Clinical Considerations of Sugammadex

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Abstract

This purpose of this research was to assess and improve the level of understanding of the newly FDA approved drug Sugammadex within the Adventist University Student Registered nurse anesthetist (SRNA) population regarding indications for use, dosing, pharmacological profile, and side effects of the new drug. Our goal was to increase knowledge of the students so that they would feel more comfortable using the new reversal agent if the opportunity presented in the clinical setting or future practice. An extensive literature review was performed to create a thorough teaching module for the SRNA students. A pre-test was administered prior to the teaching module being presented. A teaching module on Sugammadex was presented to the SRNA students and was followed by a post-test. The pre-test and the post-test were given to evaluate whether the teaching on Sugammadex had been effective. Statistical analysis using a paired t-test showed that average scores increased significantly between pre-test and post-test administrations. The mean pre-test score was 5.9 with a standard deviation of 2.30718. In comparison, the mean post-test score was 9.275 with a standard deviation of 1.37724. Therefore, the average scores increased significantly between pre-test and post-test administrations. The Sugammadex teaching module was an effective tool that can be used to educate SRNAs and possibly CRNAs in the future.

Problem Statement

The FDA approved Sugammadex for use in the United States in December 2015. Sugammadex has been used outside of the U.S. for many years. Sugammadex was first patented in 2001, with the first human study published in 2005 (Murphy, 2016). As of March 2015, Sugammadex had been approved in 57 countries with more than 11 million patients having received the drug (Murphy, 2016). When a new drug comes out on the market, providers are often uncomfortable with its use due to lack of knowledge and experience with the new drug, making them less likely to use the new drug when indicated or beneficial in certain clinical scenarios.

Sugammadex is very different from the traditionally used reversal agents such as Neostigmine. Our goal is to increase knowledge so that anesthesia providers, specifically, Student Registered Nurse Anesthetists (SRNAs), will be able to use Sugammadex for complex patient's providing them with the best perioperative outcomes possible. SRNAs will eventually be administering anesthesia care on their own, and understanding the clinical applications of Sugammadex will enable them to provide the best care possible during situations in which Sugammadex may prove beneficial.

The purpose of this project was to create a teaching module to educate the SRNA population at Adventist University of Health Sciences (ADU) regarding the clinical considerations of Sugammadex. Upon talking to other SRNAs in our class, we discovered that little is known about how Sugammadex is administered, the indications for it, and its pharmacological profile. Clinically there are circumstances where reversal with Sugammadex would be superior to Neostigmine; however, the anesthetist must be cognizant of the dosing and the pharmacological effects of the drug. A pretest was administered prior to a teaching module

being presented to assess baseline knowledge of Sugammadex. A thorough teaching module was then presented to the SRNA students. A post-test (same test) was given after the teaching module. Our anticipated outcome was that the posttest scores would be higher than the pretest scores, indicating that the teaching module on Sugammadex was effective.

Review of Literature

Neuromuscular blocking drugs (NMBDs) are used everyday in anesthesia for tracheal intubation and to facilitate optimal surgical conditions providing muscle relaxation for surgery. Until recently, NMBDs were only reversed with acetylcholinesterase inhibitors such as Neostigmine and Edrophonium. Such drugs carry a risk for unwanted side effects such as bradycardia, bronchoconstriction, and increased risk of post-operative nausea and vomiting (PONV) (de Boer et al., 2007). Additionally, anticholinergics must be given to counteract the negative side effects of anticholinesterase inhibitors. Those too carry unwanted side effects. Sugammadex works differently from traditional reversal agents. It is a cyclodextrin selective binding agent that binds to steroidals by forming a tight complex, encapsulating the unbound steroidal molecule, thus preventing action at the neuromuscular junction (Jones et al., 2008). Now that Sugammadex is available, there are more options for reversal of NMB. However, the anesthetist must be aware of the indications of Sugammadex, dosing, and its pharmacological profile.

A multi-centered study by de Boer et al. (2007) was conducted with 43 patients induced with Rocuronium 1.2 mg/kg. The study found that Sugammadex given 5 minutes after Rocuronium administration reduced the mean recovery time by 122 minutes. A study by Jones et al. (2008) compared the efficacy and safety of Sugammadex to Neostigmine. Sugammadex reversal was achieved within 5 minutes whereas Neostigmine reversal took 60 minutes (Jones et

al., 2008). Faster recovery leads to improved outcomes for patients. In addition, Sugammadex reduces risk of residual neuromuscular paralysis, thus improving post-operative patient outcomes.

In anesthesia practice, providers are commonly presented with scenarios in which paralytic effects are only desired for a short duration. Up until the FDA approval of Sugammadex, the only known paralytic that would suffice under these circumstances was Succinylcholine. The ability to administer Sugammadex, now offers providers the ability to rapidly reverse longer acting steroidal NMB drugs. Therefore, decreasing their duration of action to rates similar to that of Succinylcholine. This opportunity now allows providers an alternative to Succinylcholine with steroidal paralytics in situations where muscle paralysis is only desired for a short duration. Studies have shown that the mean time to recovery from profound Rocuronium induced neuromuscular block were reduced to 4.4 minutes to 6.2 minutes, therefore, significantly shorter than the respective times to spontaneous recovery from succinylcholine muscular blockade, which was 7.1 to 10.9 minutes (Lee et al., 2009).

Geldner et al. (2012) conducted a different study with 140 participants evenly distributed into two groups, one receiving Sugammadex and the other Neostigmine. This study revealed that Sugammadex achieved recovery 3.4 times earlier than those that received Neostigmine. TOF recovery times were significantly decreased in the Sugammadex group when compared to those in the Neostigmine group. In comparison, return of the TOF ratio to 0.9 in the Sugammadex group was 2.4 minutes versus 8.4 minutes in the Neostigmine group (Geldner et al., 2012). The patients in both groups remained in the operating room (OR) for a similar period of time. However, tracheal extubation was achieved earlier in the Sugammadex group by a clinically significant mean time of 6.5 minutes, $p < 0.001$ (Geldner et al., 2012).

This study offers anesthesia providers the potential benefits of providing deep neuromuscular blockade towards the end of surgery without fear of incomplete reversal with the use of Sugammadex. These benefits include providing the surgeon with improved surgical conditions while decreasing potential surgical complications and pain for the patient. Studies have shown, patients undergoing laparoscopic cholecystectomy may experience less pain postoperatively due to decreased pneumoperitoneum pressures achieved with deep neuromuscular blockade (Geldner et al., 2012).

Another scenario in which Sugammadex is extremely beneficial is the "can't intubate, can't ventilate scenario" (Paton et al., 2013). Administering Rocuronium in this scenario is never ideal, however, Sugammadex can be life saving in the event that this does occur. An actual case study by Paten et al. (2013) discussed the usefulness of Sugammadex in the can't intubate, can't ventilate scenario. The administration of Sugammadex saved the patient from significant hypoxia or the back up plan of having an emergency surgical tracheal access. The patient had a history of difficult airway, and it was predicted that mask ventilation would be possible. Plan A, B, C, and D was devised for this patient. The patient was induced with Propofol, and Rocuronium was given after unsuccessful mask ventilation, in hopes of ventilation being possible after the patient was relaxed. After failure to ventilate and administration of Rocuronium, Sugammadex was given to reverse the patient. The patient had return of spontaneous ventilation within 1 minute. This would not have been possible if Succinylcholine had been given. The authors pointed out that they could be criticized for not attempting to instrument the airway.

Another valuable use for Sugammadex is for the complex patient with a neuromuscular disorder. Anesthesia providers constantly struggle determining the appropriate dose of paralytic to administer, if any to patients with myasthenia gravis (MG). Furthermore, there is a strong

debate of whether the anesthesia provider should continue or suspend anticholinergic therapy along with determining appropriate doses to administer when reversing previously administered paralytic. In patients with MG, the risks are higher for prolonged ventilatory support and residual neuromuscular blockade. Fortunately, a study by Sungur et al. (2013) has now supported evidence that the administration of Sugammadex for reversal of Rocuronium can provide a complete and rapid recovery of neuromuscular blockade for such patients.

While Sugammadex has many benefits, it also has some side effects that the anesthetist must be aware of. The most common reported adverse side effects include nausea, headache, pain, and hypotension (Merck, 2015). Although rare, hypersensitivity may be a major concern with Sugammadex. Anaphylaxis has occurred in 0.3% of healthy volunteers (Merck, 2015). Such cases of anaphylaxis were reported within 4 minutes or less of administration of Sugammadex (Ledowski, 2015). The anesthetist must be vigilant in monitoring for signs of a reaction immediately after administration. Marked bradycardia has been reported within minutes after administration of Sugammadex, in some cases cardiac arrest was noted. It is important to be astute to hemodynamic changes and treat with an anticholinergic if needed. However, a study conducted by Geldner et al. (2012), determined that serious adverse events were less likely with the administration of Sugammadex in comparison to Neostigmine. Out of 1,321 patients in 18 clinical trials, the occurrence of documented adverse events was less than 1% (Welliver et al., 2015).

Another consideration for the use of Sugammadex is postoperative nausea and vomiting history (PONV). In a study by Koyuncu et al. (2015), nausea and vomiting scores were found to be significantly lower with Sugammadex administration when compared to Neostigmine upon arrival to PACU; $P<.05$. In review of the 24-hour postoperative period there was no statistical

significance of PONV among the two groups; P>.05. Another significant finding of the study was that patients receiving Neostigmine in comparison to Sugammadex experienced a higher incidence of bradycardia within a 24-hour postoperative period, 14% versus 2% respectively. The study concluded patients that received Sugammadex were noted to only have a slight reduction in PONV when compared with the patients receiving Neostigmine and Atropine. Additionally, no benefits were noted in terms of oral intake, ambulation, and return of gastrointestinal function (Koyuncu et al., 2015).

Also, drug-to-drug interactions may occur with Sugammadex. It is important to understand that Sugammadex binds to steroids. Patients taking oral contraceptives must be informed of the possibility of reduced efficacy. Displacement interactions can cause delayed recovery from NMB, in patients taking toremifene when Sugammadex is given (Merck, 2015). It is important to note concerns regarding interactions with Dexamethasone. Recent research has shown prophylactic Dexamethasone for PONV does not interfere with reversal of moderate NMB (Buonanno et al., 2016). Another important consideration when administering Sugammadex is compatibility. It is physically incompatible with ondansetron, verapamil, and ranitidine, so flushing of the line is important when administering Sugammadex (Merck, 2015).

Sugammadex comes in 100 mg/ml either in 2 mL or 5 mL vials. It is administered as a single bolus injection. Merck recommends for Rocuronium and Vecuronium induced paralysis a dose of 4 mg/kg for zero twitches on a train-of-four (TOF) response and spontaneous recovery of the twitch response of 1-2 post tetanic counts. If the reappearance of a second twitch has occurred on TOF, then Merck (2015) recommends a dose of 2 mg/kg for reversal of Vecuronium and Rocuronium. A dosage of 16 mg/kg is only recommended for Rocuronium when reversal needs to be achieved within 3 minutes after a dose of Rocuronium 1.2 mg/kg has been given**.**

The literature is conflicting on whether Sugammadex dosing should be based on ideal or total body weight in the obese patient. However, high dose Sugammadex of up to 96 mg/kg has been found to be safe and effective (Welliver et al., 2015). Sugammadex cost correlates with the dose administered to the patient. Therefore, providers have attempted to reduce the overall cost of Sugammadex by administering the drug based on ideal body weight rather than total body weight. Studies have shown that dosing Sugammadex on ideal body weight has the potential for producing an incomplete reversal of NMB. Merck and Welliver recommend dosing Sugammadex based on total body weight.

After reversal by Sugammadex, re-administration with a steroidal NMB is possible but may be difficult due to the necessity to occupy the remaining Sugammadex molecules. Therefore, a larger dose of steroidal paralytics must be administered. It is important for the provider to be aware of the pharmacokinetics of Sugammadex prior to dosing and re-administration of NMB. The renal elimination time in an anesthetized patient with normal renal function is 8 hours (Welliver et al., 2015). Additionally, no metabolites have been observed in studies, and renal excretion remains the only route of elimination (Merck, 2015). Sugammadex has an expected elimination time of 8 hours in patients with normal renal function. After complete elimination of Sugammadex has occurred, it is easy for providers to re-establish NMB if necessary.

Merck (2015) suggests a minimum wait time of 5 minutes after the administration of Rocuronium 1.2 mg/kg prior to the re-administration of NMB. If the re-administration occurs within 30 minutes of reversal with Sugammadex, the onset of the NMB may be delayed approximately 4 minutes and the duration of NMB may be decreased approximately 15 minutes

(Merck, 2015). If Sugammadex 16 mg/kg was administered for the reversal of Rocuronium or Vecuronium a waiting period of 24 hours is suggested for the re-administration of a steroidal NMB. Additionally, if a NMB is necessary prior to the recommended waiting period, the use of a nonsteroidal neuromuscular blocking agent should be administered. It is also important for the provider to be aware that the onset for a depolarizing NMB may be slower than expected due to a substantial amount of post-junctional nicotinic receptors remaining occupied by NMB agents (Merck, 2015).

Project Description

The purpose of this capstone was to provide an educational presentation regarding Sugammadex for 25 SRNAs in the junior class and 20 SRNAs in the senior class at ADU. Once a thorough literature review of Sugammadex was completed, areas regarding dosage, indications, side effects, and contraindications were identified and focused on in the teaching module. This information was extrapolated to identify potential benefits to the administration of Sugammadex in the anesthesia setting. Prior to presentation of the material and evaluation of the SRNAs at ADU, informed consent of all participants was obtained.

Once the informed consent was obtained from a convenience sample of 45 SRNAs, an anonymous pre-test and post-test was administered. The pre-test was given to the 2017 and 2018 ADU SRNA cohorts prior to the power point presentation. After completion of the pre-test a detailed power point presentation for the ADU SRNAs regarding Sugammadex was given. Once the presentation was completed, a post-test was administered using an identical test to compare the difference in scores and understanding. A numbering system was incorporated into the pre and post-test to protect the privacy of the participants. No identifying data was collected to ensure the participant's privacy. The primary goal of this capstone was to increase the level of

understanding of Sugammadex among the ADU SRNA population in regards to dosing, indications, side effects, adverse effects, contraindications, and potential benefits.

Evaluation Plan

This capstone project was submitted to the ADU Scientific Review Committee (SRC) and the Institutional Review Board (IRB). After approval from both committees was obtained and the informed consent was signed by all participants, the study was carried out. The success of this capstone project was evaluated and determined through the use of a multiple-choice pre and post-test. The testing evaluated the level of understanding the ADU SRNAs in the 2017 and 2018 cohorts have regarding Sugammadex after having received a teaching module. The tests presented to the students contained questions related to the dosing, indications, side effects, adverse effects, contraindications, and potential benefits for the use of Sugammadex in anesthesia practice. Additionally, the pre-test was anonymous and a numerical identification system was used to help link the pre-test to the post-test to allow for comparison of the results.

Once the presentation was complete the presenters administered the post-test. Once the post-test was completed, the numerical identifiers were acknowledged and compared appropriately. The data was analyzed using a paired t-test. This comparison allowed the presenters to determine the effectiveness of the presentation, therefore, indicating an effective teaching module on Sugammadex was given.

Results and Conclusions

A total of 40 SRNAs participated in the study, completing a pre-test and post-test (Appendix B). This was less than the anticipated 45 students. Five students were excluded from the study, due to arriving late in the presentation and missing the pre-test. Statistical analysis was completed using a paired t-test (Figure 1). A paired samples t-test was conducted to analyze the

data (Figure 2). The obtained t-value was 10.009 with an associated p-value of less than the .05 level of confidence. The mean pre-test score was 5.9 with a standard deviation of 2.30718. In comparison, the mean post-test score was 9.275 with a standard deviation of 1.37724. Therefore, it can be concluded that the average scores increased significantly between pre-test and post-test administrations.

Figure 1: Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-Test	5.9000	40	2.30718	.36480
	Post-Test	9.2750	40	1.37724	.21776

Figure 2: Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Pre-Test - Post-Test	-3.37500	2.13262	.33720	-4.05705	-2.69295	-10.009	39	.000

In evaluating the success of this Capstone Project, the anticipated outcomes were achieved. The results of the pre-test indicated that the students' knowledge of Sugammadex could be improved. Overall, post-test scores were improved indicating that the Power Point presentation on Sugammadex had been effective in increasing knowledge of the SRNAs at

Adventist University of Health Sciences. One limitation of the study was time constraints; as long-term learning could not be evaluated. It is important to note, that the students had just received education in the clinical setting on Sugammadex from a drug representative, as the drug had just become available in the clinical setting the same week the presentation was given. Despite the additional education the students received, the students still had room for learning, which was reflected in the pre-test scores. With this being noted, it would be interesting to see what long term learning could have been achieved from this project. In future studies, one might give a pre-test later on, rather than right after the teaching module to assess whether long term learning was achieved. Despite recent exposure, the students test scores reflected there was still room for improvement. The Power Point presentation is an effective teaching module that can be used for SRNAs and possibly CRNAs in the future for management of complex patients and clinical scenarios.

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Appendix A: Informed Consent

ADU NAP CAPSTONE PROJECT – INFORMED CONSENT

Our names are Ashley Casey and Trevor McCarty, and we are MSNA students in the Nurse Anesthesia Program (NAP) at Adventist University of Health Sciences (ADU). We are doing a Capstone Project called *Clinical Considerations of Sugammadex.* This project is being supervised by Steve Fowler, DNP, CRNA. We would like to invite you to participate in this project. The main purpose of this form is to provide information about the project so you can make a decision about whether you want to participate.

WHAT IS THE PROJECT ABOUT?

The purpose of this project is to create a teaching module to increase the knowledge of Sugammadex as is pertains to the student registered nurse anesthesia (SRNA) population at Adventist University of Health Sciences (ADU) regarding the clinical considerations of Sugammadex.

WHAT DOES PARTICIPATION IN THIS PROJECT INVOLVE?

If you decide to participate in this project, you will be asked to complete an anonymous pre-assessment, attend a classroom presentation, and then complete an anonymous post-assessment. The assessment will address the pre and post presentation knowledge and understanding regarding the clinical considerations of Sugammadex. Your participation by attendance at the presentation and completion of the survey is anticipated to take approximately one hour.

WHY ARE YOU BEING ASKED TO PARTICIPATE?

You have been invited to participate as part of a convenience sample of students currently enrolled in the ADU NAP. Participation in this project is voluntary. If you choose not to participate or to withdraw from the project, you may do so at any time.

WHAT ARE THE RISKS INVOLVED IN THIS PROJECT?

Although no project is completely risk-free, we don't anticipate that you will be harmed or distressed by participating in this project.

ARE THERE ANY BENEFITS TO PARTICIPATION?

We don't expect any direct benefits to you from participation in this project. The possible indirect benefit of participation in the project is the opportunity to gain additional knowledge about clinical considerations of Sugammadex.

HOW WILL THE INVESTIGATORS PROTECT PARTICIPANTS' CONFIDENTIALITY?

The results of the project will be published, but your name or identity will not be revealed. To maintain confidentiality of assessments, the investigators will conduct this project in such a way to ensure that information is submitted without participants' identification. Using a number system for both pre-test and post-test will protect anonymity of the participants. Thus, the investigators will not have access to any participants' identities.

WILL IT COST ANYTHING OR WILL I GET PAID TO PARTICIPATE IN THE PROJECT?

Your participation will cost approximately 30-45 minutes of your time, but will require no monetary cost on your part. You will not be paid to participate.

VOLUNTARY CONSENT

By signing this form, you are saying that you have read this form, you understand the risks and benefits of this project, and you know what you are being asked to do. The investigators will be happy to answer any questions you have about the project. If you have any questions, please feel free to contact Ashley Casey Ashley.casey@my.adu.edu or Trevor McCarty at trevor.mccarty@my.adu.edu. If you have concerns about the project process or the investigators, please contact the Nurse Anesthesia Program at (407) 303-9331.

_____ _____

Participant Signature **Date**

_____

Participant Name (PRINTED LEGIBLY)

Appendix B: Pre/post Test

1.) Sugammadex is a _____.

a. Acetylcholinesterase inhibitor

b. Cyclodextrin

c. Antimuscarinic

2.) Patients using hormonal contraceptives must use an additional, non-hormonal method of contraception for the next _____ days following Sugammadex administration.

a. 3 days

b. 7 days

c. 10 days

d. 14 days

3.) Sugammadex is indicated for the reversal of neuromuscular blockade induced by _____.

a. Atracurium

b. Vecuronium

c. Phase II depolarizing blockade

d. Cisatracurium

4.) Sugammadex should be administered _____.

a. IM

b. IV as a single bolus

c. IV over 1 minute

d. IV over 3 minutes

e. None of the above

5.) A dose of _____ of Sugammadex is recommended if spontaneous recovery of the twitch response has reached 1 to 2 post-tetanic counts and there are no twitch responses to train of four (TOF) stimulation following Rocuronium or Vecuronium induced neuromuscular blockade.

a. 2 mg/kg

b. 4 mg/kg

c. 8 mg/kg

d. 16 mg/kg

6.) A dose of _____ of Sugammadex is recommended if spontaneous recovery has reached the reappearance of the second twitch in response to TOF stimulation following Rocuronium or Vecuronium induced neuromuscular blockade.

a. 2 mg/kg

b. 4 mg/kg

c. 8 mg/kg

d. 16 mg/kg

7.) A dose of _____ of Sugammadex is recommended if there is a clinical need to reverse neuromuscular blockade soon (approximately 3 minutes) after administration of a single dose of 1.2 mg/kg of Rocuronium.

a. 2 mg/kg

b. 4 mg/kg

c. 12 mg/kg

d. 16 mg/kg

8.) Sugammadex is not recommended in patients with which of the following? (Select one)

a. Hepatic impairment

b. Severe renal impairment

c. Chronic heart failure

d. Ischemic heart disease

9.) Which of the following is Sugammadex physically compatible with? (Select one)

a. 5% dextrose

d. Verapamil

c. Ondansetron

d. Ranitidine

10.) What is the suggested waiting time for the re-administration of Rocuronium or vecuronium after reversal with 16 mg/kg of Sugammadex has been administered?

a. 3 minutes

b. 5 minutes

c. 4 hours

d. 24 hours

Appendix C: Power Point Presentation

1/7/17

Clinical Considerations of Sugammadex

Ashley Casey, RN, BSN, SRNA and Trevor McCarty, RN, BSN, SRNA

Project Mentor Elizabeth Hausaman, CRNA, JLR Medical Group

Project Chair Steve Fowler, DNP, CRNA

Learning Objectives:

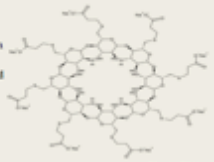
- Increase knowledge and comfort of Sugammadex use for SRNA population at ADU for complex patients and clinical scenarios
- Discuss current anesthetic indications
- Review of current literature

Characteristics of the Ideal Reversal Drug?

- Ability to rapidly reverse a deep neuromuscular blockade
- Minimal negative side effect profile
- Decreased risk of residual neuromuscular paralysis
- Cost effectiveness

History of Sugammadex

- Initially it was found that Rocuronium formed complexes with cyclodextrins, however, the bonds were weak, easily allowing Rocuronium to disassociate from the complex
- Modifications of the cyclodextrins added side chains to each sugar unit to allow a tight complex to form
- In 1999, the first batch of Org 25969 (which is now known as Sugammadex) was produced showing a desired profile



(Murphy, 2016) (Merck, 2015)

History of Sugammadex Approval

- Sugammadex was first patented in 2001, with the first human study published in 2005
- Submitted for FDA approval in U.S. in 2007, however, it was not approved due to hypersensitivity and anaphylactic concerns
- In the initial FDA submission there was one case of anaphylaxis and 31 cases of hypersensitivity
- Further studies regarding surgical bleeding, QT prolongation, and arrhythmias were requested
- The FDA approved Sugammadex for use in the United States in December 2015
- As of March 2015, Sugammadex has been approved in 57 countries with more than 11 million patients having received the drug (Murphy, 2016)

(Merck, 2015)

Sugammadex Mechanism of Action

- Modified gamma-cyclodextrin selective binding agent that binds to aminosteroidals by forming a tight complex encapsulating the unbound steroidal molecule, thus, preventing action at the neuromuscular junction (Jones et al., 2008).
- Sugammadex was developed to selectively bind to Rocuronium.
- Other steroidal muscle relaxants, such as Vecuronium and Pancuronium, can bind to Sugammadex but with much lower affinity.
- No affinity with non-steroidal NMBs.
- Avoids the need for using anticholinergic and acetylcholinesterase inhibitors for reversal.

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1/7/17

Elimination

- Formed complex is eliminated via the kidneys
- No metabolites have been observed in studies, and renal excretion remains the only route of elimination
- Elimination time of 8 hours in patients with normal renal function.
- Sugammadex is not recommended for patients with severe renal impairment
- After complete elimination of Sugammadex has occurred, it is easy for providers to re-establish NMB if necessary.

(Merck, 2015)

Indications

- Rapid reversal of neuromuscular blockade (NMB) of Rocuronium and Vecuronium and different levels of blockade
- May be used when rapid reversal is necessary and paralytic effects are only desired for a short duration.
- Neuromuscular diseases
- Difficult airway
- "Can't intubate, ventilate" scenario
- Rescue of residual paralysis
- Neurophysiological monitoring
- Considerations in ECT
- Concerns of MH with Succinylcholine
- When avoidance of anticholinesterase side effects are desired.
- May be beneficial in anaphylactic reaction to amino-steroidal muscle relaxants

(Wallace et al., 2015)

Contraindications & Adverse Reactions

- Only true contraindication is known hypersensitivity
- Anaphylaxis has occurred in 0.3% of healthy volunteers (Merck, 2015).
- Cases of anaphylaxis were reported within 4 minutes or less of administration of Sugammadex (Ledowski,(2015).
- Vigilant in monitoring for signs of a reaction immediately after administration
- Marked bradycardia has been reported within minutes
- Be astute to hemodynamic changes and treat with an anticholinergic if needed.

Most common hypersensitivity adverse reactions reported were nausea, pruritus and urticaria

(Merck, 2015)

Risk of Bleeding

- An increase in coagulation parameters of up to 25% for up to one hour in healthy volunteers were reported with a Sugammadex dose of 16 mg/kg
- Bleeding risk has only been studied systematically with heparin and low molecular weight heparin (LMWH) thromboprophylaxis with 4 mg/kg doses of Sugammadex.
- Coagulation parameters should be closely monitored in patients with coagulation disorders.
- Patients receiving thromboprophylaxis drugs that receive a dose of 16 mg/kg should also have coagulation parameters monitored.

(Merck, 2015)

Dosing & Administration:

- 200 mg/2 mL (100mg/mL) in a single-dose vial for bolus injection
- 500 mg/5 mL (100mg/mL), in a single-dose vial for bolus injection
- Given as a single bolus injection over 10 seconds, with line flushed
- Dosing is based on actual or total body weight
- **Physically incompatible** with verapamil, ondansetron, and ranitidine

Compatible with LR & Dextrose

(Merck, 2015)

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Recommended Dosing for Rocuronium and Vecuronium:

- 2 mg/kg if spontaneous recovery a TOF ratio of at least 2/4 twitches.
- 4 mg/kg if no TOF twitches (0/4) and at least 1 to 2 post-tetanic counts.

Dosing for Rocuronium Only:

- 16 mg/kg if no TOF, no post-tetanic counts, within 3 minutes of administering Rocuronium.

**This dose has not been studied for Vecuronium.*

Train-of-Four	Post-Tetanic Count	Sugammadex Dose, mg/kg
2/4	-	2
0/4	1-2	4
0	0	16

(Merck, 2015)

Possible Drug Interactions?



Drug Interactions

- Patients taking oral contraceptives must be informed of the possibility of reduced efficacy
- One dose of Sugammadex is equal to one missed dose of oral contraceptives
- Patients need to be educated to use back up contraceptives for 7 days after receiving Sugammadex
- Recent research has shown prophylactic Dexamethasone for PONV does not interfere with reversal of moderate NMB (Ikonomou et al., 2016)
- Toremifene can cause delayed recovery from Sugammadex

Re-administration of NMB After Sugammadex

- After reversal by Sugammadex, re-administration with a steroidal NMB is possible but may be difficult due to the necessity to occupy the remaining Sugammadex molecules.
- A large dose of steroidal paralytic is required to achieve relaxation
- If Sugammadex 16 mg/kg was administered, a waiting period of 24 hours is suggested for the re-administration of a steroidal NMB
- If a NMB is necessary after Sugammadex reversal prior to the recommended waiting, use of a non-steroidal NMB is recommended
- Be aware that onset for a depolarizing NMB may be slower than expected due to a substantial amount of postjunctional nicotinic receptors remaining occupied by NMB agents

(Merck, 2015)

Table 1: Re-administration of Rocuronium or Vecuronium after Reversal (up to 4 mg/kg BRIDION)

Minimum Waiting Time	NMBA and Dose to be Administered
5 minutes	1.2 mg/kg rocuronium
4 hours	0.6 mg/kg rocuronium or 0.1 mg/kg vecuronium

Onset of NMB may be delayed up to approximately 4 minutes and the DOA of NMB may be decreased by up to approximately 15 minutes if for any reason neostigmine 1.2 mg/kg is administered within 30 minutes after reversal with Sugammadex

Take Home: Prolonged onset and shorter DOA of NMB

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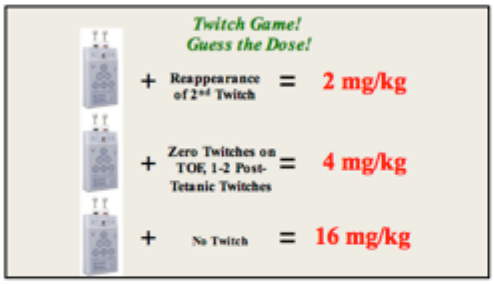
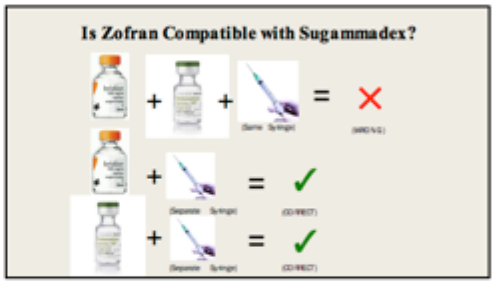
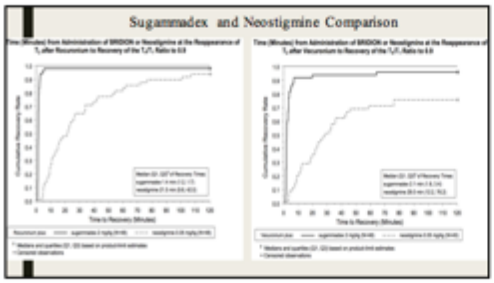
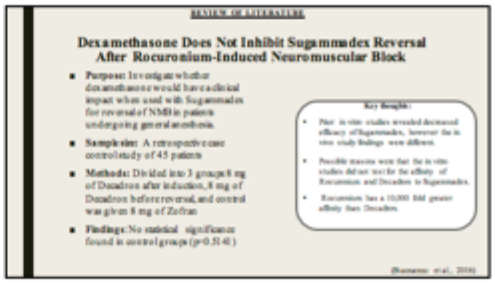
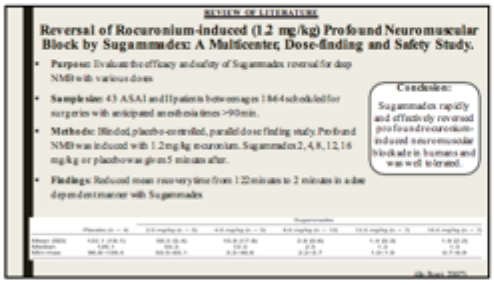
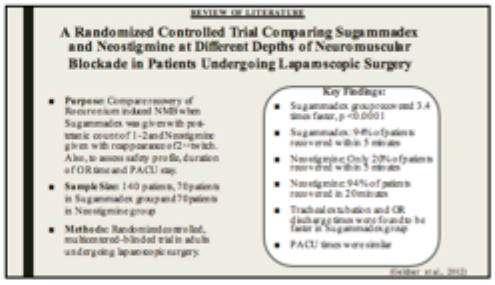

Twitch Game!
Guess the Dose!
+ Reappearance of 2nd Twitch = 2 mg/kg
+ Zero Twitches on TOF, 1-2 Post-Tetanic Twitches = 4 mg/kg
+ No Twitch = 16 mg/kg


Is Zofran Compatible with Sugammadex?


Sugammadex and Neostigmine Comparison


REVIEW OF LITERATURE
Dexamethasone Does Not Inhibit Sugammadex Reversal After Rocuronium-Induced Neuromuscular Block
Purpose: To investigate whether dexamethasone would have a clinical impact when used with Sugammadex for reversal of NMB in patients undergoing general anesthesia.
Sample size: A retrospective case control study of 45 patients
Methods: Divided into 3 groups: 8 mg of Dexadron after induction, 8 mg of Dexadron before reversal, and control was given 8 mg of Zofran
Findings: No statistical significance found in control groups (p=0.5146)
Key Insights:
Recuronium has a 10,000 fold greater affinity than Dexadron.


REVIEW OF LITERATURE
Reversal of Rocuronium-Induced (1.2 mg/kg) Profound Neuromuscular Block by Sugammadex: A Multicenter, Dose-finding and Safety Study.
Purpose: Evaluate the efficacy and safety of Sugammadex reversal for deep NMB with various doses
Sample size: 43 ASA I and II patients between ages 18-64 scheduled for surgeries with anticipated anesthesia times >90 min.
Methods: Blinded, placebo-controlled, parallel dose finding study. Profound NMB was induced with 1.2 mg/kg rocuronium. Sugammadex 2, 4, 8, 12, 16 mg/kg or placebo was given 5 minutes after.
Findings: Reduced mean recovery time from 122 minutes to 2 minutes in a dose dependent manner with Sugammadex
Conclusion:
Sugammadex rapidly and effectively reversed profound rocuronium-induced neuromuscular blockade in humans and was well tolerated.


REVIEW OF LITERATURE
A Randomized Controlled Trial Comparing Sugammadex and Neostigmine at Different Depths of Neuromuscular Blockade in Patients Undergoing Laparoscopic Surgery
Purpose: Compare recovery of Rocuronium-induced NMB when Sugammadex was given with post-tetanic count of 1-2 and Neostigmine given with reappearance of 2nd twitch. Also, to assess safety profile, duration of OR time and PACU stay.
Sample Size: 140 patients, 70 patients in Sugammadex group and 70 patients in Neostigmine group
Methods: Randomized controlled, multicentered-blinded trial in adults undergoing laparoscopic surgery.
Key Findings:
Sugammadex group recovered 3.4 times faster, p <0.0001
Sugammadex: 94% of patients recovered within 5 minutes
Neostigmine: Only 20% of patients recovered within 5 minutes
Neostigmine: 94% of patients recovered in 20 minutes
Tracheal extubation and OR discharge times were found to be faster in Sugammadex group
PACU times were similar

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REVIEW OF LITERATURE

Comparison of Sugammadex and Conventional Reversal on Postoperative Nausea and Vomiting: A Randomized, Blinded Trial

- **Purpose:** Determine whether Sugammadex causes less PONV than Neostigmine
- **Sample size:** 100 ASA 1 & 2 patients for extremity surgery
- **Methods:** Patients were randomly assigned to Neostigmine and atropine or Sugammdex 2 mg/kg when 4 twitches in response to TOF were present with visible fade.
- **Findings:** PONV rates were lower in Sugammadex group upon PACU arrival ($p<0.05$) but similar thereafter. Post operative antiemetic and analgesic consumption were similar. Post operative HR was significantly lower in Neostigmine group.

Conclusion

- Sugammadex speeds recovery time but only slightly decreases PONV compared with Neostigmine and Atropine.
- Bradycardia occurred 14% in Neostigmine vs 2 % in the Sugammadex group.

(Kopman et al., 2010)

REVIEW OF LITERATURE

Successful use of Sugammadex in a 'Can't Ventilate' Scenario

- **Case Study:** A 53-year-old man with hypopharyngoesophagostomosis following curative chemo radiotherapy for a tongue base tumor presented three years later for an attempt at pharyngoesophagostomy dilatation.
- First attempt had been abandoned 6 months previously when awake fiberoptic intubation failed due to partial airway obstruction and desaturation when the fiberscope was advanced.
- As mask ventilation was anticipated to be possible, a further attempt at intubation after induction of anesthesia was judged appropriate.

(Peters et al., 2013)

REVIEW OF LITERATURE

Successful use of Sugammadex in a 'Can't Ventilate' Scenario

- Mallampati score of 2
- Mouth opening of 3 cm
- Full dentition
- Softtissues of the neck was fibrotic with limited cervical spine movement
- Previous difficult airway
- All these factors led to the prediction that tracheal intubation would be difficult

(Peters et al., 2013)

Plan A, B, C, and D

- Plan A: Place awake cricothyroid cannulation with topical anesthesia followed by intravenous induction with Propofol and Rocuronium (Suitsopioid), prior to performing direct laryngoscopy
- Plan B: Would be executed if Plan A resulted in a failed intubation, Sugammadex would be administered to restore spontaneous ventilation and the patient allowed to wake
- Plan C: If mask ventilation also failed, would be to employ jet ventilation via the already established cricothyroid cannula, give Sugammadex and awaken the patient
- Plan D: ENT to perform an rescue emergency surgical airway

(Peters et al., 2013)

REVIEW OF LITERATURE

Successful use of Sugammadex in a 'Can't Ventilate' Scenario

- The cricothyroid cannula was inserted with ENT assistance to identify the anatomical landmarks. Correct placement was confirmed by aspiration of air and capnography.
- After pre-oxygenation for 3 min, anesthesia was induced with Propofol 200 mg followed by Rocuronium 40 mg.
- Neither mask nor jet ventilation proved possible after the induction of anesthesia and NMB with Rocuronium and the decision was made to not instrument the airway.
- Despite use of an oropharyngeal airway and five handed technique mask ventilation proved impossible. This remained in case at 2 min after induction, when optimum NMB was thought to be established.
- At this stage (with oxygen saturation still 100%), failed ventilation was declared and the procedure aborted.
- Sugammadex 400 mg was administered and the patient allowed to awaken.
- Jet ventilation was attempted, but despite firm airway opening maneuvers and an oropharyngeal airway, there was no exhalation. Therefore, only two jet ventilation breaths were given.
- Administration of Sugammadex with a thorough pre-oxygenation allowed return of spontaneous breathing before the development of hypoxia and avoided the need for a surgical airway rescue.

(Peters et al., 2013)

REVIEW OF LITERATURE

Reversal of Profound Neuromuscular Block by Sugammadex Administered Three Minutes After Rocuronium: A Comparison with Spontaneous Recovery from Succinylcholine.

- **Purpose:** To compare the time of Sugammadex reversal of profound Rocuronium NMB to the time of spontaneous recovery from Succinylcholine.
- **Sample size:** 115 ASA Class I-II patients.

Methods: Anesthesia induced and maintained with propofol and an opioid. NMB and tracheal intubation was achieved with 1.2 mg/kg of Rocuronium or 1 mg/kg of Succinylcholine. Sugammadex 16mg/kg was then administered 3 minutes after Rocuronium administration. NM function was monitored by acceleromyography. The primary efficacy endpoint was the time from the start of relaxant administration to the recovery of the first TOF twitch (T1) to 10%.

(Lee et al., 2009)

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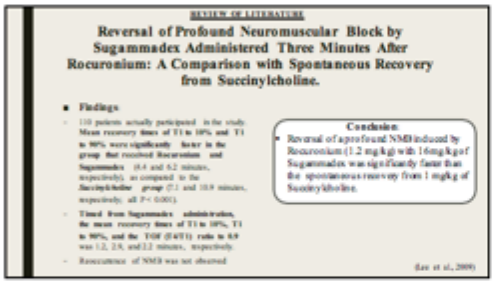
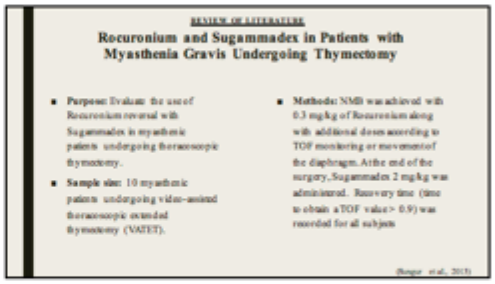
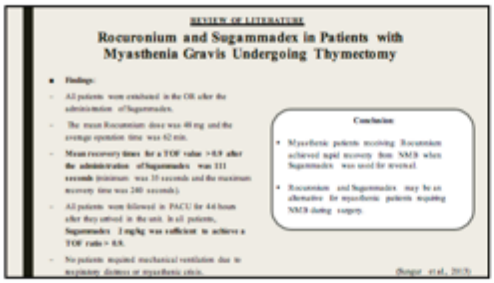
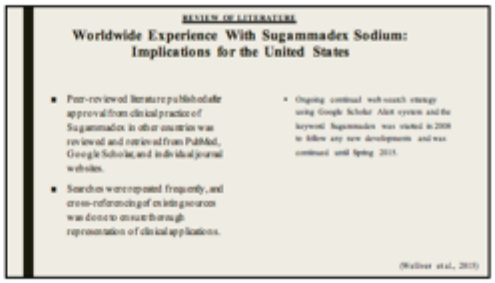
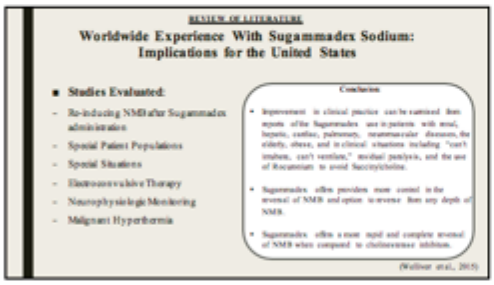
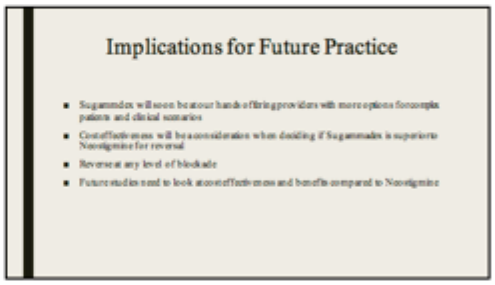

REVIEW OF LITERATURE
Reversal of Profound Neuromuscular Block by Sugammadex Administered Three Minutes After Rocuronium: A Comparison with Spontaneous Recovery from Succinylcholine.
Findings:
Conclusion:
(Lee et al., 2009)


REVIEW OF LITERATURE
Rocuronium and Sugammadex in Patients with Myasthenia Gravis Undergoing Thymectomy
Purpose:
Sample size:
Methods:


REVIEW OF LITERATURE
Rocuronium and Sugammadex in Patients with Myasthenia Gravis Undergoing Thymectomy
Findings:
Conclusion
(Berger et al., 2013)


REVIEW OF LITERATURE
Worldwide Experience With Sugammadex Sodium: Implications for the United States


REVIEW OF LITERATURE
Worldwide Experience With Sugammadex Sodium: Implications for the United States
Studies Evaluated:
Re-Inducing NMB after Sugammadex administration
Special Patient Populations
Special Situations
Electroconvulsive Therapy
Neurophysiologic Monitoring
Malignant Hyperthermia
Conclusion
(Wolfson et al., 2015)


Implications for Future Practice
Sugammadex will soon be at our hands offering providers with more options for complex patients and clinical scenarios
Cost effectiveness will be a consideration when deciding if Sugammadex is superior to Neostigmine for reversal
Reverse at any level of blockade
Future studies need to look at cost effectiveness and benefits compared to Neostigmine

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The End

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Appendix D: Capstone Poster