

# Muscle Relaxants: Block assessment and reversal

By the perioperativeCPD team

## **Introduction**

Neuromuscular blocking agents or muscle relaxants enable anaesthetists to relax skeletal muscles therefore improving anaesthetic management, increasing safety and quality of tracheal intubation, and to provide favourable operating conditions for certain surgical procedures\*.

While the types of muscle relaxants and how they work are covered in a separate module, this article discusses residual block, why, when and how muscle relaxants are reversed, and the importance of using a peripheral nerve stimulator when assessing the depth of block. It also covers the different patterns the stimulators use to assess how deep a neuromuscular block is.

\*While muscle relaxant is a commonly used term the correct description is neuromuscular blocking agent (NMBA) or neuromuscular blocking drug (NMBD).

## What is residual neuromuscular blockade?

Residual neuromuscular blockade occurs when the patient is still partially paralysed while emerging from anaesthetic. This is specifically when a neuromuscular blocking agent has been administered, but has not been totally metabolised or eliminated. It is also called residual paralysis.

Multiple studies have proved that residual neuromuscular blockade is more common than many anaesthetists think and may affect between 10-40% of patients in the post-anaesthetic care unit (PACU) particularly when the neuromuscular blocking agent (NMBA) has not been reversed or antagonised at the end of surgery. Residual neuromuscular block is associated with a reduced respiratory response, an increased chance of aspiration, airway obstruction and reintubation; as well as the risk of a prolonged length of stay in PACU. It can also be very distressing for the patient.

On a practical level adequate neuromuscular recovery is considered the return to a baseline muscular function, particularly the ability to breathe normally, maintain a patient airway and retain protective airway reflexes. Residual neuromuscular block can be assessed and prevented through the use of a peripheral nerve stimulator and a reversal agent such as neostigmine.

## Can we assess the block clinically?

Many clinical methods of assessing residual block have been tried. These include sustained head lift for five seconds, adequate tidal volume size, tongue protrusion, and grip strength. All are unreliable, and except tidal volume, none are useful if the patient is anaesthetised. A patient may open their eyes and stick out their tongue but still have considerable neuromuscular blockade.

The sustained head lift was the most established method but it has been shown to be inaccurate as some patients can achieve this goal with considerable residual block. Also if a patient cannot perform a head lift there can be other reasons such as communication issues and residual sedation due to opiates or benzodiazepines.

## What does a peripheral nerve stimulator do?

Peripheral Nerve Stimulators (PNS) are used to monitor neuromuscular blockade:

- During induction of anaesthesia for intubation
- During surgery to guide repeated doses of muscle relaxants and to assess the depth of the block
- To differentiate between different types of block (if using repeated doses of suxamethonium)
- At the end of surgery to assess the ability to reverse
- At the end of anaesthesia or in recovery to assess the degree of residual blockade



A fisher & paykel peripheral nerve stimulator

## How does a peripheral stimulator work?

A nerve stimulator works by applying an electrical current or stimulus to a peripheral nerve to produce a supramaximal stimulus (explained below) and associated motor response. This stimulus is applied through the skin, normally through ECG electrodes with the negative (black) electrode positioned over the nerve.

It is the size or magnitude of the current that determines whether the nerve depolarises or not, so delivering a constant current is more important than delivering a constant voltage as the skin resistance is variable (Ohm's Law\*). The current is measured in milliamperes (one thousandth of an ampere). A current of 60 mA is sufficient for most patients.

The stimulus produced should produce a monophasic and rectangular waveform, and the length of the pulse should not exceed 0.2 to 0.3 msec. A pulse exceeding 0.5 msec may stimulate the muscle directly or cause repetitive firing. In this context monophasic means a current that is negative or positive but not both.



A monophasic rectangular waveform

Also, for safety reasons, the nerve stimulator should be battery-operated, include a battery check, and be able to generate 60 to 70 mA, but not more than 80 mA as this can cause tissue damage.

\*Ohm's law states that electric current is proportional to voltage and inversely proportional to resistance.

## What is a supramaximal stimulus?

A supramaximal stimulus is one with sufficient current to cause 100% of the motor neurons within the nerve to be depolarised every time.

Supramaximal stimuli are required so that any variation in the twitch strength (i.e. fade) must be due to a factor other than the number of neurons recruited during repeated stimulation.

A current setting of 60 mA will achieve supramaximal stimulation in most cases. However, supramaximal electrical stimulation hurts, which is not a concern during anaesthesia, but during recovery the patient may be awake enough to experience severe discomfort or pain.

## Where can we attach the stimulator?

The ideal nerve for supramaximal stimulus must be able to be stimulated through the skin i.e. superficial and accessible, it must be a motor nerve, and the contraction desired must be able to be visible.

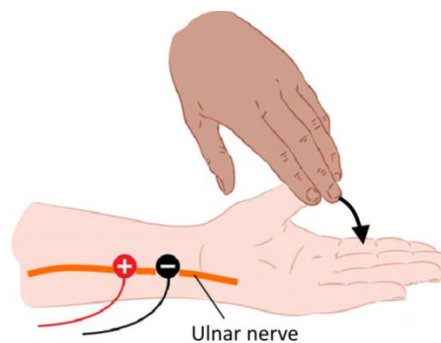
The three commonly used nerves that meet these requirements are the **ulnar, facial and posterior tibial nerve**.

### a) Ulnar nerve

The most popular site is the ulnar nerve. Stimulation of the ulnar nerve at the wrist will cause the thumb to pull toward the little finger (adduction). The adductor pollicis muscles, which are responsible for this movement, are in the hand at the base of the thumb.

The two electrodes are placed over the path of the ulnar nerve, on the opposite side to the thumb. The negative (black) activating electrode is placed about 1 cm from the point at which the wrist flexes (the wrist crease) and the positive (red) electrode is placed 3-4cm proximally. Polarity is important as significantly less energy is needed to stimulate a nerve with a negative electrode than a positive electrode. That is because the outside of a 'resting' nerve is charged positive and if you add sufficient negative charge to the outside it will cause a wave of depolarisation to travel down the nerve. An easy way to remember is the red goes closest the heart.

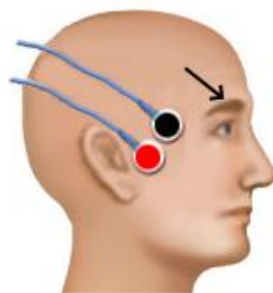
Note: because the patient is breathing does not mean they are reversed. The large muscles in the diaphragm recover first from the effects of NMBAs. Measurement of the adductor pollicis muscles response correlates well with the tone in the upper airway and upper oesophageal muscles. If the adductor pollicis muscles have fully recovered, both the diaphragm and the air upper airway muscles should have fully recovered.



Ulnar nerve electrode placement

### b) Facial nerves

The temporal branch of the facial nerve is a popular site to stimulate and evaluate for muscle blockade if the arms are unavailable during surgery due to positioning, drapes, equipment etc. The temporal branch of the facial nerve travels under the skin on the side of the face between the eye and ear. It supplies the muscles of the eyes, around the ear, and on the side of the forehead. Stimulating these will result in the contraction of the eyelid and the eyebrow. It is not as accurate as monitoring the adductor pollicis muscle in the hand and direct stimulation of the muscles can be an issue.



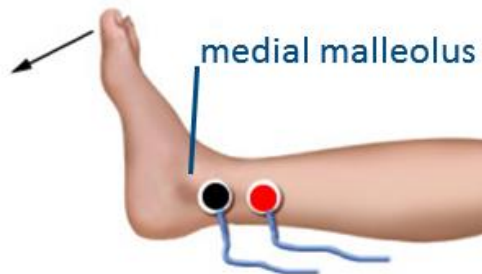
The temporal branch of the facial nerve

The negative electrode should be placed over the temporal branch of the facial nerve. The muscles around the eye (orbicularis oculi and corrugator supercilii) recover earlier than those in the hand, more similar to the diaphragmatic muscles. This means even with no fade here, the airway muscles may still have some residual block.

### c) Posterior tibial nerve

The final nerve that is commonly used is the posterior tibial nerve. It is easy to locate, especially on infants, often easier to access during surgery and is not at high risk of direct muscle stimulation. Positioning electrodes over posterior (rear) aspect of medial malleolus (ankle bone) above the posterior tibial artery results in a stimulation over the posterior tibial nerve.

When stimulated this result in the plantar flexion of the great toe.



The posterior tibial nerve

### Patterns of stimulation.

There are five different patterns that are used to measure the depth of neuromuscular block:

- Single twitch
- Train of four (TOF)
- Double burst stimulation (DBS)
- Tetanic stimulation
- Post-tetanic count

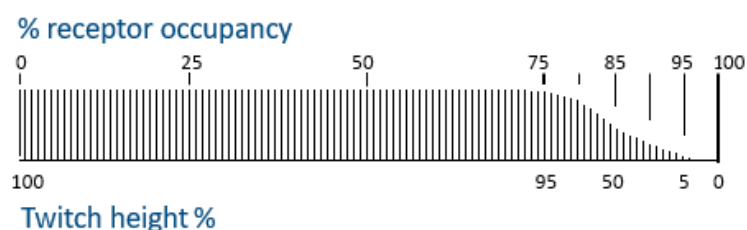
### Single twitch

The single twitch is only useful at the beginning of a neuromuscular block and it can be used to tell when optimal intubating conditions have been achieved (no twitches). A single stimulation is repeatedly delivered, usually once every 10 seconds (0.1Hz). It can be used for both depolarising and non-depolarising NMBA. Its use during surgery is limited as there is a need for it to be calibrated with a control twitch before administering the NMBA.



Single twitches at one every 10 seconds

When 75% of the receptors are occupied by NMBA twitch magnitude starts to decrease. When there is 100 % occupation, there is no twitch.



Single twitch height in relation to receptor occupancy

## Train of four (TOF)

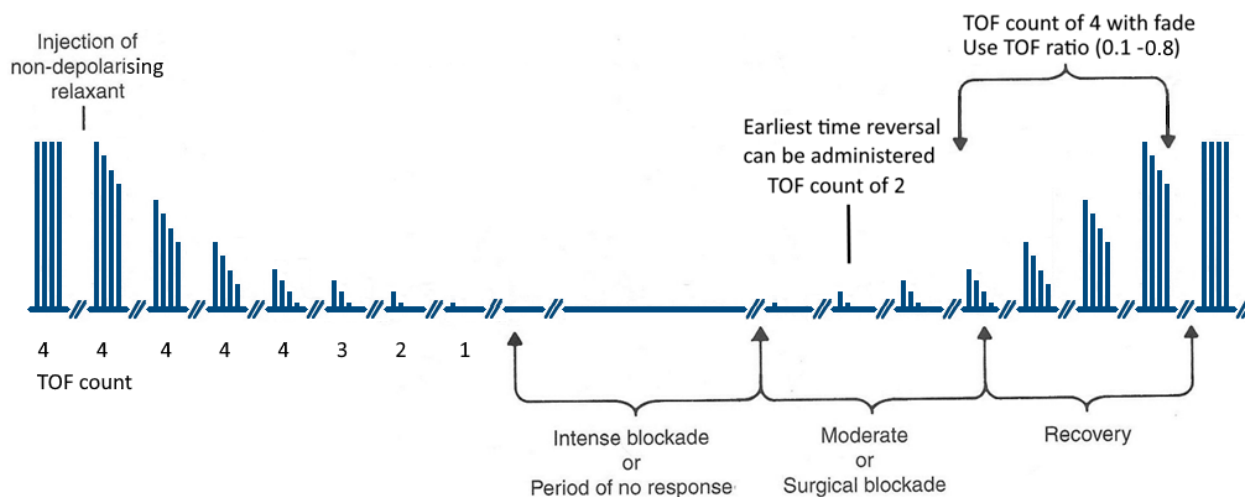
TOF has been the most common pattern used for more than 40 years because it is simple and easy to assess.

The train of four (TOF) involves the delivery of four successive stimulations at a frequency of 2 Hz (two a second). The speed of the four stimulations is sufficiently slow to distinguish individual contractions, and sufficiently fast to show fade. There should be a minimum 10 second gap before repeating either the TOF ratio or count.



The train of four pattern

Prior to administration of a non-depolarising muscle relaxant, all the twitches in the train of four are of equal amplitude. During onset of a non-depolarising block there is reduction in twitch amplitude. T4, the last twitch, is the first to be affected, followed in order by T3, T2 and T1. Eventually T4 will disappear completely, followed by T3, T2 and finally T1. This process is reversed as the muscle relaxant wears off.



TOF pattern, onset and recovery

## What is the TOF count and what is it used for?

Counting the number of twitches is quite a good guide to monitoring the levels of paralysis throughout surgery and also to assess whether or not a patient is able to be reversed.

- **1 twitch** is sufficient for intubation
- **1-2 twitches** during the maintenance of anaesthesia for general anaesthesia
- **2/3 twitches** before reversal of neuromuscular blockade (many texts differ over which is correct, 2 or 3)

## If they are breathing do they have to be reversed?

An otherwise healthy anaesthetised person can maintain good gas exchange while intubated with 3 twitches on the TOF count. If extubated, the patient would almost certainly require re-intubation because although the diaphragmatic muscles have recovered the laryngeal muscles are more sensitive to NMBA's and would be almost completely paralysed.

Even when four twitches reappear, up to 75% of receptors at the neuromuscular junction may be blocked and the patient's respiratory effort may still be insufficient for safe extubation. It is therefore advised to give neostigmine (with glycopyrrolate), prior to weaning and extubation.

No. of twitches seen (TOF count)	% of receptors blocked	Block depth
4	0-75%	Light: Onset or Recovery Phase
3	At least 75%	Moderate block
2	At least 80%	" " "
1	At least 90%	" " "
0	100%	Intense block

The reversal agent (i.e. neostigmine with glycopyrrolate) should be administered no earlier than return of the second twitch (T2) to be effective, but ideally not until all four twitches are present as this provides an additional margin of safety. No amount of neostigmine will reverse an intense block (no twitches) and it is worthwhile remembering that the action of reversal agent is not instantaneous and can take up to ten minutes to reach peak action.

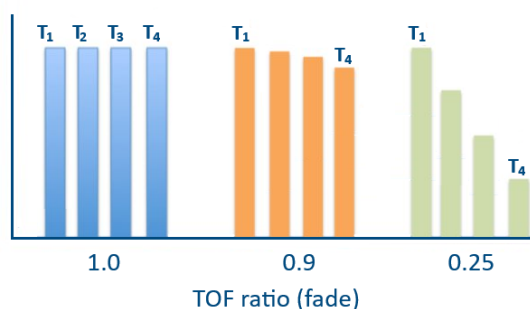
If you need to reverse an intense block or reverse a block caused rocuronium or vecuronium quickly sugammadex maybe an option (if it is stocked).

### What is the TOF ratio and when is it used?

The TOF count is not very sensitive to assessing how well the reversal has worked. The TOF ratio is more suited for assessing the adequacy of reversal.

TOF ratio uses the same TOF simulation pattern but is used at the very end of the surgery once the patient has been reversed and all four twitches have returned. The TOF ratio measures the level of fade between four twitches and any fade indicates that there is still some residual block.

The TOF ratio is calculated by comparing the magnitude of the fourth twitch (T4) to that of the first (T1). In the unblocked state, the TOF ratio (T4/T1) should be 1.0 (100%).



TOF Ratio

The obvious advantage of using TOF ratio is that responses can be easily measured or quantified without calibration as the first twitch (T1) is used as a control for the others.

Historically a TOF ratio of 0.7 or higher was an indication of sufficient reversal but more recent evidence suggests that the TOF ratio of 0.9 should be present before extubation to prevent any residual effects of the neuromuscular block. It should be noted that there can be large variations between patients. Some patients with a TOF ratio of 0.9 can display obvious muscle weakness, while many others will have full muscle strength.

Estimating the TOF ratio or fade subjectively by feel or sight is very difficult and is rarely accurate. TOF ratios around 0.25 are commonly estimated anywhere between 0.1 and 0.7 and at a TOF ratio of 0.7 fewer than 10% of observers can reliably detect any fade at all, consequently the presence of any detectable fade indicates the presence of some residual paralysis.

Remember that the use of nerve simulators on awake patients is painful, so although TOF ratio is a reliable method of detecting residual paralysis it can only be used on anaesthetised patients.

### What is quantitative monitoring?

There are many quantitative or objective monitoring devices such as the ToFscan® Neuromuscular Transmission Monitor and these are the only reliable way to get an accurate TOF ratio measurement.

Acceleromyography is the most popular method used to quantitatively measure residual block. It is easy and convenient to use, inexpensive and can be interfaced with other patient monitors. Acceleromyographs measure the acceleration of the stimulated muscle with a piezoelectric sensor. A voltage is created in the sensor when the muscle accelerates and that acceleration is proportion to force of contraction.

Where quantitative monitoring is used the desired goal for adequate reversal is TOF >0.9. If the TOF is less than 0.9 a reversal agent should be used and extubation not performed until TOF >0.9 and clinical criteria are satisfied.

While most anaesthetic regulating bodies recommend the use of quantitative monitoring devices, their use is far from universal. This may be because they are expensive and most need calibrating for use, normally between induction and the first dose of NMBA.

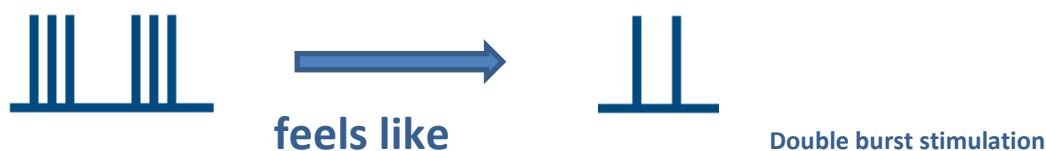


ToFscan® Neuromuscular Transmission Monitor



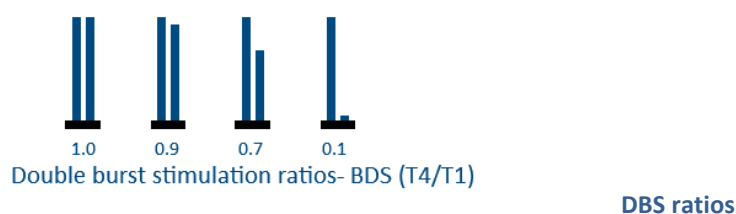
## Double burst stimulation (DBS)

DBS was developed with the specific aim of allowing manual detection of small amounts of residual blockade, similar the TOF ratio, but is considered easier to assess accurately. It consists of 2 bursts of 3 stimuli with each burst separated by 750 ms. In practice it feels like 2 separate twitches T1 and T2.



In an unparalysed muscle, two separate muscle contractions of equal intensity will occur. In muscle partially paralysed the response to the second burst is reduced. This is the same principle of fade as in the TOF ratio and it is calculated the same way. Only having two twitches is supposed to make it easier to measure the fade then over the four twitches used in TOF.

T2/T1 gives a ratio between 1.0 (no fade) and 0.1 (maximum fade) which is known as the DBS ratio.



## Tetanic stimulation

A very rapid delivery of multiple stimulations for 5 seconds will cause a sustained (tetanic) contraction of the muscle. If any muscle relaxant is still present at the neuromuscular junction, the sustained contraction will fade over the period of the stimulus. This pattern of stimulation is very sensitive and can detect very minor degrees of neuromuscular block, which is potentially useful in the postoperative recovery room. However its use is prevented by the fact that tetanic stimulation is extremely painful. In reality tetanic stimulation is only clinically used as part of post-tetanic count.

## Post-tetanic count (PTC)

Post-tetanic count (PTC) is used for evaluating the degree of a very deep neuromuscular blockade when there is no reaction to TOF count after administration of large dose of non-depolarising muscle relaxant. It can be used when an intense deep neuromuscular block must be maintained, such as in ophthalmic or neurological surgery.

This pattern involves a 5 second tetanic stimulation (as above), followed by a pause of 3 seconds and then 20 pulses at 1 per second (1 Hz). The number of twitches that are observed in response to the 20 pulses is counted and can be used to predict how deep neuromuscular blockade is. A post-tetanic count of 8-9 suggests that the return of a twitch is imminent.



PTC relies on the principle that mobilisation and synthesis of acetylcholine caused by tetanic stimulation continues for some time after discontinuation of stimulation. As a result there is an increased, immediately available store of acetylcholine which causes an enhanced response to subsequent single twitch stimulation.

Note: respiratory muscles including the diaphragm are harder to block with neuromuscular blocking agents than the peripheral muscles. To guarantee paralysis of the diaphragm, the neuromuscular blockade must be so intense the PTC stimulation is zero at the thumb.

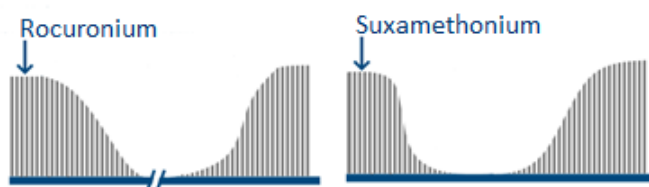
### What nerve stimulator mode to use when?

	Single twitch	TOF Count	Post-tetanic count - PTC	TOF Ratio	Double Burst - DBS
<b>Anaesthetic Room</b>					
Induction					
Intubation					
<b>During surgery</b>					
Intense block					
Moderate block					
Recovery					
<b>PACU</b>				*	*

\* Using a nerve stimulator on an awake patient is painful and not recommended

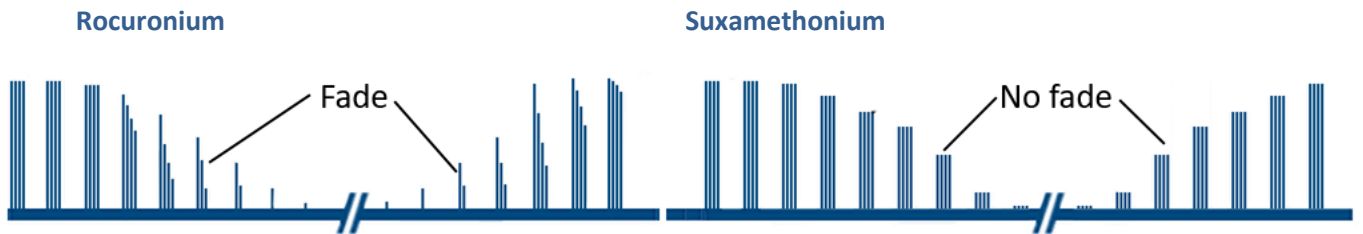
### Can I use a nerve stimulator with depolarising NMBAs?

Yes, as seen below the onset and recovery of depolarising and non-depolarising NMBAs are similar when using single twitches. When the block level is total with both depolarising and non-depolarising NMBAs, the muscles will not respond (twitch) to a stimuli sent by a nerve stimulator. As the neuromuscular block begins to wear off, the muscle will begin to respond to a stimulus, but the twitch will be less than full strength.



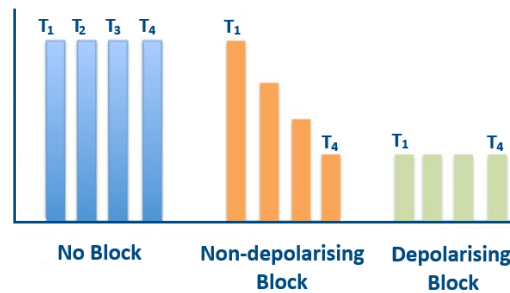
The onset and recovery of muscle relaxants monitored using single twitches

The difference between how depolarising and non-depolarising NMBAs react to nerve stimulation becomes clear when TOF stimulation is used. While non-depolarising NMBAs show not only a reduction in the size of the twitches produced, there is also a distinct fade between the first and last of the four twitches.



Pattern of muscle responses after both depolarising and non-depolarising NMBA

This fade is absent in depolarising NMBA, such as suxamethonium, which show a uniform decrease in size of all four twitches.



Showing absence of fade to TOF stimulation when using non-depolarising NMBA

Therefore, while a peripheral nerve stimulator can be used to monitor the depth of block when using depolarising muscle relaxants, the train-of-four pattern of stimulation is of no use.

If using a nerve stimulator for a depolarising block it is normally only used to check that the block is wearing off, therefore indicating there is no suxamethonium apnoea, or if repeated doses of suxamethonium are used and the anaesthetist wants to be aware of the start of a phase 2 block.

### Reversal of neuromuscular blockade- Spontaneous

Without the use of a reversal agent the concentration of the NMBA declines over time as the drug is displaced from the receptor sites by acetylcholine and moves down the concentration gradient from the neuromuscular junction into the plasma. Plasma concentrations fall as the drug is redistributed and metabolised.

Eventually sufficient NMBA will have been displaced to restore neuromuscular transmission (No fade on TOF ratio). This can take up to an hour or more after the last dose depending on the properties of the particular NMBA used. The actual duration of action of NMBA is extremely variable and an intubating dose of Rocuronium (0.6-1.0mg/kg) can last between 30 and 120 minutes. Remember factors such as advanced age, obesity and hypothermia can prolong the action of muscle relaxants.

### Reversal of neuromuscular blockade

#### - Neostigmine/glycopyrrolate (2.5mg/0.5mg) as a premixed ampoule

Although NMBA will wear off over time, this process can be sped up by using an anticholinesterase drug such as neostigmine. There must be at least two but ideally four twitches on a train of four before attempting reversal as early administration may be ineffective due to high receptor occupancy by the NMBA. Neostigmine starts to take effect after approximately 2-3 minutes but has its maximal effect at 7-10 minutes and its duration of action is about 45 minutes.

t does not metabolise or inhibit muscle relaxants. Neostigmine binds to the enzyme acetylcholinesterase which is responsible for breaking down acetylcholine. This prevents the rapid breakdown of acetylcholine and as the levels of acetylcholine quickly build up around the neuromuscular junction, they compete with and displace the NMBA.

Once displaced, the NMBA enters the systemic circulation where it is metabolised. The pharmacologically correct term is that neostigmine antagonises neuromuscular blocking agents rather than reversing them.

There are other anticholinesterase drugs besides neostigmine but they are not used in clinical practice.

The pharmacology of how NMBAs work is covered in detail in the earlier module 'Muscle Relaxants: the fundamentals'.

Unfortunately, anticholinesterase drugs such as neostigmine have side effects. These are called muscarinic effects and include bradycardia, nausea and vomiting, blurred vision and salivary secretions. To counter the side effects of neostigmine, particularly the bradycardia, it is always given with either glycopyrrolate or atropine. Glycopyrrolate is preferred as it has a slower onset of action, producing less tachycardia and less central nervous system effects with a longer duration of action. Beware that over dosing of neostigmine can also lead to muscle weakness.

### **Recurarisation**

Recurarisation is defined as an increase in neuromuscular block after a period of recovery. It occurred when a long-acting NMBA was antagonised with an anticholinesterase that had a shorter duration of action.

Recurarisation is largely a historical issue which was particularly common with the older long lasting NMBAs such as gallamine, tubocurarine and pancuronium. The problem was reduced with improved neuromuscular monitoring and the advent of atracurium, rocuronium and vecuronium, which have shorter durations.

### **Sugammadex**

Any depth of neuromuscular block, even a profound block, caused by rocuronium and vecuronium can be reversed quickly by sugammadex (tradename Bridion). This drug is covered in a separate module 'Sugammadex: an overview'.

### **Summary**

With residual neuromuscular block historically affecting between 10- 40% of post-operative patients it is essential to assess all patients who have been given a NMBA to see if they needed to be reversed or antagonised at the end of surgery. This assessment can only be accurately done with a peripheral nerve stimulator and using the correct pattern. The anaesthetic assistant should know which pattern to use when, and especially the difference between the TOF count and TOF ratio. The gold standard is the quantitative nerve monitor such as TOFscan® although these are not universally available or used as they should be.

Finally remember the duration of action of muscle relaxants is highly variable and if there is any doubt a reversal drug should be given.

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