Neuromuscular blocking agents and their reversal

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The introduction of neuromuscular blocking agents (NMBAs) produced vastly superior operating conditions, facilitating tracheal intubation and maintaining muscle relaxation during surgery. The downside of this improvement in surgical conditions is the anaesthesia nightmare of awareness and inability to ventilate and intubate a paralysed patient. It is also a challenge to completely eliminate the effect of the NMBA at the end of surgery and residual neuromuscular blockade may lead to post-operative complications. These agents are associated with an increase in the risk of mortality, due principally to the need to manage the airway, their unpredictable nature and often poor post-operative recovery facilities where residual blockade and its sequelae may go undetected.

The recovery from neuromuscular blockade (NMB) remains markedly variable between patients, due to individual patient pharmacokinetics, adjuvant agents administered, varying drug metabolism and timing of the drug dose. As a result, many patients experience residual NMB during the early post-operative period, which can result in significant patient morbidity. Therefore, a more certain method for muscle relaxation during surgery is required. The ideal muscle relaxant is an agent that not only has a rapid onset, but a controllable duration of action, ranging from a few minutes to hours which can be quickly terminated, while having no side effects. No currently available agent or combination of agents meets these criteria.

Succinylcholine is still in use, as it probably comes closest to fulfilling these criteria, with its rapid onset and short duration of action. However, its side-effect profile and risk of prolonged blockade in patients with deficiencies in butyrylcholinesterase (pseudocholinesterase) have led to suggestions that it should be withdrawn from routine use in anaesthesia.

The non-depolarising muscle relaxants currently in use have a much slower onset and longer, very unpredictable offset, but they do have the advantage of a much more favourable safety profile than succinylcholine. Thus, NMB is currently, usually achieved using NMBAs that require administration of a reversal agent to improve the predictability of offset at the end of surgery. However, NMB reversal is not without problems of its own: Reversal utilizes a competitive mechanism, using acetylcholinesterase inhibitors, such as neostigmine. This process allows the NMBA to be freed from the neuromuscular cleft by increasing the concentration of acetylcholine at the neuromuscular junction, promoting metabolism of the NMBA by the liver, kidneys or plasma esterases. The result is both unpredictable termination of the NMB and an excess of acetylcholine which not only affects the nicotinic receptors, but also muscarinic receptors causing a wide range of side effects, such as bradycardia, nausea, vomiting, abdominal cramps, excessive secretions, bronchospasm and miosis. These in turn must be treated with the concomitant administration of glycopyrrolate or atropine.

Timing of reversal administration is important as the onset of action of acetylcholinesterase inhibitors is slow and a certain degree of spontaneous recovery is required for these agents to be effective. In addition, profound NMB may not be reversible through this competitive mechanism.

Sugammadex is a novel reversal agent which has recently been introduced onto the South African market. It directly binds rocuronium, vecuronium and, to a lesser extent, pancuronium. This agent has the potential to improve the predictability of NMBAs.

Classification

1. Depolarising muscle relaxants
   - Quaternary amines – Suxamethonium

2. Non depolarising muscle relaxants
   - Amino steroids (Pancuronium, vecuronium, rocuronium)
   - Benzylisoquinolinium diesters (Atracurium, cisatracurium, mivacurium)
Mechanism of action

- **Depolarising muscle relaxants**
  Succinylcholine has a double methonium group that resemble the structure of acetylcholine. These methonium heads bind acetylcholine receptor α subunits mimicking the action of acetylcholine to cause depolarisation of the muscle. These subunits remain bound, preventing further contraction until the succinylcholine molecule is metabolised.

- **Non depolarising muscle relaxants**
  These massive agents bind a single site on the acetylcholine receptor and prevent further binding to the receptor due to their size.

Potency and onset

A sufficient number of post synaptic receptors (75%) must be blocked to produce neuromuscular paralysis. If an agent is particularly potent this will occur slowly as the amount of agent needed to produce a profound block is low and the result is that only a few receptors will be blocked per unit time resulting in a slow onset. Due to the agents potency if a quicker block is required, more agent must be given increasing the block duration.

Pancuronium and cisatracurium are the most potent agents available to us (Intubation dose =0.1mg/kg) and have onset times of around 4 minutes while rocuronium (Intubation dose = 0.6mg/kg) has an onset of less than 90 seconds.

Offset

Offset is initially dependent on redistribution, but after repeated (“top up”) or large doses it is totally dependent on elimination, which can be aided to some degree by reversal. In general offset follows the following pattern:

- Ultra-short acting agents (less than 15 minutes) – Plasma esterase metabolised (Succinylcholine and mivacurium)
- Short acting agents (15 to 30 minutes) – Hofmann elimination and plasma esterases (Atracurium)
- Intermediate acting agents 30 to 60 minutes) - Liver metabolised (Vecuronium (40%), rocuronium (70%))
- Long acting agents (60 minutes plus) – Renal excreted (Alcuronium and pancuronium (80%))

Hofmann elimination was first described in 1841 in which carbon radicals were eliminated from quaternary molecules at high temperature and pH. In atracurium and its more potent isomer cis-atracurium an acyl group breaks away from the molecule at physiological pH and temperature leaving laudanosine, a compound with potential of neurotoxicity in large amounts.

Neuromuscular blocking drugs due to their long duration of action and rapid accumulation are not ideal agents to be used in infusions. The ability to comprehensively reverse blockade with sugammadex may introduce this as an alternative technique where complete, prolonged paralysis is desired.

Summary of current NMBAs clinical properties

<table>
<thead>
<tr>
<th>Drug</th>
<th>2 x ED₉₅ mg/kg</th>
<th>Onset (min)</th>
<th>Offset (25% recovery) min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quaternary amines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Succinylcholine</td>
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<td>45sec</td>
<td>7.6</td>
</tr>
<tr>
<td><strong>Benzylisoquinolium diesters</strong></td>
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<tr>
<td>Atracurium</td>
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<td>Mivacurium</td>
<td>0.15</td>
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<td>Cis-atracurium</td>
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<td>7.7</td>
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<tr>
<td><strong>Amino steroids</strong></td>
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<tr>
<td>Pancuronium</td>
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</tr>
<tr>
<td>Vecuronium</td>
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</tr>
<tr>
<td>Rocuronium</td>
<td>0.6</td>
<td>1.0</td>
<td>43</td>
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</table>
Doses
ED$_{95}$ – is the dose needed to produce 95% twitch depression. As a safety measure to ensure we have optimal intubating conditions 2x ED$_{95}$ is used as the intubating dose. Additional “top up doses” of 10% of the initial dose are usually used producing around 10 minutes of additional paralysis. Dosing alterations should be considered in the following conditions:

- Females appear to be more sensitive to the effects of neuromuscular blockade with aminosteroidal compounds.
- Paediatric responses to neuromuscular blocking drugs differ between age groups:
  - Neonates and infants less than 2 years require adult doses, while older children requires doses up to 2 times greater than adults with top up doses given more frequently.
- Elderly
  - Initial dose is unchanged, with no change in onset time. Duration of action is longer because of slowed metabolism. Top up doses should be decreased and given less frequently.
- Obesity: Dosing is calculated using ideal body weight.

Indications for use:
1. Intubation, especially in rapid sequence techniques.
2. To provide surgical paralysis.
3. To ensure a patient does not move during precision surgical techniques.
4. To ventilate a patient using non physiological ventilatory modes such as prone positioning or high frequency jet ventilation.

Neuromuscular monitoring
Monitoring of neuromuscular blockade is often neglected but has not been shown to decrease the incidence of post-operative paralysis, but is the only method of detecting it. Monitoring is recommended when using sugammadex, to determine the sugammadex dose.

How to select a neuromuscular blocking drug:
In choosing which drug to use in a particular case the following 4 questions need to be matched to the individual agent’s characteristics.

1. How fast do I need to get this patient paralysed?
2. How long will the paralysis need to last?
3. How is the drug metabolised and will this patient be able to metabolise this drug in that way?
4. Is there any side effect that may harm this patient, or unique property that may benefit them?

Non-depolarising muscle relaxants

Atracurium (Tracrium®)
Atracurium, an intermediate acting drug with organ independent metabolism is broken down by Hofmann elimination and plasma esterases, at physiological pH and temperature. It is made up of 10 isomers. It does not display cumulative effects with repeated doses. It can cause histamine release especially in larger doses, resulting in hypotension, bradycardia and bronchospasm while allergic reactions, skin rash and hypertension have been reported.

Cisatracurium (Nimbex®)
The cis-cis isomer of atracurium, which has many of the same properties as atracurium, despite being 3 times more potent. Its slow onset and long duration of action, coupled with its organ independent elimination, make it an ideal drug for long term use in ICU. Cisatracurium has similar elimination to atracurium. Like atracurium, cisatracurium is reversed by neostigmine but not sugammadex.

Mivacurium (Mivacron®)
Mivacurium is a short acting drug with a long onset time, properties that have hampered its clinical usefulness. Metabolism is similar to succinylcholine through pseudocholinesterase (butyrylcholinesterase) in plasma. It is therefore also contraindicated in “scoline apnoea”. It lends itself to administration via infusion due to its short half-life and lack of accumulation. Doses of 8 -10 µg/kg/hr
will maintain moderate paralysis. Neostigmine has been shown to accelerate recovery from a block with mivacurium but recovery is so rapid it is rarely used. Sugammadex has no effect on mivacurium. Histamine release may be seen after rapid administration of mivacurium.

**Vecuronium (Norcuron®, Muscuron®)**
Vecuronium is an intermediate acting aminosteroid having a similar structure to pancuronium but needs to be diluted in sterile water prior to administration. With repeat doses a small cumulative effect is exhibited. About 40% of vecuronium is metabolised in the liver with the remainder being excreted unchanged via the kidney and bile. Vecuronium is reversed by both neostigmine and sugammadex. Sugammadex has a slightly lower affinity for vecuronium than rocuronium (90% vs 95%).

**Rocuronium (Esmeron®)**
Rocuronium is a steroidal agent with a fast onset and intermediate duration of action. It is a versatile NMBA having dose dependent onset times ranging from 3 minutes with a 0.3mg/kg dose to 45 seconds with a 1.2mg/kg dose. It is used as an alternative to suxamethonium in rapid sequence inductions where its action can be terminated by reversal with 16mg/kg of sugammadex almost immediately. Recovery to all end points for all doses displays wide variation. Accumulation occurs with both repeat bolus dosing and infusions. Repeat maintenance doses are 0.1mg/kg at around 20 minute intervals. It can be reversed by both neostigmine and sugammadex with sugammadex being designed specifically to bind and reverse rocuronium.

Tachycardias have been described with doses of 1.2mg/kg and above and allergy and anaphylaxis has been reported with a preponderance in certain nations (France, Australia and Norway).

**Pancuronium (Pavulon®)**
Pancuronium was a mainstay of muscle relaxation from its introduction in 1967 to the early part of the 21st century. It is still used for cases requiring prolonged muscle relaxation or where tachycardia may be beneficial. It is slow acting with a long duration of action due to renal excretion (80%). It can be reversed by both neostigmine and sugammadex. Sugammadex only binds 60% of pancuronium. Like all drugs having long half –lives, reversal should only be attempted once evidence of spontaneous recovery is present to prevent recurarisation.

**Alcuronium (Alloferin®)**
A long acting still used sporadically around the world with a very slow onset and offset due to its renal excretion. It accumulates with repeat doses and releases histamine causing bronchospasm, hypotension and a reflex tachycardia.

**Depolarising muscle relaxants**

**Suxamethonium (Succinylcholine) (Scoline®)**
It is the only depolarising agent available. It has the shortest onset and duration of action of all neuromuscular blocking agents, and organ independent metabolism. It produces unmatched intubating conditions and the ability to breathe soon after an unsuccessful attempt. It can be given intravenously, intra-muscularly and as an infusion. If it were not for its potentially fatal side effect profile it would be the perfect muscle relaxant. (Hyperkalaemia, trigger of malignant hyperthermia, Scoline apnoea, muscle pains, bradycardia, allergy and anaphylaxis.)
Reversal of neuromuscular blockade
The current method of reversal of neuromuscular blockade involves the use of indirect acting competitive acetylcholinesterase (AChE) inhibitors that raise the level of ACh in the synaptic cleft. ACh competes with neuromuscular blocking agents in the neuromuscular junction. The increase in ACh displaces the neuromuscular blocking agent, which moves into blood from where it can be metabolised and eliminated by plasma esterases, the liver and kidneys. AChE inhibitors do not metabolise or inhibit neuromuscular blocking agents.

Neostigmine
Neostigmine is the only acetylcholinesterase inhibitor available. It acts in an indirect competitive manner. Neostigmine binds acetylcholine esterase preventing the metabolism of acetylcholine which then competes with the neuromuscular blocking agent to displace it from the neuromuscular junction allowing it to be metabolised in the blood, liver or excreted by the kidneys. A dose of 0.04 - 0.07mg/kg is effective in about 1 minute with a peak effect at 9 minutes. It is given with Atropine (0.1mg per 1mg neostigmine) or glycopyrrolate (0.2mg per 1mg neostigmine) to counteract the excess ACh producing muscarinic side effects. Glycopyrrolate is preferred as it has a slower onset of action, producing less tachycardia, less central nervous system effects with a longer duration of action.

Due to its competitive action neostigmine should not be administered until spontaneous recovery to at least 2 twitches on a TOF has occurred.

Sugammadex (Bridion®)
Is a selective relaxant binding agent designed to bind rocuronium (95%) irreversibly, and due to their similar structures vecuronium (90%) and pancuronium (61%) are also encapsulated, but in lesser amounts, resulting in slightly slower recovery. Sugammadex and its complex are not metabolized and are eliminated exclusively by renal excretion or dialysis in renal failure. Atracurium, its isomers, suxamethonium and mivacurium, are hardly bound by sugammadex.

Dosing
3 dose regimens are recommended, depending on the degree of recovery of blockade.
- Moderate block - 2mg/kg if at least 2 twitches are present on a TOF after rocuronium or vecuronium. Recovery to TOF of 0.9 occurs in about 2 minutes.
- Deep or profound blockade - 4mg/kg with 1 or 2 twitches on a PTC for rocuronium or vecuronium. Recovery to TOF of 0.9 occurs in about 3 minutes.
- Immediate or emergency reversal of rocuronium - 16mg/kg. Recovery to a TOF ratio of 0.9 takes about 90 seconds when sugammadex is given 3 minutes after 1.2mg/kg of rocuronium.

Administration of neuromuscular blocking agent after sugammadex:
If a patient needs to be re-paralysed after a dose of sugammadex, it is recommended that rocuronium, vecuronium and pancuronium are not used within 24 hours. Atracurium and its isomers will be effective. Administration of rocuronium (1.2mg/kg) 5 minutes after reversal with 4mg/kg sugammadex is effective, but results in a slower onset [mean 3 minutes (2-5 minutes)] and shorter duration [mean 25 minutes (17-46 minutes)] of blockade.

Its side effect profile appears to be relatively benign: Coughing, bucking and movement while under anaesthesia have been reported due to the sudden reversal of block. Hormonal contraception is bound by sugammadex and should be treated like a missed dose of the oral contraceptive pill. Its clinical effect on coagulation and its allergenic potential have not yet been fully described. Isolated cases of its use in aborting rocuronium-induced anaphylaxis have been described.
Further reading

2. Lee C. Goodbye suxamethonium! Anaesthesia 2009; 64: 73-81