The influence of drugs used in therapeutics on the action of muscle relaxants

by

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When one considers the many types of chemical compound used in modern therapeutics, it is not surprising that some of these modify the action of muscle relaxants. In general such substances may interfere with neuromuscular transmission, or may influence relaxants by actions at other sites. Some such side effects are well known. Others, based on animal experiments on many different species and under varying conditions, are more difficult to assess precisely. Nevertheless, it would be unwise for the anaesthetist to ignore the possible risks they suggest.

Although it is difficult to classify drugs accurately according to their pharmacological action at the neuromuscular junction, they may be grouped under the following headings. It must, however, be remembered that one drug may have several effects.

1. Drugs influencing the release or metabolism of acetylcholine.
2. Drugs altering the sensitivity of the motor endplate.
3. Drugs affecting the metabolism and excretion of muscle relaxants.

Drugs influencing the release or metabolism of acetylcholine

Magnesium. Magnesium ions block the release of acetylcholine at the neuromuscular junction. They may also stabilize the endplate, making it resistant to the effects of acetylcholine. These actions, together with the accelerating action of magnesium ions on the action of the true cholinesterases (del Castillo and Engbaek, 1954), potentiate the actions of the antidepolarizing relaxants which in turn will also potentiate the action of magnesium. However, high enough concentrations of this ion are unlikely to be encountered except perhaps in the magnesium treatment of eclampsia. The neuromuscular block produced by magnesium is reversed by calcium ions.

Procaine. Procaine and other local anaesthetics have many effects at the neuromuscular junction and consequently they are difficult to place in any one group. Procaine inhibits the release of acetylcholine at the endplate (Harvey, 1939) and it would therefore potentiate the action of antidepolarizing relaxants. However, the action of procaine at the neuromuscular junction is complex and as will be seen it has other effects on the action of relaxant drugs given with it.

Adrenaline. The anticholinergic effect of adrenaline has been recognized for many years, and it is probable that this substance causes increased secretion of acetylcholine at the neuromuscular junction. However, the excitability of the muscle fibre may be reduced by it, and these opposing effects may account for the conflicting experimental results, which are in any case unlikely to have any clinical significance.

Ephedrine. Ephedrine diminishes the rate of destruction of adrenaline and would therefore be expected to have the same anticholinergic effect. Before the era of the anticholinesterases it was used in the treatment of myasthenia gravis. It is therefore not surprising that ephedrine combined with neostigmine may be a more effective curare antagonist than neostigmine alone (Burn, 1957; Zuck, 1957).

Antibiotics. Antibiotics probably act in the same way as magnesium ions (Brazil and Corrado, 1957). It seems that streptomycin reduces acetylcholine release while neomycin is an antidepolarizing blocker.

A large number of cases have been reported in which intraperitoneal neomycin or streptomycin has been responsible for postoperative apnoea (Emery, 1963). In some cases the amount of the antibiotic given was in excess of the maximum safe dose, but in others a relatively small dose markedly potentiated the action of the muscle relaxant. There is also much experimental evidence which both confirms the neuromuscular blocking
properties of antibiotics and demonstrates the potentiation of the antidepolarizing relaxants. It appears that neomycin sulphate, streptomycin sulphate, dihydrostreptomycin sulphate, polymyxins A and B, kanamycin, colomycin, viomycin and paromomycin all have some neuromuscular blocking effects. Although Timmerman et al. (1959) found no neuromuscular blocking effect of penicillin G and tetracycline, others have demonstrated that these substances potentiate d-tubocurarine experimentally in the cat if given in very large doses intravenously (Baisset et al., 1962).

The reversal of this block has been investigated (Brazil and Corrado, 1957; Pittinger et al., 1958; Timmerman et al., 1959; Adamson et al., 1960, 1961). Neomycin, streptomycin, viomycin and paromomycin are reversed by neostigmine, but not kanamycin, colomycin, polymyxin A or B. Calcium antagonizes the block of neomycin, streptomycin, viomycin and paromomycin, but not that of polymyxin A or B, or colomycin.

Great caution must thus be observed if antibiotics are to be placed in the peritoneal or pleural cavity at operation.

Paraldehyde, methyl pentynol (Oblivon), carbromal. The exact position of these hypnotics is not clear. They have a definite action on the frog nerve-muscle preparation leading to neuromuscular block, which is not reversed by eserine (Quilliam, 1955). The response to acetylcholine is retained, and the explanation may be decreased acetylcholine release. The dosage of paraldehyde and carbromal to produce an effect was comparable to that used clinically and therefore an additive effect might be expected with antidepolarizing relaxants.

Bretylium and Guanethidine. Decreased acetylcholine release may be the explanation of the potentiation of the neuromuscular blocking action of d-tubocurarine found experimentally (Dixit et al., 1961).

Anticholinesterase drugs. These drugs inhibit the breakdown of acetylcholine by acetylcholinesterase, and therefore the action is that of excess acetylcholine. Evidence suggests that neostigmine and edrophonium also have a direct depolarizing action at the endplate (Riker and Wescoe, 1950; Wescoe and Riker, 1951). Commonly used anticholinesterases include neostigmine, pyridostigmine and edrophonium. Diisopropyl fluorophosphate (DFP) is too toxic to use systemically, but even after conjunctival instillation in the treatment of glaucoma, cholinesterase levels may be reduced. These drugs antagonize antidepolarizing relaxants, and potentiate depolarizers. They may precipitate a cholinergic crisis in cases of myasthenia gravis if used in excessive doses as a result of the effects of the excess acetylcholine at the endplate.

Other drugs with anticholinesterase properties include:

Tetrahydroaminoacridine (Tacrine hydrochloride, T.H.A.). This drug, used in combination with large doses of morphine in the treatment of intractable pain, counteracts respiratory depression. The powerful anticholinesterase actions of Tacrine have been used to prolong the action of suxamethonium clinically (Benveniste and Dyrberg, 1962), and to reverse d-tubocurarine though in fact this drug is not by any means as complete an antagonist as neostigmine. It is wise to take note of the anticholinesterase actions of this drug if patients receiving it are to be submitted to surgery.

Dimethylurethimine (AB-132). This cytotoxic drug has powerful anticholinesterase activity and has been associated with postoperative apnoea in patients subsequently receiving suxamethonium (Wang and Ross, 1963).

DRUGS ALTERING THE SENSITIVITY OF THE MOTOR ENDPLATE

Although experimental results are confusing as many drugs have more than one neuromuscular action, it appears that there are two groups of drugs—one group increases and the other decreases the sensitivity of the motor endplate. They act either by enhancing or inhibiting the effect of acetylcholine at the receptor sites. The muscle membrane sensitivity may also be affected.

Drugs enhancing the effect of acetylcholine at the receptor sites or increasing the sensitivity of the motor endplate.

The clinical importance of this group is negligible, although some chemicals have this action and antagonize antidepolarizing blocks experimentally. This is true of phenol and its derivatives (Mogey and Young 1949), and also of heparin and related compounds (Cheymol et al., 1955). There are controversial results concerning the neuromuscular effects of thiamine (Gjone, 1955; Cheymol et al., 1957; di Palma and Hitchcock, 1958).
Drugs inhibiting the effect of acetylcholine at the receptor sites or decreasing the sensitivity of the motor endplate.

Magnesium. This effect has already been mentioned.

Procaine and other local anaesthetics. The curare-like effect of procaine has been recognized for many years (Niljestrand and Magnus, 1919; Fulton, 1921; Harvey, 1939), but there are points of difference between the two drugs (Jaco and Wood, 1944). These are probably due to the several effects of procaine at the endplate and to the action on plasma cholinesterase. It has been shown with nerve-muscle preparations that d-tubocurarine is always potentiated, whereas depolarizing blocks are increased only if procaine is given immediately after the relaxant. There is antagonism if procaine is given first (Ellis et al., 1953). Clinically there is no observed effect although an additive effect might develop in a patient with a subclinical neuromuscular abnormality where infiltration of local anaesthetic had been combined with general anaesthesia and muscle relaxants.

Barbiturates. There is clinical and experimental evidence to suggest that barbiturates affect neuromuscular transmission (Gross and Cullen, 1943) and potentiate antidepolarizing relaxants (Pick and Richards, 1947). This is probably due mainly to the combination of a central effect and an action on muscle. With frog nerve-muscle preparations, small doses increased the response to indirect stimulation and there was a reduced response to acetylcholine. With larger doses the response decreased leading to a complete neuromuscular block (Quilliam, 1955). It has been suggested that barbiturates antagonize the anticholinergic effect of neostigmine and could give rise to postoperative apnoea (Sirnes, 1954). These effects must be considered in patients receiving large doses of barbiturates.

Chlorpromazine. It is not clear whether the potentiation by chlorpromazine of d-tubocurarine and gallamine observed experimentally (Dyberg and Hougs, 1958) is due to central effects, the anti-acetylcholine effect or the action on the muscle fibres (Kopera and Armitage, 1954). Clinically these actions are not of significance but prolonged treatment with chlorpromazine may produce liver dysfunction and low plasma cholinesterase levels, which could in theory at least produce an abnormal response to the depolarizing relaxants.

Promethazine. Promethazine has an action at the neuromuscular junction similar to that of chlorpromazine but less powerful (Kopera and Armitage, 1954).

Opiates. Although some patients receiving large doses of analgesics occasionally seem to be resistant to the curare-like drugs (Dundee, 1958), there is evidence that morphine acts synergistically with d-tubocurarine in mice (Lang et al., 1951).

Tribromethanol (Avertin). In very large doses a weak curariform action has been demonstrated experimentally (Gross and Cullen, 1943).

Pitocin. It has been claimed that the prolonged infusion of pitocin alters the sensitivity of the endplate to depolarization by suxamethonium (Hodges et al., 1959). The resulting block is alleged to be associated with minimal or absent muscle fasciculations. It is said that the onset of block is slower but duration is prolonged and recovery may be hastened by neostigmine. This has not been confirmed but perhaps the danger lies in overdosage and depolarizing drugs should be used with caution in these cases.

Ganglion blocking drugs. These drugs also compete with acetylcholine for the cholinergic receptors at the neuromuscular junction and could present a clinical problem.

Hexamethonium. In large doses pentamethonium and hexamethonium produce an antidepolarizing type of block, reversed by neostigmine, they potentiate, therefore, d-tubocurarine (Deacock and Davies, 1958) and are antagonistic to depolarizing agents.

Phenactropinium (Trophenium). This is capable of producing paralysis and respiratory arrest in animals (Robertson et al., 1957). This block like hexamethonium is antidepolarizing in type, and can be produced with doses comparable to those used clinically.

Trimetaphan (Arfonad). This can also produce a weak antidepolarizing block potentiating d-tubocurarine in doses similar to those used clinically (Payne, 1957; Deacock and Davies, 1958). In addition to an inhibitory action on cholinesterase activity, trimetaphan is possibly broken down by plasma cholinesterase (Tewfick, 1957). This latter action may potentiate suxamethonium and it has been suggested that they should not be used together (Pearcy et al., 1960).

Mecamylamine. The weak curariform action of mecamylamine (Stone et al., 1956) has been ques-
tioned (Bennett et al., 1957). These workers considered the action to be unlike competition with acetylcholine for the receptor sites. However, mecamylamine does potentiate d-tubocurarine, possibly due to an increased endplate threshold or to a mechanism involving inhibition of acetylcholine synthesis which allows d-tubocurarine to have a more marked effect (Payne, 1957). If given before decamethonium, mecamylamine alters the block to an antidepolarizing type reversed by neostigmine (Bennett et al., 1957). Mecamylamine and hexamethonium act synergistically on neuromuscular transmission in cats (Payne, 1957).

The evidence is such that care should be exercised when using ganglion blockers and muscle relaxants.

**Quinidine and quinine.** Quinidine has been shown to be capable of producing recurarization after recovery from dimethyl tubocurarine (Schmidt et al., 1963). Further investigations using the rabbit head-drop test have shown that although quinidine alone produces no effect, it markedly potentiates the effect of d-tubocurarine. There appears to be synergism with all muscle relaxants and the mechanism is not clear although there may be an alteration in the endplate sensitivity.

**DRUGS AFFECTING THE METABOLISM AND EXCRETION OF MUSCLE RELAXANTS**

**Metabolism.** Procaine and trimetaphan are broken down by plasma-cholinesterase and if used with suxamethonium may produce a prolonged effect (Foldes et al., 1953; Salgado, 1961). Anticholinesterases such as tetrahydroaminoacridine and hexafluorenium have been used for this very purpose (Foldes et al., 1960).

**Excretion.** Diuretics might decrease the activity of relaxants such as gallamine and decamethonium which are excreted unchanged.

In addition to these three main groups there are other drugs indirectly affecting muscle relaxants.

**Mephenesin.** Although this drug which is used as a spasmolytic and tranquillizer produces muscle relaxation by depressing synapses in the spinal cord, there would be an additive effect with other muscle relaxants.

**Chlorothiazide.** Depletion of potassium may potentiate the action of antidepolarizing relaxants.

This list of drugs is doubtless incomplete, and the number will increase as more chemical compounds are used therapeutically especially with current interest in enzyme-inhibiting drugs. The neuromuscular side effects of some of these will be discovered accidentally; others will be elucidated as the pharmacology of new compounds is studied. To this end the anaesthetist must be familiar with modern drug therapy and the pharmacology of new agents. The drugs any patients has been receiving or is to receive postoperatively must be known to the anaesthetist and scrutiny of this list must be an integral part of the pre-operative visit.


