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Literature Review

Articles That May Change Your Practice: Sugammadex

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Neuromuscular blocking agents (NMBAs) are typically used to facilitate tracheal intubation and mechanical ventilation and provide appropriate conditions for surgery. Prompt reversal of neuromuscular blockage is desired in some situations. Until recently, acetylcholinesterase inhibitors such as neostigmine were the only reversal agents available. These agents are often associated with bradycardia, bronchospasm, and other side effects because of their muscarinic activity. Anticholinergic agents used to relieve these muscarinic side effects are themselves associated with other unacceptable side effects.

Sugammadex is a selective NMBA binding agent with a modified gamma-cyclodextrin, a chemical structure with a hydrophilic exterior and hydrophobic core. It was specifically designed to reverse rocuronium-induced paralysis by encapsulating rocuronium. However, its inner cavity is large enough to also encapsulate other aminosteroidal NMBAs such as vecuronium and, to a lesser extent, pancuronium. Upon binding, it creates a complex formation between itself and the NMBA, resulting in rapid reversal of the neuromuscular blockage, with no cholinergic effect. Sugammadex does not bind to plasma proteins, is not metabolized, and is excreted unchanged by the kidneys. Sugammadex was approved by the US Food and Drug Administration in December 2015 and is currently approved for use in more than 80 countries.

Sugammadex's properties make it potentially useful in the transport setting where NMBAs are used to induce and maintain neuromuscular blockage for lifesaving interventions and ongoing patient management. In this issue of articles, the efficacy and safety of sugammadex for reversing NMBA-induced neuromuscular blockade are summarized.

Hristovska A-M, Duch P, Allingstrup M, Afshari A. The comparative efficacy and safety of sugammadex and neostigmine in reversing neuromuscular blockade in adults. A Cochrane systematic review with meta-analysis and trial sequential analysis. *Anaesthesia*. 2018;73:631-641.

The authors of this systematic review included randomized clinical trials of adult patients classified as American Society of Anesthesiologists physical status 1 to 4 who received a nondepolarizing NMBA for an elective surgical procedure. Trials were included if they compared sugammadex with neostigmine, regardless of the dose of either agent and the time point of drug administration. This systematic review was an update of a previously published Cochrane review[1] regarding sugammadex. The outcomes were recovery time from moderate or deep neuromuscular blockade and the risk of adverse and serious adverse events.

Forty-one trials with a total of 4,206 participants were included, of which 31 trials with 2,559 participants were eligible for the meta-analysis. The remaining 10 trials with 1,647 participants were included in the qualitative review. The time to reversal of moderate neuromuscular blockade with sugammadex (2.0 mg/kg intravenously) was 2.0 minutes versus 12.0 minutes with neostigmine (0.05 mg/kg). The time to reversal of deep neuromuscular blockade was 2.9 versus 48.8 minutes for sugammadex (4.0 mg/kg) versus neostigmine (0.07 mg/kg). The authors noted there were significantly fewer composite adverse events (bradycardia, nausea and vomiting, and residual paralysis) in the sugammadex group compared with neostigmine (risk ratio = 0.60, 95% confidence interval [CI], 0.49-0.74). There were no differences regarding the risk of significant adverse events. The authors concluded sugammadex reverses neuromuscular blockade more rapidly than neostigmine and is associated with fewer adverse events.

This systematic review provides a sound assessment of the comparative efficacy and safety between sugammadex and neostigmine, with all outcomes favoring sugammadex. There were some limitations to the analysis. The analysis included only published trials, only those with adult patients, with no trial judged to have a low risk of bias, and the quality of findings ranked only as high as moderate across outcomes. However, the analysis provides the best evidence to support the conclusion that sugammadex reverses neuromuscular blockade faster than neostigmine, regardless of depth, and is associated with fewer side effects.

Herring WJ, Woo T, Assaid CA, et al. Sugammadex efficacy for reversal of rocuronium- and vecuronium-induced neuromuscular blockage: a pooled analysis of 26 studies. *J Clin Anesth*. 2017;41:84-91.

The authors pooled data from 26 multicentre, randomized phase 1 and 2 studies, all sponsored by the manufacturer of sugammadex, to compare the ability of the drug to reverse neuromuscular blockage with either placebo or neostigmine. Patients were included if they were adults (≥ 18 years), American Society of Anesthesiologists class 1 to 3, and undergoing surgery requiring general anesthesia with neuromuscular blockage. Patients received rocuronium (0.6-1.2 mg/kg) or vecuronium (0.1 mg/kg), with additional doses as required. Data from pediatric patients (age < 18 years) or those with severe renal impairment (creatinine clearance < 30 mL/min) were not included in the analysis. The analysis focused on recovery times with sugammadex doses of 2 mg/kg (for moderate neuromuscular blockade), 4 mg/kg (for deep neuromuscular blockage), and 16 mg/kg (at 3 minutes after neuromuscular blockade for purposes of evaluating effects in the situation of clinical need to rapidly reverse a large single dose of rocuronium).

The times to recovery for sugammadex and neostigmine were 1.9 minutes (95% CI,

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1.8-2.0) versus 10.6 minutes (95% CI, 9.8-11.6), respectively, for moderate blockade with rocuronium and 2.9 (95% CI, 2.5-3.4) versus 17.4 (95% CI, 13.4-22.6) minutes for vecuronium. For deep blockade, recovery with sugammadex was also significantly faster than with neostigmine (2.2 vs. 3.8 minutes with rocuronium and 3.8 vs. 67.6 minutes with vecuronium). Sugammadex (16 mg/kg) administered 3 minutes after rocuronium (1.2 mg/kg) resulted in rapid recovery (1.7 minutes), but there was no neostigmine comparator group. The authors concluded that sugammadex provides rapid reversal of rocuronium- and vecuronium-induced moderate and deep neuromuscular blockade and effective reversal 3 minutes after high-dose rocuronium administration.

Although this pooled analysis includes only data derived from studies sponsored by the manufacturer of sugammadex, its findings are consistent with systematic reviews and meta-analyses. Of note, the authors did not perform a safety analysis on the pooled data. The authors did include 1 key finding that was relevant to the prehospital and transport setting, namely, the ability for a large sugammadex dose (16 mg/kg) to rapidly reverse neuromuscular blockade when administered shortly ($\leq$ 3 minutes) after an “intubating” dose (1.2 mg/kg) of rocuronium. The authors found that 95% of patients administered sugammadex within 3 minutes of receiving rocuronium recovered from neuromuscular blockage within 5 minutes after the initiation of neuromuscular blockade. This is relevant in the setting where attempts at intubation have failed and rapid reversal of neuromuscular blockage is desired.

Liu G, Wang R, Yan Y, Fan L, Xue J, Wang T. The efficacy and safety of sugammadex for reversing postoperative residual neuromuscular blockade in pediatric patients: a systematic review. *Sci Rep*. 2017;7:5724.

Systematic reviews and meta-analyses have summarized the efficacy and safety of sugammadex in the reversal of neuromuscular blockade induced by steroidal neuromuscular blockade in adult patients. However, its use has not been reviewed in pediatric patients. The authors of this systematic review evaluated the efficacy and safety of sugammadex for reversing neuromuscular blockade in pediatric patients. They included randomized clinical trials that compared sugammadex with neostigmine or placebo in pediatric patients undergoing surgery involving the use of rocuronium or vecuronium. The primary outcome was the time to reversal of neuromuscular blockade.

The authors identified 10 studies with 580 participants. The results suggest that sugammadex can reverse rocuronium-induced neuromuscular blockade more rapidly (weighted mean difference = −8.51 minutes for pooled results) than neostigmine or placebo. In addition, sugammadex results in a lower incidence of bradycardia than neostigmine (risk ratio = 0.08; 95% CI, 0.01-0.42), but there were no significant difference in other adverse events. The authors conclude sugammadex at doses studied ranging from 0.5 to 4 mg/kg can rapidly and safely reverse rocuronium-induced neuromuscular blockade.

This study is limited because of its high heterogeneity given a variety of patient age ranges, a variety of or lack of reported concentrations of inhaled anesthetics used (which can enhance the effects of NMBAs), and the low numbers of adverse events. However, the review includes the largest number of included pediatric patients in an attempt to determine the efficacy and safety of sugammadex in this population. This provides suitable guidance in the use of this drug to reverse NMBAs in the pediatric population, but more data regarding the safety in this population are still required.

Min KC, Woo T, Assaid C, et al. Incidence of hypersensitivity and anaphylaxis with sugammadex. *J Clin Anesth*. 2018;47:67-73.

Studies to date support the view that sugammadex is generally safe and well tolerated. However, hypersensitivity reactions and anaphylaxis are uncommon events, and their true incidence may not be well characterized in individual trials. The authors conducted a retrospective analysis of sugammadex’s clinical development program and postmarketing data to evaluate the incidence of hypersensitivity and anaphylaxis after the administration of sugammadex. They pooled data from 42 phase 1 to 3 trials and 1 phase 5 trial involving adult patients and healthy volunteers in which sugammadex (2, 4, and 16 mg/kg), placebo, and/or comparator was administered together with anesthesia and/or NMBA for surgery under general anesthesia. All included trials were sponsored by the manufacturer of sugammadex.

The pooled data included 3,519 subjects who received sugammadex and 544 who received placebo. The groups were similar in age, sex, race, and baseline body weight and height. There was no evidence of a dose response with sugammadex. The overall incidence of hypersensitivity was less than 1%, with no differences in hypersensitivity or anaphylaxis with sugammadex compared with neostigmine or placebo. There were no confirmed cases of anaphylaxis in the pooled studies, but postmarketing use identified 155 reported cases of serious hypersensitivity and 259 reported cases of anaphylaxis in approximately 11.5 million patients exposed to sugammadex.

This study represents the largest population of subjects in controlled clinical trials in which hypersensitivity and anaphylaxis associated with the use of sugammadex were evaluated. However, given the low incidence of these events and the retrospective nature of the study, the findings may not represent the true incidence. Given the available evidence, it is reasonable to assess the risk for hypersensitivity and anaphylaxis related to sugammadex as low.

The available evidence suggests that, in comparison with neostigmine, sugammadex can more rapidly reverse rocuronium-induced neuromuscular blockade regardless of the depth of blockade. Patients receiving sugammadex also have fewer adverse events, particularly bradycardia, but there was no difference in the risk of adverse events between groups. Future trials with large sample sizes and a low risk of bias are needed to confirm the findings currently available, particularly in terms of adverse events and serious adverse events, as well as on patient-related outcomes.

Virtually all published studies involve patients, adult or pediatric, undergoing surgical procedures with general anesthesia. How this evidence translates to the prehospital and transport setting remains to be seen. There are currently no meaningful studies specifically examining the use of sugammadex in this setting. Translating the available evidence to this setting is not unlike other situations in which hospital-based evidence is adapted, as best as possible, using data and outcomes from comparable patient populations, conditions, and scenarios.

What is clear is that sugammadex is effective in quickly reversing the effects of NMBAs. This can be useful when neuromuscular blockade is no longer required, such as prompt resumption of spontaneous respirations or when considering extubation. Sugammadex may be particularly useful in a failed rapid sequence intubation with rocuronium, when the “cannot intubate, cannot ventilate” situation arises. There is some evidence that sugammadex at high doses (16 mg/kg) administered promptly after NMBA administration may be useful in this circumstance. Fortunately, these life-threatening situations are rare, but their rarity makes direct study in a clinical trial somewhat challenging. More robust evidence will be needed to establish the efficacy and safety of sugammadex in such emergency situations and how readily that evidence can be translated to the prehospital and transport setting.

Reference

1. Abrishami A, Ho J, Wong J, Yin L, Chung F. Sugammadex, a selective reversal medication for preventing postoperative residual neuromuscular blockade. *Cochrane Database Syst Rev*. 2009;4:CD007362.

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