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Drug interactions in the context of neuromuscular blockade: clinical implications and safety issues

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**UNIVERSITÉ
DE GENÈVE**

FACULTÉ DE MÉDECINE

Clinical Medicine Section
Department of Anesthesiology,
Pharmacology and Intensive Care

Drug interactions in the context of neuromuscular blockade: clinical implications and safety issues

Thesis submitted to the Faculty of Medicine of
the University of Geneva

for the degree of Privat-Dozent

by

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Geneva

2017

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ABSTRACT

Neuromuscular blocking agents (NMBAs) are a central part of modern anesthesia. Drug interactions with NMBAs can be divided into those that are pharmacodynamic and pharmacokinetic in nature. Pharmacodynamic interaction occurs when the action of a NMBA at the receptor site is altered by a second drug, whereas pharmacokinetic interaction involves changes in the absorption, distribution, metabolism or excretion of a NMBA by a previously or concomitantly administered second drug. The various sites of interactions involve motor nerve conductance, the synthesis and release of acetylcholine, the pre- and postsynaptic receptors, various enzymes in the neuromuscular junction, in the blood and in the liver, and those substances that bind the relaxant molecules in the plasma (i.e. albumin, cyclodextrins and calabadiol). Drug interactions may enhance or lessen the effect of NMBAs. Some drug interactions may induce adverse events, such as the prolongation or recurrence of neuromuscular block, or can be useful, such as the improvement of intubation conditions. The understanding of the physiology of neuromuscular transmission, the properties of modern NMBAs and their antagonists, and the basics of quantitative neuromuscular monitoring are a cornerstone of the safe administration of NMBAs.

1. INTRODUCTION

1.1 History and general considerations

The development and public demonstration of ether narcosis by William Thomas Green Morton on 16 October 1846 established the first of the three pillars of modern surgery. Subsequently, Semmelweis pioneered antisepsis procedures in 1847 for the prevention of infections and Landsteiner disclosed ABO blood groups in 1901, thus making blood transfusion possible, and was awarded the Nobel Prize in Physiology or Medicine in 1930 “for his discovery of human blood groups”.^{1,2} Ether narcosis fulfilled the basic requirements of a general anesthetic (hypnosis, antinociception and immobility),³ successfully protecting humanity from suffering for more than one century. In 1942, a new era in anesthesia and surgery was ushered in when Griffith and Johnson introduced d-tubocurarine into clinical practice.⁴ The supplementation of general anesthetics with neuromuscular blocking agents (NMBAs) facilitated access to body cavities and allowed to have patients immobilized, ventilated and relaxed at less profound narcosis, assuming less “toxicity”. However impressive the effect of relaxants appeared to be, combined anesthesia based on ether or thiopental supplemented with NMBAs was not a matter of course. In 1954, Beecher and Todd analyzed the outcome of anesthesia from 10 university hospitals in the USA and revealed a mortality rate 6-fold higher (1:370) in patients who were given NMBAs compared with those who were anesthetized without relaxants.⁵

This early analysis of anesthesia outcome clearly demonstrated the complexity of anesthetic pharmacotherapy and the risk of introducing new therapeutics in combination with those already established. The authors assumed “inherent toxicity” of the relaxants in the background of the lethal hypoxia or hypotension observed, since no knowledge was available about the interactions between thiopental or ether anesthetics and d-tubocurarine, for example. The safety of anesthesia was gravely compromised and only intense research was able to save NMBAs from being withdrawn from clinical use. The negative cardiovascular effect of ether or thiopental and the sympathetic ganglion blocking effect of d-tubocurarine in addition to histamine release were the reasons explaining cardiovascular “collapse” due to drug interaction. The occurrence of severe hypoxia, the other lethal complication of the epoch, occurred most probably due to potentiation of the residual effect of d-tubocurarine by ether in patients without respiratory support. These examples serve to illustrate the relevance of drug interactions of anesthetics and NMBAs.

Nevertheless, an immense progress has been achieved in anesthesia over the past 60 years: new inhaled and intravenous anesthetics and NMBAs have appeared, the instrumental survey of vital functions (including neuromuscular transmission monitoring) has been elaborated, and the number of drugs given to patients undergoing anesthesia and surgery has increased significantly. The more medication administered, the more interference observed and drug interactions have remained a relevant clinical problem. Anesthesia today is a complex applied pharmacological intervention with the potential of large-scale drug interactions. An increasing number of new drugs are introduced, requiring a permanent adaptation of anesthesia to maintain patient safety, while the number of interventions constantly increases. Today, more than 400 million patients receive general anesthesia each year worldwide, which is supplemented with NMBAs in approximately 30–60% of intensive

care patients and in 66.8% of elected surgeries. Thus, the safe use of muscle relaxants has evolved to become a public health issue.⁶

1.2 Concept and aim of the current review

Induction of muscle paralysis using NMBA results in respiratory depression or apnea, necessitating artificial respiration in order to maintain normal gas exchange during anesthesia and surgery. Securing the patient airway often requires tracheal intubation. To prevent the development of hypoxia during laryngoscopy and tracheal intubation, a rapid onset neuromuscular block is preferable, particularly in cases with a difficult airway or full stomach. In our clinical practice at our unit for neurosurgery, maxillofacial, plastic and ear-nose-throat (ENT) surgery, difficult airway occurs more often than in the average surgical population due to the fact that head and neck, ENT and neurosurgical patients whose pathology may extend to the airways have to be anesthetized. It is generally recognized that this patient population is particularly at risk for difficult airway and therefore rapid onset and offset of neuromuscular block is highly desirable in order to regain spontaneous respiration in case of difficulties of gas exchange. Although succinylcholine has been the gold standard used to facilitate tracheal intubation in patients with recognized difficult airway or full stomach, it has several side effects and therefore alternatives have been sought to replace it.

Based on previous investigations by our team, which showed that magnesium sulfate enhances the neuromuscular block induced by nondepolarizing NMBAs, we developed the concept of “magnesium priming”. This consists of the intravenous administration of magnesium before the injection of a non-depolarizing NMBA in order to accelerate the onset of block similar to that of succinylcholine. In addition, we studied how the amount of gastric content could be reduced in order to prevent regurgitation and pulmonary aspiration during induction of anesthesia and awakening. We were also curious to see how drug interactions influenced the duration of neuromuscular block. Furthermore, recovery from the block may also be influenced by drug interactions, which may hamper or help it, and this also aroused our interest. Pharmacological reversal of neuromuscular block was also studied with a focus on postoperative residual neuromuscular blockade (PORNB).

The objective of this review was to demonstrate the large scale of drug interactions with NMBAs and their impact on the intensity and duration of neuromuscular block. We aimed to resume the underlying mechanisms and discuss patient safety issues.

2. SCIENTIFIC BACKGROUND

Drug interactions with NMBAs can be divided into those that are pharmacodynamic and pharmacokinetic in nature.⁷ Pharmacodynamic interaction occurs when the action of a NMBA at the receptor site is altered by a second drug. Pharmacokinetic interaction involves changes in absorption, distribution, metabolism or excretion of a NMBA by a previously or concomitantly administered second drug. The various sites of interactions involve motor nerve conductance, the synthesis and release of acetylcholine (ACh), the pre- and postsynaptic receptors, various enzymes in the neuromuscular junction (NMJ), in the blood and in the liver, and those substances that bind the relaxant molecules in the plasma (i.e. albumin, cyclodextrins and calabadiol). Drug interactions may enhance or lessen the effect on NMBAs and may also elicit non-neuromuscular effects.

2.1 Morphology of the NMJ

The NMJ is responsible for the transmission of signals from the motor nerve to the muscle, allowing appropriate muscle contraction and muscle tone.⁸ The NMJ consists of three parts: the presynaptic part (distal motor nerve ending), the synaptic cleft, and the postsynaptic part (motor endplate), which is part of the muscle cell membrane.⁹ Each motor neuron innervates one to multiple muscle fibers forming motor units (Fig. 1), but each muscle fiber receives inputs only from one motor neuron. This ensures the synchronized contractions of the multitude of muscle fibers necessary for coordinated movement.

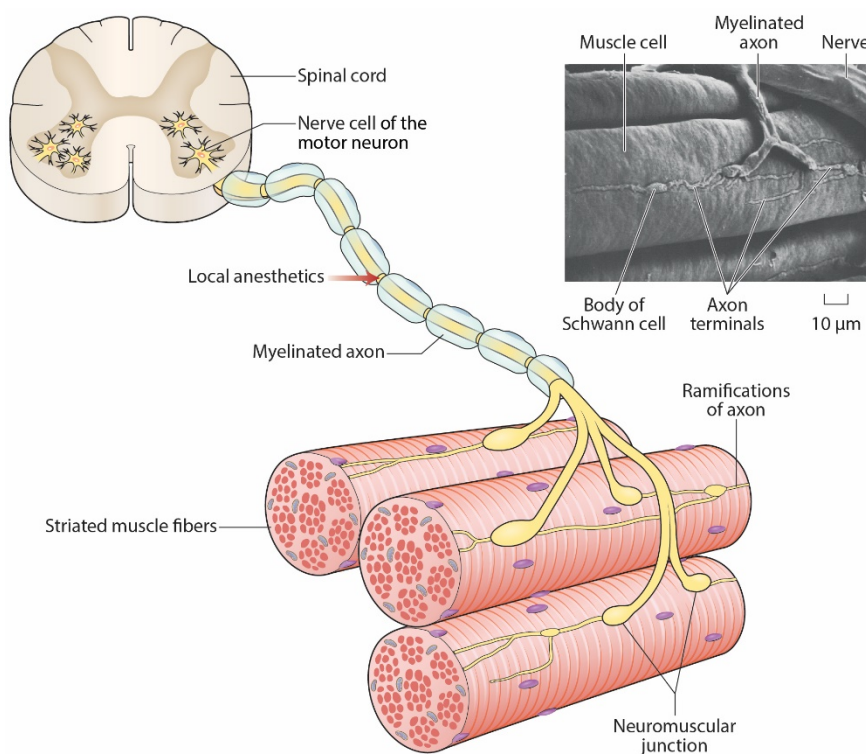


Fig. 1. Electronmicroscopic image of the muscle cell with the nerve and axon ramification from the article of Desaki (with permission)¹⁰ and schematic image of the motor unit (adapted from Tortora, G.J. and Grabowski, S.R. (1993). *Principles of Anatomy and Physiology*, 7th Ed., Page 240, Figure 10.2.).¹¹

The distal part of the motor neuron is demyelinated and surrounded by Schwann cells anchoring the nerve ending into the muscle membrane. Schwann cells ensure the survival of the motor neuron by releasing nerve growth factor and neuregulin by trophic factors released by the nerve ending. The key role of Schwann cells is to maintain the motor nerve terminal and to protect the NMJ.¹² Butyrylcholinesterase enzyme (BChE) is abundant around the terminal Schwann cell and has a regulatory function in ACh release.¹³ Within the nerve terminal, ACh is packed in vesicles located near the terminal cell membrane (the active zone) ready for release. Reserves of ACh can be found deeper in the cytoplasm.¹⁴ The nerve terminal is also involved in the maintenance of the appropriate architecture of NMJ. The cytoplasm of the nerve terminal contains a large population of mitochondria, the source of energy for the ion exchange across the cell membrane. Among the vesicles longitudinally arranged in this active zone, protein particles considered as voltage-gated calcium channels have

been observed during electron microscopy.¹⁵

The synaptic cleft spans about 50 nm from the nerve ending to the muscle membrane. The cleft contains a basal lamina made up of large molecules forming a matrix that aid the signal transmission. The enzyme acetylcholinesterase (AChE) is located here, anchored to the basal lamina.¹⁵ The postsynaptic membrane (motor endplate) consists of multiple folds located opposite the nerve terminal. These folds increase the surface of the endplate many times over. At the top of these folds, nicotinic ACh receptor (nAChR) clusters can be found in high density (about 5 million in each NMJ) anchored into the muscle cell membrane by a complex system of cytoskeletal proteins.¹⁶ Neurotransmitter release has been found to also play a role in the ultrastructure of the postsynaptic membrane. In the depth of the folds, voltage-gated sodium channels can be found, similar to the peri-junctional zone around the motor endplate (Fig. 2).⁹

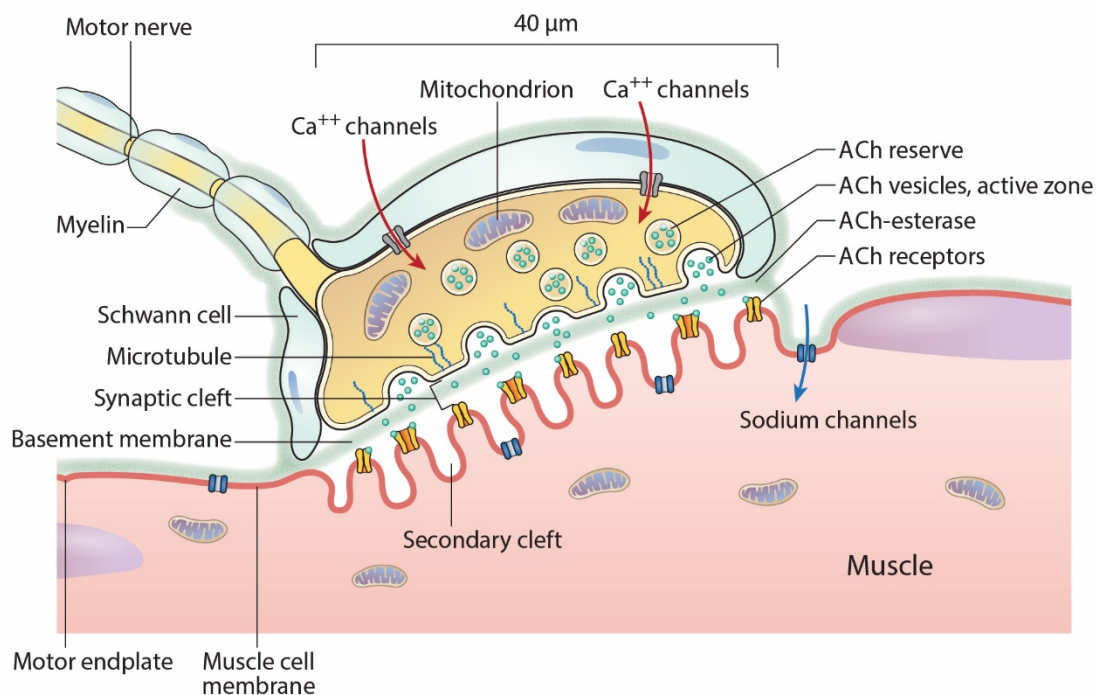


Fig. 2. Schematic structure of the NMJ with the most important components (adapted from Martyn *et al.*).⁹

2.2 Physiology of neuromuscular transmission

In the NMJ, information from the nerve to the muscle is transmitted via the release of ACh and activation of postsynaptic nAChRs. ACh is synthesized, stored and released by the nerve ending. Upon the arrival of the nerve action potential, the voltage-gated calcium channels located among the vesicles are activated. An inward calcium flux leads to intracellular calcium concentration increase sensed by vesicle membrane-associated synaptotagmins.¹⁵ Sensitive-factor-attachment-receptor (SNARE) proteins attach the vesicles to the cell membrane and have a key role in their fusion and, ultimately, in the synchronized release of ACh from hundreds of vesicles (exocytosis) (Fig. 3).¹⁷

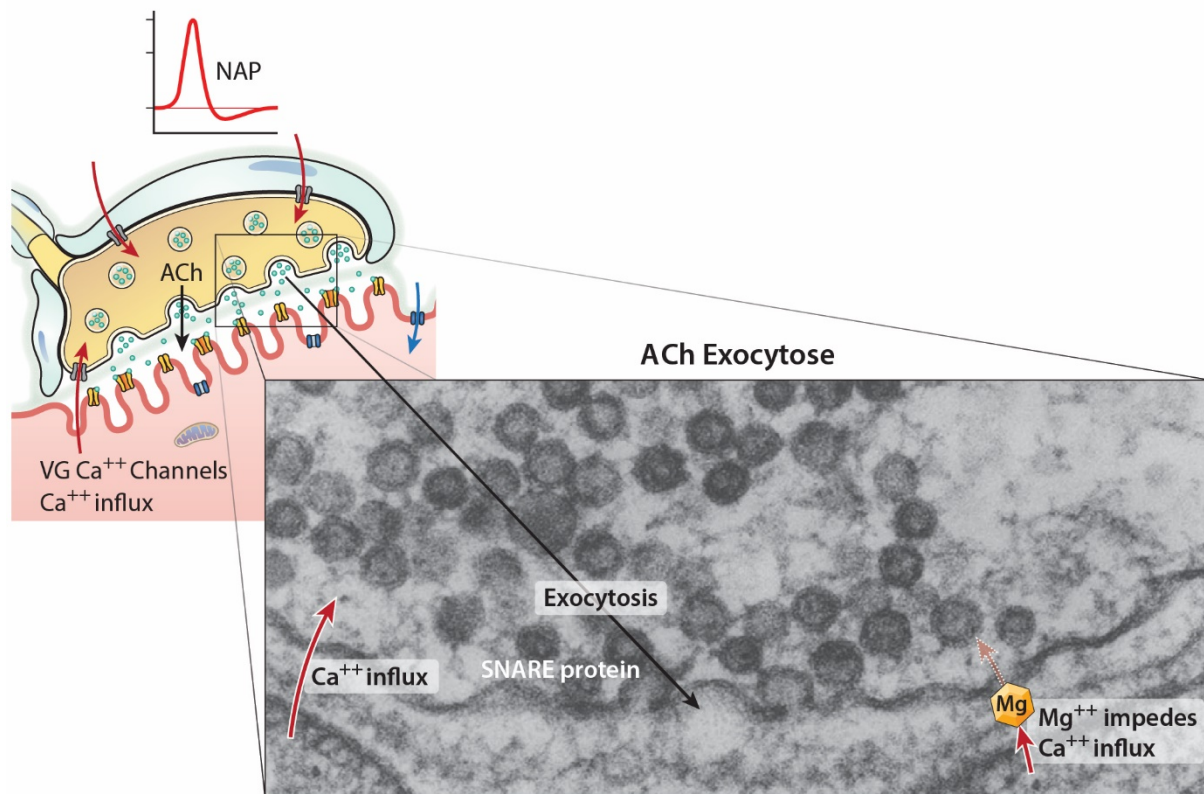


Fig. 3. Electron microscopic of a frog's neuromuscular junction showing the transmission of nerve impulses across a synaptic cleft from the article of Heuser et al. (with permission).¹⁸ Magnesium impedes Ca-influx through voltage gated calcium channels and diminishes ACh exocytose.

Furthermore, Schwann cells also sense and control ACh spillover by the BChE located around them.¹³ ACh molecules pass through the synaptic cleft to the postsynaptic receptors and are degraded by AChE to acetate and choline. The lifetime of ACh is approximately 1.0 ms and its rapid metabolism prevents repetitive receptor activation. The metabolites are actively taken up by the nerve terminal and resynthesized to ACh. ACh turnover is energy-dependent and may be altered by certain drugs, chemicals, toxins or temperature changes. For example, SNARE proteins are inhibited by botulinum toxin, or intracellular influx of calcium is inhibited by magnesium, both resulting in muscle paralysis.¹⁹ Thus, adequate ACh turnover is the *sine qua non* for satisfactory neuromuscular transmission. Under physiological conditions, the amount of ACh released by a nerve action potential is more than sufficient to evoke muscle contractions and there is a reserve in the transmitter capacity. During rapid nerve stimulation (2 to 100 Hz), a positive feedback mechanism maintains the release of ACh, which itself activates the neuronal nicotinic autoreceptors ($\alpha 3\beta 2$) at the nerve terminal.^{20, 21} NMBAs inhibit these receptors and lessen the liberation of ACh per stimulus, resulting in progressively reduced muscle contractions (muscular fade) (Fig. 4).²²

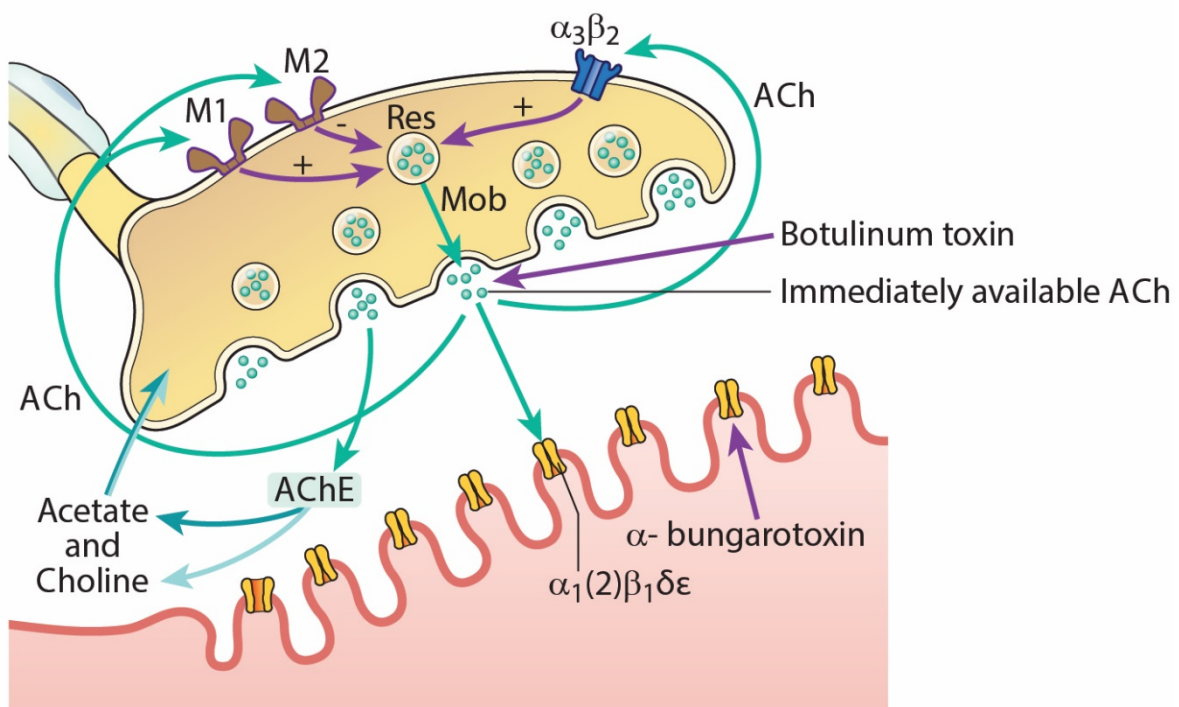


Fig. 4. Presynaptic neuronal nicotinic and muscarinic receptors modulate positive and negative feedback mechanisms in the NMJ and regulate the release of ACh from the motor nerve terminal (adapted from Vizi et al.).²³

However, a caveat is the presence of a partial postsynaptic block. Recent investigation demonstrated that selective presynaptic block in the presence of full postsynaptic receptor capacity does not result in fade because the reserve of receptor capacity will compensate for the reduction in ACh release.²⁴ Consequently, stimulation-induced fade cannot be regarded as an exclusively presynaptic phenomenon and this should be taken into account while evaluating responses to nerve stimulation (monitoring). A different physiologic occurrence is the so-called “post-tetanic facilitation”. During high frequency nerve stimulation (i.e. 50 Hz), there is no time for membrane repolarization, thus calcium freely flows into the cell where it accumulates. The result will be an increased ACh release in the “post-tetanic phase”, resulting in enhanced muscle contractions.⁹ This can be exploited for the monitoring of deep level neuromuscular block when a breakthrough is required in order to evoke muscle contractions. In contrast, under resting conditions (absence of nerve action potential), only small amounts of ACh are released and miniature endplate potential can be recorded at the postsynaptic part of the NMJ.¹⁵

Once ACh has traversed the synaptic cleft and has bound postsynaptic muscular nAChRs, the configuration of the receptors changes and their ion channel opens, allowing the extracellular sodium and, to a lesser extent, calcium ions, enter the cell. The resulting motor endplate potential activates the voltage-gated sodium channels located at the bottom of the endplate folds and at the perijunctional zone, allowing the propagation of action potential to the muscle fiber. The muscle membrane action potential then spreads to the sarcoplasmic reticulum and increased calcium concentration triggers muscle contractions through the intermediary of ryanodine-sensitive calcium channels (Fig. 5).

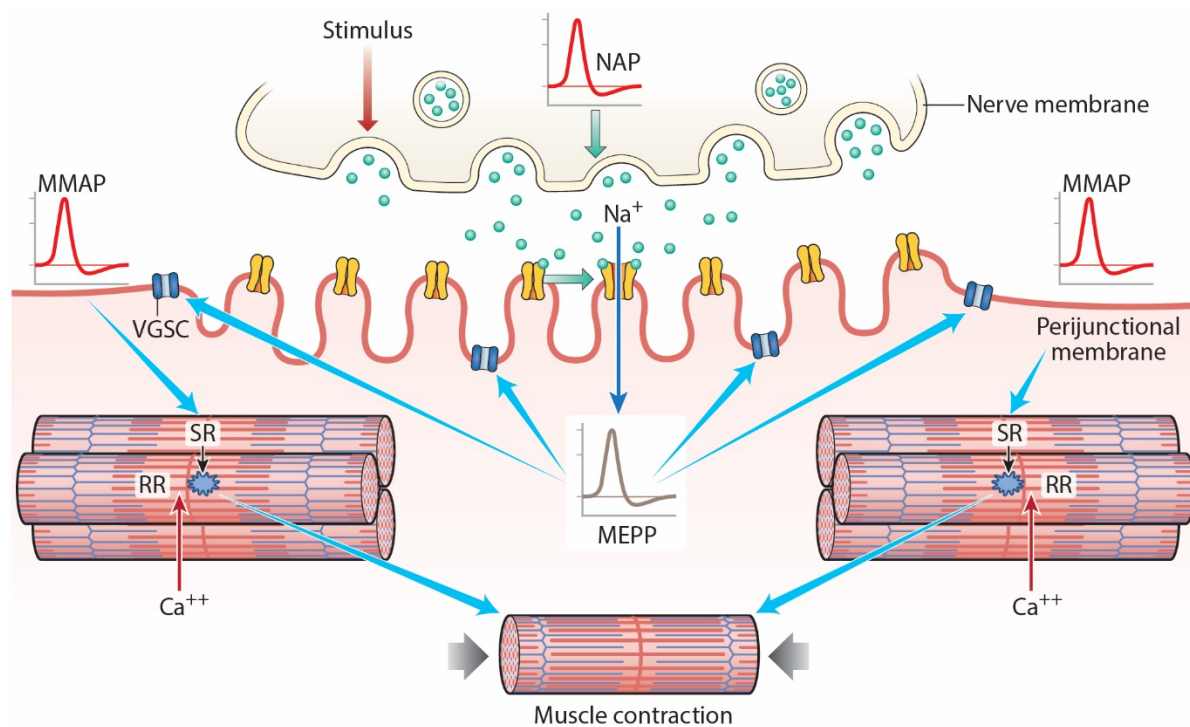
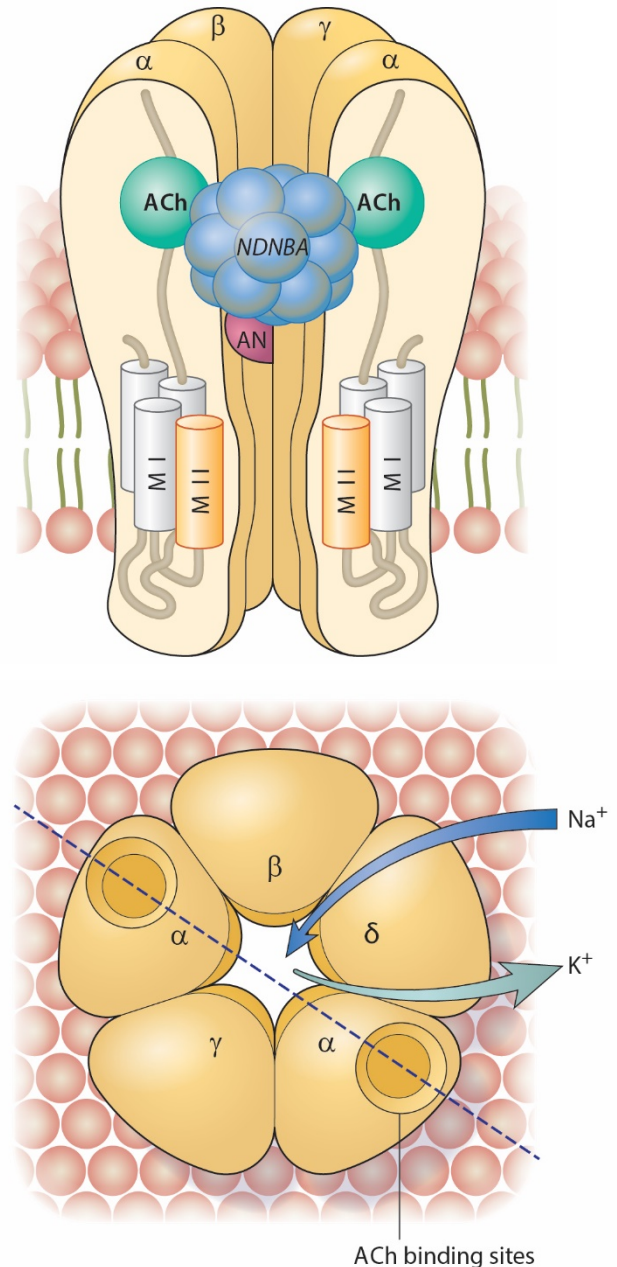


Fig. 5. The nerve action potential initiates the release of ACh, which then induces the process of signal transmission from the nerve to the muscle by the intermediary of several steps leading to muscle contraction (adapted from Tortora, G.J. and Grabowski, S.R. (1993). *Principles of Anatomy and Physiology*, 7th Ed., Page 250, Figure 10.10.).¹¹

Various nAChRs are present at the pre- and postsynaptic parts of the NMJ. They have a determinant role in signal transmission from the nerve to the muscle and have traditionally been divided into muscle and neuronal types. Muscle-type receptors are built up of $\alpha 1$, $\beta 1$, δ , γ and ϵ subunits and the neuronal receptors contain $\alpha 2$ to $\alpha 10$ and $\beta 2$ to $\beta 4$ subunits.²⁵ The most important are the muscle-type nAChRs located at the motor endplate, which mediate fast signal transmission by the action of ACh. In addition, neuronal nAChRs ($\alpha 3\beta 2$) were identified at the motor nerve terminal. $\alpha 7$ homomeric neuronal nAChRs are also expressed on the muscle membrane and on the Schwann cell.¹³ All nAChRs are members of the cys-loop superfamily of ligand-gated ion channels and share a common structure with gamma-aminobutyric acid (GABA), glycine and 5-HT₃ receptors.²⁵ They have five subunits surrounding a central pore. Each subunit consists of four transmembrane segments where the second membrane segment lines the pore (Fig. 6).

Fig. 6A and B. nAChR showing that non-depolarizing agents attach to the ACh sites on the α -subunit and compete with ACh (A). The mature muscle-type receptor consists of 5 subunits: $2\alpha 1\beta 1\epsilon \delta$. Curare can cause different actions on the receptor. Na^+ and K^+ pass through the channel once open (B). (adapted from Tassonyi et al.).²⁵

The binding site of ACh is found on the α subunit. Two types of muscular nAChRs can be distinguished: the fetal ($2\alpha 1\beta 1\delta \gamma$) and the adult ($2\alpha 1\beta 1\epsilon \delta$) types; both require two ACh molecules for activation. During the formation of the synapse, the developing neuron secretes a protein called agrin, which binds different receptors on the surface of the muscle. The receptor, called muscle-specific kinase (MuSK) protein, is required for the formation of the NMJ. This enzyme receptor causes the phosphorylation of different proteins, which then bind to the receptor. Upon activation by its ligand agrin, MuSK signals via two proteins (Dok-7 and rapsyn) to induce AChR clustering. Other proteins are then gathered to form the endplate to the NMJ (Fig. 2). During normal adult life the $\alpha 1(2)\beta 1\epsilon \delta$ receptor is expressed at the postsynaptic site. The mature receptor is more stable and more rapid in reacting to the agonist than the fetal receptor. However, during immobilization, inflammation, burn or denervation, the γ subunit re-appears on the muscle membrane.²⁶ These conditions may cause receptor upregulation when the number of both mature and fetal receptors increase exhibiting resistance to the non-depolarizing NMBAs and increased sensitivity to succinylcholine. Receptor downregulation is seen in myasthenia gravis or in anticholinesterase poisoning. The $\alpha 3\beta 2$ autoreceptors located on the nerve terminal facilitate ACh release during high frequency stimulation and thus maintain steady muscle contractions.^{21, 22} The $\alpha 7$ neuronal receptors are also present on the muscle membrane and have a stabilizing role. In addition, Alfa-7 receptors can be found on the Schwann cell. They sense the ACh and participate in the control of its release together with the BChEs and AChE.¹³



Muscarinic ACh receptors (mAChRs) are also present at the nerve terminal. M1 and M2 mAChRs have opposite presynaptic functions (negative feedback) to nAChRs in modulating quantal ACh release (Fig. 4).^{20, 27} Furthermore, adenosine triphosphate (ATP) and adenosine are endogenous neuromodulators at the NMJ through their receptors at the presynaptic site.²⁸ NMBAs have distinct effects on nAChRs, their main target being the

muscle-type receptor at the motor endplate. Three-quarters of these receptors serve as a reserve capacity (safety margin) of neuromuscular transmission. However, at least 75% of the receptors have to be occupied to obtain significant muscle weakness and 95% must be blocked for surgical relaxation.²⁹ The safety margin of presynaptic receptor capacity is unknown.²² Neuronal type nAChRs outside the NMJ are present in the brain ($\alpha 2\beta 4$), the sympathetic ganglia ($\alpha 3\beta 4$) and in the *glomus caroticum*, and $\alpha 7$ receptors are located at the inflammatory pathway.²⁵ A distinct effect of NMBAs at these receptors outside the NMJ has been demonstrated, resulting in hypotension due to ganglion blockade and lack of ventilator response to hypoxia due to *glomus caroticum* inhibition.³⁰ Some of the NMBAs are known to exert also an inhibitory effect of the mAChRs and induce side effects (i.e. tachycardia, bronchospasm) (Fig. 3).²³ In addition to ACh, other messengers have also been identified in the NMJ, such as glutamate.³¹ NMDA receptors were found in the depths of the postsynaptic folds in rat striated muscles.³² Glutamate may play a role in receptor development and may have a regulatory and trophic function as well.

2.3 Pharmacology of NMBAs

Two different classes of clinically useful NMBAs can be distinguished according to their mechanisms of action. The non-depolarizing drugs comprise aminosteroid compounds (pancuronium, vecuronium, pipecuronium and rocuronium), several benzyloquinolinium compounds (d-tubocurarine, doxacurium, mivacurium, atracurium, cis-atracurium) and the recently developed fumarate (olefinic isoquinolinium diesters) compounds (gantacurium, CW 002).³³⁻³⁵ The depolarizing muscle relaxants are represented solely by succinylcholine as decamethonium is no longer in clinical use.³⁶ The mechanism of action of non-depolarizing NMBAs is competitive antagonism³⁷; these agents compete with ACh for the binding sites of the nAChR (Fig. 6). While two ACh molecules are needed to activate muscular nAChR, one relaxant molecule is sufficient to block it, thus inhibition is preferable.⁹ In addition to the competitive block, large molecules of non-depolarizing NMBAs may directly occlude the receptor channel and thus prevent ion exchange (open channel block).³⁷ Although muscle-type nAChR is the main target of the NMBAs, non-depolarizing NMBAs also inhibit presynaptic neuronal nAChR. However, the sensitivity of the presynaptic nAChR to NMBAs seems to be of a smaller order of magnitude (μM) than that of postsynaptic receptors (nM).²² Nevertheless, the presynaptic activity of non-depolarizing NMBAs is clinically relevant because it induces muscle fade during neuromuscular monitoring, which is a reliable indicator of neuromuscular transmission and block. Postsynaptic receptor inhibition in itself does not exhibit fade. Nevertheless, fade is not possible without a certain degree (partial block) of postsynaptic inhibition.²⁴

The mechanism of the effect of succinylcholine is complex and not entirely clear even today. Succinylcholine consists of two ACh molecules and has a partial agonist effect at the postsynaptic ACh receptor site, thus it depolarizes the muscle membrane and causes fasciculation. Since AChE does not metabolize succinylcholine, its molecules remain sufficiently long at the proximity of nAChR receptors to bind them repetitively. It is assumed that desensitization of the voltage-gated sodium channels, as well as the inactivation of ACh receptors contribute to the relaxation state. The desensitized receptors do not react to the transmitter because their configuration is altered. Some receptors may contain $\alpha 8\beta 2$ subunits instead of $\alpha 1\beta 1$. This facilitates calcium influx, resulting in protein kinase C activation and $\alpha 1\beta 1$ receptor desensitization by phosphorylation. High dose or repetitive succinylcholine administration preferentially causes phase II block, which resembles a non-depolarizing block.³⁸ The reason for this may be desensitization or the accumulation of succinylmonocholine, the primary metabolite

of the drug, which behaves like a non-depolarizing substance. To differentiate between pre- and postsynaptic inhibition, succinylcholine may serve as an example. It has been shown that succinylcholine has no effect on the presynaptic nAChR and thus does not elicit fade. When stimulating the nerve during partial succinylcholine block, the force of contractions may be reduced, but there is no fade.³⁹ The differentiation between pre- and postsynaptic inhibition is important for studies on drug interactions, including the antagonism of neuromuscular block. While the effect of non-depolarizing NMBAs can be reversed by increasing ACh concentrations at the NMJ, the effect of succinylcholine cannot be reversed by AChE inhibitors (see also below), but is degraded by the BChE in the plasma. Indeed, administration of AChE inhibitors may enhance the succinylcholine block by inhibition of the plasma cholinesterase enzyme.³⁴ This is a classic example of drug interaction through the intermediary of metabolism. Metabolism is also a key component in drug interactions with non-depolarizing NMBAs. Steroid-type NMBAs are metabolized by the liver and excreted by the kidneys. Metabolism of the benzylisoquinolinium-type relaxants, atracurium and cis-atracurium, is organ-independent and happens in the blood through Hofmann elimination and ester hydrolysis.⁴⁰ Mivacurium-like succinylcholine is hydrolysed by BCh⁴¹ and therefore anticholinesterase agents may enhance its effect. The fumarate compounds undergo alkaline hydrolysis.³⁵ Interactions via metabolic pathways are further discussed below.

Both the metabolism and the autonomic nervous system effects of NMBAs exhibit wide variations and comprise both the stimulation and inhibition of sympathetic ganglia, inhibition of muscarinic receptors, histamine release and the inhibition of neuronal reuptake of noradrenalin.⁴² Sympathetic ganglionic stimulation was described with succinylcholine as a cause of elevation in blood pressure and heart rate, but bradycardia and decreased blood pressure were also observed, depending on the basal activity of the autonomic nervous system after succinylcholine administration.³⁸ The ganglion-blocking and histamine-releasing effect of d-tubocurarine is close to its neuromuscular effect and causes arterial hypotension, especially if administered with volatile anesthetics. Modern non-depolarizing NMBAs are more selective than older ones and are devoid of this kind of side effects. Cardiac muscarinic receptors mediate parasympathetic influence to the heart through the vagal nerve. Pancuronium and, to a lesser extent, rocuronium inhibit cardiac muscarinic receptors (M1) and thus exert a vagolytic effect. In addition, pancuronium inhibits reuptake of norepinephrine by cardiac adrenergic nerve terminals. In the case of superficial anesthesia, pancuronium may contribute to an exaggerated cardiovascular reaction by interacting with endogenous catecholamine release.³⁴ Interaction of halothane and pancuronium may generate cardiac arrhythmia (Fig. 7).

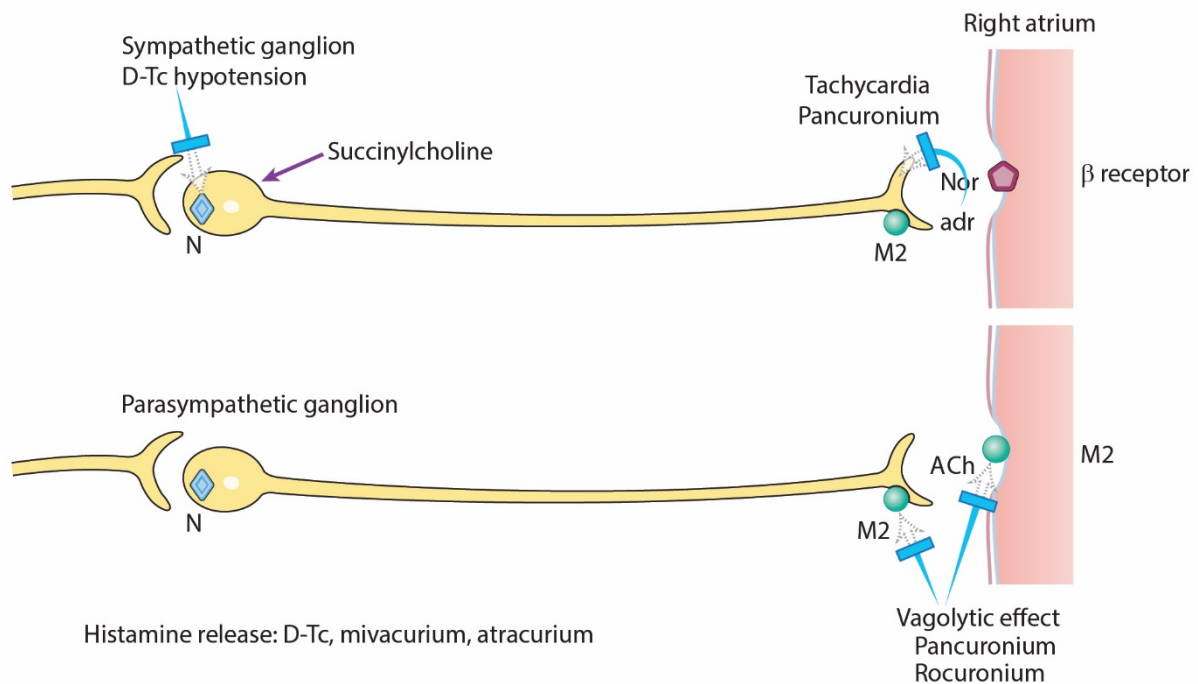


Fig. 7. NMBAs may act outside of the NMJ and induce side effects such as hypotension, tachycardia and hypertension. In addition, histamine release and allergic reactions may occur during their use. Drug interactions may influence the autonomic effects of NMBAs (adapted from Vizi et al.).²³

On the other hand, pipecuronium and vecuronium do not act at the cardiac muscarinic receptor level and thus do not compensate for the parasympathetic effect of opioids on the heart, thereby bradycardia may occur during their administration. Furthermore, M3 receptors are located on airway smooth muscle and their stimulation by ACh causes bronchoconstriction. Presynaptic M2 receptors in the airways mediate negative feedback to ACh release from postganglionic neurons. The relaxants that block both M2 and M3 receptors prevent smooth muscle constriction in the airway. However, relaxants with selective M2 antagonism may cause severe bronchospasm (i.e. rapacuronium) through inhibition of this negative feedback.⁴³ Therefore, the effect of NMBAs to M receptors is an important element of drug interaction.²³ Quaternary ammonium compounds, like NMBAs, are weak histamine-releasing substances. Steroidal agents do not liberate histamine. D-tubocurarine, mivacurium and atracurium have moderate to slight histamine-liberating effect. Succinylcholine is a slight histamine liberator. Autonomic and histamine-releasing effect will determine the safety profile for each relaxant, which includes interactions irrespective of their neuromuscular effect. While the neuromuscular transmission block by NMBAs is temporary, α -bungarotoxin selectively and irreversibly blocks the postsynaptic AChRs, and therefore has been widely used in experimental settings for studies of the NMJ. Another substance causing irreversible neuromuscular block is the botulinum toxin (commonly known as Botox), which acts presynaptically by interfering with ACh exocytosis. Botox is currently used in cosmetics and for the treatment of painful muscle spasm or other spastic disorders.

Table 1. Pharmacological characteristics of selected NMBAs (personal contribution).

NMBAs Properties	Succinylcholine	Rocuronium	Cisatracurium	Mivacurium	Atracurium	Pancuronium	Vecuronium
Drug type	Depolarizing 2 ACh molecules	Non-depol aminosteroid	Non-depol benzylizochin	Non-depol benzylizochin	Non-depol benzylizochin	Non-depol aminosteroid	Non-depol aminosteroid
ED 95 mg/kg	0.3	0.3	0.05	0.075	0.25	0.07	0.05
Duration 25 (min)	5 to 8	30 to 40	45 to 60	10 to 20	25 to 35	90 to 100	35 to 45
Renal excretion %	none	30	Hofmann elimination	10 to 20	Hofmann elimination	45 to 70	30
Hepatic excretion %	none	70	Hofmann elimination	none	Hofmann elimination	30 to 40	70
Active metabolite	Succinyl monocholine	none	none but laudanosine	none	none	3-OH 17-OH Pancuronium	3-desacetyl Vecuronium
Autonomic effect	Tachycardia, bradycardia, elevated BP	Vagolytic effect	none	Slight histamine release	Slight histamine release	Vagal block tachycardia	none
Reversal	degraded by plasma-ChE	Anti-ChEs Sugammadex	Anti-ChEs	degraded by plasma-ChE	Anti-ChEs	Anti-ChEs	Anti-ChEs
Side effects	MH, hyperkalaemia, Anaphylaxia, Myopathy	Anaphylaxia rarely	none	Histaminerg reaction	Anaphylactoid reaction	Arrhythmia, tachycardia, hypertension	Anaphylaxia rarely

BP: blood pressure; MH: malignant hyperthermia; ChE: cholinesterase; duration 25: recovery to 25% twitch height; ED95: 95% effective dose; non-depol: nondepolarizing; benzylizochin: benzylizochinolinium

2.4 Antagonists of NMBAs

2.4.1 Anticholinesterases

Two types of cholinesterase enzymes exist in the human body: AChE and BChE.⁴⁴ AChE is responsible for the metabolism of ACh at the NMJ, while BChE metabolizes succinylcholine, mivacurium and ester-type local anesthetics among other substances. Conventionally, the effect of non-depolarizing NMBAs has been reversed indirectly through inhibition of the AChE enzyme at the NMJ.⁴⁵ AChE is located in the synaptic cleft and agents such as neostigmine, edrophonium and pyridostigmine temporarily inhibit its activity.

Neostigmine and edrophonium are the most often used cholinesterase inhibitors in clinical practice. Both form a reversible attachment to AChE. Neostigmine forms a covalent bond to the esteric site and edrophonium an ionic bond to the anionic site on the AChE molecule, respectively.⁴⁵ The inhibition of the enzyme AChE augments the concentration of the neurotransmitter in the synaptic cleft. In addition, edrophonium has a presynaptic effect and increases the release of ACh from the nerve terminal, unlike neostigmine, which has a smaller presynaptic effect.⁴⁶ Increased concentrations of ACh molecules compete with the relaxant molecules for the receptor sites and dislocate them from the receptors. The NMBAs are not broken down by AChE and may re-occupy the receptors.

By contrast, in the absence of relaxants, ACh has a direct agonist effect on the receptors. The higher the amount of ACh molecules in the synaptic cleft, the higher the chance for reversal of the block, provided that the relaxant concentration is not too elevated, i.e. the block is not deep. This is the first premise of successful reversal with AChE inhibitors. The second is that the duration of AChE inhibition should not be shorter than the elimination of the relaxant from the blood. The AChE inhibitors have a ceiling effect, which means that a given dose, e.g. 0.07 mg/kg of neostigmine and 1.5 mg/kg of edrophonium, completely blocks the enzyme and further doses do not enhance their effect. Consequently, the use of these agents is limited to the reversal of blocks that has returned to a superficial level (presence of 2 to 4 “train-of-four” [TOF] responses).⁴⁵

The speed of recovery from the block is determined by the rate of spontaneous recovery plus the effect of the antagonist. Recovery after neostigmine given at a deep block does not differ from spontaneous recovery.⁴⁷ The rank order of the speed of action of anticholinesterases is edrophonium>neostigmine>pyridostigmine; the peak effect of edrophonium and neostigmine is about 3 and 10 min, respectively, and the duration of action is around 20 to 30 min (metabolized by the liver).⁴⁵ This may be insufficient for reversing the effect of long duration NMBAs. By contrast, when neostigmine is administered after complete elimination of the block, it induces neuromuscular inhibition⁴⁸ and may depress the upper airway dilator muscles and cause weakness of the genioglossus muscle.⁴⁹ Furthermore, the increase in ACh concentration induced by an anticholinesterase agent is not limited to the NMJ, but also occurs at the muscarinic sites where ACh is the transmitter.⁴⁵ In order to prevent severe muscarinic side effects, antimuscarinic drugs (atropine and glycopyrrolate) are administered in association with neostigmine. Muscarinic side effects include nausea and vomiting, bradycardia, Q-T interval prolongation, bronchospasm, salivation, miosis and increased intestinal peristalsis (see also chapter 4.1).⁴⁵ It is of interest to note that edrophonium is more selective to AChE than neostigmine and thus can be used for reversal of mivacurium, a benzilzocholinium relaxant, which is degraded by BChE, although the benefit is small.⁵⁰

Other substances with antagonistic effects have also emerged for the reversal of NMBAs, but they have not received general acceptance. 4-aminopiridine is a substance with presynaptic effect due to its K⁺ channel-blocking properties. It increases nerve terminal depolarization time and leads by sustained calcium influx to increased acetylcholine liberation.⁵¹ However, it possesses pro-epileptic properties, which exclude its use in anesthesiology.

2.4.2 Cyclodextrins: sugammadex

Although neostigmine has been the main reversal agent to non-depolarizing NMBAs for more than 70 years, many anesthetists are now reluctant to use it due to its limited efficacy and numerous side effects.

Sugammadex, a modified γ cyclodextrin compound, has emerged as a new and promising reversal agent readily reversing the effect of steroidal NMBAs.⁵² The compound is a cyclic molecule containing eight glucopyranoside units in a ring creating a hollow truncated cone known as a doughnut.⁴⁵ Hydroxyl groups line the primary and secondary faces of the doughnut, rendering the exterior surface of the sugammadex molecule water-soluble.⁴⁵ The hydrophobic interior of the doughnut is able to encapsulate appropriate size lipophilic molecules, such as aminosteroid NMBAs. Thermodynamic (van der Waals force), hydrophobic and electrostatic interactions promote the formation of a complex with steroidal relaxants. Negatively-charged sulphated carboxyl side chains

attach the quaternary nitrogen of the relaxants, contributing to the formation of a stable inclusion complex. The encapsulated relaxant molecule is pharmacologically inactive and leaves the body via the kidneys (Fig. 8).⁵³

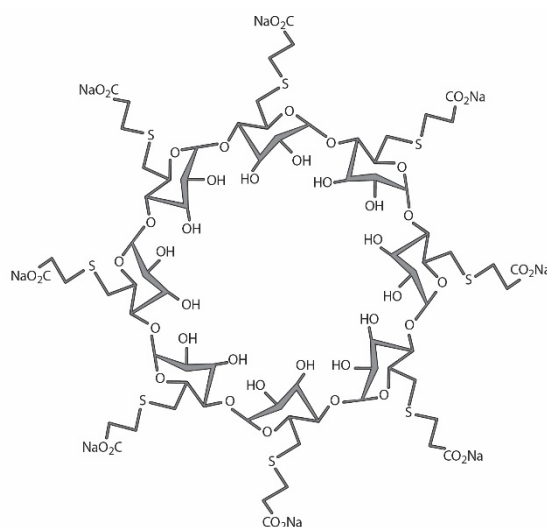


Fig. 8. Chemical structure of sugammadex showing eight sulphated side chains. The interior of the molecule is hydrophobic while the exterior is hydrophilic because of the polar hydroxyl groups (from Naguib et al.)⁵⁴

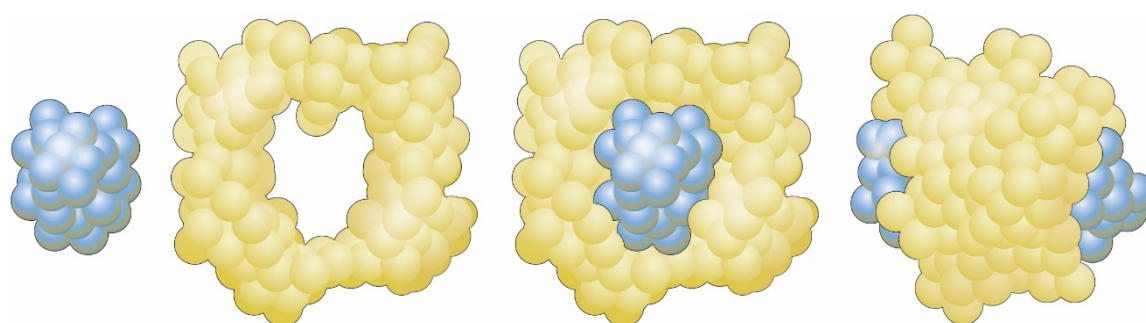


Fig. 9. Structure of a rocuronium molecule (blue) and a sugammadex molecule (yellow) and anterior and lateral view of the sugammadex and rocuronium complex (adapted from Gijzenbergh et al.).⁵³

Sugammadex reverses the neuromuscular block by encapsulating free relaxant molecules in the blood and thus creates a concentration gradient between the plasma and NMJ.⁵⁴ This induces the movement of the relaxant molecules from the NMJ toward the plasma where sugammadex molecules continue to encapsulate them and thus maintain a low free relaxant concentration in the plasma.⁵⁴ This is the driving force that liberates the receptor sites from the relaxants all over the body, including the NMJ, while the total amount of the relaxant in the plasma increases.⁴⁵ However, a caveat is in order when fewer sugammadex than relaxant molecules are present in the plasma. The encapsulation occurs at a 1:1 ratio, which means that one molecule of sugammadex inactivates one relaxant molecule (Fig. 10).

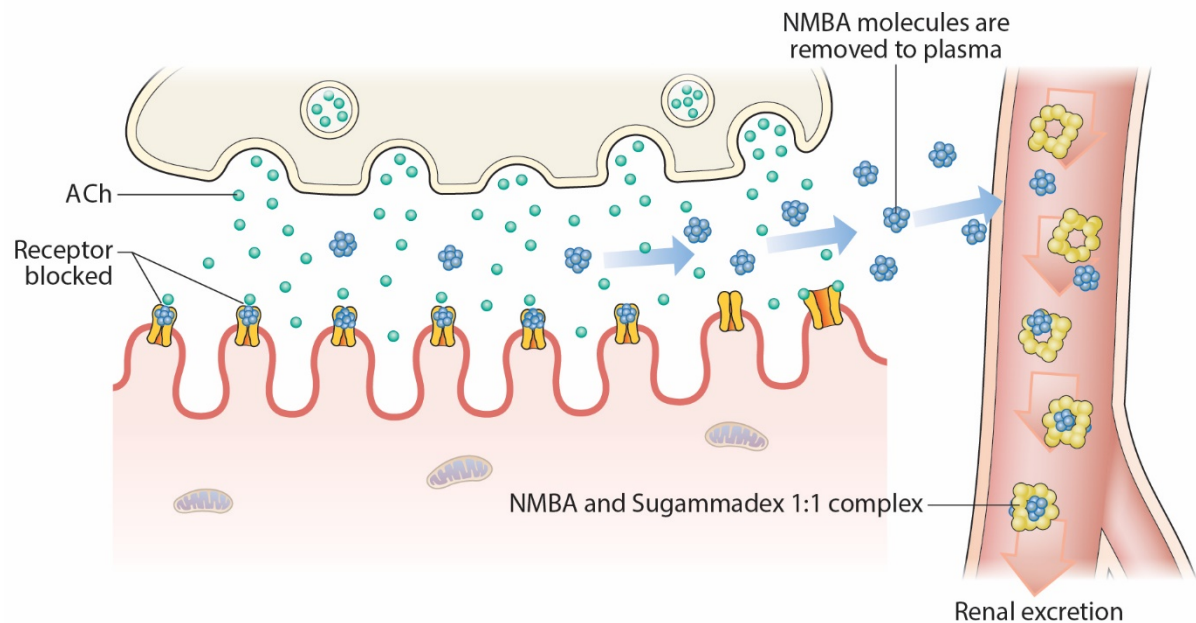


Fig. 10. Sugammadex binds the relaxant molecules in the plasma and creates a concentration gradient to the NMJ, which takes away the relaxants from the NMJ (adapted from Welliver et al.).⁵⁵

The dose of sugammadex must therefore be adapted according to the regimen of the relaxant in order to achieve adequate reversal from the block. Of note, sugammadex binds neither succinylcholine nor benzylizocholine NMBAs. As it does not exhibit a cholinergic effect, it does not require atropine administration.⁵⁶ Unlike neostigmine, sugammadex has few side effects. Among these, the prolongation of activated partial thromboplastin time and international normalized ratio (INR) deserves clinical attention.⁵⁷ Nevertheless, increased surgical bleeding due to sugammadex has not been described.⁵⁸ Arterial hypotension, electrographic QT prolongation and coughing have also been reported.⁴⁵ Furthermore, several cases of anaphylaxis related to sugammadex are reported in the literature, mainly in Japan; the estimated incidence rate is approximately 3:100,000.^{59, 60} Owing to the risk of allergic reaction, approval by the United States Food and Drug Administration was delayed, but finally granted in December 2015. Sugammadex preferentially binds steroidal muscle relaxants. Nevertheless, interaction with flucloxacillin and progesterone oral contraceptives occurs, necessitating modification of their administration.⁵⁷

Although sugammadex has been specifically designed to encapsulate rocuronium molecules, it also binds to other steroidal NMBAs, such as vecuronium, pancuronium and pipecuronium to various degrees. The association constant of rocuronium has been found to be $15.1 \pm 1.9 \times 10^6 \text{ M}^{-1}$, higher than for vecuronium or pancuronium (8.8 ± 0.4 and $2.6 \pm 0.2 \times 10^6 \text{ M}^{-1}$, respectively) and less than the association constant of pipecuronium ($161 \pm 28.1 \times 10^6 \text{ M}^{-1}$).⁶¹ The association constant describes numerically the affinity of one molecule to bind with another. These characteristics of molecular interactions correlate well with the EC₅₀ values of sugammadex as determined at the mouse hemi diaphragm-phrenic nerve preparation: pipecuronium < rocuronium < vecuronium < pancuronium. The greater the affinity, the lesser the EC₅₀. This rank of efficacy has also been retrieved under clinical circumstances and is discussed later.

2.4.3 Calabation

Calabation, a member of the cucurbit[n]uril family, is a new reversal agent. In the rat, calabation 1 rapidly and completely reversed rocuronium- and cisatracurium-induced neuromuscular transmission block.⁶² Calabation, similarly to cyclodextrins, forms host-guest complexes with specific targets and modifies the properties of drugs bound to it. The calabation molecule is flexible and can expand its cavity and thereby accommodate guests of different sizes (Fig. 11).⁶²

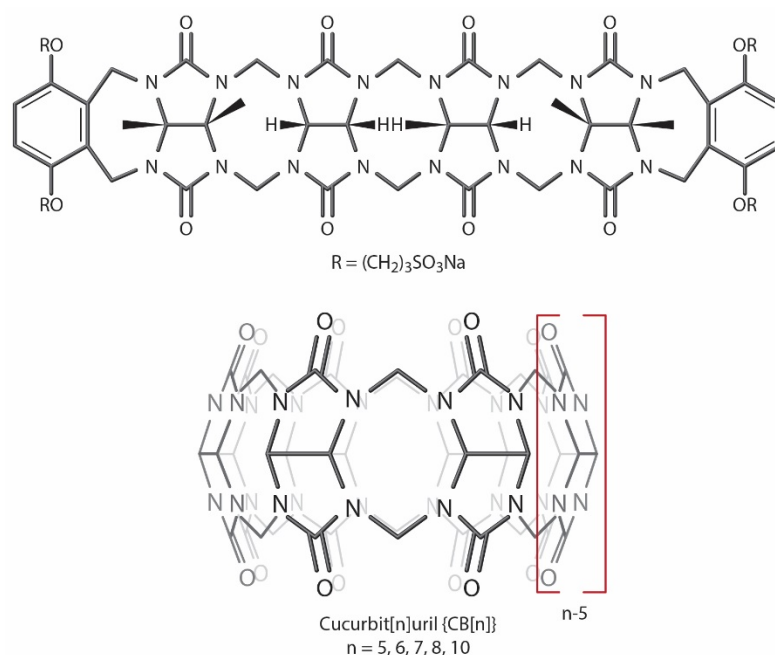


Fig. 11. Chemical structure of calabation showing the large flexible molecule capable of hosting several molecules, including NMBAs (from Hoffmann et al.).⁶²

In the rat, calabation 1 caused a rapid dose-dependent reversal of complete rocuronium- and cisatracurium-induced neuromuscular block without apparent effects on heart rate, blood pressure or gas exchange.⁶² Re-paralysis did not occur and the majority of the substance was eliminated by the kidneys within one hour. The mechanism of action of calabation resembles sugammadex, but it encapsulates both rocuronium and cisatracurium. However, the binding constant for cisatracurium is 10-fold smaller than for rocuronium ($9.7 \pm 0.8 \times 10^5 \text{ M}^{-1}$ vs. $8.4 \pm 0.9 \times 10^6 \text{ M}^{-1}$, respectively), which explains the shift of the dose-response curve of cisatracurium to the right.⁶³ By contrast to AChE inhibitors, calabation does not interfere with the release and metabolism of ACh and does not appear to have toxic effects.⁶² However, it may bind other molecules than NMBAs, including anesthetics. Calabation has not been studied in humans as yet.

2.4.4 Cystein

Gantacurium and CW 002 are new non-depolarizing NMBAs not yet in clinical use. They are fumarate compounds and their elimination does not involve the kidneys or the liver. The adduction of the non-essential amino acid cysteine changes the stereochemistry of gantacurium so it is no longer able to bind the nAChR.³⁵ The two NMBAs studied in human volunteers have a rapid onset of effect and a predictable duration of action.³⁵

Gantacurium is ultra-short; CW 002 is intermediate and is shortened in animals by adding cystein. CW 002 was recently tested in volunteers with a clinical duration of less than 40 minutes and only minimal cardiopulmonary side effects.⁶⁴ Table 2 summarizes the different reversal agents and their properties.

Table 2. Summary of reversal agents to neuromuscular blockade (personal contribution).

Agents	Neostigmine	Edrophonium	Pyridostigmine	Sugammadex	Calabadiol	Cystein	Galanthamine
Mechanism of action	cholinesterase inhibitor	cholinesterase inhibitor	cholinesterase inhibitor	encapsulation	encapsulation	chemical neutralization	cholinesterase inhibitor
Antagonist to NMBAs	all non-depolarizing	all non-depolarizing	all non-depolarizing	rocuronium, vecuronium, pipecuronium	all types of relaxants	gantacurium CW 002	all non-depolarizing
Dosage (mg/kg)	0.04 to 0.07	1.5	0.1 to 0.25	1 to 16	not yet in clinical use	not yet in clinical use	0.01 to 0.12
Duration of action (min)	30 to 40	20 to 30	200 to 300	120 to 240	-	-	20 to 30
Side effects	muscarinic PONV	muscarinic PONV	muscarinic PONV	rarely allergy	-	-	analeptic

NMBAs neuromuscular blocking agents; PONV: postoperative nausea and vomiting.

2.5 Types and mechanisms of drug interactions

Several factors may influence the effect of NMBAs among which drug interactions play a leading role. The outcome of drug interaction may be synergistic, potentiation, additive or antagonistic, depending on the individual drugs. Synergism can be defined as an interaction of drugs resulting in a total effect greater than the sum of the individual effects (i.e. $2+2=5$). For example, a synergistic interaction can be observed between rocuronium and sevoflurane or isoflurane,⁶⁵ and between steroidal relaxants given together with benzilzocholinium-type agents (i.e. rocuronium and cisatracurium).⁶⁶ Lysakowski demonstrated a synergistic interaction between propofol and opiates for the depth of anesthesia.⁶⁷ In potentiation, only one drug is effective in producing the desired or non-desired action. The other drug does not produce this action, but just augments the action of the first drug (i.e. $1+0=3$). For example, low concentrations of magnesium and local anesthetics themselves do not cause neuromuscular block, but they do enhance the effect of muscle relaxants. In additive interaction, the combined effect of two or more drugs is equal to the sum of their separate effects (i.e. $1+1=2$). For instance, an additive effect can be seen when two non-depolarizing relaxants with a similar structure are given together, or succinylcholine is followed by a non-depolarizing agent. However, succinylcholine's interaction with other relaxants is variable and depends on the timing of administration. Finally, in antagonism, the effect of two or more drugs given in combination is less than the sum of their individual effects (i.e. $2+1=1$). As an example, this definition pertains to neostigmine, which itself may also cause neuromuscular block. Of note, other agents such as sugammadex, calabadiol and cysteine are inactive in the absence of relaxants ($2+0=1$ to 0). Table 3 summarizes the nature and types of pharmacokinetic and pharmacodynamic interactions with neuromuscular blockade.

Table 3. Examples of the nature and types of pharmacokinetic and pharmacodynamic interactions with neuromuscular blockade (personal contribution).

Pharmacokinetic/pharmacodynamic interactions			
Synergism	Potentiation	Additive	Antagonism
$2+2 = "5"$	$0+1 = "2"$	$1+1 = "2"$	$2+1 = "1"$ or $2+0 = "0"$
succinylcholine + neostigmine	low-level pseudocholinesterase + succinylcholine	pancuronium+ succinylcholine	carbamazepine + rocuronium
rocuronium + cisatracurium	Mg+ NMBA's or volatile agents + NMBA's	residual succinylcholine + rocuronium	rocuronium + neostigmine or sugammadex

NMBA's: neuromuscular blockage agents; Mg: magnesium.

Drug interactions with NMBA's can be pharmacodynamic or pharmacokinetic in nature. In pharmacodynamic interactions, alterations in dose response and the time course of the block are not the result of blood concentration changes and happen at the receptor level. The potentiation of neuromuscular blockers by volatile anesthetics is one example of pharmacodynamic interaction. Volatile anesthetics enhance the effect of relaxants by the inhibition of postsynaptic nAChRs^{65, 68} that augment the affinity of the receptor site to the agonist⁶⁹ and decrease spinal cord excitability.⁷⁰ A second example of pharmacodynamic interaction with NMBA's is magnesium.⁷¹ MgSO₄ decreases presynaptic ACh release and inhibits postsynaptic potential, thus enhancing the effect of relaxants, irrespective of their blood concentration. By increasing the amount of ACh in the NMJ, neostigmine induces competition between relaxants and ACh for the receptor sites and decreases the depth of the block. This is a typical pharmacodynamic interaction.

The most frequent cause of drug interactions with NMBA's in clinical practice is a pharmacokinetic action delaying metabolism and excretion of the drugs. In pharmacokinetic interactions, a second drug alters the distribution, elimination or metabolism of the NMBA's and changes their usual onset and duration of effect. Pharmacokinetic interaction happens when steroidal relaxants are reversed with sugammadex. When sugammadex is injected intravenously, it encapsulates the free rocuronium molecules in the plasma and inactivates them, causing a shift from the receptors to the plasma and thus reverses the neuromuscular block.⁴⁵ Another example is the potentiation of succinylcholine and mivacurium by substances, which are also degraded by the enzyme BChE (i.e. ester-type local anesthetics). The capacity of this enzyme is limited and therefore the relaxants' metabolism decreases and their effects are prolonged. Any drug that reduces renal or hepatic blood flow will increase the duration of steroidal relaxants.⁷² The cytochrome P3A4 enzyme is responsible for the metabolism of many drugs, including steroidal NMBA's. Induction or inhibition of CYP450 enzymes by drugs, nutrients and temperature will change the metabolism of steroidal relaxants and may enhance or lessen their effect.⁷³

Pharmacogenetics also plays a role in drug interactions, e.g. in the case of succinylcholine and mivacurium that are enhanced in subjects with an abnormal BChE enzyme. Pharmacogenetic disorders are behind the triggering

of malignant hyperthermia by inhaled anesthetics alone or, especially in association with succinylcholine.⁷⁴ Interaction between statins and succinylcholine may cause severe muscle damage.⁷⁵ Although the origin of this interaction is unknown, pharmacogenetic alteration cannot be excluded. Physiological alterations such as cardiac output, pH changes as well as hypothermia and electrolyte imbalance have to be taken into account in addition to drug-drug interactions when unusual depth and duration of block is apparent.^{72, 73}

3. NEUROMUSCULAR DRUG INTERACTIONS FROM A CLINICAL PERSPECTIVE

Over 70 different drugs have been reported to interact with various neuromuscular blockers, potentially affecting their actions.⁷ However, only a few of these interactions are clinically relevant. The effect of interaction may be on the magnitude of the block (degree) or the onset time and duration of the block (time course). The degree of the block and its time course can be quantified with neuromuscular monitoring, allowing disclosure of drug interactions.

3.1 Measurement of neuromuscular block

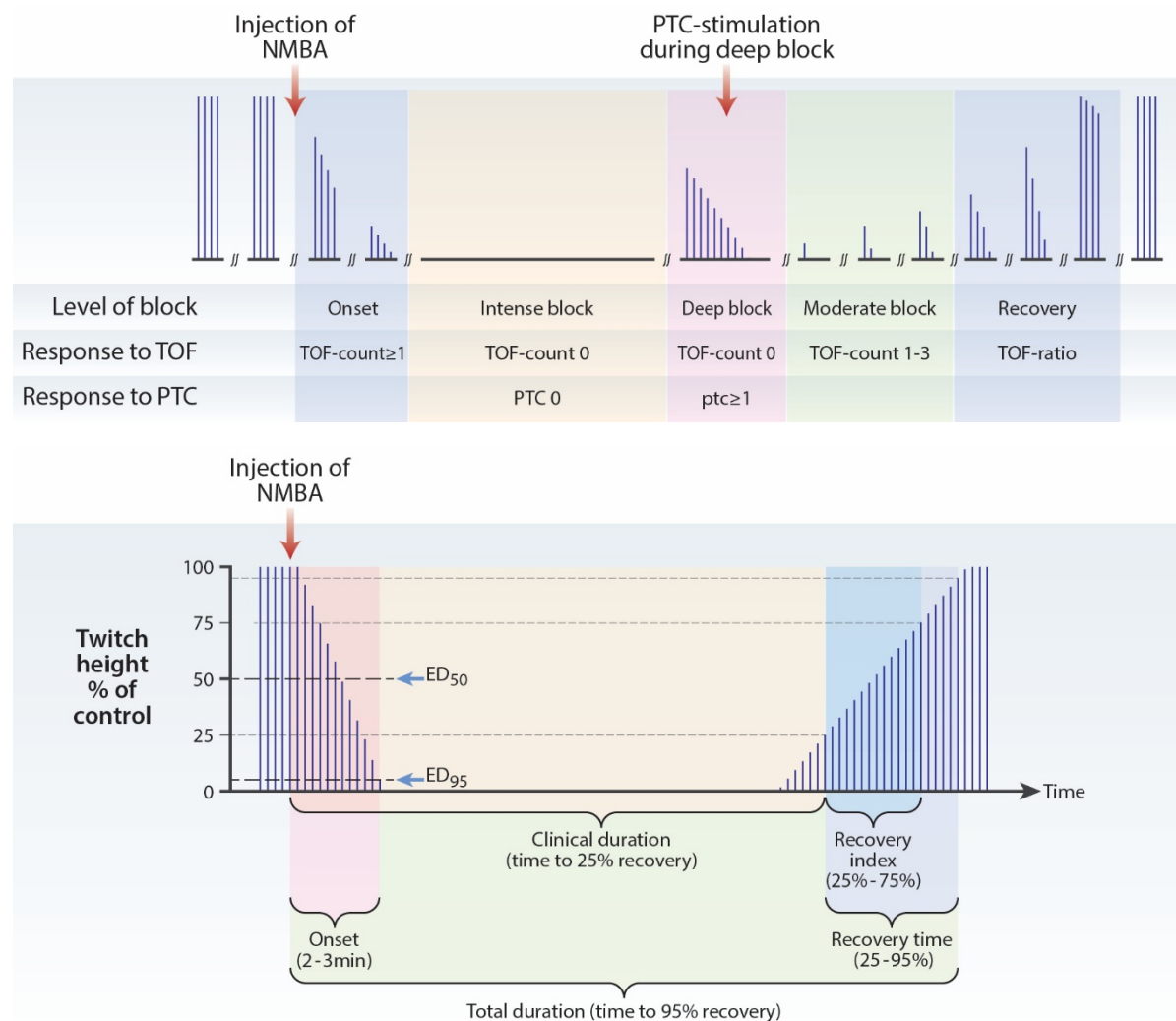
The effect of NMBA can be measured on a scale from zero to 100%. In brief, electrical stimuli are applied to a motor nerve and the contractions of the innervated muscle are evaluated.⁷⁶ Monitoring is based on the physiological characteristics of NMJ described in chapter 2.2. The adequacy of monitoring depends on the intensity of nerve stimulation, the stimulation pattern, the mode of evaluation of the evoked muscle responses, the characteristics of the examined nerve-muscle, the device used and the temperature of the muscle.⁷⁷

The detailed description of all options for neuromuscular monitoring is beyond the scope of this review and we limit ourselves to the description of acceleromyography with the TOF-WATCH SX® device, which we have used for many years in studies of drug interactions and monitoring in daily practice. This method has been validated and generally accepted for clinical research purposes according to good clinical practice guidelines.⁷⁸

During acceleromyography the ulnar nerve is stimulated proximal to the wrist using surface electrodes placed on the skin after it is cleaned. Supramaximal square wave electric stimuli of 0.2 ms duration are delivered to the nerve. A piezoelectric piece fixed at the tip of the thumb senses the movements of the thumb due to the contractions of the adductor pollicis muscle and transforms them into electric signals, which are displayed on the screen of the acceleromyograph and recorded on a computer via special software (TOF-Watch SX® version 2.2, Organon, Dublin, Ireland). The device is calibrated (CAL 2) to deliver supramaximal stimuli in order to evoke contractions of all muscle fibers. After calibration, we wait until the signals stabilize and control measurements are then carried out prior to NMBA administration. Data obtained during the monitoring are analyzed offline. The depth of block and its time course are evaluated using the following stimulation patterns. Single twitch stimulation comprises continuous delivery of supramaximal stimuli with a frequency of 0.05 to 1.0 Hz. Responses to single twitch stimulation represent postsynaptic drug action.

TOF stimulation consists of four separated stimuli delivered in 2 s (2 Hz) with a periodicity of 15 s. The first of the four twitches is considered a single twitch response and expressed as T1 height (twitch height) in percent of control. Twitch height is used for the quantification of the time course of the block and for the description of its changes due to drug interactions. The muscle responses to TOF stimulation (TOF response) without relaxant

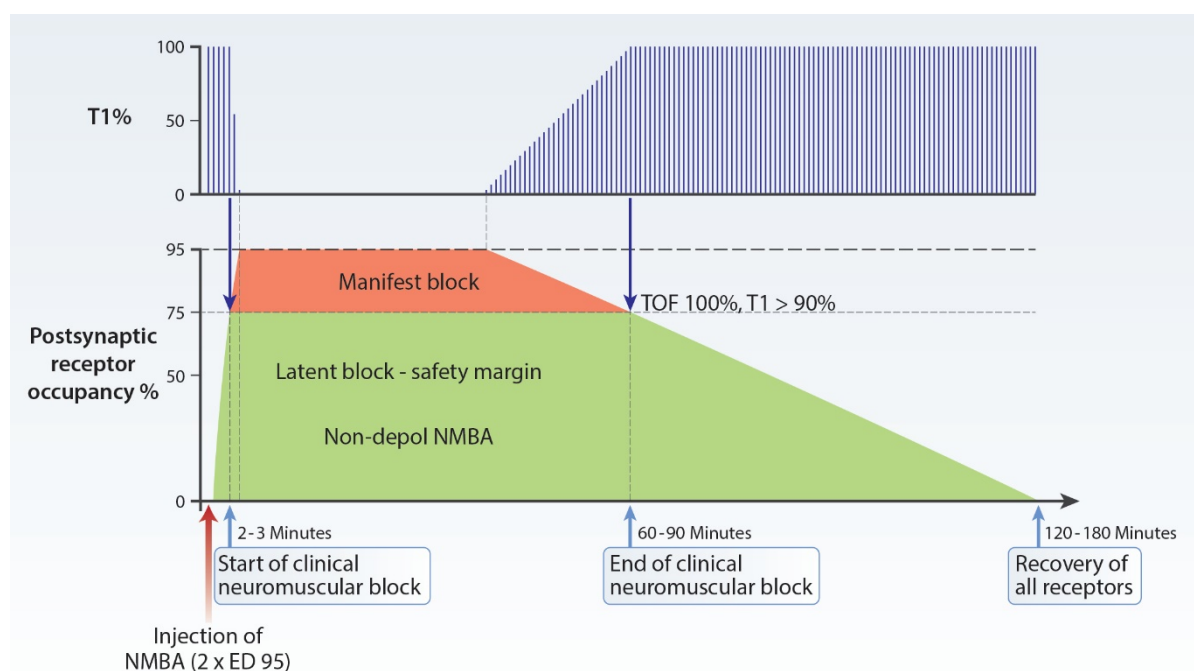
administration (control) are four equal contractions. However, with acceleromyography the fourth signal may be higher than the first (staircase effect) and this must be taken into account when evaluating the TOF ratios at recovery. After administration of NMBA in effective doses, the TOF responses disappear. The time interval from injection of the relaxant to the maximal effect is the onset time. With the elimination of the relaxants, the TOF responses progressively reappear in form of 1, 2, 3 or 4 twitches described as the TOF-count, indicating the beginning of recovery from the deep block. When the height of the first twitch reaches 25% of control, the clinical duration of the block is ended. Once four responses are present and the T1 reaches 20%, the ratio of the fourth to the first response is calculated by the device and displayed as the TOF ratio (or TOF %). TOF ratios less than 1.0 represent muscle fades due to decreased ACh release during TOF stimulation. The explanation for fade is the inhibitory effect of non-depolarizing NMBA at the presynaptic nAChRs, which mediate positive feedback to ACh release.²² Considering TOF fade and T1 depression together, both pre- and postsynaptic drug effects can be evaluated. The TOF ratio is the main parameter for the measurement of recovery from the block when the TOF-count four has been obtained. Fig 12 illustrates quantitative evaluation of neuromuscular block after TOF and single twitch stimulation.



NMBA: neuromuscular blocking agent; TOF: train-of-four; PTC: post-tetanic count.

Fig. 12A and B. Quantitative evaluation of neuromuscular block after TOF and single twitch stimulation (adapted from Fuchs-Buder et al.)⁷⁸

TOF-count 1, 2 and 3 are used as measures of residual block (i.e. T2 block). When the block is deeper, the TOF stimulation does not evoke muscle response. Nevertheless, the depth of block can also be determined in this situation by measuring the post-tetanic count (PTC). This stimulation mode can be set on the acceleromyograph and consists of 5 s train of 50 Hz followed by 15 single stimuli of 1 Hz. The number of evoked single responses is the PTC. When there are 1 or 2 evoked twitch responses following tetanization, the block is deep. In the case of 7 or more contractions, the recovery of TOF responses can be soon expected. The time interval from T1 25-75% is the recovery index and from T1 25-90% is the recovery time. Total duration of the block is the time from injection of the relaxant to recovery of T1 and the TOF ratio to 90% or 0.9, respectively. It is important to note that using TOF monitoring, the block can be perceived only after the safety margin is abolished. At recovery from the block, normal TOF responses are obtained when 25% of receptors are liberated from the relaxant molecules. With TOF monitoring, only the tip of the iceberg is visible. Thus, TOF recovery means only a partial elimination of the relaxants and not a full relief of neuromuscular transmission.²⁹



NMBA: neuromuscular blocking agent; non-depol: non-depolarizing.

Fig. 13. A correlation of receptor occupancy and clinically manifest muscle relaxation showing that 25% of receptor capacity is sufficient to elicit normal TOF or T1 response (this illustration is a personal contribution based on the concept of neuromuscular reserve from Waud et al.).⁷⁹

In this situation, even small amounts of drugs, which are not normally effective will cause manifest block.⁸⁰ Therefore, patients may be vulnerable in the immediate postoperative period and need close supervision. Any administration of medication in the acute postoperative period comprises the risk of drug interactions and patients should be closely monitored in order to prevent PORNB and respiratory complications. Fig 13. Is a graphic illustration of manifest and latent block and percentage of receptor occupancy and Fig 14. Is an example of magnesium potentiation of the residual effect of rocuronium after full recovery of T1.

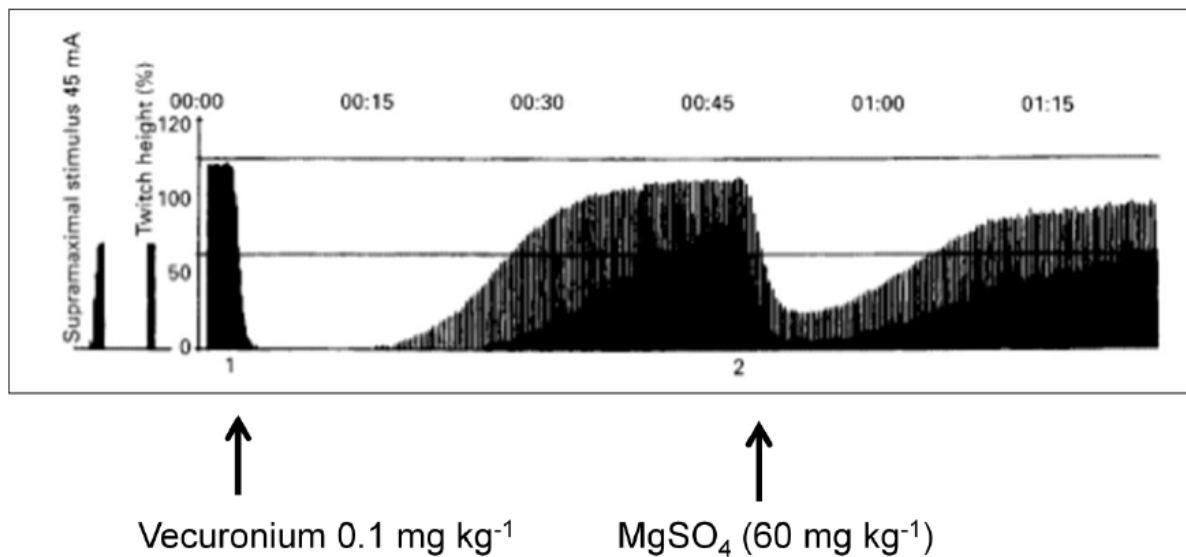


Fig. 14. Magnesium causes recurarization when given immediately after recovery of T1 following vecuronium administration (illustration from Fuchs-Buder et al.)⁸⁰

Unterbuchner reported about a case of magnesium induced recurarisation after reversal of rocuronium-induced neuromuscular block with sugammadex in a patient undergoing desflurane and remifentanyl anesthesia (fig. 15).⁸¹ One possible explanation is that the given dose of sugammadex did not bind all rocuronium molecules. Thus the safety margin was not re-established and magnesium potentiated the residual effect of rocuronium. But it is to note that desflurane such as sevoflurane strongly interacts on neuromuscular transmission and the effect measured might be a magnesium-desflurane interaction.⁸²

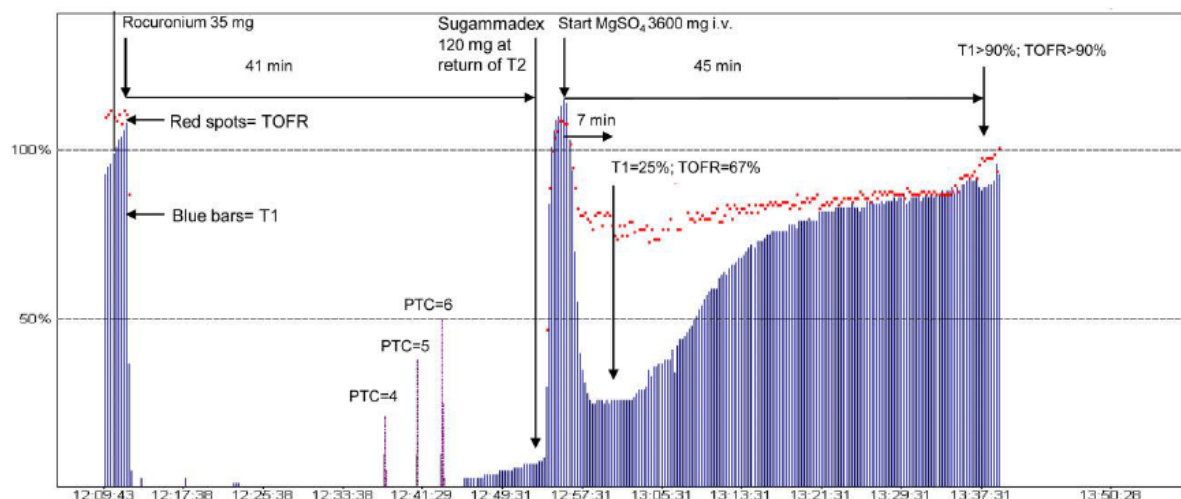


Fig. 15. Magnesium administered immediately after sugammadex reversal of rocuronium enhanced the neuromuscular block (illustration from Unterbuchner et al.).⁸¹

3.2 Interaction between muscle relaxants

Administration of two non-depolarizing NMBAs can be additive or synergistic; antagonism has not been reported in this class of drugs. Additive interaction occurs between agents of the same chemical family of relaxants, e.g. atracurium and mivacurium.⁸³ Interaction between steroidal and benzyliisoquinolinium-type compounds has been described as synergistic, e.g. pancuronium and d-tubocurarine, rocuronium and cis-atracurium.^{66, 84} Inhibition of plasmacholinesterase by pancuronium decreases the metabolism of mivacurium and enhances its effect.⁸⁵ Differences in presynaptic effects, in addition to non-equivalent binding affinities to postsynaptic nAChRs, may explain the synergism. When two relaxants are subsequently administered, the characteristic of the one injected first will prevail and three half-lives are required for takeover for the second drug. Through repetition of the second drug for maintenance of the block, the profile of the second drug will progressively prevail. There is a non-specific “competition” between both drugs for the receptor-binding sites, which is governed by the sequence of administration and their concentrations. Formerly, a mixture of relaxants was administered in order to reduce side effects by giving lower doses from each, e.g. pancuronium and metocurine or pancuronium d-tubocurarine.⁸⁴ With the appearance of more selective NMBAs, the need for mixing them decreased and, therefore, the clinical relevance of interaction between non-depolarizing NMBAs is marginal.

Succinylcholine has been the primary NMBA for decades, facilitating tracheal intubation. For the maintenance of neuromuscular block, non-depolarizing relaxants were given subsequent to succinylcholine. The interaction of depolarizing and non-depolarizing relaxants is clinically relevant because it alters the depth and duration of both drugs. For example, when vecuronium was administered after recovery from a decamethonium block, the effect of vecuronium was potentiated seven-fold compared to vecuronium alone.⁸⁶ A similar, but less dramatic effect can be observed with succinylcholine. It has been suggested that this interaction results from the presynaptic effect of decamethonium on the nAChRs, leading to decreased ACh release. This can be excluded in the case of succinylcholine, which has no effect on presynaptic ACh receptors.³⁹ Although the exact mechanism of potentiation of non-depolarizing agents after succinylcholine remains unclear, the most probable explanation is the development of phase II block. The administration of a depolarizing drug after recovery from a non-depolarizing block results in resistance to blockade and necessitates an increased dose of depolarizing agent. This is explained as an interaction between a residual antagonist and a newly administered agonist.⁸⁷ The attenuation of the depolarizing effect of succinylcholine by a priming dose of non-depolarizing agents has been used for the prevention of fasciculation and muscle pain due to succinylcholine administration.⁸⁸

3.3 The succinylcholine dilemma

The history of succinylcholine is closely related to Geneva as Daniel Bovet, who developed succinylcholine in 1951,⁸⁹ had graduated from the University of Geneva and then worked in the department of physiology for some years before joining the Pasteur Institute in Paris. His research focused on the pharmacology of the autonomic nervous system and he identified several substances, such as histamine, norepinephrine, and ACh and synthesized succinylcholine and antihistamines among others. For this work, he was awarded the Nobel Prize in Physiology and Medicine in 1957.

Owing to unique pharmacodynamic properties (rapid onset and short duration of action),⁹⁰ succinylcholine is the drug of choice for the management of difficult airway and in cases of increased risk for bronchoaspiration when rapid sequence intubation (RSI) of the trachea is required. The short duration of apnea (about 5 min) after succinylcholine is life-saving if the patient cannot be intubated and ventilated. However, succinylcholine has numerous adverse effects,⁹¹ some of which may be lethal, e.g. hyperkalaemia, cardiac arrest, malignant hyperthermia and anaphylaxis.⁹² Therefore, alternatives have been sought to replace it for RSI.⁹³ The use of rocuronium has been suggested for this purpose as its onset of action is the most rapid among non-depolarizing NMBAs.⁹⁴ Rocuronium was successfully used for RSI in severe head trauma patients. When compared to succinylcholine, in-hospital mortality was lower in patients who received this compound.⁹⁵ Several studies demonstrated that rocuronium in combination with propofol provides conditions for RSI that are similar to succinylcholine.⁹⁶ However, the dose regimen of rocuronium and the effect of background anesthesia on intubation conditions were not clear. Furthermore, different techniques have been advocated for RSI.

We performed a systematic review of randomized trials in order to establish the impact of these elements on the efficacy of RSI.⁹⁶ We retrieved 21 relevant randomized trials reporting on 922 patients who had received rocuronium and 889 who had received succinylcholine. It was found that both rocuronium and succinylcholine provided good or excellent intubation conditions after 60 s, but the doses of rocuronium should be 0.9 to 1.2 mg/kg (3 to 4 times ED₉₅) if thiopental is used for induction. In combination with propofol, 0.6 to 0.7 mg/kg of rocuronium was sufficient for acceptable intubation conditions. No significant relationship was found between the use of opioids and intubation conditions. We concluded that rocuronium combined with propofol induction may be an alternative to RSI when succinylcholine is contraindicated, but the long duration of rocuronium limited its use. These results are in accordance with the Cochrane Database Systematic Review (2003) that reported similar intubation conditions between rocuronium and succinylcholine when propofol was used for induction.⁹⁷ However, we found that 1 mg/kg or higher doses of rocuronium were necessary for similar intubation conditions when thiopental was the induction agent. In the 2008 survey, the Cochrane Database Systematic Review reported superior intubation conditions with succinylcholine in the propofol group, but no statistical difference was seen when 1.2 mg/kg rocuronium was compared to succinylcholine.⁹⁸

Once sugammadex was introduced in 2008, a new paradigm emerged advocating the replacement of succinylcholine by rocuronium in view of its rapid reversibility with sugammadex even in cases of intense block. However, this suggestion has not been supported by high-quality evidence. A Cochrane Database Systematic Review surveyed the period between 2008 and 2015 after the introduction of sugammadex.⁹⁹ Fifty trials including 4151 participants were analyzed. The dose of rocuronium was at least 0.6 mg/kg and the dose of succinylcholine was at least 1 mg/kg. Overall, succinylcholine was superior to rocuronium in terms of achieving excellent and clinically acceptable intubation conditions. Succinylcholine was more likely to produce excellent intubating conditions when using thiopental as an induction agent.⁹⁹ This result is different from the 2003 survey, where propofol was superior to thiopental, but confirms the results of the 2008 report.⁹⁸ When 1.2 mg/kg rocuronium was compared to succinylcholine, there was no difference in intubation conditions with no occurrence of severe adverse events. The authors concluded that succinylcholine was superior to rocuronium from a clinical perspective as it has a shorter duration of action.

The apparent “survival” of succinylcholine led us to perform a systematic review of randomized trials aiming to compare the standard dose of succinylcholine (1 mg/kg) with lower and higher dose regimens in order to obtain excellent intubation conditions and reasonable apnea times.¹⁰⁰ Our aim was to find the optimal dose regimen of succinylcholine for RSI. Compared with 1.0 mg/kg succinylcholine, 2.0 mg/kg provides excellent intubation conditions significantly more often. Apnea times are shortened with regimens <1.0 mg/kg, but the risk of unacceptable intubation conditions was significantly increased with doses of succinylcholine lower than 0.5 mg/kg. We concluded that in cases where excellent intubating conditions are required for safety reason, 2 mg/kg succinylcholine is indicated. When short apnea must be ensured and acceptable intubating conditions suffice, 0.5 mg/kg succinylcholine should be administered.

3.4 The priming principle using magnesium

Magnesium sulfate (MgSO₄) at the usual clinical concentrations does not cause muscle weakness, but it does enhance the effect of relaxants. Therefore, we studied the effect of MgSO₄ for priming purposes. We investigated whether MgSO₄ administration before rocuronium shortens the onset of action of rocuronium and, if so, by how much. We conducted a randomized study including 80 patients who received 60 mg/kg MgSO₄ or placebo (saline) intravenously for 15 min before induction of anesthesia with propofol and sufentanil.¹⁰¹ For tracheal intubation, 0.6 mg/kg of rocuronium was administered in an intravenous bolus once the acceleromyography was stabilized and control measurements were executed. Onset time was measured as the time in seconds from the start of the injection of rocuronium to 95% depression of the first twitch (T1) of the TOF. In patients who had received MgSO₄, the average onset time was 77 (SD 18) s versus 120 (48) s in those receiving placebo ($p < 0.001$). These results are in contrast to the study by Kussman et al. who did not find a shortening of the onset time of rocuronium due to prior MgSO₄ administration, despite similar doses to those used in our study.¹⁰² However, they injected the MgSO₄ as an intravenous bolus immediately before the administration of rocuronium and there was probably no time for magnesium ions to penetrate the NMJ and exert a measurable effect. Although our study was not designed to draw conclusions pertaining to intubation conditions after MgSO₄ pre-treatment, magnesium not only shortened the onset time of rocuronium, but also improved the predictability of the onset of the block compared to placebo (SD 18 s vs. 48 s, respectively).

Magnesium priming appears to be a promising method that may improve intubation conditions. For that reason, we have chosen to further evaluate the magnesium-rocuronium combination. We hypothesized that during a RSI procedure, intubation conditions with a magnesium-rocuronium combination are superior (in terms of speed of onset and quality of intubation conditions) to succinylcholine. We conducted a prospective, randomized, double-blinded trial from September 2012 to July 2015 at the University Hospitals of Geneva and Lausanne in Switzerland. Two hundred and eighty patients were randomized to two groups. In one group (MR), patients received a 15 min preoperative perfusion of MgSO₄ 60 mg/kg-1. RSI was done with propofol and sufentanil and neuromuscular block induced at loss of consciousness with 0.6 mg/kg-1 of rocuronium. Patients were intubated 50 s after by a blinded investigator and intubation conditions graded following an internationally recommended score. In the other group (PS), patients received a perfusion of placebo and neuromuscular block was induced with 1 mg/kg-1 of succinylcholine. The primary endpoint was the intubation conditions. Secondary endpoints were any minor/major adverse events up to 24 h postoperatively.

Primary outcome could be evaluated in 113 patients in group MR and in 126 patients in group PS. There was no significant difference in intubation conditions between the two groups (Fig. 16). Excellent intubation was encountered in 61 (46%) patients in the MR group and in 57 (45%) patients in the PS group. In addition, the variables for evaluation of the intubation conditions (vocal cord position ($p=0.3$) and reaction to the insertion of tracheal tube and cuff inflation ($p=0.77$) were also similar in both groups. Only the conditions at laryngoscopy appeared to be discretely superior in the MR group ($p=0.01$) (Fig. 17). Table 4 summarizes the adverse events for each of the two treatment groups including the 280 randomized patients. Fifty-one patients (18%) had at least one adverse event. The number of adverse events was greater in the PS group (20%; 95% CI [10; 30]; $p < 0.001$). The most common adverse event was the occurrence of erythema after the injection of curare. At the 24 h postoperative visit, significantly more patients in the PS group complained of myalgia (17%; 95% CI [10; 25]; $p < 0.001$). There were no major adverse events. The stratified analysis showed divergent results between the two study centers with a reduction in excellent intubation conditions in the MR group in men in Lausanne (RR=2.48; 95% CI [1.22, 6.09]; $p=0.022$). There was a non-statistically significant trend of superiority of magnesium rocuronium for intubation conditions in women. We concluded that the magnesium-rocuronium combination appeared to be an interesting alternative to succinylcholine. However, there seems to be an influence of gender on the effectiveness of this association for RSI that needs to be studied further and quantified.¹⁰³

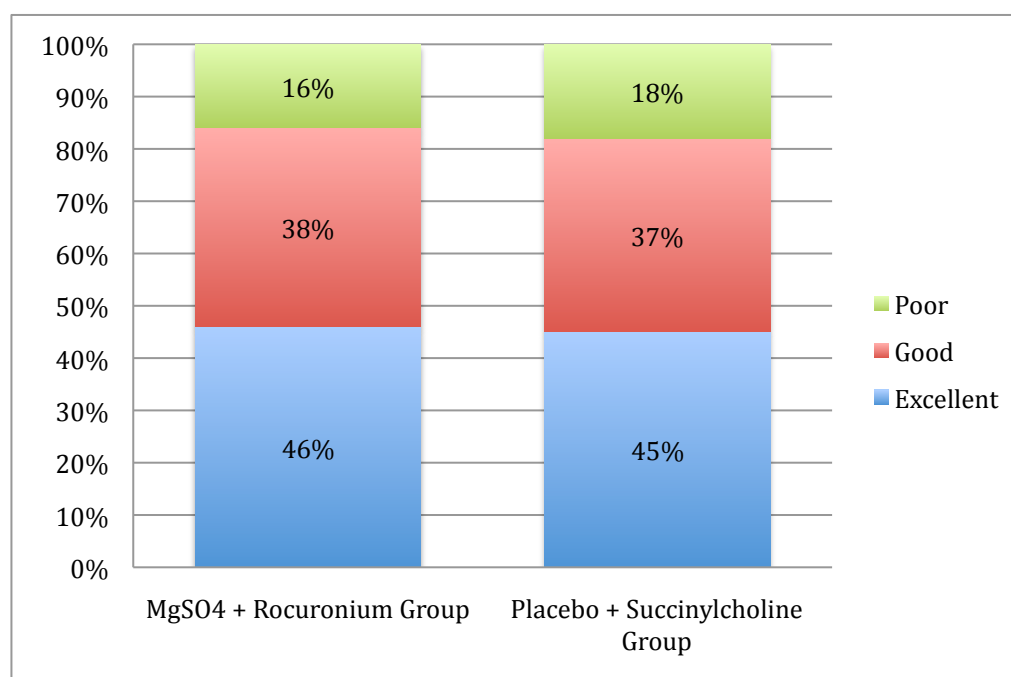


Fig. 16. Diagram of intubation conditions according to study treatment (from the dissertation for the diploma in anesthesia of M. Robin)¹⁰³

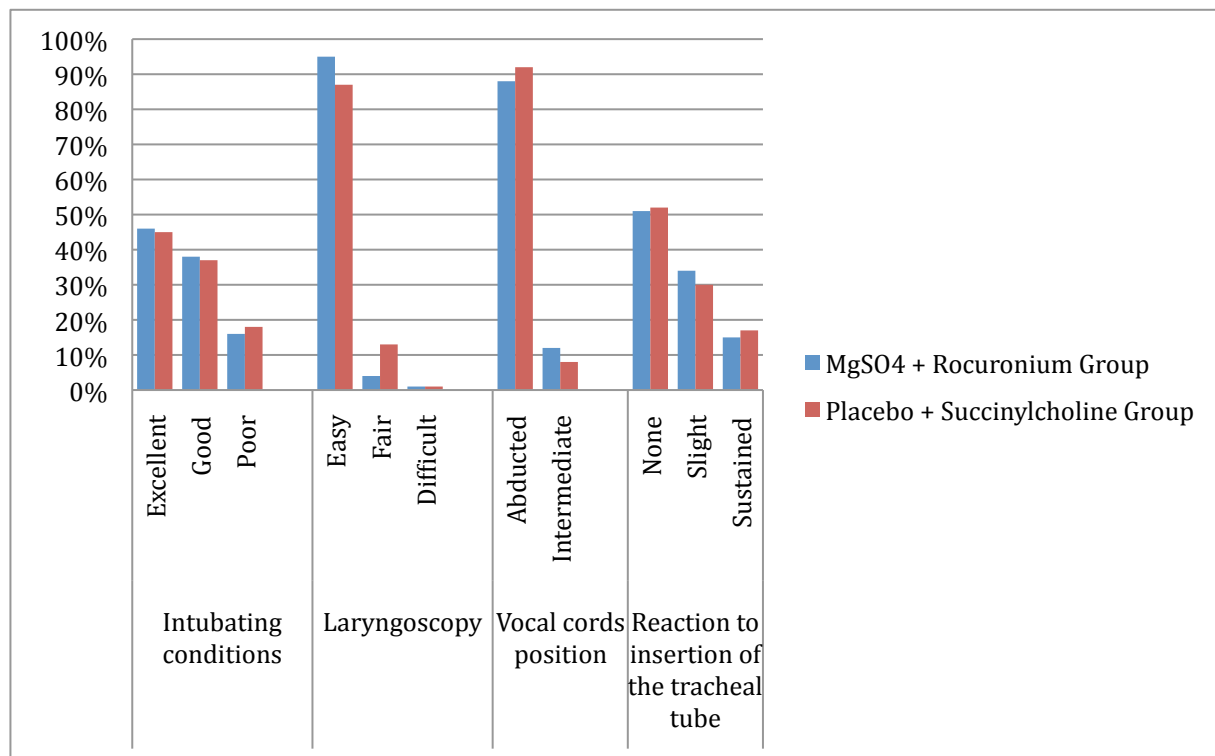


Fig. 17. Variables for assessing intubation conditions by treatment received (from the dissertation for the diploma in anesthesia of M. Robin)¹⁰³

Table 4. Adverse events for each of the two treatment groups including the 280 randomized patients (from the dissertation for the diploma in anesthesia of M. Robin)¹⁰³

	N=280	Group MR (N=141)	Group PS (N=139)	Diff (95%CI)	p value
Adverse event (at least one)	51 (18%)	14 (10%)	37 (27%)	20% [10; 30]	<0.001
Related to the study intervention	22 (8%)	10 (7%)	12 (9%)	2% [-5; 9]	0.797
Pre-treatment		5	0		
Nausea and vomiting		3			
Skin redness		1			
Pain at injection		1			
Injection of rocuronium or succinylcholine		5	12		
Bronchospasm [#]		0	1		
Skin redness [#]		4	10		
Hypotension [#]		1	1		
Postoperative complications*	28 (10%)	2 (1%)	26 (19%)	17% [10; 25]	<0.001
Unrelated to the study intervention	6 (2%)	3 (2%)	3 (2%)	0% [-3; 3]	1

MR: magnesium sulfate; PS: placebo + succinylcholine; Diff:

* All postoperative complications were muscle pain.

[#] Two patients had missing data (both in the MR group)

Among the 16 patients with skin redness, the symptoms of two patients were moderate to severe. The only observed bronchospasm was mild.

3.5 Gastric emptying for the prevention of bronchoaspiration

Aspiration is defined as the inhalation of oropharyngeal or gastric content into the respiratory tract. There is a correlation between the administration of NMBA and bronchoaspiration because relaxants abolish the coughing reflex and inhibit swallowing, thus increasing the risk of inhalation of regurgitated gastric content into the bronchus during laryngoscopy and tracheal intubation or extubation. Regurgitation of liquid or solid food occurs most often in emergency situations, in trauma patients and during general anesthesia. Patients are most at risk with reduced gastric emptying or a full stomach. Aspiration can lead to infectious pneumonia, chemical pneumonitis or respiratory distress syndrome with significant morbidity and mortality. It occurs in 3 to 10/10,000 general anesthesia patients.¹⁰⁴ The likelihood of massive aspiration can be reduced by fasting and correct anesthetic management (such as RSI) using cricoid pressure (Sellick manoeuvre) and an adequate reversal of neuromuscular block at the end of surgery.¹⁰⁵ As nonacidic gastric liquid is considered less deleterious, premedication with antacids, histamine 2 receptor antagonists or proton pump inhibitors have been recommended to ameliorate the outcome of aspiration. A preventive approach would be the emptying of the stomach through a nasogastric tube, but it does not guarantee complete emptying and its preoperative insertion is not without its hazards; therefore, it is not recommended except in the case of bowel obstruction. Acceleration of gastric emptying with pharmacologic intervention before induction of anesthesia would be an alternative for diminishing the volume of gastric content.

Erythromycin, a macrolide antibiotic and motilin receptor agonist, induces antral contractions and increases lower esophageal sphincter tone, which is an important factor in hampering regurgitation. Erythromycin has been used to ameliorate gastric emptying in different settings, but has not been studied in patients undergoing emergency surgery where the risk of bronchoaspiration is imminent.¹⁰⁶ To answer the question whether erythromycin clears the stomach of patients undergoing general anesthesia for emergency surgery, we conducted a randomized study, which included 132 patients stratified into those undergoing trauma-related surgery and others undergoing acute abdomen-related surgery (66 in each arm).¹⁰⁷ Participants received intravenously 3 mg/kg dose of erythromycin or placebo (saline) as a 5 min infusion 15 min prior to the induction of general anesthesia. After RSI, three senior gastroenterologists performed an endoscopy for qualitative and quantitative assessment of gastric content. We were looking for a clear stomach (<40 ml liquid and no solid) immediately after intubation. The pH level of residual content was also measured. A clear stomach was found in 42 of 66 patients (64%) who received placebo compared with 53 of 66 (80%) receiving erythromycin. In non-trauma patients the association of clean stomach and receipt of erythromycin was statistically significant ($p=0.029$), whereas in the trauma population it was not ($p=0.26$). Among non-trauma patients, 61% had no liquid or solid in the stomach after erythromycin prevention. The average pH value of residual gastric liquid was significantly higher after erythromycin treatment. These results show that erythromycin is effective in decreasing gastric content mainly in patients undergoing non trauma-related emergency surgery. Thus, erythromycin can be added to the armamentarium of bronchoaspiration preventing therapy in patients at risk due to receiving NMBA.

3.6 Maintenance surgical relaxation: interactions with inhaled anesthetics, magnesium, local anesthetics and adrenaline

3.6.1 Inhaled anesthetics

Inhaled anesthetics alone do not inhibit neuromuscular transmission as measured by tetanus or TOF stimulation. However, compared to intravenous anesthetics, they potentiate the effect of non-depolarizing NMBA and shift their dose response curves to the left and thus prolong the duration of the block.^{108, 109} For example, maintenance of adequate neuromuscular block in the presence of volatile anesthetics requires about 25% to 30% less NMBA than with propofol anesthetic.¹¹⁰ It is well known that equivalent relaxant doses result in a longer duration of the block in the presence of volatile anesthetics than with intravenous ones.¹¹¹ The ranking order of volatile anesthetics in potentiating NMBA is: desflurane > sevoflurane > isoflurane > halothane > N₂O. The interaction of inhaled anesthetics with non-depolarizing NMBA is of a pharmacodynamic nature. Volatile agents inhibit postsynaptic nAChRs by causing open channel block, receptor desensitization and receptor “flickering” and augment the affinity of the receptor sites to the relaxants.^{68, 112} In addition, a recently published investigation revealed presynaptic effects of sevoflurane and isoflurane through inhibition of exocytosis from synaptic vesicles at the mouse NMJ.¹¹³

Although the pharmacodynamic nature of the interaction is generally accepted, pharmacokinetic factors cannot be neglected. Low blood-gas and tissue-gas solubility of desflurane and sevoflurane result in a faster muscular uptake and elimination of these agents than that of isoflurane and halothane, which are more soluble. The greater muscle-relaxing effect produced by desflurane and sevoflurane is mainly due to their larger aqueous concentration. In addition, blood supplies of the muscles, the temperature and the duration of anesthesia further modify the muscle response to stimulation. Long-duration muscle relaxants (i.e. pancuronium and pipecuronium) are more susceptible to be prolonged by volatile agents, which may even hamper complete spontaneous recovery.⁶¹ There are also gender differences in susceptibility to steroid-type relaxants as females need 30% less rocuronium than men to achieve the same degree of neuromuscular block.¹¹⁴ Therefore, neuromuscular monitoring is a must in this clinical setting in order to adjust the maintenance doses of relaxants to individual patients and to specific surgery (i.e. presence of one twitch, or PTC 2). An overdose of NMBA in the presence of volatile agents may result in postoperative muscle weakness and associated complications (see below).

We were particularly interested to investigate how the effect of rocuronium changes under volatile anesthetics as we use single-dose rocuronium for the intubation of patients undergoing ENT surgery with propofol, isoflurane and sevoflurane maintenance anesthesia. We use acceleromyography for monitoring neuromuscular function routinely in daily clinical practice. This enabled us to compare the duration of 0.6 mg/kg single bolus doses of rocuronium between patients receiving isoflurane, sevoflurane or propofol anesthetics for usual ENT surgery. The primary endpoint of this non-randomized study was the time from rocuronium injection to a TOF ratio of 0.9 (total duration). Secondary endpoints were the time from rocuronium injection to re-appearance of the first twitch (deep block) and time from T1 25% to T1 75% (recovery index). We evaluated the recordings of the neuromuscular block of 323 patients. Of these, 235 had received a single dose of rocuronium of 0.6 mg/kg and had evaluable recordings. One hundred and forty-eight (63%) had received propofol, 24 (10%) isoflurane and 63

(27%) sevoflurane anesthesia. The total duration of the neuromuscular block (mean $\pm$ SD) was 58 $\pm$ 17 min in the propofol group, 77 $\pm$ 20 min in the isoflurane group and 101 $\pm$ 46 min in the sevoflurane group ($p < 0.001$) (Fig. 18).¹¹⁵ The pharmacodynamic interaction with rocuronium was most pronounced with sevoflurane with a large variation of recovery times (± 46 min), thus indicating poor predictability and supporting the need for neuromuscular monitoring and pharmacological reversal to prevent PORNB. The duration of the deep block was 26 $\pm$ 7, 28 $\pm$ 7 and 33 $\pm$ 12 min under propofol, isoflurane and sevoflurane, respectively ($p < 0.001$). The recovery index was 12 $\pm$ 7 min under propofol, 19 $\pm$ 12 min under isoflurane and 26 $\pm$ 15 min under sevoflurane ($p < 0.001$). This indicates a synergistic interaction between residual concentrations of rocuronium and sevoflurane, which was similar in intensity at low and higher concentrations of rocuronium.

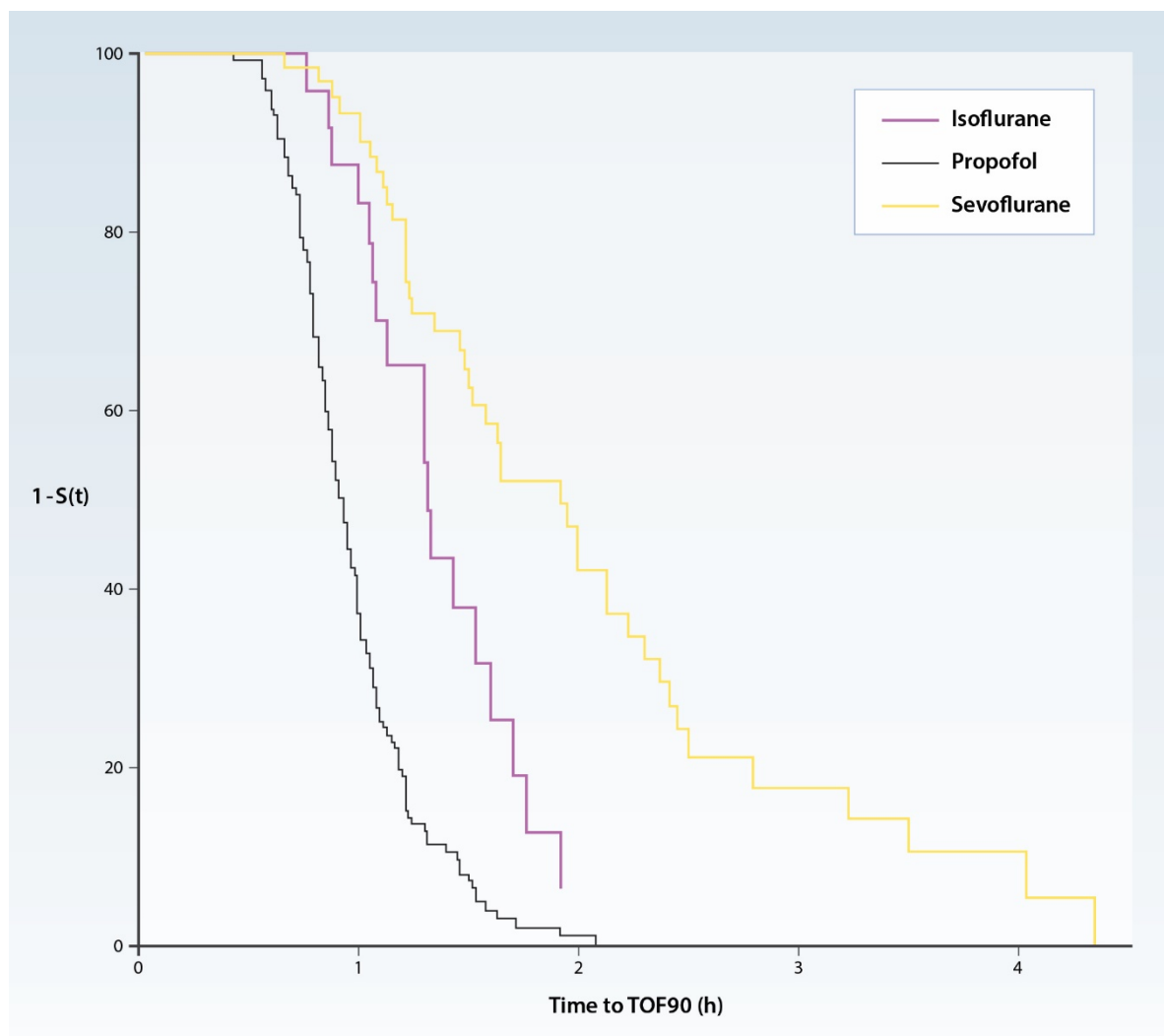


Fig. 18. Potentiation of residual rocuronium block by isoflurane and sevoflurane compared to propofol (from the 3rd year medical student master thesis of E. Chaix).

3.6.2 Magnesium

Magnesium has a prominent place among substances known to interact with NMBAs. In clinical concentrations, magnesium does not cause neuromuscular block, but it potentiates the effect of NMBAs. An excess of magnesium ions has at least three distinct effects on the NMJ.⁷¹ The most important is a reduction in the amount of the released transmitter, which causes a drastic fall in the amplitude of end-plate potential. In addition,

magnesium diminishes the depolarizing action of ACh at the endplate and depresses the excitability of the muscle membrane. Magnesium decreases transmitter release by inhibition of voltage-gated Ca^{++} channels at the motor nerve terminal. Under these circumstances, even small concentrations of NMBAs depress the neuromuscular transmission and prolong the duration of the block. An excess in Ca^{++} ions relieves the effect of magnesium and antagonizes the block. Magnesium has been shown to contribute to postoperative pain alleviation and has an opiate-sparing effect.¹¹⁶ This will lead to the increase in perioperative MgSO_4 administration and the likelihood of postoperative neuromuscular depression. However, only few studies have investigated the time course of neuromuscular block in the context of perioperative MgSO_4 treatment.

We conducted an electrophysiological investigation with the aim to determine the modification of the time course of rocuronium block due to MgSO_4 .¹⁰¹ Eighty patients were randomized to receive 60 mg/kg MgSO_4 or placebo (saline) as a short infusion for 15 min before induction of anesthesia with propofol, sufentanil and rocuronium 0.6 mg/kg. Anesthesia was maintained with target-controlled propofol. The neuromuscular block was measured by acceleromyography using TOF-Watch SX® device. Spontaneous recovery from the block was allowed and different time intervals were measured as follows: the time from the injection of rocuronium to T1 25% was “clinical duration”; from 25% to 75%, “recovery index”; and from 25% to 90% , “recovery time”. Full recovery from the block was defined as a TOF ratio 0.9 and the time taken from the injection of rocuronium until TOF 0.9 was “total recovery time”. The average total recovery time was 73 [22] min [mean and SD] with magnesium and 58 [14] min with saline ($p < 0.003$). The clinical duration was 45 [14] min with magnesium and 33 [8] min with placebo ($p < 0.0002$). The recovery index was 14 [6] min with magnesium and 11 [5] min with placebo ($p < 0.02$). The recovery time was 28 [11] min with magnesium vs. 24 [8] min with saline ($p = 0.28$). Thus, MgSO_4 given 15 min before rocuronium administration prolonged “total recovery time” by about 25%. This prolongation was mainly due to longer clinical duration because recovery time from 25% to TOF 0.9 was not different. The prolongation of the block by magnesium has not been fully investigated. A case report described prolongation of the block by 10 hours after cardiac surgery.¹¹⁶ Another study reported unchanged recovery times in elderly patients with MgSO_4 during recovery from rocuronium block.¹¹⁷ Other studies did not differentiate between time periods during recovery as in our trial and they cannot be compared with our data.¹⁰² One possible explanation why the recovery time (25% to 90% recovery) with magnesium and placebo did not differ significantly in our study would be the elimination of MgSO_4 from the body. We did not measure plasma magnesium concentrations and, thus, we cannot prove this assumption. The duration of the neuromuscular effect of magnesium has been reported to be about 45 min,¹¹⁸ which corresponds to the time of clinical duration in our study and suggests the duration of a neuromuscular effect of 60 mg/kg MgSO_4 as approximately 45 min. Nevertheless, measurements of plasma magnesium levels would be desirable whenever MgSO_4 is administered to patients receiving NMBAs.

3.6.3 Local anesthetics

Local anesthetics are widely used not only for local and regional anesthesia, but also as intravenous adjuvants to general anesthesia to minimize perioperative pain or to treat cardiac arrhythmia. Pharmacologic properties of local anesthetics predestine them to act on the presynaptic site (depressing ACh), postsynaptic site (reducing AchR channel open time), and muscle cell membrane (reducing muscle contractility) in the NMJ.⁷ However, their interaction with NMBAs is not clear. Procaine is metabolized by the plasma-cholinesterase and may

augment the effect of succinylcholine and mivacurium by decreasing their enzyme degradation. Epidural bupivacaine prolonged the duration of atracurium in adults,¹¹⁹ but did not affect the duration of vecuronium in children.¹²⁰ Another study has found prolongation of vecuronium block by epidural mepivacaine.¹²¹ The action of intravenous lidocaine on rocuronium-induced block was reported by Cardoso (2005) who found that a 1.5 mg/kg lidocaine bolus prolonged the block.¹²²

To establish the interaction between lidocaine and rocuronium, we performed a randomized study including 54 patients receiving 1.5 mg/kg of lidocaine intravenous bolus followed by an infusion of 2 mg/kg/h versus placebo (saline). Target-controlled propofol and sufentanil anesthesia was given with 0.6 mg/kg rocuronium for intubation. The effect of rocuronium was measured by acceleromyography according to the methodology described previously in this review. We found no differences between lidocaine and placebo in any of the variables of neuromuscular block.¹²³ Thus, the intravenous infusion of plain lidocaine had no impact on the time course of rocuronium-induced neuromuscular block. However, in ENT surgery, infiltration of the operation field with lidocaine containing adrenaline is usual practice for the prevention of bleeding and nociception. We observed potentiation of the neuromuscular block in several patients in which 2-5 ml of lidocaine 1% containing 5 µg/ml adrenaline was injected under the mucosa of the nasal septum. Figure 19 shows an example of the acceleromyographic recording of a 67-year-old female patient undergoing septoplasty under sevoflurane anesthesia. One min after the injection 3 ml of the lidocaine-epinephrine mixture, the TOR ratio and the twitch height lessened by about 30% to 40% over 10 min.

30 mg lidocaine + 15 µg epinephrine under nasal mucosa

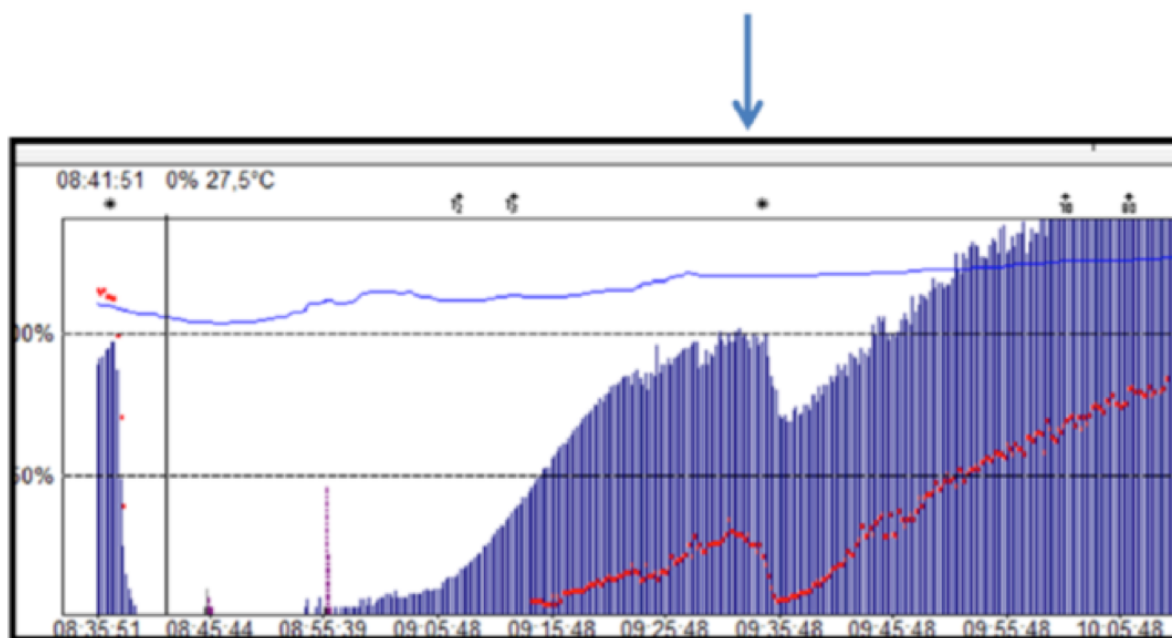


Fig. 19. Acceleromyographic recording of the effect of 0.6 mg/kg rocuronium showing the enhancement of the block by epinephrine (arrow). Blue tracings are T1, red dots are TOF responses. Upper horizontal blue line indicates the muscle temperature at the site of monitoring (personal contribution with permission of the cantonal ethics committee of Geneva).

3.6.4 Adrenaline

In his classical pharmacological experiments carried out 50 years ago, Bowman demonstrated a biphasic effect of 10 µg/kg intravenous epinephrine on the d-Tc-induced block in the cat. An initial antagonism (presynaptic facilitation: α -effect) was followed by a postsynaptic potentiation of the block (β -effect), probably due to hyperpolarization of the muscle membrane.¹²⁴ However, smaller doses of epinephrine (0.5-1.0 µg/kg) augmented the paralysis of the tibialis anterior muscle of the cat without producing any initial anti-curare effect (lack of α -effect with low doses). This was similar to our findings where the subjects also received small amounts of epinephrine (about 0.3 µg/kg), thus explaining the lack of antagonism prior to potentiation. Ninomiya et al. observed both antagonism and potentiation of rocuronium block by oral mucosal injection of epinephrine in 16 patients,¹²⁵ which confirms the biphasic effect of locally-injected epinephrine on the neuromuscular block. Further studies are warranted, including plasma concentration measurements of lidocaine and epinephrine, to explore the interaction of epinephrine with NMBAs in the clinical settings where the systemic effect of locally administered epinephrine is expected.

4. REVERSAL OF NEUROMUSCULAR BLOCKADE

Owing to the low predictability of the duration of action of NMBAs, reversal of their effect at the end of anesthesia and surgery is recommended in order to prevent PORNB and related complications. Two concepts have prevailed during the last 50 years concerning the issue of pharmacological reversal of neuromuscular transmission block. One suggested the administration of neostigmine as a rule once the patient had received a non-depolarizing NMBA. The other preferred selective administration of reversal agents was based on the monitoring of neuromuscular function or on the clinical signs of muscle weakness. The use of reversal with neostigmine has been the subject of ongoing debate. With the introduction of sugammadex for the reversal of steroidal NMBAs, a new era began in the management of neuromuscular block based on quantitative monitoring.

4.1 Reversal of neuromuscular blockade with neostigmine

As described in chapter 2.4.1, the interaction of neostigmine with non-depolarizing NMBAs is competitive antagonism. Neostigmine can be used for the reversal of both steroidal and benzylisocholinium-type relaxants. Neostigmine dose dependently inhibits the activity of AChE enzyme up to 0.07 mg/kg, which is its ceiling dose. However, in current clinical practice, lower doses of neostigmine (0.02 to 0.04 mg/kg) are also used with an aim to prevent side effects, but this may increase the risk of unsatisfactory reversal. Nevertheless, in superficial block (TOF ratio 0.4 to 0.6) induced by atracurium and rocuronium, low doses of neostigmine (0.02 mg/kg) have provided adequate reversal.^{126, 127} Indeed, many anesthetists are reluctant to administer neostigmine fearing muscarinic side effects, such as bradycardia, QT prolongation, arrhythmia, salivation, bronchospasm, increased bowel peristalsis, miosis, and nausea and vomiting, and prefer spontaneous recovery from the block instead of pharmacological reversal.⁴⁵ Anticholinergic drugs given together with neostigmine to reduce muscarinic side effects may also cause tachycardia or arrhythmia. However, spontaneous recovery may take too long to take place, necessitates monitoring to ensure completion of recovery, and is difficult to perform during busy operating schedules. Maintaining normal gas exchange during reversal with neostigmine is a key element in avoiding cardiac side effects and assisted ventilation is recommended during the recovery period. The time to peak effect of neostigmine is about 10-15 min, provided that the dose regimen is adapted to the depth of the block. Therefore, the quantification of the block is indispensable when using neostigmine. Originally, the

presence of two twitches to TOF stimulation (TOFC-2) was recommended as a minimum requirement for neostigmine reversal.^{128, 129} This concept was challenged by Kirkegaard et al. who demonstrated that 0.07 mg/kg neostigmine was unable to adequately reverse cis-atracurium-induced block in a reasonable time, even if four twitches were present.¹³⁰ Similar results were reported by Kopman et al. using 0.05 mg/kg of neostigmine to reverse TOFC 2 level cis-atracurium and rocuronium block under desflurane anaesthetic. In 20% of patients, 30 min was necessary to achieve a TOF ratio of ≥ 0.9 (criteria of adequate recovery from the block).¹³¹ Volatile anesthetics prolong the duration of recovery after neostigmine. Kim et al. compared the times necessary to achieve TOF ratio 0.9 with the administration of 0.07 mg/kg neostigmine to reverse TOFC 1, 2, 3 and 4 degree rocuronium block under propofol and sevoflurane anaesthetic.¹³² The reversal of TOFC-1 block took 8.6 min on average under propofol and 28.6 min under sevoflurane anesthesia to take place, while 4.7 min and 9.7 min, respectively, were necessary for the reversal of TOFC 4 degree block ($p < 0.0001$). The authors recommended achieving three twitches with propofol anesthesia and four TOF responses with sevoflurane for adequate reversal with neostigmine within 10-15 min. The prolongation of time to 0.9 TOF ratios by volatile agents has since been confirmed by several other studies.¹³³ Pongrácz et al. found that 20% of patients who were relaxed with rocuronium and received sevoflurane did not reach TOF ratio 0.9 within 15 min after neostigmine administration at threshold TOFC 4.¹³⁴ Thus, if volatile anesthetics are used together with NMBAs, the appearance of four responses to TOF stimulation is highly recommended before neostigmine is given. However, unsatisfactory recovery in a reasonable time may occur and monitoring is mandatory.

Routine administration of neostigmine at the end of surgery has not been confirmed and there are several reasons for this. First, because neostigmine has been shown to cause “re-curarisation” in patients who had completely recovered from the block ($\text{TOF} \geq 0.9$).⁴⁸ Caldwell observed a decrease in TOF ratios after neostigmine in eight patients in whom TOF ratios were ≥ 0.9 , indicating that in the absence of a block, neostigmine depresses neuromuscular transmission. Second, Eikermann et al. demonstrated in animal experiments the inhibitory effect of neostigmine on the diaphragm and on the upper airway dilation muscles once the animals fully recovered from the block.¹³⁵ Third, Herbstreit et al. examined the effect of 0.03 mg/kg neostigmine in volunteers who recovered from rocuronium block to TOF ratio 1.0.⁴⁹ The upper airway closing pressure increased and the genioglossus muscle activity decreased; both are known to facilitate upper airway occlusion. Other clinical signs of neuromuscular transmission inhibitory effects (double vision, difficulty in swallowing, fasciculation) of neostigmine were also observed. Finally, Grosse-Sundrup et al. (2012) identified an increased risk for postoperative hypoxia and critical respiratory events due to routine administration of neostigmine after relaxation with intermediate acting agents.¹³⁶

These data support the view that appropriate neuromuscular monitoring is a *sine qua non* of adequate reversal with neostigmine. One may argue for the use of a simple nerve stimulator able to deliver TOF stimuli ad hoc, allowing to observe the number of evoked muscle contractions and checking the TOF ratio by palpation in order to determine the point in time of the administration of the antagonist and its dose. However, this method is not suitable to confirm the adequacy of recovery from the block because TOF ratios > 0.4 cannot be sensed by palpation or visually.^{137, 138} Therefore, the sensitivity and specificity of simple nerve stimulators for the detection of residual block is insufficient. Currently, objective quantitative monitoring, i.e. acceleromyography, is

recommended for the adequate reversal of neuromuscular block (see chapter 3.1.) and the use of neostigmine should always be based on objective monitoring.

4.2 Reversal of neuromuscular blockade with sugammadex

With the introduction of sugammadex in Europe in 2008 into clinical anesthesia, a new era began in the management of neuromuscular blockade induced by steroidal-type relaxants. From a clinical perspective, the novelty of the new paradigm consists of its quantitative feature, taking into account the depth of the block to determine the dose of sugammadex in order to achieve optimal recovery. To quantify the depth of block, objective monitoring is indispensable. It is known that 3.75 mg of sugammadex binds 1 mg rocuronium.¹³⁹ Calculating with a 70 kg bodyweight and 0.6 mg/kg rocuronium for intubation, 42 mg rocuronium has to be encapsulated and requires 157.5 mg of sugammadex, which is 2.25 mg/kg. Indeed, the lowest dose of sugammadex is 2.0 mg/kg, which is recommended for the reversal of moderate (T2 degree) or superficial (> T3 degree) rocuronium block. This is the lowest dose recommended by the manufacturer. However, several investigators tested less than 2 mg/kg sugammadex regimens for the reversal of superficial rocuronium blocks, such as threshold TOFC-4 or TOF ratio 0.5 degree.^{127, 134} Pongrácz et al. demonstrated that at threshold TOFC-4 rocuronium block 1.0 mg/kg sugammadex was as effective as 2.0 mg/kg to achieve TOF ratio 1.0 within 2 min, and 0.5 mg/kg reversed the block in less than 8 min.¹³⁴ Schaller et al. described that a shallow rocuronium block of TOF ratio 0.5 can be reversed within 2 min using only 0.25 mg/kg sugammadex.¹²⁷ Residual postoperative block was not reported by these investigators. However, using low doses of sugammadex comprises the risk of insufficient reversal if the depth of the block is not precisely determined or the dose is not correctly adapted to the depth of the block or when drug interaction occurs.¹³⁹ It is of note that the side effects of sugammadex are not dose dependent; the reason for using low doses is exclusively economic. Further experience is required before a low sugammadex regimen can be recommended for general use. In contrast to neostigmine, sugammadex is able to reverse any depth of rocuronium block. For reversal (within 2 to 3 min) of PTC 2 degree rocuronium block, 4 mg/kg sugammadex is recommended and, in the case of no response to PTC mode of stimulation, 8 mg/kg of sugammadex is necessary to obtain satisfactory recovery.^{140, 141} Furthermore, successful reversal of the effect of 1.2 mg/kg rocuronium was achieved in 2 min with 16 mg/kg of sugammadex given 5 min after relaxant administration, which can be life-saving in “cannot intubate, cannot ventilate” situations.¹⁴² This is unique for the rocuronium-sugammadex paradigm pertaining to RSI and to the management of difficult airway. The possibility to regain spontaneous respiration in case of difficult airway provides an alternative to succinylcholine in critical intubation situations and the speed of recovery of intense rocuronium block enhanced by sugammadex is illustrated in Figure 20.

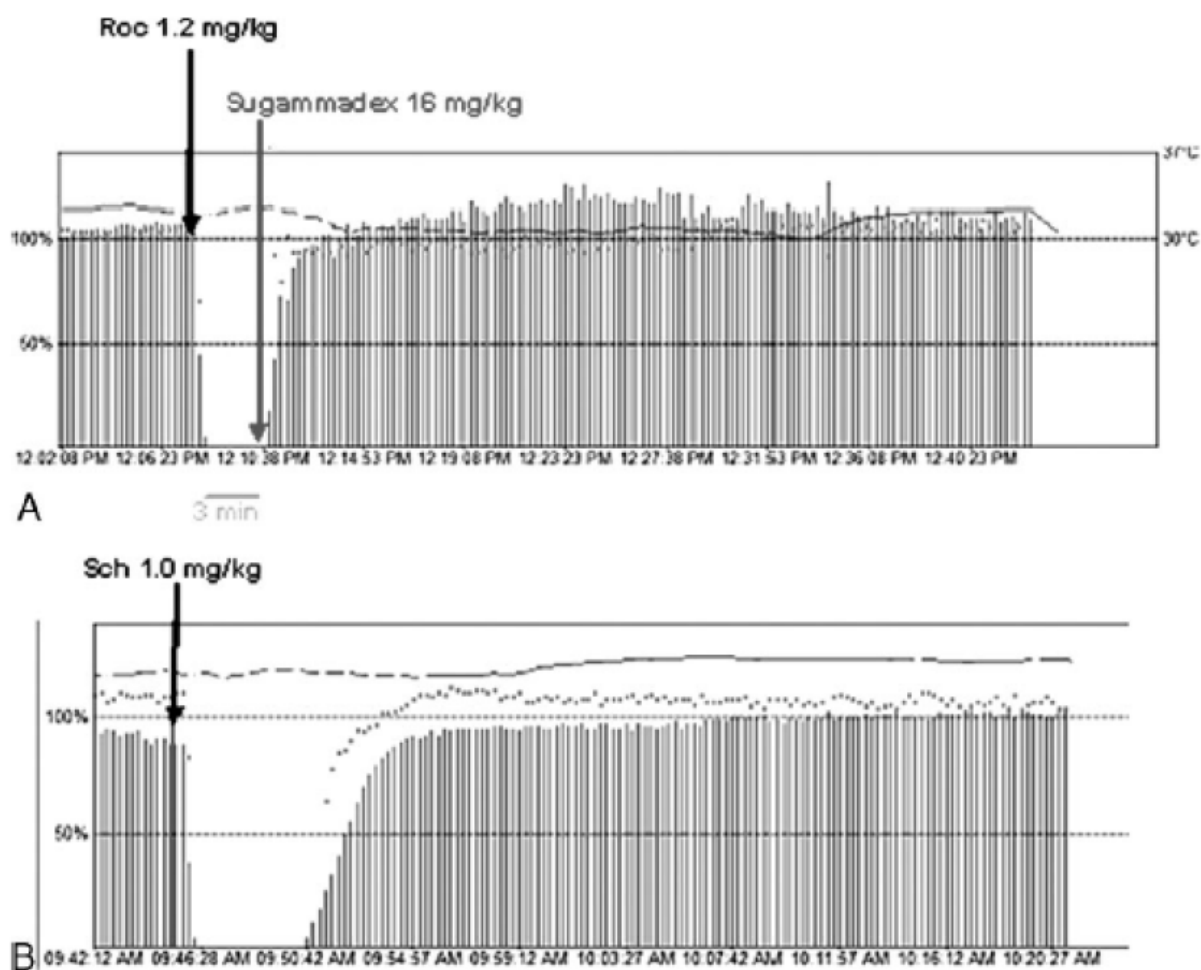


Fig. 20. Comparison of the speed of recovery from intense rocuronium block (1.2 mg/kg) enhanced by sugammadex (16 mg/kg), versus spontaneous recovery from succinylcholine (1.0 mg/kg) induced block (illustration from Naguib et al.).⁵⁴

The dose-finding studies cited above indicate that the deeper the block, the higher the dose of sugammadex to ensure rapid recovery (<5 min average). According to the above calculation, 4.5 mg/kg sugammadex should be sufficient to encapsulate 1.2 mg/kg of rocuronium. However, this would take too long for recovery to take place and therefore sugammadex is intentionally overdosed. Not only rocuronium, but also vecuronium, is reversible with sugammadex. Although the affinity of sugammadex to vecuronium is less than that of rocuronium, deep and residual vecuronium block (PTC 2 and T2 degree) was adequately reversed with 4 and 2 mg/kg of sugammadex, respectively.^{141, 143} By contrast, sugammadex has low affinity to pancuronium and cannot be suggested for its reversal. An additional steroidal NMBA with long duration of action is pipecuronium, which has an excellent cardiovascular profile. In addition, histamine release does not appear to be a problem with this compound.¹⁴⁴ Although pipecuronium is no longer on the approved medication list in Switzerland, a Hungarian team investigated the reversal of its effect in surgical patients and found that moderate pipecuronium block (T2 degree) can readily be reversed with 1 mg/kg of sugammadex, similarly to 2 mg/kg or higher doses.⁶¹ The reason explaining the efficacy of sugammadex in this context may be the high affinity of sugammadex to pipecuronium, which is 10 times superior to rocuronium. The authors suggest a more frequent use of pipecuronium for long

surgical relaxation because its residual effect can be eliminated at any time with sugammadex albeit in the presence of sevoflurane anesthetic.

It is generally recognized that volatile anesthetics prolong the recovery time from the block and attenuate the efficacy of neostigmine. Vanacker et al. compared the time intervals to 0.9 TOF ratios after sugammadex and neostigmine during sevoflurane and propofol anesthetics.¹⁴⁵ The average recovery times were similar (1.8 min) after sugammadex, while sevoflurane significantly prolonged the time of neostigmine-induced recovery.^{133, 145} Other studies have also confirmed that sugammadex is effective in reversing neuromuscular block induced by rocuronium, pipecuronium or vecuronium in the presence of volatile anesthetics without the risk of PORN. ^{134, 141}

In addition to the reversal of neuromuscular block, the encapsulation of relaxants by sugammadex augments the safety margin of NMJ. Since about 75% of the amount of the relaxant administered to the patients is “consumed” without causing muscle relaxation (“safety margin”), only the supplementary 25% of the molecules induce measurable block. Indeed, one-fourth of the total amount of sugammadex calculated above (2.25 mg/kg) should be able to reverse the block at least to its measurable level. Furthermore, the dosage of sugammadex has been determined aside from the elimination of relaxant molecules during the time from relaxant injection to sugammadex administration and, therefore, the recommended doses of sugammadex are “oversized”. Indeed, as demonstrated by Pongrácz et al., 0.5 mg/kg sugammadex was sufficient to achieve full reversal from threshold TOFC 4 block within 8 min and without PORN.¹³⁴ We also described an electrophysiological difference between sugammadex and neostigmine reversal and confirmed the observation of Staals et al. in that during spontaneous recovery or neostigmine reversal T1 reaches normal values before the TOF fade would have ceased.¹⁴⁶ The contrary can be observed with sugammadex reversal when twitch recovery is lagging behind TOF fade. This may be explained by augmented concentrations of ACh at the NMJ due to the inhibition of AChE and the lack of the presynaptic effect of neostigmine. When sugammadex is administered, both pre- and postsynaptic receptors are liberated from the relaxants and since the presynaptic nACh receptors are less sensitive to relaxants than the postsynaptic ones, TOF fade is attenuated while the postsynaptic receptor inhibition still exists. Only when T1 has reached the control value can the recovery be considered complete. This may take several minutes to take place after TOF recovery to 1.0. With neostigmine antagonism, the relaxant molecules are not taken away from the NMJ in contrast to sugammadex, which forms a neutral complex with them in the plasma. Therefore, theoretically speaking, drug interactions should not influence the reversal with sugammadex because there are no relaxant molecules left in the NMJ to interact with magnesium or volatile anesthetics, for instance.

As no study has examined this hypothesis to date, we conducted a randomized double-blind trial aiming to verify whether magnesium pre-treatment has an impact on sugammadex reversal of rocuronium block.¹⁴⁷ Thirty-two male patients were randomized to receive MgSO₄ 60 mg/kg or placebo intravenously before induction of anesthesia with propofol, sufentanil and rocuronium 0.6 mg/kg. We included only male patients to exclude the confounding effect of gender differences. Neuromuscular transmission was monitored using TOF-Watch SX® acceleromyography. In 16 patients, sugammadex 2 mg/kg was administered intravenously at the reappearance of the second twitch of TOF (moderate block). In a further 16 patients, 4 mg/kg sugammadex was administered at

PTC 1 to 2 (deep block). The time from injection of sugammadex to normalized TOF ratio 0.9 was measured. The recovery time to final T1 was also determined. Plasma magnesium levels were measured from freshly-drawn venous blood specimens before administration of pre-treatments and thereafter, as well as at the time of sugammadex injections at deep and moderate block. The average time for the reversal of moderate block was 1.69 min (SD 0.81) in patients pretreated with magnesium and 1.76 min (1.13) in those pretreated with placebo ($p=0.9$). The average time for reversal of deep block was 1.77 min (0.83) in patients pretreated with magnesium and 1.98 min (0.58) in those pretreated with placebo ($p=0.57$). Times to final T1 were longer compared with times to normalized TOF ratio 0.9, without any difference between patients pretreated with magnesium or placebo. We concluded that 60 mg/kg of MgSO₄ administered before induction of anesthesia does not decrease the efficacy of recommended doses of sugammadex for reversal of deep and moderate rocuronium-induced neuromuscular block. Intravenously-administered MgSO₄ is used for a variety of indications in perioperative medicine. Elevated plasma concentrations of magnesium enhance the effect of non-depolarizing NMBAs and lessen the efficacy of reversal with neostigmine.¹⁴⁸ However, when higher doses of MgSO₄ are administered, elevated concentrations of magnesium ions may cause neuromuscular block, which cannot be antagonized with sugammadex, but may react to calcium.⁸² Therefore, when magnesium, muscle relaxants and sugammadex are administered together during the perioperative period, quantitative relationships and timing are as important as objective monitoring to obtain correct diagnoses in cases of persisting neuromuscular block. Human data on MgSO₄- induced neuromuscular block are lacking and should be obtained in the near future.

4.2.1 Attenuation of pseudoallergic reactions to rocuronium with sugammadex

We recently published three cases of pseudoallergic (anaphylactoid) reactions to perioperatively-administered rocuronium, which rapidly resolved after sugammadex injection.¹⁴⁹ One of our cases was particularly well documented due to our electronic anesthesia record system (Fig. 21). A 48-year-old female was scheduled for surgical resection of an unexplained left parietal cerebral mass. A few minutes after induction with propofol and fentanyl and injection of 40 mg of rocuronium, she developed tachycardia and a generalized urticarial rash, followed by profound hypotension. An anaphylactic shock was suspected and hydrocortisone and clemastine were administered once. Despite repeated epinephrine injections and intravenous fluids, the patient remained hypotensive and the surgical procedure was cancelled. Fifty-three min after the induction, 200 mg of sugammadex were injected, resulting in rapid hemodynamic normalization, disappearance of the urticarial rash and extubation 15 min later.

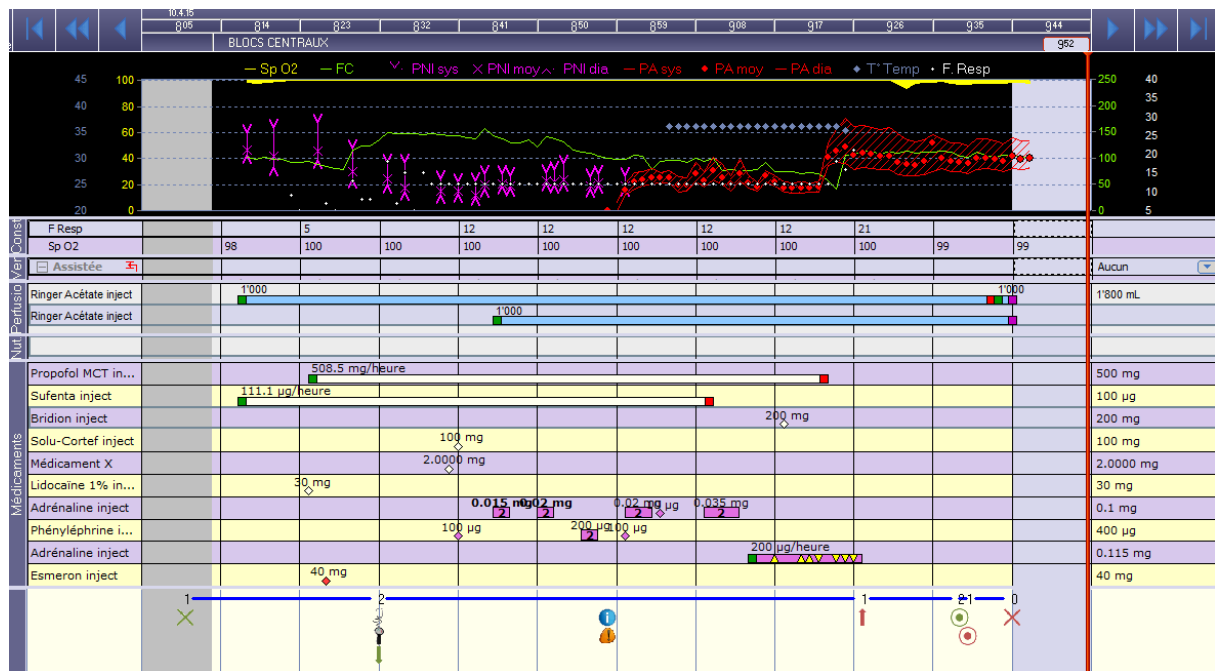


Fig. 21. Sugammadex reverses rocuronium induced pseudoallergic reaction, image of the electronic anesthesia record system (with permission from the patient).

Allergological workup showed no evidence for immediate-type hypersensitivity to rocuronium. However, rocuronium induced an irritative reaction in skin tests in all three patients and in three healthy individuals. This reaction was specifically suppressed by adding sugammadex at a 1:1 molecular proportion to rocuronium before the skin tests. This observation suggests that the patients suffered from a pseudoallergic reaction and indicates that sugammadex might act via the inhibition of recently discovered non-IgE-mediated Mas-related G-protein-coupled receptor member X2 (MRGPRX2)-triggered mast cell degranulation induced by rocuronium.¹⁵⁰ It is possible that the high rate of anaphylactic reactions reported in NMBA-naïve patients, as well as the high percentage of cross-reactivity reported in NMBA-allergic patients (mostly based on skin test results), might be due to the effects of NMBA on the MRGPRX2 receptor and be pseudoallergic and not anaphylactic. This mechanism may also explain the irritative reaction in skin tests with NMBAs. Therefore, we proposed a reclassification of anaphylaxis to NMBAs.¹⁵¹

4.3 PORN

PORN is an anesthetic complication due to the use of NMBAs, which may have severe consequences on patient outcome.

4.3.1 Definition of PORN

Currently, PORN is defined as TOF ratios less than 0.9 after extubation of the trachea or later during the acute postoperative phase.¹⁵² Formerly TOF ratio of 0.7 was considered adequate recovery from neuromuscular block, because at this value of TOF ratio patients were able to breathe with normal tidal volume, open eyes, cough, lift their head, shoot out their tongue and produce vital capacity of 15-20 ml/kg.^{153, 154} This is explained by the fact that the sensibility of different muscles to NMBAs is not uniform. Since the diaphragm is the less sensible muscle of the body to curare-like agents and because it ensures 60-80% of inspiratory force and 60% of vital

capacity, its early recovery from the block results in normal respiratory tidal volume. However, the pharyngeal muscles, the upper esophageal sphincter, the genioglossus muscle and the geniohyoideus muscle, which are more sensitive to the relaxants, recover much later.^{155, 156} The sensibility to NMBAs of the peripheral muscles like the adductor pollicis is intermediary. Therefore monitoring at the ulnar nerve/adductor pollicis muscle only indirectly indicates the inhibition of the pharyngeal muscle function.¹⁵⁷ It has been demonstrated in volunteers that swallowing was inhibited at TOF ratios 0.6 to 0.8.¹⁵⁶ The dysfunction of the pharyngeal muscles decreases the protection of the airway and facilitates bronchoaspiration. At TOF ratio 0.8, the upper esophageal muscle function and the coordination of swallowing are disturbed, particularly in elderly patients who are more susceptible to aspiration.^{158, 159} The protection of the airway further deteriorates by the attenuated coughing reflex due to the residual effect of opioids and volatile anesthetics.^{159, 160} The intubation of the trachea may also contribute to the depression of reflex activity, thus facilitating pulmonary aspiration after extubation.¹⁶¹ Partial neuromuscular block causes functional disturbance of upper airway dilator muscles. For the prevention of upper airway obstruction and bronchoaspiration, recovery to TOF ratio to 1.0 has been recommended, particularly in patients with sleep apnoea,¹⁶² obesity and upper abdominal surgery, who are at increased risk for airway obstruction.⁴⁹ It should also be kept in mind that after full recovery of the abductor pollicis muscle other, more sensitive muscle groups still recover from neuromuscular block. Amongst these are the pharyngeal muscles which are responsible for effective swallowing (fig. 22).¹⁶³

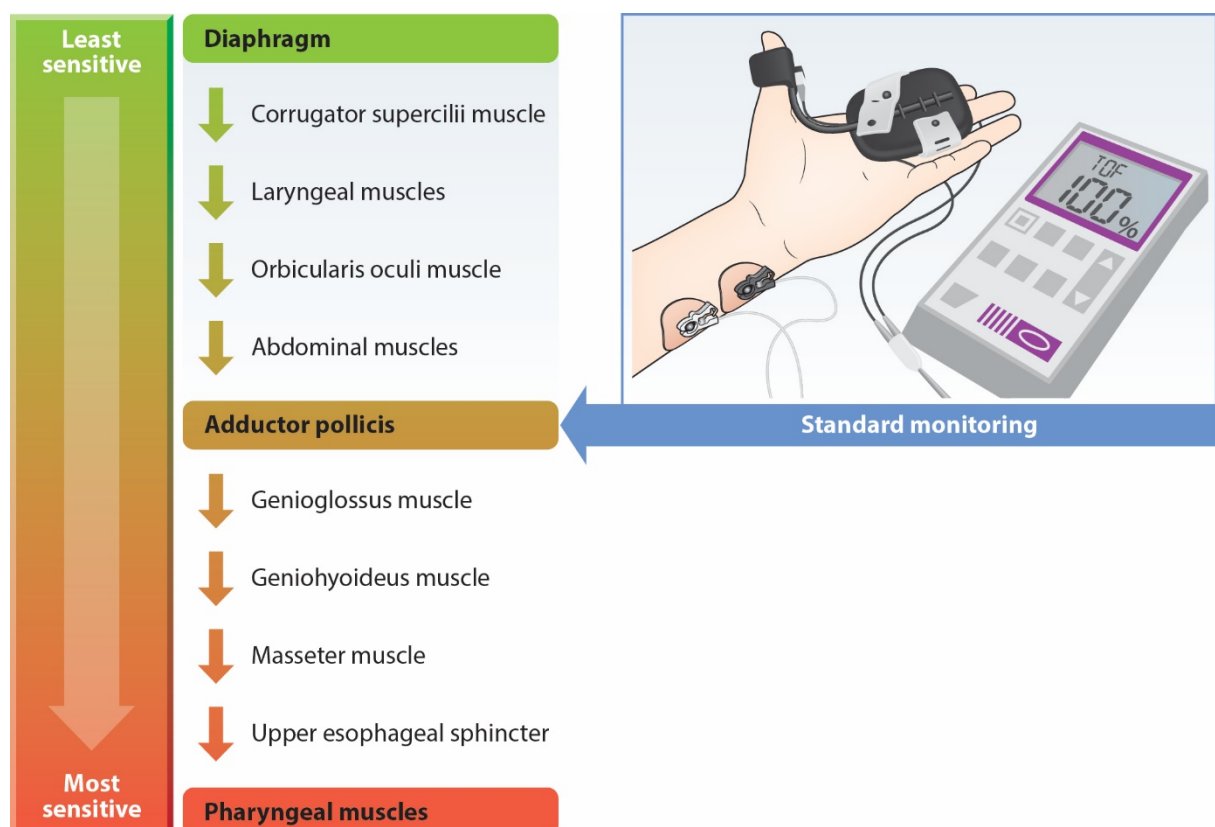


Fig. 22. Sensitivity of different muscles to the NMBAs. The diaphragm is the less sensitive, the pharyngeal muscles are the most sensitive (adapted from Fuchs-Buder).¹⁶³

Nicotinic ACh chemoreceptor can be found in the glomus caroticum, where it contributes to the modulation of respiratory response to acute hypoxia. It has been shown that a partial effect of vecuronium attenuates the respiratory response to hypoxia through inhibition of these receptors.¹⁶⁴ Also, atracurium and pancuronium decreased the hypoxic respiratory response by about 30%. When the TOF ratio returned to 0.9, the respiratory response became normal.¹⁶⁵ The residual effect of NMBAs may be potentiated by residual anesthetic and opiate effects, causing severe hypoxia.¹⁶⁶ This interaction can be prevented by adequate reversal of neuromuscular block with sugammadex, which sweeps out the relaxant molecules from all active sites including the glomus caroticum receptors, thus may help to prevent hypoxia. PORNB in conscious patients is subjectively unpleasant because muscle weakness, double vision, difficulty speaking and swallowing are difficult to tolerate.¹⁶⁷ At TOF ratio 0.5 respiratory depression is apparent.¹⁵⁷ Therefore, adequate antagonism of residual block controlled by objective monitoring is an important quality and safety measure.

4.3.2 The impact of PORNB on patient outcome

In the introduction to this review, we cited the classical work of Beecher and Todd published in 1954 and we emphasized the risk of the use of NMBAs on patient safety. Twenty years later in the UK and Ireland, a survey of postoperative mortality revealed respiratory depression as cause of death in 16% of anesthesia-related mortality.¹⁶⁸ In France during the 1980s the incidence of coma and death associated with anesthesia was 1/7924, of which half was due to respiratory depression.¹⁶⁹ Cooper et al reported that 60% of admissions to the intensive care unit (ICU) were due to inadequate reversal of the effect of NMBAs.¹⁷⁰ Berg et al. carried out a randomized study examining the occurrence of pneumonia and/or atelectasia on the second postoperative day in patients who received pancuronium for muscle relaxation during surgery. Positive thoracic radiography was associated with lower TOF ratios (0.65 ± 0.16) than negative radiography (TOF ratio 0.81 ± 0.14).¹⁷¹ In the Netherlands, an analysis of approximately 800,000 anesthetics revealed an 8.8/10,000 24 h mortality rate and emphasized the benefit of antagonism of neuromuscular block, which significantly and independently reduced mortality.¹⁷² Murphy et al reported critical respiratory events requiring re-intubation in 0.82% among 7459 patients due to hypoxia and upper airway obstruction in whom the postoperative TOF ratio was 0.62 ± 0.3 .¹⁷³ A recently published investigation identified intermediate duration NMBAs as an independent risk factor for postoperative respiratory complications in a patient population including 57,000 anesthetics. When re-intubation was necessary due to desaturation, pulmonary edema, atelectasia and aspiration, the mortality increased 90 fold.¹³⁶ Other studies support the findings that TOF ratios <0.7 at extubation are more often (35%) associated with positive thoracic radiology of atelectasia, pneumonia or both than TOF ratios >0.7 (5%).¹⁷⁴

4.3.3 The incidence rate of PORNB

The recognition that NMBAs with a long duration of action are responsible for postoperative respiratory complications brought to the fore the use of intermediate duration relaxants, such as vecuronium, rocuronium, atracurium and cis-atracurium, prevailing in clinical practice today. However, as mentioned above, the expected reduction of PORNB with the use of these agents has not become a reality. In a meta-analysis comparing PORNB after long- and intermediate-acting drugs, Naguib et al demonstrated that no significant difference occurred between them when TOF <0.9 was the criterion.¹⁷⁵ Regarding published data for the last 10 years, the incidence rate of PORNB varies between 3.5 to 88% with an average of 38%.¹⁵² That said and as demonstrated by several investigators, using intermediate NMBAs does not prevent PORNB.^{48, 176, 177} Indeed, the duration of

action of these relaxants is unpredictable and drug interactions, low body temperature, electrolyte imbalance, age and deficiencies in organ functions may influence the speed of offset of effect. We also measured large variations in the duration of rocuronium, in particular when administered together with sevoflurane anesthetic (see chapter 3.6.1). Thus, using intermediate-acting relaxants *per se* does not mean an absence of PORNB and further measures are required to avoid this complication. Ideally, clinical tests should allow excluding or confirming PORNB at the end of the interventions. However, head-lifting, leg-lifting, hand grip or tongue protrusion tests are not sensitive and not specific enough to achieve this aim. Kopman et al. demonstrated that lifting of the head for 5 s was successful at TOF ratios 0.62 on average, similarly to leg-lifting (TOF 0.59).¹⁷⁸ The “tongue depressor” test was the most successful at TOF ratios of 0.86 on average.¹⁷⁸ Cammu et al. reported low sensitivity (0.18 to 0.35) and specificity (0.78 to 0.89) of these tests compared to TOF ratio 0.9.¹⁷⁹ Although many anesthetists rely on clinical evaluation for antagonism, appropriate assessment of PORNB requires objective neuromuscular monitoring. With acceleromyography, normalized TOF ratio 0.9 can be regarded as equivalent to 0.9 TOF ratio measured with mechanomyography, the gold standard of neuromuscular monitoring.^{180, 181} Data are divergent with regard to the question whether monitoring decreases the incidence of PORNB. By contrast to Baillard et al. who reported a decrease from 62% to 3%,¹⁸² Naguib et al. reported no difference in the occurrence of PORNB, irrespective of whether monitoring was or was not used.¹⁷⁵ Murphy achieved reduction of PORNB from 50% to 14.5% by using neuromuscular monitoring.¹⁸³ When PORNB has been diagnosed using neuromuscular monitoring, it can be adequately antagonized and, thus, theoretically, the related complications should be avoided. In our clinical practice, neuromuscular monitoring is regularly used and the reversal of residual NMB is based on the degree of the block. The education of the residents in our department comprises the use of neuromuscular monitoring and evaluation of its results. A description of quantitative monitoring can be found in chapter 3.1 of this review. Table 5 provides an overview of the clinical signs of PORNB at different acceleromyographic TOFR values.

Table 5. Clinical signs and symptoms of PORNB at different TOFR values (personal contribution).

Clinical signs	TOFR 0.5	TOFR 0.8	TOFR 1.0
Tidal volume	normal	normal	normal
Forced vital capacity	rather reduced	rather normal	normal
Swallowing	major impairment	impaired	rather normal
Upper airway integrity	major impairment	impaired	rather normal
Acute hypoxic respiratory response	often impaired	rather normal	normal
Subjective symptoms	significant	rather present	rather absent

TOFR: train-of-four ratio.

5. MISCELLANEOUS DRUG INTERACTIONS WITH NMBAS

Drugs administered to patients undergoing anesthesia may complicate the use of NMBAs. The various sites of interaction include action on the motor nerve conduction, ACh synthesis and release, sensitivity of motor endplate to ACh and the ease of propagation of motor endplate potential. In addition, many drugs affect the pharmacokinetics of NMBAs. Numerous substances and therapeutics have been found to interact with NMBAs, although only a few of these interactions are clinically relevant. Familiarity with these agents is important for patient safety reasons, since the dose regimen of the relaxants and their reversal has to be adapted accordingly so as to avoid overdoses or insufficient relaxation during surgery, as well as to prevent PORN. In order to try to obtain an overall picture without presenting a non-informative list, we considered the mechanisms of action and the most relevant interactions in addition to those already discussed above (magnesium, volatile agents, local anesthetics, adrenaline, etc.).

5.1 Plasma cholinesterase inhibitors

Succinylcholine and mivacurium are metabolized by the plasma cholinesterase enzyme and the deficit of the enzyme or its inhibition potentiate the effect of these relaxants. Cyclophosphamide, ecothiopate iodide, metoclopramide, ester-type local anesthetics, organophosphate insecticides, propanidid, tacrine and trimethaphane possess enzyme inhibitory effects.⁷ Pancuronium and neostigmine are also known to decrease the activity of pseudocholinesterase.¹⁸⁴ In hepatic cirrhosis, the production of plasma cholinesterase is lessened and the effect of succinylcholine and mivacurium is enhanced.¹⁸⁵ In patients with severe postoperative infections, plasma cholinesterase is decreased, similar to patients with cirrhosis. The clinical importance of this finding has still to be investigated.¹⁸⁶

5.2 Intravenous anesthetics

Thiopental may cause a fall in cardiac output with a prolongation of the onset of effect of the relaxant administered immediately thereafter. Induction agents that produce less hemodynamic depression, such as etomidate, are less likely to alter the onset time of NMBAs. Propofol produces flaccid areflexia, which facilitates tracheal intubation, particularly when used together with rocuronium. However, it is not the result of drug interaction, but rather an independent characteristic of propofol. Otherwise, propofol does not exert any effect on neuromuscular transmission or block and can be used as a control for studying interactions of other drugs with NMBAs, such as volatile anesthetics. Benzodiazepines do not affect neuromuscular transmission and cause little pharmacokinetic change by circulatory effect.¹⁸⁷ Etomidate and ketamine are considered not to interact with NMBAs in a clinically significant manner.¹⁸⁸ Many intravenous anesthetic agents are believed to possess slight AChR channel-blocking propensity, resulting in an increase in sensitivity to ACh. On the other hand, they diminish the transmitter release to some extent, resulting in a balance in the final effect.¹⁸⁹

5.3 Antibiotics

Following large doses or prolonged use of antibiotics, significant interaction with NMBAs may occur. Aminoglycoside antibiotics have long been recognised as powerful potentiators of non-depolarizing NMBAs and as a cause of prolonged paralysis that is not reversible by neostigmine. This is due to their effect at the motor nerve terminal through inhibition of the transmitter release similar to magnesium. Indeed, electrophysiological imaging obtained with TOF or tetanic stimulation during antibiotic block fade is not observed, but the strength of the muscle contractions diminishes and depressed twitch responses of equal height appear. This indicates that

presynaptic nAChRs are not involved and the mechanism may rather be attributed to Ca^{++} channel block and postsynaptic membrane stabilisation.¹⁹⁰ All aminoglycoside antibiotics potentiate the effect of non-depolarizing NMBAs and neostigmine reversal is not effective, but the block may respond to Ca^{++} administration and 4-aminopiridine.¹⁹¹ In addition to aminoglycoside antibiotics, lincosamide antibiotics (clindamycin, lyncomycin) are also known to potentiate NMB. Clindamycin causes endplate ion channel blockade and interacts synergistically with gentamicin, which acts presynaptically.¹⁹² Penicillin and cephalosporin are devoid of neuromuscular blocking effects.

5.4 Antiarrhythmic drugs

Quinidine potentiates the non-depolarizing NMB and calcium channel blockers theoretically may also enhance the effect of muscle relaxants, but the clinical significance of this interaction is marginal. Magnesium sulfate is also used as an anti-arrhythmic substance during perioperative care and its interaction with NMBAs has been described above. The effect of magnesium on neuromuscular transmission can be attenuated, but not reversed by calcium administration.

5.5 Corticosteroids

There have been reports on resistance to NMBAs in patients receiving chronic corticosteroid therapy, although the mechanism is not entirely clear. Pre- and postsynaptic sites are supposed to be involved in the development of resistance to NMBAs, including increased ACh synthesis and postsynaptic receptor channel block. Critically ill neuropathy may develop in ICU patients treated with muscle relaxants and corticosteroids.

5.6 Anticonvulsants

Long-term phenytoin treatment has been reported to cause resistance to steroidal NMBAs by increasing the sensitivity of postsynaptic receptors to ACh through receptor upregulation. However, its metabolite depresses presynaptic ACh release and may enhance the block.⁷

5.7 Other drug interactions

Furosemide may increase the renal excretion of NMBAs, apart from succinylcholine, mivacurium, atracurium and cis-atracurium, and may result in a more rapid recovery from the block. There have been occasional reports of resistance to non-depolarizing NMBAs in patients under atenolol and propranolol treatment due to their hemodynamic effect. Aminophylline has been reported to antagonize non-depolarizing block by interfering with ACh synthesis and release through cAMP-related mechanisms. Lithium carbonate in high concentration decreases ACh release and causes magnesium-type potentiation of non-depolarizing NMBAs.⁷ Dantrolene, a drug used in the treatment of malignant hyperthermia, potentiates the effect of NMBAs by blocking intracellular Ca^{++} release in the muscle cell and thereby decreasing the force of muscle contractions. Table 6 summarizes the most important drug interactions with neuromuscular blockade.

Table 6. Summary of the most important drug interactions with neuromuscular blockade (adapted from Feldman et al.).⁷

Drugs enhancing the effect of muscle relaxants	Drugs decreasing the effect of muscle
Inhaled anesthetics: desflurane, sevoflurane, isoflurane, halothane	Phenytoin
Magnesium	Carbamazepine
Antibiotics: aminoglycosides, clindamycin, vancomycin	Ranitidine
Plasma-cholinesterase inhibitors: cyclophosphamide, ecothiopate iodide, metoclopramide, ester-type local anesthetics, organophosphate insecticides, propanidid, tacrine, trimethaphane	Atenolol, propranolol
Antiarrhythmic drugs: quinidine, β -blockers, calcium channel antagonists, procainamide	Furosemide
Adrenaline	Aminophylline, caffeine
Lithium	Corticosteroids
Dantrolene	Anticholinesterases

5.8 Body temperature

Hypothermia is frequently encountered during anesthesia and increases the effect of non-depolarizing NMBAs by slowing their metabolism and by direct effects on muscle contractility. It significantly reduced the plasma clearance of rocuronium without changing its volume of distribution.¹⁹³ In humans, in the absence of neuromuscular blocking drugs, a reduction of the twitch response by 2–10% per 1°C reduction in muscle temperature has been reported.¹⁹⁴ As a rule, a 2°C reduction in body temperature doubles the duration of neuromuscular blockade.¹⁹⁴ A surface temperature >32°C at the monitoring arm is necessary in order to avoid misinterpretation.¹⁹⁵ Neostigmine reversal of vecuronium-induced neuromuscular block, is significantly delayed by hypothermia, even when administered at 10% spontaneous recovery.¹⁹⁶ With sugammadex, a deep rocuronium-induced NMB might be securely reversed during mild hypothermia, taking an additional 46 s for recovery in the hypothermic group.¹⁹⁷ Maintaining normal body temperature and neuromuscular monitoring during surgery and anesthesia are essential to prevent PORN.

6. PERSONAL WORK IN THE DOMAIN OF DRUG INTERACTIONS AND PERIOPERATIVE PATIENT CARE

Table 7 and 8 summarize our achievements in the domain of drug interactions with neuromuscular blockade and attempts to improve patient safety during the perioperative period. Table 9 lists ongoing research projects in the field of NMBAs and neuromuscular monitoring.

Table 7. Summary of publications: 2007-2017.

Issues	Publications	Conclusions
Bronchoaspiration	■ <i>Czarnetzki C et al</i> : Erythromycin for gastric emptying in patients undergoing general anaesthesia for emergency surgery: A randomized clinical trial. JAMA Surg 2015; 150:730-7	■ Erythromycin increased the proportion of clean stomach and decreased the acidity. It was more effective in non-trauma patients.
Airway management	▲ <i>Lysakowski C, Suppan L, Czarnetzki C et al</i> : Impact of the intubation model on the efficacy of rocuronium during rapid sequence intubation: systematic review of randomized trials. Acta Anaesthesiol Scand 2007; 51:848:57	▲ For an alternative to succinylcholine, a true RSI model with rocuronium should be used.
Time course of neuromuscular block	■ <i>Czarnetzki et al</i> : Time course of rocuronium-induced neuromuscular block after pre-treatment with magnesium sulphate: a randomized study. Acta Anaesthesiol Scand 2010; 54:299-306	■ Magnesium sulfate reduced the onset time by 35% and prolonged the duration by 25%. This may facilitate intubation.
	▲ <i>Czarnetzki et al</i> : Intravenous lidocaine has no impact on rocuronium-induced neuromuscular block: randomized study. Acta Anaesthesiol Scand 2012; 56:474-81	▲ Effect of standard intubation dose of rocuronium is not influenced by the intravenous infusion of lidocaine.
Antagonisation of residual neuromuscular block	■ <i>Czarnetzki et al</i> : Efficacy of sugammadex for the reversal of moderate and deep rocuronium-induced neuromuscular block in patients pretreated with magnesium: a randomized controlled trial. Anesthesiology 2014; 121:59:67	■ Pretreatment with 60 mg/kg magnesium sulfate does not decrease the efficacy of sugammadex reversal.
Hypersensitivity to rocuronium and NMBAs	▲ <i>Spoerl D, D'incan S, Roux-Lombard P, Harr T, Czarnetzki C</i> : Non-IgE-dependent hypersensitivity to rocuronium reversed by sugammadex: report of three cases and hypothesis on the underlying mechanism. Int Arch Allergy Immunol 2016; 169:256-62	▲ Three cases of anaphylactoid reactions after rocuronium rapidly resolve after sugammadex injection.
	■ <i>Spoerl D, Nigolian H, Czarnetzki C, Harr T</i> : Reclassifying anaphylaxis to neuromuscular blocking agents based on the presumed patho-mechanism: IgE-mediated, pharmacological adverse reaction or an "innate hypersensitivity"? Int J Mol Sci 2017 (<i>in press</i>)	■ Mas-related G-protein coupled receptor member X2 is responsible for anaphylactoid reactions.

Table 8. Summary of 3rd year medical student master thesis and dissertation for the diploma in Anesthesia (articles for the submission in peer reviewed journals are in redaction).

Issues	Publications	Conclusions
Rapid sequence induction	▲ <i>Giffa M et al.</i> : The optimal dose of succinylcholine for rapid sequence induction. A systematic review and meta-analysis. Dissertation for the diploma in Anesthesia. Faculty of Medicine of Nancy and Geneva 2015.	▲ Compared with 1.0 mg/kg-1, succinylcholine 2.0 mg/kg-1 provides significantly excellent intubation conditions more often. Apnea times are shortened with regimens <1.0 mg/kg-1, but the risk of unacceptable intubation conditions was significantly increased with doses lower than 0.5 mg/kg.
	■ <i>Robin M et al.</i> : Rapid sequence intubation with magnesium-rocuronium compared with succinylcholine - a randomized clinical study. Dissertation for the diploma in Anesthesia. Faculty of Medicine of Nancy and Geneva 2017.	■ Magnesium sulfate pre-treatment before a standard intubation dose of rocuronium produces identical intubation conditions for RSI compared with succinylcholine with less adverse effects.
Volatile anesthetics and rocuronium interaction	▲ <i>Chaix E</i> : The impact of total intravenous propofol anesthesia versus isoflurane and sevoflurane anesthesia on the spontaneous recovery from rocuronium-induced neuromuscular block: a retrospective cohort study. 3rd year medical student master thesis. Faculty of Medicine of Geneva 2017	▲ Compared to propofol, isoflurane and sevoflurane anesthesia significantly extended the duration of rocuronium-induced neuromuscular block. The effect was most pronounced under sevoflurane anesthesia with the highest variability.

Table 9. Summary of accepted protocols and ongoing research projects.

Issues	Publications	Conclusions
Neuromuscular monitoring	■ The validity and tolerability of awake calibration of the TOF Watch SX® Monitor: An interventional prospective single-center study. <i>Cantonal ethics committee of Geneva approval 6.6.2017 (CCER 2017-00195).</i>	■ The primary objective is to validate the measurements of the TOF Watch SX® monitor calibrated in awake patients by comparing them with the measurements obtained with the TOF Watch SX® monitor calibrated after anesthesia induction (gold standard). The secondary objective is to evaluate the tolerability of the awake calibration process of the TOF Watch SX® monitor.
	▲ The comparison of the TOF Cuff Monitor® with the TOF Watch SX® Monitor: an observational prospective single-center study. <i>Cantonal ethics committee of Geneva approval 15.5.2017 (CCER 2017-00415).</i>	▲ The objective of this study is to validate the recovery parameters of neuromuscular block obtained with the TOF Cuff® monitor with those obtained with the TOF Watch SX® monitor (reference).

**Reversal with
sugammadex vs
neostigmine**

■ Interaction between intravenous magnesium sulphate and neostigmine or sugammadex for the reversal of a rocuronium-induced neuromuscular block - a randomized, double blinded, electrophysiological study.

Cantonal ethics committee of Geneva approval 2.2.2017 (CCER 2016-00018); Swissmedic approval pending.

■ The primary objective of the study is to show that after reversal with sugammadex, there is no or only very little re-occurrence of neuromuscular block after a magnesium perfusion. After reversal with neostigmine, we suspect that there will be a re-occurrence of neuromuscular block.

7. CONCLUSIONS

Curare, a poison used for hunting and as a weapon, was discovered many centuries ago by the Indians living in the dense jungles of South America. Today, curare is an irreplaceable part of modern anesthesia for muscular relaxation at intubation and during surgery. Its use in medicine nearly came to an abrupt end when it was discovered that patients who died from its use would have survived if they had not received curare during anesthesia. It is only due to the intense research conducted by dedicated clinical investigators, scientists and technicians that curare as an NMBA is still in use and given to millions of patients worldwide. Today, our newer NMBAs are shorter-acting with a more favorable side effect profile and we have finally an antagonist at hand, which can terminate the action of rocuronium at any given moment of anesthesia. Modern quantitative neuromuscular monitoring has become a standard of clinical practice. However, NMBAs still remain a dangerous and deadly weapon in the hands of clinicians and a threat to patient safety when expected or unexpected drug interactions lead to a prolongation or recurrence of its effect.

A cornerstone to its safe use is the understanding of the concept of neuromuscular reserve. After spontaneous recovery from neuromuscular block, patients still remain myasthenic as long as the neuromuscular reserve recovers. The remaining molecules on the NMJ will be of relevance when drugs are given that influence the liberation of ACh or interact directly with pre- and postsynaptic ACh receptors. Full instauration of clinical neuromuscular block happens rapidly after only a few minutes. However, in general, recovery to the end of manifest block takes hours and the duration of recovery of the neuromuscular reserve even longer, but this has never been investigated in detail. When we think of safety related to the application of NMBAs, we must keep in mind this “iceberg” phenomenon of neuromuscular block and look at the submerged part of the iceberg.

The aging population is the most significant trend of the 21st century worldwide. Thus, patients of the anesthesiologist are becoming older, with multiple chronic diseases and an unending list of medications. These fragile patients undergo complex and sometimes risky interventions. Given the increased potential for drug interactions with NMBAs, we have to be constantly vigilant about potential harm to these patients. Much has been discovered in the field of NMBAs, but there remain many issues to be investigated and elucidated. Our knowledge increases daily about the complex physiology of the NMJ and the ultimate quest is to find the ideal neuromuscular agent, which reacts very fast with an ultra-short action of some minutes and devoid of any side effect. Nevertheless, we should keep in mind that we have already achieved an important cornerstone in the safe application of NMBAs because we are able to inactivate rocuronium with sugammadex. In this way, we can not only terminate the clinical effect of NMBAs, but also restore the neuromuscular reserve of our patients and preserve them from possible drug interactions. The safe application of NMBAs needs fully-trained anesthesiologists who have a perfect knowledge of the medications they use, are aware of possible drug interactions and side effects, and are able to correctly use quantitative neuromuscular monitoring. The role of our teaching hospitals is to favor clinical research in the field of NMBAs in order to foster progress in medicine, to improve patient safety and quality of care, and form clinical teachers with a profound knowledge in this field.

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