THE INITIAL TRANSIENT STIMULATING ACTION OF NEUROMUSCULAR
BLOCKING AGENTS IN THE CAT

BY

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An initial transient increase in the size of the muscle twitch before the onset of paralysis has been described as characteristic following the intravenous injection of a depolarizing neuromuscular blocking agent. During several series of experiments undertaken in the study of different aspects of neuromuscular block this typical response was confirmed, but it was also noted that occasionally a similar brief stimulant effect followed the intravenous injection of competitive blocking agents. The observation was sufficiently interesting to justify an examination of all records in an attempt to explain this rather unexpected finding.

MATERIAL AND METHOD

The analysis of previous records was made easy by the fact that a standard technique for the administration of relaxants had been adopted throughout all the experiments. The results obtained were therefore comparable. The method was as follows. All experiments were performed in cats; after induction with ethyl chloride and ether, anaesthesia was established with intravenous chloralose. A dose of 80 mg/kg was injected through a cannula in the right external jugular vein in a strength of 10 mg/ml. The same cannula was used for the injection of the relaxant drug dissolved in physiological saline. A tracheostomy was established to facilitate ventilation with a positive pressure respirator.

After the sciatic nerve had been located in the posterior aspect of the thigh, it was crushed and tied as far proximally as possible to avoid interference with its blood supply. Its medial division was dealt with likewise. The tendon of the right anterior tibialis muscle was avulsed from its insertion and attached to a flat steel spring myograph recording on smoked paper. The animal was placed in a supine position with the right leg horizontal and held rigidly by a drill inserted immediately above the ankle joint. The muscle was stimulated indirectly once every 10 seconds by a square wave pulse of 0.5 m.sec duration applied to the nerve through platinum electrodes at 1–3 volts.

The muscle relaxants covered by this survey were tubocurarine and dimethyl-tubocurarine, gallamine, benzoquinonium, laudexium and mecamylamine, as well as two tropine derivatives DF.596 and DF.648 and suxamethonium and decamethonium.

RESULTS

As was to be expected, initial stimulation was most marked with the depolarizing agents suxamethonium and decamethonium. In 12 cats given suxamethonium the effect was observed in all of them but it was also noted in 7 of the 12 that there was a progressive decrease in the extent of the initial stimulation with successive series of injections. Transient increased twitches were noted in all 8 cats given decamethonium and, of these, 6 showed a progressive decrease in the amount of activity with successive series of injections.

Among the competitive blocking agents, tubocurarine was given to 13 cats of which 3 showed evidence of initial stimulation. In those 3 animals the effect was noted after the first injection and was not seen again. The pattern was similar when dimethyl-tubocurarine was used, although the percentage showing initial stimulation was greater as it appeared in 4 out of 8 cats. The incidence of the response was even higher with gallamine; of 20 cats tested 13 showed a transient enhanced...
Suxamethonium: 10 µg/kg
Decamethonium: 5 µg/kg
Gallamine: 0.5 mg/kg
Tubocurarine: 100 µg/kg
Dimethyl-tubocurarine: 10 µg/kg
Benzoquinonium: 50 µg/kg
D.F. 596: 0.25 mg/kg
Mecamylamine: 10 mg/kg

FIG. 1
Showing the transient increase in the size of the anterior tibialis twitch before the onset of neuromuscular block.
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Effect before the onset of paralysis on the first injection only. Benzoquinonium was used in 2 cats only and both showed a brief initial increase in twitch size before paralysis developed during the first series of injections. In 2 of 3 cats given DF.596 there was a transient increase in twitch size before neuromuscular block became established. With subsequent series of injections it was still apparent but became progressively weaker and disappeared about the fourth or fifth series.

Mecamylamine is used primarily for its ganglion blocking effect but in large doses it has a weak neuromuscular blocking action of competitive type. In 8 cases given this drug all showed a transient increase in activity before the onset of paralysis.

Laudexium was given to 3 cats as was DF.648 but no evidence of initial stimulation was seen with either drug.

DISCUSSION

It has previously been reported without comment that the intravenous injection of gallamine into the cat may be followed by a brief initial increase in excitation before the onset of paralysis (Riker and Wescoe, 1951; Payne, 1958). The work described here establishes that such a stimulation is not uncommon after the first injection of most competitive blocking agents. Such an observation is hard to understand if the classical interpretation of competition block is accepted in its entirety and any attempt to do so is complicated by the fact that the analysis of the problem must prove difficult if for no other reason than that in most instances the effect is seen only in any one animal.

However, the facts reported are in accordance with the theory of drug action recently propounded by Paton (1960) which suggests, (1) that the stimulant action of a drug is dependent on the rate of its combination with tissue receptors; (2) that the stimulant action is maximal on first exposure when all receptors are free from combination with the drug; later the presence of occupied receptors will slow down the rate of combination and thereby reduce or abolish it; (3) that when dissociation of the drug from receptors is slow the stimulant effect is correspondingly feeble; (4) that for any antagonist its initial combination should lead to some degree of excitation not necessarily detectable.

This theory explains why stimulation occurs, why it is most marked with the first injection, why it is weaker with some drugs than with others and why in some instances no stimulant action is seen. The theory also implies that strictly speaking there is only a quantitative and no qualitative difference between drugs classified as depolarizers and competition blockers although the quantitative differences may be very large. In particular it excludes the use of the terms “antidepolarizer” and “nondepolarizer”.

The theoretical considerations are substantiated by considerable experimental and clinical evidence in favour of a transition from depolarization to competition block.

In 1953 Paton and Perry showed that, when nicotine was used to block the superior cervical ganglion in the cat, they could obtain direct electrical evidence of a change from depolarization to competition block. Later, Zaimis (1953) showed that in the dog, hare, monkey and rabbit the nature of depolarization block with decamethonium was changed with time and repeated dosage so that the block was ultimately antagonized by neostigmine and tetanic stimulation and enhanced by tubocurarine. In man, Brennan (1956) demonstrated that in a series of 62 patients given suxamethonium by continuous infusion, neostigmine antagonized and gallamine enhanced the neuromuscular block in most patients. The transition was gradual and seemed to be related to the duration of exposure and dose of drug employed. By demonstrating that the prolonged administration of either suxamethonium or decamethonium sensitized the motor endplate to the effects of d-tubocurarine and gallamine in the dog, cat and man, Foldes et al. (1957) confirmed and amplified the findings of Zaimis and Brennan.

There is no evidence to suggest that competition block ever precedes depolarization block.

An increase in the size of individual muscle twitches may result from cholinesterase inhibition and as many relaxants possess anticholinesterase activity (Foldes, 1957) this offers an alternative explanation. But the evidence that inhibition of cholinesterase occurs in vivo with the doses employed here is not convincing and the inability in most instances to demonstrate enhanced activity
with other than the first injection does not support this interpretation.

The possibility of other factors such as the influence of the drugs on the nerves and muscles as distinct from the motor endplate has to be considered. In the dosage used there is no known action of relaxant drugs on nerve fibres and spinal reflex activity can be excluded because the nerve was crushed and tied proximal to the point of stimulation. This, of course, does not exclude axon reflexes but the nature of the response makes it unlikely that such reflexes are involved.

The behaviour of muscle fibres can be altered by drugs and could conceivably produce the effect described, but again it is difficult to understand how the activity could be altered so consistently and yet so rarely under the conditions of the experiments.

**SUMMARY**

The division of relaxants into depolarization and competition blockers is less well defined than had previously been believed and evidence has been presented which, though not conclusive, suggests that all neuromuscular blocking agents pass through a depolarizing phase which is later followed by competition block if the action of the drug is prolonged. The depolarizing phase is extremely short with drugs like tubocurarine and competition block develops early, but with decamethonium and suxamethonium competition block may never be seen unless the block is unduly prolonged.

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**REFERENCES**


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**F.F.A.R.C.S.I.**

The first examination for the Primary Fellowship of the Faculty of Anaesthetists of the Royal College of Surgeons in Ireland will commence on November 13, 1961.

Entries must be lodged with the Registrar R.C.S.I., St. Stephen's Green, Dublin 2, twenty-one days beforehand.