decurarization can similarly be observed on intravenous administration of decamethononium in doses which, given alone, produce complete neuromuscular block. In Fig. 2*b* the result of injection of 60 μg./kg. of decamethonium iodide into the saphenous vein is shown. The twitch tension increased gradually to about 80 per cent of its value at the beginning of the experiment and remained there for some minutes before declining again. In the same preparation, at somewhat deeper curarization, the effect of five similar doses, given in close succession, was tested (Fig. 2*c*). It can be seen that the first two injections progressively increased the twitch tension, but that subsequent doses did so only transiently and, in the main, had the opposite effect. In this experiment we thus traversed the whole cycle, from block by *d*-tubocurarine to block by decamethonium. The fact that decamethonium, when enough is given, will block transmission even in the presence of tubocurarine is, no doubt, the reason why its decurarizing property has been overlooked so far, and it probably underlies yet another curious feature of its action. Under our experimental conditions we have never seen complete restoration of transmission, as judged by the response to a single shock, and it seems likely that decamethonium, in the concentration required to decurarize the most resistant neuromuscular junctions, blocks those junctions most sensitive to it.

It is known that decamethonium is a weak inhibitor of cholinesterase (Barlow and Ing, 1948; Paton and Zaimis, 1949). To test whether the decurarization

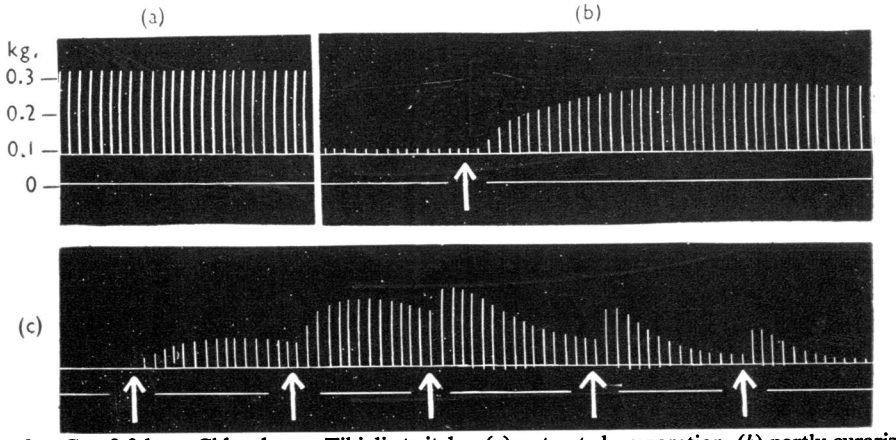

FIG. 2.—Cat, 3.3 kg. Chloralose. Tibialis twitches (*a*) untreated preparation, (*b*) partly curarized; at arrow intravenous injection of 200 μg. decamethonium iodide; (*c*) 2 hr. later; at each arrow intravenous injection of 200 μg. decamethonium iodide.

described here can be attributed to this property of the compound the following experiment was made. A heavily curarized preparation was treated, by retrograde injection into the opposite femoral artery, with 250 μg. physostigmine sulphate. The resulting decurarization is shown in Fig. 3*a*. More tubocurarine was then given until complete block was re-established and the process then repeated four times. The fifth dose of physostigmine no longer restored transmission, but subsequent doses of decamethonium decurarized effectively (Fig. 3*b*). Hence the two compounds do not act in the same manner.

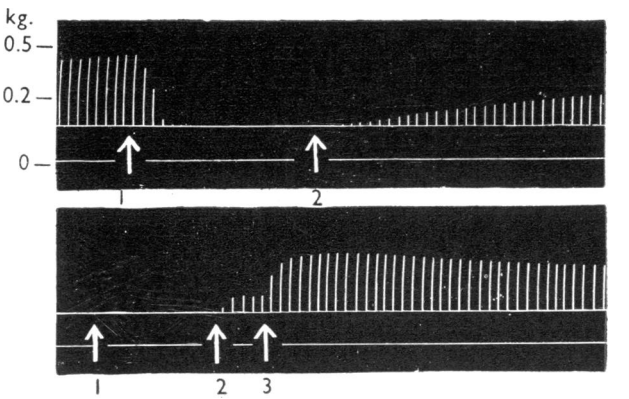

FIG. 3.—Cat, 3.0 kg. Chloralose. Contractions of tibialis. (*a*) At arrow 1, intravenous infusion of *d*-tubocurarine chloride; at arrow 2, "distant" arterial injection of 250 μg. physostigmine sulphate; (*b*) 30 min. later, after treatment described in text, "distant" arterial injections of, at arrow 1, 250 μg. physostigmine sulphate, at arrow 2, 50 μg., at arrow 3, 100 μg. decamethonium iodide.

In order to obtain better insight into these phenomena we studied the electrical responses in gracilis. The muscle was stimulated through its motor nerve at 10-second intervals either by a single supramaximal shock or by a pair of shocks 1.2 msec. apart. Curarization was taken to the stage at which both forms of stimulation failed to evoke muscle action potentials (Fig. 4*a, b*): that is a good deal further than in most of the preceding experiments. Continuous recording of endplate potentials was then made while decamethonium was injected at an even rate into a

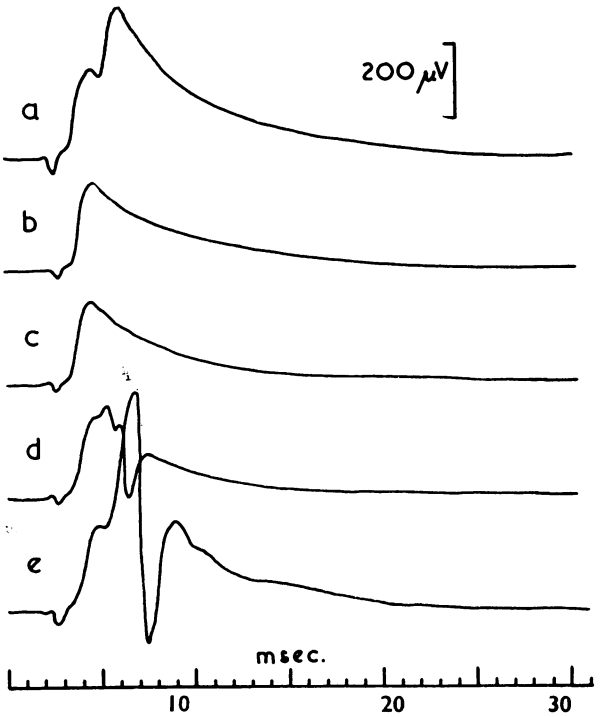

FIG. 4.—Cat, 3.2 kg. Chloralose. Curarized. Endplate potentials recorded from gracilis. (*a*) Response to two supramaximal stimuli to nerve 1.2 msec. apart; (*b–e*) responses to single supramaximal stimuli to nerve; (*a*) and (*b*) before decamethonium; (*c–e*) during slow infusion of decamethonium, 0.35 mg. per min.; (*c*) 3 min. 20 sec., (*d*) 3 min. 30 sec., (*e*) 3 min. 50 sec. after commencement of infusion.

vein. This procedure was adopted in order to make sure that an effective concentration was reached slowly so that we might observe any change in the endplate potentials before their form became distorted by spikes. In all 1.4 mg. decamethonium iodide was given in the course of 4 minutes. Records (Fig. 4*c, d, e*) taken 3 minutes 20 seconds, 3 minutes 30 seconds, and 3 minutes 50 seconds after commencement of injection demonstrate that muscle action potentials appear without any detectable increase in the height of the endplate potentials or prolongation of their time course.

DISCUSSION

Paton and Zaimis (1949) have shown that a dose of decamethonium which, given alone, produces neuromuscular block is without effect when given to a preparation which has just recovered from a small dose of *d*-tubocurarine. We have used enough tubocurarine to cause almost complete block and found that under those conditions the most striking action of decamethonium is to restore transmission.

Decurarization by decamethonium takes place without change in the peak voltage or time course of the endplate potential, indicating that both the intensity of the transmitter action and the activity of the cholinesterase remain unaltered. The site of action must therefore be more peripheral. This agrees with what is already known about this compound. Decamethonium blocks neuromuscular transmission by depolarizing the motor endplate region (Burns, Paton, and Dias, 1949), and this property provides an explanation for its anticurare activity as well, if it is assumed that in the curarized preparation it exerts a slight depolarization only.

The amount of further depolarization required for initiation of endplate potentials would then be reduced. Such an additive effect accounts satisfactorily for the observation that an endplate potential which previously failed to reach threshold will, after decamethonium, set up action potentials without any detectable increase in its size.

When very large doses of decamethonium were given restoration of transmission was poor. There is thus an optimal concentration for decurarization beyond which a stage is no doubt reached where an increasing number of fibres becomes blocked by too much depolarization. Moreover, the less deep the level of curarization the more readily does the blocking action of decamethonium become apparent.

Recently the pharmacology of a series of phenolic quaternary ammonium compounds has been studied in some detail (Riker, Wescoe, and Brothers, 1949 ; Randall, 1950 ; Riker and Wescoe, 1950). These compounds share with decamethonium the property of being both neuromuscular blocking and anticurare agents, and it seems likely that they act in a similar manner. Their anticurare activity has received special attention and has been tested on anaesthetized surgical patients (Artusio, Riker, and Wescoe, 1950) and on conscious volunteers (MacFarlane, Pelikan, and Unna, 1950). The last group of authors have also reported that these compounds were effective in alleviating muscular weakness in a myasthenic patient. If a case for the use of decurarizing agents which act by virtue of their direct effect on the motor endplates can in fact be made, then decamethonium should be the compound of choice, since it is free from the undesirable side-effects on the heart and circulation which the phenolic quaternary ammonium compounds display in varying degrees. Our experiments point, however, to an inherent difficulty in the use of anticurare agents of this type. Their action is of short duration, compared with anticholinesterase drugs, yet any attempt to prolong it by increasing the dose entails the risk of reaching concentrations in which these agents will themselves block transmission.

SUMMARY

In suitable doses decamethonium restores neuromuscular transmission after block by *d*-tubocurarine. This decurarization is not due to inhibition of cholinesterase by decamethonium. Transmitted responses appear without detectable increase in size or prolongation in time course of the endplate potential. These experiments emphasize the inverse relationship between the two neuromuscular blocking agents.

This work was aided by an equipment grant from the Central Research Fund of the University of London to one of us (O. F. H.).

REFERENCES

Artusio, J. F., Riker, W. F., and Wescoe, W. C. (1950). *J. Pharmacol.*, **100**, 227.
Barlow, R. B., and Ing, H. R. (1948). *Brit. J. Pharmacol.*, **3**, 298.
Brown, G. L. (1938). *J. Physiol.*, **92**, 22 *P*.
Brown, G. L., and Burns, B. D. (1949). *J. Physiol.*, **108**, 54 *P*.
Burn, J. H., and Dale, H. H. (1924). *J. Physiol.*, **59**, 164.
Burns, B. D., Paton, W. D. M., and Dias, M. V. (1949). *Arch. Sci. physiol.*, **3**, 609.
Castillo, J. C., Phillips, A. P., and de Beer, E. J. (1949). *J. Pharmacol.*, **97**, 150.
MacFarlane, D. W., Pelikan, E. W., and Unna, K. R. (1950). *J. Pharmacol.*, **100**, 382.
MacFarlane, D. W., Unna, K. R., Pelikan, E. W., Cazort, R. J., Sandove, M. S., and Nelson, J. T. (1950). *J. Pharmacol.*, **99**, 226.
Paton, W. D. M., and Zaimis, E. J. (1949). *Brit. J. Pharmacol.*, **4**, 381.
Randall, L. O. (1950). *J. Pharmacol.*, **100**, 83.
Riker, W. F., and Wescoe, W. C. (1950). *J. Pharmacol.*, **100**, 454.
Riker, W. F., Wescoe, W. C., and Brothers, M. J. (1949). *J. Pharmacol.*, **97**, 208.
Winter, C. A., and Lehman, J. T. (1950). *J. Pharmacol.*, **100**, 489.