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Yearbook *of* Anesthesiology-9



Yearbook

Indian College of Anaesthesiologists

Editors
Raminder Sehgal
Anjan Trikha

Foreword
Baljit Singh

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CHAPTER

4 Sugammadex and Beyond

Vinh Nguyen, Kumar Belani

INTRODUCTION

A major advance in the clinical practice of anesthesia to improve the reversal of steroidal nondepolarizing neuromuscular agents (NDNMA) was introduced by the drug, sugammadex. Sugammadex is a modified cyclodextrin, and its chemical structure was designed to from an inclusion complex with steroidal compounds rendering the molecule inactive. Sugammadex was modified from its parent compound to encompass all four hydrophobic rings of the neuromuscular blocking agent (NMBA) in its lipophilic cavity. Within the cavity, there is an electrostatic interaction between the negatively charge acidic groups (COO^-) and the positively charge nitrogen of the NMBA. In a rocuronium-induced blockade, these sequestration mechanisms encapsulate free floating rocuronium causing a diffusion gradient to allow rocuronium-bound nicotinic receptor to dissociate as free plasma and be further neutralized by sugammadex. This process is immediate and continues to create a diffusion gradient until all the rocuronium is uncouple from the neuromuscular junction.[1]

SUGAMMADEX VERSUS ANTICHOLINESTERASE INHIBITORS

Sugammadex was first approved in the European Union in 2008 for clinical usage and other countries followed suit.[2] It had been recently approved for clinical use in the United State of America by the Food and Drug Administration (FDA) in 2015.[3] Prior to sugammadex, the only effective reversal agent was the anticholinesterase (AChE) inhibitors, in particular neostigmine and pyridostigmine. Some of the disadvantage of AChE inhibitors included their limited efficacy in reversing deep blockade, which caused the speed of recovery to be unpredictable and a ceiling effect reached when the AChE inhibitors are 100%. Therefore, AChE inhibitors can only be used if the neuromuscular function returned to some degree. Numerous unwanted adverse effects such as bradycardia and hypersalivation have been linked to AChE inhibitors thus, a coadministration of an anticholinergic is required.

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Overall, sugammadex is a new and novel reversal agent which may be the answer to previous old problems.

Although the reversal of sugammadex is rapid, neuromonitoring is still essential to ensure a return of motor function. Residual muscle paralysis still remains a complication even with the use of sugammadex. Multiple case reports of recurarization have occurred after sugammadex when it was given to an intensive care patient postrocuronium infusion, an obese individual, and a pediatric patient undergoing cardiac catheterization.[4-6] Train of four ratio (TOFR) should be monitored exclusively during any NDNMAs and reversed with the appropriate dose. Patient with a deep block, no train of four (TOF) but a post-tetanic count (PTC) of 1–2 will require 4 mg/kg^{-1}. Full recovery at TOF 0.9, was 17 times faster (2.7 min) than 0.07 mg/kg^{-1} neostigmine (49 min) at the recommended dose of 4 mg/kg^{-1}.[7] A recent observational study reported that sugammadex was significantly faster compared to neostigmine independent of the level of blockade, shallow block: 2.2 versus 6.9 min and deep block: 2.7 versus 16.2 min respectively.[8] Pongracz et al. looked at the appropriate dose for four twitches of TOF and found that 1.0 mg/kg^{-1} was appropriate for a TOF >0.9 recovery in 2.1 min.[9] Furthermore, sugammadex at 0.22 mg/kg dose effectively and comparably reverse a rocuronium-induced shallow residual neuromuscular block at a TOF ratio of 0.5 (Table 1).[10] Currently, there is no dose recommendation for vecuronium-induced neuromuscular block. Sugammadex affinity for vecuronium-induced blockade is less compared to rocuronium. In fact, sugammadex had approximately 2.5 times the affinity for rocuronium.[11] Vecuronium took twice as long as rocuronium (3.0 min vs 1.5 min) after sugammadex reversal.[12] Similarly, Duvaldestin et al. showed a slow speed of recovery of 3.3 min with vecuronium when the PTC of 1–2.[13] A dose-response

Table 1: Recommended sugammadex dose to reverse rocuronium blockade.

Sugammadex dose	*Depth of NMBA*	*Mean recovery time to TOF 0.9*	*Studies*
16 mg/kg^{-1}	After 1.2 mg/kg^{-1} of rocuronium	1.5 minutes	De Boer et al.[56]
4 mg/kg^{-1}	Deep block, PTC 1–2	3 minutes	Jones et al.[7] Della Rocca et al.[8]
2 mg/kg^{-1}	Moderate block, two twitches to TOF	2 minutes	Pland et al. Della Rocca et al.[8]
1 mg/kg^{-1}	Four twitches to TOF	2 minutes	Pongracz et al.[9]
0.22 mg/kg^{-1}	TOF 0.5	2 minutes	Schaller et al.[10]

(kg: kilogram; mg: milligram; NMBA: neuromuscular blocking agent; PTC: post-tetanic count; TOF: train of four)

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relationship between vecuronium and rocuronium at different dose of sugammadex was done and consistently showed a slower recovery from vecuronium.[14]

SPECIAL CONSIDERATIONS

Morbid Obesity

The use of NMBAs in morbidly obese patients can cause significant postoperative complications in the recovery phase, if reversal is inadequate. Critical respiratory events include airway obstruction, hypoventilation, hypoxia, hypercapnia, and aspiration, and these can lead to acute respiratory failure. Sugammadex had shown promising effect to rescue postoperative residual recurarization after neostigmine was ineffective in the recovery room for a morbidly obese patient.[15] Patient receiving sugammadex compared to neostigmine recovered (TOFR 0.9) three time faster, 2.7 min versus 9.6 min, respectively.[16] Furthermore, patients undergoing laparoscopic removal of adjustable gastric banding demonstrated faster postanesthesia care parameters; improved TOFR, ability to swallow, ability to get into bed independently, and discharge to surgical ward earlier.[17] Thus, rapid recovery from sugammadex can be beneficial for morbidly obese patient to fast-track bariatric surgery and in ambulatory setting. Although the reversal of NMBAs with sugammadex was faster than neostigmine, postoperative respiratory complications had not been fully elucidated. Ezri et al. had found no difference in the incidence of respiratory complications but rather a higher SpO_2 in the sugammadex group. Despite the statistical difference in SpO_2, its clinical importance seemed to be minimal and no postoperative respiratory events were noted.[18] There will need to be more large, prospective, randomized trials to evaluate the benefit of sugammadex to decrease postoperative respiratory complications in this population.

Pediatric Population

Sugammadex has been widely studied in adults but has not received FDA approval in the pediatric population. The appropriate dose-response studies in the pediatric group have not been well defined. The pharmacokinetic (PK) and pharmacodynamic profile of rocuronium in infants and children differ from adult patients. In infants and children, the clinical duration was longer and the potency of rocuronium was greater compared to adults. The group from Europe employed a multicenter, randomized group study to explore the efficacy and safety in infants, children, adolescent, and adults. When the reappearance of T2 of the TOF was seen, either placebo or sugammadex was randomly assigned and the median recovery time to TOF 0.9 was measured. The placebo group recovery time was 21, 19, 23.4,

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and 28.5 min in infants, children, adolescents, and adults, respectively. After 2.0 mg/kg sugammadex, the TOF 0.9 was 0.6, 1.2, 1.1, and 1.2 min, respectively. Therefore, this initial dose-response study explained the similarities in the recovery of neuromuscular blockade between the pediatric and adult group.[19] Furthermore, a systematic review of nine studies comparing sugammadex to neostigmine indicated that sugammadex can reverse rocuronium-induced neuromuscular blockade more rapid with a lower incidence of bradycardia.[20] One area that sugammadex may benefit pediatric patients was those with neuromyopathic conditions. In myotonic dystrophy patients, reversal with neostigmine can precipitate myotonia crisis therefore making sugammadex an attractive alternative. Sugammadex was successful in reversing myotonic dystrophy without perioperative complications or exacerbation.[21,22] Certain other underlying conditions including Duchenne muscular dystrophy, myotonic dystrophy, and myasthenia gravis caused the neuromuscular junction to be highly sensitive to NMBAs and experience residual weakness.[23-25] These case reports highlighted the importance of using sugammadex for a safe and rapid recovery from NMBAs. In another report, the role of sugammadex was essential for airway rescue and this needs to be entertained in the difficult airway algorithm. Woloszczuk-Gebicka B et al. reported a case in a 9-month-old infant who fell into the "cannot intubate-cannot ventilate" scenario. Sugammadex (8 mg/kg^{-1}) was administered and spontaneous ventilation was achieved within 25 sec.[26]

Elderly Population

The increasing number of elderly patients with comorbidities has greatly impacted the clinical practice of anesthesia. The elderly patients are at high risk for postoperative residual neuromuscular blockade resulting in muscle weakness, airway obstruction, respiratory failure, hypoxemia, atelectasis, and pneumonia. Therefore, reversal drugs are an important part of the anesthetic practice. The use of neostigmine has reduced the risk of residual neuromuscular blockade but has not eliminated this complication in the recovery period. In the elderly group, the increase chronic disease and receptor sensitivity may alter the PKs of sugammadex. McDonagh et al. demonstrated a prolong recovery time to a TOFR 0.9 with old-elderly patients (>75 years) compared to adults (18–64 years) 3.6 min versus 2.3 min, respectively.[27] In a recent prospective study by Yazar et al., TOF 0.9 recovery in older elderly (greater than 75 years) versus young elderly (65–74 years) was prolonged, 5.5 min versus 3.27 min, respectively.[28] Muramatsu et al. suggested that elderly patients were at the greatest risk for recurarization and residual muscle paralysis when low dose sugammadex was administered. The slower spontaneous TOFR and impaired renal function were two major contributing factors that decreased TOFR change rate in response

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to low-dose sugammadex.[29] In a clinical series performed by Suzuki et al., a complete reversal of deep muscle paralysis using 4 mg/kg took longer in elderly patients.[30] All these studies were consistent demonstrating a prolonged recovery in the older patient with either a moderate or deep block. On average, the rocuronium-induced NMBA reversal is prolonged by at least 1–2 minutes in the elderly than in young adults.

ADVERSE EFFECTS

Hypersensitivity and Anaphylaxis

The approval of sugammadex for USA was delayed until 2015 due to hypersensitivity concerns. In general, perioperative anaphylaxis is a life-threatening condition most commonly reported occurring with NMBAs. Among the steroidal NMBAs, rocuronium has a higher rate of IgE-mediated anaphylaxis.[31] With the availability and widespread use of sugammadex to encapsulate and reverse steroidal NMBA, there had been confirmed cases of allergic anaphylactic reactions with clinical doses triggering significant shock.[32,33] However, the number of reported sugammadex-induced anaphylaxis was much less than those associated with NMBAs. Dose-related hypersensitivity reactions had been reported with its use. A joint study by de Kam et al. reported hypersensitivity or anaphylaxis reactions to sugammadex to be dose dependent. Hypersensitivity occurred in 0.7% and 4.7% after sugammadex 4 mg/kg^{-1} and 16 mg/kg^{-1}, respectively.[34] The incidence of hypersensitivity and anaphylaxis with sugammadex had a low overall score (<1%) compared to placebo or neostigmine. The incidence of spontaneous reports of anaphylaxis was similar in a perioperative setting in which NMBAs had been administered. Approximately, 15–34 confirmed cases per 100,000 operations occur corresponding to a risk of 0.015–0.034%. On the other hand, sugammadex might be a novel drug to manage rocuronium-induced hypersensitivity or anaphylaxis. Sugammadex was used successfully to rapidly resolve the pseudo-allergic reaction as seen during intradermal testing on three patients.[35] There were several reports that suggested the possibility of hemodynamic improvement in a rocuronium-induced anaphylaxis by the administration of sugammadex.[35-37]

Whether this beneficial effect was due to the inhibition of IgE-mediated activation of mast cells remains unknown. Despite this potential therapy rescue by sugammadex, there had been suspicion that the sugammadex-rocuronium inclusion complex may give rise to an allergic response. The physical and chemical properties of a drug and its host carrier can be altered, thus exposing certain molecule groups to be an antigen. There had been a few reported cases of this nature via positive skin testing for the inclusion complex while the same subjects demonstrated a negative skin

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test for the individual drug of sugammadex and rocuronium.[38-40] Although sugammadex can cause hypersensitivity or anaphylaxis, its incidence was similar to that generally observed in the perioperative suite in the setting of NMBA use. The likelihood was greatest at higher dose and can occur within 4 min.

Myth of Anticoagulation

Preclinical *in vitro* studies demonstrated that sugammadex can increase activated partial thromboplastin time (aPTT) and prothrombin time (PT).[41] Two sugammadex clinical doses, 16 mg/kg^{-1} and 4 mg/kg^{-1}, were analyzed for its coagulation effects. Both caused a transient increase in aPTT and PT but resolved quickly (<30 min).[41] In a prospective observational study, 131 patients in either the 2 mg/kg^{-1} or 4 mg/kg^{-1} sugammadex groups were tested for coagulation tests and bleeding in a clinical setting. The authors concluded that neither groups were associated with a longer clotting time or decreased hemoglobin concentration.[42] The results obtained with thromboelastography (TEG), however, provided a different result but only at high blood concentrations of sugammadex. The two highest concentrations of sugammadex 16 and 32 mg/kg^{-1}, significantly altered all TEG parameters. However, the therapeutic concentration of 4 mg/mg^{-1}, did not induce any clinical changes in any TEG parameters.[43]

RELATIVE CONTRAINDICATIONS AND CAUTIONS

Renal Dysfunction

Sugammadex is exclusively excreted by the kidneys in healthy volunteers with minimal radioactive 14 C-labeled sugammadex in blood, feces, and exhaled air.[44] Trials had been done to evaluate the safety of sugammadex on rocuronium-induced blockade in renal failure. The PK relationship of sugammadex reflected a large difference in severe and end-stage renal disease compared to normal renal function patients. Although the clearance is decreased, these renally impaired patients were monitored for 48 hours without any sign of recurarization.[45] Two independent studies measured the efficacy and safety of sugammadex in severe renal impairment after reversing a deep neuromuscular block with 4 mg/kg^{-1}. In the renal impairment group, neuromuscular recovery was slower than the healthy patients and neither of the studies demonstrated recurrence of blockade.[46,47] After binding with rocuronium, the sugammadex-rocuronium complex is highly stable. It has a very low dissociation rate ($K_d = 0.1 \times 10^{-6}$ M) due to the strong binding forces.[48] As a result, the complex may remain intact in the plasma for days, thus limiting any clinical complications or recurrence of neuromuscular blockade. The muscle relaxant reversal is dependent on the encapsulation

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by sugammadex to neutralize muscle blockade effect and not the excretion of the complex in the urine.[49] One should note, however, that the current literature does not specify the appropriate safe use of sugammadex for patient with creatinine clearance <30 mL/min.

Contraceptive Use

Since the FDA approval of sugammadex in 2015, multiple institutions are changing their anesthesia consents to caution childbearing women about the interaction of sugammadex and contraceptives. Sugammadex had been shown to interact with progesterone, as found in progesterone only and combined oral contraceptive preparations, vaginal rings, implants, and intrauterine devices. A dose of 4 mg/kg^{-1} sugammadex had been predicted to decrease progesterone exposure by 34%, similar to a daily oral dose taken 12 hours too late. According to the package from Merck & Co, Inc., section 5.6, specified a potential lowering of the free plasma concentrations of hormonal contraceptive. Furthermore, section 7.3 stated that a dose of sugammadex is equivalent to missing a dose of oral contraceptives. Those patients taking oral hormonal contraceptive must refer to the package label and follow the directions for a missed dose. Those women using nonoral hormonal contraceptives must be advised to use additional nonhormonal contraceptive methods or a backup method of contraception (e.g. condoms) for the next 7 days.

FUTURE REVERSAL AGENTS

Sugammadex has been a novel discovery in revolutionizing the reversal of NMBAs. Over the past decade, a newer class of drug called calabadion has been tested for anesthetic usage. This drug came from an acyclic member of the Cucurbit[n]urils family of "molecular containers", similar to the cyclodextrins class of host-guest complexes. The structure contains a central glycoluril tetramer backbone which forms a C-shaped configuration to capture specific targets. The flexibility of the molecule allows the cavity to expand and accommodate different drug targets of various sizes.[50] Two different cucurbiturils compounds, calabadion 1 (CB1) and calabadion 2 (CB2), have been reported to reverse both steroidal and benzylisoquinoline NMBAs via encapsulation in the same 1:1 binding ratio as sugammadex. Originally, the first generation CB1 was the first used to reversed deep cisatracurium-induced NMB. The newer second-generation formulation, CB2, was shown to have a five times higher affinity toward cisatracurium.[51] Although calabadions successfully bind to benzylisoquinolines NMDAs, they have a much lower affinity than steroidal NMBAs group. The *in vitro* study of CB1 has a high affinity for rocuronium but inferiorly compared to

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sugammadex. On the other hand, CB2 affinity for rocuronium was nearly 20,000 times that for acetylcholine compared to CB1, which was only 350 times that for acetylcholine.[52] A head-to-head comparison of CB2 potency to sugammadex has been established. CB2 binds rocuronium 89 times stronger than sugammadex, as it requires a lower number of molecules to allow a faster recovery phase compared to sugammadex.[53] Since calabadions have a more effective binding capacity for other classes of drug beside NMBAs, they should be considered a broad-spectrum reversal agent. Unlike sugammadex, calabadions have no coagulation inhibitory effect and lower allergenic profile due to the lack of sugar moiety. These less adverse effects make calabadions an idea reversal agent in the near future.

Other Novel Reversal Drugs

Gantacurium, the first isoquinolinium muscle relaxant group described in the early 1990s, was found to have a rapid and a wide safety margin. It was considered an ultrarapid nondepolarizer muscle blocker due to its quick chemical degradation. Unlike cisatracurium or atracurium, gantacurium is rapidly hydrolyzed by a nonenzymatic chemical reaction which involves endogenous cysteine adduction. A cysteine adduction is due to a replacement of chlorine (native gantacurium) by cysteine, which forms a heterocyclic ring (modified gantacurium). This chemical ring formation prevents the interaction of modified gantacurium to the neuromuscular junction, rendering it inactive.[54] Due to the fact that the drug had a poor safety profile (histamine release and bronchospasm), gantacurium was modified to prevent these adverse effects. An intermediate isoquinolinium muscle relaxant group, CW002, was developed and designed to interact more slowly with endogenous L-cysteine and degraded in the same fashion as gantacurium. CW002, a benzylisoquinolinium fumarate diester, was studied in human subjects with no cardiopulmonary side effects or histamine release but rapidly reversed with L-cysteine administration.[55] Exogenous L-cysteine is nontoxic and commonly administers in human as an essential component of parenteral nutrition. In the new age of reversal agents, sugammadex has begun a new wave of customized reversal with a higher safety profile (Table 2).

Although the FDA has approved the use of sugammadex, the concerns over the potential for hypersensitivity or anaphylactic reactions, bradycardia and even asystole have made clinicians more aware of its potential adverse effects. Therefore, this newer NMBA and its exclusive reversal using L-cysteine may play an essential role for an emerging family of selective relaxant binding agents with limited adverse effects.

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Table 2: Summary of the new reversal agents for neuromuscular blocking drugs.

Agents	*Structure*	*Target*	*Mechanism*	*Developmental stage*
Sugammadex	Cyclodextrin	Steroidal compounds	Envelops NMBA with high affinity binding	FDA approval USA in 2015
Calabadion	Acyclic Cucurbit[n]uril	All NMBAs	Promote binding affinity to NMBA and then engulf	Not approved yet
Cysteine	Amino acid with thiol side chain	Novel isoquinoliniums	Cysteine adduction	Not approved yet

(FDA: food and drug administration; NMBA: neuromuscular blocking agents; USA: United States of America)

CONCLUSION

Sugammadex is the most recent approved drug to reverse the effect of rocuronium. It can also, reverse vecuronium but the reversal is slower. As a benefit, its use does not require the addition of anticholinergics. The usual clinical dose ranged from 2 mg/kg^{-1} to 4 mg/kg^{-1} and is based upon the TOF recovery profile. The drug has an acceptable side effect profile with a low incidence of an allergic response. The hypersensitivity or anaphylaxis mechanism is still undetermined but may be considered as a rescue agent for rocuronium-induced anaphylaxis. The speed of onset of rocuronium-induced neuromuscular block is based upon the dose of sugammadex. Larger doses have been used successfully to rapidly reverse a strong rocuronium-induced neuromuscular block. In the different generation classes, pediatric patient showed similar results as adult unlike elderly patients, sugammadex reversal is prolonged up to 2 min. The drug may promote fast-tracking in the morbidly obese patient especially for same day surgery. The coagulation profile was not elevated unless dose is higher than 4 mg/kg^{-1} as reported with TEG. Sugammadex forms a strong bond with rocuronium that is exclusively excreted by the kidneys. The strength of its interaction did not demonstrate any sign of recurarization in renal dysfunctional patient. Although the data is limited for patient with stage 4 kidney disease or higher, caution is still needed for these types of patients. In addition, those patients who are using oral or nonoral contraceptives need to perform abstinence or to use other forms of contraception for 7 days after sugammadex administration. Sugammadex has been the cornerstone and prototype for other reversible agents. The future is bright for newer reversal

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agent such as calabadion, a broad spectrum NBMAs for steroidal and benzylisoquinoline molecules. As well, exogenous L-cysteine has a unique mechanism that promotes adduction of a new NMBA, isoquinoliniums, to impair its function and inactive the molecule.

KEY POINTS

- Sugammadex acts by encapsulating only steroidal nondepolarizer muscular relaxants and eliminating them as an inclusion complex via the kidneys.
- The reversal is rapid compared to anticholinesterase inhibitors thereby limiting potential adverse outcomes.
- Clinical recovery time from sugammadex is similar in adult and children.
- In obese patients, it may improve fast recovery in an outpatient setting but may not eliminate postoperative respiratory complications.
- In elderly patients, recovery from sugammadex is prolonged by 1–2 minutes.
- Hypersensitivity to sugammadex has the same incidence rate as other potential drug allergens.
- Delayed blood coagulation by sugammadex has a limited effect at clinical dose.
- Sugammadex efficacy on renal dysfunction patient is still unknown.
- Sugammadex may lower the efficacy of hormonal contraceptives because of its interaction with progesterone.
- Calabadion is a new broad-spectrum drug that engulfs all types of nondepolarizer muscle relaxants.
- Exogenous L-cysteine rapidly inactivates isoquinolinium type non-depolarizer.

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