NEUROMUSCULAR BLOCK IN MAN

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In 1942 Griffiths and Johnson (1) introduced d-tubocurarine chloride into anaesthesia and since that time many synthetic muscle relaxants have been developed for use in clinical practice. For simplicity of description they have usually been classified into two main groups: (1) those drugs which produce neuromuscular block in a like manner to d-tubocurarine, that is, competitive inhibition (non-depolarisation) drugs, and (2), those which act in a manner similar to acetylcholine and bring about depolarisation of muscle; this group is represented by decamethonium (C 10) and succinylcholine.

Recent findings, in cases of myasthenia gravis, that both decamethonium and succinylcholine give rise to a block having some of the characteristics of both groups suggest that this rigid classification is no longer strictly tenable. It has undoubtedly led to some confusion, and the purpose of this paper is to present a brief survey of relevant findings of the investigation into the effect of the muscle relaxants on neuromuscular transmission in man.

NORMAL NEUROMUSCULAR TRANSMISSION

The present conception is based on the chemical theory of normal neuromuscular transmission in that acetylcholine is the all important link in the transmission of an impulse from motor nerve to muscle fibre.

The neuromuscular junction comprises three important components, namely, the end of the nerve fibre, the protein membrane between the nerve and muscle fibre (often referred to as the "end-plate" or "receptor") and finally, the muscle fibre. On the arrival of a motor nerve impulse at the end of the nerve fibre, acetylcholine is liberated from an inactive precursor (2). The acetylcholine ions rapidly become attached to the end-plate and bring about a change in the electrical potential normally present on either side of this membrane. The negation of this change is termed "depolarisation" and this process acts as a trigger mechanism to produce the same change in the adjacent part of the muscle fibre, so that a wave of depolarisation followed by contraction spreads along the whole muscle fibre. Meanwhile the acetylcholine molecules have been almost instantly hydrolysed to acetic acid and choline by the cholinesterase present in the tissues, and the end-plate region has regained the resting potential across the membrane and is now in the resting state of polarity.

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This description, for purposes of simplicity, completely ignores the movement of sodium and potassium ions which are the effective part in carrying the electrical charges. Kuffler (3) suggested that the attachment of acetylcholine to the protein molecules of the end-plate membrane resulted in an alteration of the membrane permeability, rendering it freely permeable to ions; thus potassium ions on the outside and sodium ions on the inside can freely interchange.

Methods of Study of Neuromuscular Transmission in Man

There are two main methods of studying neuromuscular block in man: by (1) volitional activity, and (2) electromyographic studies.

Volitional Activity. The muscle strength of a conscious subject after varying doses of a relaxant is recorded. The commonest method used is the measurement of hand grip-strength by squeezing a bulb attached to a column of mercury. Each determination requires the maximum possible effort on the part of the subject, and this is sometimes difficult to obtain.

Electromyographic Studies. The main nerve to a muscle or group of muscles is stimulated a variable number of times per second and the resultant contraction of the muscle fibres is recorded either electrically or mechanically. The height of the action potential from peak to peak is taken as an index of the number of muscle fibres contracting. The synchronous contraction of 150 to 300 muscle fibres representing a motor unit gives rise to an action potential similar to that recorded on the electrocardiograph. This method can be used on either conscious or anaesthetized patients, but the results obtained are not strictly comparable with those of volitional activity.

Neuromuscular Block

Deficiency Block. Any factor that interferes with the liberation of acetylcholine is capable of producing a block of this type; for example, procaine (4), botulinus toxin, and calcium deficiency act in this way. There is a failure of neuromuscular transmission, but both the nerve and the muscle will respond to direct stimulation.

Depolarisation Block. This process is similar to that produced by acetylcholine in normal neuromuscular transmission but there is an increased duration and extent of depolarisation. Succinylcholine lasts only a few minutes because it is rapidly hydrolysed by the plasma into succinylmonocholine, which in turn is broken down to succinic acid and choline. In contrast, the action of decamethonium is prolonged because it is not hydrolysed in vivo but is excreted unchanged in the urine.

A depolarisation block due to either C10 or succinylcholine is preceded by muscle twitches, which represent the contraction of the
muscle fibres before the onset of persistent depolarisation and neuromuscular block. There are certain features of these fasciculations which are worth recalling:

Firstly, decamethonium produces a characteristic tightness of the jaw and calf muscles which occurs soon after the injection and may persist for many hours. Secondly, succinylcholine leads to widespread fasciculations which are particularly prominent if the injection is given rapidly. Recovery is complete, but if the subject is ambulant after recovery a high proportion of patients (66 per cent) will develop generalised muscle stiffness after moving about on rising the following morning. This stiffness is similar to that experienced by an untrained subject the morning after some violent exercise (5). Finally, electromyographically (using a recording needle deeply placed in a muscle) it can be shown that these twitches are not, as might be expected, single muscle fibre potentials but are full-action potentials, representing a whole motor unit of 150 to 300 muscle fibres contracting simultaneously. This might be taken as suggestive evidence of a central action of the drug, but the more likely explanation is that both succinylcholine and C 10 stimulate a single motor end-plate which, in turn, by an antidromic reflex, fires off all the other fibres in the motor unit—the Masland-Wigton phenomenon (6).

Non-depolarisation Block. This term is preferred to competitive inhibition because d-tubocurarine and decamethonium both compete with acetylcholine for the end-plate receptor. The distinctive factor is that curare combines with the receptor protein without causing depolarisation; it simply prevents the acetylcholine from combining with the receptor, thereby stopping depolarisation from taking place and producing a block of neuromuscular transmission. If the concentration of acetylcholine can be raised by inhibiting the action of choline-esterase with neostigmine or Tensilon® to a level at which the excitation threshold of the end-plate is reached, then the neuromuscular block is overcome. d-tubocurarine, di-methyl ethyl-d-tubocurarine, gallamine (Flaxedil®), Laudolissin® and Mytolon® chloride act in this manner.

Dual block.—This type of block occurs in cases of myasthenia gravis and possibly, in certain circumstances, after the intravenous injection of decamethonium or succinylcholine in normal subjects. The mechanism is complex and requires knowledge of the response of cases of myasthenia gravis to both d-tubocurarine and decamethonium.

D-tubocurarine and Myasthenia. Bennet and Cash (7) were the first to suggest the injection of d-tubocurarine as a diagnostic test for the presence of myasthenia, based on the finding that some of these patients showed a hypersensitivity to the drug. A re-evaluation of this test has shown that only those muscles which are clinically weak have this hypersensitivity, whilst the other muscles will give a similar response to that of normal subjects. Consequently, respiratory paraly-
sis is unlikely to follow a small test dose of \textit{d}-tubocurarine unless the myasthenic patient has clinical signs of weakness in the muscles concerned with breathing.

\textit{Decamethonium and Myasthenia.} To understand the response to decamethonium in patients with myasthenia gravis there are two findings in normal subjects which must be emphasized: (1) the average normal subject shows a profound degree of muscular weakness after the intermittent injection of a total dose of 2.5 to 3.0 mg. \textit{C} 10 over six minutes, and (2) once this paresis is present an injection of an anticholinesterase (such as neostigmine or Tensilon) leads to a severe increase in the weakness.

In myasthenia the response to \textit{C} 10 varies with the degree of myasthenic weakness already present. For example, a 21 year old woman who only had minimal myasthenic symptoms limited to her eyelids, showed no signs of paralysis even after the injection of 10 mg. \textit{C} 10. Further studies suggest that if an even greater dose had been given the eyelid muscles would have been the first eventually to show signs of paresis. The fact that every motor end-plate showed resistance to the depolarizing activity of \textit{C} 10 is evidence of the generalized character of this disease despite the fact that, clinically, it is only detectable in a limited group of muscles—in this patient, the eyelids.

At the other extreme, a severe case of myasthenia with generalised signs of weakness may show paralysis after the injection of as little as 1.5 to 2.5 mg. \textit{C} 10. The failure of neuromuscular transmission, however, is not due to a block of the depolarisation type but to one of non-depolarisation (like \textit{d}-tubocurarine); it is therefore readily reversible by neostigmine or Tensilon. There is also evidence that a brief period of depolarisation precedes the change-over to this non-depolarisation block (5).

These two types of response to decamethonium (\textit{C} 10) identical to those observed in myasthenia, have been described as occurring physiologically in various species of animals (8). Thus, whereas the muscles of the cat, bird, and frog respond to \textit{C} 10 by pure depolarisation, those of the monkey, dog, and hare can exhibit features, not only of depolarisation, but also of non-depolarisation block with this substance. In the light of this work it appears that the muscles of normal subjects respond to \textit{C} 10 in a similar manner to those of the cat, whereas the myasthenic muscle-response resembles that of the dog.

From time to time a case of prolonged action following the use of one of the muscle relaxants has been reported in the literature. Soon after the introduction of \textit{d}-tubocurarine a number of cases of persistent apnoea were concluded to be due to "latent myasthenia," yet with the introduction of decamethonium and succinylcholine the abnormal responses have continued to occur.

\textit{Causes of Prolonged Apnoea.} The causes of prolonged apnoea in
clinical anaesthesia are many and various, and they are not always associated with the use of a muscle relaxant. The factors concerned fall naturally into two groups:

**Central action.** An overdose of any anaesthetic drug, or a wide fluctuation in the plasma carbon dioxide level, depresses the activity of the respiratory centre and can lead to a prolonged apnoea.

**Peripheral action.** Again, the commonest cause of a prolonged response is probably an overdose of the muscle relaxant. The correct dosage will necessarily vary with the amount of muscle tissue and the state of the circulation of the patient. A poor peripheral blood flow, such as often occurs at the end of a long operation, will be attended by a prolonged action of the drug. Similarly, delayed renal excretion, as in hypotension and hypothermia, theoretically could lead to a longer action, but this is not very evident in clinical practice. The fact that the diaphragm, the principal muscle of respiration, is always (except in myasthenia) the last muscle to become paralyzed may well be due to the excellent circulation resulting from its constant exercise.

The administration of two drugs, both of which have a similar action on the neuromuscular junction, may lead to summation and a persistent apnoea. For example, a combination of ether and \(^7\)-tubocurarine or decamethonium and neostigmine have been known to bring about this result.

Succinylcholine, particularly when given as a continuous intravenous infusion, is apt to lead to a persistent apnoea or weak respiratory activity in the occasional patient. As far as is known it is hydrolyzed in two stages: First, one molecule of choline is quickly split off, leaving succinylmonocholine. In the second stage, which takes place more slowly, succinylmonocholine is hydrolysed to sucurinic acid and choline. The process of hydrolysis is controlled by the enzyme pseudo-cholinesterase. Thus, on the one hand, a low plasma cholinesterase level may lead to a slower breakdown to the monocholine derivative (9, 10). A low pseudo-cholinesterase activity is known to be associated with a number of factors, such as liver damage, undernutrition, cachexia and anti-cholinesterase drugs, but this may also occur in an otherwise apparently normal person (11).

On the other hand, succinylmonocholine, like its dicholine derivative, is capable of producing neuromuscular block if a sufficient concentration is reached—for animals this varies from 2.5 to 5.0 mg./Kg. (12). On a molar basis the activity of the monocholine varies from 1/24 to 1/62 of the dicholine (13). Since the ratio of the molecular weights of the monocholine to the dicholine is 0.8, hydrolysis of 100 mg. of dicholine will lead to 80 mg. of the monocholine. Although it is unlikely that such a small amount of monocholine could have any effect, when doses in the region of 1.5 to 2.0 Gm. are used, then the accumulation of monocholine may well be responsible for the prolongation of the paralysis.
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Finally, the prolonged apnoea may be due to the presence of a dual block caused by either decamethonium or succinylcholine. Although this type of response is rare, it must be seriously considered in view of the increasing number of reports in the literature of a prolonged paralysis, due to a depolarising drug, which has been completely and rapidly reversed by the injection of an anti-cholinesterase drug (14–16). The presence of a dual block due to a depolarising drug is known to occur in cases of myasthenia gravis. It is therefore possible that the end-plate response of normal subjects may change under persistent bombardment from one of pure depolarisation to one of dual response.

DIAGNOSIS OF THE ABNORMAL RESPONSE

In the event of a case of prolonged apnoea occurring during clinical anaesthesia the treatment of this condition must rightly come before anything else. Yet, if we are ever to establish the true causation, some attempt to isolate the causative factor must be made. Most reports in the literature offer only tentative suggestions of the responsible factor. There are, however, a number of tests that can be made at the time which will help later to establish the true diagnosis.

To distinguish between depression of the respiratory centre (central) and neuromuscular block (peripheral), or a combination of both, it is necessary to stimulate a main nerve trunk with an electrical stimulus. If the muscle fibres contract vigorously, then neuromuscular transmission cannot be affected. The prolonged paralysis, therefore, must be due to some central cause: either an overdose of the anaesthetic agent or an altered carbon dioxide tension of the blood. The latter may readily be calculated if a sample of blood is collected in a syringe without coming in contact with air (that is, under oil). Prior to the determination the sample should be kept cool.

If, on the other hand, the cause is diagnosed as some abnormality of neuromuscular transmission due to the depolarizing drugs, then again a blood sample should be taken in a plain syringe for determination of the plasma-cholinesterase level. Following this, an intravenous injection of 10 mg. of Tensilon will help to elicit the possible presence of a dual block. Tensilon is used, in preference to neostigmine, because it acts for only a few minutes, and were the block one of pure depolarisation then it would be potentiated briefly whereas a dual block would be completely reversed.

SUMMARY

There are three types of neuromuscular block that may be encountered in man: (1) depolarisation, (2) non-depolarisation, and (3) dual block. This last type of block occurs in cases of myasthenia gravis, and possibly, in certain circumstances, in normal subjects after a depolarising drug has been given. The possible causes of prolonged
apnoea following one of the muscle relaxants are reviewed and some suggestions to aid in the diagnosis of this condition are made.

REFERENCES