Neuromuscular blocking drugs (NMBDs) have become an established part of anaesthetic practice since Griffith and Johnson in Montreal first described the use of curare to facilitate muscle relaxation in a healthy man undergoing an appendicectomy in 1942.

Structure of NMBDs

All the NMBDs available in the UK are quaternary ammonium compounds. They are structurally related to acetylcholine (ACh), which contains a quaternary nitrogen group (\(\text{N}^+ (\text{CH}_3)_3\)). As with ACh, the positive nitrogen atoms of NMBDs are attracted to the \(\alpha\)-subunits of the postsynaptic nicotinic receptor. Many NMBDs (e.g. succinylcholine, pancuronium and atracurium) contain two quaternary ammonium cations. These bisquaternary amines are more potent than monoquaternary amines (e.g. rocuronium, tubocurarine and vecuronium), which have only one permanent quaternary cation and one tertiary amine. However, at physiological pH, and especially in acidotic conditions, the tertiary amine can become protonated and therefore positively charged, increasing the potency of monoquaternary NMBDs. This factor has clinical significance; the effect of such NMBDs is potentiated in acidic patients.

The two quaternary ammonium groups are separated by a bridging structure that is lipophilic and varies in size. The bridging structure varies with different series of NMBDs and is a major determinant of their potency. NMBDs are classified as depolarizing and non-depolarizing drugs according to their action at the postjunctional nicotinic receptor.

Depolarizing NMBDs

Mechanism of action

Depolarizing drugs are agonists at ACh receptors. Succinylcholine is the only depolarizing NMBD in clinical use. It is effectively two ACh molecules joined through the acetate methyl groups. The two quaternary ammonium radicals bind to the two \(\alpha\)-subunits of one nicotinic receptor, and depolarization occurs. When voltage-sensitive sodium channels sense membrane depolarization (as a result of activation of the ACh receptors), they first open (Fig. 1A(b)) and thereafter close and become inactivated (Fig. 1A(c)). The membrane potential must be reset before the sodium channels can be reactivated (Fig. 1A(a)). This is a very rapid process with ACh (1 ms), as it is hydrolysed by acetylcholinesterase (AChE) within the synaptic cleft. However, succinylcholine is not metabolized by AChE, so a prolonged activation of the ACh receptors is produced. The sodium receptors at the end-plate and the perijunctional zone remain inactivated (Fig. 1A(c)) and junctional transmission is blocked. The muscle becomes flaccid.

Depolarization block is also called Phase I or accommodation block and is often preceded by muscle fasciculation. This is probably the result of the prejunctional action of succinylcholine, stimulating ACh receptors on the motor nerve, causing repetitive firing and release of neurotransmitter. Recovery from Phase I block occurs as succinylcholine diffuses away from the neuromuscular junction, down a concentration gradient as the plasma concentration decreases. It is metabolized by plasma cholinesterase (previously called pseudocholinesterase). Prolonged exposure of the neuromuscular junction to succinylcholine can result in (i) desensitization block or (ii) Phase II block.

Desensitization block

Desensitization occurs when ACh receptors are insensitive to the channel-opening effects of agonists, including ACh itself. Receptors are in a constant state of transition between resting and desensitized states, whether or not agonists are present (Fig. 1B). Agonists do promote the transition to a desensitized state or trap receptors in that state, as desensitized receptors have a high affinity for them.
Normally, ACh is hydrolysed so rapidly that it has no potential for causing desensitization. Desensitization block may be a safety mechanism that prevents overexcitation of the neuromuscular junction.

**Phase II block**

Phase II block differs from desensitization block. It occurs after repeated boluses or a prolonged infusion of succinylcholine. In patients with atypical plasma cholinesterase, Phase II block can develop after a single dose of the drug. The block is characterized by fade of the train-of-four (TOF) twitch response, tetanic fade and post-tetanic potentiation, which are all features of competitive block. After the initial depolarization, the membrane potential gradually returns towards the resting state, even though the neuromuscular junction is still exposed to the drug. Neurotransmission remains blocked throughout.

Possible explanations for the development of Phase II block include presynaptic block reducing the synthesis and mobilization of ACh; postjuncional receptor desensitization; and activation of the sodium-potassium ATPase pump by initial depolarization of the postsynaptic membrane, which repolarizes it. Inhalation anaesthetic drugs accelerate the onset of Phase II block. Anticholinesterase drugs can be used to antagonize it, but the response is difficult to predict. Therefore, it is advisable to allow spontaneous recovery.

**Pharmacology of succinylcholine**

The dose of succinylcholine required for tracheal intubation in adults is 1.0–1.5 mg kg\(^{-1}\). This dose produces profound block within 60 s, which is faster than any other NMBD presently available (Table 1). Neuromuscular block starts to recover within 3 min and is complete within 12–15 min. Plasma cholinesterase has an enormous capacity to hydrolyse succinylcholine, such that only a small fraction of the injected dose actually reaches the neuromuscular junction.

Succinylcholine has several undesirable side-effects which limit its use. It stimulates muscarinic and nicotinic receptors (as does ACh).

**Cardiovascular effects**

Stimulation of muscarinic receptors in the sino-atrial node produces bradycardia, especially in patients with a high vagal tone (e.g. children). In adults, bradycardia is seen more commonly after repeated increments. Anticholinergic drugs (e.g. atropine) are effective in preventing or treating the bradycardia. Nodal rhythm or ventricular arrhythmias may develop.

**Muscle pain**

Muscle pain is most often experienced the day after surgery and is worse in ambulatory patients. It is more common in the young and healthy with a large muscle mass. Children, elderly and pregnant women complain less frequently. The pain is thought to be a result of the initial fasciculations and occurs in unusual sites, such as the diaphragm, intercostal muscles and between the scapulae. The pain is not relieved by conventional analgesics. Various preventive measures have been recommended, but none is effective in all cases. These include precurarization, whereby a small dose of a non-depolarizing NMBD is given 2–3 min before the administration of succinylcholine (e.g. atracurium 2.5 mg). This technique reduces the potency of succinylcholine, requiring a larger dose to
produce the same effect. Other drugs that have been used include benzodiazepines, lidocaine, calcium, magnesium and repeated doses of thiopental.

**Increased serum potassium**

Administration of succinylcholine 1.0 mg kg\(^{-1}\) produces a small increase (\(<0.5\) mmol litre\(^{-1}\)) in serum potassium concentration in patients undergoing halothane anaesthesia. This effect is thought to be a result of muscle fasciculation, but it is not abolished by precurarization. A similar increase occurs in patients with renal failure, but these patients may already have an increased serum potassium concentration, and the further increase may precipitate cardiac arrhythmias. There are several conditions in which the release of potassium may be exaggerated. These include burns, muscular dystrophies (particularly relevant in undiagnosed paediatric patients), and paraplegia. The underlying mechanism may be increased release of potassium from swollen or damaged muscle cells or due to proliferation of extrajunctional receptors. Fatal hyperkalaemia after succinylcholine has also been reported in patients with muscle wasting secondary to chronic arterial insufficiency, prolonged immobilization, severe trauma and closed head injury.

**Malignant hyperthermia**

Succinylcholine is a recognized trigger factor for malignant hyperthermia and may also precipitate muscle contracture in patients with myotonic dystrophies.

**Hypersensitivity**

Hypersensitivity reactions occur with all NMBDs. However, unlike the non-depolarizing drugs which produce non-immunologically mediated (anaphylactoid) reactions, succinylcholine reactions generally represent classic Type 1 anaphylaxis (IgE-antibody mediated) and are more common after repeated exposure to the drug. Succinylcholine accounts for about 50% of hypersensitivity reactions to NMBDs. The incidence is estimated to be 1 in 4000 administrations.

### Increased intra-ocular pressure

The average increase in intra-ocular pressure after succinylcholine 1.0 mg kg\(^{-1}\) is 4–8 mm Hg. The increase occurs promptly after intravenous injection, peaking at 1–2 min and lasting as long as the neuromuscular block. The cause is multifactorial, including increases in choroidal blood volume, extra-ocular muscle tone and aqueous humour outflow resistance. There is concern that the increased intra-ocular pressure may be sufficient to cause expulsion of vitreal contents in the patient with a penetrating eye injury. This is unlikely.

### Increased intragastric pressure

Succinylcholine-induced increase in intragastric pressure is thought to be a result, in part, of the fasciculation of abdominal muscles and a direct increase in vagal tone. The increase in intragastric pressure is highly variable. However, there is a corresponding increase in lower oesophageal sphincter pressure, resulting in an increase in barrier pressure. Thus, there is no increased tendency to regurgitation in subjects with an intact lower oesophageal sphincter after succinylcholine.

### Prolonged paralysis

Reduced plasma cholinesterase activity, a result of inherited or acquired factors, may alter the duration of action of succinylcholine, leading to prolonged paralysis.

The structure of plasma cholinesterase is determined by a single gene that is located on chromosome 3 (3q26). Normal plasma cholinesterase, the gene of which is designated E\(_1^a\), is a tetrameric glycoprotein consisting of four identical subunits. Each subunit consists of 574 amino acids. Several variations in the amino acid sequence are recognized. The atypical gene, E\(_1^a\), produces the most common variant, where Asp-70 to Gly-70 substitution significantly decreases the binding capacity of the enzyme for succinylcholine. A standard dose of succinylcholine given to a patient who is a heterozygote for the atypical gene (E\(_1^a\), E\(_1^a\)) will have a clinical effect for about 30 min. In a patient who is a homozygote for the atypical gene (E\(_1^a\), E\(_1^a\)), succinylcholine may have an effect for more than 2 h. Other rarer variants of plasma cholinesterase genes are recognized [e.g. fluoride (E\(_1^a\)) and silent (E\(_1^a\)) genes]. The silent gene produces plasma cholinesterase that has virtually no capacity to hydrolyse succinylcholine; thus, paralysis in the homozygous patient (E\(_1^a\), E\(_1^a\)) may last for several hours. In such patients, non-specific esterases gradually clear the drug from the plasma.

Plasma cholinesterase activity may be reduced despite a normal structure. In these circumstances, reduced activity does not cause

![Table I Pharmacodynamic properties of neuromuscular blocking drugs](http://ceaccp.oxfordjournals.org/)

<table>
<thead>
<tr>
<th>Drug</th>
<th>ED(_{95})a (mg kg(^{-1}))</th>
<th>Intubating dose (mg kg(^{-1}))</th>
<th>Onset time(^b) (s)</th>
<th>Clinical duration(^c) (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
<td>0.3</td>
<td>1.0d</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>Benzylisoquinolines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>0.5</td>
<td>0.5-0.6</td>
<td>220</td>
<td>80+</td>
</tr>
<tr>
<td>Atracurium</td>
<td>0.23</td>
<td>0.5</td>
<td>110</td>
<td>43</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>0.08</td>
<td>0.15-0.2</td>
<td>170</td>
<td>16</td>
</tr>
<tr>
<td>Doxacurium</td>
<td>0.025</td>
<td>0.05</td>
<td>250</td>
<td>83</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>0.05</td>
<td>0.1</td>
<td>150</td>
<td>45</td>
</tr>
<tr>
<td>Aminosteroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancuronium</td>
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<td>0.1</td>
<td>220</td>
<td>75</td>
</tr>
<tr>
<td>Vecuronium</td>
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<td>0.1</td>
<td>180</td>
<td>33</td>
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<tr>
<td>Pipecuronium</td>
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<td>0.08</td>
<td>300</td>
<td>95</td>
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<td>0.6</td>
<td>75</td>
<td>33</td>
</tr>
<tr>
<td>Rapacuronium</td>
<td>1.2</td>
<td>1.5</td>
<td>&lt;75</td>
<td>15</td>
</tr>
</tbody>
</table>

\(a\)The dose that depresses the twitch height by 95%.

\(b\)Time to 25% depression of first twitch of train-of-four.

\(c\)Time to 25% recovery of first twitch of train-of-four.

\(d\)This is about three times the ED\(_{95}\).
markedly prolonged neuromuscular block. In one series, plasma cholinesterase activity as low as 150 u litre\(^{-1}\) (normal range 677–1560) did not cause the clinical duration of succinylcholine to exceed 22 min. Causes of reduced plasma cholinesterase activity include reduced enzyme synthesis (e.g. liver disease, carcinomatosis, starvation and renal disease); enzyme inhibition by other drugs (e.g. neostigmine, organophosphorus compounds and metolazopridine); and reduced availability of the enzyme in the presence of other substrates (e.g. etomidate, ester local anaesthetics, methotrexate and esmolol).

**Non-depolarizing NMBDs**

**Mechanism of action**

Non-depolarizing NMBDs antagonize the action of ACh in a competitive manner at the postsynaptic nicotinic receptor. They do not produce conformational changes in the receptor, unlike depolarizing drugs. Binding to one or both \(\alpha\)-subunits prevents access by ACh to depolarize the receptor. The binding of antagonists to the receptors is dynamic, with repeated association and dissociation. If the concentration of ACh is increased, it has a higher chance of occupying the receptor sites than the antagonist. With antagonist block, there is a gradual reduction in end-plate potential until it fails to reach the threshold to fire off a propagating action potential to produce muscle contraction. Under normal physiological conditions, more molecules of transmitter than are needed generate the end-plate potential, evoking a response that is greater than needed. At the same time, only a fraction of the available receptors are used to generate the signal. Neuromuscular transmission therefore, has a substantial margin of safety.

Neuromuscular block, expressed as depression of the single twitch height, only becomes evident when 70–80% of receptors are occupied by non-depolarizing NMBDs. To produce complete block, at least 92% of receptors must be occupied. Non-depolarizing NMBDs, like the depolarizing drugs, also exhibit desensitization block. They bind tightly to desensitized receptors and can trap them in these states (Fig. 1B). This is a non-competitive block. When more receptors are in the desensitized state, the margin of safety of transmission is reduced. Many drugs used during anaesthesia increase the proportion of receptors in the desensitized state (e.g. inhalation anaesthetics, thiopental and local anaesthetics).

**Prejunctial action of non-depolarizing antagonists**

ACh acts on prejunctial nicotinic receptors in a positive feedback manner to increase its own release during high-frequency (>2 Hz) stimulation. These presynaptic receptors differ from postsynaptic receptors and from autonomic ganglionic receptors. Non-depolarizing NMBDs block prejunctial receptors, resulting in failure of mobilization of ACh to keep pace with the demands of the stimulation frequency. Clinically, this is manifest as tetanic fade and TOF fade, in which there is a reduction in twitch height with successive stimuli.

**Other non-competitive mechanisms of neuromuscular block**

Several drugs can interfere with the nicotinic receptors directly or via their lipid environment to change neuromuscular transmission. Besides desensitization block, ion-channel block occurs, in which some drugs block the flow of ions through the ACh receptor. There are two types of ion-channel block – open or closed. In closed-channel block, the drug molecules occupy the mouth of the receptors. By their presence, ions are prevented from passing through the channel to depolarize the end-plate. It has been proposed as the mechanism of action of tricyclic antidepressants, naltrexone and naloxone in potentiating neuromuscular block.

In open-channel block, the molecules enter the open ion channel and occlude it. It is use-dependent, which means that the molecules can enter the channel only when it is opened by an agonist. With the channels blocked, influx of sodium ions is obstructed. This prevents depolarization, and weaker or complete block of neurotransmission results. NMBDs cause open-channel block when present in high concentration. It is not likely that open-channel block is of great importance in clinical practice, but it may explain why it is difficult to antagonize profound neuromuscular block. It may also play a role in interactions of NMBDs and steroids, local anaesthetics, antibiotics, calcium-channel blockers or inhalation anaesthetics.

**Benzylisoquinolinium compounds**

Benzylisoquinolinium compounds include atracurium, mivacurium, doxacurium and cisatracurium; tubocurarine and other toxiferine derivatives (e.g. alcuronium) are also classified as benzylisoquinolines. They consist of two quaternary ammonium groups joined by a thin chain of methyl groups. They are more liable to breakdown in the plasma than the aminosteroid compounds. They lack any vagolytic effect but are more likely to release histamine. The methyl chain contains one or more chiral atoms, which leads to the existence of several stereoisomers of these drugs.

**Tubocurarine**

Tubocurarine has a long onset of action and a prolonged duration of effect (Table 1). It causes marked histamine release and thus hypotension, with compensatory tachycardia. In large doses, it may produce ganglion block, which potentiates these cardiovascular effects. It is excreted unchanged in the urine with some biliary excretion. Its duration of action is increased in renal failure and in elderly patients. It is no longer available in the UK.

**Atracurium**

Atracurium has an intermediate duration of action (Table 1). It is presented as a racemic mixture of 10 stereoisomers and geometric isomers. It has no direct cardiovascular effects but may release histamine. Renal or liver impairment does not prolong its duration.
of action, as its metabolism is largely organ-independent. The drug undergoes Hofmann degradation (45%) and ester hydrolysis by non-specific esterases in the plasma. Only about 10% is excreted in the urine. A metabolite of Hofmann degradation (laudanosine) is a tertiary amine that has epileptogenic properties in high concentration, although this complication has not been reported in humans during general anaesthesia.

**Mivacurium**

Mivacurium is a short-acting drug with a duration of action twice that of succinylcholine (Table 1). It is useful for short surgical procedures requiring muscle relaxation and can be given as a continuous infusion for prolonged procedures. It has little direct cardiovascular effect. However, it causes histamine release, which leads to significant hypotension in doses greater than 0.2 mg kg\(^{-1}\). This is reduced by slow injection of the drug over 15–30 s.

Mivacurium is a racemic mixture of three isomers. The more potent \( cis\)-\( trans \) and \( trans\)-\( trans \) isomers form 95% of the drug; they are rapidly hydrolysed by plasma cholinesterase. The \( cis\)-\( cis \) isomer, which has 10–15 times less neuromuscular blocking activity than the other two, is slowly hydrolysed, mainly excreted in the urine and not likely to contribute to neuromuscular block. Mivacurium is hydrolysed at 88% of the rate of succinylcholine. Its duration of action is increased in patients with atypical plasma cholinesterase activity. The action of the drug may also be prolonged in patients with hepatic and renal disease if they have reduced plasma cholinesterase activity.

**Doxacurium**

Doxacurium is the most potent non-depolarizing NMBD; the intubating dose is 0.05 mg kg\(^{-1}\) (Table 1). It is only available in the USA. It produces no histamine release or cardiovascular effects over the clinical dose range. It has a long onset of action and a prolonged duration of effect (Table 1). It is excreted mainly in the urine and the bile.

**Cisatracurium**

Cisatracurium is the 1\( R \)-\( cis \) 1\( R \)-\( cis \) isomer of atracurium. It constitutes 15% of the mixture of atracurium. It is four times more potent than atracurium and has a slightly longer onset and duration of action (Table 1). It does not release histamine and has no direct cardiovascular effect. About 77% of the drug undergoes Hofmann degradation, and 15% is excreted unchanged in the urine. Renal failure is associated with a slight reduction in its plasma clearance, but its duration of action is not prolonged. As a lower dose is given, it produces less laudanosine than an equipotent dose of atracurium.

**Aminosteroid compounds**

Aminosteroid compounds contain an androstane skeleton to which ACh-like moieties are introduced at the A ring and D ring. They tend not to cause histamine release. Most depend on organ function for their excretion. Some undergo deacetylation in the liver, and the deacetylated metabolites may possess neuromuscular blocking properties.

**Pancuronium**

Pancuronium was the first steroid NMBD used clinically. It has a long duration of action, which is prolonged in the presence of renal impairment, as 60% of the drug is excreted unchanged through the kidney. A small amount undergoes deacetylation in the liver. The 3-hydroxy metabolite is about half as potent a neuromuscular blocking compound as the parent drug. Pancuronium does not release histamine but has direct vagolytic and sympathomimetic properties. It causes an increase in heart rate, blood pressure and cardiac output.

**Vecuronium**

Vecuronium is unstable in solution, so it is supplied as lyophilized powder. An intubating dose of 0.1 mg kg\(^{-1}\) has an onset of action of 3 min and a duration of action of about 30 min (Table 1). Compared with pancuronium, it is more lipid-soluble; this promotes significant hepatic uptake and biliary excretion. About 30–40% of the drug undergoes deacetylation in the liver, and one of the metabolites (3-desacytyleucuronium) is nearly as potent (\sim 80%) as the parent drug. In patients with renal failure, 3-desacytyleucuronium can accumulate and contribute to neuromuscular block during prolonged infusion of vecuronium. Vecuronium does not release histamine and has no direct effect on the cardiovascular system.

**Pipacuronium**

Pipacuronium resembles pancuronium in its chemical structure, onset of action and clinical duration of effect (Table 1). However, it is more potent – an intubating dose is 0.08 mg kg\(^{-1}\). In contrast to pancuronium, it has no vagolytic or sympathomimetic effects. Most of the drug undergoes renal elimination, and its duration of effect is prolonged in renal failure. It is not available in the UK.

**Rocuronium**

Rocuronium is a monoquaternary amine with a rapid onset and intermediate duration of action (Table 1). It is 6–8 times less potent than vecuronium. An intubating dose of 0.6 mg kg\(^{-1}\) produces satisfactory intubating conditions within 60–90 s, and it can be used as an alternative to succinylcholine in larger doses for rapid sequence intubation. It is more lipophilic than vecuronium; most of the drug is taken up by the liver and eliminated via the bile. The only metabolite detected in plasma (17-desacytyleucuronium) is 20 times less potent than the parent drug and not likely to contribute to neuromuscular block. Rocuronium has no direct sympathomimetic effects but, in high doses, has a mild vagolytic property. It is
more likely to cause anaphylactoid reactions than pancuronium or vecuronium.

**Rapacuronium**

Rapacuronium was introduced in the USA over 4 years ago. However, it was withdrawn in March 2001 because of serious adverse effects. It is less potent than the other aminosteroids and thus given in a larger dose (Table 1). Consequently, it has a rapid onset of action.

Rapacuronium has a short duration of effect; it is rapidly cleared from the plasma by hepatic uptake and deacetylation. Its 3-desacetyl metabolite has more potent neuromuscular blocking effects than the parent drug and may prolong the block if repeated boluses or a prolonged infusion are given. Rapacuronium causes histamine release, which is associated with an increase in heart rate and a decrease in blood pressure. It was the high incidence and severity of bronchospasm that led to its withdrawal.

**Key references**


King JM, Hunter JM. Physiology of the neuromuscular junction. *BJA CEPD Rev* 2002; 2: 129–33


See multiple choice questions 1–5.