Preliminary Indications for the Use of Sugammadex After Its Addition to a Formulary at a Tertiary Care Children's Hospital

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OBJECTIVES Neuromuscular blocking agents (NMBAs) are administered to facilitate endotracheal intubation and provide skeletal muscle relaxation in surgical procedures. Sugammadex (Bridion) recently received approval by the United States Food and Drug Administration for reversal of rocuronium and vecuronium-induced neuromuscular blockade thereby providing an alternative to acetylcholinesterase inhibitors such as neostigmine. This quality improvement analysis sought to investigate the clinical reasons and common clinical perceptions for choosing sugammadex over neostigmine to reverse NMBAs.

METHODS One hundred cases were reviewed where sugammadex was used for neuromuscular blockade reversal in the operating room. Cases were identified from electronic medical record reports. Anesthesia providers responsible for administering sugammadex were interviewed to obtain rationales for sugammadex use in the perioperative setting. Responses were reviewed to identify distinct reasons for using sugammadex. Two independent raters ranked the reasons according to prevalence. The study was exempt from Institutional Review Board approval as a quality improvement (QI) project.

RESULTS Forty-two anesthesia providers (15 Certified Registered Nurse Anesthetists, 5 anesthesiology trainees, and 22 attending anesthesiologists) were interviewed to identify reasons why sugammadex was administered intraoperatively in 100 surgical cases (69/31 male/female patients, age 9.4 ± 6.5 years). The author identified the top 19 common reasons respondents chose to use sugammadex for each case, and independent raters reviewed the response summaries for those 19 primary reasons sugammadex was used. The most common reasons for choosing sugammadex were: 1) beneficial pharmacokinetics of the agent; 2) sugammadex's perceived superior efficacy over neostigmine; and 3) concerns regarding adverse effects of neostigmine and/or the anticholinergic agent.

CONCLUSIONS Sugammadex has recently been introduced for clinical use to reverse NMBAs at our institution. Primary reasons and perceptions for its use over neostigmine included a limited adverse effect profile, a greater sense of control and predictability of patients' response, and a limited incidence of residual neuromuscular blockade.

ABBREVIATIONS EMR, electronic medical record; FDA, Food and Drug Administration; NMBA, neuromuscular blocking agent; PT, prothrombin; PTT, partial thromboplastin; QI, quality improvement

KEYWORDS neostigmine; neuromuscular blocking agents; NMBA; sugammadex

J Pediatr Pharmacol Ther 2018;23(1):48–53

DOI: 10.5863/1551-6776-23.1.48

Introduction

Aminosteroid, non-depolarizing, neuromuscular blocking agents (NMBAs) such as rocuronium or vecuronium are often administered during the perioperative period to facilitate endotracheal intubation and provide pharmacologically induced skeletal muscle paralysis for surgical procedures. At the completion of the surgical procedure, reversal of residual neuromuscular blockade is necessary to allow for tracheal extubation and resumption of normal respiratory function. Neostigmine inhibits acetylcholinesterase, increasing the concentration of acetylcholine at the neuromus-

cular junction, thereby competitively antagonizing the effects of residual neuromuscular blockade.¹ Although neostigmine has been in clinical use since the 1930s, concerns with its use include inadequate reversal of neuromuscular blockade leading to residual paralysis and the potential for cholinergic side effects such as bronchospasm, bradycardia, and postoperative nausea. While the clinical sequelae of residual paralysis may be limited in pediatric patients, concerns in the adult population include effects on respiratory function as well as upper airway patency, thereby compromising postoperative ventilation and increasing the incidence of critical postoperative respiratory events, including

upper airway obstruction, respiratory insufficiency, and pneumonia.²⁻⁷

Sugammadex (Bridion, Merck & Co, Kenilworth, NJ) is a novel pharmacologic agent, which was approved for clinical use by the United States Food and Drug Administration (FDA) in December 2015. Its mechanism of action differs from acetylcholinesterase inhibitors in that it encapsulates rocuronium or vecuronium, providing rapid and complete recovery from neuromuscular blockade.⁸⁻¹⁰ As such, it represents a novel pharmacologic agent, being the first non-competitive antagonist for the reversal of neuromuscular blockade. Given its potential efficacy and clinical advantages over acetylcholinesterase inhibitors such as neostigmine, many institutions have chosen to add sugammadex to the hospital formulary. While practices vary among institutions, we have allowed the unrestricted use of sugammadex to our anesthesia providers. Given that there remains a choice as to which agent can be used for reversal of residual neuromuscular blockade, this quality improvement (QI) analysis sought to investigate the clinicians' reasons for choosing sugammadex over neostigmine including its perceived clinical advantages.

Methods

In April 2016, sugammadex was added to our hospital formulary and available for unrestricted use in the operating room for the reversal of neuromuscular blockade. To provide educational background for this initiative, the use of this agent was discussed at our monthly departmental grand rounds and morning conferences. These monthly conferences are attended by the faculty, CRNAs, and trainees to discuss morbidity and mortality, interesting cases, and updates on various educational and QI initiatives of the department. During these conferences, preliminary information was provided for the clinical staff regarding the reversal of neuromuscular blockade, concerns with neostigmine, and potential use of sugammadex, including dosing, the economic profile of sugammadex versus neostigmine within our institution, product availability (vial size), and when it would be available in the Pyxis (Becton, Dickinson and Co., Franklin Lakes, NJ) anesthesia machines (automated operating room dispensing cabinets). The faculty and staff were also informed of the 2 prospective QI projects that would be initiated with the implementation of the medication. This was followed in March 2016 by a 1-hour Grand Rounds presentation regarding the use of sugammadex, including its pharmacology, dosing schemes, potential adverse effect profile, and reports of its use from the pediatric literature. The faculty and staff were also provided with reprints of a review article regarding the use of sugammadex in the pediatric population.⁹

The study was deemed exempt from the need for Institutional Review Board approval as it was a QI project with no potential for added physical risks to the

patients or study participants. Cases were identified via an "Operating Room Medication List for Sugammadex" report generated from the electronic medical record (EMR), over a 6-month period. The study was initiated within 1 to 2 months of the approval of sugammadex by our Pharmacy & Therapeutics committee. A randomly selected 100 cases were reviewed where sugammadex was used for reversal of neuromuscular blockade. The anesthesia provider responsible for the decision to use sugammadex was identified, and they were asked to participate in the study and provide verbal consent. The anesthesia provider was approached by the lead author and was asked to describe the case in which they administered sugammadex, as identified from the weekly EMR report. All interviews were conducted in a semistructured format, guided by a consistent list of prompts and questions, and responses were recorded on a study source document for each participant. As appropriate, probing questions were used to further clarify respondents' opinions regarding the use of sugammadex. After all data were collected, the lead author reviewed participant responses to extract a list of the most common reasons for using sugammadex. Two blinded raters separately reviewed and rated participants' recorded responses according to whether each reason was mentioned or not. Subsequently, reasons for using sugammadex were ranked according to the average of the independent ratings. The lead author and both independent raters separately reviewed each interview response for any mention of patient adverse events.

Results

One hundred cases where sugammadex was used during cases conducted in the operating room were reviewed. The use of sugammadex for these 100 cases involved a total cohort of 42 anesthesia providers. The anesthesia providers included 22 pediatric anesthesiology attendings, 5 pediatric anesthesiology fellows, and 15 CRNA anesthesia providers. Patients who received sugammadex ranged in age from 10 days to 21.2 years (mean of 9.4 ± 6.5 years). While provider observations were not prospectively verified, there were no adverse events related to use of sugammadex as reported by anesthesia providers during the course of this project. Select responses to the question of why providers chose sugammadex are illustrated in Table 1. Nineteen reasons for using sugammadex were extracted from the responses shared, and were then ranked by 2 blinded and independent raters (Table 2). The most common reasons why sugammadex was chosen over neostigmine included a perceived beneficial pharmacokinetic pattern including rapid reversal with limited residual neuromuscular blockade, provider preference primarily based on their understanding of the literature, a limited adverse effect profile, and clinical efficacy especially in patients where reversal of neuromuscular block-

Table 1. Examples of Providers' Responses Regarding Decision to Use Sugammadex**Why Did You Choose Sugammadex?**

1. "Did not want to give neostigmine to avoid bradycardia episodes; could not use atropine and glycopyrrolate; they do not work to treat patients with bradycardia that have had heart transplants, and this was a heart transplant patient."
2. "Used rocuronium to intubate; I try to avoid succinylcholine; sugammadex assists with neuro-monitoring, especially used with thyroid cases; I always use with thyroid cases since it has been available at NCH."
3. "Short case; more efficient reversal than neostigmine with fewer hemodynamic side effects and no parasympathetic concerns; I do not like tachycardia with glycopyrrolate; a cleaner side effect profile with sugammadex."
4. "I gave sugammadex because...I wanted the patient to be strong at extubation because he was so young (<6 months of age)."
5. "I like it, and there is less PONV with sugammadex versus neostigmine immediately postoperatively; we try to get patients discharged same day per hospital laparoscopic appendectomy protocol and sugammadex helps to facilitate quicker discharge."
6. "I wanted the best fighting chance to make sure the baby was strong enough to be extubated safely; be certain that it was not the paralytic causing the extubation to be unsuccessful."
7. "No post-tetanic twitches; For duration of case there was over use of paralytic agent; I decided to try to see if we could reverse with sugammadex so I gave 4 mg/kg, and she was reversed literally within 15 seconds; I gave glycopyrrolate to prevent bradycardia associated with sugammadex because she was already on the low side with HR."
8. "Because it was a 6-week-old, and these babies can be slow to wake up, and I didn't want the baby to be weak...and weakness possibly be the reason the baby did not wake up quickly."
9. "Length of case (case done within 20 minutes); hard to say if patient had twitches back or was breathing spontaneously; history of renal transplant (because we do not want the patient's kidney to take a hit because of the metabolism of neostigmine and sugammadex does not appear to pose such concerns for patients with end-stage renal failure."
10. "Because everything about her preoperative history (hypoalbuminemia, iron deficiency, depression) and risk of nausea/vomiting; wanted to avoid PONV; cleaner reversal of sugammadex than with neostigmine and glycopyrrolate."
11. "Because she was a CT chest protocol; we paralyzed the patient with rocuronium; procedure was short (<30 minutes.); we only had 1 twitch on train-of-four so 4 mg/kg sugammadex dosing; because of nature of procedure... ready to extubate and sugammadex provided a much quicker reversal to extubate the patient sooner (it would take 15–20 minutes with neostigmine and glycopyrrolate versus 2 minutes with sugammadex)."
12. "Gave atropine with first dose to prevent bradycardia because the patient was heart rate dependent; choice for sugammadex because with little children it is quite challenging to get extubation because of weakness (when they have poor muscle development), so we tried sugammadex to give the patient the best possible chance to extubate. We gave 2 mg/kg on first dose, but the baby was still too weak to extubate, so we gave another 2 mg/kg dose; baby was strong enough after second dose and was successfully extubated."

CT, computed tomography; HR, heart rate; NCH, Nationwide Children's Hospital; PONV, postoperative nausea and vomiting

ade might be problematic. This latter group included neonates, patients with neuromyopathic conditions, or those with profound blockade.

Discussion

Over the past 20 to 30 years, several new medications have been introduced into the practice of clinical anesthesia. A select few of these agents such as propofol or sevoflurane have been met with enthusiasm and have gained widespread use in clinical anesthesia to the point that they have replaced previously used agents, such as halothane and thiopental. Others have seen limited use, and may have even disappeared from clinical use for various reasons, such as rapacurium, doxacurium, and levobupivacaine. The decision to

adopt new medications and incorporate their use into clinical practice includes many factors, such as improved clinical efficacy, perceived pharmacokinetic advantages with respect to onset or offset times, an improved or limited adverse effect profile, and cost advantages in certain parts of the world.

Sugammadex is a novel pharmacologic agent with a new mechanism of action for reversal of neuromuscular blockade. The current study identified common clinical reasons why our anesthesia group at a large tertiary care children's hospital have chosen to use sugammadex in clinical practice. While we identified 19 distinct reasons for using sugammadex from anesthesia providers' responses, the most common reasons for choosing sugammadex were perceived benefits of the

Table 2. Common Themes for Using Sugammadex*

Reason	Percentage of Responses Mentioning Each Reason	
	Rater 1	Rater 2
1. Availability (automated operating room dispensing cabinets)	8	6
2. Number of twitches present	10	11
3. Dosing ease (1 drug versus 2 drugs)	18	12
4. Pharmacokinetics	32	38
5. Case duration	16	10
6. Side effects	23	17
7. Procedure type	17	19
8. Price (cost)	14	17
9. Efficacy	30	7
10. Diagnosis	11	8
11. Safety	11	17
12. Patient size	7	5
13. Teaching opportunity	9	6
14. To avoid postoperative nausea and vomiting	4	6
15. Provider preference	27	88
16. Medical status	1	6
17. Weakness of patient	5	3
18. Patient age	7	1
19. Superior drug	9	14

* Total percentage in each column exceeds 100% as the responses could include more than 1 reason.

pharmacokinetic profile of sugammadex, a personal preference for the use of this agent, sugammadex efficacy, and concerns regarding neostigmine side effects. In particular, clinicians identified several specific clinical scenarios or patient profiles where sugammadex was used, including patients with profound neuromuscular blockade (no twitches on the train-of-four [TOF]), patients with neuromyopathic conditions such as muscular dystrophy, heart transplant recipients (due to concerns of bradycardia with neostigmine), and infants. While clinical experience with sugammadex has been limited to date, many clinicians expressed their acceptance of this novel agent, given its perceived limited adverse effect profile when compared to neostigmine. Clinical concerns expressed when reversing with neostigmine and an anticholinergic agent included residual neuromuscular blockade or limited efficacy, tachycardia due to the anticholinergic agent, bradycardia due to neostigmine, and the potential to increase the incidence of postoperative nausea and vomiting. During preclinical trials and in our initial clinical experience, the adverse effect profile with sugammadex has been generally minor and self-limited, including a list of non-specific complaints such as nausea, vomiting, pain, hypotension, and headache. Although no clinical effect was noted, a previous study found mild prolongation of the prothrom-

bin (PT) and partial thromboplastin (PTT) time following a dose of 16 mg/kg.¹¹ It has been postulated that the prolongation of the coagulation times is the result of a laboratory artifact and not a true *in vivo* effect. Severe adverse effects during preclinical trials have included rare reports of bradycardia and anaphylaxis.¹² Although not mentioned in responses to our survey, another issue to consider when using sugammadex is its potential to interfere with oral contraceptive medications and the recommendations to use alternative methods of birth control for 7 days after its administration.

Other less common yet frequently mentioned reasons for choosing sugammadex in the current study included case duration or the procedure type. In both of these scenarios, the duration of neuromuscular blockade with rocuronium was felt to be too long to allow for effective reversal, or the procedure itself mandated normal neuromuscular function for either neurophysiological monitoring (motor evoked potential monitoring during spinal surgery or vocal cord monitoring during thyroid surgery), or computed tomography imaging of the chest. For the latter, our institutional practice and policy includes avoidance of, or rapid reversal of neuromuscular blockade to limit atelectasis which may obscure small metastatic lesions. The current options available to provide effective neuromuscular block-

ade for endotracheal intubation with prompt return of neuromuscular function within 5 minutes are limited to succinylcholine. Given concerns regarding its potential adverse effect profile, pediatric anesthesia providers may choose to avoid the use of succinylcholine.¹³ While alternatives exist for providing acceptable conditions for endotracheal intubation without the use of NMBA, these techniques have not gained significant popularity in clinical practice.¹⁴ In our clinical practice, we have noted that some providers now freely use rocuronium for endotracheal intubation during short procedures or even when neuromuscular blockade should be avoided as rapid reversal of even profound blockade is feasible with sugammadex.

The current project may aid anesthesia providers and clinical departments in identifying opportunities, limitations, and trade-offs in the use of either neostigmine or sugammadex for the reversal of neuromuscular blockade. It may also identify specific areas of future clinical research to clarify or provide additional evidence-based recommendations and evidence for using sugammadex in the clinical scenarios mentioned by our providers. This project has also identified specific clinical scenarios in which reversal of neuromuscular blockade is viewed as problematic or in which rapid reversal is needed following the provision of neuromuscular blockade for endotracheal intubation. This ongoing clinical experience with sugammadex showing its efficacy may also ease reservations for using NMBAs to achieve the desired conditions for endotracheal intubation and neuromuscular blockade during surgical procedures.

Limitations of the current study include a limited number of participating providers, lack of a standardized forced-choice questionnaire to elucidate additional reasons for using sugammadex in the perioperative setting, and a few areas where there was interrater variability when identifying the prevalence of common themes for use of sugammadex. Furthermore, cost and institutional restrictions did not influence the conduct of this study. The cost of medications varies widely from institution to institution, and moreover, from country to country. Given the current acquisition costs associated with the use of neostigmine and glycopyrrolate, which was our previous primary combination of medications for reversal of neuromuscular blockade, there was limited or increased clinical cost when using sugammadex. Furthermore, at our institution, there was no institutional restriction to the use of sugammadex. It was readily available in the automated operating room dispensing cabinets in all anesthetizing locations. Variations in these factors may limit the generalizability of our findings to other settings.

As a disclaimer, we would like to note that this retrospective review is not meant to endorse the use of sugammadex or to provide safety or outcomes data in comparing it to acetylcholinesterase inhibitors such as neostigmine. The impetus behind our manuscript was

an investigation into the subjective decision-making process of adopting new medications into clinical practice. In particular, we hoped to provide some insight into why anesthesia providers chose to use sugammadex and in particular why it was chosen over acetylcholinesterase inhibitors (neostigmine). We hope that identifying these perceptions may help formulate future studies to provide evidence-based method regarding choice of agents to reverse neuromuscular blockade in specific clinical scenarios. Furthermore, when adopting new medications, cost must be balanced into the equation and our manuscript is not meant to provide pharmacoeconomic data to help in this decision process.

This qualitative QI project identified several clinical scenarios and provider preferences that influenced the rapid adoption of a novel medication in our operating rooms. Reasons for the use of sugammadex include perceived advantages of this new agent, as well as ongoing issues with the time-honored combination of neostigmine and glycopyrrolate. The most commonly identified reasons for choosing sugammadex were perceived benefits of the pharmacokinetic profile of sugammadex, sugammadex efficacy in specific clinical scenarios, personal preferences (as explicitly stated by respondents), and concerns regarding adverse effects related to neostigmine or the anticholinergic agent. Clinical concerns that were expressed when reversing with neostigmine and an anticholinergic agent included residual neuromuscular blockade or limited efficacy, tachycardia due to the anticholinergic agent, bradycardia due to neostigmine, and the potential to increase the incidence of postoperative nausea and vomiting. Specific clinical scenarios or patient profiles in which sugammadex was judged to be beneficial included clinical scenarios where reversal may be problematic, such as patients with profound neuromuscular blockade (no twitches on the train-of-four), patients with neuromyopathic conditions, and neonates. Of note, cost was not considered as a decision point in our clinical practice, as sugammadex is currently available in the automated operating room dispensing cabinets for unrestricted use. As purchasing contracts and prices vary from region to region, a direct cost comparison is difficult. However, in our current setting, the cost of 2 mL or 200 mg vial of sugammadex (\$700–\$800) compares favorably with the cost of reversal using neostigmine and glycopyrrolate.

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Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. This research was carried out without funding. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgments The authors wish to thank Heather Delinger, RN who served as Clinical Research Coordinator, and Hina Walia and Mumin Hakim who were Response Raters.

Accepted November 20, 2017

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