ADVERSE EFFECTS OF NEUROMUSCULAR BLOCKING DRUGS

J. M. HUNTER

Neuromuscular blocking drugs are not as notorious for producing adverse reactions as the i.v. induction agents; nevertheless, to a varying degree they all produce unfavourable or harmful effects. The newer non-depolarizing neuromuscular blockers, atracurium and vecuronium, have been developed in an attempt to overcome the disadvantages of the earlier drugs, but although much more specific agents, they are not completely free from side-effects. The adverse effects of the neuromuscular blocking drugs available in Great Britain today will be discussed in this paper. Those which are not available in this country (such as pipecuronium and metocurine), and obsolete agents (such as decamethonium) will not be discussed. Although what follows is concerned mainly with the non-depolarizing agents, suxamethonium is included where appropriate, whilst what might be regarded as the unique features of the drug are discussed later in the article.

DIRECT CARDIOVASCULAR EFFECTS

With the possible exception of vecuronium, all the neuromuscular blocking drugs have some effect on the cardiovascular system. Such effects are described usually in terms of the degree of ganglionic blockade, sympathetic stimulation, vagal stimulation and vagolytic effect, and are summarized in Table I. It must be emphasized, however, that histamine release caused by administration of a blocking agent may well have a much greater effect on the cardiovascular system than any direct effect of the drug itself; this is particularly pertinent in the case of tubocurarine.

The ganglionic blockade caused by tubocurarine and the synthetic derivative of tubocurarine, alcuronium, results in a decrease in peripheral vascular resistance and hence a reduction in arterial pressure. This effect is dose related and is probably of clinical significance only when using larger doses of the drugs (such as tubocurarine 0.6 mg kg⁻¹) and in a hypovolaemic patient. As tubocurarine also releases histamine to a significant degree, the two unrelated effects may combine, even when using smaller doses of this drug to produce a decrease in arterial pressure, an effect which is often used to clinical advantage when hypotension is desired.

The sympathomimetic effect characteristic of some neuromuscular blocking drugs is thought to be an indirect response attributable to release of noradrenaline from adrenergic nerve endings in the heart; it has been demonstrated with both gallamine (Brown and Crout, 1970) and pancuronium (Nana, Cardan and Domokos, 1973). The

<table>
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<tr>
<th>Drug</th>
<th>Ganglion blockade</th>
<th>Sympathetic stimulation</th>
<th>Vagolytic effect</th>
<th>Vagal stimulation</th>
<th>Histamine release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suxamethonium</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>-</td>
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<tr>
<td>Atracurium</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Alcuronium</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Gallamine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>-</td>
<td>+</td>
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subsequent development of tachycardia and hypertension is potentiated by the vagolytic effect of these two drugs, for they also produce an atropine-like blockade of the cardiac muscarinic receptors (Goat and Feldman, 1972).

In contrast, of all the neuromuscular blocking drugs, suxamethonium is most likely to produce a reduction in heart rate as a result of stimulation of the cholinergic receptors in the heart, either directly or indirectly from reflex activity following stimulation of peripheral sensory receptors in the carotid body. There has been much discussion in the literature over these alternative mechanisms and the relative importance of each is still not clear (Goat, 1972). Bradycardia and asystole have been described clinically after a single dose of suxamethonium (Sorenson et al., 1984), but this effect on muscarinic receptors is more pronounced after repeated dosage, in the presence of an inhalation agent and in the younger patient (Leigh et al., 1957). In such circumstances, the resultant bradycardia frequently necessitates the use of an anticholinergic drug such as atropine.

In a patient with severe cardiovascular disease the cardiovascular effects produced by a neuromuscular blocker can be of clinical importance: for instance gallamine might be contraindicated because the combination of a vagolytic effect with sympathetic stimulation may cause an unacceptable increase in heart rate and hence cardiac rate-pressure product (Stoelting, 1973). The same effect, to a lesser extent, may also be seen with pancuronium.

Atracurium and vecuronium are free from direct cardiovascular effects within the clinical dose range (Crul and Booji, 1980; Sokoll et al., 1983), although the histamine releasing properties of atracurium may produce some degree of hypotension and tachycardia, especially when used in large bolus doses, greater than 0.6 mg kg\(^{-1}\) (Hughes and Payne, 1983). Only when very large doses (2 mg kg\(^{-1}\)) were used in animal work has a vagolytic effect been reported with atracurium (Hughes and Chapple, 1980). Because of the possibility of histamine release with atracurium, vecuronium is the neuromuscular blocking agent causing the least cardiovascular side effects. It is therefore the best drug when considering the most suitable form of anaesthesia for the patient with severe myocardial disease.

The virtual absence of direct cardiovascular effects associated with vecuronium and atracurium, however, does allow other anaesthetic agents such as halothane and the opioid analgesics to exert an unopposed effect on the myocardium. In addition, surgical manoeuvres which result in vagal stimulation such as peritoneal traction or cervical stimulation may lead to an unopposed reduction in heart rate. These factors probably explain the occurrence of bradycardia which has been reported during the use of both atracurium (Carter, 1983) and vecuronium (Robertson, et al., 1983) which provoked much debate in the literature (Madden, 1983; Macrae, 1985). It is pertinent that a similar case of sinus arrest during peritoneal traction has also recently been reported when tubocurarine was the neuromuscular blocking agent used (Nandi and Astley, 1985); there is always the possibility of a bradycardia during vagal traction, whatever the anaesthetic technique used.

**HISTAMINE RELEASING PROPERTIES**

Most neuromuscular blocking agents cause histamine release and the results of this release are seen in three ways: first, by a local erythematous reaction, like nettle rashing, sometimes accompanied by a widespread flush but without a reduction in arterial pressure; second by systemic effects such as tachycardia and hypotension, which may well be of clinical importance; and third, and rarely, as a life threatening anaphylactic or anaphylactoid reaction.

Basic compounds are more disruptive of mast cells, and thus more prone to release histamine than are acidic substances. Of the neuromuscular blocking agents, tubocurarine is the most potent in this respect: the free hydroxyl groups on the molecule are thought to enhance histamine release. Atracurium (Hilgenberg, 1983), alcuronium and gallamine have only about one-third of the histamine releasing potency of tubocurarine. However, several severe anaphylactic reactions to all these agents have now been described (Salem, Kim and El Etr, 1968; Fisher, 1978; Fisher, Hallowes and Wilson, 1978; Mercer, 1984). Although pancuronium and vecuronium, which are acidic compounds, are relatively free from histamine releasing properties, cardiovascular collapse has been reported following the administration of pancuronium, as has an incident of acute bronchospasm following administration of the drug (Heath, 1973; Mishima and Yamamura, 1984). More recently, localized histamine release
has been reported after an injection of vecuronium (Spence and Barnetson, 1985). It has been suggested that atracurium does not cause histamine release when doses of less than 0.6 mg kg\(^{-1}\) are used. It has also been demonstrated that histamine liberation is less likely to become evident when the speed of administration of atracurium is reduced and when pretreatment with \(H_1\) and \(H_2\)-receptor antagonists is used; cimetidine 4 mg kg\(^{-1}\) and chlorpheniramine 0.1 mg kg\(^{-1}\) i.v. were given successfully for this purpose (Scott et al., 1985). It is probable that the same histamine antagonists would have similar beneficial effects with the other histamine releasing neuromuscular blockers, especially tubocurarine.

The incidence of the localized erythema and urticaria occasionally produced when atracurium is injected to a peripheral vein may be reduced by injecting the drug separately from the induction agent, either by flushing the needle used with saline between the administration of two drugs or by injecting them both to a free flowing peripheral i.v. infusion. This observation suggests that the precipitate formed by the mixture of the two drugs is responsible at least in part for the localized response (Hughes, 1985).

There is some evidence that allergic cross reactivity between different myoneural blockers can develop, exposure to a second blocker more commonly producing any abnormal reaction when sensitivity to another relaxant has already occurred (Harle, Baldo and Fisher, 1985). There are isolated reports of anaphylactoid reactions to suxamethonium (Assem, Frost and Levis, 1981; Royston and Wilkes, 1978), but these are generally considered to be much less common than with tubocurarine (Lim and Churchill-Davidson, 1981).

**Impaired Metabolism and Excretion**

Any pathological process which impairs the route of metabolism or excretion of a neuromuscular blocking drug may result, not only in prolongation of the effect of the drug, but also in difficulty in antagonizing the residual neuromuscular blockade. Apart from the enzymatic or spontaneous breakdown of suxamethonium and atracurium that occurs in plasma and extracellular fluid, the liver and kidney are the two main organs involved in metabolism and excretion of neuromuscular blockers. (The metabolism of suxamethonium may be prolonged either by inherited abnormalities of pseudocholinesterase or by several acquired factors which will be discussed later.)

Non-depolarizing neuromuscular blockers are highly ionized, water soluble substances which are filtered by the renal glomerulus and, unlike lipid-soluble substances, are not reabsorbed in the proximal tubule. The kidney is, therefore, the main route of excretion of gallamine, tubocurarine, alcuronium and pancuronium (Table II). In addition, some excretion of all these drugs (except for gallamine) occurs into the bile (Table III) together with metabolic transformation to more water soluble, less pharmacologically active breakdown products in the liver, the resultant metabolites also being excreted both into the bile and through the kidney. In contrast, vecuronium is mainly metabolized in the liver by deacetylation, in a manner similar to the metabolism of pancuronium, but much more extensively. So extensively, indeed, that the proportion of free drug excreted in the urine is much smaller than in the case of other conventional non-depolarizing neuromuscular blocking agents (Upton et al., 1982).

**Hepatic disease**

The need for abnormally high doses of competitive blockers such as tubocurarine in cirrhotic liver disease to obtain a satisfactory effect (resistance) has long been recognized (Dundee and Gray, 1953). A similar phenomenon has been reported.

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**Table II. The percentage of each neuromuscular blocker excreted in the urine (Miller, 1985)**

<table>
<thead>
<tr>
<th>Neuromuscular blocker</th>
<th>Percent excreted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallamine</td>
<td>&gt; 95</td>
</tr>
<tr>
<td>Alcuronium, pancuronium</td>
<td>60-90</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>25-60</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>3.5</td>
</tr>
<tr>
<td>Suxamethonium, atracurium</td>
<td>None</td>
</tr>
</tbody>
</table>

**Table III. The percentage of each neuromuscular blocker recovered in the bile over 24 h after a bolus dose (Duvaldestin, Lebrault and Chauvin, 1985)**

<table>
<thead>
<tr>
<th>Neuromuscular blocker</th>
<th>Percent recovered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcuronium</td>
<td>15-20</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>12</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>10</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>12</td>
</tr>
<tr>
<td>Gallamine</td>
<td>&lt; 0.5</td>
</tr>
</tbody>
</table>
in cirrhotic patients, together with difficulty in antagonism of block following pancuronium (Duvaldestin et al., 1978) and following the use of large doses of vecuronium (0.2 mg kg\(^{-1}\)) (Hunter, Parker et al., 1985; Lebrault et al., 1985). Resistance to atracurium has also been encountered in a patient with a large liver abscess and abnormal liver function (Gyasi and Naguib, 1985).

In obstructive liver disease an increased volume of distribution of pancuronium has been shown with consequent prolongation of effect (Westra, Keulemans et al., 1981; Westra, Vermeer et al., 1981). In contrast gallamine, which is excreted entirely by the kidney, was found by the same workers to have a pharmacokinetic profile in obstructive liver disease similar to that of healthy subjects.

In clinical practice, the difference in the pharmacokinetics and pharmacodynamics of non-depolarizing neuromuscular blocking drugs in patients with cirrhotic as opposed to obstructive liver disease is probably unimportant. It seems probable that, in all these oedematous patients, an increased volume of distribution of the loading dose of the drug results in apparent initial resistance to the effects of the blocker. The impairment of liver function in these cases, however, results in a decreased rate of metabolism of any drug metabolized in that organ. Prolonged action of the blocker thus ensues as the elimination of the agent then depends mainly on the kidney, although redistribution, perhaps to non-specific receptors, will influence clinical antagonism. Such redistribution is usually sufficient to ensure clinical recovery after a single dose of blocker, but after repeated incremental doses difficulty in obtaining satisfactory antagonism of residual blockade frequently ensues.

In addition to the altered pharmacodynamics of non-depolarizing neuromuscular blocking agents in the presence of liver disease, a great variation between patients in the duration of action of equivalent doses of such drugs is recognized. For many years attempts have been made to relate altered plasma protein concentrations, and the degree of plasma protein binding, to this marked variation. Unfortunately, different methods of assay appear to give widely different results and it now seems that there is little difference in the percentage of plasma protein binding of either tubocurarine, pancuronium or vecuronium in cirrhotic patients compared with healthy controls (Meijer et al., 1979; Duvaldestin and Henzel, 1982).

**Renal disease**

With the exception of suxamethonium and atracurium, which are broken down in plasma, all neuromuscular blocking drugs are excreted at least in part by the kidney (table II).

Before the advent of atracurium and vecuronium, tubocurarine was widely considered to be the drug of choice in patients with renal failure, albeit in reduced dosage, because this was the only agent for which biliary excretion had been shown to be increased in the absence of renal function (Cohen, Brewer and Smith, 1967). The obvious problem with all the neuromuscular blockers which are largely excreted by the kidney is that prolonged curarization may be seen after their use, and this is particularly so after repeated incremental doses (Gibaldi, Levy and Hayton, 1972). This manifests itself as a poor antagonism of residual neuromuscular blockade in the presence of a residual amount of the relevant blocker in the plasma, with resultant respiratory embarrassment and acidosis.

There is a wide range in the degree of residual blockade that may remain: in some patients it may be minimal, being manifest only as diplopia (Hunter, Jones and Utting, 1984) or it may be extreme and require artificial ventilation for several hours, or even days (Riordan and Gilbertson, 1971). As gallamine is almost totally excreted by the kidney, it is not surprising that there are reports in the literature of renal transplant patients receiving artificial ventilation for several days after a single dose of the drug (Churchill-Davidson, Way and de Jong, 1967). It is contraindicated in the anephric patient.

**Atracurium and laudanosine.** There are now several reports of the successful use of atracurium in anephric patients (Hunter, Jones and Utting, 1982b; Fahey et al., 1984). Concern has been expressed, however, that the major break-down product, laudanosine, which in large doses is known to produce epileptiform seizures in dogs (Chapple, Miller and Wheatley, 1985) may have similar adverse effects in humans, especially in renal failure patients, since it is excreted mainly by the kidney (Fahey et al., 1985). The concentrations of laudanosine detected by these workers in renal transplant patients were, however, much smaller than those necessary to induce seizures in experimental animals. Prolonged infusions of
atracurium to patients in renal failure, for example, in the intensive therapy unit might result in high blood concentrations of laudanosine, however. A recent report suggests that such infusions can be used safely, even in patients with renal failure, for up to 36 h (Griffiths, Hunter and Jones, 1986). Nevertheless, further study is needed to establish the safety of long-term infusions of atracurium in such patients, particularly with regard to serum laudanosine concentrations.

As a result of animal studies it has also been suggested that, in the presence of plasma concentrations of laudanosine comparable to those found in humans after the administration of a bolus dose of atracurium, the MAC value for halothane is increased (Shi et al., 1985). These workers suggest that laudanosine may increase cerebral irritability and be responsible for an increase in anaesthetic requirement. There are at present, however, no clinical reports of experience in humans to support this hypothesis.

Vecuronium, which is only excreted unchanged to a small extent in the urine (Upton et al., 1982), also offers a significant advance in the treatment of patients with renal failure (Fahey et al., 1981; Hunter, Jones and Utting, 1984). There has, however, been a report of two cases of resistance to the drug in renal failure patients, both of whom were very sick; this phenomenon has not been satisfactorily explained (Hunter, Jones and Utting, 1984). Atracurium is probably the best drug for use in patients in renal failure.

**Age**

The duration of action of non-depolarizing neuromuscular blocking agents varies with the age of the patient. Neonates have been shown to be sensitive to tubocurarine (Bush and Stead, 1962), alcuronium (Bush, 1965) and pancuronium (Bennett et al., 1975) and, to a lesser extent, to atracurium and vecuronium (Brandom et al., 1983; Nightingale and Bush, 1983). Compared with adults, children of school age appear to be resistant rather than sensitive to non-depolarizing neuromuscular blocking drugs, and then with advanced age an increasing sensitivity develops. In the elderly this increased sensitivity is probably accounted for by slower metabolism and excretion of drugs, in contrast to the neonate, in whom it is more likely to be related to a decreased number of post-synaptic receptors. Thus a decreased clearance of pancuronium (McLeod, Hull and Watson, 1979), alcuronium (Stephens et al., 1984) and tubocurarine (Matteo et al., 1985) have all been demonstrated in the elderly. Both the onset and the duration of action of vecuronium 0.07 mg kg\(^{-1}\) have been shown to be prolonged in old age (d'Hollander et al., 1982; d'Hollander, Nevelsteen et al., 1983). D'Hollander's group did not find such prolongation with atracurium (d'Hollander, Luyckx et al., 1983), for which the responses were compatible with those reported clinically in the elderly for atracurium by Rowlands (1983). A recent pharmacokinetic study of single dose-response curves for vecuronium, using smaller doses of the drug (up to 0.04 mg kg\(^{-1}\)) has, however, suggested that there is no significant difference between the younger and older patient within this lower dose range (O'Hara, Fragen and Shanks, 1985). It would seem that the sensitivity to vecuronium in old age is probably partly related to dosage. It is possible, therefore, that atracurium is the drug of choice in elderly patients, but it is imperative that, with any neuromuscular blocker, care is exercised, particularly in respect to the need for a reduced dose in this age group.

**NEUROMUSCULAR DISORDERS**

Neuromuscular blocking agents act primarily at the post-synaptic membrane of the neuromuscular junction. It is therefore to be expected that patients who have a pathological process at this site, such as myasthenia gravis or those with muscle disorders, frequently show an abnormal response to neuromuscular blocking drugs. The primary problem in patients with these diseases is that the response to both depolarizing and non-depolarizing blockers is unpredictable. In addition, worse problems may occur when the disease is undiagnosed in the patient being anaesthetized. The subject has been fully reviewed by Azar (1984).

**Myasthenia gravis**

In this disease, which occurs more commonly in females, patients frequently present with weakness of cranial muscles, especially the ocular and oro-pharyngeal groups. Typically, this muscle weakness gradually spreads throughout the body, involving not only the limbs, but also the muscles of respiration. The degree of weakness varies from day to day, but is associated with excessive fatiguability of the muscle groups involved. No neurological deficit is demonstrable and patients
show consistent improvement after therapy with cholinergic drugs. There is great variability in the rate of progression of the disease, and if resistance to cholinergic agents develops, steroids or other immunosuppressant drugs such as azathioprine are often introduced. Myasthenia gravis is frequently associated with hyperplasia of the thymus and, if tolerance also develops to immunosuppressant agents, thymectomy may be performed.

In pathological terms, myasthenia gravis is an autoimmune disease affecting the neuromuscular junction, in which the patients develop antibodies to the post-synaptic acetylcholine receptors, leading to a decrease in both their number and half-life. As the disease progresses, presynaptic receptors sites may also become affected and fade of the train-of-four twitch response may then be seen even before any blocking agent is given. The response of such patients to both depolarizing and non-depolarizing neuromuscular blocking drugs is unpredictable, depending to a certain extent on the degree and duration of the disease process. Churchill Davidson and Richardson (1953) were the first to report that myasthenia patients showed initial resistance to depolarizing neuromuscular blockers, followed by a dual block; this was later substantiated by Foldes and McNall (1962). In contrast, marked sensitivity was demonstrated to non-depolarizing blocking agents; for example, it was found that tubocurarine, in doses as small as 2 mg, produced a clinical block (Foldes and McNall, 1962).

It seems, however, that when myasthenic patients are in remission they may tolerate normal doses of non-depolarizing blockers; certainly this has been demonstrated in the case of pancuronium (Blitt, Wright and Peat, 1975). This may explain the normal response of some myasthenic patients to suxamethonium. Because of this variability in response, continuous neuromuscular monitoring is necessary when a neuromuscular blocking drug is required in the myasthenic patient.

Small doses of both atracurium (Baraka and Dajani, 1984; Bell et al., 1984) and vecuronium (Hunter, Bell et al., 1985) have been used safely in myasthenic patients and these agents appear to offer a substantial advantage over tubocurarine. The new blocking drugs may become the preferred agents in patients with myasthenia gravis in whom a neuromuscular blocker is required; certainly there is no longer an indication for deep inhalation anaesthesia in these patients.

There is a wide variation amongst clinicians in regard to the question of continuation or otherwise of anticholinesterase therapy immediately before surgery in the myasthenic patient. If therapy is stopped before operation then the patient is often very weak on presentation for surgery and, therefore, is less likely to need a blocking drug, or will need less of it. By the end of surgery, however, the patient is even weaker, and then larger doses of anticholinesterase may be indicated. It is probably preferable, therefore, to continue routine therapy until induction of anaesthesia.

**Myasthenic syndrome**

The appearance of proximal muscle weakness, having many of the features of myasthenia gravis, in patients with advanced carcinoma was first described by Henson, Russell and Wilkinson (1954) and the particular association of oat-cell carcinoma of the bronchus (in up to 1% of patients) with a similar myopathy was then noted by Eaton and Lambert (1957). In this syndrome, unlike myasthenia gravis, the patients are very sensitive to suxamethonium, in addition to the non-depolarizing neuromuscular blocking drugs, and they respond poorly to treatment with anticholinesterase. Also in contrast to myasthenia gravis, a growth in electromyograph potential on low frequency tetanic stimulation is seen, together with marked post-tetanic facilitation (Wise, 1962). This pattern probably explains the transient increase in muscle strength which may be seen on exertion in this condition, although this may be followed by a prolonged period of excessive fatigue. A typical anaesthetic presentation of such a case consists of a male patient undergoing bronchoscopy for possible carcinoma of the bronchus with failure to resume effective respiratory muscle action in the normal way following a single dose of suxamethonium.

**Myotonic dystrophy**

This is the commonest muscle dystrophy of adult life which also varies greatly in severity between patients, the mild form being associated with few symptoms or signs. It presents typically with facial weakness, producing an expressionless facies, ptosis, dysarthria, wasting and weakness of the sternomastoids and initially of the proximal muscle groups, followed later by progressive distal muscle involvement. Classically, the myotonia produces an inability to relax the grip. Myotonia dystrophia is a multisystem disease: other features
include premature frontal balding and cataracts, testicular atrophy, low intelligence and myocardial conduction defects.

The use of neuromuscular blocking drugs in this inherited condition (autosomal dominant) has been recently reviewed by Aldridge (1985). Suxamethonium should be avoided as it may accentuate the myotonia, causing respiratory muscle spasm and subsequently airway problems, because the rigidity may make endotracheal intubation impossible. It has been suggested that the increase in serum potassium concentration produced by suxamethonium may be responsible for this increased rigidity, as marked hyperkalaemia has been shown experimentally to produce spontaneous myotonic discharges. As neostigmine has been reported to worsen the myotonia in myotonic dystrophy, it is probably more appropriate to allow spontaneous recovery after the use of a non-depolarizing neuromuscular blocker (Buzello, Krieg and Schlickewei, 1982). It has, therefore, been suggested that atracurium or vecuronium, which have shorter half-lives than the conventional myoneural blockers, are very useful agents in this condition (Nightingale, Healy and McGuinness, 1985). Finally, it must be remembered that these patients have a reduced muscle mass and therefore smaller doses of all blocking drugs are still indicated if excessive blockade is to be avoided.

**Duchenne muscular dystrophy**

This is another inherited condition, resulting from a sex-linked recessive gene and, therefore, seen mainly in males. It presents early in life, usually between 2 and 6 years, initially with a clumsy gait which gradually progresses to a complete inability to walk and confinement to a wheelchair by 8–11 years. In addition to the progressive musculo-skeletal deformity, which spreads to the shoulder girdle muscles and causes fatty replacement of muscle tissue, obstructive cardiomyopathy frequently develops, evidence for which is detectable on the electrocardiogram and is accompanied by evidence of cardiac enlargement on the chest x-ray. The resting plasma creatinine phosphokinase concentration is frequently increased.

Affected patients often require orthopaedic surgical procedures (e.g. for the associated kyphoscoliosis) or surgery for incidental operations such as dental extraction. Following administration of suxamethonium or halothane they may develop a hyperpyrexic response similar to that characteristic of malignant hyperthermia, associated with a further increase in serum creatinine phosphokinase concentration, myoglobinuria and a metabolic acidosis which may lead to cardiac arrest. Not only may this occur during anaesthesia, but delayed respiratory insufficiency may occur several hours after a full recovery from an anaesthetic (Smith and Bush, 1985).

**Malignant hyperthermia**

It is now well accepted that suxamethonium should be avoided in this condition (Gronert, 1980). For many years pancuronium was considered to be the drug of choice in susceptible patients (Cain and Ellis, 1977), although, as neostigmine may precipitate a cholinergic crisis, it is considered preferable to allow spontaneous recovery from any non-depolarizing neuromuscular blocking agent (Ellis, 1980). In the case of the older non-depolarizing agents, this practice may prolong anaesthesia inconveniently and atracurium and vecuronium possess advantages in this respect. Satisfactory use of both agents has been reported in patients susceptible to malignant hyperpyrexia (Buzello et al., 1985; Michel and Fronfield, 1985), although prolongation of the duration of action of vecuronium has been observed in a susceptible patient pretreated with dantrolene (Driessen, Wuis and Gielen, 1985). Dantrolene, which mainly acts by interfering with calcium uptake into or release from the sarcoplasmic reticulum, has been shown, when given alone, to produce a dose-dependent depression of the mechanical twitch response and a prolonged decrease in grip strength (Flewelling et al., 1983). It is possible that similar problems may be encountered when other neuromuscular blocking agents are administered in the presence of this drug.

**MISCELLANEOUS EFFECTS**

**Burns**

A variety of causes were initially postulated for the cardiac arrests that were recognized to occur, albeit rarely, when the severely burned patient was anaesthetized; these included vagal stimulation, acidosis, fluid depletion, reduced concentrations of pseudocholinesterase, and overdosage of anaesthetic agents. Gradually it became apparent that hyperkalaemia induced by suxamethonium was the usual cause; in burned patients suxa-
methonium causes a more marked increase in serum potassium concentrations than in the healthy control, probably because of the extensive cellular damage produced by the thermal injury (Bush, 1964; Tolmie, Joyce and Mitchell, 1967). For this reason suxamethonium should be avoided in the severely burned patient.

The burned patient may show an increased requirement for non-depolarizing muscle relaxants. This has certainly been reported repeatedly with tubocurarine (Bush, 1964; Martyn et al., 1980), but the phenomenon has proved difficult to explain. Resistance appears not to result from an increased volume of distribution of tubocurarine, or from an increased plasma protein binding, leakage through the burned area or increased renal excretion of the blocker. It is possible that there may be an increased number of acetylcholine receptors at the neuromuscular junction following thermal injury which have an increased affinity for non-depolarizing neuromuscular blocking drugs (Martyn et al., 1982).

Acid-base disturbances

It has long been accepted that respiratory acidosis potentiates the neuromuscular blockade produced by tubocurarine and pancuronium (Baraka, 1964; Norman, Katz and Seed, 1970), whilst respiratory alkalosis had a slight antagonist effect (Payne, 1958). There is more controversy, however, about the effect of metabolic acidosis on the duration of neuromuscular blockade produced by non-depolarizing neuromuscular blocking drugs: it was thought that potentiation could occur in this condition too (Brookes and Feldman, 1962; Bush and Baraka, 1964), but more recently this has been denied (Miller et al., 1978); these workers found more marked potentiation of tubocurarine and pancuronium in conditions of metabolic alkalosis and a similar picture was reported with gallamine in animals (Hughes, 1970).

In a fashion similar to the older agents, the duration of action of vecuronium has also been shown to be increased by respiratory acidosis and reduced by respiratory alkalosis (Gencarelli et al., 1983). Although the breakdown of atracurium is pH dependent, the range of plasma pH is small whatever the disease state, compared with that required to have an effect on the degradation of the drug sufficient to be of clinical significance. Indeed, the clinical significance of any change in acid–base status on the duration of action of a non-depolarizing neuromuscular blocking agent is probably slight.

Electrolyte disturbance

The normal resting membrane potential is dependent primarily on the distribution of potassium ions between the intracellular and extracellular compartments. A reduction in extracellular potassium results in hyperpolarization of the cell membrane and, therefore, a potentiation of neuromuscular blockade. This hyperpolarization would not occur if the intracellular potassium decreased to the same extent. Unfortunately the serum potassium, measured clinically, gives no indication of the changes in trans-membrane potential and Feldman (1963) has suggested that, in chronically depleted states, such as occur with regular diuretic therapy, it is probable that both extracellular and intracellular potassium concentration is reduced and therefore there is minimal effect on neuromuscular blockade. However, Miller and Roderick (1978) have demonstrated potentiation of pancuronium induced paralysis in cats in a state of diuretic-induced potassium depletion. Care must, therefore, be exercised in the use of a non-depolarizing neuromuscular blocking agent in the hypokalaemic patient to avoid a prolonged effect.

Release of acetylcholine from the nerve ending is reduced by an increase in magnesium ion and a reduction in calcium ion concentration and hence these electrolyte changes may well potentiate non-depolarizing neuromuscular blockade (Ghoniem and Long, 1970; Waud and Waud, 1978). This has been demonstrated clinically when magnesium sulphate has been used to treat pre-eclampsia patients (de Silva, 1973).

Hypothermia

In this state, both the degree and duration of block produced by the conventional non-depolarizing neuromuscular blocking agents such as tubocurarine and pancuronium are augmented (Park and MacNamara, 1979) and hypothermia has also been demonstrated markedly to prolong the action of atracurium in patients undergoing cardiac by-pass surgery (Flynn, Hughes and Walton, 1984). This is to be expected, since the spontaneous breakdown of this drug in the plasma is temperature dependent, even within the clinical range of body temperature.
A wide range of antibiotics is well recognized to potentiate the neuromuscular blockade produced by non-depolarizing neuromuscular blockers. Aminoglycosides, including streptomycin, neomycin, gentamycin and kanamycin were first to be incriminated and have now all been shown to reduce presynaptic quantal release of acetylcholine, although this effect can be reduced by the administration of calcium ions (Rawlins, 1978). Other antibiotics, including the polymyxins, lincosamides and tetracyclines have been shown to have not only pre-junctional, but also post-synaptic effects which, by decreasing the sensitivity of the receptor site to acetylcholine, will potentiate the action of neuromuscular blocking agents (Singh, Marshall and Harvey, 1982). There has even been a suggestion that metronidazole may augment neuromuscular blockade produced by vecuronium, although any such effect is probably of limited clinical significance, as only at exceptionally high concentrations has it been demonstrated that metronidazole may have a weak anticholinesterase effect. Certainly, such interaction has not been demonstrated to occur between metronidazole and pancuronium (McIndewar and Marshall, 1981).

Potentiation of the action of non-depolarizing neuromuscular blocking agents has been reported with a wide range of other drugs. Lithium carbonate has been shown to reduce pre-synaptic release of acetylcholine, especially potentiating the neuromuscular blocking properties of pancuronium in comparison with gallamine and tubocurarine (Hill, Wong and Hodges, 1977). Local anaesthetic agents such as lignocaine and bupivacaine, barbiturates, magnesium and quinidine not only reduce acetylcholine release, but in addition they stabilize the post-synaptic membrane for, by blocking the end-plate ionic channel which opens after acetylcholine has combined with the end-plate receptor, they prevent propagation of the action potential from the end-plate to the muscle fibre and thus potentiate neuromuscular blockade. Calcium ions are essential for presynaptic release of acetylcholine and it is not surprising, therefore, that prolonged neuromuscular blockade has been reported after the administration of calcium antagonists to treat cardiac arrhythmias in an anaesthetized patient who has received a non-depolarizing neuromuscular blocking drug. The interaction of calcium antagonists and non-depolarizing blockers has recently been reviewed by Jones (1985).

A range of other drugs has been shown in occasional reports to potentiate non-depolarizing neuromuscular blockers. In animal studies, trimetaphan has been shown to enhance the blockade produced by tubocurarine (Deacock and Hargrove, 1962) and it has been suggested that nitroglycerine is able to potentiate the block produced by pancuronium, although the mechanism of action is not clear (Glisson, El-Etr and Lim, 1979).

Diuretics too have been incriminated. Large doses of frusemide (1 mg kg$^{-1}$) have been shown to potentiate the action of tubocurarine, probably by presynaptic inhibition of transmitter release (Miller, Sohn and Matteo, 1976), although mannitol seems to be free of such side effects. In contrast, azathioprine and corticosteroids, which are used as immunosuppressants in transplantation surgery, have both been shown to reduce the potency of non-depolarizing myoneural blockers, necessitating the administration of larger doses of the drugs to produce satisfactory paralysis. The mechanism of action of these drugs in this respect is not, however, clear (Vetten, 1973; Hall, 1983), although it is possible that, like theophylline, they facilitate calcium transport across the cell membrane, thus potentiating muscle contraction.

It is also well recognized that the combination of two or more non-depolarizing neuromuscular blockers may produce a prolonged effect either by simple additivity, as with gallamine and tubocurarine and gallamine and pancuronium, or by true potentiation, as with pancuronium and tubocurarine (Waud and Waud, 1985). These effects are probably attributable to the multiple sites for acetylcholine binding on the post-synaptic membrane which the different blockers combine with and compete for to differing extents. The complexity of the effect is such as to suggest that the use of only one non-depolarizing neuromuscular blocker during the course of an anaesthetic is preferable.

Prior administration of a depolarizing agent such as suxamethonium is known to potentiate the duration of action of tubocurarine (Katz et al., 1969) and pancuronium (Katz, 1971), but this effect, although still present, is less marked when vecuronium (Kreig, Hendrickx and Cruyl, 1981) or atracurium is used (Hunter, Jones and Utting, 1982a).
The interaction between neuromuscular blockers and other drugs has recently been reviewed by Viby-Mogensen (1985).

**SUXAMETHONIUM**

This is now the only depolarizing neuromuscular blocking agent available in Great Britain and, although it is undoubtedly the drug of choice in some situations, for example when rapid endotracheal intubation is required or difficulty is anticipated, it is certainly not an ideal agent. It has certain side effects which are peculiar to itself and these will be discussed separately in this section.

**Muscle pains.** Patients commonly complain of aching and painful muscles following administration of the drug (Churchill-Davidson, 1954). The complaint is especially likely to arise in the unpremedicated young patient who is allowed out of bed soon after surgery, although they may occur in virtually any patient. Such pains act as a relative contraindication to the use of the drug, especially in the day case patient. As the likelihood of development of these pains is worsened by repeated doses of the drug, the use of intermittent boluses of suxamethonium must be of limited benefit, especially since the introduction of the shorter acting non-depolarizing agents makes the technique largely obsolete. Symptoms can be very distressing and the patient should be forewarned about them, and told that they may occur in such unexpected sites as the shoulders, the middle of the back and the upper abdomen.

The cause of the muscle pain is unknown and this makes prophylaxis difficult. Small doses of non-depolarizing neuromuscular blocking drugs are frequently used for this purpose and it has been suggested that an adequate interval, of the order of 3 min, must be allowed for significant receptor occupancy to occur after administration of the small dose of tubocurarine or gallamine before suxamethonium is given (Miller and Way, 1982a). Inherited abnormalities of the chemical structure of pseudocholinesterase can result in delayed metabolism of suxamethonium, however, and the prolonged apnoea which follows, although not life-threatening, represents a marked but uncommon inconvenience. Artificial ventilation must be adequately maintained in such circumstances and it is also essential to keep the patient anaesthetized throughout the apnoeic period.

**Prolonged apnoea.** Suxamethonium is metabolized in the plasma by the enzyme pseudocholinesterase, usually resulting in 90% recovery of neuromuscular function within 10 min of administration of a 50-mg dose (Hunter, Jones and Utting, 1982a). Inherited abnormalities of the chemical structure of pseudocholinesterase can result in delayed metabolism of suxamethonium, however, and the prolonged apnoea which follows, although not life-threatening, represents a marked but uncommon inconvenience. Artificial ventilation must be adequately maintained in such circumstances and it is also essential to keep the patient anaesthetized throughout the apnoeic period.

Several different genetic defects cause the action of suxamethonium to be prolonged, because the serum cholinesterase enzyme is polymorphic in nature. The molecular structure is determined by several different genes, abnormalities of which can produce an abnormal chemical structure of pseudocholinesterase. Phenotyping, that is the determination of any abnormality produced by the different genes, is based on the inhibition of activity of pseudocholinesterase by different substances, such as cinchocaine, fluoride, chloride and suxamethonium itself. The genes responsible are known as the normal (E\text{I}\text{a}), usual, atypical (E\text{I}\text{a}), fluoride-resistant (E\text{I}\text{a}), and silent (E\text{I}\text{a}) gene, respectively. Inheritance of these genes is autosomal in nature, with heterozygote patients manifesting less sensitivity to suxamethonium than
homozygotes. Thus approximately 94% of the population are homozygote for the normal genes (E₁, E₁), 4% are atypical heterozygotes (E₁, Eᵡ) in whom suxamethonium 50 mg would last approximately 30 min and less than 2% of the population have one of the other heterozygote or homozygote abnormalities which result in prolongation of the action of the drug, of which being homozygote for the fluoride (Eᵢu, Eᵢ) or silent gene (Eᵢ, Eᵢ) are the most common (Lim and Churchill-Davidson, 1981).

Non-inherited (acquired) factors can result in low plasma concentrations of pseudocholinesterase of normal molecular structure; for example, this occurs in pregnancy and the puerperium. Indeed, it may take as long as 6 weeks after delivery for the plasma concentrations of pseudocholinesterase to return to normal, although this is probably exceptional, a return usually occurring within 2 weeks (Whittaker and Selwyn-Crawford, 1983). Reduced concentrations have also been reported in chronic liver disease, malignancy, burns, hypothyroidism, blood dyscrasias and renal failure and such factors are thought to account for up to 17% of cases of prolonged apnoea (Bauld et al., 1974). The problem has been reviewed by Lim and Churchill-Davidson (1981).

Several drugs may also interfere with the activity of serum cholinesterase; these include amethocaine, phenothiazines, ketamine, oral contraceptives, propanidid, and trimetaphan in addition to the often quoted, but now rarely used ecbithiolate iodide eye drops. Tetrahydroaminoacrine (tacrine) and hexafluorenium should be mentioned: both inhibit pseudocholinesterase and were once used deliberately to prolong the action of suxamethonium, but this technique is now obsolete. It should be added that, whether the cause of the prolonged apnoea is an inherited or acquired defect in the plasma cholinesterase, there is little evidence to suggest that administration of fresh frozen plasma which contains some cholinesterase, is of any practical benefit.

Increased intraocular and intracranial pressure. There is much debate about the degree and duration of the increased intraocular pressure (IOP) produced by suxamethonium, an increase now thought to be explained by sustained contracture of the extraocular muscles which, having a large number of end-plates, respond to suxamethonium in a manner different from other muscle groups which show fasciculations, but similar to the contracture described in avian muscle.

This increase in intraocular pressure can be damaging, especially in the case of a penetrating eye injury, where expulsion of the vitreous humour can ensue. The subject has recently been reviewed by Adams and Salt (1985). Non-depolarizing neuromuscular blocking drugs do not increase the IOP and are therefore less damaging to the open eye, but in patients with a full stomach requiring emergency surgery suxamethonium may still be the safest drug. It is important to note that the effect of endotracheal intubation in increasing the IOP in an incompletely paralysed patient can be much greater than that produced by suxamethonium (Wynands and Crowell, 1960).

The effect of suxamethonium on intra-cranial pressure (ICP) is less clear: some studies have demonstrated an increased ICP after the drug was administered (Marsh et al., 1980), but others have not (Bormann et al., 1980). Although non-depolarizing neuromuscular blocking drugs do not increase ICP directly, the tachycardia produced by gallamine and pancuronium may have adverse effects on intracranial vascular pathology. Furthermore, the potent histamine releasing properties of tubocurarine may produce cerebral vasodilatation. Thus suxamethonium may not be contraindicated if blocking agents are required. Atracurium has been shown to have little effect on ICP in patients with a cerebral tumour (Minton et al., 1985). This subject has recently been reviewed by Murphy (1985).

Increased intragastric pressure. This occurs during the voluntary muscle fasciculations which follow the administration of suxamethonium, pressures of up to 40 mm Hg being recorded. However, as the lower oesophageal sphincter pressures have also been shown to increase to an even greater extent at this time, the risk of regurgitation is probably reduced. This subject has been reviewed by Smith, Dalling and Williams (1978).

Hyperkalaemia. Injection of suxamethonium 1 mg kg⁻¹ in humans increases the serum potassium concentration by approximately 0.5 mmol litre⁻¹ (Paton, 1959). In patients with an already increased serum potassium concentration, such as those in renal failure, the administration of this drug may therefore precipitate life-threatening
cardiac arrhythmias. In addition to the hyperkalaemia caused by suxamethonium in patients with muscle disorders, to which reference has already been made, marked hyperkalaemia has also been reported to occur following suxamethonium in a range of neurological disorders in which muscle denervation and atrophy occurs. These include hemiplegia, following diffuse head injury, encephalitis, ruptured cerebral aneurysm, tetanus and paraplegia (Azar, 1984) and, as has been mentioned previously, in burned patients.

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NEUROMUSCULAR BLOCKING DRUGS


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