Abstract: Non-depolarizing neuromuscular blocking agents (NMBAs) produce neuromuscular blockade by competing with acetylcholine at the neuromuscular junction, whereas depolarizing NMBAs open receptor channels in a manner similar to that of acetylcholine. Problems with NMBAs include malignant hyperthermia caused by succinylcholine, anaphylaxis with the highest incidence for succinylcholine and rocuronium, and residual neuromuscular blockade. To reverse these blocks, anticholinesterases can act indirectly by increasing the amount of acetylcholine in the neuromuscular junction; sugammadex is the only selective relaxant binding agent (SRBA) in clinical use. At all levels of blockade, recovery after sugammadex is faster than after neostigmine. Sugammadex potentially also has some other advantages over neostigmine that are related to neostigmine's increase in the amount of acetylcholine and the necessity of co-administering anticholinergics. However, hypersensitivity reactions, including anaphylaxis, have occurred in some patients and healthy volunteers after sugammadex and remain an issue for the FDA.

In the near future, we may see the emergence of new SRBAs and of easier-to-use technologies that can routinely monitor neuromuscular transmissions in daily practice. The nature of the effect of sugammadex on freeing nicotinic acetylcholine receptors located outside the neuromuscular junction from NMBAs is unknown. Moreover, it is uncertain whether the full removal of the competing antagonists (by SRBAs) at the neuromuscular junction impacts the efficiency of acetylcholine transmission. In a recent pilot study in healthy volunteers, we demonstrated increased electromyographic diaphragm activity after sugammadex, compared to neostigmine. Further research is needed to elucidate the role of NMBAs and their reversal agents in the central control of breathing, respiratory muscle activity, and respiratory outcomes.

Key words: Diaphragm; neuromuscular block; neuromuscular blocking agents; nicotinic acetylcholine receptor; sugammadex.

Pharmacology of neuromuscular blocking agents (1, 2)

At the adult human neuromuscular junction, two different populations of nicotinic acetylcholine receptors can be found, as follows: a α₁β₁εδ receptor at the postsynaptic (muscular) portion of the neuromuscular junction and a α₁β₁-subunit-containing presynaptic (neuronal) nicotinic receptor. Non-depolarizing neuromuscular blocking agents (NMBAs) produce a neuromuscular blockade by competing with acetylcholine for the postsynaptic α subunits; each of the two α subunits contains an acetylcholine-binding site. Succinylcholine produces a prolonged depolarization resulting in the decreased sensitivity of the postsynaptic receptor, such that there is no progression of the action potential across the muscle membrane.

Succinylcholine is the only available depolarizing NMBA and provokes a rapid onset and short duration of action by rapid hydrolysis (butyrylcholinesterase). Non-depolarizing NMBAs can be categorized by chemical class (steroidal, benzylisoquinoline, other) or by the onset or duration of action of equipotent doses (short-acting, intermediate-, long-acting). The speed of onset is inversely proportional to the potency of the non-depolarizing NMBAs; that of rocuronium is low so that its onset is more rapid than in the other non-depolarizing NMBAs. Neuromuscular blockades have a faster onset and recover more quickly in more centrally located muscles, such as the diaphragm and laryngeal adductors, than in the more peripherally located adductor pollicis, for example. Long-acting NMBAs are primarily eliminated, unchanged, via renal excretion, whereas intermediate-acting NMBAs have multiple pathways of breakdown or elimination. Mivacurium is almost entirely metabolized by butyrylcholinesterase.
PROBLEMS WITH NMBAs

Although it is a critical disorder, the incidence of malignant hyperthermia caused by succinylcholine is low. The overall prevalence of malignant hyperthermia due to anesthesia in surgical patients treated in New York State hospitals is approximately 1 per 100,000 (3). In a recent issue of The Association of Anesthetists of Great Britain and Ireland (AAGBI) safety guidelines, it appears that, in the UK, approximately 60% of anesthesia-related anaphylaxis is caused by NMBAs (4). It is well known that, in a country such as Denmark, the causes of anaphylaxis during anesthesia are completely different, with <10% being attributed to NMBAs (5). Some of the reasons behind these huge differences in incidence between populations may lie in the use of pholcodine (6, 7). Based on the different studies by the French group of Laxenaire, it has become clear that the ratio between the number of reactions and number of patients exposed is the highest for succinylcholine and rocuronium but the lowest for cisatracurium (8). Of the retrieved cases of NMA hypersensitivity in a recent analysis, 4.1% were fatal. Obese males with a history of cardiovascular disease receiving ongoing beta-blocker treatment and undergoing surgery in an emergency setting were at high risk of a fatal outcome after NMBAs-induced anaphylaxis (9). In the UK, several cases of allergic reactions linked to anesthetics have been identified, but only 35 anaphylaxis-related deaths were recorded there over the past 10 years, among which 19 were attributed to succinylcholine (4). This and other drawbacks of the drug kept the discussion alive regarding whether succinylcholine should ever disappear in anesthetic clinical practice. Several experts have discussed this issue in editorials, and many concluded that succinylcholine still has a place in emergency procedures (such as an emergency cesarean section under general anesthesia) or in cases where a difficult airway is expected and needs to be managed (10). Apart from the high dose of rocuronium, there is thus far no real alternative for muscle relaxation during rapid sequence induction. Rapacuronium (Org 9487) had a fast onset due to its low potency and a short-to-intermediate duration of action. It is eliminated mainly by the liver and, to a lesser extent, the kidney. However, side effects, such as a decrease in blood pressure and bronchospasms, made it necessary to be withdrawn from clinical use just 19 months after it had been approved. A potential mechanism by which rapacuronium may potentiate bronchoconstriction is by blockade of M2 muscarinic receptors on prejunctional parasympathetic nerves, leading to increased release of acetylcholine and thereby resulting in M3 muscarinic receptor-mediated airway smooth muscle constriction (11).

RESIDUAL NEUROMUSCULAR BLOCKADE

Naguib et al. showed in a meta-analysis that the pooled rate of postoperative residual curarisation (PORC) when considering TOF<0.9 as the cutoff value for PORC was 0.4 for intermediate-acting NMBAs (12). When an intermediate-acting NMBA was given only for tracheal intubation, Debaene et al. showed that 45% of their patients had a TOF<0.9 in the post-anesthesia care unit (13). Following repeated doses of intermediate-acting vecuronium, 42% of patients had a TOF<0.7 (14). After the shorter-acting mivacurium, more than 20% of patients had PORC (15). The huge variation in response to NMBAs between individuals may partly explain these important incidences of PORC. A study by Arai et al. showed that the durations of action (range, min) were 37-81 for cisatracurium, 35-137 for vecuronium, and 33-119 for rocuronium (16). The variability in responses between individuals is partly genetically determined and partly by age, possible organ dysfunction, female gender, and the use of volatile anesthetic agents, among others. Moreover, the margin of safety for NMBAs is small. For a fraction of occupied receptors varying between 0.7 and 0.9, the clinical effect, i.e., the neuromuscular blockade, goes from zero to maximal (17).

RESIDUAL NEUROMUSCULAR BLOCKADE HAS A CLINICAL IMPACT ON THE PATIENT

Because randomized controlled trials on PORC are ‘difficult’ to perform, it becomes correspondingly complicated to convince clinicians who believe PORC cannot cause harm of opposing results. In this context, the fact that parachutes reduce the risk of injury after jumping out of an airplane, despite the effectiveness of this strategy never having been proven by randomized controlled trials, is often referenced. Moreover, there are many causes of postoperative critical respiratory events other than PORC alone, including the lingering effects of opioids, age, emergency surgery, long duration of surgery, abdominal surgery, and others, such as body mass index (BMI) and vascular surgery, both of which have been recently described (18-20).
In 2012, Grose-Sundrup et al. published a propensity-matched retrospective analysis of patients who received or did not receive intermediate-duration NMBAs. In their retrospective study, NMBA use was associated with a 40% increase in the relative risk of reintubation, which itself increased the risk of hospital mortality 90-fold (21). Far earlier, Eriksson et al. showed that the hypoxic ventilator control was impaired at partial neuromuscular blockade (TOF 0.7) (22), whereas Berg et al. showed that the risk of pulmonary complications following surgery increased with age and was considerably greater when patients had a TOF < 0.7 (18). Fortunately, we also have access to several nice volunteer studies that have confirmed the clinical consequences of PORC (defined as a TOF < 0.9), including the following: upper airway obstruction and impaired ability to swallow, impaired coordination of pharyngeal muscles and reduced upper esophageal muscle tone, increased risk of aspiration, and unpleasant symptoms of muscle weakness (23-25). Finally, PORC also affects postoperative pulmonary function tests. Interestingly, in that study, the authors showed that, regardless of the presence of PORC, anesthesia itself resulted in postoperative reductions to the peak expiratory flow (PEF) and forced vital capacity (FVC), compared with the preoperative status. However, the postoperative PEF and FVC reductions were greater in patients with PORC than in those without PORC (26).

**Neuromuscular Transmission is Insufficiently Monitored in Daily Clinical Practice**

In those patients for whom only ‘clinical criteria’ (e.g. head lift, leg lift, hand grip) were considered before tracheal extubation, more than 40% had a TOF < 0.9 (15). Moreover, the sensitivity of these different ‘clinical tests’ has been found to be very low. Still, in general, neuromuscular transmission monitoring is only rarely used. In a study of 12 large anesthesia departments in the UK, TOF monitors were only routinely used in 9% of cases; in 62% of cases, the monitors were never used (27). Although these data are from 2007, they may still represent the actual practices in many hospitals. In a recent study from a Brazilian group, the most important rule of thumb clinicians seem to use to decide whether a neuromuscular block should be antagonized was found to be the ‘time since the last NMBA dose’, followed by the ‘breathing pattern’ and the ‘muscular strength’. The TOF only took the 7th place (28). However, in a French study between 1995 and 2004, the authors found that there was a significant decrease in PORC in the recovery room when they increased the use of neuromuscular transmission monitoring and/or antagonization of blocking (29). In our institution, likewise, the incidence of PORC after NMBAs strongly decreased from 39% in 2005 to 14% in 2011 (15, 20).

**Reversal Agents: Anticholinesterases and Selective Reversal Binding Agents**

The mechanism of action of sugammadex, which is the only selective relaxant binding agent (SRBA) in clinical use, is the chemical encapsulation of the NMBA molecule; sugammadex does not directly interact with the cholinergic system. Neostigmine, the anticholinesterase most frequently used, acts indirectly by increasing the amount of acetylcholine in the neuromuscular junction. The effectiveness of anticholinesterases depends on the degree of blockade recovery at the moment it is administered. It can only be effective when administered at the moment at which 2-4 twitches are visible on the TOF monitor (30). The doses of neostigmine need to be adapted depending on the degree of recovery, from 20-50 (70) µg/kg (31, 32). The drug is very cheap and has existed since 1931. Neostigmine may have adverse effects by itself and in occasions of co-administration with anticholinergics. However, these drawbacks should not be exaggerated; as is evident in the controversial literature on many of those issues, this drug has been used widely without too many clinical problems (33). A deep block cannot be antagonized with neostigmine; in such cases, one must wait until an appropriate level of blocking is reached before neostigmine can be administered (at least 2 visible TOF twitches) (30).

At all levels of blockade, recovery after sugammadex is faster than after neostigmine, including deep and moderate or shallow blocks (34). The most impressive action of sugammadex is surely its capability to reverse a deep block (35). It is possible that sugammadex has certain other advantages over neostigmine, which might be related to neostigmine’s increase in the amount of acetylcholine and necessity for the co-administration of anticholinergics. However, so far, there is insufficient literature to support these ‘other advantages’. For example, the difference in the percentage change in heart rate after the administration of sugammadex vs. neostigmine/glycopyrrolate is only apparent in the first 10 min after administration; it could not be shown.
that neostigmine/glycopyrrolate attenuates the QT interval more so than sugammadex (36). Sugammadex should be given in a block-dependent-dose: 2 mg/kg when the TOF count is 2; 4 mg/kg for a block that recovered to at least a PTC of 1-2; and 16 mg/kg for reversal of a rapid sequence induction-dose of rocuronium (37).

**Why should the anesthetist prefer sugammadex over an anticholinesterase?**

At all levels of blocking, sugammadex has a faster onset-to-peak; however, due to pharmacoeconomic reasons, it is hard to defend the use of sugammadex for levels of blockage that could easily be reversed with an anticholinesterase. Theoretically, sugammadex could be advantageous in those specific patients for whom muscarinic effects (or the anti-muscarinic effects of the co-formulation) could cause problems. However, so far, there are only limited data that could ‘isolate’ patient populations deriving significant clinical (outcome) benefits from sugammadex instead of an anticholinesterase. Recently, a retrospective investigation of postoperative outcomes after the reversal of PORC in patients receiving sugammadex, neostigmine, or neither showed that sugammadex-reversed elderly patients with ASA physical status 3 and 4 showed reduced pulmonary complications relative to neostigmine-reversed or non-reversed patients (38). Another study on routine anesthetic practices showed that respiratory monitoring results and respiratory events in the post-anesthesia care unit tend to favor patients reversed with sugammadex relative to spontaneously recovered patients or those reversed with neostigmine; however, an important bias in that study emerged. In patients reversed with neostigmine, more abdominal surgeries were performed than in the other patients (20). Other authors showed that a deep intraoperative neuromuscular block (at the end reversed with sugammadex) may improve surgical conditions during laparoscopic surgery, compared with a moderate neuromuscular blockade (39-41). One study (40) only included 24 patients; a more recent study (41) in 102 women of ASA physical status 1 or 2, was more convincing. However, an intraoperative, continued, deep neuromuscular blockade is rarely indicated and should never be an aim unto itself. Still, in the case of a ‘dose-time mismatch’ (shorter procedure than expected, short procedure after a rapid-sequence-dose of rocuronium, etc.), sugammadex is valuable as the sole reversal agent able to reverse deep neuromuscular blockades. The safe use of sugammadex in patients with neuromuscular disorders who require general anesthesia with neuromuscular blockades has been nicely shown (42). Finally, whether sugammadex can save a patient who received an intubating dose of rocuronium in a ‘cannot intubate, cannot ventilate’ situation, is far from guaranteed, as it takes time to collect and prepare the appropriate dose of sugammadex. Lingering effects of any co-administered hypnotics and opioids during the induction of anesthesia may also impair airway mechanisms (43, 44).

**Why should the anesthetist restrict the use of sugammadex?**

Until quite recently, certain sugammadex issues have remained unanswered, such as the possible drug interactions with sugammadex, QTc prolongation by sugammadex, sugammadex and renal failure, and muscle relaxation after sugammadex. However, most of these have been addressed and published in scientific papers over recent years. The manufacturer found that the interaction between 4 mg/kg sugammadex and a progestogen could lead to a decrease in progestogen exposure, potentially leading to a reduction in its effectiveness. Therefore, the administration of a bolus dose of sugammadex is considered to be equivalent to one missed daily dose of oral contraceptive steroids. Dr Kam et al. found that sugammadex 4 mg/kg does not cause clinically relevant QTc interval prolongation versus placebo when combined with propofol or sevoflurane (36). In a study investigating the dialysability of sugammadex and its complex with rocuronium in intensive care patients with severe renal impairment, reduction ratios indicated mean reductions of approximately 70% in the plasma concentration of sugammadex during the first dialysis episode and of 50% during sequential dialysis (45). However, as far as we know, sugammadex is not advocated by the manufacturer to be used in renal failure patients. Finally, the rapid re-onset of neuromuscular blockade can be achieved after a repeated dose of rocuronium 1.2 mg/kg as early as 5 min after sugammadex in healthy volunteers. In that study, the re-onset of the block took longer if the second rocuronium dose was < 25 min after sugammadex, and the duration of action of a second rocuronium dose increased with later repeated dose time points (46).

What remain to be addressed are the adverse effects of sugammadex. Hypersensitivity reactions,
including anaphylaxis, have occurred in some patients and healthy volunteers. In clinical trials of surgical patients, these reactions have been reported uncommonly; for post-marketing reports, the frequency is unknown, despite some case reports having been published (47). Hypersensitivity reactions remain an issue for the FDA, as the drug is still not approved by the US authorities to date. Interestingly, these reactions have occurred in patients with no prior exposure to sugammadex. A recent review identified 15 cases of hypersensitivity following sugammadex administration. Thirteen cases were with routine doses of sugammadex; two cases with higher doses than the approved ones (48). Second, the administration of sugammadex is associated with a dose-related, limited and transient prolongation of APTT and PT(INR) that is unlikely to be of clinical relevance (49). Cost price also remains a crucial factor. In that context, we are convinced that it is naïve to think that any time saved in the reversal of the blockade would translate to extra surgical time to perform more cases. Further, one must remain cautious towards the individual onset time of sugammadex and not become overconfident in its effectiveness. Thus, one should continue to monitoring the neuromuscular block, even when using sugammadex. As far as we know, the only reports that show PORC after sugammadex are those cases where monitoring was not used (20, 50). Indeed, extreme (and unexpected) maximum onset times have been described in studies, even among healthy subjects, showing that even sugammadex may have interindividual pharmacological variability (51).

DO NOT FORGET THE EVIDENCE

Moving away from the discussion as to whether sugammadex should be used, certain simple measures can be used to prevent PORC. First, it is critical to use the smallest amounts of NMBAs possible; an intubating dose of 2x ED95 should suffice for intubation and for most surgical procedures. Although this approach results in a somewhat increased onset time, even smaller amounts (than the 2x ED95 dose) may be used if the NMBA is only required for intubation of the patient’s trachea. Longer-acting NMBAs should be avoided; as far as we know, pancuronium is no longer on the Belgian market. There is little evidence supporting the use of continuous infusions of NMBAs. Extremely high incidences of PORC were recorded after continuous infusions of rocuronium and cisatracurium (52); cisatracurium is most likely the preferred choice for any exceptional indication of prolonged muscle relaxation in the ICU (due to its particular non-organ dependent breakdown mechanism) (53). Even during cardiopulmonary bypass surgery, continued muscle relaxation is no longer withheld (54).

If it cannot be prevented, then PORC must be treated. Evidence-based management of residual blockade at the end of surgery was nicely described in a paper by Plaud et al., and NMT monitoring is crucial for decision-making (37). In our own in-hospital practice, we are somewhat more liberal towards the administration of neostigmine. Where Plaud et al. only administer neostigmine at the reappearance of 4 twitches on the TOF, we provide neostigmine from the moment that 2 twitches on the TOF are visualized at a 70 µg/kg dose. Provided that it is given in time, neostigmine administered at that dose and at that particular level of blocking has been shown to be effective (30). On the other hand, neostigmine-induced neuromuscular blockade may occur in patients who receive a fixed 2.5-mg dose as part of a routine vial-based reversal practice (55). Neostigmine 30 µg/kg is an appropriate dose if a patient has recovered to a block level of 4 equal responses to TOF stimulation (32). In our hospital, between 2009 and 2012, 3% of patients who received a NMBA for general anesthesia and planned to be extubated in the operating room received sugammadex. Such administrations occurred predominantly after spine neurosurgery, vascular surgery, and abdominal surgery; in > 70% of cases, it was administered at a 2 mg/kg dose (56).

WHAT CAN BE EXPECTED?

1. Beyond sugammadex

In the near future, we will see the emergence of new SRBAs, with calabadion most likely being the next agent of interest. Calabadion, an acyclic member of the family of Cucurbit[n]urils, is a new broad spectrum agent for the rapid and complete reversal of steroidal (rocuronium) and of benzylisoquinoline (cisatracurium) NMBAs. The structure of Calabion features a central glycoluril tetramer to create a C-shaped cavity suitable for binding to the hydrophobic steroidal nucleus, aromatic walls, and four sulfonate groups, promoting cation binding and enhancing solubility in water. Calabion has been tested in rats (57).
2. Beyond the TOF watch

For many years, little progress has been made in developing new technologies to monitor the neuromuscular blockade. Last year, the TOF-Cuff® was launched as an alternative for the TOF-watch (58). This new device integrates neuromuscular monitoring in a blood pressure cuff and does not require the installation of a separate sensing element to function. It stimulates the ulnar nerve at the level of the upper arm and records the resulting neuromuscular activity through the changes in pressure generated at the inner part of the cuff. Easier-to-use technologies can lower the threshold for anesthesiologists to routinely implement the monitoring of neuromuscular blockades in daily practice. Nevertheless, a full understanding of neuromuscular blockade reversal and PORC will always remain the basis of good clinical practice, regardless of technological advancements.

3. Beyond the neuromuscular junction

As mentioned earlier, NMBAs act at the neuronal nicotinic acetylcholine receptors as well. These receptors are located in various places in the human body. The best known site is on the neurons in the neuromuscular junction, where they provide a molecular basis for the fade in the TOF (2, 59). Furthermore, nicotinic transmission plays a key role in both the central and peripheral control of breathing, and the neuronal nicotinic acetylcholine receptors are expressed in the respiratory center in the brainstem and in carotid bodies, as well. At the central level, in the brainstem, NMBAs possess a centrally mediated inhibitory effect on breathing through these receptors (60). All NMBAs are highly charged molecules and normally do not cross the blood-brain barrier. Still, it has been demonstrated that some NMBAs can cross the blood-brain barrier when it has been disrupted, e.g., during brain surgery (61). This is true for rocuronium as well, as was proven by Fuchs-Buder et al. in 2004 (62). Nevertheless, the concentrations needed to produce a centrally mediated respiratory depression were around 1000-fold greater than those detected in the cerebrospinal fluid.

Peripheral, in the carotid bodies, nicotinic transmission is equally well documented, and NMBAs block nicotine-induced carotid body chemoreceptor responses in a dose-dependent manner (63). This inhibition of nicotinic acetylcholine receptors in the carotid bodies provides a molecular explanation of the reduced hypoxic respiratory response in patients with PORC (22, 64). Although these are interesting findings, more neurotransmitters and pathways link the carotid bodies with the brain, providing a back-up mechanism (65).

To our best knowledge, the effect of sugammadex on freeing those receptors located outside the neuromuscular junction from NMBAs is unknown. The control of respiration is a highly complex mechanism, and the interacting effects of hypnotics, opioids and NMBAs hinder the progression of clinical research in this domain.

4. Beyond TOF 0.9 and anticholinesterases

Research is ongoing to explore the potential benefits of sugammadex over anticholinesterases (or no reversal). We currently accept a TOF ≥ 0.9 as clinically acceptable, as decades of research have noted that muscle tone and activity baseline values have returned at this point. Nevertheless, both major and minor respiratory complications remain numerous after the use of NMBAs, even after strict compliance to the current standards of care (21). A subgroup analysis of this last study by Grosse-Sundrup et al., published later as a letter, showed a counterintuitive increase in respiratory complications after the use of neostigmine (66). The reasons behind these remarkable findings remain debatable. If all other reasons (e.g., lingering opioid effects or inadequacy in monitoring) can be ruled out, future research with SRBAs will have to evaluate whether reversal from a shallow block with anticholinesterases is as good as a reversal with a SRBA or as a spontaneous reversal.

After all, approximately 70%-75% of all nicotinic acetylcholine receptors in the neuromuscular junction remain occupied with the NMBa when TOF values are 0.9 during spontaneous or anticholinesterase-enhanced recovery (67). It is still unknown whether the full removal of the competing antagonists (by SRBAs) at the neuromuscular junction impacts the efficiency of acetylcholine transmission. One of the locations where neuromuscular transmission matters the most is at the level of the diaphragm. A link between diaphragm excursion and respiratory outcomes was first demonstrated in 1948 (68). Furthermore, neuromuscular transmission at the diaphragm plays an independent role in diaphragm function during loaded breathing (69). We have conducted a pilot study in healthy volunteers to study the electromyographic diaphragm activity during neostigmine- or sugammadex-enhanced recovery from neuromuscular blockade. Our study demonstrated greater electromyographic
diaphragm activity after sugammadex administration compared to neostigmine. The associated tidal volumes and post-extubation PaO₂ levels were higher in the sugammadex group (70). Figure 1 (A: neostigmine and B: sugammadex) contains screenshots of the ventilator during spontaneous breathing at the end of anesthesia, demonstrating this difference in electromyographic diaphragm activity.

**Conclusion**

For the first time, anesthetists have the possibility to free all nicotinic acetylcholine receptors in the human body from NMBAs. This result may have consequences for neuromuscular transmission mechanisms. Many opportunities lay ahead, and further research may well give us further insight into the roles that NMBAs and their reversal agents play in the central control of breathing, respiratory muscle activity, and respiratory outcomes.

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