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EXPERT REVIEW

A Review of the Safety and Efficacy of Sugammadex in Anesthetic Practice

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Abstract: Sugammadex, the first in a novel class of medications termed selective relaxant binding agents, was developed to rapidly and completely encapsulate aminosteroid neuromuscular blocking agents, thus removing them from the neuromuscular junction. When used properly, sugammadex has the potential to decrease the incidence of residual neuromuscular block and it's associated complications, as well as, avoid the side effects associated with cholinesterase inhibitors. Sugammadex may also have a role in the management of patients with difficult airways and rocuronium- induced anaphylaxis. Currently available in over 70 countries worldwide, fears of hypersensitivity reactions have delayed it's release in the United States. The article looks to examine the role of sugammadex in anesthesia and detail its pharmacologic profile.

Keywords: sugammadex, neuromuscular blocking agents, reversal agents, cyclodextrins, rocuronium, nondepolarizing agents

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Introduction

Neuromuscular blocking agents are used daily to attain ideal intubating and surgical conditions in operating rooms around the world. Yet, despite an ever-improving understanding of neuromuscular function and the clinical use of modern neuromuscular monitoring techniques, residual paralysis still remains a significant problem in post anesthesia care units (PACU).[1,2] In fact, Yip et al showed the incidence of patients arriving in the PACU with residual weakness (residual paralysis) to be 31%. Interestingly, in this study the incidence of residual weakness was not significantly lower in patients who received neostigmine,[1] suggesting that we may need to rethink our management of patients who receive neuromuscular blocking agents (NMBAs). Sugammadex sodium (Merck and Co, Inc, Whitehouse Station, NJ, USA) is a novel drug that appears to provide clinicians a novel and superior way to reverse neuromuscular blockade and perhaps prevent the complications associated with residual neuromuscular block.

Sugammadex is the first in a new class of medications known as selective relaxant binding agents (SRBAs). These agents act to encapsulate free aminosteroid relaxants and effectively prevent them from interacting at the neuromuscular junction. Questions about its potential for hypersensitivity reactions and coagulation interference have prevented sugammadex from entering the US market; however it is currently approved for use in over 70 countries worldwide, and its Food and Drug Administration (FDA) re-review for approval is expected in 2012.

Neuromuscular Transmission and Residual Block

Under normal conditions, neuromuscular transmission occurs at the interface between the motor neuron and the muscle fiber, termed a motor endplate. When an action potential travels anterogradely along a nerve and reaches the endplate, acetylcholine (ACh) is released from the pre-synaptic nerve terminal stores and diffuses across the synaptic cleft towards the muscle fiber membrane. There, it interacts with postjunctional ACh receptors (via a specialized recognition site on the α subunit of the receptor), inducing a conformational change in the receptor, and allowing sodium and potassium to move along their respective concentration gradients. If enough ACh receptors are activated, an action potential will occur in the muscle fiber resulting in muscle contraction. Over time ACh dissociates from the receptor leading to repolarization. Additionally, acetylcholinesterase enzymes located with the synaptic cleft rapidly and efficiently degrade ACh.

Currently available neuromuscular blocking agents act on the postjunctional ACh receptor. *Depolarizing* agents (such as succinylcholine) mimic ACh and result in activation of the ACh receptors. However, since succinylcholine is not metabolized by acetylcholinesterases, its effects on the receptors are prolonged. This interaction of succinylcholine and the postsynaptic muscle receptors presents clinically as initial muscle contractions (fasciculations) followed by flaccid paralysis, as the receptors are rendered inactive by the persistence of succinylcholine at the neuromuscular junction. *Nondepolarizing* neuromuscular agents (such as curare, alcuronium, doxacurium, pipecuronium, pancuronium, vecuronium, atracurium, cisatracurium, mivacurium, rocuronium, etc) act by competitive inhibition of the postjunctional ACh receptor (ie, they compete with ACh for the α subunit recognition site of the receptor). Two structurally different classes of nondepolarizing agents exist, the aminosteroid compounds (rocuronium, vecuronium, pancuronium, and pipecuronium) and the benzylisoquinolinium compounds (d-tubocurarine, atracurium, cisatracurium, doxacurium, and mivacurium).

The nondepolarizing agents can be further subdivided based on their duration of action into short-, intermediate-, and long-acting agents. Nondepolarizing neuromuscular blocking agents have a competitive advantage over ACh as only one α subunit of the ACh receptor needs to be bound to prevent activation, whereas ACh must bind both α subunits to open the same ion channel.

Currently, practitioners rely on either spontaneous or pharmacological reversal to restore muscular strength after neuromuscular blocking agents have been administered. Spontaneous reversal is achieved over time as the NMBA redistributes away from the synaptic cleft and is metabolized. This process can be highly variable and depends on several factors such as the agent used, drug interactions, body temperature, acid-base status, and comorbid conditions.[3–6] Anticholinesterases (such as neostigmine, pyridostigmine and edrophonium) are used to pharmacologically

reverse neuromuscular blockade. These medications act to inhibit the cholinesterase enzyme, thereby blocking destruction of ACh, and increasing the amount of ACh in the synaptic cleft. This increase in ACh shifts the balance to favor normal muscle function and "displaces" the neuromuscular blockers from the receptor site (ie, renders them less likely to bind to the recognition site).[7] Unfortunately, pharmacologic reversal has several disadvantages. The increase in ACh concentrations affects muscarinic receptors and may result in a variety of undesirable cardiovascular, pulmonary, and gastrointestinal side effects.[8–10] Additionally, anticholinesterases have a ceiling effect,[11] such that once the anticholinesterase enzyme is maximally inhibited, additional neostigmine will not be effective. The anticholinesterase inhibitory effects are relatively short-lived, and their clinical effect may abate before the neuromuscular blocking agent has been fully metabolized, resulting in reappearance of neuromuscular weakness ("recurarization").

Proper monitoring of the neuromuscular junction function is essential to evaluate successful reversal and prevent re-paralysis in the recovery room. This often entails a combination of subjective clinical signs and objective neuromuscular monitoring devices. Subjective signs such as head lift and grip strength are commonly employed but are inadequate in determining a return of normal muscle strength.[12,13] Objective means of assessment of neuromuscular blockade classically include the use of a peripheral nerve stimulator placed on the ulnar nerve and measuring the force of contraction of the adductor pollicis muscle. Commonly, the ratio between the fourth twitch strength and first twitch strength is compared, resulting in a train-of-four (TOF) ratio. In the past, TOF ratios of 0.7 and above were considered to be indicative of adequate neuromuscular function; however, recent evidence suggests that a TOF of at least 0.9 should be used as the threshold for adequate recovery.[14,15]

Often undiagnosed, inadequate reversal of neuromuscular block can have significant patient safety implications in the postoperative care unit. Pulmonary aspiration, hypoxemia, need for emergent tracheal reintubation, and extended recovery times have all been attributed to residual neuromuscular weakness.[15–19] Despite this morbidity, significant numbers of clinicians still do not routinely monitor neuromuscular function.[20] It is hoped that improved awareness of residual neuromuscular weakness through education, coupled with improved monitoring equipment, proper use of current reversal agents and introduction of new, safer and more effective reversal agents may lessen the occurrence of this complication.[21,22]

Pharmacodynamics and Pharmacokinetics

Sugammadex is the first in a new class of reversal agents known as selective relaxant binding agents or SRBAs. Formed from a modified γ-cyclodextrin, sugammadex was specifically designed to tightly bind the intermediate acting neuromuscular blocker rocuronium.[23] Subsequent work revealed that there was an affinity, though to a lesser degree, for the other aminosteriods, vecuronium and pancuronium.[24,25] Formed by adding eight lipophilic side chains with acidic functional groups to a γ-cyclodextrin core, researchers developed a compound that is highly water soluble and able to tightly encapsulate the rocuronium molecule in a 1:1 molecular ratio.[26,27] The encapsulation is extremely stable with a very low dissociation rate.[28]

By rapidly encapsulating free aminosteroid molecules in plasma, sugammadex creates a concentration gradient that drives the movement of neuromuscular blocking agents from the neuromuscular junction back into the plasma.[29,30] This redistribution occurs rapidly even in the presence of profound block.[31–33] Since the complex is highly stable, the risk of re-paralysis is low when sugammadex is administered in appropriate clinical doses.

Although it has been developed for binding to, and reversal of, rocuronium, sugammadex also effectively reverses the actions of vecuronium. The threefold lower affinity of sugammadex for vecuronium is countered by the greater potency of vecuronium, which results in fewer number of vecuronium molecules administered in an equipotent dose; for instance, the molar ratio of a sugammadex dose of 32 mg/kg and rocuronium dose of 1.2 mg/kg is 8:1. Conversely, the molar ratio of a sugammadex dose of 32 mg/kg and vecuronium dose of 0.1 mg/kg is 102:1.[34] This means that although the affinity of sugammadex for vecuronium is lower (than for rocuronium), fewer vecuronium molecules are needed (and available) to be bound by sugammadex to effect reversal of neuromuscular block.

Sugammadex follows linear elimination kinetics and appears to have no active metabolites. Given the hydrophilic properties of sugammadex, it rapidly distributes throughout the extracellular fluid compartments and has a volume of distribution of approximately 18L.[35] Sugammadex has an elimination half-life of 1.8 hours and a clearance rate between 88–120 mL/hr.[35] Sugammadex is excreted primarily unchanged by the kidneys. Up to 70% of the administered dose is excreted in the first 6 hours and approximately 90% within 24 hours.[36] Less than 0.02% of sugammadex is eliminated in the feces and exhaled via the lungs.[35–37] In patients with renal failure, the elimination of sugammadex and rocuronium-sugammadex complex was decreased, and the drug should be avoided in patients with creatinine clearances less than 30 mL/min.[37]

Clinical Trials Examining Efficacy and Safety

After promising results in animal studies,[38–41] Gijsenbergh and colleagues first described the safe use of sugammadex in humans in 2005.[35] The investigators enrolled 29 healthy male volunteers to determine the pharmacokinetics and safety of sugammadex. They found the medication to be well tolerated and effective in reversing neuromuscular block produced by rocuronium. Side effects were generally mild, with taste perversion (dysgeusia) and dry mouth occurring in two volunteers. Eight subjects had prolonged corrected QT interval (QT_c), three of which occurred in volunteers receiving sugammadex. The longest measured prolonged QT_c was 461 ms, occurring 30 minutes after administration of a 4 mg/kg dose.

Several studies followed that investigated the safety profile and dosing requirements of sugammadex. Cammu et al found sugammadex, at doses of 16, 20, or 32 mg/kg, to be safe when administered to non-anesthetized patients, as well as those receiving propofol/remifentanil anesthesia.[34] Shields and colleagues found sugammadex to be effective in reversing deep and prolonged neuromuscular blockade (at least 2 hours) produced by rocuronium.[42] The muscle relaxant reversal effective dose was determined to be between 2–4 mg/kg. Sorgenfrei noted that at doses above 2 mg/kg, sugammadex reversed rocuronium-induced blockade in a dose dependent manner.[43] Early work done by Cammu and Suy involved patients who received 0.1 mg/kg of vecuronium. These studies found sugammadex to have similar efficacy when used to reverse vecuronium-induced neuromuscular blockade[34,44] as studies documenting the efficacy in reversing rocuronium-based neuromuscular block. Additionally, Cammu found that plasma levels of sugammadex decline slower that rocuronium, suggesting that the likelihood of residual block (or re-paralysis) may be lessened.

Questions concerning QT_c prolongation were investigated by de Kam et al.[45] This randomized, double-blinded study examined 80 adult males and females who received sugammadex doses of 4 mg/kg and 32 mg/kg with and without neuromuscular blocking agents. The investigators found the largest change in QT_c to be 4.3 msec in a patient receiving sugammadex 32 mg/kg following vecuronium 0.1 mg/kg.[45] This prolongation is well below the threshold established by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E14 guidelines. There was also one episode of ventricular tachycardia in a test subject that spontaneously terminated and was deemed to not be related to sugammadex administration. The investigators concluded that sugammadex was not associated with QT_c prolongation.

Dahl, et al examined the safety of sugammadex in patients with cardiovascular disease undergoing non-cardiac surgery. The investigators concluded that sugammadex was safe to use in patients with ischemic heart disease, chronic heart failure, or arrhythmia categorized as New York Heart Association (NYHA) Functional Class II or III.[46] There were 3 episodes of QT_c prolongation among the included patients, but it could not be determined conclusively whether or not the prolongation was associated with sugammadex administration. Overall mean QT_c prolongation occurred in all groups, though to a greater extent in the placebo group as compared with the sugammadex groups.[46] The investigators suggested that the QT_c prolongation may have been a direct effect of the anesthetic, rather than sugammadex. Sugammadex has been shown to precipitate in vitro when combined with protamine in situations, for instance, in which protamine and sugammadex are injected sequentially in the same intravenous tubing.[47] In order to avoid this complication, either separate intravenous access should be used for each medication, or care should

be given to properly flush the IV tubing with saline between sequential administration of protamine and sugammadex.

Sugammadex has also been evaluated in patients with pulmonary disease. Amao evaluated 77 American Society of Anesthesiologists (ASA) physical status II–III patients with underlying pulmonary disease who received sugammadex either 2 or 4 mg/kg. The investigators reported two episodes of bronchospasm occurring in patients with a known history of asthma after administration of a 4 mg/kg dose.[48] Arashi et al compared the safety and side effects prophiles of sugammadex and neostigmine in 69 patients. The investigators found no significant differences in postoperative decreases in pulmonary functional parameters such as forced vital capacity (FVC) or forced expiratory volume in 1 sec (FEV_1).[49] The investigators reported no respiratory complications in their patients.

Staals examined the pharmacokinetics and safety of sugammadex in patients with preexisting kidney disease.[50] In this study, 15 patients with renal failure (defined as a creatinine clearance, $Cr_{cl} < 30$ mL/min) were compared to 15 patients with normal creatinine clearance. Each group received sugammadex 2 mg/kg at the reappearance of the second twitch following paralysis with rocuronium. The investigators found that sugammadex effectively reversed paralysis in patients with renal disease. Furthermore, no instances of recurarization occurred in the test subjects, confirming that the sugammadex-rocuronium complex is extremely stable and that extrarenal clearance of rocuronium occurs in spite of the tight complexation. This was reconfirmed in a second study by Staals who investigated the incidence of reparalysis ("recurarization") 48 hours postoperatively in patients with renal failure.[37] Reversal of neuromuscular block was slightly slower in the renally impaired patient group, but the difference was not found to be clinically significant. More recently, Staals and colleagues ligated the renal pedicle in cats that received rocuronium followed by sugammadex, in order to simulate an acute renal failure study condition.[51] In this situation, the investigators concluded that the speed of reversal was not dependent on the renal elimination of the sugammadex-rocuronium complex, but rather that it was the formation of the complex leading to the redistribution of rocuronium that contributed most significantly to the speed of reversal.[51] Sugammadex was safe and effective in reversing neuromuscular block. There was no recurrence of blockade for 90 minutes after sugammadex administration, and recovery time was no different between the controls and the test (acute renal failure) cats.

Sugammadex also appears to be safe in the pediatric population. Plaud et al examined sugammadex in a wide range of age groups, from 28 days to 65 years old.[52] Their study included 8 infants, 24 children, and 31 adolescents. While this study included relatively small number of patients, sugammadex was well tolerated and the authors recommended further evaluation of the medication in children less than two years old, especially in neonates.[52] Uematsu and colleagues found that sugammadex in doses of 2 mg/kg and 4 mg/kg were equally efficacious in reversing rocuronium-induced blockade in 38 pediatric patients aged 1–23 months.[53] The investigators suggested that the lower dose (2 mg/kg) was effective because plasma level increased rapidly due to the high cardiac output seen in the pediatric population. Sugammadex was used successfully as a rescue medication in a 7-month old patient with a difficult airway.[54] In this case report, the authors used a dose of 4 mg/kg of sugammadex to re-establish spontaneous breathing, after mask ventilation became difficult and they were unable to secure the airway following administration of rocuronium.

McDonagh and colleagues were among the first to evaluate sugammadex in elderly surgical patients.[55] This study enrolled 162 patients, of which, 62 were between 65–74 years of age, and 40 patients were older than 75 years. The investigators found that reversal with sugammadex was rapid in the elderly, but the times were slightly slower in the elderly compared to younger adults. The authors hypothesized that the difference might be due to a less dynamic circulation in the elderly compared with the adults, or to changes in the acetylcholine receptor.[55] Suzuki et al also found slightly slower recovery times in 15 patients over 70 years of age when compared to patients less than 50 years old.[56] Like McDonagh and colleagues, Suzuki's group hypothesized that the difference in recovery times might be attributed to decreased muscle perfusion due to declining cardiac output, and age-associated atherosclerosis that might reduce regional blood flow. In a subsequent study, Suzuki and

colleagues evaluated 43 patients aged 65–86 years and found that the time to recover to a train-of-four ratio of 0.9 was, in fact, dependent on cardiac output.[57]

Van Lancker and colleagues examined sugammadex dosing in the morbidly obese patients. In one of their studies, 100 morbidly obese patients were randomly assigned to received sugammadex at 2 mg/kg based on ideal body weight (IBW), IBW+ 20%, IBW+ 40%, or real body weight.[58] The authors found that morbidly obese patients can be successfully reversed from rocuronium-induced paralysis with sugammadex doses based on ideal body weight without residual weakness or recurrence of paralysis. Furthermore, IBW+ 40% dosing resulted in the fastest recovery times of the 4 groups.[58] Gaszynski compared sugammadex to neostigmine in 70 morbidly obese patients with body mass indexes (BMI) greater than 40.[59] This group found sugammadex to be superior to neostigmine when administered in doses of 2 mg/kg of corrected body weight, as long as a minimum of two twitches are present on the train-of-four monitoring.

Sugammadex has been compared to neostigmine in multiple studies.[59–68] Overall, sugammadex has been shown to be superior to neostigmine in the reversal of shallow and profound rocuronium- or vecuronium-induced blockade. The efficacy and speed of recovery typically follow a dose-response curve. As anticipated, cardiovascular side effects were more frequent in the neostigmine patient groups compared to sugammadex-treated patients.

Safety

Sugammadex generally has been well tolerated in Phase I-III trials.[31,33–35,37,42–79] In all, over 1800 ASA I-III study patients received sugammadex in doses ranging from 0.1 mg/kg to 96 mg/kg. The most common side effect was altered taste (dysgeusia) often described as a metallic or bitter taste.[a] These side effects occurred most commonly with sugammadex administered in doses greater than 32 mg/kg.[b] Other common side effects include throat pain, fatigue, nausea, vomiting, flatulence, dry mouth, sleep disturbances, headache, and pruritis.

Recurrence of weakness ("recurarization") occurred on several occasions in dose-finding studies when sugammadex was administered in doses less than the clinically recommended dose of 2 mg/kg.[31,69] In the study by Duvaldestin and colleagues, five patients in the rocuronium arm developed recurrent neuromuscular blockade. Two of these patients received 1 mg/kg of sugammadex for reversal, and initially had an improvement in the train-of-four ratio to 0.9; however, the ratio decreased over time, resulting in re-paralysis. Three additional patients never attained train-of-four ratios of 0.9: two patients who received 0.5 mg/kg of sugammadex, and one who received a dose of 1 mg/kg.[69] Groudine and colleagues reported one patient with incomplete reversal after receiving rocuronium 1.2 mg/kg and sugammadex 0.5 mg/kg for reversal of block.[31] There were no reported episodes of residual block occurring at sugammadex doses greater than 2 mg/kg, although one study patient was reported to have required 16 minutes[65] and the second patient required 24 minutes to fully recover to a train-of-four ratio of 0.9 after sugammadex administration.[70] Patients with decreased cardiac output or elderly patients may have a slightly slower time of onset of sugammadex action.[55–57]

Other studies have shown the relative safety of sugammadex administration. In a study in which patients were followed for 7 days postoperatively, Sparr and colleagues reported that sugammadex was well tolerated and patients had minimal effects on heart rate and blood pressure after sugammadex administration.[70] However, some patients receiving sugammadex exhibited insufficient depth of anesthesia. This was reported in 18 of 88 patients receiving propofol/fentanyl—based anesthesia.[70] In this study, "light anesthesia" was defined as an increase in the patients' Bispectral Index, suckling, grimacing, moving, and coughing on the endotracheal tube. The researchers attributed the increased movement to the cerebral arousal reaction (the "muscle spindle theory" in which neostigmine was shown to alter the depth of propofol-remifentanil based anesthesia and hasten recovery as assessed by Bispectral Index), coupled with external stimulation and light plane of anesthesia.[70] Another potential explanation for the light plane of anesthesia after sugammadex administration was the theoretical binding of narcotics and/or intravenous anesthetics by sugammadex. However, this theory is very unlikely, since encapsulation of these agents by sugammadex is minimal.

[a]http://www.bridion.com Last accessed 11/10/2011.
[b]http://www.bridion.com Last accessed 11/10/2011.

In a study conducted by Peeters et al a patient who received 32 mg/kg of sugammadex developed flushing, visual changes and a rash.[71] This patient subsequently underwent intradermal skin testing and was found to have had a probable hypersensitivity reaction. Following this finding, retrospective review of other phase I-III studies suggested an additional six patients may have exhibited hypersensitivity reactions.[c] More recently, a 17 year-old healthy male, with no prior exposure to sugammadex, developed an anaphylactic reaction to a clinically relevant dose. In this case, 3.2 mg/kg of sugammadex resulted in hypotension, tachycardia, wheezing, edema, and erythema one minute after its administration. The patient subsequently underwent intradermal testing, which resulted in a positive result for sugammadex allergy.[80] The authors propose that exposure to oral cyclodextrins present in many foods may have led to this sensitization.

While no studies to date have been conducted in pregnant women, sugammadex should pose no risk to the fetus based on animal studies.[d] In animals, sugammadex is excreted in breast milk, however no studies have been conducted in humans. Since oral absorption of cyclodextrins is generally low, no untoward side effects are anticipated in suckling infants.[e] Sugammadex has been shown safe in infants and adolescents, however due to lack of large, controlled, prospective studies, the manufacturer has recommended against routine use of sugammadex in term-newborns and infants up to the age of 2 years. Furthermore, sugammadex at a dose of 2 mg/kg should be used for routine reversal only in infants $>$ 2 years old and in adolescents.[f] At this time, immediate reversal of profound neuromuscular block has not been studied sufficiently.

While no formal studies have been conducted, pharmacodynamic models suggest that sugammadex may interact with progesterone-based contraceptives. This minimal interaction is equivalent to missing one daily dose of an oral contraceptive.[g] For non-oral hormonal contraceptives, the manufacturer recommends that an alternative means of contraception be used for a minimum of seven days following sugammadex exposure. Zwiers, using a mathematical pharmacokinetic- pharmacodynamics model suggested a potential for displacement of rocuronium from sugammadex by toremifene, flucloxacillin, and fusidic acid.[81] This could potentially lead to recurarization under the correct conditions. More recently, Kam et al studied the effects of administration of flucloxacillin and diclofenac following a suboptimal dose of sugammadex to reverse neuromuscular blockade.[82] In this study, no recurrence of neuromuscular block occurred within 90 minutes after administration of the test medications.

Sugammadex may result in prolongation of the prothrombin time and partial thromboplastin time according to bench studies performed by the manufacturer. This interaction, however, has not been reported in any phase I-III study involving humans. According to the manufacturer, ongoing studies are investigating more fully the potential effect of sugammadex on clotting. Sugammadex has been associated with elevation of plasma aspartate aminotransferase[34] and γ-glutamyltransferase[34] levels, with abnormal urinalysis,[43] and elevation of urinary N-acetyl glucosaminidase.[66]

Sugammadex is excreted renally and should be used with caution in patients with end-stage renal disease (see above). The manufacturer recommends that alternative medications be used in patients with GFR $<$ 30 mL/min.[h] Sugammadex does not appear to be removed with low-flux hemodialysis, but the sample size was too small to draw definitive conclusions.[37]

Place in Therapy

Sugammadex has the potential to revolutionize the field of anesthesiology. At a dose of 2 mg/kg, sugammadex is effective in reversing rocuronium- and vecuronium-induced shallow neuromuscular blockade, defined as the reappearance of the second twitch on train-of-four. Profound neuromuscular block, defined as the presence of 1–2 posttetanic contractions, can be reversed with 4 mg/kg of sugammadex. If immediate reversal is needed, 16 mg/kg can be given 3 minutes after administration of 1.2 mg/kg of rocuronium.

[c]http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4346b1-02-Organon.pdf Last accessed 11/27/2011.
[d]http://www.bridion.com Last accessed 11/10/2011.
[e]http://www.bridion.com Last accessed 11/10/2011.
[f]http://www.bridion.com Last accessed 11/10/2011.
[g]http://www.bridion.com Last accessed 11/10/2011.
[h]http://www.bridion.com Last accessed 11/10/2011.

The ability to immediately and effectively reverse neuromuscular blockade with sugammadex should make the use of older reversal agents obsolete. This will allow for a more predictable time to recovery of neuromuscular function and eliminate the side effects associated with anticholinesterases, including incomplete reversal. The ability to quickly and completely antagonize aminosteroid-induced neuromuscular block may also have salutary effects in surgery. Thus, a deeper plane of neuromuscular block could be maintained throughout surgical procedures in which complete neuromuscular block is beneficial: robotic, intracranial and intraocular procedures. In such cases, complete neuromuscular block may improve patient safety by preventing hemodynamic instability and inadvertent patient movement that may occur without the use of neuromuscular blockers.[83,84] Similarly, a deep degree of neuromuscular block may allow lesser intra-abdominal pressures during laparoscopic procedures and pneumoperitoneum. Lower intra-abdominal pressures have been associated with lower postoperative surgical pain and decreased analgesic requirements.[85,86] Finally, surgical closure may be facilitated by better neuromuscular relaxation, especially during thoracic and large abdominal incisions, and results in more stable hemodynamics.[87] These improvements can be facilitated by the ability to quickly, effectively and predictably reverse deep degrees of neuromuscular block by sugammadex. Such reversal is impossible using the currently-available anticholinesterase reversal agents. In all clinical settings, however, objective measurement of neuromuscular function will be essential to ensure appropriate, reliable return of appropriate neuromuscular function.

Additionally, the use of succinylcholine for rapid sequence inductions, and the dreaded "cannot-intubate, cannot-ventilate" difficult airway scenarios could be eliminated. Succinylcholine is associated with a variety of serious, potentially lethal, side effects, but is favored in the aforementioned situations due to its rapid onset, short duration and high reliability in producing profound neuromuscular block. Rocuronium has a comparable time of onset to succinylcholine when given in equivalent doses (four times the effective dose to achieve 95% reduction in twitch response, ED_{95}). Unfortunately, at this dose, rocuronium has a long duration of action, making it a poor choice for difficult airway cases. Sugammadex can effectively reverse deep rocuronium-induced blockade and allow return of spontaneous ventilation in a failed intubation scenario. This obviously improves the margin of safety of rocuronium in an unstable environment and avoids the dangers associated with the use of succinylcholine. While the use of sugammadex shows promise for difficult airway cases, it should not be deemed the "magic bullet" for all these scenarios. Curtis et al described a case of laryngeal edema from multiple airway manipulations resulting in a "cannot intubate, cannot ventilate" scenario, despite adequate reversal with sugammadex. The authors recommend early use of sugammadex in rescue situations prior to repeated airway instrumentation.[88]

It has also been suggested that sugammadex may play a role in the treatment of rocuronium- induced anaphylaxis. Case reports by Kawano, McDonnell and Motamed describe rapid improvement in vital signs with the use of sugammadex in patients with hemodynamic instability.[89–91] Recent studies, however, suggest that sugammadex cannot stop anaphylaxis, but rather can only prevent further basophil activation.[92,93] This would not result in a rapid cessation of anaphylaxis as described in the case reports, as once mast cells are activated, propagation of the hypersensitivity reaction is allergen-independent.[93] Further work is needed to evaluate the potential role of sugammadex in rocuronium- mediated anaphylaxis and to delineate the mechanism by which patients appear to improve following its administration.

Cost Considerations

The cost of sugammadex in the US has not been announced, since sugammadex has not yet been FDA-approved. However, it is likely that the pricing structure will be similar to the European structure, which is €70 ($90) per 4 mg/kg dose. There are no currently available data on the cost of complications associated with residual neuromuscular weakness, but some broad calculations and inferences can be made. The latest available data on the total annual number of surgeries in the US come from the National Health Statistics Reports (http://www.cdc.gov/nchs/data/nhsr/nhsr011.pdf). These data indicate that in 2006, there were a total of 100 million ambulatory and inpatient procedures and surgeries. Of these, 30.7% involved general anesthesia (or 30.7 million general anesthetics). If we assume only half of these

cases would receive a nondepolarizing neuromuscular blocking agent, then 15.4 million patients might be exposed to the potential for residual block. Studies have shown that 41% of patients receiving neuromuscular blockers experience residual weakness (TOF $<$ 0.90) in the postoperative care unit, so this represents a total of 6.3 million patients. Of the patients with residual weakness, 0.8% will have a critical respiratory event.[16] Extrapolation from these data indicates that of the 6.3 million patients, 50,500 patients will experience a critical respiratory event. The magnitude of the residual neuromuscular weakness as a postoperative complication, patient safety and economic burden is better evaluated as a public health issue, and patients, economists, healthcare agencies and payors will ultimately have to decide whether sugammadex will be "worth" the cost. Finally, it must be pointed out that the ultimate cost/benefit analysis will depend entirely on whether the use of sugammadex will result in eradication of postoperative residual neuromuscular weakness. Without such improved safety outcomes, sugammadex will become a "niche" drug used for rare, selected ("rescue") indications.

Conclusions

Sugammadex is the first in a new class of selective relaxant binding agents that work to encapsulate aminosteroid muscle relaxants (rocuronium $>$ vecuronium $>>$ pancuronium). The ability to rapidly reverse neuromuscular blockade improves the safety margin of these medications. When used in clinically appropriate doses, residual neuromuscular blockade can be eliminated, the time to full muscle recovery becomes more predictable, and the side effects associated with modern reversal agents can be avoided. Additionally, succinylcholine can be avoided in difficult airway situations. While sugammadex has been used clinically in over 70 countries around the world, fears of hypersensitivity reactions have held up its approval in the United States. It is hoped that the safety data obtained from clinical use of sugammadex around the rest of the world in the past 2 years will prove its safety and allow its introduction into clinical practice in the United States.

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Competing Interests

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Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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