Neuromuscular blocking drugs (NMBDs) are quaternary ammonium compounds structurally similar to acetylcholine (ACH); they act mostly at the post-junctional nicotinic receptor of the neuromuscular junction. NMBDs may be agonists (‘depolarising’ NMBDs) or antagonists (‘non-depolarising’ NMBDs) at the nicotinic receptor. Anticholinesterase drugs (also known as acetylcholinesterase inhibitors) are used to reverse the effects of non-depolarizing NMBDs. These drugs increase the concentration of ACh at the neuromuscular junction by inhibiting the enzyme acetylcholinesterase.

**INTRODUCTION**

Neuromuscular blocking drugs (NMBDs) are used in anaesthesia to impair neuromuscular transmission and provide skeletal muscle relaxation. These drugs enable the anaesthetist to perform tracheal intubation, facilitate ventilation and to provide optimal surgical operating conditions, for example during laparotomy.

**DEPOLARIZING NMBDS - SUXAMETHONIUM**

Suxamethonium (succinylcholine) is the only depolarizing NMBD in clinical use. Structurally it is two ACh molecules joined together and it acts as an agonist at the nicotinic receptor. Suxamethonium binds with the two alpha sub-units of the receptor mimicking ACh resulting in membrane depolarization. When depolarization occurs it causes muscle contraction, which occurs rapidly and is observed clinically as muscle fasciculation. After depolarization the membrane potential must be reset before further depolarization can occur and skeletal muscle remains in a state of flaccid relaxation until this occurs.

An intravenous dose of suxamethonium of 1.0–1.5mg.kg⁻¹ produces profound neuromuscular block within 60 seconds, this is faster than with any other NMBD. The blockade typically resolves spontaneously after approximately 10 minutes. Suxamethonium results in a phase I block, characterised by absence of fade and post-tetanic facilitation on peripheral nerve stimulation. Suxamethonium is hydrolysed rapidly by plasma cholinesterase to succinyl monocholine and choline. Prior to use it is stored at 4°C to prevent hydrolysis.

Although not commonly used, an infusion of suxamethonium can be used to produce prolonged neuromuscular blockade. 500mg of suxamethonium are put in a 500ml bag of saline (0.1% solution). The rate of infusion is adjusted to achieve the desired degree of relaxation, usually 5-15mg.kg⁻¹.h⁻¹ (5-15ml.kg⁻¹.h⁻¹). Pre-treatment with atropine is required if this technique is used.

Suxamethonium can be given intramuscularly at a dose of 3-5mg.kg⁻¹. The onset is considerably slower that when given intravenously. This route is usually used only in infants where venous access is not possible.

**Indications and side effects**

Suxamethonium has the most rapid and predictable onset of action of all the NMBDs. It also has a short duration of action, with recovery commencing at about 4 minutes and complete by about 10 minutes. This means that it is the drug of choice for anaesthesia when rapid tracheal intubation is required, for example in an emergency situation, or when a rapid sequence induction (RSI) is indicated in patients at risk of aspiration. It is also indicated when rapid recovery of neuromuscular function may be required.

Suxamethonium has several side effects:

**Bradycardia**

- Occurs due to stimulation of muscarinic receptors in the sino-atrial node.
- Bradycardia is more common in children and after repeated doses of the drug.
- Increased intra-ocular pressure.
- There is a theoretical risk of expulsion of vitreal contents with the use of suxamethonium in patients with a penetrating eye injury.
- This risk must be balanced with the risk of aspiration of gastric contents in emergency surgery.

**Muscle pain**

- Occurs commonly, especially in young, fit adults with early ambulation.
- Strategies such as precurarization exist to reduce the incidence but no strategy is fully preventative. This is where a small dose of a non-depolarising NMBD is given at least three minutes before suxamethonium, but is not recommended for routine use.

**Hyperkalaemia**

- Average serum potassium levels increase by 0.5mmol.l⁻¹ on administration of suxamethonium. Patients with pre-existing hyperkalaemia are at risk of cardiac arrhythmias and death.
- Life threatening hyperkalaemia can occur in patients with burns, muscular dystrophies, and

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**Summary**

Neuromuscular blocking drugs (NMBDs) are quaternary ammonium compounds structurally similar to acetylcholine (ACH); they act mostly at the post-junctional nicotinic receptor of the neuromuscular junction. NMBDs may be agonists (‘depolarising’ NMBDs) or antagonists (‘non-depolarising’ NMBDs) at the nicotinic receptor. Anticholinesterase drugs (also known as acetylcholinesterase inhibitors) are used to reverse the effects of non-depolarizing NMBDs. These drugs increase the concentration of ACh at the neuromuscular junction by inhibiting the enzyme acetylcholinesterase.

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over 90% of receptors must be occupied. 70-80% of receptors are antagonised, to produce a complete block and dissociation occurs. Neuromuscular blockade starts to occur when at least 50% of antagonists to the receptor is reversible and repeated association of the receptor and prevent depolarization due to ACh. The binding postsynaptic nicotinic receptor. They bind to one or both α-subunits.

Non-depolarizing drugs are competitive antagonists of ACh at the junctional receptors. Maximal risk of hyperkalaemia in burn patients occurs during days 9-60 after the burn.

Increased intragastric pressure
The rise in intragastric pressure following administration of suxamethonium is counteracted by a concomitant elevation in the lower oesophageal sphincter pressure.

Phase II block
This phenomenon may occur after large or repeated doses of suxamethonium. Neuromuscular block is prolonged and peripheral nerve stimulation results in fade of the train-of-four twitch height response and post tetanic facilitation.

Anaphylaxis
Suxamethonium is responsible for over 50% of anaphylactic reactions to NMBDs.

Prolonged block due to reduced plasma cholinesterase activity
This may be due to inherited or acquired causes.

Inherited causes of prolonged block after suxamethonium occur due to production of atypical plasma cholinesterase. The structure of the cholinesterase enzyme is determined genetically by a gene on chromosome 3, this gene is described as the usual gene (94% of the population homozygotes). Several variants from the usual gene exist - the three commonest are known as the atypical, silent and fluoride resistant genes. Individuals with variant genes have atypical cholinesterase enzyme, and develop prolonged neuromuscular block after suxamethonium. Duration of prolonged block varies from 30 minutes (e.g. people heterozygous for the atypical gene) to several hours (e.g. homozygotes for the silent gene.)

Acquired causes include reduced enzyme synthesis, which may occur in liver disease, carcinoma, pregnancy or starvation (hypoproteinaemic states), cardiac failure, renal failure, and burns. The co-administration of other drugs such as etomidate, ester local anaesthetics, methotrexate, remifentanil and esmolol can result in a reduction in plasma cholinesterase activity.

Malignant hyperthermia
This condition may be triggered by suxamethonium and therefore its use is absolutely contraindicated in susceptible patients.

NON-DEPOLARIZING NMBDs
Non-depolarizing drugs are competitive antagonists of ACh at the postsynaptic nicotinic receptor. They bind to one or both α-subunits of the receptor and prevent depolarization due to ACh. The binding of antagonists to the receptor is reversible and repeated association and dissociation occurs. Neuromuscular blockade starts to occur when 70-80% of receptors are antagonised, to produce a complete block over 90% of receptors must be occupied.

Non-depolarizing NMBDs are also believed to have an action at pre-junctional receptors at the neuromuscular junction. Stimulation of pre-junctional receptors by ACh normally results in further mobilisation of ACh to cope with increasing stimulation frequency. Non-depolarizing NMBDs antagonise these receptors and inhibit this process.

When assessing the block caused by non-depolarizing NMBDs with a peripheral nerve stimulator a characteristic response is observed. Fade of twitch height response occurs during a train of four or tetanic pattern of stimulation. Fade is due to the action of these drugs at the presynaptic receptor resulting in reduced availability of ACh with repeated nerve stimulation. Post tetanic facilitation of neuromuscular transmission is another feature of non-depolarizing neuromuscular blockade and is due to increased quantities of ACh in the synapse of the junction after tetanic stimulation.

Non-depolarizing NMBDs are not metabolised at the neuromuscular junction and resolution of block is due to a dilutional effect of the drug with time. They are highly ionised, water-soluble drugs and their volume of distribution approximates to that of plasma and extracellular fluid. There are two groups of non-depolarizing NMBDs, benzylisoquinolinium compounds and aminosteroid compounds.

Benzylisoquinolinium compounds
These drugs consist of two quaternary ammonium groups joined by a chain of methyl groups. They are more liable to break down in the plasma and often cause release of histamine; examples include tubocurarine, atracurium, cisatracurium and mivacurium.

Tubocurarine
A drug with a long onset and prolonged duration of action (see Table 1). It causes marked histamine release, with hypotension and tachycardia.

• Ganglion blockade may occur with large doses.
• Tubocurarine is excreted unchanged mostly in the urine but also in bile. Its effects are prolonged in renal failure. It has been superseded by agents with better side effect profiles and is no longer available in the UK.

Atracurium
A racemic mixture of 10 stereoisomers and geometric isomers. Atracurium has an intermediate onset and duration of action. It causes release of histamine but has no direct cardiovascular effects.

• Metabolism is by Hofmann degradation and ester hydrolysis in the plasma, hence its duration of action is independent of renal and hepatic function.

Cisatracurium
The R-cis R′-cis isomer of atracurium. It constitutes 15% of the parent compound and is four times more potent with a longer duration of action.

• Unlike atracurium it does not release histamine. It is metabolised by Hofmann degradation and does not accumulate in renal failure.

Mivacurium
Mivacurium is a drug with a short duration of action of
approximately 15 minutes, making it potentially useful for short procedures. It is a racemic mixture of three isomers that is hydrolysed by plasma cholinesterase.

- Mivacurium is associated with histamine release causing significant hypotension with doses greater than 0.2mg.kg$^{-1}$.
- Like suxamethonium its duration of action is increased in patients with atypical plasma cholinesterase.

**Aminosteroid compounds**

- All aminosteroid NMBDs possess at least one quaternary ammonium group attached to a steroid nucleus. They tend not to cause histamine release and most are metabolised in an end organ before excretion.

**Pancuronium**

- The first steroid NMBD in clinical use has a slow onset and long duration of action.
- It does not cause histamine release but has weak sympathomimetic properties and causes tachycardia.
- It is partly de-acylated in the liver to a metabolite with neuromuscular blocking properties, and partly excreted unchanged in the urine. Its action is prolonged in renal and hepatic impairment.

**Vecuronium**

- Vecuronium is structurally similar to pancuronium but has a slightly faster onset and shorter (intermediate) duration of action. It does not release histamine or have any cardiovascular effects.
- Metabolism in the liver occurs to active metabolites before being excreted in the bile and urine.
- Vecuronium is unstable in solution and is stored as powder and requires mixing with water prior to administration.

**Rocuronium**

- This monoquaternary amine has the most rapid onset of the clinically available non-depolarizing NMBDs.
- Intubating conditions can be achieved in 60-90 seconds after an induction dose of 0.6mg/kg. Rocuronium has an intermediate duration of action and is metabolised in the liver and excreted in the bile.
- Rocuronium has minimal cardiovascular effects and does not release histamine, however, it has a higher incidence of anaphylactic reactions than other aminosteroid NMBDs.

**ANTICHLINESTERASES**

Anticholinesterases (also known as acetylcholinesterase inhibitors) are agents that inhibit the action of the acetylcholinesterase enzyme at the neuromuscular junction. Enzyme inhibition leads to a reduction in the breakdown of ACh and potentiates its action.

Anticholinesterases are used in anaesthesia to reverse the effects of non-depolarizing NMBDs. Reversal of non-depolarizing neuromuscular blockade usually occurs at the end of surgery, and should not take place before some resolution of the block has already occurred. Early administration of anticholinesterase may be ineffective due to high receptor occupancy by the NMBD. Reversal of intermediate acting NMBDs with anticholinesterase should be at least 20 minutes after giving the drug. If peripheral nerve stimulation is used, at least 2 twitches on a train of four should be detected before attempting reversal. The most reliable sign that a block is fully reversed by anticholinesterase is a sustained response to tetanic stimulation with a peripheral nerve stimulator (i.e. no fade). However tetanic stimulation can be painful to apply in awake individuals. Clinical tests of adequate resolution of neuromuscular block include the ability to lift the head from the bed for 5 seconds, although this is a much less reliable assessment.

Anticholinesterases will augment the Phase I block due to depolarizing NMBDs and there is no role for anticholinesterases in reversing the effects of suxamethonium.

**Side effects of anticholinesterase agents**

Anticholinesterases cause a build up of ACh that results in potentiation of its effects at muscarinic receptors. This can cause bradycardia, miosis, GI upset, nausea, bronchospasm, increased bronchial secretions, sweating and salivation. For this reason an antimuscarinic such as glycopyrronium or atropine must be administered along with the anticholinesterase to minimise these effects.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg.g$^{-1}$)</th>
<th>Onset time (min)</th>
<th>Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
<td>1.0-1.5</td>
<td>&lt; 1</td>
<td>5-10</td>
</tr>
<tr>
<td>Tubocurarine</td>
<td>0.5</td>
<td>3-5</td>
<td>30-50</td>
</tr>
<tr>
<td>Atracurium</td>
<td>0.5</td>
<td>2-3</td>
<td>20-30</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>0.1</td>
<td>2-3</td>
<td>30-40</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>0.15-0.20</td>
<td>2-3</td>
<td>10-20</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>0.1</td>
<td>3-5</td>
<td>40-60</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.1</td>
<td>2-3</td>
<td>20-30</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>0.6</td>
<td>1-2</td>
<td>30-40</td>
</tr>
</tbody>
</table>
Anticholinesterase drugs

Neostigmine

- The most commonly used anticholinesterase in anaesthesia is neostigmine. This is a water-soluble quaternary ammonium compound that combines reversibly with the esteratic site of the acetylcholinesterase enzyme rendering it inactive for about 30 minutes.
- Neostigmine is given as an intravenous injection at a dose of 0.05mg.kg\(^{-1}\) (maximum 5mg), and should be administered with glycopyrronium 0.01mg.kg\(^{-1}\) or atropine 0.02mg.kg\(^{-1}\). Neostigmine starts to take effect after approximately 2 minutes but has its maximal effect at 5-7 minutes. It is excreted unchanged by the kidney and has a half-life of about 45 minutes.

Edrophonium

- This anticholinesterase forms an ionic bond at the anionic site of the enzyme. Bonding is reversible and short lived in the order of a few minutes.
- Edrophonium is used as a diagnostic test for myasthenia gravis. ACh potentiation by the drug results in a transient increase in muscle power in the patients with this autoimmune disease.
- Edrophonium is rarely used to reverse the effects of NMBDs as its effects are short lived and neuromuscular block may increase after an initial recovery.

Pyridostigmine

- This agent has a longer onset than neostigmine and lasts for several hours. It is used more frequently as a therapy for myasthenia gravis.

Physostigmine

- Like neostigmine and pyridostigmine, physostigmine acts reversibly at the esteratic site of the acetylcholinesterase enzyme.
- As it is more lipid soluble than the other agents it can be absorbed from the GI tract and crosses the blood brain barrier.

Organophosphorous compounds

- These substances are found in some pesticides and agents used in chemical warfare.
- Organophosphorous compounds form an irreversible bond with the enzyme and recovery only occurs after generation of new enzyme, which takes weeks. Poisoning results in salivation, sweating, bradycardia, bronchospasm and muscle weakness.
- Treatment is with atropine and supportive measures.

OTHER “REVERSAL” DRUGS

Sugammadex is a novel drug designed to antagonize the effects of aminosteroid NMBDs, particularly rocuronium. It is a cyclodextrin molecule, and rapidly reverses the effects of NMBDs by encapsulation.

FURTHER READING

- Pete Ricketts. Malignant hyperthermia. Update in Anaesthesia (2008); 24,1: 13-17
- Ackroyd C, Gwinnutt C. Physiology of the neuromuscular junction. Update in Anaesthesia (2008); 24,2: 38-40