Sugammadex: Efficacy and Practicality in the Dental Office

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Sugammadex is a novel drug capable of reversing paralysis induced by the common steroidal nondepolarizing neuromuscular blocking drugs, rocuronium and vecuronium. Reversal is complete at any depth of blockade dependent on the dose of sugammadex administered. This allows rocuronium to be used as a rescue agent in scenarios where succinylcholine is contraindicated. Sugammadex is considered a safe drug with minimal side effects compared with traditional reversal with neostigmine and glycopyrrolate. This article features a case report where succinylcholine was undesirable and rapid reversal of paralysis with sugammadex was used during general anesthesia for dentistry.

Key Words: Sugammadex; Reversal; Rocuronium; Paralysis.

Advanced anesthesia techniques such as general anesthesia and deep sedation have become an integral part of modern dentistry. General anesthesia is frequently utilized to provide ideal operating conditions during orthognathic surgery, full mouth rehabilitation, implant placement, and other invasive dental procedures. Additionally, some of the most challenging patient demographics in dentistry do not have access to care in a safe and efficacious manner without general anesthesia. Patient populations include those with special needs or severe psychological impairments, pronounced dental phobia, allergy or ineffectiveness to local anesthesia, and preoperative or uncooperative children. Furthermore, the use of general anesthesia and sedation in these patient populations continues to grow.^{1,2} The provision of office-based anesthesia offers many benefits in comparison to hospital-based anesthesia to both providers and patients, including decreased cost, greater access to care, and improved autonomy. Sedation and general anesthesia are not without risk; therefore, dental anesthesia providers are obligated to ensure the safest and most responsible care possible.² Office-based anesthesia providers must be aware of the latest developments in hospital-based anesthesia and determine if new drugs and modalities offer improvements to the uniquely challenging aspects of office-based dental anesthesia. Sugammadex, a new drug gaining popularity in hospital anesthesia,

has great potential to influence the way office-based dental anesthesia is practiced.

ABOUT SUGAMMADEX

In December 2015, the US Food and Drug Administration (FDA) approved sugammadex (Bridion) for the reversal of neuromuscular blockade induced by rocuronium or vecuronium. Sugammadex is a gamma cyclodextrin ring made up of 8 conjoined sugar molecules. It works by encapsulating a neuromuscular blocking drug (NMBD) in a 1:1 ratio. This encapsulation of the NMBD by sugammadex renders the NMBD unable to bind to acetylcholine nicotinic receptors. As plasma levels of the NMBD decrease, a rapid shift in the concentration gradient causes remaining NMBD to diffuse away from the neuromuscular junction. If enough sugammadex is used, a complete reversal of paralysis will result.³ The dose of sugammadex required to reverse neuromuscular blockade is dependent on the depth of blockade. If spontaneous recovery from neuromuscular blockade has reached 2 twitches on a train of 4 (TOF), then a dose of 2 mg/kg is recommended. If there are zero twitches on a TOF, but there are 1–2 posttetanic twitches, then a dose of 4 mg/kg is recommended. If immediate reversal of complete neuromuscular blockade is needed, such as following anesthetic induction with inability to ventilate or intubate, then a dose of 16 mg/kg is recommended. Dosages are based on actual body weight, not ideal body weight.⁴ Essentially, rocuronium can be reversed at any time by adjusting the dose of sugammadex to the depth of blockade. With sugammadex, the duration of action of rocuronium is completely modifiable. Sugammadex is

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indicated for reversal of vecuronium as well, but efficacy for immediate reversal with the 16 mg/kg dose has not been verified. The sugammadex-NMBD complex is excreted unchanged by the kidneys within 24 hours.^{3,4}

SAFETY OF SUGAMMADEX

Sugammadex has been used in the European Union and other countries since 2008, but was only recently approved by the FDA because of concerns about immunologic hypersensitivity, bradycardia, and potential cardiac arrhythmias.⁴ A randomized, double-blind, placebo-controlled hypersensitivity trial of 375 awake patients exposed to sugammadex was conducted. Doses of 4 and 16 mg/kg were associated with a higher incidence of hypersensitivities (6.6 and 9.5%, respectively) when compared with placebo (1.3%).⁵ The majority of reactions were mild (91%), and only 3 cases, all of which had doses of 16 mg/kg, required acute treatment with an antihistamine and/or corticosteroid.⁵ Epinephrine was not needed for any of these cases. Larger pooled studies of more than 3000 patients show the incidence of sugammadex hypersensitivity (0.2%) to parallel placebo (0.6%).⁵ Safety trials concluded true anaphylaxis to be a rare occurrence (<0.1%).⁵ Regarding the cardiac safety of sugammadex, the FDA safety trials demonstrated no evidence of prolongation of the QT interval when examining sugammadex alone. Cardiac arrhythmias associated with sugammadex are similar to placebo (~5 and 4% respectively), and occur less frequently than with neostigmine (8%) and succinylcholine (Sch; 9%).⁵ Several case reports of bradycardia immediately following administration of sugammadex have been reported.⁶ The FDA safety trials found a lower incidence of sugammadex-induced bradycardia (0.5%) when compared to neostigmine with glycopyrrolate (4.8%). Bradycardia resulting from sugammadex responds well to classical treatment with atropine.⁵ The cause of bradycardia associated with sugammadex is unknown. Sugammadex is chemically inert and has no direct effects on cholinergic muscarinic receptors.³ A transient increase in the partial thromboplastin time has been reported.⁵ Sugammadex may interfere with steroid oral contraceptive drugs, so women taking these medications must be advised to use an alternative form of birth control for 7 days.⁷

COMPARISON WITH TRADITIONAL NEUROMUSCULAR BLOCKADE REVERSAL

Reversal of nondepolarizing NMBDs is typically accomplished by administration of an acetylcholinester-

ase inhibitor and an anticholinergic agent such as neostigmine (0.05–0.8 mg/kg) and glycopyrrolate (0.01 mg/kg).⁸ This method of reversal can safely be used only once 2–3 twitches have spontaneously returned on a TOF to prevent recurrence of paralysis.^{8,9} Furthermore, neostigmine and glycopyrrolate have potentially severe side effects. Neostigmine may cause acute bradycardia, asystole, increased secretions, bronchospasm, residual neuromuscular blockade, and recurrence of neuromuscular blockade. Glycopyrrolate may cause tachyarrhythmias, xerostomia, miosis, and urinary retention.^{8–10} Carron et al¹⁰ conducted a meta-analysis comparing the efficacy and safety of sugammadex versus neostigmine and glycopyrrolate in reversal of moderate (1–2 twitches on TOF) and deep neuromuscular blockade (posttetanic twitch only) with rocuronium. Thirteen randomized controlled trials and a total of 1384 patients met their inclusion criteria. The following statistically significant results refer to the comparison of the sugammadex group with the traditional reversal group. Sugammadex had the following characteristics:

- Faster at reversing moderate neuromuscular blockade (mean difference, –1.82 minutes)
- Faster at reversing deep neuromuscular blockade (only 3 randomized controlled trials, so not enough to perform a subgroup analysis)
- Higher TOF ratio values at extubation (mean difference, 0.18 ratio value)
- Lower risk of postoperative residual curarization (odds ratio, 0.05)
- Lower risk of all adverse events (11.4 vs 21.1%)
- Lower risk of serious adverse events (0.15 vs 1.27%)

The authors defined adequate reversal as a TOF ratio >0.9. Serious adverse events were defined as marked fatigue, anxiety, depression, acute lung failure, severe hypoxemia, bradycardia, and postoperative upper abdominal pain.¹⁰

A randomized, double-blind study demonstrated a more favorable reversal of general anesthesia with sugammadex when compared to neostigmine with glycopyrrolate. Patients given sugammadex demonstrated significantly decreased time to head lift (4 vs 8 minutes) and extubation (3 vs 4 minutes) when compared to patients receiving neostigmine with glycopyrrolate. The sugammadex group experienced significantly less postoperative nausea and vomiting when initially arriving at the postanesthesia care unit; unfortunately, differences in postoperative nausea and vomiting scores did not persist, and there were no significant difference in postoperative nausea and vomiting scores during the initial 24-hour postoperative period. Postoperative heart rates were also significantly lower for patients receiving neostigmine as a reversal

agent; bradycardia was much more pronounced and occurred much more frequently (14 vs 2%) in patients who received neostigmine.¹¹

COST COMPARISON WITH TRADITIONAL NMBD REVERSAL

Because drug costs vary greatly depending on numerous factors, it is hard to compare costs for all providers in different areas of the country and in different venues, such as hospitals, ambulatory surgery centers, and office anesthesia providers. For office anesthesia providers who must pay for their medications directly, cost frequently needs to be a consideration. Review of costs at the University of Pittsburgh Department of Dental Anesthesiology reveals standard reversal with sugammadex at a dose of 2 mg/kg to be very comparable to the standard cost of neostigmine with glycopyrrolate. Therefore, costs for the 4 mg/kg and 16 mg/kg dose are correspondingly higher. Our current cost in 2017 for a 16 mg/kg emergency reversal dose is approximately \$700.00. Of course, neostigmine is not indicated for reversal at these greater degrees of paralysis for which sugammadex is indicated.

NEUROMUSCULAR BLOCKADE IN DENTISTRY

Although paralysis is frequently not necessary for many dental and oral surgeries, especially with concomitant regional anesthesia, there are several indications for neuromuscular blockade in dental anesthesia. Paralysis in dentistry is desired by surgeons to obtain ideal and safe operating conditions during delicate operations. Patients who exhibit hypotension at even modest levels of general anesthetic agents may require paralysis to allow only amnestic doses of sedative/general anesthetic agents to be used in order to maintain cardiovascular stability. Neuromuscular blockade facilitates intubation and is used for emergency management of acute laryngospasm. Sch is the prototypical drug in these situations because of its rapid onset and short duration. However, Sch has many undesirable side effects, including but not limited to acute bradycardia, tachycardia, myalgias, prolongation of the QT interval, and hyperkalemia. Hyperkalemia is of particular concern in patients with upregulation of nicotinic receptors. Patients with upper motor neuron lesions, denervation of skeletal muscle, certain congenital muscle disorders, and severe burns are at increased risk of developing hyperkalemia. Hyperkalemia in these populations can potentially be so severe that cardiac arrest ensues. For this reason, the use of Sch is contraindicated in these

patients.^{4,12} Sch is also a triggering agent for malignant hyperthermia (MH).^{4,12} Male children under the age of 8 pose the risk of undiagnosed congenital muscular disorders. Sch in this patient population can lead to rapid rhabdomyolysis, hyperkalemia, and cardiac arrest.¹² Additionally, patients may have undiagnosed butyrylcholinesterase deficiency. The incidence of butyrylcholinesterase activity resulting in prolonged apnea is around 1 in 2500.¹² Lastly, the possibility of residual paralysis for patients reversed with conventional acetylcholinesterase inhibitors and anticholinergics is of particular concern in the office-based and other ambulatory settings. Use of sugammadex almost completely eliminates this concern for dental office general anesthesia where rocuronium or vecuronium is used.

Even though rocuronium lacks most of the adverse effects seen with Sch, it typically is not used as a rescue paralytic in laryngospasm because of its longer duration of action. Several studies have compared rocuronium to Sch and found that intravenous (IV) onset times are comparable when using 0.9–1.2 mg/kg of rocuronium and 2 mg/kg of Sch.^{13,14} Schultz and Ibsen¹⁵ found that 60 seconds after administration of 0.9 mg/kg of rocuronium, intubating conditions were good or excellent, with no further benefit in intubating conditions when the dose was increased to 1.2 mg/kg.⁵ With similar onsets of action and intubating conditions, the advent of sugammadex may negate concerns regarding duration of action and allows rocuronium to be a viable alternative to Sch without the associated side effects. Lee et al¹⁶ found that reversal of high-dose rocuronium blockade (1.2 mg/kg) with sugammadex (16 mg/kg) proved to be faster than spontaneous recovery from an intubating dose of Sch (1 mg/kg).

The following case report, conducted by the Department of Dental Anesthesiology at the University of Pittsburgh School of Dental Medicine, illustrates the use of rocuronium and sugammadex in an ambulatory surgical environment to achieve ideal intubating conditions and subsequent immediate reversal of neuromuscular blockade in a patient where Sch was relatively contraindicated.

CASE REPORT

A wheelchair-bound 31-year-old, 5'1", 65-kg Caucasian woman presented to the University of Pittsburgh School of Dental Medicine's Center for Patients with Special Needs for restorative dental procedures under general anesthesia. The patient's medical history included cerebral palsy with spastic quadriplegia, scoliosis, intellectual disability, seizure disorder, and severe gastroesophageal reflux disease. Current medications

included clobazam, clonazepam, diazepam, docusate, lamotrigine, levocarnitine, lorazepam, melatonin, pantoprazole, and quetiapine. Surgical history was significant for placement of a vagal nerve stimulator and fusion of the lumbar vertebrae. Family and social histories were noncontributory. The patient was NPO appropriate.

Although cerebral palsy is not an absolute contraindication to the use of Sch, some studies have found the incidence of extrajunctional acetylcholine receptors to be as high as 30% in cerebral palsy patients.¹⁷ Additionally, the use of Sch in this patient poses the risk of severe postoperative myalgia and/or aspiration at induction due to Sch-induced increased intragastric pressure with known poor lower esophageal sphincter tone. For these reasons, we felt Sch was relatively contraindicated. Ideal intubating conditions were desired because of the presence of a restrictive lung condition resulting in a reduced functional residual capacity and a decreased oxygen reserve. The anesthetic plan was to induce anesthesia with fentanyl and propofol, establish neuromuscular blockade with rocuronium to facilitate intubation, and immediately reverse the neuromuscular blockade using sugammadex. We chose to immediately reverse the NMB with sugammadex for 2 primary reasons:

1. The planned procedures (routine 6-month dental exam with dental prophylaxis) were anticipated to be completed in well less than an hour, so the patient would require mechanical ventilation for only a short period of time and higher-dose sugammadex would likely be necessary for NMBD reversal.
2. The University of Pittsburgh Medical Center and the affiliated dental school are teaching facilities. The current dental faculty and residents at the University of Pittsburgh Medical Center had no clinical experience using sugammadex for the purpose of immediate reversal after an intubating dose of rocuronium. Therefore, this case allowed the anesthesia faculty and residents to benefit from the clinical experience of using this novel medication for immediate reversal of NMBD, such as would be indicated in a “can’t intubate, can’t ventilate” (CICV) scenario, or following the use of rocuronium to manage a laryngospasm in a patient for whom Sch is either relatively or absolutely contraindicated.

Standard American Society of Anesthesia monitors were placed. In addition, a peripheral nerve stimulator was placed on the adductor pollicis muscle to monitor neuromuscular blockade of the ulnar nerve. IV access was obtained with a 20-gauge catheter on the right dorsal hand. General anesthesia was induced using fentanyl 100 mcg and propofol 120 mg. A baseline TOF

was taken and 4 strong twitches without fade were observed. The peripheral nerve stimulator was then placed on continual twitch mode in order to monitor the onset of paralysis. Rocuronium 80 mg (1.2 mg/kg) was administered, and twitches disappeared 33 seconds later. Direct laryngoscopy with a Macintosh 3 blade was performed, resulting in a Cormack grade I view of the vocal cords. A 6.0-mm nasal Ring-Adair-Elwyn endotracheal tube was placed via the right naris. The cuff was inflated and successful intubation was confirmed with the detection of end-tidal CO₂ and equal bilateral breath sounds. The endotracheal tube was secured with tape at 23 cm at the right naris and mechanical ventilation was initiated. Profound neuromuscular blockade was confirmed by lack of posttetanic twitches in response to a tetanic stimulus at 50 Hz. After intubation, a 1000-mg (15.4 mg/kg) sugammadex bolus dose was administered. Return of twitch was observed 14 seconds later. Four strong twitches without fade were noted 1 minute and 36 seconds later, indicating complete reversal of paralysis.

No adverse events occurred throughout the duration of treatment. Heart rate and blood pressure remained constant following the use of a large dose of sugammadex. Dental treatment lasted an additional 45 minutes. The patient was then extubated without incident and released to her caregiver after meeting discharge criteria.

DISCUSSION

Utilization of general anesthesia and deep sedation in dentistry is increasing in order to safely treat challenging patient populations and for various oral and maxillofacial procedures.^{1,2} Dental anesthesia providers should assess whether new developments in anesthesia care are applicable to office-based anesthesia. Sugammadex is a novel NMBD reversal agent that has the potential to impact the practice of dental anesthesia in an office-based setting.

An acute laryngospasm may occur at any time during deep sedation/general anesthesia when an endotracheal tube is not properly in place and requires prompt emergency management. Paralysis of the vocal cords to facilitate adequate ventilation is included in laryngospasm management algorithms.¹⁸ As previously noted, the use of Sch has many adverse effects and may be contraindicated in specific populations that present to the dental office, including certain pediatric patients and patients with special needs. Rocuronium should be available to use when Sch is absolutely contraindicated. Rocuronium does not share the negative side effects of Sch, and the duration of action may now be controlled with immediate reversal by administering sugammadex. Rocuronium given at a dose of 0.9 mg/kg has shown to

be effective in rapidly breaking a laryngospasm and is a viable alternative to Sch when sugammadex is available.¹⁸ Following the use of sugammadex, redosing of rocuronium becomes unpredictable and is dependent on the dose of sugammadex administered.¹⁹ Therefore, clinical judgment must be used to continue elective cases requiring emergency pharmacologic intervention with rocuronium to break a laryngospasm with sugammadex reversal in which intubation was not carried out. Where intubation is performed, extubation should occur with the patient clearly awake. In the event that a laryngospasm occurs prior to gaining IV access, intramuscular (IM) administration of Sch (3–4 mg/kg) is considered as part of the algorithm.²⁰ There is currently conflicting evidence regarding the efficacy of IM rocuronium administration.^{21,22} Reynolds²¹ found that all children who received 1.8 mg/kg rocuronium IM had good to excellent intubating conditions with an onset time similar to IM Sch (4 minutes). Kaplan et al²² replicated the study by Reynolds, and found that only 56% of patients demonstrated good to excellent intubating conditions following IM administration of rocuronium. More research is needed regarding the efficacy of IM injection of rocuronium. In an emergency situation when IV access is not possible, the consideration of intraosseous access may result in better outcomes than IM injection. However, time and personnel issues need to be taken into consideration. Regardless, the use of pharmacologic agents in a crisis is secondary to proper airway management. If rocuronium is used, once the patient is intubated, available dental personnel can easily ventilate the patient with a bag-valve-mask device. Even without intubation, use of an oropharyngeal airway should allow available dental personnel to adequately ventilate the patient, allowing time for IV or other access to be established by the anesthesia provider.

Many dental anesthesia providers do not use volatile anesthetics and use Sch only as an emergency drug in the event of laryngospasm. By replacing Sch as an emergency drug with rocuronium and sugammadex in practice, these practitioners can avoid using any MH-triggering agents. Avoidance of all MH-triggering agents would enable these providers to no longer carry dantrolene and all the other medications and ancillary equipment necessary to manage an MH crisis.²³ This results in the elimination of the excessive cost associated with dantrolene, but more importantly, it also eliminates the rare complication of MH, which can be fatal or lead to renal failure even with prompt and appropriate management. The provider may consider instead carrying rocuronium and sugammadex as a replacement. However, it should be noted that the Society for Ambulatory Anesthesia recently published a position

statement regarding rescue Sch use for laryngospasm when no other MH triggers are present in ambulatory settings. They stated, “If succinylcholine is stocked and its availability is strictly limited solely for emergency use only, the mandate for carrying dantrolene in facilities that do not have inhaled anesthetics is unnecessary and may, in fact, compromise patient safety.”²⁴ Despite this, however, some doctors may still not be comfortable using an MH-triggering agent (Sch) without dantrolene readily available, so for these anesthesia providers the replacement of emergency Sch with rocuronium/sugammadex is an option.

Another emergency situation encountered during anesthesia is the CICV scenario. It has been suggested that rapid reversal of paralysis with sugammadex can help mitigate a CICV scenario. Rapid reversal of complete paralysis allows the patient to regain control of breathing through spontaneous ventilation. Sugammadex may serve as an important adjunct to accomplish the goal of returning the patient to ventilation and reoxygenation. CICV can, however, be a multifactorial development occurring independently from simple muscle relaxation resulting in airway obstruction. Other causes of CICV may include oversedation, airway obstruction not caused by muscle relaxation, edema of the airway, iatrogenic trauma, etc. Sugammadex will not be of value in these scenarios and preparation for emergency surgical airway management with the goal to reoxygenate the patient must also be included in the CICV algorithm.²⁵

The FDA has not approved the use of sugammadex for pediatric patients at this time. However, sugammadex has been used to reverse neuromuscular blockade for pediatric patients with difficult clinical scenarios as discussed in this article, including in CICV and patients with muscular dystrophy and myotonic dystrophy. Case studies suggest that it is equally efficacious and safe in pediatric patients, but further research needs to be conducted before these off-label uses become FDA approved.²⁶

CONCLUSION

Sugammadex has the potential to change the way nondepolarizing NMBDs are used in anesthesia. The duration of action of rocuronium is now modifiable and can be tailored to different scenarios, including routine reversal of paralysis and emergency crisis management. The high cost of sugammadex is a concern. Office-based anesthesia providers are encouraged to become familiar with sugammadex because it has the potential to improve the quality of care provided to patients, especially when Sch is contraindicated.

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