Sugammadex Use in Infants and Children
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On December 15, 2015, the Food and Drug Administration approved sugammadex for the reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults undergoing surgery. Sugammadex is the first noncompetitive antagonist for nondepolarizing neuromuscular blocking agents. It offers an alternative to neostigmine for reversal of neuromuscular blockade, producing a more rapid return to normal function, reduced time to extubation following surgery, and less risk for adverse effects. When administered after rocuronium for endotracheal intubation, the duration of neuromuscular blockade is comparable to that of succinylcholine. With these advantages, the use of sugammadex has expanded in clinical practice to include use in infants and children.

Mechanism of Action
Sugammadex sodium is a modified gamma-cyclodextrin, containing eight dextrose units that form a sphere-like shape with a lipophilic core and hydrophilic exterior. Sugammadex forms a complex with aminosteroid neuromuscular blocking agents, encapsulating them in the plasma and reducing the amount of drug available at nicotinic cholinergic receptors at the neuromuscular junction. As the available neuromuscular blocking agent declines, reversal of the blockade occurs and normal function of the neuromuscular junction is restored. Sugammadex is indicated only for reversal of vecuronium and rocuronium. It is not recommended for use with the benzylisoquinolinium compounds such as cisatracurium. It does not reverse the effects of succinylcholine, a depolarizing neuromuscular blocking agent.

Pharmacokinetics
After IV administration, the volume of distribution of sugammadex ranges from 11-14 liters in adults. Neither sugammadex nor the sugammadex-neuromuscular blocking agent complex bind to plasma proteins. Sugammadex is deposited in areas of active mineralization, with studies of release from teeth and bone revealing half-lives of 8 and 172 days, respectively. Sugammadex is renally excreted as unchanged drug, with an elimination half-life in adults of approximately 2 hours and a clearance of 88 mL/min. Clearance of sugammadex is reduced in patients with renal impairment, with prolongation of the half-life to 4 hours in patients with mild impairment, 6 hours in those with moderate impairment, and 19 hours in those with severe impairment.

Pharmacodynamics
In clinical trials of adults undergoing surgery, sugammadex reverses neuromuscular blockade produced by vecuronium or rocuronium approximately 3 to 8 times faster than
neostigmine. In clinical trials, effectiveness is typically determined by evaluating time to recovery of muscle function using train-of-four (TOF) testing. Four consecutive stimulations are given and the response of the muscle is measured. In the absence of neuromuscular blockade, four equal muscle contractions will result. If a nondepolarizing blocking agent has been given, there will be a loss of twitch height and number which will indicate the degree of blockade, with four twitches representing no neuromuscular blockade and zero being complete blockade.

The pharmacodynamics of sugammadex were studied in a multicenter, randomized controlled study of 189 adult patients who received either 2 mg/kg sugammadex or 50 mcg/kg neostigmine as a single injection at the completion of surgery. The primary endpoint was time from administration to recovery of a TOF ratio (T4/T1) of 0.9, representing adequate recovery of neuromuscular function to allow spontaneous breathing. Median recovery times, with Q1 and Q3 quartiles, were significantly shorter with sugammadex, 1.4 min (1.2, 1.7) compared to 21.5 min (9.8, 42.0) for neostigmine.

Recovery from neuromuscular blockade during endotracheal intubation was evaluated in a comparison study of 110 adults given rocuronium 1.2 mg/kg followed 3 minutes later with 16 mg/kg sugammadex for reversal, or succinylcholine 1 mg/kg given alone. The primary outcome for the study was time from recovery of the first twitch (T1) to 10% of baseline. Recovery was more rapid in the patients given rocuronium followed by sugammadex, 4.4 ± 0.7 min, compared to 7.1 ± 1.6 min for succinylcholine.

**Clinical Experience in Pediatrics**

The first reports of sugammadex in children date back to 2009. Among the reports that year, Plaud and colleagues described their phase 3A trial of its efficacy in reversing rocuronium-induced neuromuscular blockade in infants, children, adolescents, and adults. A total of 84 surgical patients were evaluated in this international dose-ranging study. All patients received 0.6 mg/kg rocuronium, with sugammadex (0.5, 1, 2, or 4 mg/kg) or placebo given at the reappearance of T2 at the end of the case. The primary endpoint was the time from administration to return of the T4/T1 ratio to 0.9. The median recovery time after the 2 mg/kg dose was 0.6, 1.2, 1.1, and 1.2 min in the infants, children, adolescents, and adults, respectively. In comparison, the median recovery time after placebo was 21.0, 19.0, 23.4, and 28.5 min in the four groups. A dose-response relationship for sugammadex was demonstrated in all age groups except the infants. The infant group had too few patients to evaluate. Plasma concentrations were similar in all groups across the dosage range. There were no cases of inadequate reversal, recurrence of neuromuscular blockade, or serious adverse effects.

In 2016, Won and colleagues performed a systematic review and meta-analysis of sugammadex reversal of rocuronium-induced neuromuscular blockade in children. The authors included six randomized controlled trials, with a total of 253 children from 2 to 18 years of age (studies with infants were excluded). Five of the studies were conducted in Europe, with the remaining study from Egypt. The mean time to reach a T4/T1 ratio of 0.9 was significantly shorter in the sugammadex groups (2 or 4 mg/kg) than in the neostigmine or placebo groups. The weighted mean differences of the 2 mg/kg group was -7.15 (95% CI -10.77, -3.54, p = 0.0001) and in the 4 mg/kg group was -17.32 (95% CI -29.31, -5.32, p = 0.005).

There are several clinical trials currently listed on www.ClinicalTrials.gov, including the completed study, Reversal with sugammadex from deep neuromuscular blockade induced by rocuronium in children: randomized clinical trial (SUGAPED-01), described at https://clinicaltrials.gov/ct2/show/NCT01809886?term=sugammadex+pediatric&rank=2. The only study currently enrolling patients is the Depth of neuromuscular blockade and the perioperative conditions in laparoscopic surgery in pediatric population (PedLapBlock), https://clinicaltrials.gov/ct2/show/NCT02546843?term=sugammadex+pediatric&rank=3.
While most of the studies conducted to date have included few or no infants, there are several case reports and one retrospective study describing the use of sugammadex in this population.\textsuperscript{8-11} In 2015, Langleby and colleagues described a 2-day-old male given rocuronium during surgery to repair a tracheal esophageal fistula who experienced prolonged neuromuscular blockade.\textsuperscript{8} General anesthesia had included desflurane, remifentanil 0.1-0.2 mg/kg/min, and rocuronium 1 mg/kg/hr for the first 3 hours of surgery, then reduced to 0.5 mg/kg/hr for 1 hour prior to discontinuation 30 minutes before the completion of the case. The baby received a total of 10.5 mg rocuronium over 4 hours. The case proceeded without incident.

Upon arrival to the pediatric intensive care unit, the patient was noted to be profoundly hypotonic, with fixed dilated pupils. Epidural levobupivacaine was discontinued and a cranial ultrasound was performed to exclude an intracranial event. Train of four testing revealed no peripheral neuromuscular activity. Neostigmine was administered with no significant improvement. A 16 mg/kg dose of sugammadex, administered 4 hours after discontinuation of rocuronium, produced spontaneous breaths on the ventilator, limb movement, and pupil reactivity within 90 seconds. The patient was extubated the following morning and experienced an otherwise uneventful recovery. The authors proposed that sugammadex produced a rapid response by binding peripheral rocuronium stores and prompting diffusion of rocuronium from the central nervous system to the plasma to reduce CNS rocuronium concentrations.

In the December issue of the \textit{Journal of Clinical Anesthesia}, Ozmete and colleagues described their retrospective study of 26 infants from 2 to 12 months of age (mean 6.15 ± 3.52 months) who received sugammadex following neurosurgical procedures.\textsuperscript{9} All of the patients received 5 mg/kg thiopental, 1 mcg/kg fentanyl, and 0.6 mg/kg rocuronium for intubation, followed by sevoflurane with doses of rocuronium repeated as needed. A 3 mg/kg dose of sugammadex was administered at completion of the case. The mean time to recovery, \textit{Td}/\textit{T1} ratio of 0.9, was 112 seconds. There were no patients with residual or recurrent neuromuscular blockade. None of the patients experienced adverse effects attributed to sugammadex.

In addition to these papers, sugammadex has been found to be effective in cases where intubation is not achieved and rapid reversal of neuromuscular blockade is necessary. Woloszczuk-Gebicka and colleagues describe a case in which administration of vecuronium during induction in a 10-month-old patient with stridor being evaluated for upper airway obstruction resulted in a “cannot intubate, cannot ventilate” scenario.\textsuperscript{12} The procedure was abandoned and an 8 mg/kg dose of sugammadex was administered to reverse neuromuscular blockade. Spontaneous ventilation occurred within 25 seconds and normal muscle tone within 90 seconds. The authors acknowledge the additional safety in managing these scenarios that sugammadex may provide.

\textbf{Warnings and Precautions}

Severe hypersensitivity reactions, including anaphylaxis and anaphylactoid reactions, have been reported after sugammadex administration during clinical trials and in routine clinical practice.\textsuperscript{2,5} Concern for these reactions delayed its approval in the United States and led the FDA to require additional data from the manufacturer to better estimate their frequency. A randomized, double-blind, placebo-controlled, parallel-group study was conducted in 375 adults randomized to receive 3 doses of sugammadex or placebo with a 5 week washout period between doses. The frequency of anaphylaxis in the two treatment groups (4 or 16 mg/kg) was 0.3%. A single patient in the 16 mg/kg group experienced urticaria, conjunctival edema, erythema, swelling of the uvula, and a reduction in peak expiratory flow within 5 minutes of the dose. Another similar trial of 298 patients reported three cases of anaphylaxis, resulting in an incidence of 1%.

In their 2014 case series, Takazawa and colleagues, estimated the occurrence to be 29 cases per 1,000,000 population.\textsuperscript{13} The authors described three cases, including that of a 13-year-old boy, the first pediatric anaphylaxis case reported. The case reports and case series describing the results of skin prick and intradermal testing in their patients have revealed
that while some patients react to sugammadex alone, others have reacted only to the sugammadex-rocuronium inclusion complex. Recommendations for evaluating potential cases of sugammadex-induced anaphylaxis, including appropriate skin testing, were published last year by Ue and colleagues in the Annals of Allergy Asthma and Immunology.

Clinically significant bradycardia has also been reported after sugammadex administration, including cases in adults that have progressed to cardiac arrest. All patients should be closely monitored for hemodynamic changes during and after neuromuscular blockade. Atropine should be available for administration in cases of significant bradycardia. Delayed or inadequate response to sugammadex has also occurred. Respiratory function monitoring should be continued until full recovery from neuromuscular blockade has occurred.

Adverse Effects
Data from 2,914 adults participating in clinical trials were used to determine the most commonly reported adverse effects following administration of sugammadex. Those occurring in 10% or more of patients included nausea, vomiting, headache, pain, and hypotension. After sugammadex doses of 2, 4, or 16 mg/kg, nausea was reported in 23-26%, with vomiting occurring in 11-15%. Headache was reported in 7-10% of patients, with pain reported in 36-52%. Hypotension occurred in 4-13%. There were no clear dose-related differences, other than a greater incidence of hypotension in the 16 mg/kg group. Hypersensitivity reactions were not common, with pruritus or erythema reported in only 1-2% of patients. Bradycardia was found in 1-5% of the patients.

Drug Interactions
Although sugammadex has a high binding affinity for aminosteroid nondepolarizing blocking agents, it may also bind endogenous or exogenous steroidal compounds. It binds estrogen and progestogens, potentially reducing the effectiveness of hormonal contraceptives. The manufacturer recommends use of a back-up or alternative form of contraception for 7 days following sugammadex administration. Toremifene, an oral selective estrogen receptor modulator used in the treatment of advanced (metastatic) breast cancer, has a high binding affinity for sugammadex and may displace vecuronium or rocuronium. Patients taking toremifene on the day of surgery may have a delayed response to sugammadex and should be monitored for residual neuromuscular blockade.

There is a potential for exogenous corticosteroids to impair the ability of sugammadex to reverse neuromuscular blockade. In an early in vitro study, dexamethasone was found to produce a dose-dependent inhibition of sugammadex reversal of neuromuscular blockade in innervated human muscle cells. In a recent double-blind randomized controlled study, Gulce and colleagues enrolled 60 children (3-8 years of age) undergoing tonsillectomy and/or adenoidectomy to study this drug interaction. The children received either 0.5 mg/kg dexamethasone IV or saline during surgery. All patients had received rocuronium 0.6 mg/kg. At the end of surgery, when a second twitch (T2) had reappeared, a single 2 mg/kg dose of sugammadex was administered. The time from sugammadex administration to achievement of a T4/T1 ratio of 0.9 was not significantly different between the groups, with a mean of 23.9 seconds (95% CI, 19.8-28.0) in the dexamethasone group and 23.0 seconds (95% CI, 18.8-27.1) in the controls. Heart rate and systolic and diastolic blood pressures were also similar between the groups. The authors concluded that dexamethasone produced no significant effect on sugammadex administration.

Availability and Dosing
Sugammadex is available in 200 mg/2 mL and 500 mg/5 mL single-use vials and may be stored at room temperature. A 4 mg/kg sugammadex dose is recommended for reversal in rocuronium- or vecuronium-induced neuromuscular blockade at a level of no twitch responses on TOF stimulation (T0), with a dose of 2 mg/kg recommended for patients with evidence of a second twitch response to TOF stimulation (T2). A single sugammadex dose of 16 mg/kg is recommended for rapid reversal of neuromuscular blockade produced by a single 1.2 mg/kg dose of rocuronium. Sugammadex is not recommended for use in patients...
with severe renal impairment. No dosage adjustment is needed in patients with mild to moderate renal impairment or hepatic impairment.

Sugammadex should be dosed using actual body weight and administered over 10 seconds into an existing IV line. It is compatible with most IV fluids, including 0.9% sodium chloride, 5% dextrose, 5% dextrose and 0.9% sodium chloride, 2.5% dextrose and 0.45% sodium chloride, Ringer’s lactate solution, and Ringer’s solution. It is not compatible with ondansetron, ranitidine, or verapamil.2

Summary
Sugammadex offers a unique alternative to neostigmine for reversal of aminosteroid nondepolarizing neuromuscular blocking agents. It provides a rapid return of function, facilitating earlier extubation. While it is currently approved by the FDA only for use in adults, early off-label experience in infants and children has been positive. Controlled trials, as well as continued post-marketing surveillance studies and larger case series, will be needed to confirm the safety of sugammadex in both children and adults.

References

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