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Muscle relaxants

By the perioperativeCPD team

Introduction

The introduction of neuromuscular blocking drugs revolutionised the practice of anaesthesia. Before the advent of muscle relaxants, anaesthesia was induced and maintained by intravenous or inhalation agents. Tracheal intubation was uncommon, and muscle relaxation, if needed was secured by deep inhalation anaesthesia with its attendant risks of respiratory or cardiac depression.

After the introduction of muscle relaxants, anaesthesia underwent a conceptual change. Anaesthesia was redefined as a triad of narcosis, analgesia and muscle relaxation, specific drugs being used to produce each of these effects.

History

The first European explorers to South America brought back reports of an arrow poison used by the indigenous Indians. In 1780, Abbe Felix Fontana discovered that this poison acted on the voluntary skeletal muscles rather than nerves and the heart.

Early in the 1800's Sir Benjamin Collins Brody experimented with one of these poisons called curare. He was the first to show that curare does not kill the animal and the recovery is complete if the animal's respiration is maintained artificially.

In 1850 Claude Bernard showed how the site of action of curare is neither on the nerve nor on the muscle, but on the neuromuscular junction.

The active constituent of curare, d-tubocurarine, was first used in the 1940's and from then on muscle relaxants became an essential part of anaesthesia
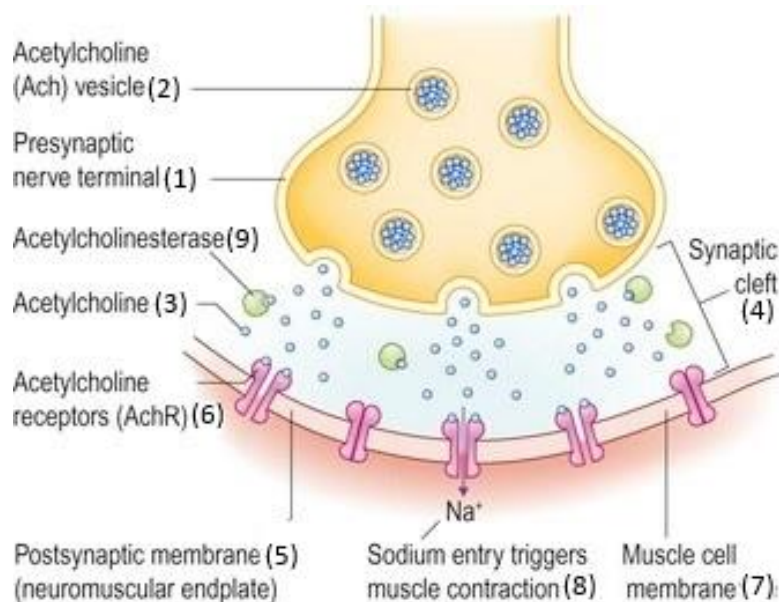
Suxamethonium, a depolarising muscle relaxant was introduced into clinical practice in 1951.

Neuromuscular Transmission

The passage of an impulse down a nerve fibre is an electrical phenomenon. Similarly, the spread of an impulse across a muscle fibre causing it to contract is also electrical.

However, the transmission of the impulse from the nerve fibre to the muscle fibre is a chemical process actioned by the acetylcholine. This occurs at the special junctional areas between the nerve fibres and muscle fibres which is called the neuromuscular junction.

The neuromuscular junction.

The nerve-ending part of the neuromuscular junction is called the presynaptic area or terminal (1). Acetylcholine is manufactured, stored (2) and, when a nerve impulse arrives, released from the of the nerve ending.

The acetylcholine (3) then crosses the extremely narrow gap or synaptic cleft (4) to arrive at the muscle side of the neuromuscular junction. This is called the postsynaptic area or neuromuscular end-plate (5).

The neuromuscular end-plate contains special acetylcholine receptor sites (6). On the arrival of sufficient acetylcholine the muscle membrane (7) becomes briefly permeable to sodium ions, which pass into the muscle cell and produce electrical depolarisation (8).

If the current of depolarisation (also called the motor end-plate potential) reaches a certain magnitude the depolarisation spreads to the adjacent part of the muscle fibre and travels across the surface of the muscle fibre, causing the contraction of the fibre and then the muscle.

In the meantime the acetylcholine disassociates from the receptor site and is broken down in a fraction of a second by an enzyme called acetylcholinesterase (9), which is present at the motor end-plate. The neuromuscular junction is then ready to receive and transmit the next nerve impulse. The whole process is nearly instantaneous.

There are two classes of neuromuscular blocking drugs; depolarising and non-depolarising.
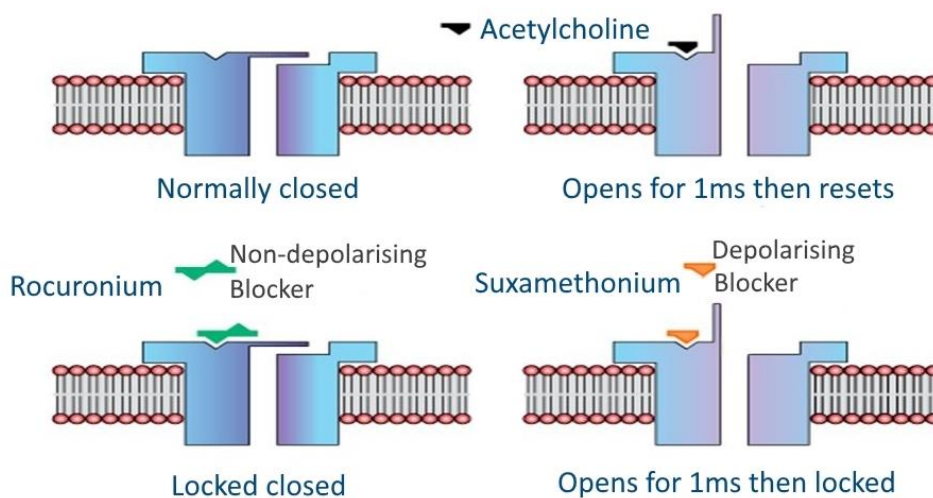
Depolarising Muscle Relaxants

Depolarising muscle relaxants produce depolarisation at the postsynaptic membrane in the same way as acetylcholine. They do this by having a similar structure to acetylcholine and binding to the same receptors, briefly opening the sodium channels.
The block is preceded by a short period of muscle fasciculation (uncoordinated muscle contractions) as the drug produces depolarisation.

It however is not rapidly metabolised like acetylcholine and blocks the receptor site producing a prolonged period of depolarisation. Further muscle contraction cannot occur while the site is blocked and the muscle stays relaxed and paralysis occurs.

Depolarising relaxants are metabolised through hydrolysis and by plasma cholinesterase which is an enzyme produced by the body.

Mechanism of non-depolarizing and depolarizings muscle relaxants

Acetylcholine

Normally closed   Opens for 1ms then resets

Rocuronium Non-depolarising Blocker   Suxamethonium Depolarising Blocker

Locked closed   Opens for 1ms then locked

Suxamethonium chloride (succinylcholine)

Suxamethonium is a very short-acting muscle relaxant and is the only depolarising agent still in use. It was described as early as 1906 and introduced into use in 1951.

It is commonly used for rapid sequence inductions (RSI) where fast intubation is a priority.

Usually 75-150mg (1-2 mg/kg) is given to intubate an adult. The onset of muscle relaxation is rapid after intravenous injection (<60 seconds) and lasts for 3-5 minutes.

Suxamethonium should not be reversed as it is very short acting. Giving neostigmine can prolong the block as it inhibits plasma cholinesterase as well as the acetycholinesterases.

Adverse effects of suxamethonium:

- **Muscle fasciculations** which occur before paralysis may be violent and may cause post-operative muscle pain. They are more commonly seen in women, the young and in those ambulant early in the postoperative period.
- **Increased intraocular pressure** which may be dangerous in certain eye procedures (i.e. penetrating eye injuries or intracranial disease).
- **Increased in serum potassium** which is a concern in severe burns patient's after the first 24 hours as the potassium will already be high.
- **Malignant hyperthermia**: suxamethonium can trigger the onset of malignant hyperthermia in those patients who have this genetic muscle disorder. Non-depolarising muscle relaxants are considered safe.
- **Anaphylaxis**: suxamethonium can cause allergic reactions, which range in severity from minor flushing of the skin to cardiac arrest and severe bronchospasm.
- **Cardiovascular:** suxamethonium can cause bradycardia, especially if second or further doses are given.
- **Increased intragastric pressure:** Suxamethonium results in increased intragastric pressure, although this is counteracted by a corresponding increase in lower oesophageal pressure.

Suxamethonium apnoea

Suxamethonium is metabolised by an enzyme in the blood called plasma cholinesterase. Metabolism is normally complete within 5-10 minutes. Some patients lack this enzyme or have an altered enzyme that does not metabolise suxamethonium as rapidly.

These patients may remain paralysed hours after a standard dose of suxamethonium, and must be kept anaesthetised and ventilated until the suxamethonium has been eliminated by other, slower methods (alkaline hydrolysis) that do not play a significant role in normal patients.

Dose

Intravenous 1-2 mg/kg
Intramuscular 3 mg/kg (emergencies only)

In an emergency, suxamethonium may be administered intramuscularly, but the onset of action is slower and less predictable than when given intravenously.

Phase II Block (Dual block)

Suxamethonium should not be given repeatedly as it can change its nature. With multiple doses desensitisation occurs at the nerve terminal, and the receptors becomes less sensitive to acetylcholine; the membrane repolarises and cannot be depolarised again.

The block increasingly shows the properties of a non-depolarising block, in particular it being possible to at least partially to reverse the block by an anticholinesterase.

Non-depolarising muscle relaxants (NDMR)

Non-depolarising muscle relaxants (or competitive blockers) have a slower onset and therefore are slower at achieving intubating conditions than depolarising muscle relaxants but they do not provoke muscle fasciculations or any of the associated complications of depolarising relaxants. They also have longer duration of action.

Mechanism of action

1. They attach themselves to the receptor sites on the postsynaptic membrane to which the acetylcholine molecules normally become attached, blocking them and preventing them from opening.
2. These competitive blockers reduce the number receptors available to acetylcholine resulting in endplate depolarisation falling below a level that is necessary for a muscle action to be generated and therefore causing paralysis.
3. Blockade starts when 70–80% of receptors at the junction are blocked, and is complete with 90% blocked. Small rapidly moving muscles (eyes, fingers) are paralysed first, then the larger trunk and abdominal muscles. Finally the intercostals and diaphragm.

Muscle function returns as the drug diffuses out into the plasma where it is metabolised; none is metabolised within the neuromuscular junction.

When a block is wearing off it is the respiratory muscles that recover first. Just because a patient is breathing does not mean they are fully reversed and they could still have a significant level of block present.

The effective duration of action ranges from around 15 minutes for mivacurium to more than an hour for pancuronium although this is highly dose dependant.

Paediatrics

When giving NDMR to children and infants they are more sensitive in terms of requiring a lower plasma concentration to produce a given effect but this is countered by an increased volume of distribution. This means that the dose does not have to vary significantly.
The adult dose per kg is appropriate for children and infants. The same is true for reversal with anticholinesterases but they do have a faster effect than in adults.

Elderly

Conversely, in the elderly with a less dynamic circulation, the speed of onset may be delayed. Also as both kidney and liver functions are expected to decrease with age they will be expected to have a prolonged action.

Pregnancy

Pregnancy has minimal effects on the pharmacodynamics and pharmacokinetics of muscle relaxants. NDMR are highly ionised which impedes placental transfer, resulting in minimal effects on the foetus. (Magnesium used in the treatment of pre-eclampsia will increase muscle relaxant effects).

Obesity

In severely obese individuals, administration of a NDMR based on actual body weight results in a rapid onset of action and a longer duration of action; thus, the dose should be modified down to account for this.

Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune disease in which neuromuscular transmission is defective. This causes muscle weakness due to a loss of functional acetylcholine receptors in skeletal muscle.

Patients with MG have a relative resistance to suxamethonium, a depolarizing muscle relaxant and have an increased sensitivity to non-depolarising muscle relaxants.

Because of this unpredictability some anaesthetists avoid muscle relaxants and depend on deep inhalational anaesthesia, for tracheal intubation and maintenance of anaesthesia. If a NMBA must be used atracurium is recommended.

Full recovery of intercostal and diaphragmatic muscles may be prolonged so close monitoring of respiratory function is essential.

Other factors lengthening the duration of action of non-depolarising muscle relaxants

- Prior administration of suxamethonium.
- Volatile anaesthetic agents i.e. sevoflurane, desflurane etc,
- pH changes – metabolic and respiratory acidosis.
- Hypothermia – including cardiac surgery.

Types of Non-depolarising muscle relaxants

NDMR fall into two groups based on their chemical structure:

Aminosteroid compounds (-ronium)

Aminosteroid relaxants tend not to cause histamine release and most are metabolised in the liver or excreted unchanged by kidneys.

They include vecuronium, rocuronium & pancuronium.

Benzylisoquinolinium compounds (-curium)

These drugs typically break down in the plasma and can often cause release of histamine release. Histamine release can cause skin flushing, hypotension, tachycardia and bronchospasm.

This group includes atracurium, cisatracurium and mivacurium.

Table 1. Dose, speed of onset and duration of neuromuscular blocking drugs.

	Dose (mg/Kg)	Typical Dose (75kg)	Onset time (min)	Duration (min)
Suxamethonium	1.0-2.0	75-150mg	< 1	5-10
Atracurium	0.3-0.6	25-50mg	2-3	15-30
Mivacurium	0.10-0.20	7.5-15mg	2-3	10-20
Cisatracurium	0.15	10-15mg	2-3	30-40
Vecuronium	0.1	7.5-10mg	2-3	20-30
Pancuronium	0.1	7.5-10mg	3-5	45-65
Rocuronium	0.6-1.2	50-100mg	1-2	20-40

Depolarising ☐   NDMR (Aminosteroid) ☐   NDMR (Benzylisoquinolinium) ☐

Benzylisoquinolinium NDMR

Atracurium

It is a commonly used intermediate acting relaxant which is predominantly broken down by Hoffman elimination (spontaneous decomposition in plasma and tissue at normal body pH and temperature) which makes it ideal for patients with renal and hepatic impairment.

This also makes atracurium very predictable and it wears off rapidly compared with the longer-acting relaxants. The main side effect is histamine release which is usually mild but severe reactions have been reported.

An intubating dose of 0.3-0.6 mg/kg (25-50mg in 75kg patient) will provide relaxation for 15-30 minutes.

Cisatracurium

Cistatracurium is a newer version of atracurium which was introduced in 1995. Compared to atracurium it has less histamine release although its onset time is longer than for and it has a longer duration of action. Like atracurium it is metabolised predominantly by Hoffmann elimination.

Its uptake has been patchy due to the higher cost for limited perceived benefit however with its price now dropping its use may show an increase.

An intubating dose of 0.15mg/kg (12mg in a 75kg patient) will provide relaxation for 30-40 minutes.

Mivacurium

Mivacurium has a structure similar to that of atracurium but a shorter duration of action (10-20 minutes) due to its metabolism by plasma cholinesterase (the same as suxamethonium). It may have histamine release with rapid injection.

Although initially popular for quick surgical cases it has developed a reputation for producing inconsistent blocks. Reversal is not routinely indicated due to its short duration of action but neostigmine can be used. However, there is debate to its effectiveness as neostigmine can inhibit the action of plasma cholinesterase.

An intubating dose of 0.2 mg/kg (15mg in a 75kg patient) will provide relaxation for 10-20 minutes.

Aminosteroid NDMR

Rocuronium

Rocuronium has an intermediate duration of action at a standard intubating dose. Although at higher doses (1.2mg/kg) you can achieve intubating conditions very rapidly, similar to suxamethonium.

Rocuronium has minimal cardiovascular effects although with large doses there is an increase in heart rate and mean arterial pressure. There is considered to be a risk of allergic reaction to the drug in some patients (particularly those with asthma), but studies show rates are similar to other relaxants of the same class.

It has a rapid onset (1-2 minutes) with an intubating dose of 0.6mg/kg (45mg in 75kg patient). The block last 20-40 minutes but is very dose dependant.

Vecuronium

Vecuronium is structurally similar to rocuronium and pancuronium but has a shorter duration of action. Vecuronium is called a 'clean' drug as it does not affect the cardiovascular system or precipitate the release of histamine.

Vecuronium is unstable in solution and is stored as powder which requires mixing with water prior to administration. Anecdotally this extra step of mixing prior to use may have contributed to it not being as widely used as expected.

An intubating dose of 0.1 mg/kg (7.5mg in a 75kg patient) will provide relaxation for 20-30 minutes.

Pancuronium

The first steroid based relaxant in clinical use has a slow onset and longest duration of action of available NDMR. It does not cause histamine release but can have a small positive sympathetic effect. Its use presently is limited to cardiac and transplant surgery although it is still popular in low resource countries due to its low cost.

An intubating dose of 0.1 mg/kg (7.5mg in a 75kg patient) will provide relaxation for 45-65 minutes.

Reversal

Although NDMRs will wear off over time, this process can be sped up by using an anticholinesterase drug such as neostigmine.

Neostigmine binds to the acetylcholinesterase which is responsible for breaking down the acetylcholine. It prevents this breakdown and as the levels of acetylcholine build up around the neuromuscular junction, they compete with and displace the muscle relaxant off the neuromuscular junction.

Once displaced, the muscle relaxant enters the systemic circulation where it is metabolised.

Reversal of intermediate acting muscle relaxants with anticholinesterase drugs should be at least 20 minutes after giving the drug. Early administration may be ineffective due to high receptor occupancy by the NMBD and can result in a residual blockade. If peripheral nerve stimulation is used, at least three twitches on a train of four should be detected before attempting reversal.

Neostigmine starts to take effect after approximately 2-3 minutes but has its maximal effect at 5-7 minutes and it its half-life is about 45 minutes.

Unfortunately, anticholinesterase drugs such as neostigmine have side effects. These are called muscarinic effects and include bradycardia, blurred vision and salivary secretions. To counter the side effects neostigmine is always given with either glycopyrolate or atropine.
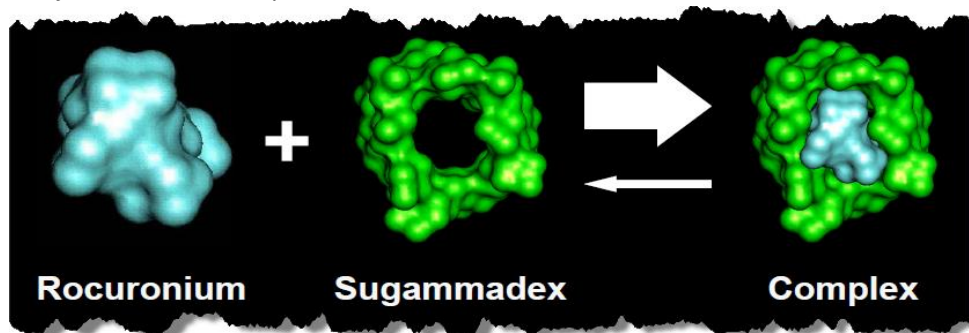
Without the use of an anticholinesterase drug the plasma concentration of the muscle relaxant declines over time as the drug moves down the concentration gradient from the neuromuscular junction into the plasma. Eventually sufficient relaxant will have left to restore neuromuscular transmission.

The reversal of muscle relaxants using nerve stimulators is covered in a separate module.

Sugammadex

Sugammadex is a newer drug and is the first of its type which is able to directly reverse neuromuscular blockade by rocuronium and vecuronium. It is unique as it is very fast acting and can reverse any depth of block.

It works by encapsulating the rocuronium. One molecule of sugammadex will encapsulate one molecule in a very strong bond and the rocuronium is unable to bind to the acetylcholine receptor at the neuromuscular junction. The complex is metabolised as a whole.

Dose

Due to one-to-one binding capacity with rocuronium, sugammadex has the ability to reverse any depth of rocuronium induced neuromuscular blockade. The dose of sugammadex required to ensure complete reversal is dependent upon the depth of block, the timing and dose of rocuronium.

Type of Block	Dose of Sugammadex	Time to TOF >0.9
Routine – TOF count 2	2mg/kg	2 minutes
Moderate – Post tetanic count 1-2	4mg/kg	3 minutes
Profound – 3-5 minutes post NMBD	16mg/kg	1.5 minutes

Although sugammadex has been available since 2008 its use has been restricted due to its very high costs.
(There is a separate module covering sugammadex in depth)

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