Emerging considerations in the reversal of neuromuscular blockade and residual block

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ABSTRACT
Incomplete recovery following reversal of neuromuscular blockade can present as a clinical problem in surgical patients. Emerging pharmacologic solutions may prevent such adverse outcomes in the future. We briefly review two methods of pharmacologic reversal of neuromuscular blockade. Both methods of reversal are effective. However the early studies of the new compound, sugammadex has been shown to achieve a more rapid, stable reversal of steroidal based neuromuscular blocking agents compared to neostigmine. Due to the novel mechanism of action of this agent, sugammadex has been demonstrated to be effective even when administered during profound neuromuscular block, without evidence of recurarization.

Key words: sugammadex, Org 25969, cyclodextrin, rocuronium, cholinesterase inhibitor

Introduction
Spontaneous recovery from neuromuscular block occurs through redistribution, buffered diffusion, or metabolism of the neuromuscular blocking agent (NMBA) administered. Acetylcholinesterase inhibitors (e.g., neostigmine) are often given at the end of surgery to speed the rate of recovery from non-depolarizing NMBA. However, residual block may persist. In the absence of such reversal agents, residual paralysis may persist for 2 hours or more after the administration of an intermediate duration muscle relaxant. Concomitant use of magnesium, local anesthetics, antibiotics, and calcium channel blockers has also been shown to increase the risk of prolonged paralysis after reversal of neuromuscular blockade.

Residual block may be associated with serious adverse events, such as respiratory depression, pharyngeal dysfunction, hypoxemia and prolonged length of stay in the recovery room. While the use of acetylcholinesterase inhibitors may reduce these risks by accelerating reversal of neuromuscular blockade, they are themselves associated with unwanted effects resulting from muscarinic receptor activation. Co-administration of anticholinergic agents (e.g., glycopyrrolate) may attenuate these effects but at the potential cost of further side effects, such as tachycardia and QT interval prolongation.

Sugammadex (Organon, USA Inc.) is a new reversal agent currently under clinical investigation. A modified gamma cyclodextrin, sugammadex is a selective relaxant binding agent (SRBA) specifically designed to reverse the effects of the aminosteroidal non-depolarizing NMBA, rocuronium. Unlike the acetylcholinesterase inhibitors, sugammadex does not achieve reversal via competitive cholinergic mechanisms but, rather, acts non-competitively by forming a complex with rocuronium, thereby lowering its effective concentration. As a result, sugammadex does not require the co-administration of anticholinergic agents for the management of muscarinic side effects.

Pharmacology
Pharmacological considerations explain the clinical differences between the two agents with regard to the onset and stability of reversal. Acetylcholinesterase inhibitors are agonists that act indirectly to increase endogenous concentrations of acetylcholine. This excess acetylcholine competes with the non-depolarizing NMBA at the nicotinic receptor at the neuromuscular junction. At the same time, these agents inevitably increase the availability of acetylcholine at muscarinic receptors,
resulting in parasympathetic adverse effects such as bradycardia and hypersalivation. Furthermore, there is a relative "ceiling effect" with acetylcholinesterase inhibitors, such that some recovery of neuromuscular function is required prior to their administration. If these conventional agents are given to patient with a higher degree of neuromuscular blockade, inadequate reversal may ensue.

Sugammadex is a selective relaxant binding agent (SRBA) that is pharmacologically unrelated to conventional methods of reversal. Since its mechanism of action does not involve an endogenous increase in acetylcholine, reversal of neuromuscular block by sugammadex is not accompanied by the side effects associated with acetylcholinesterase inhibitors. Sugammadex acts, instead, by encapsulating the NMBA, lowering its effective concentration. By acting as a "pharmacologic sink", sugammadex prevents the interaction between the aminosteroidal NMBA and the nicotinic receptor at the neuromuscular junction. Due to the specificity of the sugammadex molecule, NMBA of the benzylisoquinolinium class are not antagonized.

**Clinical Trials**

Several clinical studies have illustrated the effectiveness of this mechanism of action for rapid reversal of rocuronium-induced neuromuscular blockade without evidence of recurarization. Efficacy was measured by acceleromyography (figure 1) and the time to achieve the train of four (TOF) ratio of 0.9 was the endpoint. Gijsenbergh et al. showed full reversal without recurarization within 2 min, when sugammadex 8mg/kg was administered 3 min after rocuronium 0.6mg/kg. Other studies have demonstrated similar efficacy with sugammadex at doses of 2.0 mg/kg or higher, administered at reappearance of T2 following rocuronium 0.6 mg/kg. The onset and stability of reversal with sugammadex appear to be related to several factors: the dose of NMBA administered, the timing of sugammadex administration in relation to NMBA administration, and the dose of sugammadex. In a dose-finding study by Groudine et al. (22), the two lowest doses of sugammadex (0.5 and 1.0mg/kg) were found to achieve inadequate reversal of profound neuromuscular block. Although there was some variability in effectiveness between the doses administered in this study, reversal of profound rocuronium-induced block was more successful with sugammadex ≥ 2 mg/kg. Low-dose sugammadex was also the topic of a recent case report which described a transient decrease in train of four (TOF) response after a small dose (0.5mg/kg) of sugammadex for reversal of neuromuscular block induced by rocuronium 0.9 mg/kg. Using the data from this patient, the investigators developed a simple pharmacokinetic-pharmacodynamic model of rocuronium, sugammadex and their interaction. Simulations using this model indicated that rebound of muscle relaxation may occur with sugammadex doses "in a limited critical range". The authors concluded that administration of sugammadex in a sufficiently large dose eliminates the possibility of muscle relaxation rebound.

In a direct comparison, sugammadex 4 mg/kg has been shown to reverse rocuronium-induced neuromuscular blockade more rapidly and effectively compared with neostigmine 70 μg/kg or edrophonium 1 mg/kg. It has also been demonstrated that reversal of neuromuscular block achieved with sugammadex does not depend on the type of anesthetic maintenance employed. Vanacker et al. studied reversal of rocuronium with sugammadex in patients receiving either propofol or sevoflurane, and found the recovery time of the TOF ratio to 0.9 to be comparable in both groups. In contrast, neostigmine has been shown to achieve slower reversal of rocuronium-induced block under sevoflurane compared to propofol anesthesia.

**Discussion**

Recovery of the TOF ratio to 0.9 prior to tracheal extubation has been clinically advocated as important for patient safety. Although the incidence...
of “recurarization” declined with the introduction of shorter acting NMBAs in the 1990s (29), residual curarization may still occur. (30) In order to avoid complications related to the use of muscle relaxants, precise assessment of neuromuscular transmission would be beneficial. (31,32) However, acceleromyography is not currently used routinely to determine a TOF ratio but remains primarily a tool for research. More conventional spot monitoring with TOF stimulation is unlikely to provide the clinician with an adequate assessment of peri-operative neuromuscular function. The availability of a reversal agent with predictable effectiveness, and which fully prevents residual block, is therefore highly desirable.

**Conclusions**

The pharmacological comparison described here illustrates the rapid recovery of neuromuscular function permitted by the novel mechanism of action of sugammadex. Studies have also demonstrated the ability of sugammadex to reverse profound neuromuscular blockade, such that timing of sugammadex administration is not an issue, as it is with the use of conventional reversal agents. The rapid reversal can be attributed to the stability of the complex formed between sugammadex and the aminosteroidal NMBA. In conclusion, with the arrival of sugammadex in clinical practice, residual neuromuscular block may become extinct as a clinical feature.

**REFERENCES**

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