Neuromuscular physiology and pharmacology: an update

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Rashmi Khirwadkar MBBS MD (India) FRCA
Jennifer M Hunter MB ChB PhD FRCA FCARCSI

Key points

The functioning of the neuromuscular junction (NMJ) and the release of acetylcholine to stimulate the post-synaptic nicotinic receptors is dependent on the interaction of several proteins such as agrin and muscle-specific tyrosine kinase, which are responsible for the formation and maintenance of the NMJ.

A new non-depolarizing agent, gantacurium, is being investigated as a replacement for succinylcholine. It is degraded in the plasma non-enzymatically by endogenous L-cysteine.

The new antagonist to rocuronium, sugammadex, can reverse profound block when given in the correct dose immediately after rocuronium.

Postoperative residual curarization is still common. A train-of-four ratio of >0.9 is necessary before extubation to prevent postoperative respiratory complications.

Rashmi Khirwadkar MBBS MD (India) FRCA

ST5 Anaesthesia
Royal Liverpool and Broadgreen University Hospital
Prescot Street
Liverpool L7 8XE
UK
Tel: +44 (0)7899665846
Fax: +44 (0)1517065884
E-mail: rashmikhirwadkar@aol.com
(for correspondence)

Jennifer M Hunter MB ChB PhD FRCA FCARCSI

Professor of Anaesthesia
University Clinical Departments
Duncan Building
Daulby Street
Liverpool L69 3GA
UK

Neuromuscular physiology

The neuromuscular junction (NMJ) consists of a presynaptic nerve terminal, the synaptic cleft, and post-synaptic nicotinic receptors on the muscle membrane. An electrical impulse is transmitted along the motor nerve causing presynaptic acetylcholine (ACh) release with binding of the neurotransmitter to the post-synaptic ACh receptor (AChR).

Presynaptic nerve terminal

This consists of the terminal part of the motor neurone which originates from the ventral horn of the spinal cord, losing its myelin as it nears the muscle fibre. Here, the Schwann cell (SC) anchors the nerve to the muscle membrane. SCs play an important role in the maintenance of nerve homeostasis. In addition to providing stability and secreting growth and trophic factors, they also participate in axon development and synaptic formation from the fetal state and throughout life. SCs control the number of NMJs and remove superfluous pre-synaptic nerve terminals, especially during re-innervation, for instance, after crush injury. The mechanism involves interaction with the immune molecules, major histocompatibility Class 1a (MHC Class 1a), present in motor neurones which mediate non-immune modulation of synaptic function and plasticity. In the absence of MHC Class 1a, NMJ organization is disturbed, and recovery of motor nerve lesions is delayed.[1]

The presynaptic terminal also contains AChRs on the surface of the nerve membrane. These are nicotinic receptors identified as neuronal nAChR ($\alpha 3\beta 2$).[2] Non-depolarizing and depolarizing neuromuscular blocking agents (NMBAs) act on these receptors, altering the mobilization of ACh: the former inhibit them and the latter stimulate them. Such mobilization involves the acquisition and synthesis of ACh, its storage in reserve vesicles, and its release by a nerve action potential.

ACh is stored in two pools: in vesicles in the reserve pool which contain abundant mitochondria and microtubules to synthesize neurotransmitter; and as readily releasable vesicles. The release of ACh from the readily releasable pool on arrival of a nerve impulse results in sodium channel activation on the prejunctional nerve membrane. This in turn activates voltage-dependent calcium channels (P-type fast channels) on the motor neurone causing an influx of calcium into the nerve cytoplasm that promotes further ACh release. Three proteins, synaptobrevin, syntaxin, and synaptosome-associated protein SNAP-25, are involved in the attachment of ACh vesicles to the presynaptic cell membrane. These proteins along with vesicle membrane-associated synaptotagmins cause the docking, fusion, and release (exocytosis) of neurotransmitter from the vesicles.[2]

The P-type calcium channels are in contrast to the L-type (slow channels) which are present in the heart. There is evidence that L-type calcium channels may also be present on the nerve terminals which could explain why the action of non-depolarizing NMBAs is prolonged by calcium channel blockers. By blocking the L-type channels, these drugs may prevent calcium accumulation within the prejunctional membrane and thus release of ACh from the vesicles. The P-type calcium channels are blocked by cations such as magnesium, cadmium, and manganese. By blocking calcium entry, magnesium sulphate reduces ACh release from the vesicles, resulting in a reduction in muscle tone. Antibodies to the calcium channels may develop in some forms of cancer (Eaton–Lambert syndrome in small cell lung cancer) causing muscle weakness.

An increase in calcium concentration in the prejunctional cytoplasm triggers ACh release. The calcium inflow is balanced by

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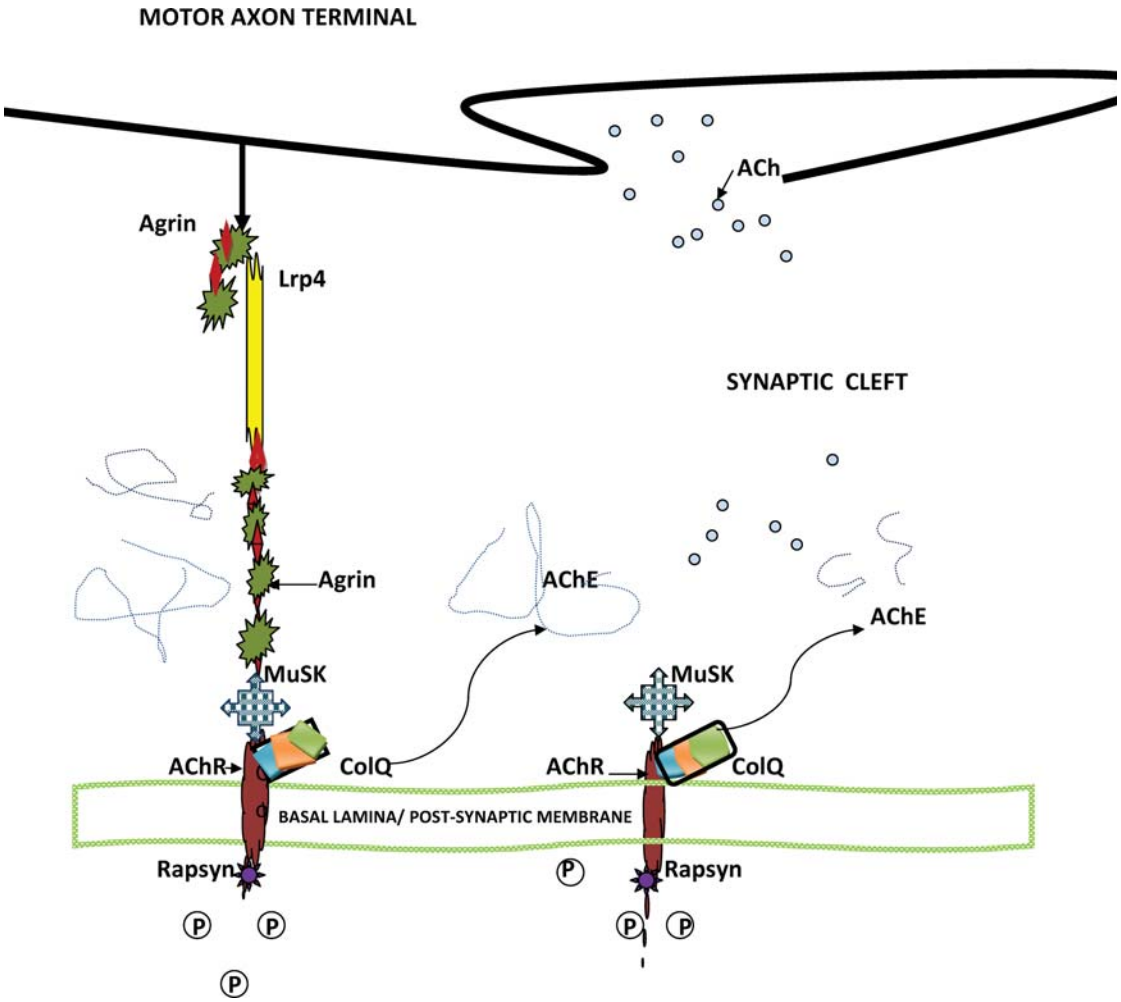

Fig 1 The glycoprotein, agrin, is released from the motor nerve terminal into the synaptic cleft and binds to the Lrp4. This causes the activation of MuSK which binds to AChR. One domain of ColQ in the synaptic cleft binds to AChE and the other to activated MuSK which through a rapsyn-dependent pathway then causes the phosphorylation of proteins (P) in the skeletal muscle cells, leading to the anchoring and clustering of AChRs. (Modified with permission from Burden.[3])

potassium ion outflow through potassium channels to maintain equilibrium across the nerve membrane. Drugs such as 4-aminopyridine or tetraethyl ammonium which are potassium channel blockers cause accumulation of high concentrations of intracellular calcium in the presynaptic nerve cytoplasm with prolonged release of ACh.

Synaptic cleft

The synaptic cleft measures 50 nm from the motor neurone to the post-synaptic muscle membrane. Variants of acetylcholinesterase (AChE), lipoprotein receptor-related protein 4 (Lrp4), agrin, and several collagens including collagen Q (ColQ) interact in the cleft not only to enhance neuromuscular transmission but also to contribute to the prepatterning of muscles in respect of AChR formation on the crests of the post-junctional folds.[3] The basal lamina of the post-synaptic membrane is also made up of proteins which contribute to cell adhesion and aid neuromuscular signalling. The most important molecule is muscle-specific tyrosine kinase (MuSK) on the muscle membrane. Agrin is a glycoprotein which binds to Lrp4 and stabilizes post-synaptic differentiation of AChRs by causing MuSK activation (Fig. 1).

The normal variant of $AChE_T$ which is abundant in the synaptic cleft binds to ColQ, a non-fibrillar protein with three domains. The ColQ C domain also binds to muscle MuSK which then recruits rapsyn, a membrane-associated cytoplasmic protein to produce AChR clustering. MuSK association is essential to NMJ formation and triggers AChR clustering even before the nerve contacts the muscle during development. Its actions are regulated by ColQ. The absence of ColQ results in reduced levels of MuSK on the muscle cell surface. Patients with ColQ mutations develop congenital myasthenic syndrome with AChE deficiency.

Post-junctional membrane

This consists of multiple folds with shoulders bearing the high-density clusters of AChR (10 000 receptors μm^{-2}), and clefts containing voltage-gated sodium channels. The high density ensures that ACh elicits sufficient depolarization across the muscle membrane for muscle contraction. The density is achieved by two mechanisms: anchoring the receptors through rapsyn and other critical muscle proteins into the post-synaptic membrane;[3] and selectively increasing expression of the genes coding for these receptors in the myofibre nuclei positioned near the synaptic site. This process is called 'synapse-specific transcription'.

AChRs exist in two forms:

(i) Mature/adult junctional receptors: these are pentameric proteins with five subunits ($2\alpha\beta\delta\varepsilon$) which are present in high concentration, exhibit high conductivity, and remain open for a very short time (ms). They have a half-life of 14 days. They remain anchored to the post-synaptic membrane by rapsyn dystroglycans.

(ii) Immature/fetal extrajunctional receptors: these are present mainly in the fetus. They can proliferate in adult life secondary to upper or lower motor neurone nerve injury, sepsis, or in burns. They also have a pentameric structure but differ from the adult form, in that one of the subunits (ε) is replaced by γ ($2\alpha\beta\delta\gamma$). They appear within 18–24 h of injury and have a shorter half-life of <24 h. These receptors are resistant to non-depolarizing NMBAs and sensitive to succinylcholine. When stimulated, these channels have a 2- to 10-fold longer mean channel open time than mature receptors, promoting greater efflux of potassium ions with the risk of hyperkalaemia.

Neuromuscular pharmacology

NMBAs are quaternary ammonium compounds, with positively charged radicals [N^+ $(CH_3)_3$] mimicking the quaternary nitrogen radical of ACh. It is this similarity in structure which attracts NMBAs to nicotinic receptors. NMBAs can be classified according to their mechanism of action.

Depolarizing agents

These drugs are agonists at AChRs, the classic example being succinylcholine. Decamethonium is another depolarizing NMBA which is no longer available due to its renal excretion and tendency to produce tachyphylaxis. It is used only for research purposes.

Non-depolarizing agents

These are competitive antagonists at the AChR and grouped according to their chemical structure:

(i) steroidal compounds: pancuronium, vecuronium, and rocuronium;

(ii) benzylisoquinolinium compounds: atracurium, cisatracurium, and mivacurium.

In the early 1980s, vecuronium and atracurium revolutionalized clinical practice as non-depolarizing NMBAs of intermediate duration with minimal side-effects.

Rocuronium with its faster onset of action (<75 s) can be used to facilitate rapid sequence intubation if succinylcholine is contraindicated.

New non-depolarizing drugs

Gantacurium is a diester derivative of chlorofumaric acid belonging to the family of tetrahydroisoquinoliniums. It is undergoing phase III trials in the USA. A dose of $1.8–4\times ED_{95}$ (0.19 mg kg^{-1}) has a fast onset of action of 1.5 min with spontaneous recovery of the train-of-four (TOF) ratio to 0.9 in 10–14 min.[4] It is being considered as a replacement for succinylcholine. Gantacurium is degraded non-enzymatically to inactive derivatives by the endogenous amino acid, L-cysteine, in the plasma. L-cysteine conjugates with the central double-bond carbons in gantacurium causing alkaline hydrolysis. This drug is associated with less histamine release than succinylcholine. Its neuromuscular blocking effects can rapidly be antagonized by edrophonium 0.5 mg kg^{-1} with atropine, or possibly cysteine if it becomes commercially available.

Anaphylaxis to NMBAs

NMBAs are the most common cause of anaphylaxis under general anaesthesia (50–70% of all cases), with succinylcholine thought to have the highest risk. Atracurium and rocuronium are the next most commonly implicated agents. The flexible structure of drugs such as succinylcholine and mivacurium allows these drugs to interact with the mast cell receptor more easily than the steroidal agents which have a more rigid structure. IgE antibodies to these receptors may have been previously induced after exposure to environmental or microbial antigens, including the quaternary ammonium radicals in soaps and perfumes and also NMBAs.

This may explain why anaphylaxis is more common in females and why prior exposure to NMBAs is not needed to cause an anaphylactic reaction.

Incidence

In the UK, the incidence of anaphylaxis is one in 10 000–20 000 general anaesthetics per year and in Australia, it is similar. In Norway, it is higher at one in 6000, which is 20 times greater than that in neighbouring Denmark or Sweden. It was suggested that the increased prevalence in Norway may be due to the unrestricted sale of *over the counter* cough mixtures containing pholcodine, a drug which also has a quaternary ammonium group which could stimulate antibody formation. This cough mixture is not available in Denmark and Sweden and has now been withdrawn from sale in

Norway. It is thought that the increasing incidence of anaphylaxis to rocuronium has paralleled its increasing usage.

Investigations

Blood sampling for enzyme assays should be carried out as soon as possible after an acute event. Histamine which is the mediator in mast cells is difficult to measure because of its short half-life (15 min). Tryptase is a serine protease in mast cells which reaches a peak in plasma between 15 min and 1 h after an allergic reaction and then declines over the next 2 h. A marked increase in its plasma concentration is highly suggestive of an anaphylactic reaction and plasma tryptase concentration should be estimated in all suspected cases. After the event, suspected cases must be screened by skin testing.

Skin testing is a two-stage process: first, the skin prick test (PT) is performed which if negative in the presence of a good clinical history and raised serum tryptase is followed by an intradermal test (IDT), using a stepwise increase in the concentration of the relevant NMBA starting with a dilution of one in 10 000. The dilutions of NMBA used for these skin tests are a cause of confusion: different studies use different concentrations. Some studies have suggested that PT results are not reliable for rocuronium and hence only IDT should be performed. If the IDT is negative for rocuronium, then an IgE radioimmunoassay can be used. Specific IgE assays are also available for succinylcholine, but the sensitivity of these assays compared with skin testing is low. It has been shown that although correlation between skin reactivity (cellular immunity) and IgE reactivity (humoral immunity) to succinylcholine is high, this is not the case for rocuronium. Measuring the amount of *in vitro-activated basophils* (CD*63* and CD*203*c) using flow cytometric analysis after a reaction may also serve as a useful diagnostic test, but this technique is still experimental.

Cross-reactivity between NMBAs in patients who have had anaphylaxis is high at 70%. Patients should be skin tested not only with the suspect NMBA but also with other NMBAs to identify the NMBA most suitable for future use.

Antagonizing neuromuscular block

The action of NMBAs can be terminated either by increasing the concentration of ACh at the NMJ or by enhancing the disposition of NMBAs from the plasma.

AChE antagonists

These prevent the degradation of ACh by hydrolysing the enzyme AChE in the synaptic cleft. The enzyme has two active sites: the esteratic site (positively charged) and the anionic site (negatively charged).

Reversible inhibitors

Edrophonium competes with ACh for AChE. It has a short duration of action as it only forms an ionic not a covalent bond with AChE. It binds to the negatively charged site on the enzyme by the electrostatic attraction of its positively charged nitrogen atom.

Edrophonium is less potent than neostigmine and not commonly used in the UK.

Neostigmine hydrolyses AChE by forming a carbamylated enzyme complex at the esteratic site. It has a slower rate of hydrolysis than edrophonium.

The action of these antagonists is not limited to the NMJ, for they also cause cholinergic effects such as bradycardia and are given with anticholinergic agents.

Irreversible inhibitors

Organophosphorous compounds irreversibly phosphorylate the esteratic site of AChE forming a stable complex that is resistant to hydrolysis or reactivation. They are not used in clinical practice as they cause autonomic and central nervous system instability.

Drugs which encapsulate NMBAs

Traditional pharmacological strategies only reverse residual neuromuscular block, once recovery has commenced, for example, a TOF ratio of 0.2, or a TOF count of 2. A reversal agent that could reverse profound block soon after an NMBA had been given was considered beneficial.

This led to the development of sugammadex as a specific antagonist for rocuronium.

Sugammadex

This drug is a cyclodextrin. It consists of eight oligosaccharides, each composed of α-D-glucopyranoside units attached by alpha 1–4 linkages in a circular arrangement to create a hollow, spatially arranged toroid (Fig. 2).[5] A toroid is a geometric figure that can rotate around its axis without crossing the axis path.

Cyclodextrins are hydrophilic on the outer surface due to tails of negatively charged hydroxyl groups and lipophilic on their inner surface (Fig. 2). They have been used in foods to trap hydrophobic and less hydrophilic compounds such as cholesterol. The irreversible encapsulation or chelation of lipophilic molecules such as the steroidal NMBAs, rocuronium and vecuronium (but not pancuronium), incorporates the drugs within the toroid, eliminating them from plasma. Once captured, there is an array of interactions (thermodynamic, van der Waals forces, and charge transfer) which irreversibly hold the drug in the toroid.

Pharmacokinetics

Sugammadex exhibits three-compartment kinetics similar to rocuronium.[5] Protein binding, and blood–brain barrier and placental transfer are minimal. The drug and its complex are eliminated unchanged by the kidneys. Sugammadex has a volume of distribution of 10–15 litres with a plasma clearance of 91 ml min^{-1} (similar to the glomerular filtration rate), and an elimination half-life of 2.2 h.

Mechanism of action

Sugammadex encapsulates free plasma rocuronium molecules in a ratio of 1:1. As the free concentration of rocuronium in the plasma

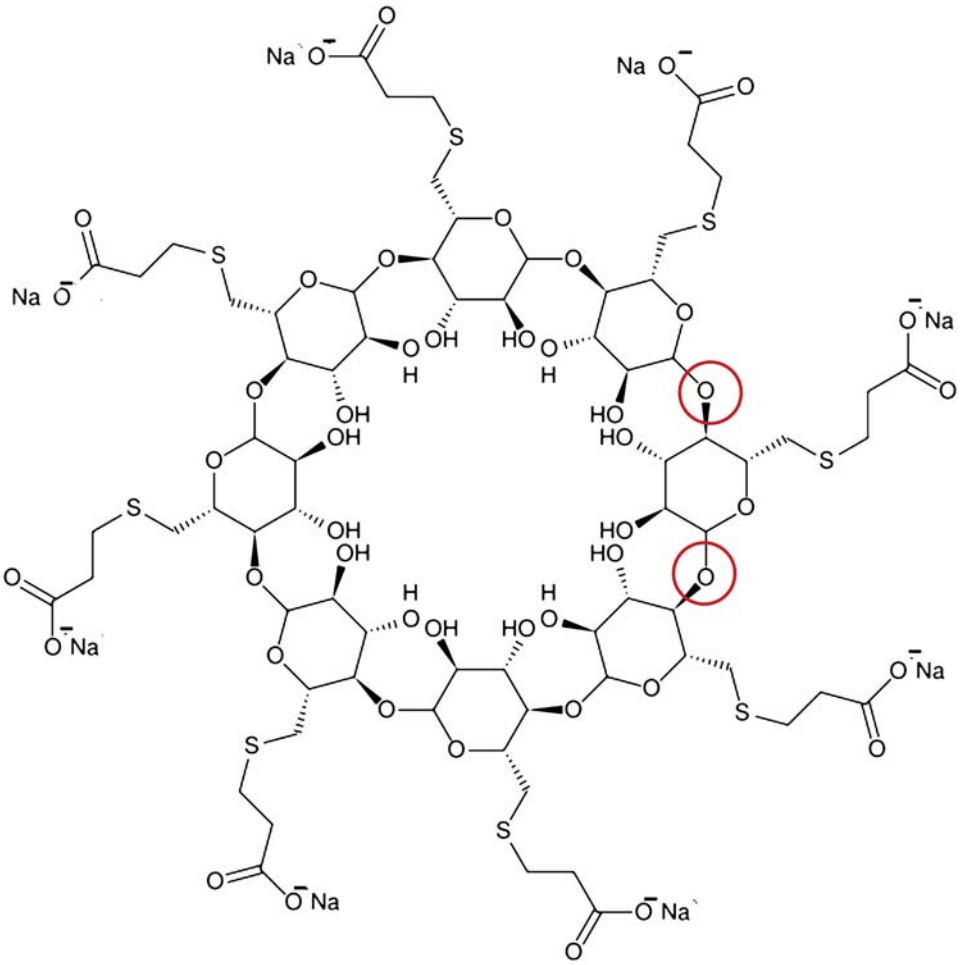

Fig 2 The cyclical structure of sugammadex which consists of eight glucopyranoside units attached by oxygen radicals (marked by circle). The negatively charged hydrophilic chains attract rocuronium to the core of the toroid.[5] (Downloaded from Wikipedia, freely accessible.)

decreases, its dissociation from the NMJ increases down a concentration gradient, thus restoring normal muscle tone. Sugammadex has no effect on AChE, so co-administration of anticholinergics is not required. It is ineffective against depolarizing NMBAs and benzylisoquinolinium compounds.

Dose

The dose depends on the degree of neuromuscular block. If two twitches of the TOF response are detectable (when anticholinesterases can be used), a dose of 2 mg kg^{-1} is recommended. If there is profound block (post-tetanic count of 2–4), then sugammadex 4–8 mg kg^{-1} should be given. For immediate reversal within a few minutes of giving the relaxant, the dose is 16 mg kg^{-1}.

Drug interactions

Sugammadex has minimal interaction with endogenous steroids, for example, hydrocortisone which lack a charged quaternary ammonium group that is attracted to the negatively charged tails on sugammadex. Most endogenous steroids are also tightly bound to carrier proteins in the plasma obviating the possibility of their interaction. However, in patients on the oral contraceptive, sugammadex may *encapsulate* these progestogens reducing their concentration in the plasma. Patients should follow the missed dose advice provided in the drug package leaflet. It is also recommended that caution be exercised when administering sugammadex to patients who are receiving flucloxacillin, fusidic acid, or toremifene (a non-steroidal oestrogen receptor modulator used in breast cancer). Laboratory data suggest that these drugs may *displace* rocuronium from sugammadex, potentiating block.

Side-effects

Concern has been expressed about possible prolongation of the QT interval of the ECG after sugammadex, and hyper- and hypotension have been reported after large doses (32 mg kg^{-1}). One report described accidental administration of a very large dose of sugammadex (40 mg kg^{-1}), however, without any adverse effect on the cardiovascular system.

From phase I studies, allergic reactions to sugammadex were reported to the American Food and Drug administration (FDA) in six volunteers in August 2008, 2 days after the drug had been approved for use in Europe. The FDA therefore requested more volunteer exposures to sugammadex. Recently, reports of anaphylaxis to sugammadex have occurred including one in a patient with a raised plasma tryptase and a positive skin PT.[6]

In contrast, it has been suggested that sugammadex could be given to mitigate the effects of rocuronium in anaphylactic shock, although this is not recommended in the sugammadex data sheet. Its use was reported in a 33-yr-old, female patient undergoing a laparoscopic procedure who developed anaphylaxis to rocuronium. The patient was resuscitated using the standard ALS protocol, but was showing no response 19 min later, when sugammadex 500 mg was given as a last resort. The patient rapidly improved, making an uncomplicated recovery.[7]

Postoperative residual curarization

Postoperative residual curarization (PORC) is a term used to describe residual paralysis or recurarization after anaesthesia in which NMBAs have been used with or without AChE inhibitors. The adverse effects of residual block were recognized in the 1960s, mainly in patients with chronic renal failure who had been reversed with neostigmine. It occurred because these patients were given too large a dose of relaxant, or the anticholinesterase had been given too soon after the last dose of relaxant or before recovery from neuromuscular block was detectable. The patients showed signs of incomplete reversal after operation such as facial twitching or in extreme cases respiratory failure.

Ali and colleagues[8] introduced a clinical tool for monitoring recovery from neuromuscular block in 1971. They suggested that if the degree of the block was assessed using the TOF twitch technique, inadequate reversal could be prevented. They recommended that a TOF ratio of 0.7 after operation indicated adequate clinical recovery from muscle relaxation as it correlated with a sustained head-lift for 5 s, ability to protrude the tongue and grip the hand, and a vital capacity of 15–20 ml kg^{-1}. Following this work, a TOF ratio of >0.7 was considered an indicator of adequate recovery before extubation for over two decades.

In 1997, Berg and colleagues[9] reported a significant incidence of postoperative pulmonary complications, if the TOF ratio was ≤ 0.7 in the recovery room. In this study, the incidence of a TOF ratio <0.7 was higher after the long-acting NMBA, pancuronium (26%), compared with those who had received the intermediate-acting relaxants, atracurium and vecuronium (5.3%). At that time, Eriksson and colleagues[10] measured the strength of the pharyngeal constrictor muscles in 14 volunteers after vecuronium-induced neuromuscular block. He concluded that pharyngeal tone only returned to normal when the TOF ratio at the adductor pollicis muscle was ≥ 0.9: a TOF ratio <0.9 increased the chance of pulmonary aspiration of stomach contents. It is now considered that a TOF ratio >0.9 is required before extubation.

Incidence

The frequency of PORC in present-day clinical practice ranges from 4% to 50% depending on: the duration of action of the NMBA used; whether or not a reversal agent is given; the type of neuromuscular monitoring used peroperatively; and the diagnostic tests used for assessing PORC. Even 2 h after a single dose of atracurium, vecuronium, or rocuronium, the TOF ratio has been shown to be ≤ 0.7 in 10% of patients, if no reversal agent is given.[11] Even after reversing the intermediate-acting NMBAs, the incidence of PORC is similar (TOF ratio <0.8) to when no reversal agent is used.[12] Using NMBAs as continuous infusions rather than in bolus doses also increases the incidence.[13]

The magnitude of the TOF ratio at the time of reversal is positively correlated with the time elapsed since the last dose of relaxant, and the incidence of PORC is greater in patients in whom the duration of the surgery was shorter than anticipated. Murphy and colleagues[14] collected data on critical respiratory events (CREs) in 7459 patients after operation. Sixty-one (0.8%) developed hypoxaemia and upper airway obstruction with eight patients needing re-intubation. Of these 61 patients, 42 had signs or symptoms of residual block. The mean TOF ratio was 0.62 in the CRE group *vs* 0.98 in the control group. No postoperative follow-up with respect to respiratory complications was reported.

Monitoring

In 2007, the AAGBI issued Guidelines, stating that a nerve stimulator must be available whenever NMBAs are used. But a survey of 12 UK anaesthetic departments in 2007 showed that only 9.4% of anaesthetists use nerve stimulators routinely with 62% never using them in practice. PORC can be minimized by accurate neuromuscular monitoring perioperatively. This is now done using acceleromyography. *Bedside clinical tests* such as postoperative head-lift, tongue-depressor tests, or vital capacities[8] are no longer considered adequate.

Subjective monitoring

Subjective monitoring with a peripheral nerve stimulator (PNS) should at least be used to evaluate the TOF response or double-burst stimulation (DBS) visually or tactilely. A major limitation of this method is that even experienced clinicians are unable to detect TOF fade visually or manually once the TOF ratio exceeds 0.4. Even DBS fade can only be detected in this way up to a TOF ratio of 0.6: much lower than the required TOF ratio of 0.9 for extubation.

Objective monitoring

The TOF watch series of monitors (TOF, TOF-S, TOF-SX) work on the principle of acceleromyography and allow better detection of residual block than older PNSs. The acceleration of the thumb after stimulation of the ulnar nerve is converted by a transducer

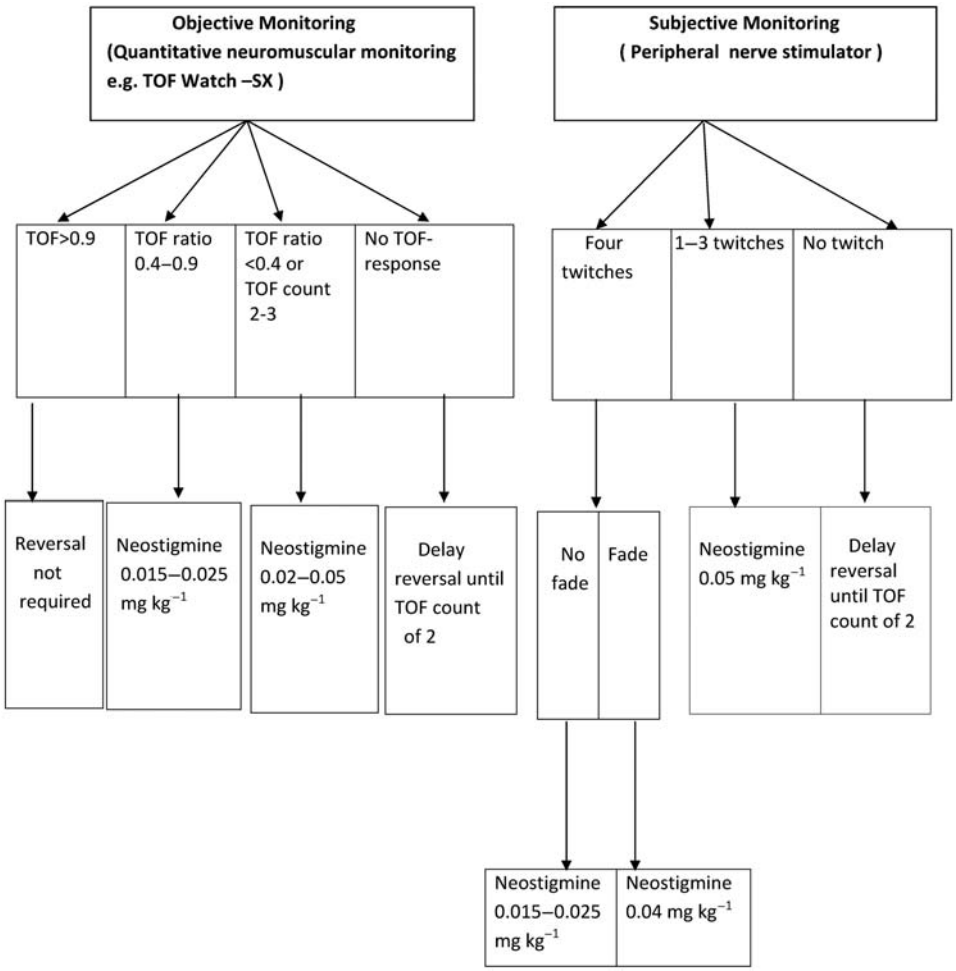

Fig 3 The recommended dose of neostigmine for use in adults based on the type of neuromuscular monitoring available and the response obtained. (Reproduced with permission.[15])

into an electrical signal which is amplified to give a numerical TOF ratio. The most recent equipment, the TOF-SX, is the best clinical neuromuscular monitoring tool available as it gives a direct read-out of the TOF ratio.

Kopman and Eikermann[15] made recommendations on whether to reverse residual block based on the equipment available in the operating theatres which are detailed in Fig. 3.

Conclusions

In this review, some recent developments in our understanding of neuromuscular physiology have been described, as has the study of a new non-depolarizing NMBA, gantacurium, which has been designed to replace succinylcholine. The pharmacology of the new selective relaxant binding agent, sugammadex, has been detailed and the persisting problem of residual postoperative curarization with its attendant risks has been outlined.

Declaration of interest

None declared.

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Please see multiple choice questions 9–12.