Actions and clinical assessment of drugs which produce neuromuscular block / W.D.M. Paton and Eleanor J. Zaimis.

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ACTIONS AND CLINICAL ASSESSMENT OF DRUGS WHICH PRODUCE NEUROMUSCULAR BLOCK

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THAT decamethonium may be used clinically to produce muscular relaxation in anæsthesia and in convulsion therapy, as suggested by us (Paton and Zaimis 1948a), is now well established (Organe 1949, Davies and Lewis 1949, Hobson and Prescott 1949, Hewer et al. 1949, Davies 1950). But it is clear from some reports that the fundamental differences in mechanism of action between decamethonium and drugs resembling *d*-tubocurarine are not sufficiently appreciated, and that this lack of understanding may interfere with assessment of the value of such drugs.

MODE OF ACTION OF DECAMETHONIUM AND *d*-TUBOCURARINE

The fundamental action of decamethonium on skeletal muscle is a specific depolarisation of the muscle membrane at the motor end-plate (where the motor nerve-fibre ends on the muscle membrane) (Burns and Paton 1950). The first effect of this depolarisation, particularly if the decamethonium is injected rapidly into a muscle by an arterial route, is to excite a brief contraction. But the depolarisation then persists and spreads to adjacent regions of the muscle. Two further effects follow: (1) because the end-plate is already partly depolarised, a nerve impulse can no longer evoke so large an "end-plate potential" (the electrical response by which the muscle-fibre is excited); and (2) the surrounding depolarised area becomes electrically inexcitable, with the result that there is a zone of inexcitable muscle membrane 2–3 mm. in width between the point at which the end-plate potential is set up and the nearest normally excitable part of the muscle-fibre. The net result of the reduction of the end-plate potential, and of the inexcitability of the end-plate zone, is neuromuscular block.

This action of decamethonium is analogous to that exerted by acetylcholine. Normally, in mammalian

muscle, acetylcholine released at the nerve terminals depolarises the end-plate for only a few thousandths of a second, so giving rise to the normal end-plate potential, and its liberation and removal are so rapid that only excitation is seen. But if acetylcholine is caused to persist either by giving anti-cholinesterases or by injecting large doses into a muscle, so that the depolarisation which it causes is prolonged, neuromuscular block follows, with the same characteristics as block due to decamethonium (Zaimis 1949).

In short, it may be said that, so far as skeletal muscle is concerned, decamethonium can be regarded as an acetylcholine that cannot be hydrolysed, and its actions are the same as those of persisting acetylcholine. Thus the contractions sometimes evoked by decamethonium are precisely analogous to those of any voluntary movement but are less coördinated. Decamethonium does not share the other (muscarine-like and ganglion-stimulating) actions of acetylcholine ; but its properties are simply those exerted by acetylcholine at the myoneural synapse, displayed in singularly pure form.

In contrast with decamethonium, *d*-tubocurarine cannot depolarise the muscle, and its actions depend on its ability to prevent other agents, especially acetylcholine, from doing this. In this way it makes the end-plate potential, evoked by the discharge of acetylcholine at the nerve terminals, too small to excite the muscle-fibre, although the muscle-fibre is still normally excitable by electrical stimulation.

The actions of decamethonium can therefore be regarded as due to an abnormally persistent end-plate depolarisation, and those of *d*-tubocurarine to the blocking of the normal depolarising action of acetylcholine ; thus the mechanisms of action are diametrically opposed. This is elegantly illustrated by the fact that *d*-tubocurarine can antagonise the effects of decamethonium. The terms " curarising " or " curariform " are now seen to be words that must be used with care, and are best restricted to those drugs which, like *d*-tubocurarine, act simply by raising the threshold of the motor end-plate to acetylcholine.

CONSEQUENCES OF DIFFERENCE IN ACTION

The divergence in the ways by which decamethonium and *d*-tubocurarine act inevitably leads to many detailed differences in their behaviour. For instance, it follows at once that it is not to be expected that anti-cholinesterases should antagonise decamethonium, since prolongation of the action of acetylcholine in a muscle paralysed with decamethonium can do little more than intensify the block slightly. So too there are many other differences : in the mode of onset and passing of the paralysis, in the influence of anæsthetics, in the

response to repetitive nerve stimulation, to mention only a few.

The use of neuromuscular blocking agents has evolved over a period of years, around preparations containing *d*-tubocurarine. Decamethonium is the first, and so far the only, "depolarising" blocking agent to be used clinically. A technique developed with *d*-tubocurarine will therefore need adaptation if it is to be used to full advantage with decamethonium. Seriously misleading results may be obtained if the differences between the drugs are not borne in mind, and the following examples have been chosen to exemplify this.

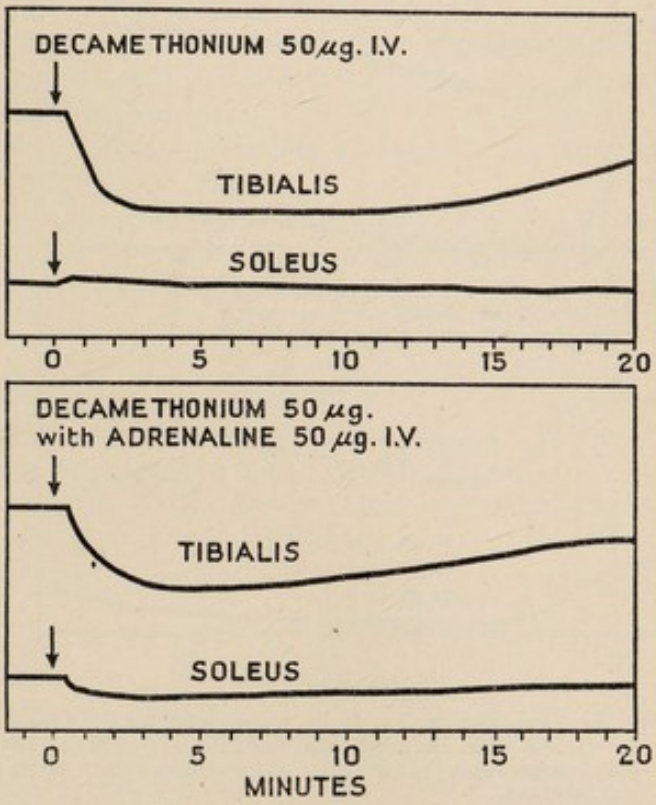

Fig. 1—Tracings of maximal twitch tension from records of the contraction of tibialis and of soleus excited by single maximal nerve shocks every 10 sec., in a cat weighing 3·3 kg., in chloralose anæsthesia, after injections of decamethonium and of decamethonium with adrenaline.

Muscle Specificity

It has long been known that muscles vary in their sensitivity to *d*-tubocurarine, the muscles of the eyes, pharynx, and larynx being particularly susceptible. Hence it is not surprising that decamethonium should also display differences in its effect on different muscles. But the significant point is that these differences are not the same as with *d*-tubocurarine. Figs. 1 and 2 illustrate this point on the tibialis anterior and the soleus in the cat; with *d*-tubocurarine the soleus is the more easily paralysed (fig. 2), whereas with decamethonium the tibialis is paralysed first (fig. 1). Similarly, in the cat, the respiratory muscles are paralysed before the tibialis with *d*-tubocurarine and after the tibialis with decamethonium (Paton and Zaimis 1948b).

This varying sensitivity to the two drugs may be seen in another aspect when different species are compared. We then find that in the rat, on which *d*-tubo-

curarine is more than usually potent, decamethonium is particularly ineffective; whereas in the cat, on which *d*-tubocurarine is less effective, decamethonium reaches its highest potency.

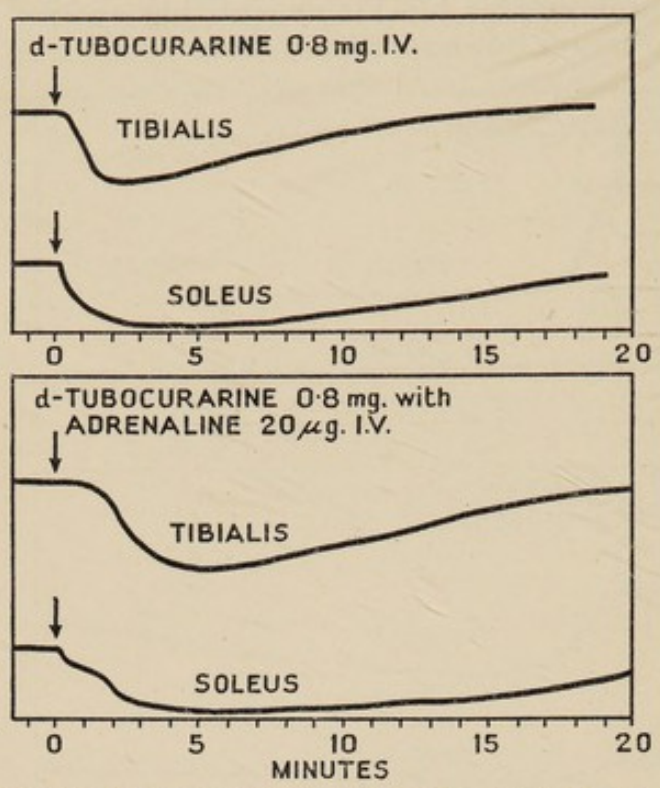

Fig. 2—Tracings as fig. 1, in a cat weighing 3·5 kg., in chloralose anæsthesia, after injections of *d*-tubocurarine and of *d*-tubocurarine with adrenaline.

Yet another difference is that ether anæsthesia slightly potentiates *d*-tubocurarine, but slightly antagonises decamethonium (Paton and Zaimis 1949).

In short, one may say that the circumstances in which *d*-tubocurarine is particularly effective are likely to be those in which decamethonium is ineffective, and vice versa. This inverse relationship between the two drugs springs naturally from the difference in their modes of action, and provided an important clue to that difference. But it also has an important bearing on clinical comparisons between the drugs.

Effects of Adrenaline

(1) In an anæsthetised animal the stimulant effects of decamethonium on a muscle are usually restricted to a few transient fasciculations, with more or less potentiation of the nerve-excited muscle twitch. If a dose of adrenaline is given beforehand, however, this excitatory phase may be distinctly increased, and the fasciculations become quite vigorous. This effect may be observed whether the adrenaline is given arterially or intravenously, and with noradrenaline.

(2) Adrenaline also influences the depth of paralysis of the muscle by decamethonium. Fig. 1 shows how, with the tibialis muscle of the cat, the injection of adrenaline intravenously lessens the maximum paralysis by decamethonium from 95% to 78%. On the other hand, with *d*-tubocurarine (fig. 2) an intravenous dose of adrenaline just before the injection increases the

blocking effect on tibialis from 60% to 75% block and prolongs it.

(3) But these changes of potency of decamethonium and *d*-tubocurarine do not affect different muscles equally or in the same direction. Fig. 1 shows, for instance, that with the soleus muscle adrenaline has quite opposite effects to those on tibialis; here it actually augments the action of decamethonium. With *d*-tubocurarine, however, adrenaline hardly modifies the action on soleus and increases it on tibialis (fig. 2).

The presence of circulating adrenaline, therefore, has three effects: (1) it increases the stimulant action of decamethonium; (2) it changes the potency of *d*-tubocurarine and of decamethonium on a given muscle; and (3) it changes the pattern of muscle susceptibility to these two drugs in opposite ways, increasing the proportionate effect of decamethonium on the "red" muscle, soleus, and decreasing that of *d*-tubocurarine on soleus. There can be little doubt that tests of these compounds in conscious people will be seriously influenced by the secretion of adrenaline that accompanies trials of this nature.

Idiosyncrasy

Among the precautions taken in the administration of *d*-tubocurarine is that of giving an initial small dose, so as to detect those occasional persons who are particularly susceptible to it, and who (it has been suggested) may be regarded as latent or subclinical myasthenics. The same technique has been used with decamethonium (Gray 1950). But when we consider the modes of action of the two drugs, and the evidence already cited that conditions favouring the action of *d*-tubocurarine usually oppose that of decamethonium, it seems reasonable to expect that those patients who are susceptible to *d*-tubocurarine would be, if anything, resistant to decamethonium. Some slight support for this suggestion that there is no idiosyncrasy of this kind to decamethonium comes from the experience of Davies (1950) in which, out of 973 administrations of decamethonium, every patient required 3–5 mg., and none appeared to be particularly sensitive. It would be of great interest to know what the sensitivity of a myasthenic is to decamethonium, since it would not only determine whether idiosyncrasy of this kind occurred to decamethonium but would also throw light on the pathogenesis of myasthenia.

It therefore seems probable that precautionary small initial doses are unnecessary with decamethonium. They may also be somewhat confusing to an inexperienced anæsthetist. The effects of a small dose of decamethonium in a conscious patient with (no doubt) a liberal supply of circulating adrenaline due to the approaching operation

are likely to be solely those of muscle stimulation. These contractions are, as we have said above, perfectly harmless, being analogous to an incoördinated voluntary contraction ; they pass off within a minute or two, or with the administration of more decamethonium.

CLINICAL ASSESSMENT

The considerations and evidence which we have advanced have one particularly important consequence ; that, for practical purposes, a comparison of the clinical usefulness of such drugs as *d*-tubocurarine and decamethonium can only be made under the conditions of actual use. If it is desired to know, for instance, whether one or other of such drugs has (say) less effect on the respiration than on the abdominal muscles in an anæsthetised patient, then the comparison must be made on the muscles concerned and in anæsthetised patients. It is instructive to compare two attempts at such a comparison, with this requirement in mind.

The first is that of Davies and Lewis (1949), who wished to compare the effects on the respiration of decamethonium and *d*-tubocurarine when given to abate the convulsions of shock therapy. The comparison was made directly, in the course of normal treatment. By a simple but careful system of scoring the intensity of the convulsions, doses of each drug which were equally active were obtained ; using these doses, these workers determined the maximum inspiratory capacity of the patients just before the convulsion. They found that, for the third and fourth minutes after the injection, this was 1160 c.cm. and 1110 c.cm. respectively with decamethonium, and 835 c.cm. and 700 c.cm. with *d*-tubocurarine (average of six patients). This was not an elaborate study, but its findings were clear and directly applicable to practice ; they have been borne out by later experience. It remains the only satisfactory clinical comparison yet made between two such drugs.

In contrast one may cite the relatively complicated experiments of Unna et al. (1950). These workers wished to assess the usefulness in surgical anæsthesia of three blocking agents, paying particular attention to the respiratory effects. They were careful to emphasise the danger of arguing from experiments on one species to another ; but they underestimated the equally great danger of arguing from one muscle to another. So far from studying the abdominal muscles, they chose the muscles of the hand for analysis. They obtained, as doses giving 95% paralysis of the grip strength, the following average doses for a man weighing 70 kg. : *d*-tubocurarine chloride 9·4 mg. ; decamethonium iodide 2·8 mg. If these doses are compared with the amounts that have been found to give equivalent maximum relaxations in anæsthesia (*d*-tubocurarine chloride 15 mg., decamethonium iodide

3 mg.), it is seen at once that the hand must be relatively more sensitive than the abdominal muscles to *d*-tubocurarine. Roughly speaking, then, the dose of *d*-tubocurarine required to paralyse the hand was only 65% of that needed for abdominal relaxation, whereas for decamethonium the dose was 95% of the effective dose for anæsthesia. The comparison of the effects on the respiration was therefore between a full anæsthetic dose of decamethonium and a two-thirds anæsthetic dose of *d*-tubocurarine. Such a comparison is obviously irrelevant to the conditions of surgical anæsthesia, although of some interest for manual physiology.

Further, instead of using anæsthetised persons, Unna et al. used conscious volunteers, in whom adrenaline must have been secreted in appreciable amounts (these workers themselves state that " an increase in pulse-rate and blood-pressure in the subjects was seen frequently during the first few minutes after the injection of any of the drugs "). We have shown how circulating adrenaline profoundly alters the comparison between decamethonium and *d*-tubocurarine, in a way which seems likely to increase the respiration-sparing effects of *d*-tubocurarine and to decrease those of decamethonium. The comparison by Unna et al. was made under conditions different from those of anæsthesia and probably those least favourable to decamethonium. To the presence of circulating adrenaline may be attributed also the muscular twitches and muscle cramps recorded with decamethonium by these observers. We ourselves observed in the first trials of decamethonium (Organe et al. 1949) that the incidence of the cramps was in proportion to the rise in blood-pressure during the experiment.

It is clear, therefore, that the experiments by Unna et al., through an unfortunate chance, were made in such a way that the respiratory depressant effects of decamethonium were likely to be exaggerated, its muscle-specificity reduced, and its muscle-stimulating action increased. It is not surprising that these workers were unable to confirm the finding of Davies and Lewis (1949) that decamethonium has a less depressant action than has *d*-tubocurarine on respiration.

DISCUSSION

We have emphasised particularly the difficulties in making comparisons between *d*-tubocurarine and decamethonium. But the difficulties of assessments of this sort are not restricted to these two drugs ; they will appear when any two or more drugs that produce neuromuscular block are studied, and will certainly also have to be faced in the clinical evaluation of the dimethyl ether of *d*-tubocurarine, and of ' Flaxedil,' not to mention that of the blocking agents still to be discovered. Although it is considerably harder to make

quantitative comparisons during clinical practice than in the laboratory, there seems no escape from the conclusion that either this task must be undertaken or we must remain in doubt about the relative usefulness of these drugs in practice. Such trials, however, have an interest greater than that of simple clinical evaluation of a new medicament, for they reveal differences between the drugs that may be, in time, capable of exploitation in other directions; in particular, it seems possible that the varying muscle specificity may prove useful. Further, there is slowly accumulating a substantial body of information relating the physiology of the human neuromuscular junction—about which we have little detailed knowledge—to the well-established and extensive information at our disposal in animals.

SUMMARY

Decamethonium and *d*-tubocurarine cause neuromuscular block by fundamentally different mechanisms. Block by decamethonium is due to a persistent end-plate depolarisation, analogous to an exaggeration of the normal excitant action of acetylcholine; block by curare is due to an antagonism to the normal action of acetylcholine.

These differences in mode of action reveal themselves in many ways, particularly in differing muscle-susceptibility. Further, circulating adrenaline modifies the pattern of muscle-susceptibility both of *d*-tubocurarine and of decamethonium.

The relevance of these findings to clinical assessment of such drugs is discussed. Such assessment can be valid only if made under the actual conditions in which the drug is to be used.

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