23 March 2018
No. 03

A FISH OUT OF WATER - Post-operative residual neuromuscular blockade

K Kistan

Moderator: K Allopi

UNIVERSITY OF
KWAZULU-NATAL

INYUVESI
YAKWAZULU-NATALI

School of Clinical Medicine
Discipline of Anaesthesiology and Critical Care

CONTENTS

INTRODUCTION

“I couldn’t breathe”
“I was hungry for air”
“I felt like I was going to die”
“I could see you looking at me wondering if I knew what was happening”
“I needed you to save me”
“I felt helpless”
These are words that no anaesthesia care provider would ever like to hear from their last patient.

To witness the distressing sight of a fish out of water is both distressing for the fish and for the observer. To witness this phenomenon in our fellow patients//friends/family/brothers and sisters can be equally distressing for both the patient and peri-operative physician. This is a memory that will stay with both parties for a long time to come, if not forever – an unpleasant emotional experience for all those involved.

One would think that in this day and age of highly advance medical technology, we should not be having such occurrences, but we still encounter such situations not that uncommonly. These are (highly preventable) morbidities and one that can go a long way with routine implementation of simple techniques.

DEFINITION AND CONTEXT

Residual neuromuscular blockade is defined as "inadequate neuromuscular recovery as measured by objective neuromuscular monitoring."(1) They may also sometimes be reported as residual curarisation, residual neuromuscular block or residual paralysis. The latest internationally accepted gold standard, is defined by an objective measurement of a train-of-four ratio (TOFR) of >0.9. This is importantly different to the train-of-four count (TOFC) as will be discussed later. Less than a ratio of 0.9 is considered inadequate recovery.(2)

The 1970's saw the introduction of the train-of-four ratio. This ratio compares the height of the response of the 4th twitch of the muscle compared to that of the 1st twitch of the muscle, with the stimuli being delivered at intervals of 0.5 seconds (2Hz). Several studies were then evaluated and "acceptable recovery" was then derived to be a TOFR>0.7. Importantly, even though this ratio was an objective measure, they were based on subjective clinical signs. These included ability of patients to open their eyes widely, cough, protrude tongue, attain vital capacity breaths of 15-20ml/kg, and sustain tetanic stimulation without fade for more than 5 seconds.(2)

With further advanced monitoring and studies, the acceptable cut-off for a TOF ratio evolved to 0.9 by the year 2003.(3) This new recommendation came about after discovering increased aspiration risk and pharyngeal dysfunction from several studies at TOFR<0.9 and partial airway obstruction with impaired respiratory flow at TOFR<0.8.(2-4)

It must be borne in mind that there is a significant inter-patient variability. Obvious muscle weakness may be evident in some patients despite an acceptable TOFR of >0.9, whereas clinical recovery of muscle strength may be seen in other patients with TOFR<0.9. Perhaps even more importantly – in patients with seemingly subtle levels of neuromuscular block at TOFR>0.9, awake patient's may display distressing symptoms.(2)

To consider adequate neuromuscular recovery, a return to baseline muscular function is considered most practical, especially aims related to the pulmonary system (normal breathing patterns, airway patency and intact airway protection reflexes).

INCIDENCE

There are limited randomized controlled trials and well-designed cohort studies demonstrating a link between significant morbidity and mortality with residual curarization. The current available well of data is heteregenous in their evidence in this regard owing to the numerous confounding variables in clinical practice settings which may influence the effect of neuromuscular blockade. To curb the problem of post-operative residual curarization, further development led to the introduction of intermediate acting non-depolarizing neuromuscular blocking drugs.

For almost 4 decades, the literature reports evidence of residual neuromuscular blockade.(5) In results published of some American and European surveys, 50-65% of anaesthesiologists reported their belief that post-operative residual weakness is an extremely rare (<1%) event. However, there are published estimates in the 1970's showing that the incidence of patients arriving to the post-anaesthesia care unit (PACU) with TOFR<0.7 is in the region of 45%.(5) This number has also been proven to be significantly higher in a 2003 publication by Debaene and colleagues (TOFR<0.9 in the PACU as high as 45%) (3) and again in 2007 and 2010 by Naguib and colleagues (approximately 40%).(6,7) Building on studies showing these results, further investigations aimed at linking morbidity and mortality to post-operative residual curarization estimate that clinically apparent events would develop in approximately 1-3% of these patients.(2) Putting this into absolute numbers reveal that more than half a million people annually worldwide experience critical respiratory events.(8) Due to the large percentage of

patients arriving to the PACU with post-operative residual curarisation (PORC), one can infer that most patients would be able to tolerate a modest depth of residual block without any unfavourable effects. To this end a subset of these patients include those with limited physiological reserve and it is in these patients that serious consequences of post-operative residual neuromuscular blockade will be displayed.

The development of sugammadex has brought about significant change in PORC. In a prospective study in 2015, Brueckmann and colleagues (9) found that if sugammadex rather than neostigmine had been used, the incidence of PORC in the recovery room is significantly less (based on TOFR<0.9, zero vs 43%). These findings re-iterated those by Cammu et al earlier in 2012.(10) In an important subset of patients Gaszynski et al (11) in a 2012 publication revealed a reduced incidence of PORC in morbidly obese patients (BMI>40kg/m^2) given sugammadex 2mg/kg to reverse a moderate block (TOFC=2) compared with a similar group given neostigmine 0.05mg/kg. In another interesting take on events involving routine clinical practice *without* the use of neuromuscular monitoring, Kotake et al revealed in an observational study that the incidence of TOFR<0.9 after extubation was reported as 24% after neostigmine and only 4.3% after sugammadex.(12)

AETIOLOGY OF RESIDUAL NEUROMUSCULAR BLOCKADE

There are likely a multitude of factors responsible for this phenomenon: (7)

- use of non-depolarizing muscle relaxant agents
- confounding factors and other potentiating factors of neuromuscular blockade
- lack of intraoperative objective monitoring
- reliance on subjective assessment (visual or tactile means) or clinical tests (head-lift, grip strength, tidal volume, etc.) to judge adequacy of pharmacologic reversal prior to tracheal extubation

Characteristics of neuromuscular blocking drugs that contribute to residual blockade:

1. Administration of neuromuscular blocking drugs – these should be used only if clinically indicated.
2. Higher dosages of neuromuscular blocking drugs (3-4 times ED95) in modified rapid sequence inductions significantly prolong duration of action of blockade by 50-300% when compared with administration of a normal-dose of 1-2 times ED95.(2) The dose administered to a patient should always be calculated on an individual patient basis as dictated by surgical necessity.
3. Using long-acting neuromuscular blocking drugs (e.g. pancuronium) has been linked to a 3-fold increased risk of TOFR<0.7 in the immediate post-operative period.(6) This is the basis for the recommendation of using intermediate acting neuromuscular blocking agents (e.g. rocuronium, vecuronium) whenever this may be feasible.
4. Maintaining deep intra-operative paralysis routinely as indicated by TOFC of zero or post-tetanic count (PTC) less than 5 is linked to post-operative residual curarization.(6)

There also exists a subset of patient population that are at high risk of catastrophic complications related to post-operative residual neuromuscular blockade, and as such, extreme caution must be exercised in selecting appropriate neuromuscular blockers if required. These high risk patients include patients with respiratory disease, sleep apnoea, obesity, the elderly, and those with pre-existing neuromuscular disease.(6)

ROLE OF THE ANAESTHETIST

Being the creators of this problem, we have the power to prevent the associated morbidity and mortality. Studies have shown that objective methods of monitoring neuromuscular function used routinely in the peri-operative environment reduces the incidence of post-operative weakness.(7)

ADVERSE EFFECTS OF RESIDUAL NEUROMUSCULAR BLOCKADE (1)

Table 1 – physiological changes

Impaired muscle tone and co-ordination	Upper airway pharyngeal and oesophageal muscles	Increased aspiration risk Increased risk of airway obstruction
	Laryngeal muscles	Increased aspiration risk Impaired phonation Impaired cough
	Respiratory muscles	Impaired ventilation and oxygenation
	Impaired function of other muscles throughout the body	

Table 2 – clinical implications

Symptoms and signs of muscle weakness	Difficulty breathing Generalized weakness Difficulty speaking Visual disturbances Patient distress
Immediate critical respiratory events in PACU	Post-operative hypoxaemia Upper airway obstruction
Later respiratory events	Prolonged ventilator weaning Post-operative pulmonary complications (e.g. atelectasis, pneumonia)

Post-operative pulmonary complications (POPC)

Post-operative respiratory failure has been identified as a sequel to incomplete recovery from neuromuscular blockade. A South African report on peri-operative mortality in 1978 revealed that anaesthesia was considered responsible for 2.2% of peri-operative deaths. The second commonest cause of death was respiratory inadequacy post-neuromuscular blockade which accounted for almost 20% of the mortality.(13) In a UK study in 1981 by Lunn and colleagues, 6/32 respiratory related anaesthetic deaths had post-op residual curarization. In 1984, Cooper and colleagues demonstrated that approximately 50% of cases admitted to an ICU for anaesthesia related complications were associated with post-operative incomplete recovery from neuromuscular blockade.(14) These findings were re-affirmed by a French study in 1986, purporting that half of anaesthesia related deaths were ascribed to post-operative respiratory depression and citing incomplete recovery from neuromuscular block as the principle reason.(15) In 1997, a study by Berg et al was done demonstrating a higher incidence of POPC with TOFR<0.7 in the PACU in patients receiving pancuronium but not when TOFR>0.7; however this was not demonstrated after the use of vecuronium or atracurium. This then sparked subsequent widespread research into investigating the incidence of POPC in patients who had received non-depolarizing neuromuscular blocking drugs during general anaesthesia as well as the relationship to use of a reversal agent. Use of intermediate rather than long-acting neuromuscular blockers were then suggested to result in a significantly lower incidence of POPC in a meta-analysis in 2007 by Naguib and colleagues.(6) In a recent study by Murphy and colleagues in 2015, elderly patients (70-90yr old) also displayed a higher incidence of POPC than younger patients (18-50 year old) - 58% compared with 30%.(16) Even though the complication rates of hypoxaemia, POPC and length of hospital stay were more common in

both groups when residual neuromuscular block was detected, the elderly group displayed a significantly increased rate overall.

INVESTIGATIONS

As with any ideal test, it should be easy to use, reproducible, consistent, and preferably cheap. Specifically with regard to neuromuscular monitoring a pre-requisite should also not include an awake, co-operative patient.

Quantitative versus qualitative neuromuscular monitoring

In the past TOFC was done clinically by feeling or observing number of twitches as there was no readout by the machine of the TOF ratio comparing the strength of the 4th twitch to that of the 1st twitch (see *Figure 1*). This is referred to as qualitative monitoring. Minimal evidence exists that this reduces residual neuromuscular block post-operatively or post-operative pulmonary complications.(6)

Figure 1 – various objective quantitative readouts demonstrating TOFC and fade on TOFR (4th twitch over 1st twitch as a percentage)

Clinical factors that were used to evaluate adequacy of reversal of neuromuscular blockade included the patient's ability to maintain a sustained head lift, jaw clench, grip strength and tidal volume. These factors have been proven to be *unreliable* predictors of neuromuscular recovery. For example, some patient's are able to maintain a sustained head lift for more than 5 seconds *even with a TOFR<0.5*.(17) The majority of these tests are also not particular indicators of adequate respiratory ability.

The following table shows the limitations of some popularly used clinical tests, described by Plaud et al in 2010 (18):

Table 3 – limitations of clinical tests

Clinical test	Reliability	Findings
Tidal volume: recovery of spontaneous breathing	Not reliable	Unchanged even when peripheral muscles are fully paralyzed
Vital capacity: ability to take deep breaths	Not sensitive enough	Unchanged with significant levels of paralysis at peripheral muscles
Head or leg lift test >5 seconds	Not sensitive enough	Corresponds to TOFR>0.4. useful to determine the optimum timing of reversal
Tongue depressor test	Probably most reliable clinical sign	Corresponds to TOFR>0.8/0.9. Difficult to implement routinely

A further study by Brull and colleagues in 2011 highlights the diagnostic value of 2 commonly performed clinical tests in the table below (17):

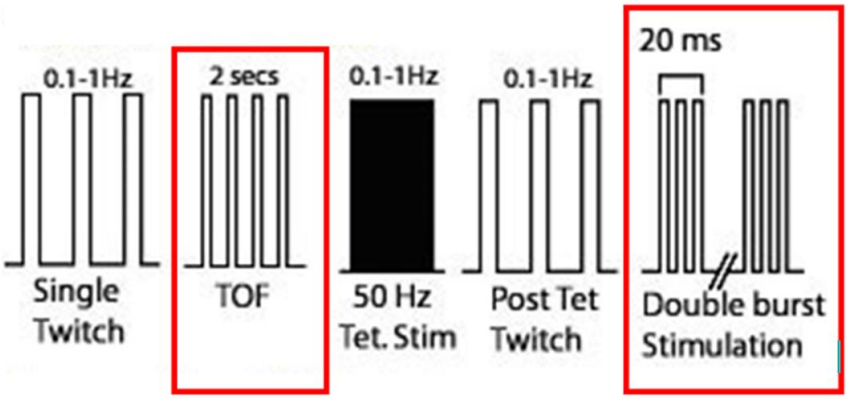
Table 4 – Diagnostic attributes of clinical tests of neuromuscular recovery

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Inability to lift head for 5 seconds	0.19	0.88	0.51	0.64
Inability to perform sustained hand grip for 5 seconds	0.18	0.89	0.51	0.63

Train-of four ratio is the gold standard in objectively proving adequate recovery of neuromuscular blockade, however when train-of-four is performed as a subjective test (either as a train-of-four count or train-of-four fade detected clinically), the results are not reliable. Clinical evaluation of fade of train-of-four is commonly either done as a tactile (assessment of the movement of the patient's thumb against the fingers of the observer) or visual assessment of movement of the patient's thumb. To detect fade clinically, the magnitude of response of the 4th twitch is compared to that of the 1st twitch and a fade between the two is either perceived or not. Even though tactile assessment is more accurate than visual assessment (17), it is still inadaquate to reliably confirm reversal of neuromuscular blockade. In a study by Viby-Mogensen and colleagues, the detection rates of fade was reported as 37% for visual versus 57% for tactile (19), *however*, the majority of evaluators were unable to detect fade when a train-of-four ratio of >0.4 was present.(20)

Other modes of neuromuscular monitoring have also been evaluated to establish detection of fade clinically. The implementation of Double Burst Stimulation (DBS) (see *Figure 2*) improves clinical detection rates of fade up to 0.6/0.7 – this is a significant improvement of 0.4 compared to clinical evaluation limitations on a TOFR, yet this improvement does not eradicate the frequency or magnitude of PORC.(21)

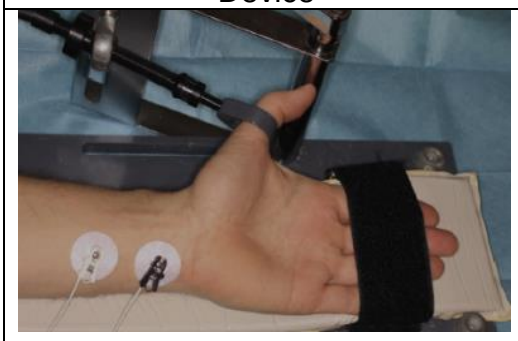
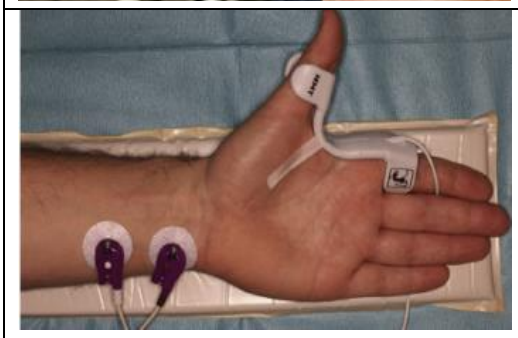
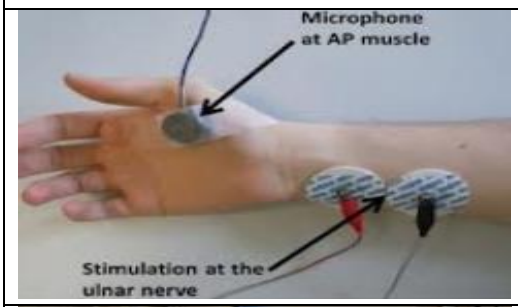
Figure 2 – Different modes of stimulation using a peripheral nerve stimulator; note specifically Train-of-four (TOF) versus Double-burst stimulation (DBS)



The sole measurement of precisely measuring residual neuromuscular blockade is objective neuromuscular monitoring. In the majority of cases, this method is employed by quantifying the measurement of the strength of contraction of a peripheral muscle. This contraction is in response to stimulation of a peripheral nerve supplying that muscle via current being transmitted from 2 stimulating electrodes. A common site employed in the clinical setting is to measure the force of contraction of the adductor pollicis muscle in the thumb after stimulation of the ulnar nerve at the wrist. To quantify the force of contraction of the muscle, various techniques can be employed – these can be either direct measurement or by measurement of some other factor that is proportional to force.

The images in the table below summarize the various methods available for objective measurement of strength of muscle contraction:

Table 5 – Different types of objective neuromuscular monitoring devices (1)

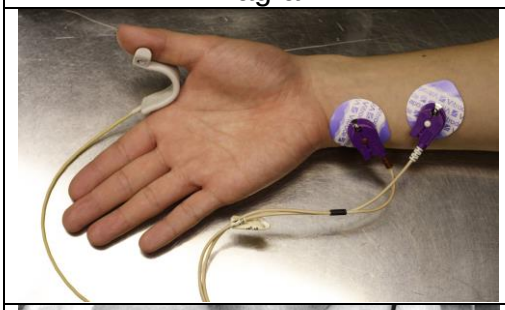
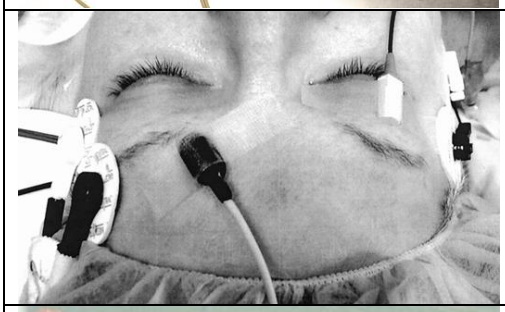
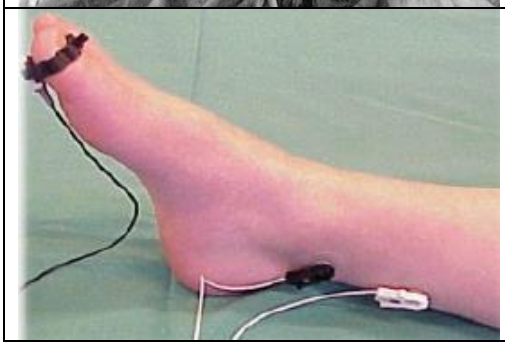
Device	Notes
	**Mechanomyography (MMG)** Sensor: force transducer Measures: force of contraction - Widely considered gold standard - Rarely used clinically because of elaborate setup and bulk of equipment
	**Electromyography (EMG)** Sensor: electrodes Measures: amplitude of compound muscle action potential - Affected by electrocautery - Considered as gold standard by some experts
	**Kinemyography (KMG)** Sensor: piezoelectric polymer sensor in groove between thumb and index finger Measures: movement of muscle (which generates voltage in sensor) - Less reproducible results than EMG
	**Phonomyography (PMG)** Sensor: high-fidelity narrow-bandwidth microphone placed alongside muscle Measures: sound intensity - Low clinical use and unclear future
	**Acceleromyography (AMG)** Sensor: piezoelectric crystal Measures: acceleration of muscle (which generates voltage in crystal) - Reliably detects TOF ratios - Can overestimate compared to EMG

Practical nerve stimulator tips

There are multiple options available in terms of the site and method of neuromuscular monitoring that is practical for the peri-operative physician to use**.** With this plethora of options, one must decide which would be the best option to use to monitor depth of adequate paralysis.

Each site is accompanied by its own advantages (see *Table 6* below). An advantage of measuring the adductor pollicis response is that there is a good correlation with upper airway as well as upper oesophageal muscle tone.(22) Comparing this to the muscles about the eye (including the orbicularis oculi as well as the corrugator supercilii), it is found that the ocular muscles recover early (in a similar manner to how the diaphragm recovers) and a TOFC of 4 in these muscles regularly correlates with a TOFC of 2 or less at the adductor pollicis muscles.(22)

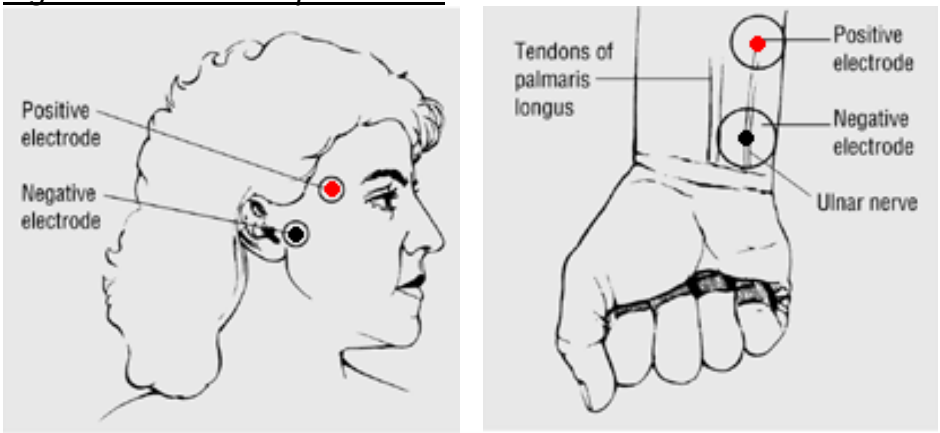
Table 6 – Common sites of peripheral nerve stimulation (1)

Diagram	Notes
	Nerve: Ulnar nerve Muscle: Adductor pollicis Action: Thumb adduction Black: 1-2cm proximal to wrist crease Red: 2-3cm proximal to black
	Nerve: Facial nerve Muscle: Orbicularis oculi and Corrugator supercilii Action: Twitching of eyelid and eyebrow Black: Just anterior to tragus Red: Lateral to outer canthus of eye
	Nerve: Posterior tibial nerve (sural nerve) Muscle: Flexor hallucis brevis Action: Plantar flexion of great toe Black: Over posterior aspect of medial malleolus, over posterior tibial artery Red: 2-3cm proximal to black

Electrode placement is a critical factor to accurately and successfully implement neuromuscular monitoring. They should be positioned over the route of a specific peripheral nerve. The most effective stimulation occurs when the negative electrode (usually black in colour) is placed as close as possible to the muscle terminus (see *Figure 3*). About 2-6cm proximally, the positive (usually red) electrode is placed. As far as possible to ensure best contact, the chosen site must be clean, shaved and dry. A supramaximal stimulus is then applied, usually in the region of around 60mA. In terms of neuromuscular monitoring for the anticipation of emergence, the ulnar nerve has shown to be the superior site for the following reasons:

1) the muscles supplied by the nerve are less likely to be stimulated directly
2) due to the fact that there is slower recovery from neuromuscular blockade as compared to the diaphragm, there is an increased safety margin
3) when monitoring muscles around the eye, the incidence of residual neuromuscular block is increased 5-fold

Figure 3 – electrode placement



REVERSAL AGENT

In order to reduce the risk of PORC, best practice is to always consider administering a reversal agent. The exception is if there is objective evidence of neuromuscular function proving a TOFR>0.9. This is because the administration of neostigmine to a patient that has fully recovered from neuromuscular blockade may actually cause a decreased in activity of muscles of the upper airway as well as tidal volume.(17) Anticholinesterases (neostigmine, pyridostigmine and edrophonium) are at present, one of the more common drugs administered for the reversal of neuromuscular blockade. It must be borne in mind that due to a multiplicity of factors, there is a range in the time taken to onset as well as duration of action of the reversal seen with neostigmine. When administered after a TOFC of 2, the mean time period to adequate reversal of neuromuscular blockade is 15 minutes, and some patients still demonstrate residual blockade of TOFR<0.9 even after 30 minutes.(17) Due to neostigmine's mechanism of action on enzyme inhibition pathways, it also has been shown to display a ceiling effect.(3) Additional safety concerns around the use of neostigmine include the side effect profile related to the blockade of muscarinic and nicotinic receptors including (but not limited to) increasing gastrointestinal and respiratory (bronchial) secretions, muscle cramps and weakness, miosis, etc. which necessitates the co-administration of an anti-cholinergic agent such as glycopyrrolate or atropine to antagonize these muscarinic effects.

A limitation to the use of an anticholinesterase reversal agent is that before they are administered, there should be evidence of adequate spontaneous recovery as seen by implementation of the train-of-four count. The recommended minimum TOFC that should be established is 2 when the implementation of anaesthetic techniques that avoid the potentiation of neuromuscular blockers is used (e.g. TIVA). On the other end of the spectrum using techniques that cause potentiation of neuromuscular blockade (e.g. volatile inhalational anaesthetic agents), 4 is the recommended number of twitches that should be elicited on a TOFC. These recommendations are to make sure that there is adequate antagonistic activity by the reversing agent of the additional depth of neuromuscular block. Refer to the table below as a reminder of the predicted physiological correlations with train-of-four count:

Table 7 - Train of four count and physiological correlation (1)

Train of four count	% neuromuscular blockade at muscle
4	0 – 75%
3	75%
2	80%
1	90%
0	100%

Regarding the administration of reversal agents for neuromuscular blockade, the following guidelines have been recommended by Brull and colleagues (17):

Reversal with subjective neuromuscular monitoring

- TOFC 1 or zero = delay reversal
- TOFC 2 or 3 = give reversal
- TOFC 4 with fade = give reversal
- TOFC 4 with no perceived fade = give reversal, consider low dose (20 µg/kg) neostigmine

Reversal with objective neuromuscular monitoring

- TOFC 0 or 1 = delay reversal
- TOFC 2 or 3 = give reversal
- TOFC 4 with TOFR< 0.4 = give reversal
- TOFC 4 with TOFR0.4-0.9 = give reversal, consider low dose neostigmine
- TOFC 4 and TOFR>0.9 = withhold reversal

Reversal guidelines with clinical neuromuscular monitoring

- Consideration of the use of reversal agents should only occur once there is demonstrated return of spontaneous muscle activity
- Always bear in mind that clinically based tests to detect adequate reversal of neuromuscular blockade are inconsistent and unreliable

MANAGEMENT OF POST-OPERATIVE RESIDUAL NEUROMUSCULAR BLOCKADE

1. ABC. Support airway, breathing and circulation as initial basic resuscitation techniques.
2. Look for other potential causes. Is this truly residual neuromuscular blockade or could it be something else? (Evaluate neuromuscular function using a nerve stimulator device; consider testing a different combination of nerve-muscle).
3. Consider the administration of a reversal agent. There are some institutions that do not employ routine reversal of neuromuscular blockade. Cholinergic side effects of neostigmine were cited as the main reason for not routinely giving reversal in a survey conducted in Europe.(3)
4. If the patient's physiology is stable enough to employ "watchful waiting" this may be considered to allow adequate duration for the reversal agent to take effect.
5. Repeat dosage of reversal agent may be considered, *however*, due to the ceiling effect owing to the enzyme inhibition mechanism of action, if complete enzyme inhibition is already present, no further benefit will be seen.
6. Other factors that potentiate neuromuscular blockade should also be ruled out. Hypoxia, hypercarbia, inhalational agents, hypothermia, impaired hepatic and renal function, electrolyte derangements (be aware of hypermagnesaemia), acidosis and opioids are further considerations to rule out.
7. Alternative agents for reversal should then be considered (for example sugammadex if available).

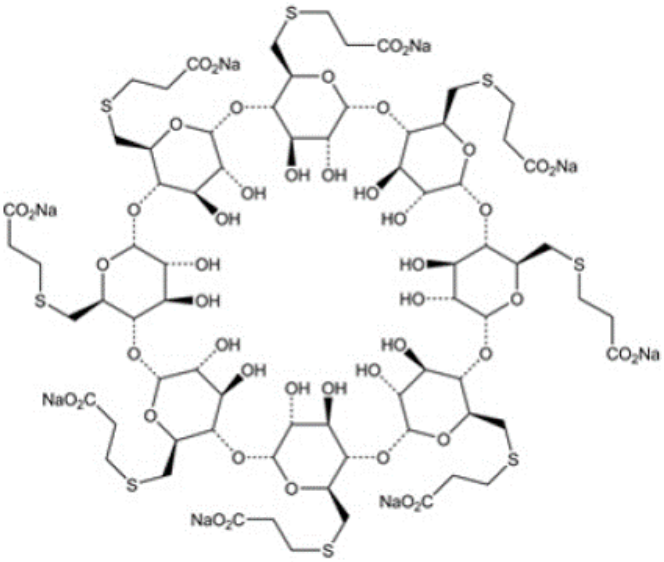
SUGAMMADEX

Further research into reversal agents for neuromuscular blocking drugs has led to the development of more effective agents to combat even profound neuromuscular blockade regarded as undetectable TOFC or PTC as low as 1 or 2.

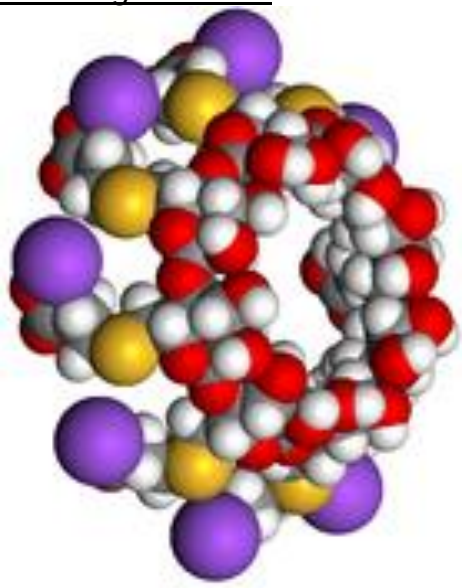
The chemical structure of sugammadex is modified gamma-cyclodextrin (a cyclic sugar) encapsulating agent (see *Figure 4*). This consists of a periphery that is hydrophilic and a

lipophilic core that is negatively charged and that is able to bind aminosteroid neuromuscular blocking drugs selectively. It's affinity for rocuronium is greater than that for vecuronium, which in turn is greater than that for pancuronium. Aminosteroid non-depolarizing neuromuscular blocking drugs are lipophilic substances and these are encapsulated into the toroidal shape of the sugammadex molecule (see *Figures 5 and 6*) in a rigid fashion made possible from a combination of charge transfer and van der Waals forces.(3)

Figure 4(a) – chemical structure; and 4(b) – 3D illustration of sugammadex

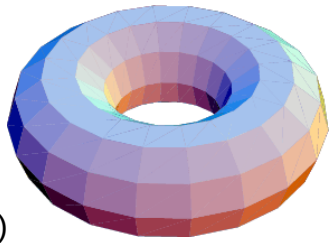


4(a)

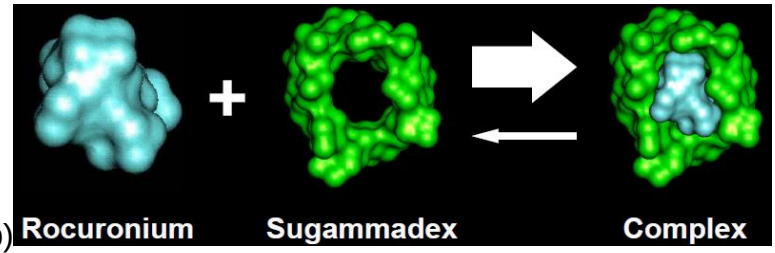


4(b)

Figure 5(a) – a toroid shape; and (b) – illustration showing complex formed with sugammadex and rocuronium



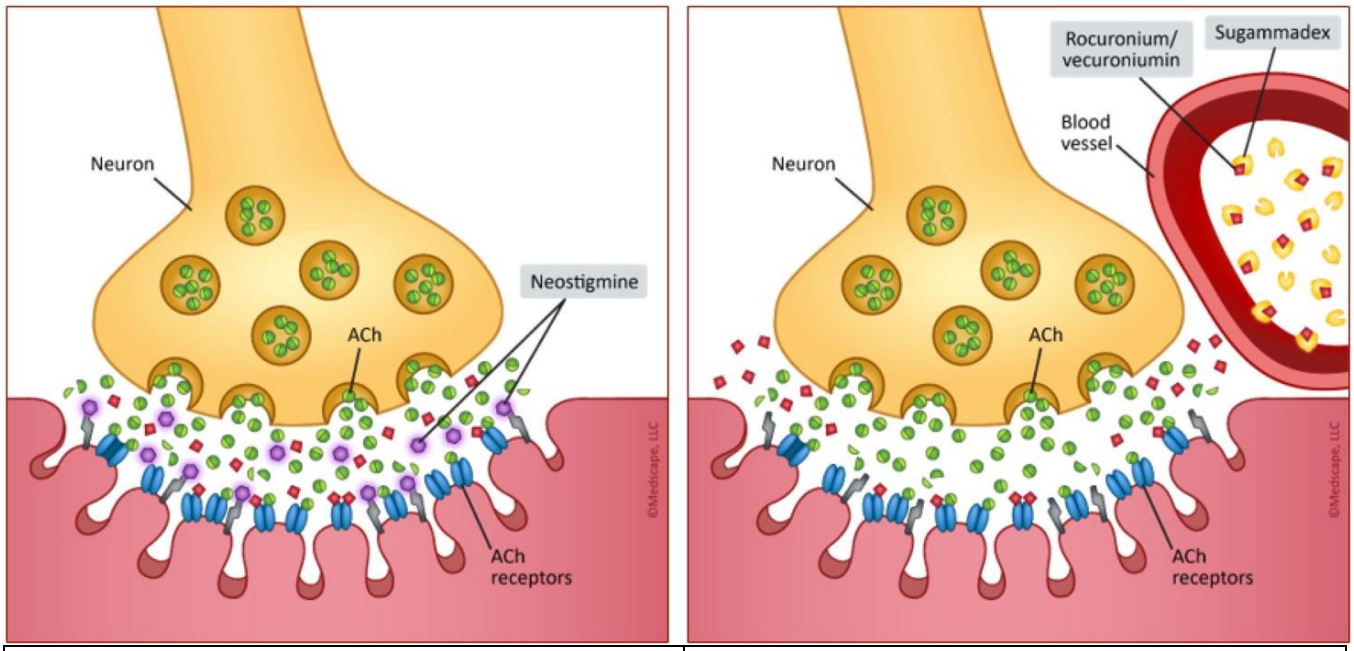
5(a)



5(b)

Figure 6 – diagrammatic illustration showing of mechanism of action of neostigmine versus sugammadex (17)

Neostigmine **Sugammadex**



Neostigmine	Sugammadex
Inhibits acetylcholinesterase at the neuromuscular junction	Encapsulates aminosteroidal neuromuscular blocking drugs
Has a ceiling effect and therefore cannot reverse deep neuromuscular blockade	Rapidly reverses any level of neuromuscular blockade

The introduction of this agent created a new category for drug classes - “Selective Relaxant Binding Agents (SRBA).” This revolutionary new drug is already available in a multitude of countries and in many other countries its approval is currently being trialled. Dosing guidelines recommend that at 2mg/kg, a TOFR>0.9 is reliably produced in 2 minutes when administered at a TOFC of 2 (for longer acting neuromuscular blocking drugs, this increases to approximately 5 minutes). In a display of superiority over neostigmine which is ineffective when there are no twitches on a TOFC or a PTC of 1-2, the recommended dosage of sugammadex here for adequate reversal is 4-8mg/kg. In the ultimate display of dominance, sugammadex can also be administered even immediately post administration of neuromuscular blockers, albeit at a larger dose of up to 16mg/kg. This is particularly appeasing in the “can’t intubate/can’t ventilate” scenario, however a limitation to its use in this setting relates to the time factor to physically draw up the required dose of the drug. Further to this, it may be necessary to antagonize any previously administered opioids or benzodiazepines in this same setting in an attempt to regain adequate spontaneous respiration.(3)

The drug does not undergo biotransformation and elimination is exclusively via renal excretion. Even though sugammadex is not recommended for use in end-stage renal failure, there is no indication of altered effect in such patients.(3)

The limited use of this drug at present is aggravated by cost and availability factors. Nonetheless, it is a landmark drug to be acquainted with due to its potential for rapid reduction of neuromuscular blockade and at the same time to decrease the incidence of residual curarization when compared to neostigmine.

In an international publication, sugammadex in a dose of 2mg/kg in the presence of a moderate block of TOFC of 2 was shown to have an improved incidence of residual neuromuscular blockade in the morbidly obese patient population (BMI>40kg/m^2) in comparison to neostigmine

given at a dose of 50mcg/kg to a similar group.(11) In a follow-on study in 2013 by Kotake and colleagues, the post-extubation incidence of TOFR<0.9 was reported as 24% with neostigmine, but only 4.3% using sugammadex and following routine clinical practice devoid of neuromuscular monitoring.(12) The following table illustrates recommended dosages and timings of reversal agents for neuromuscular blockade (23,28):

Table 8 – Dosing guidelines for reversal agents and timing of administration
(PTC – post tetanic count, TOF – train-of-four, TOFR – train-of-four ratio)

	Benzylisoquinoliniums	Aminosteroids	
	Neostigmine	Neostigmine	Sugammadex
Complete block No PTC detectable	Ineffective	Ineffective	16 mg/kg
Profound block PTC<7	Ineffective	Ineffective	4 – 8 mg/kg
Moderate block TOF count 1-2	50 mcg/kg	50 mcg/kg	2 mg/kg
Moderate block TOF count 2-3 TOFR<0.4	20 – 50 mcg/kg	20 – 50 mcg/kg	2 mg/kg
Residual block TOF count = 4 TOF fade detectable subjectively	40 mcg/kg	40 mcg/kg	2 mg/kg
No fade on TOF detectable subjectively or TOFR0.4-0.9	15 – 25 mcg/kg	15 – 25 mcg/kg	2 mg/kg
TOFR>0.9 on quantitative monitoring	No reversal agent required	No reversal agent required	

The side effect profile of this particular SRBA includes the requirement for additional contraception for 7 days post-administration if a patient is on hormonal contraception as sugammadex binds other steroidal compounds (*in vitro*) such as oestrogen-type compounds, flucloxacillin and antifungals. Even though the relevance of this *in vivo* has not been demonstrated, these are the manufacturer recommendations.(24) Larger doses of administration have also been linked to hypotension as well as prolonged Q-T interval, but the clinical relevance is yet to be elucidated.(25) Despite the fact it is yet to be reported in clinical studies, an increase in blood-clotting times in volunteer studies has been identified.(25) Largely responsible for the delay in the Food and Drug Administration (FDA) approval was the report of anaphylactic reactions, even though the incidence is rare. In contrast though, anaphylactic reactions to rocuronium have been treated with sugammadex when first-line management with sympathomimetic agents such as adrenaline and the use of metaraminol have proved fruitless, although its use in this setting is not a recommendation on the package insert. While it has been reported, the incidence of post-operative nausea and vomiting (PONV) is diminished with sugammadex when compared to neostigmine but the evidence of decreased POPC in comparison is poor, with the majority of the benefit being identified in the elderly.(26)

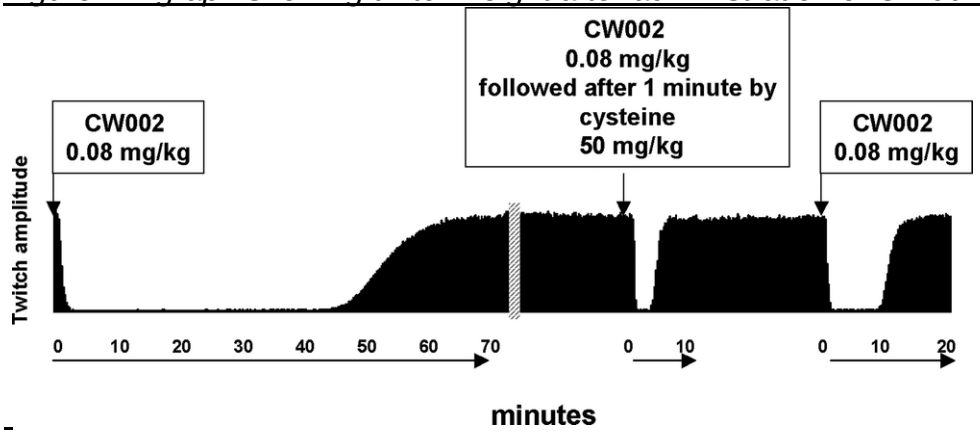
OTHER NEWER AGENTS

a) Cysteine and CW002

CW002 is a fumarate – of family tetrahydro-isoquinolinium compound. Its birth was brought about by an attempt to formulate a newer type of non-depolarising neuromuscular blocking drug characterized by a short duration of action as well as an absence of histamine release and other autonomic effects. Endogenous L-cysteine

present in plasma has been reported to be the agent responsible to degrade CW002.(27) Due to this, its onset of action has been reported to occur on average within 200 seconds, with duration of action approximating 34 minutes. Much like the combination of sugammadex and rocuronium, intense block due to CW002 can be reversed by exogenous cysteine, however CW002 has currently not yet been licenced for clinical use.

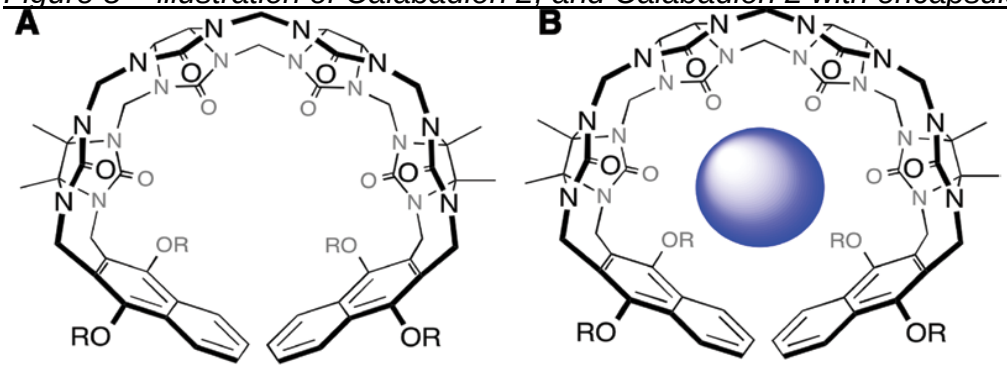
Figure 7 – graph showing twitch height after administration of CW002 as well as cysteine



b) Calabadion 1 and 2

On-going research in an attempt to create an agent that is adept at antagonizing both benzylisoquinolinium as well as aminosteroidal blockers has resulted in the introduction of calabadion 1 and 2. Again, much like sugammadex and rocuronium the mechanism of action is that of an encapsulation type as it forms host-guest complexes with non-depolarising neuromuscular blocking drugs due its molecular structure (see *Figure 8*). Calabadion 1 has been shown to reverse cisatracurium, vecuronium and rocuronium albeit with a lower affinity for rocuronium (*in vitro)* than sugammadex for rocuronium. Calabadion 2 on the other hand is dose-dependent - similar to sugammadex, however it is able to reverse deep block from cisatracurium as well as vecuronium and rocuronium, and notably, the reversibility of rocuronium occurs more rapidly than that seen with sugammadex.(3)

Figure 8 – illustration of Calabadion 2; and Calabadion 2 with encapsulated rocuronium



Calabadion 2: R = $(CH_2)_3SO_3Na$
Molecular Formula: $C_{62}H_{68}N_{16}Na_4O_{24}S_4$
Molecular Weight: 1641.51

Calabadion 2•rocuronium

CONCLUDING REMARKS

The problem of post-operative residual curarisation has been shown to occur more commonly than initially thought. This may likely be, at least in part, due to the fact that varying degrees of residual blockade is usually well tolerated in the clinical environment. However, one must always be cognisant of the fact that especially in high risk groups, residual blockade can

present potentially grave consequences. The gold standard of objective quantitative monitoring of neuromuscular blockade should be routine practice as increased morbidity has been identified in patients extubated with a TOFR up to 0.9.(17) Additional recommendations to reduce this complication include the requirement that any peri-operative anaesthesia care provider should be well versed in the pharmacology of both reversal agents as well as the neuromuscular blocking drugs, and all peri-operative staff involved in the clinical care of patients should also be familiar with steps to identify as well as manage residual neuromuscular blockade.

REFERENCES

1. Moi D. Residual Neuromuscular Blockade Anaesthesia Tutorial Of The Week 290. *www.totw.anaesthesiologists.org*. 2013
2. Murphy GS, Brull SJ. Residual neuromuscular block: lessons unlearned. Part 1: definitions, incidence, and adverse physiologic effects of residual neuromuscular block. *Anesth Analg* 2010;111:120-8
3. Hunter JM. Reversal of residual neuromuscular block: complications associated with perioperative management of muscle relaxation. *Br J Anaesth*, 119 (S1): i53–i62 (2017)
4. Eriksson, L. I., Sundman, E., Olsson, R., Nilsson, L., Witt, H., Ekberg, O., & Kuylenstierna, R. (1997). Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans: Simultaneous videomanometry and mechanomyography of awake human volunteers. *Anesthesiology*, *87*(5), 1035-1043
5. Viby-Mogensen J, Jorgensen B, Ording H. Residual curarization in the recovery room. *Anesthesiology* 1979;50:539-4
6. Naguib M, Kopman AF, Ensor JE. Neuromuscular monitoring and postoperative residual curarisation: a meta-analysis. *Br J Anaesth* 2007;98(3):302-16
7. APSF Survey Results: *Drug-Induced Muscle Weakness in the Postoperative Period Safety Initiative*. *https://www.apsf.org/newsletters/html/2014/winter/03_survey.htm*. Winter 2013-14 Survey
8. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS: Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit. *Anesth Analg* 2008; 107:130–7
9. Brueckmann B, Sasaki N, Grobara P, et al. Effects of sugammadex on incidence of postoperative residual neuromuscular blockade: a randomized, controlled study. *Br J Anaesth* 2015; 115: 743–51
10. Cammu GV, Smet V, De Jongh K, Vandeput D. A prospective, observational study comparing postoperative residual curarisation and early adverse respiratory events in patients reversed with neostigmine or sugammadex or after apparent spontaneous recovery. *Anaesth Intensive Care* 2012; 40: 999–1006
11. Gaszynski T, Szewczyk T, Gaszynski W. Randomized comparison of sugammadex and neostigmine for reversal of rocuronium-induced muscle relaxation in morbidly obese undergoing general anaesthesia. *Br J Anaesth* 2012; 108: 236–9
12. Kotake Y, Ochiai R, Suzuki T, et al. Reversal with sugammadex in the absence of monitoring did not preclude residual neuromuscular block. *Anesth Analg* 2013; 117: 345–51
13. Harrison GG. Death attributable to anaesthesia: a 10-year survey (1967-1976). *Br J Anaesth* 1978; 50: 1041–6
14. Cooper ALO, Leigh JM, Tring IC. Admission on the intensive care unit after complications of anaesthetic techniques over 10 years. *Anaesthesia* 1989; 44: 953–8
15. Tiret L, Desmonts JM, Hatton F, Vourc'h G. Complications associated with anaesthesia: a prospective survey in France. *Can J Anaesth* 1986; 33: 336–44
16. Murphy GS, Szokol JW, Avram MJ, et al. Residual neuromuscular block in the elderly: incidence and clinical implications. *Anesthesiology* 2015; 123: 1322–36

17. Brull SJ, Murphy GS. Residual neuromuscular block: lessons unlearned. Part 2: Methods to reduce the risk of residual weakness. *Anesth Analg* 2011;111:129-40
18. Plaud et al, 2010 - Plaud, B., Debane, B., Donati, F., Marty, J. (2010) Residual paralysis after emergence from anesthesia. *Anesthesiology,* 112(4), 1013-1022
19. Viby-Mogensen J, Jensen NH, Engbaek J, Ording H, Skovgaard LT, et al. Tactile and visual evaluation of the response to train-of-four nerve stimulation. *Anesthesiology* 1985;63:440-443
20. Brull SJ, Silverman DG. Visual and tactile assessment of neuromuscular fade. *Anesth Analg* 1993;77:352-5
21. Drenck NE, Ueda N, Olsen NV, Engbaek J, Jensen E, et al. Manual evaluation of residual curarization using double burst stimulation: a comparison with train-of-four. *Anesthesiology* 1989;70:578-81
22. Donati F. Neuromuscular monitoring: more than meets the eye [comment]. Anesthesiology 2012;117(5):934-6. Comment on: *Anesthesiology* 2012;117:964-72
23. Kopman AF, Eikermann M. Antagonism of non-depolarising neuromuscular block: current practice. *Anaesthesia* 2009; 64: S22–30.
24. Zwiers A, van den Heuvel M, Smeets J, Rutherford S. Assessment of the potential for displacement interactions with sugammadex. *Clin Drug Investig* 2011; 31: 101–11
25. Keating GM. Sugammadex: a review of neuromuscular blockade reversal. *Drugs* 2016; 76: 1041–52
26. Ledowski T, Falke L, Johnston F, et al. Retrospective investigation of postoperative outcome after reversal of residual neuromuscular blockade. *Eur J Anaesthesiol* 2014; 31: 423–9
27. Sunaga H, Savarese JJ, McGilvra JD, et al. Preclinical pharmacology of CW002. *Anesthesiology* 2016; 125: 732–43
28. Khirwadkar R, Hunter JM. Neuromuscular physiology and pharmacology: an update. *Br J Anaesth* CEACCP 2012; 12: 237–44