THE DIAGNOSIS OF NEUROMUSCULAR BLOCK IN MAN*

BY

H. C. CHURCHILL-DAVIDSON AND T. H. CHRISTIE

St. Thomas's Hospital, London, S.E.1

In the past neuromuscular blocking drugs have been regarded as acting at the motor endplate either by depolarization (like acetylcholine) or by nondepolarization (like d-tubocurarine). This simple classification became widely accepted. Nevertheless, the actions of some newly discovered relaxant drugs have cast doubts on this simple classification and it has been suggested that they show characteristics of both types of neuromuscular block. Furthermore, confusion has arisen from the suggestion that suxamethonium (a depolarizing drug) may actually alter its mode of action—so that after repeated doses it produces a non-depolarizing type of neuromuscular block.

Clinically, if muscle relaxants are used, it is extremely important to determine the precise type of neuromuscular block that is present. Thus, a nondepolarizing block can be reversed rapidly by an anticholinesterase drug (e.g. neostigmine) whereas a depolarizing block is merely potentiated.

Unfortunately, in man there is very little data upon the state of neuromuscular transmission in the presence of the various muscle relaxants. Almost all the available evidence is based upon animal studies. An attempt has therefore been made to measure changes in neuromuscular transmission in anaesthetized patients under the influence of the principal muscle relaxants.

METHOD

Subjects undergoing routine surgical operations requiring the use of a muscle relaxant in the course of the anaesthetic technique were chosen at random. Each patient was premedicated with papaveretum (10 mg) and hyoscine (0.45 mg); induction of anaesthesia was with 500 to 750 mg of thiopentone and maintained with nitrous oxide-oxygen (6:2 l./min) given in a semiclosed circuit. Intermittent doses of pethidine hydrochloride (totalling 20–80 mg) were given as required.

Neuromuscular transmission was measured by a modification of the method described by Harvey and Masland (1941). A supramaximal stimulus of 0.2 milliseconds duration was administered through a needle electrode in the region of the ulnar nerve at the elbow. An earth lead was firmly attached over the forearm. Surface recording electrodes were applied over the muscle mass of the abductor digitii minimi. The hand and forearm were firmly attached to a back-splint to prevent movement.

The portable electromyograph was capable of delivering a stimulus at rates of 1, 2.5, 10, 25 and 50 per second. The design also included a device enabling single twitch stimuli to be administered automatically at varying intervals before and after a train of tetanic stimulations.

The following features were specifically studied:

1. The ability of muscle to respond to varying rates of stimulation in the presence of neuromuscular blocking drugs.
2. The presence or absence of post-tetanic facilitation. (This is signified by an increase in the height of a single action potential delivered 1–5 seconds after a burst of tetanic stimulation as compared with a single control stimulus delivered beforehand.)
3. The effect of anticholinesterase drugs upon the neuromuscular block.

The following drugs were studied:

1. Decamethonium iodide.
2. Suxamethonium chloride.
3. d-Tubocurarine chloride.

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Edrophonium and neostigmine were used for anticholinesterase therapy. Whenever neostigmine was used it was always preceded by the intravenous injection of 1 mg atropine sulphate. There was no evidence that atropine alone affected neuromuscular transmission.

In each case an intravenous dose of the muscle relaxant sufficient to produce complete neuromuscular block of the hypothenar muscles was administered and the various effects upon the neuromuscular block were studied during the recovery.

Preliminary studies established that the basic anaesthetic technique (including the intravenous administration of pethidine hydrochloride) did not influence neuromuscular transmission even when continued for 2 hours or more. In the anaesthetized patient the effects of a single dose of d-tubocurarine or gallamine could readily be differentiated from a similar dose of either suxamethonium or decamethonium.

**RESULTS**

(a) *Decamethonium.*

The most characteristic feature of this type of neuromuscular block is the ability of the motor endplate to transmit successive stimuli even when very fast rates of stimulation are used (figs. 1A, B, C, D).

In the example shown in figure 1 the degree of paresis is approximately 50–80 per cent. The action potential is well maintained for short periods even with a rate of stimulation rising to 50 per second. At this fast rate signs of fatigue and ischaemia of the muscle fibre are responsible for a gradual failure of the action potential after some 30 seconds or more of repeated nerve stimulation.

There was no evidence of post-tetanic facilitation after a period of tetanic stimulation. (This is not shown in the figure.)

The findings following a single dose of suxamethonium were indistinguishable from those after decamethonium.
Neostigmine in the presence of a depolarization block.

The effect on the already existing decamethonium block (fig. 1D) of the injection of an anticholinesterase drug (2.5 mg. neostigmine) is illustrated in figure 1E.

In this instance the neostigmine was given during the recovery phase of the decamethonium block and it can be clearly seen that it produced a progressive failure of neuromuscular transmission with rapid rates of stimulation. Slow or twitch rates of stimulation were unaffected by the neostigmine. The significance of these changes can best be understood by reference to the effects of anticholinesterase drugs alone (see figs. 3 and 4).
(b) d-Tubocurarine.

In direct contrast to decamethonium, the principal feature of this type of neuromuscular block is an inability to maintain successive stimuli (figs. 2A, B, C, D).

The major proportion of this decrement takes place in the first three or four stimuli of the train, and only a very small fall is distinguishable in the remainder until finally a potential of considerably reduced amplitude is steadily maintained. This progressive failure of neuromuscular transmission can be observed with both fast and slow rates of stimulation. In man, unless the interval between successive twitch stimuli is at least 3–5 seconds, some decrement after successive stimuli will be observed.

After a train of tetanic stimuli lasting 5 to 10 seconds or longer post-tetanic facilitation is observed. The longer the duration of tetanic stimulation, the more likely facilitation is to be present: the ideal interval between the end of the tetanus and the delivery of a single twitch is 2–4 seconds.

The results with gallamine triethiodide were identical and indistinguishable from those with d-tubocurarine.
Neostigmine in the presence of a nondepolarization block.

Within 2 minutes of the administration of 2.5 mg of neostigmine in the presence of either a d-tubocurarine or a gallamine block, the rapid failure or decrement of successive stimuli started to disappear (fig. 2E). By the fourth minute the height of the single potential had shown a considerable increase over the previous value and the neuromuscular junction could now often transmit fast rates of stimulation without showing any decrement at all. If large doses of d-tubocurarine (such as 25–30 mg) had been used, the return to the control value was considerably delayed.

From these observations it was evident that the administration of neostigmine (2.5 mg) in the presence of an existing neuromuscular block provided a useful method of diagnosis of the precise mechanism underlying that block.

Neostigmine alone.

The finding that neostigmine produced changes of a different nature in the presence of either a depolarization or a nondepolarization block made it necessary to study the effect of an injection of neostigmine alone.

Under the same conditions, therefore, a group of patients were given doses of neostigmine ranging from 1.25 mg to 5 mg preceded by 1 mg of atropine sulphate. Two distinct phases of response—related to the dose level—could be recognized.

(1) Following moderate doses (1.25–2.5 mg) a failure to maintain fast tetanic rates of stimulation was observed (figs. 3A, B, C, D, E, F). At first it was only visible at rates of 50 per second (figs. 3E, F), but increasing the dose led to its appearance at 25 per second (figs. 3C, D), then at 10 per second, and finally even at 5 per second. It was not observed at 2.5 per second even when a dose level of 5 mg of neostigmine was used. Unlike the decrement produced by d-tubocurarine, in this instance a further dose of neostigmine leads to a worsening of the condition. This phenomenon could be explained upon the basis of accumulation of acetylcholine at the neuromuscular junction.

(2) Following large doses of neostigmine (2.5–5 mg) a persistent degree of neuromuscular block can be recognized even at very slow rates of stimulation (figs. 4A, B). As will be seen in figure 4B the action potential is reduced in height, signifying neuromuscular block similar to that produced by decamethonium. This may be due to a direct depolarizing action of neostigmine upon the motor endplate.
(1) Moderate dose of neostigmine

**Before neostigmine**

![Graph - Before neostigmine](image)

**Fig. 3A**
Rate of nerve stimulation: 2.5 per second

**After neostigmine**

![Graph - After neostigmine](image)

**Fig. 3B**
Rate of nerve stimulation: 2.5 per second

**Before neostigmine**

![Graph - Before neostigmine](image)

**Fig. 3C**
Rate of nerve stimulation: 25 per second

**After neostigmine**

![Graph - After neostigmine](image)

**Fig. 3D**
Rate of nerve stimulation: 25 per second
(2) Large dose of neostigmine

**Before neostigmine**

**FIG. 3e**
Rate of nerve stimulation: 50 per second

**After neostigmine**

**FIG. 3f**
Rate of nerve stimulation: 50 per second

**FIG. 4A**
Rate of nerve stimulation: 2.5 per second

**FIG. 4B**
Rate of nerve stimulation: 2.5 per second
Effect of continuous infusion of suxamethonium on neuromuscular transmission.

Following a single dose of suxamethonium (50 mg) the pattern of the neuromuscular block is clearly of the depolarization type (figs. 5A, B). Thus, the action potentials are well maintained even with fast rates of stimulation and there is no post-tetanic facilitation. Edrophonium potentiates the neuromuscular block.

If, however, the patient receives a continuous infusion of suxamethonium the pattern of the neuromuscular block gradually changes as the total dose increases. By the time a dose of 500–1,500 mg has been reached the characteristic fade in the series of action potentials—normally associated with a nondepolarizing (d-tubocurarine) block—can be clearly seen (fig. 5c).

This type of response occurred consistently in seven patients investigated. The larger the dosage used, the more obvious becomes the decrement of repeated potentials.

The effect of neostigmine on this response was also studied. Within 2 minutes of the intravenous injection of 2.5 mg the fade in the action potential started to disappear and by the fifth minute was practically negligible (fig. 5d). At the same time the height of each single potential increased, denoting a lessening of the neuromuscular block.

These results suggest that not only does neostigmine fail to potentiate the late block of suxamethonium but also that it may actually reverse it. Great caution, however, must be exercised in interpreting these results, since suitable allowance must also be made for the normal recovery of the underlying neuromuscular block due to the help of the destruction of suxamethonium by plasma cholinesterase. Alternatively, any change in the neuromuscular block might be due to a breakdown product of suxamethonium, as, for example, the monocholine derivative.

The final proof of the effect of neostigmine on the late block produced by a depolarizing drug could only be obtained by a study of its action in the presence of large doses of decamethonium, as this drug is believed to be excreted unchanged in the urine.
Neostigmine and the late block of decamethonium.

Just as it had been possible to demonstrate a change in the characteristics of neuromuscular block following the infusion of large doses of suxamethonium, so repeated intermittent doses of decamethonium led to a similar result.

After a single dose of 5 mg decamethonium (figs. 6A, B) the neuromuscular block showed the signs previously ascribed to a pure depolarization block.

There is some post-tetanic facilitation to be seen in the control (fig. 6A). This phenomenon is only rarely seen in the controls, but to some extent its presence detracts from the value of post-tetanic facilitation alone as a diagnostic measure. It will be noted that it was less in the presence of the depolarization block (fig. 6B).

Repeated additional doses (1.25 mg) led to a gradual lessening of the dose-response relationship, i.e. tachyphylaxis. By the time a dose of 15–20 mg of decamethonium (over a period of 2 hours) had been reached the characteristics of the neuromuscular block showed a marked change. A fade of successive stimuli even with twitch rates of stimulation and post-tetanic facilitation was present (fig. 6C). In other words, the block strongly resembled that seen after a dose of d-tubocurarine.

Recovery of the neuromuscular block at this time was extremely sluggish. The respiratory activity of the patient (if unassisted) was severely depressed, with a marked tracheal tug.

At this point 2.5 mg neostigmine was given intravenously. Three minutes later electromyographic measurement of the hypothenar muscles revealed an almost complete recovery from the neuromuscular block (fig. 6D).

At the same time, respiratory activity improved dramatically to full tidal volume.
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Control

Rate of nerve stimulation: 25 per second

After 5 mg decamethonium

Rate of nerve stimulation: 25 per second

After 20 mg decamethonium

Rate of nerve stimulation: 25 per second
DISCUSSION

The foregoing results lead to the following principal findings. First, electromyography reveals a distinct pattern which makes it possible to differentiate between a depolarizing and a non-depolarizing block. Secondly, neostigmine alone, in therapeutic doses, is capable of producing a neuromuscular block. Finally, evidence is presented to show that the type of neuromuscular block produced by both suxamethonium and decamethonium gradually changes as increasing doses are used.

Soon after the introduction of the depolarizing relaxant drugs into clinical anaesthesia reports began to accumulate of an abnormal response. Some patients receiving either decamethonium or suxamethonium showed a prolonged apnoea which promptly responded to neostigmine therapy. Yet it had already been firmly established that anticholinesterase drugs increased the neuromuscular block of a single injection of decamethonium and suxamethonium. It appeared, therefore, that under certain conditions the response of the motor endplate might gradually change from one of depolarization to one of non-depolarization.

The problem of the diagnosis of neuromuscular block was further accentuated by the advent of some new synthetic relaxant drugs. For example, the modes of action of benzoquinonium hydrochloride (Mytolon) (Foldes, 1957) and dioxahexadecaniumbromide (Prestonal) (Frey, 1956; Jolly, 1957) were incompletely understood. More recently, the introduction of a new relaxant drug—hexamethylene 1-6 carbinamoylcholine bromide (Imbretil)—which is claimed to act by both mechanisms, has increased the problem. The results of the application of this electromyographic technique to the latter drug are reported elsewhere (Christie, Wise and Churchill-Davidson, 1959).

Animal studies have revealed that in certain species both decamethonium and suxamethonium are followed first by a neuromuscular block showing the characteristics of depolarization and then by one of the characteristics of non-depolarization (Zaimis, 1953). A similar type of block (i.e. dual block) has been described in myasthenic patients (Churchill-Davidson and Richardson, 1953). Tidal volume studies have suggested that the neuromuscular block produced by the depolarizing drugs gradually underwent a change following successive doses (Brennan, 1956; Foldes et al., 1957; Hamer Hodges, 1958). Nevertheless, such measurements provide no direct proof that neuromuscular transmission is affected. The results reported in this paper, however, demonstrate conclusively that the neuromuscular block following the infusion of both suxamethonium and decamethonium gradually undergoes a change.

The danger of the indiscriminate use of neostigmine is emphasized by the finding that therapeutic doses are capable of producing neuromuscular block. This appears to be achieved by two possible mechanisms. First, by accumulation of acetylcholine molecules with failure of trans-
mission of rapid rates of stimulation. Secondly, by a direct depolarizing action of neostigmine on the motor endplate. It would seem unwise, therefore, to use this drug after a depolarizing one unless there is absolute proof that the neuromuscular block has undergone a change to the nondepolarizing type. Doses in excess of 2.5–3.75 mg are seldom likely to benefit neuromuscular transmission, even in the presence of severe neuromuscular block.

SUMMARY
A method of diagnosing the type of neuromuscular block in an anaesthetized patient is described.

Evidence is presented to show that the continued infusion of both suxamethonium and decamethonium leads to a change in the type of neuromuscular block.

Therapeutic doses of neostigmine can lead to neuromuscular block.

REFERENCES

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