Sugammadex Sodium:
A Synthesis of the Evidence Regarding Neuromuscular Blockade Reversal.

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Semester V, 2009.

NDNP 88080: DNP Project
Disclosure

Mark Welliver is a member of the CRNA advisory council on neuromuscular blockade reversal and has been a paid consultant for Organon/ Schering-Plough. He has received no financial or material incentives related to this project and presentation.
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Problem Statement:

Cholinesterase inhibitors have been the mainstay of neuromuscular blockade reversal for over 50 years in all patient populations undergoing surgical procedures. The indirect action of cholinesterase inhibitors increases acetylcholine at the neuromuscular junction to compete with neuromuscular blocking agents’ affinity for the acetylcholine receptors. The increase in acetylcholine is not localized to the nicotinic junction and causes numerous undesirable side effects including bradycardia, bronchospasm, increased airway secretions, nausea, vomiting, increased peristalsis, increased urination, muscle cramps/spasms, miosis, vision disturbances, and convulsions. No other method of reversing neuromuscular blocking agents’ effects has existed until now. The new pharmacology of Selective Relaxant Binding Agents that directly encapsulate neuromuscular blocking agents (drugs) to render them inactive offers a unique approach to reverse neuromuscular blockade with a possible improved efficacy and safety. With this newly available option to reverse neuromuscular blocking agent effects, clinicians must ask “In patients requiring neuromuscular blockade reversal, is the selective relaxant binding agent sugammadex sodium an improvement on cholinesterase inhibitors for more effective reversal, less side effects and greater safety profile?”.

PICO Question:

P- In patients requiring neuromuscular blockade reversal
I- is the selective relaxant binding agent (SRBA) sugammadex an improvement on
C- cholinesterase inhibitors
O- for more effective reversal, less side effects and greater safety profile?
Proposed Innovative Solution:

The proposed innovative solution to cholinesterase inhibitor limitations and side effects of neuromuscular blockade reversal is the synthesis of the research to make recommendations for practice and incorporate those practice changes in a major medical center. Dissemination of the evidence and recommendations will be conducted through in-service presentations, peer-reviewed publication, and national lecture presentations.

Methodology:

Comprehensive literature review and analysis of available evidence for the selective relaxant binding agent sugammadex compared to cholinesterase inhibitors (edrophonium, neostigmine, physostigmine). Inclusion criteria for evidence analysis include bench studies and animal and human randomized controlled trials. Exclusion criteria are expert opinion and drug reviews. Taxonomy of levels of evidence will be applied to guide the grading of recommendations for specific clinical application.

Findings:

The evidence strongly supports the incorporation of sugammadex into clinical practice for the reversal of rocuronium- and vecuronium- induced neuromuscular blockade.

Conclusion and Recommendations:

It is recommended that sugammadex be used to reverse the effects of rocuronium and vecuronium whenever profound neuromuscular blockade is present, hemodynamic and pulmonary parasympathetic effects are undesirable, or any degree of residual paralysis will be detrimental to the patient. It is also recommended that sugammadex be administered in any situation that rocuronium- or vecuronium-induced neuromuscular blockade has contributed to a “can not ventilate, can not intubate” scenario.
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CHAPTER 1

INTRODUCTION

Anesthesia is defined as the institution of amnesia, analgesia, and immobility. Often, immobility is provided by neuromuscular blocking agents (NMBAs) that interrupt the neuronal motor impulses from reaching the muscle fibers. Neuromuscular blocking agents, by attaching to specific receptors (nicotinic) located on post synaptic muscle fibers, prevent acetylcholine from stimulating these receptors and end the propagation of nerve impulses. Thus, cessation of peripheral motor nerve communication with muscle fibers causes muscle paralysis (neuromuscular blockade (NMB)). Neuromuscular blockade facilitates intubation of the trachea, airway management, surgical exposure, and manipulation of extremities. The effects of NMBAs are undesirable after surgery in patients that are to resume spontaneous ventilation and maintain protective reflexes. Neuromuscular blockade reversal is a necessity to effectively and efficiently emerge patients from the effects of anesthetic agents, specifically NMBAs. Currently, only the indirect action of cholinesterase inhibitors (CIs) is used to compete against the effects of NMBAs. A new pharmacology of encapsulation that renders NMBA inactive has been made available in the drug sugammadex and may offer a more effective and safe reversal. To fully evaluate the clinical impact sugammadex may have this manuscript will start with a review of NMBA pharmacology. The current reversal method utilizing CIs will then be reviewed and compared to sugammadex pharmacology. An analysis of the evidence regarding sugammadex capabilities to reverse NMB will be discussed and recommendations for practice made. Levels of evidence will be rated using a scoring taxonomy and recommendations for practice will be graded based on this taxonomy. Implementation of sugammadex into practice at a major medical center will be reviewed and conclusions made.
History of neuromuscular blockade

Curare, also known as warare, was a necessity for survival in the jungle. Dense vegetation and a high canopy provided a secure habitat for game and curare provided the hunters with deadly ability to overcome these obstacles. Life in the difficult environment of the Amazon was in large part enabled by curare. Thus, curare became a central element of tribal life. Curare’s importance was underscored by the high value placed on it by indigenous tribal members. The knowledge of its recipe was closely held and those who created it held high status. Often the preparer of curare was the tribal chief and leader. Derived from a natural plant alkaloid of the green leafed woody vine Chondodendron tomentosum found in South American tropics. Pharmacologic principles of potency and effect were appreciated by the original discovers of curare. Potent curare was highly desired and reflected more pure preparation. The potency of curare was determined by the amount of time it took for a darted monkey to fall from a tree. Quicker effect of action reflected greater potency and thus greater desirability. As potent curare was highly desirable, it became valued and also used as currency.

Amazon tribal Indians first introduced curare to the world during Spanish explorations. The uniqueness of this substance was not overlooked by early explorers and word spread of its apparent magical and deadly properties. Though prepared and used for untold years by the indigenous people of the Amazonian rain forest, western civilization could not recreate this unique substance and sought prepared sources for study. Explorer Baron von Humboldt is often credited with the discovery of curare by acquiring the prepared substance from tribal members but the amounts acquired were small. Larger quantities were needed to support extensive research. Scarce samples limited study and identification of curare’s suspected treatment for the underlying cause of myastinia gravis. Richard Gill, a medical student, diagnosed with early
stages of myastinia gravis believed the understanding and cure to his affliction lie with curare’s action. Gill conducted an expedition to the Amazon and was the first individual to obtain the ingredient list to prepare raw curare. With this “recipe”, curare was able to be continually prepared, studied, and ultimately synthetically produced.

After curare became available its effects were researched by many scientists including Sir Benjamin Brodie, Johann Bartholomaus Trommsdorff, Charles Waterton, and Claude Bernard. Claude Bernard is most often given credit for discovery of curare’s action on the nerve end-plate in his classical frog leg experiment (Bernard 1856; Nedargaard 2003). Dr. Bohm (1912) of Germany was first to use curare as an adjunct drug to facilitate the anesthetic procedure of placing an epidural catheter. It was not until 1942 that two Canadian anesthesiologists used curare to facilitate surgical exposure during an anesthetic. (Griffith & Johnson) Curare’s use as a NMBA led to new agent’s being synthesized to gain better control over NMB.

**Molecular action of Neuromuscular Blockade**

**Receptor Blockade**

Normal motor function occurs from the release of the neurotransmitter acetylcholine (ACh) from synaptic vesicles in the nicotinic junction. Released ACh diffuses across a nanoscopic space (synaptic cleft) to ACh receptors located along the muscle fiber, and this chemical propagation of the neuronal impulse promotes muscle contraction. (Figure 1) Pharmacologic induced NMB occurs by NMBA attachment to nicotinic ACh receptors at the neuromuscular cleft along the muscle cell. By occupying the receptors, NMBA s prevent ACh from binding to and stimulating these receptors. (Figure 2) Motor neuron impulses are blocked from reaching the muscle fiber and muscular contraction is prevented. Varying levels of ACh receptor blockade provide varying levels of muscular relaxation. Only 100% receptor
occupation by NMBAs completely prevents nerve impulses from reaching the muscle fibers. The large number of nicotinic ACh receptors requires the administration of large numbers of NMBAs to bind in a one to one or one to two ratios. This high percent of ACh occupancy required to initiate appreciable NMB reflects the resilience of the somatic nervous system. It also foretells of the difficulty related to reversing NMB with CIs.

**History of cholinesterase inhibitors**

Cholinesterase inhibitors were first used in western Africa in their natural form. Physostimine venmosum, the active ingredient of calabar beans was known to cause multiple side effects including death. Calabar beans are kidney shaped beans that grow in the pod of a woody vine found in the tropical Calabar region of western Africa now known as Nigeria. These beans, also called ordeal beans, were used by the indigenous people for a judiciary process known as “esere”. The judicial outcome of a conflict between individuals was determined by the consumption of these beans by both parties. The physiologic response determined guilt or innocence (Brossi, Pei, & Greig, 1996). Fortunately, esere has been outlawed since the early 1800s. Also outlawed was the practice among indigenous men of ingesting calabar beans to compete with one another. After eating one or two beans, the last man standing was declared the victor. Death was sometimes the final outcome of this male contrived display of masculinity.

The effects of Calabar beans did not go unnoticed by western explorers and research ultimately unlocked their pharmacologic actions. The late 1800s and early 1900s saw a dramatic increase in the knowledge known about CIs. The isolation, action, and eventual synthesis of CIs led to their use as competitive antagonists of NMBAs in the mid 1950s. Unfortunately, the progression of cholinesterase inhibitor development has not paralleled that of NMBA. Whereas, NMBAs have been developed to account for a wide range of needs such as organ independent
metabolism, varying durations, and limited side effects, CIs development has not progressed. The options available to reverse NMBA effects remain the same as they were 50 years ago. The same drugs, edrophonium (Tensilon®) and neostigmine (Prostigmin®), remain to reverse NMB.

Physostimine venmosum, the parent compound of CIs, blocks the action of cholinesterase enzymes (AChE). Cholinesterase enzymes are responsible for breaking down ACh, a neurotransmitter found in the sympathetic, parasympathetic, and somatic nervous system. Acetylcholine propagates neuronal impulses across synaptic clefts and in the case of the somatic nervous system enables muscle stimulation and contraction. Cholinesterase inhibitors, by preventing ACh breakdown, allow ACh to increase in quantity and duration. Increased quantities of ACh molecules are then capable of displacing some NMBA molecules from their attachment on the ACh receptors to restore a level of motor function. (Figure 3) By competitively antagonizing the NMBA, motor impulses are able to reach the muscle fiber and muscular contraction is enabled. Thus, NMBA are not inactivated or broken down by CIs. They are only displaced from their site of action, the nicotinic receptor. The two CIs most often used in clinical practice, edrophonium and neostigmine, form reversible, non-covalent attachments to the anionic site or esteratic site on the AChE molecule. Their duration of action is approximately 60 minutes. AChE activity returns to normal after the detachment and metabolism of CIs. The temporary increase in ACh then returns to normal levels.

Limitations of cholinesterase inhibitor drugs

Indirect action

Limitations of CIs include its indirect action and inability to completely reverse NMBA effects. Cholinesterase inhibitors are unable to displace and compete against large quantities of NMBA that have established profound levels of NMB. Complete displacement of NMBA is not
possible and as long as NMBA molecules remain in the body they are able to maintain a degree of NMB despite “reversal”. Residual paralytic effects of NMBAs may or may not be manifest as obvious and measurable continued muscle weakness after CI reversal. Higher levels of residual paralysis are clinically measurable with peripheral twitch monitors and/or patient motor function tests such as head lift, hand grasp, jaw clenching, coughing, and inspiratory effort. Low levels of residual paralysis that affect physiologic functions and contribute to post operative complications such hypoxia, hypercarbia, atelectasis, and aspiration may not be fully measurable. The inability to fully quantify low levels of residual paralysis has allowed on-going controversy concerning its clinical significance and risks.

**Residual Paralysis**

The risks of residual paralysis include: dysphagia, hypoventilation, weakened hypoxic drive, impaired coughing, compromised pharyngeal and laryngeal function and pulmonary complications (Berg, et al.1997; Eikerman, et al. 2006; Eriksson 1999; Tramer & Fuchs-Buder 1999). The primary concern in patients with residual paralysis is airway protection and adequate ventilation. Atelectasis due to volatile anesthetic agent delivery, positive pressure ventilation, hypoventilation, and patient position is compounded by residual paralysis in the post-operative period. The lingering effects of volatile anesthetic agents, benzodiazepines, and narcotics contribute to post-operative hypoventilation. Hypoventilation is worsened by residual paralysis and complicates post operative recovery (Eriksson, 1999).

Recurarization is also a significant limitation of CIs. Recurarization is the reattachment of displaced NMBA onto the motor receptors re-establishing a degree of NMB. It usually is associated with longer acting NMBAs that remain in the body longer than the duration of CIs but also has been associated with intermediate duration NMBAs (Debaene, Plaud, Dilly, & Donati
 Longer acting NMBAs such as curare, pancuronium, doxacurium are often avoided because of this risk and shorter acting agents are preferred. Hence, the progression of NMBA development that favors shorter acting agents with predictable metabolism or degradation has been pursued.

**Side effects of cholinesterase inhibitor drugs**

Cholinesterase inhibitors increase in ACh not only at the neuromuscular junction, but also throughout the body. The generalized increase of ACh stimulates the parasympathetic system and causes undesirable and potentially detrimental side effects. The CIs side effects include: bradycardia, bronchospasm, increased airway secretions, nausea, vomiting, increased peristalsis, increased urination, muscle cramps/spasms, miosis, vision disturbances, and convulsions (American Regent Laboratories Inc., 2002). To counteract these CIs side effects, anticholinergic drugs are given concomitantly. Anticholinergic drugs are effective in attenuating some of the cholinergic actions of CIs but also exert their own undesirable effects including: tachycardia, dry mouth, mydriasis, and vision disturbances (American Regent Laboratories Inc., 2002). The hemodynamic, pulmonary, gastrointestinal, and genitourinary disruption associated with CIs and anticholinergics have been well established.

The indirect action of CIs, limited ability to reverse NMB, generalized systemic effects, and numerous side effects requiring pharmacologic attenuation expresses the need for improved NMBA reversal options. The CI drugs first used to reverse curare have remained the standard for reversing all NMBAs until now. New options are emerging that may provide choice of reversal agents for NMB. Currently undergoing study, these options have sparked interest in the desire for improved safety and efficacy.
Rationale for alternative neuromuscular blocking agent reversal method.

There exists a need for a new class of drugs to overcome the limitations and side effects of CIs while improving the safety and efficacy of NMB reversal. One potential candidate is the selective relaxant binding agent (SRBA) sugammadex (sugammadex sodium, generic, Schering-Plough Corporation, formerly Organon International, Oss, The Netherlands), a modified gamma cyclodextrin (CD). Sugammadex acts by directly encapsulating, binding, and inactivating NMBAs. This pharmacology differs significantly from the indirect action of CIs. (Figure 4)

Discovery of the modified cyclodextrin sugammadex

The original motivation for the study of CD encapsulation of rocuronium was the desire to improve the NMBA’s solubility (Zhang, 2003). Rocuronium is a non-depolarizing NMBA with a steroidal backbone that is commercially prepared in an aqueous solution adjusted to a pH of 4.0 (Rocuronium package insert, 2007). Researchers at Organon Laboratories (New House, UK) originally wanted to solubilize rocuronium without the acidic mannitol phosphate buffer solvent used in its commercial formulation. A different solvent was necessary for in-vitro experiments of rocuronium’s smooth muscle effects uninfluenced by an acidic environment (Bom, Epemolu, Hope, & Mason, 2007). Previous work using CDs to solubilize lipophilic molecules precipitated its use with rocuronium (Szetjtli, 2004).

Modification of CDs alters their affinity for other molecules and researchers explored many modifications of the alpha, beta, and gamma CDs. Multiple modified CDs were synthesized and the candidate chosen to solubilize rocuronium was sugammadex (the modified gamma CD Org 25969). Sugammadex is a modified gamma CD with every 6th carbon hydroxyl group substituted with a carboxyl thioether linkage. [FIG 4] The thioether linkages extend the cavity length allowing complete encapsulation of the rocuronium molecule while increasing the
area over which thermodynamic attractions can occur (Zhang, 2003; Bom, et al. 2002). A secondary benefit provided by the negatively charged carboxyl groups is an increased aqueous solubility of the sugammadex molecule (Zhang, 2003). X-ray crystallography has shown very close size compatibility between sugammadex and the rocuronium molecule (Figure 5) (Bom, et al. 2002). Furthermore, it was found to be one of the most stable complexes of a CD and its guest molecule, with an association constant \( K_a \) of \( 1.8 \times 10^7 \text{ M}^{-1} \) (Bom, et al., 2002). Many unrelated drug/CD complexes studied previously have averaged \( K_a \)s of \( 1 \times 10^1 \text{ M}^{-1} \) to \( 2 \times 10^4 \text{ M}^{-1} \) (Challa, Ahula, Ali, & Khar, 2005).

**Selection of sugammadex sodium for further study**

The discovery of sugammadex’s extremely high binding affinity for rocuronium changed the research focus from *in-vitro* drug solubilization to the novel concept of *in-vivo* drug extraction (Bom, Epemolu, Hope, & Mason, 2007). This initiated the new concept of encapsulation termination of NMBAs.

The high lipophilic binding affinity of sugammadex motivated exploration of possible undesirable binding to endogenous and exogenous steroidal compounds. Zhang found over 40 lipophilic, steroidal, and non steroidal drugs typically given during an anesthetic case had affinities with sugammadex that ranged from 120-700 times less than that of rocuronium (Zhang, 2003). These drugs included the induction agents (propofol, thiopenthane), narcotics (fentanyl, remifentanyl), antibiotics (vancomycin, gentamycin), bronchodilators (salbutamol, aminophylline), cardiovascular drugs (atropine, digoxin, ephedrine, phenolamine, verapamil), and steroids (cortisone, hydrocortisone) (Zhang, 2003). Clinical studies also showed no evidence of interaction with or alteration of the volatile inhalation anesthetic sevoflurane or the intravenous anesthetic propofol (Vanacker, et al., 2007). It was also demonstrated that
propanolol and isoprenaline did not modify the action of sugammadex (Bom & Hope, 2007). Sugammadex has a high selectivity for the aminosteroidal NMBAs rocuronium and vecuronium.

**Sugammadex mechanism of action**

Sugammadex is unique in its application, since CDs have been used previously to encapsulate lipophilic molecules *in-vitro* in order to increase solubilization for improved drug delivery (Loftsson, Pekka, Mar, & Tomi, 2005; Thompson & Chaubal, 2002). Sugammadex is the first CD created to perform its effect *in-vivo* drug effect. The process of sugammadex reversal of NMBA effects can be broken down into two component parts, direct molecular encapsulation and mass extraction of NMBAs from the nicotinic junction into the plasma (Figure 4). Sugammadex is administered intravenously and works in the plasma and possibly the nicotinic junction. The majority of sugammadex appears to remain in the plasma. In the plasma, sugammadex encapsulates and non-covalently binds aminosteroidal NMBAs with a one-to-one ratio. Early studies explored the specifics of this encapsulation process. Using microcrystallography, Bom (2002a) determined that all four steroidal rings of the rocuronium molecule lie in close approximation to the lipophilic cavity of the sugammadex molecule. It was believed that thermodynamic interactions occurring between the sugammadex cavity and the steroidal backbone of the rocuronium molecule, along with the carboxyl group’s attractions for rocuronium’s tertiary ammonium accounted for its total high binding affinity (Zhang, 2003; Adam, Bennett, Bom, Clark, & Feilden, 2002). The plasma encapsulation of NMBA molecules prevents their diffusion into the peripheral compartment for attachment to nicotinic ACh receptors. Any NMBA molecules already attached to extracellular nicotinic receptors causing neuromuscular blockade are rapidly drawn into the plasma and encapsulated. This removal of NMBA molecules from nicotinic ACh receptors occurs because of the concentration gradient.
created by sugammadex binding of the NMBAs in the plasma (Epemolu, et al., 2003). The shift
to a low concentration of unbound NMBA molecules in the plasma causes the higher
concentration of extracellular NMBA molecules to detach from the ACh receptors and diffuse
into the plasma. Once back in the plasma, these NMBA molecules are quickly encapsulated and
bound by sugammadex. This process occurs rapidly, restoring motor function. The two-fold
process of one-to-one encapsulation/-binding in the plasma and the concentration gradient-
mediated extraction of NMBAs from the nicotinic ACh receptors results in fast and effective
termination of NMB by sugammadex.

**Overview of cyclodextrins**

The action of sugammadex is enabled by cycodextrin’s general characteristics of interior
lipophilicity and exterior hydrophylicity. It is the interior lipophilicity of sugammadex which
binds to aminosteroidal NMBAs and exterior hydrophilicity that promotes plasma solubility.
Cyclodextrins are called natural when found in nature wherever starch sources, bacteria, and
appropriate environmental conditions exist. The glucopyranose units of amylose starch are
enzymatically restructured by bacteria such as Bacillus macerans, creating the natural CDs
(Szejtili, 2004). The natural CDs consist of rings of six, seven, or eight glucopyranose units
named alpha, beta, and gamma, respectively (Figure 6). The glucopyranose units are attached by
alpha 1-4 linkages in a circular arrangement creating a truncated cone that points the hydroxyl
groups outward along the rims while directing the alpha 1-4 linkages inward (Figure 7). The
narrow opening is called the primary face, and the larger opening is called the secondary face.
The negatively charged hydroxyl groups lining the primary and secondary faces are responsible
for the water solubility of these molecules. The interior of the CD is lined by uncharged carbon
atoms and alpha 1-4 linkages creating a lipophilic cavity. The structure of CDs creates a water
soluble molecule with a cavity capable of surrounding and binding to a lipophilic molecule. The main pharmacologic benefit extracted from this structural arrangement is encapsulation of appropriately sized lipophilic molecules or drugs and the promotion of aqueous solubility (Welliver 2007).

Historically, CDs have been considered excipients (inert adjuncts) lacking pharmacologic activity but useful for improving the formulation of other active compounds (Loftsson, et al. 2005; Thompson & Chaubal, 2002). The two key characteristics of CDs - lipophilic molecule encapsulation and aqueous solubility- have multiple beneficial applications. For example, CD encapsulation of lipophilic drugs, which are difficult to solubilize, allows their dissolution in water, which is biologically better tolerated than the organic solvents currently used, such as benzyl alcohol and propylene glycol (MacPherson, 2001). The pharmacologic benefits of CD solubilization have been explored and applied successfully with many drug formulations throughout the world (Challa, et al., 2005). The solubilization characteristics of CDs, coupled with biological tolerance, make them desirable replacements for other organic solvents.

Although CDs possess aqueous solubility and an affinity for lipophilic molecules, the relative potency of these characteristics varies between different CDs. Close size approximations of lipophilic molecules to their corresponding CD is necessary to allow non-covalent thermodynamic interactions to occur promoting the formation of an inclusion complex. The approximate cavity sizes of the natural CDs are: gamma (0.8 nm) > beta (0.6 nm) > alpha (0.5 nm) (Welliver 2007). Once inside a CD cavity, thermodynamic attractions- including electrostatic interaction, van der Waals interaction, hydrophobic interaction, hydrogen bonding, release of conformational strain, exclusion of cavity-bound high-energy water, and charge–transfer interaction- may contribute to the formation of the inclusion complex (Liu & Guo,
An inclusion complex, also known as a host-guest assembly, is the newly formed molecular entity of a CD and its encapsulated lipophilic molecule. Modification of the natural CDs allows improvement of their aqueous solubility and thermodynamic attractions for a particular guest molecule. The sites available for CD modification are on the 2\textsuperscript{nd}, 3\textsuperscript{rd}, and 6\textsuperscript{th} carbon atoms of the glucopyranose sub-units. (Figure 7) Numerous substituent atoms or groups may be placed on any or all of these sites improving a CD’s affinity for a particular molecule (Svente & Szejtli 2002). The ability to improve upon the base characteristics of natural CDs has led to the discovery of a CD that promises the unique drug effect of NMBA encapsulation with resultant termination of the paralytic effect.

**Side effects of cyclodextrins**

Cyclodextrins have historically been considered inert excipients meaning they have no pharmacologic effects of their own and are used primarily to solubilize other active agents. Oral consumption of CDs are not regulated and have been proclaimed “generally regarded as safe” (GRASP) by the FDA. Despite being labeled “inert”, CDs do possess side effects. High plasma concentrations have the potential to cause acute renal failure similar to a rhabdomyolysis mechanism. Cyclodextrins are large macro molecules (2000+ atomic mass units) and may collect in the renal tubules exceeding their ability to excrete them. Because of this concern, drug formulations using CDs have been approved only for bolus administration and not continuous infusion. Sugammadex is indicated as a one time intravenous bolus administered drug and therefore acute renal failure because of it CD structure is unlikely. Allergic reactions, though rare, may also be caused by CDs.

**CHAPTER 2**

**METHODOLOGY**
The methodology utilized in this synthesis of the research incorporates a systematic review of the evidence concerning sugammadex using databases that include, Cochrane Reviews, Medline, Pub Med, Highwire, and Google Scholar. Reference lists from sources were audited to identify any relevant sources that may have been missed in the database review. Government regulatory agency clinical trial result submissions have also been reviewed to correlate with published findings and identify discrepancies or omissions that may exist. Inclusion criteria for evidence analysis include bench studies and animal and human randomized controlled trials. Exclusion criteria are expert opinion and drug reviews. Compilation and qualification of the evidence using the Oxford Centre for Evidence-Based Medicine Levels of Evidence taxonomy was completed.

**Phases of clinical trials**

After initial discovery of an active compound and bench studies to assess its characteristics, animal testing is done. Testing a new drug on animals is done to explore a drug’s actions, side effects, and minimize possible harm to humans during later clinical testing. An Investigational New Drug (IND) application to the Food and Drug Administration (FDA) follows successful preclinical bench and animal study in the United States. An IND application must be accepted and approved by the FDA before clinical trials with human subjects may begin. There are four phases of clinical trials (studies): phase I, II, III, and IV. Phase I trials are the first administration of a new drug to healthy human subjects. There are usually very few subjects (n < 100) and the purpose is to assess drug action, safety, dosage ranges, and identify possible side effects. Phase II trials incorporate larger numbers of subjects (n = 100+) to further identify safety, efficacy, and dosage ranges. Multiple study sites may be used in Phase II and phase III clinical trials. Phase III trials use a much larger number of subjects (n = 1000+) to refine the
safety, efficacy, and effective dosage ranges identified in phase II trials. Additionally, phase III trials seek to identify possible interactions with other drugs, efficacy in different patient populations, and compare the new treatment to conventional treatments. Submission to the FDA for marketability usually occurs after successful conclusion of phase III clinical trials. Phase IV is post marketing surveillance that explores long term benefits and risks as well as the efficacy of the drug compiled from its use on a large scale (n = 10,000+)

**Sugammadex clinical trials**

The pre-clinical animal studies confirmed the high affinity of sugammadex for both rocuronium and vecuronium and, to a lesser extent, pancuronium with the ability to terminate NMBA effects under multiple conditions (Welliver, 2006). Mason successfully reversed rocuronium- and vecuronium-induced NMB in guinea pigs with sugammadex 1 mg/kg in less than 1 minute (Mason & Bom, 2001). Profound NMB induced by rocuronium 500 mcg/kg in Rhesus monkeys was successfully performed by de Boer using 2.5 mg/kg sugammadex (deBoer, van Egmond, van de Pol, & Bom, 2006a). Sugammadex reversal of rocuronium was unaffected by pH changes in guinea pigs or renal impairment in cats (Bom, Mason, & McIndewar 2003; Bom, van Egmond, & Hope 2003). The initial success of sugammadex to reverse aminosteroidal NMBA effects in animals supported investigation in humans.

Phase I studies of sugammadex were first performed by Gijsenbergh in 29 healthy male volunteers. All were anesthetized and had NMB induced by rocuronium. Either placebo or sugammadex, in doses ranging from 0.1 – 8.0 mg/kg, were given, and both time and degree of reversal were recorded. Sugammadex 8.0 mg/kg reversed rocuronium-induced NMB in 1 minute, compared to 52 minutes with placebo. The investigators concluded that effective and safe reversal of rocuronium-induced NMB could be achieved with sugammadex (Gijsenbergh
Ramael, Houwing, van Iersal, 2005). A pilot study of the simultaneous administration of sugammadex (16, 20, and 32 mg/kg) with rocuronium (1.2mg/kg) or vecuronium (0.1 mg/kg) was well tolerated in 16 subjects (Cammu, et al., 2008).

**Dose-finding and safety studies**

Dose-finding studies have explored not only the effective doses for shallow levels of NMB, but also for profound levels of NMB. A shallow level of NMB is defined as 2 twitches following train-of-four neuromuscular stimulation (TOF 2/4). A profound level of NMB is defined as no twitches on TOF stimulation and only 1-2 twitches following a post-tetanic count (PTC 1-2). The target end-point (“full reversal”) for these studies was a TOF ratio of 0.9, meaning the 4th twitch of the TOF is 90% the height or strength of the 1st twitch from baseline. Reversal criteria were standardized by using a TOF-Watch® accelerometry nerve stimulator (Organon Ltd., Swords, Ireland). Accelerometry allowed the objective analysis of motor function and standardized the target end-point of the clinical studies. The sugammadex dosage ranges used were 0.5 mg/kg -16 mg/kg. Many studies also reported safety findings which were investigated along with the primary research goals of efficacy and dose-finding. The following studies were designated phase II and III.

Rocuronium-induced NMB studies have shown a dose-dependent time to full reversal. Shields et al. (2006) found safe reversal of rocuronium-induced NMB of two hours or greater duration. Dosages of sugammadex 0.5-6.0 mg/kg effectively reversed rocuronium in a dose-dependant fashion within two minutes (n=30, ASA I-III, age 18+ years). The sugammadex dose of 4.0 mg/kg effectively reversed rocuronium-induced NMB of 15 minutes duration or greater with a mean time of 1.9 minutes (Pavlin, White, Viegas, Minkowitz, & Hudson, 2007). Two studies (n=87, ASA I-III, age 18-87 years) explored reversal of different high-dose
administrations of rocuronium (1.0 and 1.2 mg/kg). These high-dose rocuronium studies, parts of an international multicenter phase II trial, delivered sugammadex (2-16 mg/kg) at 3 and 15 minutes post rocuronium administration. The average time to reversal with 8.0 mg/kg sugammadex was less than 3 minutes at both time intervals with both doses of rocuronium. A dose-response relationship in the time to recovery was concluded (Khuenl-Brady, Rex, Sielenkamper, & Puhringer, 2005, Rex, Khuenl-Brady, Sielenkaemper, Kjaer, & Puhringer, (2005). The final conclusions drawn from this multicenter trial of 176 adult patients was sugammadex provided a rapid dose-dependent reversal of profound NMB induced by rocuronium (Puhringer, et al. 2008).

Shallow rocuronium and vecuronium reversal

Vecuronium- and rocuronium-induced NMB in 100 patients (ASA1-III, age 20-65 years) was reversed with sugammadex. The sugammadex dose of 2.0 mg/kg for rocuronium and 4.0 mg/kg for vecuronium effectively reversed shallow NMB (TOF2/4) in three minutes or less (Puhringer, Blaszyk, Cammu, Sparr, & Heeringa, 2007). These findings have been supported by another study of 100 patients (ASA class I-III, age 20-64 years) (Suy, et al., 2007). Rocuronium- and vecuronium-induced shallow levels of NMB (TOF 2/4) were effectively reversed using sugammadex doses of 1.0 – 4.0 mg/kg. The recovery times displayed a dose-dependent fast time to reversal. The 4.0 mg/kg dose mean reversal time was 1.5 minutes for rocuronium and 3 minutes for vecuronium. All doses were well tolerated (Suy, et al., 2007). Shields described the dose related time to TOF ratio 0.9 from a profound rocuronium-induced NMB reversed upon a spontaneous return to TOF 2/4 (shallow blockade). The dose and corresponding median times (minutes: seconds) to TOF ratio 0.9 were: 0.5 mg/kg (6:49), 1 mg/kg (2:42), 2 mg/kg (1:42), 4 mg/kg (1:04), 6 mg/kg (2:42). The concluded effective dose was 2-4 mg/kg for shallow NMB.
(Vanacker, et al 2007). The longer duration to reversal observed for the 6 mg/kg dose was unexplained and not found in other studies.

Shallow pancuronium reversal

Despite being found in pre-clinical and clinical studies to have a lower affinity for pancuronium compared to rocuronium (Khuenl-Brady, et al., 2005; Rex, et al., 2005, Puhringer, et al., 2008; Zhang, 2003) shallow pancuronium-induced NMB reversal was attempted. Shallow pancuronium-induced NMB has been successfully reversed in 20 patients (ASA class I-II, age 18-81 years). All participants were reversed at the reappearance of 2 twitches on TOF with sugammadex doses ranging from 1.0 mg/kg to 8.0 mg/kg after pancuronium-induced NMB (0.1 mg/kg). The sugammadex dose of 4.0 mg/kg mean time to TOF ratio 0.9 was 2:46 minutes.

Larger doses (6 mg/kg and 8 mg/kg) achieved reversal to a TOF ratio 0.9 in less than 1.5 minutes (Decoopman, Cammu, Suy, Heeroinga, & Demeyer, 2007). Only one dose of pavulon was given in this study and a degree of spontaneous recovery of neuromuscular function was present before sugammadex reversal. Additional study of pancuronium reversal needs to be conducted, including reversal after repeated doses of pancuronium and at varying depths of NMB.

Profound rocuronium and vecuronium reversal

In a study of 50 patients (ASA class I-III, age ≥ 18 years) profound rocuronium-induced NMB was successfully reversed with doses ≥ 2 mg/kg. The lower dose of 2 mg/kg displayed significant variability in recovery times (1.8 -15.2 minutes). The authors concluded that the 4.0 mg/kg and 8.0 mg/kg dose were effective doses exhibiting a mean time of 1.2 minutes to full reversal from profound rocuronium-induced NMB (Sheilds, et al 2006). de Boer found profound rocuronium-induced NMB (1.2 mg/kg) given with propofol and opioid anesthesia of greater than
90 minutes duration was effectively reversed by sugammadex in a dose dependent manner in 45 patients (ASA I- II, age 18-64 years) (de Boer, Driessen, Marcus, & Kerkamp, 2007).

Others studied the ability of sugammadex to reverse profound NMB induced by rocuronium and vecuronium. In 102 patients (ASA class I-III, age 21-64 years) sugammadex doses of 0.5, 1.0, 2.0, 4.0, 8.0 mg/kg were delivered at PTC 1-2. The 2.0 mg/kg dose mean time to full recovery was 3.2 minutes (rocuronium) and 9.1 minutes (vecuronium). The 4.0 mg/kg dose mean time to full recovery was 1.6 minutes (rocuronium) and 3.3 min. (vecuronium). A dose dependent time to full recovery was found with doses 2 mg/kg and greater. The 8.0 mg/kg dose mean time to full recovery was 1.1 minutes (rocuronium) and 1.7 minutes (vecuronium) (Duvaldestin, Kuizenga, Kjaer, Saldien, & Debaene, 2007). Profound vecuronium-induced NMB (PTC 1-2) reversal by sugammadex 4.0 mg/kg was confirmed (average time of 4.5 minutes) (Lemmens, El-Orbany, Berry, & Martin, 2007).

Additional studies also explored the effectiveness of immediate reversal of rocuronium-induced profound NMB. Immediate reversal of profound rocuronium-induced NMB was performed with sugammadex 3, 5, and 15 minutes after rocuronium was administered in 98 adult males. Sugammadex doses of 1.0-8.0 mg/kg were administered. The mean recovery times for the 8.0 mg/kg dose were 1.8 min, 1.5 min, and 1.4 min respectively. The authors concluded a dose-dependent reversal of profound rocuronium-induced NMB was safe and well tolerated (Groudine, Soto, Lien, Drover, & Roberts, 2007). Similarly, rocuronium 1.0 mg/kg was administered and reversed with sugammadex after 3 or 15 minutes with sugammadex doses ranging 2.0 -16 mg/kg. A higher rocuronium dose of 1.2 mg/kg was administered and reversed after 3 or 15 minutes with sugammadex doses of 2.0 -16 mg/kg. The 12 and 16 mg/kg doses
reversed 90% of the cases within 3 minutes. A dose-dependent time to reversal was found (Sparr, et al., 2007).

Doses of 2-16 mg/kg of sugammadex have successfully reversed all levels of rocuronium- and vecuronium-induced NMB with higher doses exhibiting faster reversal times. The dose finding studies have shown a dose-dependant time to reversal of rocuronium- and vecuronium-induced NMB of varying depths. It is apparent from the clinical studies that higher sugammadex dosages are required to reverse deeper levels of NMB. The evidence for this is supported by documentation of the effects of insufficient dosages.

Insufficient dosage

A case was described of a 108 kg female (ASA class II, age 48 years) reversed with sugammadex (0.5 mg/kg) 42 minutes after profound rocuronium (0.9 mg/kg)-induced blockade (PTC 1). The TOF ratio initially improved to 0.6. With in minutes, the TOF ratio decreased to approximately 0.25 and gradually improved to 0.9 over the next 65 minutes. The authors concluded this “muscle relaxant rebound” (recurarization) was due to an insufficient dose of sugammadex (Eleveld, Kuizenga, Proost, & Wierda, 2007). Others found the low dose (0.5 mg/kg) sugammadex initially reversed the shallow NMB induced by rocuronium and vecuronium to a TOF ratio of 0.9 but was followed by a decrease to a TOF ratio <0.8 (Suy, et al., 2007). Similarly, with profound rocuronium- and vecuronium-induced NMB, the low doses (0.5 and 1.0 mg/kg) of sugammadex initially reestablished a TOF ratio ≥ 0.9 that subsequently decreased to <0.8 (Groudine, et al., 2007). This scenario has occurred in clinical trials using the low sugammadex doses of 0.5-1.0 mg/kg (Sheilds, et al., 2006; Suy, et al., 2007; Groudine, et al., 2007; Eleveld, et al., 2007).
It has been theorized by Eleveld (2007) that this recurarization was due to an insufficient dose of sugammadex that may have initially established a concentration gradient by binding central compartment (plasma) rocuronium, significantly decreased the amount of unbound rocuronium, and caused a return of motor function. The decreased concentration of unbound central compartment rocuronium then pulled peripheral compartment rocuronium into the plasma. The insufficient amount of sugammadex may not have been able to bind all of the additional rocuronium molecules drawn from the peripheral compartment and these unbound rocuronium molecules may have re-equilibrated with the effect compartment (nicotinic junction). This redistribution of unbound NMBAs back onto the nicotinic receptors was thought to be the cause of the recurarization (“muscle relaxant rebound”). This explanation may apply to the recurarization found in other studies with vecuronium and rocuronium using sugammadex doses of 0.5 -1.0 mg/kg. Regardless of the exact mechanism of this recurarization, these findings reflect the importance of proper dosing when using sugammadex. It is important to think of sugammadex reversal in terms of direct binding (encapsulation) termination of NMBAs effects, and the establishment of a concentration gradient that extracts the NMBAs off of the nicotinic receptor drawing them into the plasma. Sufficient doses of sugammadex must be given to fully encapsulate all NMBA molecules in a 1:1 ratio. The use of neuromuscular monitoring was advised to assure the correct chosen dose and adequate reversal is achieved. (Eleveld, et al., 2007)

High dosage

A sugammadex dose (40.0 mg/kg) which is 10 times the desired dose of 4.0 mg/kg was inadvertently delivered by investigators to a male (ASA class I, age 36 years) patient five minutes after receiving rocuronium 1.2 mg/kg. The error was quickly recognized and data
collection continued. Full recovery to TOF ratio 0.9 occurred in 1.31 minutes. No untoward effects were revealed apart from immediate and effective rocuronium reversal. Investigators disclosed an uneventful duration of anesthesia (150 minutes) and recovery. No adverse or serious adverse events were identified by a blinded safety assessor postoperatively, or at a seven day follow-up. The time to full reversal of rocuronium by the excess sugammadex dose was 1.31 minutes. The investigators suspected that a faster reversal time could have occurred but was dependent on cardiac output or circulation time and not the encapsulation process which is very rapid (Molina, de Boer, Klimekl, Heeringa, & Klein, 2007).

**Comparative studies**

Comparison to succinylcholine recovery

Successful, immediate reversal of rocuronium prompted the question of a comparison to succinylcholine. Spontaneous enzymatic degradation of succinylcholine restores motor function within ten minutes (Kopman, 2003). The recovery time of succinylcholine was compared to the reversal time of rocuronium after sugammadex 16 mg/kg. One hundred and ten patients (ASA class I-II, age 18-65 years) were randomized to receive succinylcholine 1.0 mg/kg or rocuronium 1.2 mg/kg. Three minutes after rocuronium administration, sugammadex 16 mg/kg was delivered and time to full reversal recorded. Spontaneous recovery time of succinylcholine was also recorded. The mean time to a TOF ratio 0.9 was 6.2 minutes for rocuronium, and 10.9 minutes for succinylcholine. The authors concluded a faster safe reversal of rocuronium-induced NMB compared to spontaneous recovery from succinylcholine (Lee, Jahr, Candiotti, Warriner, & Zornow, 2007). It is important to note that the time count to recovery began immediately after succinylcholine administration and not until after sugammadex delivery for rocuronium.
Comparison to cholinesterase inhibitors

Vecuronium-induced NMB reversal by sugammadex was compared to conventional reversal with cholinesterase inhibitors. Alvarez-Gomez (2007) found a faster time to full reversal of shallow vecuronium-induced NMB (TOF 2/4) with sugammadex (average 2.1 minutes) verses neostigmine (average 18.9 minutes). Profound vecuronium-induced NMB reversal by sugammadex was compared to both edrophonium and neostigmine. Eighty-three patients (ASA class I-III, age >18 years) received propofol, sevoflurane, opioids, anesthesia with vecuronium (maintenance doses 0.1mg/kg) to maintain profound NMB. Sugammadex 4.0 mg/kg, or neostigmine 70 mcg/kg with glycopyrrolate 14 mcg/kg, was administered. The time to full recovery averaged 4.5 minutes for the sugammadex group and 66.2 minutes for the neostigmine-glycopyrrolate group. No residual curarization was found in either group. Safe, efficient, and faster reversal by sugammadex was concluded (Jones, Caldwell, Brull, & Soto, 2007).

Sugammadex reversal of shallow rocuronium NMB was compared to neostigmine reversal of shallow cis-atracerurium blockade. Eighty-four patients (ASA class I-III) were randomized to receive sugammadex-rocuronium or cis-atracerurium-neostigmine at a TOF 2/4. The mean reversal time for sugammadex was 1.51 minutes (range 0.7-6.4) compared to 2.85 minutes (range 4.2-28.2) for neostigmine. The time to full reversal by sugammadex was significantly faster (p<0.0001) (Lemmons, et al., 2007). The wide range of reversal times associated with neostigmine reflected the individual variability of its competitive antagonism mechanism of action compared to the direct encapsulation mechanism by sugammadex.

Comparison of sugammadex to neostigmine for reversal of shallow levels of rocuronium-induced NMB was conducted. Ninety-eight patients (ASA class I-III, age >18 years) received rocuronium and at TOF 2/4, sugammadex 2.0 mg/kg, or neostigmine (50 mcg/kg) with
glycopyrrolate (10 mcg/kg) was administered. The median time to full reversal was 1.4 minutes (range 0.9-5.4 min) for sugammadex and 17.6 minutes (range 3.7-106.9 min) for neostigmine. No residual paralysis or re-curarization occurred in either group (Blobner, Eriksson, Scholz, Hillebrand, & Pompei, 2007). Moderately profound and profound rocuronium-induced NMB reversal by sugammadex was compared to edrophonium and neostigmine. Sixty patients (ASA class I-III) received desflurane, remifentanil, and rocuronium. Moderately profound NMB was not clearly described in this study but, at a “similar first twitch height” sugammadex 4.0 mg/kg, edrophonium 1 mg/kg with atropine (10 mcg/kg), or neostigmine (70 mcg/kg) with glycopyrrolate 14 mcg/kg was administered. The time to full recovery averaged 1.78 (± 1.1) minutes for sugammadex, 5.52 (± 0.45) minutes for edrophonium, and 17.44 (± 9.8) minutes for neostigmine (Sacan, White, Tufanogullari, & Klein, 2007). Similarly, Flockton (2007) found profound rocuronium-induced NMB was fully reversed faster with sugammadex 4.0 mg/kg (average 2.9 minutes) compared to neostigmine 70 mcg/kg with glycopyrrolate 14 mcg/kg (average 50.4 minutes).

Specific patient populations

Phase III clinical trials explored therapy in varied patient populations and its possible alterations in patients with differing physiologies.

Pediatric

Pediatric use of sugammadex was conducted by Plaud with infants, children, and adolescents. Eight infants (age 28 days- 23 months), 24 children (age 2- 11 years), and 31 adolescents received propofol anesthesia and caudal analgesia (infants) or opioids (children and adolescents). Rocuronium 0.6 mg/kg was administered and at TOF 2/4 sugammadex 0.5 – 4.0 mg/kg or placebo was administered. The time to full recovery ranged from 0.7 - 4.2 minutes in
the infant group. The time to full recovery ranged from 0.6 -10.9 minutes in a dose dependant manner in the children group, and from 0.7 - 43.5 minutes in a dose dependant manner in the adolescent group. Higher doses (2.0 – 4.0 mg/kg) of sugammadex had significantly faster times to full recovery. Safety was assessed by electrocardiography, laboratory values, and documentation of adverse events. The authors concluded safe and effective use of sugammadex in infant, children, and adolescent populations (Plaud, et al., 2009).

Elderly

Drug pharmacokinetics (PK) and pharmacodynamics (PD) can be altered in the elderly. McDonagh and others explored sugammadex efficacy in this patient population. A total of 150 patients were grouped by age: 48 adults (age 18-64 years), 62 elderly (age 65-74 years), and 40 old elderly (age >75 years). All received rocuronium 0.6 mg/kg and, at a return of TOF 2/4, sugammadex 2 mg/kg was administered. The mean time to full recovery in the adult group was 2.3 minutes, elderly group 2.6 minutes, and old elderly 3.6 minutes. The authors concluded that there was a significant time delay for all patients over age 65 (average 2.9 minutes) compared to patients <65 (average 2.3 minutes) (McDonagh, Benedict, Kovac, Drover, & Brister, 2007).

Renal Insufficiency

Patients with renal impairment indicated by creatinine clearance less than 30 ml/minute were compared to non-renal impaired patients who received sugammadex. All patients were anesthetized with propofol, opioids, and rocuronium 0.6 mg/kg. At TOF 2/4 sugammadex 2.0 mg/kg was administered and time to full recovery recorded. The mean time to full recovery was 2.0 minutes for the renal impaired group (n=15), and 1.7 minutes for the non-renal impaired group (n=15). The authors concluded safe and effective reversal of rocuronium-induced NMB in both normal and renal impaired patients (Staals, Snoek, Flockton, Heeringa, & Driessen, 2007).
Cardiac

Study of sugammadex reversal in 121 cardiac patients (NYHA class II-III, ASA class II-IV, age 36-90 years) was conducted in a randomized, placebo-controlled, multicenter study. All patients in this study underwent non-cardiac surgery with rocuronium-induced NMB. Baseline QTc intervals, using the Fridericia correction formula (to account for changes in heart rate), were recorded and compared to QTc intervals after sugammadex and placebo reversal. Reversal was administered at the conclusion of surgery and return of TOF 2/4 using sugammadex 2.0 mg/kg, 4.0 mg/kg, or placebo. The mean time to full recovery was 1.7, 1.4, and 34.4 minutes respectively. Analysis of QTc intervals showed no significant statistical differences (ANCOVA) between the sugammadex and placebo groups. The authors stated only two episodes of QTc interval prolongation, one in the sugammadex group and one in the placebo group, was “possibly related to study treatment” (Dahl, Pendeville, Hollman, Heier, & Blobner, 2007). The anesthetic agents used to induce general anesthesia in these patients was not disclosed. Inhalation volatile anesthetic agents have been implicated as a cause of QTc interval prolongation (Schmeling, et al., 1991; Kleinsasser, et al., 2000). Previous studies reported QTc prolongations that were “possibly related” to sugammadex; therefore, specific investigation of the phenomena was warranted (Gijsenbergh, et al., 2005; Vanacker, et al. 2006; Sorgenfei et al., 2006; de Kam, van Kuijk, Smeets, Thomsen, & Peeters, 2007).

Specific analysis of possible QTc prolongation by sugammadex was conducted. Using criteria of the International Conference on Harmonisation (ICH-E14) guidelines, (Shah, 2005) researchers eliminated agents that may prolong QTc intervals and evaluated only sugammadex. A total of 62 volunteers were randomized to receive 4.0 mg/kg or 32 mg/kg sugammadex, moxifloxacin 400 mg (known QTc prolongation), or placebo. No significant QTc prolongation
was found with the sugammadex or placebo groups. Significant (>10msec) QTc was found with
the positive control drug moxifloxacin (deKam, et al., 2007). The potential consequences of QTc
prolongation by drugs have warranted this particular study. It appears that disclosed QTc
prolongations in previous studies are more likely to be associated with concomitantly
administered agents rather than sugammadex. This finding, in association with safe and
efficacious conclusions in patients with cardiac disease, suggests sugammadex may be safely
used in the presence of cardiac disease and possibly in patients with conduction defects (Dahl, et
al., 2007). The finding that sugammadex is unlikely to cause QTc prolongation is important to
note as several studies disclosed QTc prolongation as a possible adverse event.

Pulmonary

The effects of sugammadex in patients with pulmonary disease were studied. Seventy-
seven patients (ASA class II-III, age >18 years) with a known history or diagnosis of pulmonary
disease received rocuronium (0.6 mg/kg). At a TOF 2/4, sugammadex 2.0 or 4.0 mg/kg was
administered. The mean time to full reversal was 1.8 minutes with the 2.0 mg/kg dose, and 2.1
minutes for the 4.0 mg/kg dose. Two serious episodes of bronchospasm, possibly related to
sugammadex, were observed in the 4.0 mg/kg dose group. Both of these patients had a disclosed
history of asthma. No alterations in respiratory rate or recurarization were observed in any
patients. The authors concluded sugammadex was well tolerated and effective for reversal of
rocuronium-induced NMB in patients with pulmonary disease (Amao, Zornow, Cowan, Cheng,
& Allard, 2007).

Metabolism and Excretion

Sugammadex is biologically well tolerated. It does not undergo metabolism or
breakdown and therefore does not affect blood sugar levels. It is excreted by the kidneys intact
and has been found to increase the excretion of rocuronium molecules that it encapsulates. (Sorgenfrei, et al., 2006) Sugammadex and sugammadex/NMBA inclusion complexes are excreted unchanged in the urine mirroring glomerular filtration rate (GFR) (Gijsenbergh, et al. 2005). The sugammadex/NMBA complex and it can be removed by dialysis (Hartman Smeets, deZwart, & Peters, 2007).

**Duration of action**

Once encapsulated, rocuronium and vecuronium molecules remain unable to exert their paralytic effects. The specific duration of time that sugammadex may exert its NMBA reversal effect is determined by dose as well as GFR. Early PK and PD study in Rhesus monkeys found that the half-life of sugammadex is 30 minutes but the ED$_{90}$ of rocuronium differs between rhesus monkeys and humans, 100mcg/kg vs 300 mcg/kg respectively (de Boer, et al., 2006b). The lower ED$_{90}$ for Rhesus monkeys allows less rocuronium molecules to produce an equipotent block with their human counterparts, and therefore less sugammadex molecules are needed for reversal. Lower amounts of sugammadex molecules will be cleared faster and allow sooner re-administration of rocuronium of vecuronium.

**Adverse effects**

Few adverse effects have been attributed to sugammadex. One study reported abdominal discomfort as “definitely related” to study drug (Suy, et al., 2007). Movement after sugammadex was observed in several studies which may be expected with rapid restoration of motor function and lighter anesthetic levels towards the conclusion of surgery (Sorgenfrei, et al., 2006; de Boer 2007). “Possible” adverse effects reported in clinical trials include: erythema, alterations in taste and smell, coughing, dry mouth, tachycardia, bradycardia, pyrexia, dizziness, vomiting, hypotension, abnormal urine levels of N-acetyl-glucosaminidase, and QT interval prolongation.
QT prolongation was observed by Puhringer but was considered not to be related to sugammadex (Puhringer, et al., 2008). An analysis by Vanacker determined that corrected QT prolongations, which were not arrhythmogenic, were likely to be due to the anesthetics sevoflurane and propofol (Vanacker, et al., 2007). A study by de Kam found that sugammadex doses up to 32 mg/kg were not associated with QT/QTc prolongation (de Kam, et al. 2007). The authors of a study in cardiac patients also reported that no QTc prolongations were related to sugammadex (Dahl, et al., 2007). Inadvertent over dosage occurred in one clinical study, when sugammadex 40 mg/kg was administered instead of 4.0 mg/kg, but this was not associated with any adverse effects and effective reversal of rocuronium was reported (Molina, et al., 2007).

Only one confirmed (skin patch testing) case of mild allergic reaction has been documented although skin patch testing was performed on several patients suspected of possible allergic reaction. To date, less than 8 patients out of 2000+ have been documented by investigators as “possibly” having an allergic reaction. Although most disclosed adverse effects have been expressed as only “possibly related” to the study drug, conclusive determination has yet to be made. (See Appendix A, Clinical trials summary)

Concern by the Food and Drug Administration (FDA) that adverse events described in clinical trials, when viewed as a whole, could possibly represent anaphylactic/anaphylactoid reactions caused a “not approvable” letter to be issued to Schering-Plough Pharmaceutical July 2008. Ongoing clinical studies are addressing the concerns. Re-submission of sugammadex to the FDA is expected prior to 2010. The European regulatory commission has approved sugammadex for use and it is currently being used clinically in several countries. No adverse outcomes have been disclosed since its practice incorporation date of August 2008 in Europe.
CHAPTER 3

CRITIQUE OF THE EVIDENCE

Improved Neuromuscular Blockade Management

Unique to sugammadex is the ability to reverse rocuronium- and vecuronium-induced NMB of varying depths and durations. The dose-dependent fast time to reversal permits the continuation of any level of NMB up to the time of surgical conclusion. Sugammadex reversal can then quickly re-establish neuromuscular function. Surgical closures and procedures of short duration may benefit from profound aminosteroidal-induced NMB that is not lessened by spontaneous recovery toward the end of surgery. A degree of spontaneous recovery of neuromuscular function is a necessity for CI reversal. The provision of profound NMB eliminates unacceptable operating conditions (King, et al., 2000). Abdominal rectus tone decreases surgical exposure and requires greater traction on retractors. Tissue damage may occur with excessive retraction. Only profound NMB provides total muscle laxity which optimizes surgical exposure and access. Profound NMB has been found to be associated lower incidence of nerve injury during femur pinning. In cases were lower levels or absent NMB was present the incidence of nerve injury due to excessive traction increases (Chan, Schondorf, & Brock, 1999; Giordano, Mallet, Tricoire, Nehme, Chiron, & Puget, 2003; Rajbabu, Brown, & Poulsen, 2006; Mallet, et al., 2005). Sugammadex’s ability to reverse all levels of NMB should eliminate the hesitancy of anesthesia providers to maintain profound levels of NMB. Prospective and retrospective studies may offer conclusive evidence of this suggestion. Profound NMB also prevents diaphragmatic movement during surgical procedures. Spontaneous attempts at breathing intra operatively are contraindicated during laproscopic abdominal procedures. Despite shallow NMB that may prevent skeletal muscle movement, the diaphragm is relatively resistant. Greater
levels of NMB are required to assure no diaphragmatic movement. Spontaneous diaphragm movement during surgery regularly occurs and elimination of this event may benefit open and laproscopic abdominal surgical procedures.

Procedures requiring absolute immobility will benefit from the provision of profound NMB. Diagnostic imaging, neurosurgical spinal and cranial procedures, and cases with head fixation all require assured immobility. Current NMBA reversal with CIs does not allow continual profound NMB. Undesirable patient movement during these and other procedures may have devastating consequence. It is recommended that sugammadex be used whenever profound NMB is to be reversed.

**Rapid Sequence Intubation**

Additionally, the ability of sugammadex to quickly reverse rocuronium (1.2 mg/kg) used for rapid sequence intubations (RSI) provides an alternative to succinylcholine. Succinylcholine is the only NMBA that can establish quick (60 sec.s) NMB with fast (<10 minutes) reliable termination of effect. Unfortunately, succinylcholine is associated with multiple undesirable side effects and contraindicated in numerous clinical situations. Rocuronium is a safer NMBA that provides quick (60 sec.s) NMB but with a long duration (45 + min.s) that can not be immediately reversed with CIs. Sugammadex effectively reverses rocuronium-induced NMB of any depth at any time and therefore provides a recommended to succinylcholine for RSI and procedures of ultra short duration.

**Coexisting Diseases**

The lower side effect profile of Sugammadex promotes its use in patients with co-existing cardiac and pulmonary disease. The well documented hemodynamic instability associated with CIs promotes the use of sugammadex in patients with cardiac compromise and
coronary artery disease. Sugammadex has no effect on heart rate or blood pressure. Sugammadex also has no documented effect on the pulmonary system in contrast to firmly established negative effects of CIs. Patients with acute and chronic obstructive and restrictive pulmonary disease will likely benefit from sugammadex reversal that is free of pulmonary side effects and more effective re-establishment of muscle function. Obese patients whom already have airway and respiratory function compromise related to their obesity may be provided with optimal restoration of neuromuscular function. Sugammadex reversal addresses decreased pharyngeal muscle tone that contributes to airway compromise especially in the obese and obstructive sleep apnea patients after NMB. Sugammadex is recommended for all obese patients with normal renal function.

**Dosage**

It is likely that sugammadex will be prescribed on a sliding scale based on study findings which show that time to full reversal and degree of efficacy are dose-dependent. Doses of 2-4 mg/kg have effectively reversed shallow NMB (TOF 2/4) induced by rocuronium and vecuronium. Profound levels of NMB (PTC 1-2) induced by rocuronium and vecuronium have been effectively reversed with dosages of 4-8 mg/kg. Doses of 32+ mg/kg have been used to immediately reverse profound levels of NMB 3 minutes after rocuronium (1.2 mg/kg) administration. Residual paralysis from incomplete CI reversal may also be performed with sugammadex. A case report by Lenz described the successful reversal of residual paralysis manifest as respiratory compromise in the post anesthesia care unit (Lenz, Hill, White, 2007).

**Further Study**

Few studies using sugammadex have been conducted on infants, children, and adolescents therefore only weak recommendations may be made for these patient populations.
Further study is needed in infants, children, and adolescents. The evidence has not disclosed the effect of lingering sugammadex-NMBA inclusion complexes due to inability to excrete. The clinical need for complete and reliable reversal of NMBA effects may outweigh any unknown risks with its use in renal failure patients. Until further study documents benefit and safety, sugammadex is not recommended in patients with acute or chronic renal failure. Sugammadex use in renal insufficiency is weakly recommended because it is extrapolated from the studies which showed clearance mirrors GFR.

CHAPTER 4

DISCUSSION

Evidence-based Practice Model

The Evidence-based Practice Model formulated by Rosswurm and Larrabee (1999) guided the assessment, synthesis and integration of this project. The six step model delineates a process that promotes evidence-based practice change. The six steps are:

1. Assess need for change
2. Link Problem interventions and Outcomes
3. Synthesize best evidence
4. Design practice change
5. Implement & evaluate
6. Integrate & maintain

Assess need for change (Step 1)

Steps 1, assess need for change, is described in chapter 1 which introduces the need for an improved, direct, and specific reversal of NMBAs free of unwanted side effects. The situational analysis discloses both internal and external data that highlights the contrast between
sugammadex and CI reversal of NMB. Internal data associated with effects and outcomes includes: time to extubation, PACU stay duration, reintubation rates, SpO2 trends, incidence of hypoxia, and morbidity and mortality rates. These effects and outcomes have been strengths of sugammadex and weaknesses of CIs. External data includes: JCAHO standards, pay for performance, patient satisfaction, surgeon satisfaction, practitioner satisfaction, and nurse satisfaction. Sugammadex lends itself well to improved outcomes and milestone targets for continuous quality assurance programs. The opportunity that sugammadex offers the stakeholders; anesthesia provider, surgeons, pharmacy, purchasing administrators, operating room nurses, recovery room nurses, and patients, warrants continued analysis.

*Link problem interventions and outcomes (Step 2)*

The problems associated with CI reversal of NMB are its indirect action, incomplete reversal, and numerous side effects. Because of these limitations and undesirable effects the full use of NMB is hindered. Shallow and moderate levels of NMB are the norm and profound NMB is often avoided. The delayed ability to reverse NMB and potential for residual paralysis contribute to peri-anesthetic risks. Clinical considerations addressed by sugammadex include: muscle relaxation vs muscle paralysis, shallow/moderate vs profound (Deep) NMB, reversibility, degree reversal, residual paralysis, and RSI options. Management of NMB is expanded by sugammadex while offering an improved safety and efficacy profile compared to CIs. The NMB management options made available by sugammadex compared to CIs is displayed in figure 8. The bold vertical bracket in the figure represents the range of NMB enabled by sugammadex. The horizontal bracket represents the delay to full reversal of NMB by CIs. These are two of the significant improvements offered by sugammadex, faster reversal and more complete reversal of NMB.
**Synthesize best evidence (Step 3)**

The review of the literature has disclosed significant improvement to reverse rocuronium- and vecuronium-induced NMB by sugammadex compared to CIs. A greater safety profile has been shown by hemodynamic stability and pulmonary tolerability. Fast, complete reversal of NMB by sugammadex free of the limitations and side effects associated with CIs encourages the structured synthesis of evidence to guide clinical practice.

Levels of evidence

Various types of data hold greater value than others. In general, randomized controlled trials (RCTs), meta-analysis of RCTs, and systematic reviews of RCTs are the strongest data (evidence); followed by cohort studies, non-randomized clinical trials (nRCTs), case reports, and lastly, expert opinion. High quality meta-analysis and systematic reviews of unbiased RCTs consolidate evidence that promotes reliable practice recommendations. Levels of evidence (LOE) are scored using a numerical system that ranges from 1-5. The numeric value of 1 correlates with strong, high quality data such as a well conducted double blinded RCTs, systematic reviews of homogenous RCTs, or meta-analysis of RCTs. Evidence scored at 2 consists of systematic reviews of cohort studies, cohort studies, and lower quality RCTs. Evidence scored 3 and 4 are weaker strength consisting of case-controlled studies and case-series. Expert opinion is the weakest strength of evidence and poor rationale from which to make recommendations for practice. The purpose of scoring LOE is to allow the reader/practitioner to quickly identify the quality of the evidence and the value it contributes to guiding practice.


Grades of recommendation
Recommendations for practice are graded based on the level (strength) of the evidence. Recommendations graded: “A” are the best drawn from high quality level 1 evidence, “B” are drawn from level 2 or 3 evidence, “C” are drawn from level 4 evidence or extrapolated from level 2 or 3 studies, and “D” are drawn from level 5 evidence. Strong consistent evidence such as RCTs with significant number of study subjects and findings allow recommendations to be made with an “A” grade. Appendix B describes Oxford Centre’s Evidence-based Medicine grades of recommendation based on LOE.

Sugammadex studies utilized in this review consist of RCTs. The evidence reviewed is of strong quality (LOE 1) with many RCTs consisting of 100+ subjects and using multicenter aggregate data. Consistent data collection, tools and methodology allow comparison of data from multiple studies and reflect a consistency of findings. Although many studies have been blinded, the immediate pronounce clinical effects observed with sugammadex foretold its identity. All clinical studies have been sponsored by Organon/Schering-Plough and this may introduces a bias in study design and possible data evaluation. Published peer-reviewed reports are expected to disclose unbiased findings but contractual agreements require initial review and approval by the sponsor. This may introduce bias in disseminated published research.

**Design practice change (Step 4)**

Practice Change Guidelines

In light of the safety and efficacy findings in RCTs of sugammadex, recommendations have been made to use sugammadex instead of CIs for reversal of rocuronium- and vecuronium-induced NMB. Use of sugammadex is superior to CIs in all patient groups including adult, elderly, obese, cardiac and pulmonary compromise, and acid-base disturbances. Sugammadex is superior to CIs for all depths of NMB induced by rocuronium and vecuronium. Therefore, it is
recommended that sugammadex be used instead of CIs whenever significant (moderate or profound) NMB depth exists, CIs side effects are undesirable, any degree of residual NMB would be detrimental, or a “can not intubate, can not ventilate scenario is encountered due to rocuronium- or vecuronium-induced NMB is present. The specific recommendations for practice change are delineated in Tables 1, 2, and 3 and were derived from high quality evidence (LOE 1). These recommendations have not considered cost as a factor for decision making and are based only on pharmacologic and physiologic safety, efficacy, and outcomes and associated with each treatment therapy.

Neuromuscular Monitoring

In light of the effectiveness of SRBAs, the question of continued use of neuromuscular monitoring has been raised (Kopman, 2006; Naguib, 2007). Neuromuscular monitoring should be used whenever NMBAs are administered. In the desire to maintain vigilance, and because of concerns about potentially insufficient sugammadex doses, it is recommended that use of peripheral twitch monitors (nerve stimulators) to assess the degree of NMB be continued and expanded.

Neuromuscular monitoring is of paramount importance to effectively titrate NMBAs and regulate the degree of NMB. Current neuromuscular monitoring techniques are fully capable of measuring profound NMB but are not routinely used by clinicians. Neuromuscular monitors function by transmitting an electrical impulse through a peripheral motor nerve such as the ulnar nerve. The resultant muscle contraction is assessed and the degree of NMB is estimated. The testing modes available are single twitch, continuous twitch, train-of-four (TOF), double-burst (DBS), tetanus, and post-tetanic count (PTC). Each of these modes offers unique data to be evaluated and applied to the estimation of neuromuscular function. Specifically, PTC allows the
extrapolation of the degree of profound NMB. The safer provision of profound NMB enabled by sugammadex encourages practitioners to expand their use of NMB monitoring modes to effectively measure that greater depth of blockade.

Depth of anesthesia monitoring

Sugammadex’s fast and effective reversal allowing the provision of continual profound NMB during surgery and diagnostic procedures eliminates the patient response of movement during light anesthesia. Physiologic parameters, pharmacologic principles, and patient responses provide valuable information from which the anesthesia provider determines depth of anesthesia. Patient variability and changing surgical stimuli creates a dynamic scenario in which extrapolation of patient status is not always completely reliable. Eliminating movement as a sign of light anesthesia may increase the risk of intra-operative awareness (Ghoneim, Blcok, Haffarnan, & Matthews, 2009). The use of anesthesia depth monitors is therefore encouraged. Anesthesia depth monitors measure the overall activity of brain function and provide a scaled estimation between 0-100. Estimated values ranging 40-60 have been shown to correlate with adequate suppression of cerebral function to may lessen the chance of intraoperative awareness.

The resources to facilitate introduction of into practice sugammadex include existing equipment and monitors which are able to measure outcomes. Improved utilization of these resources including neuromuscular monitors, depth of anesthesia monitors, and standard vital sign parameters provide immediate measurable outcomes and reinforce the clinical benefit to the anesthesia provider. The summary of practice recommendations is to use sugammadex to reverse rocuronium- and vecuronium-induced NMB:

Whenever profound NMB is present.

Hemodynamic and pulmonary parasympathetic effects are undesirable.
Any degree of residual paralysis will be detrimental to the patient.

“Can not ventilate, can not intubate” scenario d/t NMB.

**Implement & evaluate (Step 5)**

**Sugammadex practice incorporation**

The plan for practice incorporation of sugammadex for reversal of aminosteroidal NMBAs is to first introduce the drug as a phase III clinical trial candidate. Our institution is a University based health science center with an established reputation for conducting clinical trials. Sugammadex will be introduced to the anesthesia department by power point presentation. Its pharmacology and clinical significance will be discussed. Select anesthesia department staff will then be invited to participate in a clinical trial of sugammadex. Regular staff updates will be provided during weekly departmental meetings throughout the clinical trial process. Active Student Registered Nurse Anesthetists (SRNAs) participation will be sought to promote an educational milieu pertaining to sugammadex. Final clinical trial findings will be presented to the anesthesia department in lecture and abstract form. National presentation will be pursued at the AANA annual convention.

A clinical trial of a new drug will require interdepartmental cooperation between the anesthesia, pharmacy, and laboratory departments. This interdisciplinary cooperation for a clinical trial will allow dissemination of data pertaining to not only the pharmacology of this drug but also its clinical significance. The educational opportunities to inform individuals about sugammadex will facilitate the acquisition of sugammadex when it is evaluated for purchase. The formulary committee is composed of representatives from management, pharmacy, and clinical departments. Several committee members are likely to be well informed about sugammadex because of the clinical trial. Thus, a clinical trial of sugammadex will allow interdepartmental staff the opportunity to become familiar with the drug and its capabilities. The
interdisciplinary collaboration, educational opportunities provided to appropriate individuals, and the clinical experience obtained using this drug should improve the likelihood that this drug will be added to our formulary.

During the formulary approval process, a plan to add sugammadex to individual operating room drug trays will be initiated. The addition of sugammadex to individual operating room stock drug trays allows immediate access as opposed to requiring another person to go to a centralized pharmacy for dispensing. Immediate access of all reversal drugs promotes clinical decision making based on relevant factors affecting patient care rather than adding drug administration delay as an extraneous factor to be considered. Staff education will be conducted prior to sugammadex availability for clinical use. Pharmaceutical drug representative presentation and literature will be provided. Sugammadex pharmacology including drug actions, dosing, indications, contraindications, and side effects will be discussed. Clinical trial investigators will serve as educational resources for staff during clinical incorporation of sugammadex.

**Integrate & maintain (Step 6)**

Continued evaluation of sugammadex use will be initiated after practice incorporation and research committee evaluation of proposals. Suggested explorations include: incidence of nausea and vomiting, extubation times from end of surgery, operating room turn over times, length of post anesthesia care unit stay, patient satisfaction, nurse satisfaction, surgeon satisfaction, and increased or decreased use of neuromuscular monitoring. Administrative evaluation of cost and process improvement is also suggested. Drug acquisition costs are unknown as sugammadex is not yet FDA approved. Associated cost benefit analysis is not possible at this time but suggested for further study. Patient outcome studies comparing conventional NMBA CI reversal with reversal by means of CD encapsulation are needed to
determine the potential benefits of sugammadex beyond effective and immediate NMBA reversal.

Recommendations of sugammadex or CI use in specific clinical situations or with specific patient populations is supported by the evidence and summarized in the tables of recommendations. The promotion of more in depth neuromuscular blockade monitoring has not been shown to improve outcomes with CIs and may or may not improve outcomes with sugammadex. It will likely improve the intraoperative management of continual profound NMB. Until strong evidence suggests otherwise, intraoperative NMB monitoring remains a recommendation of practice based on expert opinion and a standard of practice incorporated into assessment and vigilance. Phase IV study may strengthen or weaken the body of evidence and lead to modification of these recommendations for practice.

CHAPTER 5

CONCLUSION

This synthesis of the research is based only on available published clinical studies; the data disclosed suggests sugammadex is a safe and effective reversal agent for rocuronium- and vecuronium-induced NMB that appears to be free of the side effects associated with CI and anticholinergic drugs. Sugammadex use in pediatric and elderly populations as well as patients with coexisting diseases of cardiac, pulmonary, and renal origin have shown safe and effective reversal of rocuronium and vecuronium but these have been single studies and, as yet, not repeated. Shallow pancuronium-induced NMB reversal has been successfully achieved, though not extensively studied. A sliding scale dosage schedule based on the degree of NMB determined by neuromuscular monitoring is recommended. As described in the dose finding studies, higher doses will be needed to reverse greater depths of NMB. A much higher dose for immediate
reversal of profound rocuronium-induced NMB after 1.2 mg/kg may enable safer rapid sequence intubations when avoiding the use of succinylcholine. Not only does it appear that fast and effective reversal may be achieved with sugammadex, but also improved surgical conditions may be provided to surgeons. The pharmacology of direct encapsulation to reverse all levels of rocuronium- and vecuronium-induced NMB unveils options that competitive antagonism has precluded. Improved surgical performance and outcomes may be found in the future with the expanded abilities in NMB management. The new management option of NMB of any depth and duration will require the continued use of neuromuscular monitoring to fully assess these varying depths. The PTC mode will likely become as standard as TOF ratio for those desiring to achieve and maintain deeper (profound) levels of NMB that sugammadex enables. The evidence leads to the conclusion that sugammadex is a more effective, safer reversal of rocuronium- and vecuronium-induced NMB at any time and at any depth compared to CIs. It is recommended that sugammadex be used to reverse the effects of rocuronium and vecuronium whenever profound NMB is present, hemodynamic and pulmonary parasympathetic effects are undesirable, or any degree of residual paralysis will be detrimental to the patient. It is also recommended that sugammadex be administered in any situation that rocuronium- or vecuronium-induced neuromuscular blockade has contributed to a “can not ventilate, can not intubate” scenario. Evidence-based practice goals are a dynamic process of continual assessment, synthesis, integration, and reassessment and will be continued after the introduction of sugammadex into clinical practice.
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Figure 1. Normal acetylcholine release and receptor stimulation causing muscle contraction.
Figure 2. Neuromuscular blockade induced by plasma administered neuromuscular blocking agent which diffuses to nicotinic synaptic cleft, occupies receptors, and prevents attachment of acetylcholine.
Figure 3. Cholinesterase inhibitor (not shown) prevents breakdown of acetylcholine allowing increased concentration to form which displace neuromuscular blocking agent from receptors allowing motor function restoration.
Figure 4. Intravenous administered sugammadex encapsulates neuromuscular blocking agent in blood stream establishing a concentration gradient that extracts neuromuscular blocking agent from the neuromuscular junction back into the plasma for the continued process of encapsulation. Neuromuscular function is fully restored.
Figure 5. Crystal spectroscopy image of sugammadex (stick figure) encapsulating rocuronium molecule (ball model). (With permission A. Bom, Organon USA, a part of Schering-Plough Corporation, and Prous Scientific).
Figure 6. Formation of natural cyclodextrins alpha, beta, and gamma.
Figure 7. General truncated cone molecular shape of a cyclodextrin showing peripheral exterior hydroxyl groups and interior alpha 1-4 linkages.
Figure 8. Comparison of sugammadex and CI NMB management.
<table>
<thead>
<tr>
<th>Goal</th>
<th>Recommendation</th>
<th>SOR</th>
<th>LOE</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Profound rocuronium NMB (PTC&lt;8) reversal</td>
<td>Sug</td>
<td>A</td>
<td>1b</td>
<td>39, 40, 44, 48, 49, 51, 52, 55, 57, 59, 62.</td>
</tr>
<tr>
<td>Moderate rocuronium NMB (TOF 1-2/4) reversal</td>
<td>Sug</td>
<td>A</td>
<td>1b</td>
<td>38, 40, 41, 45, 46, 63, 65, 66, 72.</td>
</tr>
<tr>
<td>Shallow rocuronium NMB (TOF 2-4/4) reversal</td>
<td>Sug (CI)</td>
<td>A</td>
<td>1b</td>
<td>60, 61, 69.</td>
</tr>
<tr>
<td>Profound vecuronium NMB (PTC&lt;8) reversal</td>
<td>Sug</td>
<td>A</td>
<td>1b</td>
<td>39, 49, 50.</td>
</tr>
<tr>
<td>Moderate vecuronium NMB (TOF 1-2/4) reversal</td>
<td>Sug</td>
<td>A</td>
<td>1b</td>
<td>45, 46, 58.</td>
</tr>
<tr>
<td>Shallow vecuronium NMB (TOF 2-4/4) reversal</td>
<td>Sug (CI)</td>
<td>A</td>
<td>1b</td>
<td>45, 46, 58.</td>
</tr>
<tr>
<td>Rescue residual paralysis s/p CI</td>
<td>Sug</td>
<td>C</td>
<td>1b</td>
<td>62. 82.</td>
</tr>
<tr>
<td>Full airway / Pharyngeal muscle function</td>
<td>Sug</td>
<td>A</td>
<td>1b</td>
<td>6. 9, 13. 7,81.</td>
</tr>
</tbody>
</table>

Goal summary of practice recommendation and strength of recommendation (SOR) based on referenced levels of evidence (LOE).
Table 2.

<table>
<thead>
<tr>
<th>Coexisting condition / disease</th>
<th>Recommendation</th>
<th>SOR</th>
<th>LOE</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac ischemia</td>
<td>Sug</td>
<td>A</td>
<td>1b</td>
<td>66, 70.</td>
</tr>
<tr>
<td>Unstable hemodynamics</td>
<td>Sug</td>
<td>A</td>
<td>1b</td>
<td>66, 70.</td>
</tr>
<tr>
<td>Restrictive pulmonary disease</td>
<td>Sug</td>
<td>A</td>
<td>1b</td>
<td>72.</td>
</tr>
<tr>
<td>Obstructive pulmonary disease</td>
<td>Sug</td>
<td>A</td>
<td>1b</td>
<td>72.</td>
</tr>
<tr>
<td>Renal insufficiency creatinine clearance &lt; 30 ml/hr</td>
<td>CI (Sug)</td>
<td>A</td>
<td>1b</td>
<td>37, 65.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>1b</td>
<td>73.</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>CI</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>CI</td>
<td>na</td>
<td>na</td>
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</table>

Coexisting condition or disease summary of practice recommendation and strength of recommendation (SOR) based on referenced levels of evidence (LOE).
Table 3.

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Recommendation</th>
<th>SOR</th>
<th>LOE</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants (&lt;23 months)</td>
<td>CI</td>
<td>D n=8</td>
<td>1b</td>
<td>63.</td>
</tr>
<tr>
<td>Children (2-11 years)</td>
<td>CI</td>
<td>D n=24</td>
<td>1b</td>
<td>63.</td>
</tr>
<tr>
<td>Adolescents (12-17 years)</td>
<td>CI</td>
<td>D n=31</td>
<td>1b</td>
<td>63.</td>
</tr>
<tr>
<td>Geriatric (65+)</td>
<td>Sug CI</td>
<td>A</td>
<td>1b</td>
<td>23, 41, 44, 47-57, 64, 65, 66.</td>
</tr>
</tbody>
</table>

Patient population summary of practice recommendation and strength of recommendation (SOR) based on referenced levels of evidence (LOE). Refer to tables 2 & 3 for goal and coexisting conditions recommendations.
<table>
<thead>
<tr>
<th>Reference #, Author</th>
<th>LOE</th>
<th>Study Phase, Type</th>
<th>Subject Number, Anesthesia</th>
<th>Methodology</th>
<th>Major Findings, Conclusions</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gijsenbergh F, Ramael S, Houwing N, van Iersel T. 2005</td>
<td>3a</td>
<td>I RCT Safety Efficacy PK</td>
<td>N=29 Healthy males</td>
<td>Sug (1-8mg/kg) or placebo 3 min. after Roc 0.6mg/kg</td>
<td>Roc plasma conc. and renal excretion increased after org25969. “Well tolerated, effective”.</td>
<td>No SAE 5 mild, 1 moderate (IV site parasthesia x7days)</td>
</tr>
<tr>
<td>Cammu G, de Kam P-J, Demeyer I, Decoopman M, Peeters P, Smeets JM, Foubert. 2008</td>
<td>3a</td>
<td>I RCT Pilot Safety study</td>
<td>N=16 Healthy volunteers Prop. &amp; remifent or No anesth.</td>
<td>Roc 1.2mg/kg, along with Sug 16, 20, or 32mg/kg. Vec 1mg/kg, along with Sug 16,20, or 32mg/kg.</td>
<td>Several combinations of Sug and Roc or Vec safe, well tolerated in anesthetized and non-anesthetized volunteers when given simultaneously.</td>
<td>No SAE AEs; Mild H/A, tiredness, dry mouth, oral discomfort, nausea, increased aspartate aminotransferase and gamma-glutamyltransferase levels</td>
</tr>
<tr>
<td>de Kam P-J, van Kuijk J. 2007</td>
<td>1b</td>
<td>I RCT Safety</td>
<td>N=62</td>
<td>Sug 4 or 32 mg/kg, Moxifloxacin, or placebo</td>
<td>Sug single IV doses 4 and 32 mg/kg not associated with QTc prolongation. “Safe, well tolerated”</td>
<td>No SAE</td>
</tr>
<tr>
<td>Sorgenfei IF, Norrild K, Larsen PB, Stensballe J, Ostergaard D, Prins ME, Viby-Mogensen J. 2006</td>
<td>1b</td>
<td>II RCT Safety Dose-response PK</td>
<td>N=27 Age 18-64 Prop, narc.</td>
<td>Sug 0.5-4.0mg/kg or placebo 60 min. after Roc 0.6mg/kg x1 dose.</td>
<td>Roc plasma conc. and renal excretion increased. Dose-dependent time to “full reversal.” Safe. Well tolerated”.</td>
<td>2 Hypotension 3 Coughing 3 Movement</td>
</tr>
<tr>
<td>Suy K, Morias K, Cammu G, Hans P, van Duijnhooven WGF, Heeringa M, Demeyer I. 2007</td>
<td>1b</td>
<td>II RCT Dose-finding</td>
<td>N=80 ASA I-II Age ≥ 18 Prop. &amp; remifent.</td>
<td>Roc 0.6mg/kg Vec 0.1mg/kg Sug 0.5-4 (8)mg/kg or placebo@TOF 2/4</td>
<td>Dose-dependent fast time to reversal. Dose-response relationship. Effectively reversed rocuronium and vecuronium.</td>
<td>6 SAE surgery related 1 SAE tachycardia 1 prolonged awakening 1 erythema 1 abd. discomfort</td>
</tr>
<tr>
<td>Reference #, Author</td>
<td>LOE</td>
<td>Study Phase, Type</td>
<td>Subject Number, Anesthesia</td>
<td>Methodology</td>
<td>Major Findings, Conclusions</td>
<td>Adverse Effects</td>
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<tr>
<td>Vanacker BF, Vermeyen KM, Struys MMRF, Rietbergen H, Vandermeersch E, Saldien V, Kalmar AF, Prins ME. 2007</td>
<td>1b</td>
<td>II RCT Safety Efficacy</td>
<td>N=42 ASA I-III Age 18-82 Sevo or Prop.</td>
<td>Sevoflurane grp. Propofol grp. Sug 2.0mg/kg @ TOF 2/4 after Roc 0.6mg/kg</td>
<td>Mean time to full reversal equivalent for both groups (1.8 min.). Unaffected by sevoflurane or propofol. No residual paralysis.</td>
<td>No SAE 8 QT prolongation Hypotension Bradycardia 1 N&amp;V</td>
</tr>
<tr>
<td>Puhringer F, Blaszyk M, Cammu G, Sparr H, Heeringa M. 2007</td>
<td>1b</td>
<td>II RCT Efficacy</td>
<td>N=100 ASA I-III Age 20-64</td>
<td>Roc 0.9mg/kg Vec 0.1mg/kg Sug 0.5-4 (8)mg/kg or placebo@TOF 2/4</td>
<td>Sug dose-dependent time to reversal &amp; dose-response relationship for reversal of Roc and Vec.</td>
<td>3 SAEs</td>
</tr>
<tr>
<td>Shields M, Giovannelli M, Mirakhur RK, Adams J, Hermens Y. 2006</td>
<td>1b</td>
<td>II RCT Safety Efficacy Dose-response</td>
<td>N=30 ASA I-III Age &gt; 18 Prop, narc. &amp; N2O.</td>
<td>Sug 0.5-6 mg/kg @TOF 2/4 after profound Roc block x 2hr.s</td>
<td>Reversed profound and prolonged roc block. Dose-response effect. Sug 2-4 mg/kg-full reversal within 3 min. “Safe and effective”.</td>
<td>Atrial fibrillation, resp. failure</td>
</tr>
<tr>
<td>Decoopman M, Cammu G, Suy K, Heeroinga M, Demeyer M. 2007</td>
<td>1b</td>
<td>II RCT Exploratory</td>
<td>N=20 ASA I-II Age 20-81</td>
<td>Sug 1.0-8 mg/kg @TOF 2/4 after Pancuronium 0.1mg/kg</td>
<td>Sug decreases mean recovery time of shallow pancuronium block. No dose-response relation shown. Good safety profile, well tolerated.</td>
<td>2 SAEs</td>
</tr>
<tr>
<td>Groudine SB, Soto R, Lien C, Drover D, Roberts K. 2007</td>
<td>1b</td>
<td>II RCT Dose-finding</td>
<td>N=50 ASA I-III Age ≥ 18 Prop, narc &amp; N2O.</td>
<td>Sug 0.5-8mg/kg after Roc 0.6 or 1.2 mg/kg and PTC 1-2</td>
<td>Mean time to full reversal 1.2min with Sug 8mg/kg Profound roc block reversed @doses≥2mg/kg Well tolerated</td>
<td>4 SAE undisclosed</td>
</tr>
<tr>
<td>Reference #, Author</td>
<td>LOE</td>
<td>Study Phase, Type</td>
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<tr>
<td>Duvaldestin P, Kuizenga K, Kjaer CC, Saldien V, Debaene B. 2007</td>
<td>1b</td>
<td>II RCT Dose-finding</td>
<td>N=102 ASA I-III Age 21-64 Sevo,</td>
<td>Sug 0.5-8mg/kg @ PTC1-2 after Roc 0.9mg/kg or Vec 0.1mg/kg</td>
<td>Dose-response relation. Recurarization (TOF ratio &gt;0.9 to &lt;0.8) w/Sug 0.5-1mg/kg</td>
<td>4 SAE undisclosed</td>
</tr>
<tr>
<td>Sparr HJ, Vermeyen KM, Beaufort A, Rietbergen HM, Proost JH, Velik-Salchner C, Wierda JM. 2007</td>
<td>1b</td>
<td>II RCT Safety Efficacy PK</td>
<td>N=98 Adult males Prop, narc.</td>
<td>Sug 1-8mg/kg or placebo at 3, 5 or 15 min post Roc 0.6mg/kg. Dose-response relation. Recurarization (TOF ratio &gt;0.9 to &lt;0.8) w/Sug 0.5-1mg/kg</td>
<td>Dose-dependent time to reversal. Sug enhanced renal excretion of Roc.</td>
<td>Undisclosed</td>
</tr>
<tr>
<td>Khunl-Brady K, Rex C, Siebenkamper A, Eikerman M. 2005</td>
<td>1b</td>
<td>II RCT Dose-finding</td>
<td>N=87 ASA I-III Age 18-80 Prop, narc.</td>
<td>Sug 2-16mg/kg or placebo 3 or 15 min. after profound Roc block. (1.0 mg/kg)</td>
<td>Ave time to full reversal 2.5 min with Sug 8mg/kg. Dose-response relationship. “Well tolerated, good safety profile”.</td>
<td>SAE: 6 QT prolong, 8 N&amp;V, 1 hypotension, 1 vertigo, 1 hiccups, 1 delayed awakening</td>
</tr>
<tr>
<td>Rex C, Khunl-Brady K, Siebenkamper A, Kjaer CC, Puehringer FK, 2005</td>
<td>1b</td>
<td>II RCT Dose-finding</td>
<td>N=87 ASA I-III Age 18-80 Prop, narc.</td>
<td>Sug 2-16mg/kg or placebo 3 or 15 min. after profound Roc block. (1.0 mg/kg or 1.2 mg/kg)</td>
<td>Time to full reversal &lt; 3 min. with Sug 8mg/kg. Dose-response relationship. Safe.</td>
<td>SAE: 6 (5 undisclosed) 1 QT prolong</td>
</tr>
<tr>
<td>Puehringer F, Rex C, Siebenkamper, Claudius C, Larsen PB, Prins ME, Eikerman M, Khunl-Brady K. 2008</td>
<td>1b</td>
<td>II RCT Dose-finding Safety Multicenter</td>
<td>N=176 ASA I-III Age 18-80 Prop, narc.</td>
<td>Sug 2-16mg/kg or placebo 3 or 15 min. after profound Roc block. (1.0 mg/kg or 1.2 mg/kg)</td>
<td>Median time (min.s) to full reversal: 3min 15min 1.0 1.6 0.9 1.2 1.3 1.9</td>
<td>As above</td>
</tr>
<tr>
<td>de Boer HD, Driessen JJ, Marcus M, Kerkkamp H, Heeringa M, Klimek M. 2007</td>
<td>1b</td>
<td>II RCT Safety Dose-finding</td>
<td>N=46 ASA I-II Age 18-64 Prop &amp; remifentanil</td>
<td>Sug 2-16mg/kg 5 min. after 1.2 mg/kg Roc</td>
<td>Dose-dependent fast time to reversal. All doses “well tolerated”. No recurarization.</td>
<td>No SAE 2 Movement 1 light anesthesia, 1 diarrhea</td>
</tr>
<tr>
<td>Reference #, Author</td>
<td>LOE</td>
<td>Study Phase, Type</td>
<td>Subject Number, Anesthesia</td>
<td>Methodology</td>
<td>Major Findings, Conclusions</td>
<td>Adverse Effects</td>
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<tr>
<td>Pavlin EG, White PF, Viegas OJ, Minkowitz HS, Hudson ME. 2007</td>
<td>1b</td>
<td>II RCT Efficacy Dose-response</td>
<td>N=197 ASA I-III Age 18-70 TIVA, GA</td>
<td>Sug 4.0mg/kg 15min or greater after Roc.</td>
<td>Mean time to reversal 1.9 min. “Effective, well tolerated”</td>
<td>No SAE No AE</td>
</tr>
<tr>
<td>Lee C, Jahr JS, Candiotti K, Warriner B, Zornow MH. 2007</td>
<td>1b</td>
<td>II RCT Safety Efficacy Comparative</td>
<td>N=110 ASA I-II Age 18-65</td>
<td>Sug 16 mg/kg 3min after Roc 1.2mg/kg or SCh 1 mg/kg followed by spont. recovery</td>
<td>Mean time(min.) to 0.9TOF from delivery of NMBA: Roc/Sug group- 4.4 SCh group- 7.1 min. No residual paralysis or recurarization.</td>
<td>8 AE Sug group 8 AE SCh group (AEs undisclosed)</td>
</tr>
<tr>
<td>Alvarez-Gomez JA, Wattwil M, Vanacker B, Lora-Tamayo JI, Khun-Brady KS. 2007</td>
<td>1b</td>
<td>II RCT Efficacy Comparative</td>
<td>N=100 ASA I-III Age ≥ 18</td>
<td>Sug 2.0mg/kg or Neo/glyco 50/10µg/kg after Vec and TOF 2/4</td>
<td>Median time to Vec reversal faster with Sug vs Neo (2.1 vs 18.9 min) No residual paralysis or re-curarization</td>
<td>No SAEs</td>
</tr>
<tr>
<td>Lemmens HJM, El-Orbany MI, Berry J, Martin G. 2007</td>
<td>1b</td>
<td>II RCT Efficacy Comparative</td>
<td>N= 84 ASA I-III Prop, narc.</td>
<td>Sug 2.0mg/kg after Roc or Neo/glyco 50/10µg/kg after Cis-atracurium. Both @ TOF2/4</td>
<td>Median time to Roc reversal w/Sug 1.9 min compared to Cis-atracurium reversal w/ Neo 7.2 min. No recurarization either group.</td>
<td>No SAEs</td>
</tr>
<tr>
<td>Flockton E, Scanni E, Gomar C, Shields M, Aguilera L. 2007</td>
<td>1b</td>
<td>II RCT Efficacy Safety Comparative</td>
<td>N=74 ASA I-III Age ≥ 18 Prop, sevo, &amp; narc.</td>
<td>Sug 4.0mg/kg or Neo/glyco70/14 µg/kg after Roc and PTC 1-2</td>
<td>Mean time to Roc reversal faster with Sug vs Neo. (2.9 min vs 50.4 min). “Good safety profile” Sug reversal less tachycardia.</td>
<td>No SAE</td>
</tr>
<tr>
<td>Reference #, Author</td>
<td>LOE</td>
<td>Study Phase, Type</td>
<td>Subject Number, Anesthesia</td>
<td>Methodology</td>
<td>Major Findings, Conclusions</td>
<td>Adverse Effects</td>
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<tr>
<td>Jones RK, Caldwell JE, Brull SJ, Soto R. 2007</td>
<td>1b</td>
<td>III RCT Efficacy Safety Comparative</td>
<td>N=83 ASA I-III Age ≥ 18 Prop, narc. Sevo, narc.</td>
<td>Sug 4.0mg/kg or Neo/glyco 70/14µg /kg after Vec and PTC 1-2</td>
<td>Mean time to Vec reversal faster with Sug vs Neo (4.5 min vs 66.2 min). No residual curarization or residual paralysis.</td>
<td>No SAE either group 9 AE Sug group 10 AE Neo group</td>
</tr>
<tr>
<td>Blobner M, Eriksson L, Scholz J, Hillebrand H, Pompei L. 2007</td>
<td>1b</td>
<td>III RCT Comparative</td>
<td>N=98 ASA I-III Age ≥ 18</td>
<td>Sug 2.0mg/kg or Neo/glyco 50/10µg /kg after Roc and TOF 2/4</td>
<td>Median time to reversal 1.4 min vs 17.6 for neo/glycol. No residual re-curarization.</td>
<td>2 SAE Sug grp 3 SAE Neo grp4</td>
</tr>
<tr>
<td>Sacan O, White PF, Tufanogullari B, Klein K. 2007</td>
<td>1b</td>
<td>III RCT Comparative</td>
<td>N=60 ASA I-III Desflurane &amp; remifentanil.</td>
<td>Sug 4.0 mg/kg or Edroph/atropine 1/0.01mg/kg or Neo/glycol 70/10 µg/kg after Roc and TOF 2/4</td>
<td>Mean time &amp; % achieved “full” (0.9TOF) reversal: Sug (S) 107 sec., 100% Edroph (E) 1044 sec.,25% Neostig (N) 331 sec., 10% AEs:</td>
<td></td>
</tr>
<tr>
<td>Plaud B, Meretoja O, Pohl B, Mirakhur RK, Raft J. 2007</td>
<td>1b</td>
<td>III RCT Safety Pediatric Children Adolescent Adult</td>
<td>N=8 infants N=24 child. N=31 adolsc N=28 adult ASA I-II Prop, caudal, opioid</td>
<td>Sug 0.5 – 4.0 mg/kg after Roc 0.6mg/kg and TOF 2/4</td>
<td>Median time full reversal 2.0 &amp; 4.0 mg/kg*: Infants- 0.6 &amp; 0.7 min Children-1.2 &amp; 0.6 min Adolescent-1.1 &amp; 1.1 min Adult-1.4 &amp; 1.2 min Placebo 19-28.5 min * Sug 0.5,1.0 mg/kg in text</td>
<td>SAE: 1 infant 1 child</td>
</tr>
<tr>
<td>Reference #, Author</td>
<td>LOE</td>
<td>Study Phase, Type</td>
<td>Subject Number, Anesthesia</td>
<td>Methodology</td>
<td>Major Findings, Conclusions</td>
<td>Adverse Effects</td>
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<tr>
<td>McDonagh DL, Benedict PE, Kovac AL, Drover D, Brister NW. 2007</td>
<td>1b</td>
<td>III RCT Safety Elderly</td>
<td>N=150 ASA I-III Age 18-&gt;75 GA</td>
<td>Sug 2mg/kg after Roc 0.6mg/kg and TOF 2/4</td>
<td>Mean time to reversal: Age &lt; 65 2.3 min Age 65-74 2.6 min Age &gt; 75 3.6 min Reversal slightly longer for age &gt; 65 years</td>
<td>AE: Hypotension³ Tachycardia³ Pyrexia³ Dizziness³ Oligemia³</td>
</tr>
<tr>
<td>Staals LM, Snoek MMJ, Flockton E, Heeringa M, Driessen JJ. 2007</td>
<td>1b</td>
<td>III RCT Safety Renal Disease</td>
<td>N=30 ASA II-III Age 29-81 Prop, narc.</td>
<td>Sug 2.0mg/kg after Roc 0.6mg/kg and TOF 2/4</td>
<td>Mean time to reversal 2.0 min in renal-impaired and 1.7 min in normal renal function group. Well tolerated, rapid recovery</td>
<td>No SAE disclosed</td>
</tr>
<tr>
<td>Dahl V, Pendeville PE, Hollman MW, Heier T, Blobner M. 2007</td>
<td>1b</td>
<td>III RCT Safety Cardiac Disease</td>
<td>N= 121 ASA II-IV Age 36-90 Non-cardiac surgery. Anesthesia undisclosed</td>
<td>Sug 2 or 4mg/kg or placebo after Roc 0.6mg/kg and TOF 2/4</td>
<td>NO QTc prolongation. Decrease mean QTc noted from baseline in Sug groups. “Safe and effective in cardiac patients” Time to recovery faster with Sug vs placebo.</td>
<td>2 SAE: QTc prolongation³</td>
</tr>
<tr>
<td>Amao R, Zornow MH, Cowan RM, Cheng DCH, Allard M. 2007</td>
<td>1b</td>
<td>III RCT Safety Pulmonary Disease</td>
<td>N= 77 ASA II-III Age ≥ 18 Anesthesia undisclosed</td>
<td>Sug 2 or 4mg/kg after Roc 0.6mg/kg and TOF 2/4</td>
<td>“Generally well tolerated and effective” Mean time to reversal: Sug 2mg/kg 2.1min Sug 4mg/kg 1.8min</td>
<td>2 SAE: Bronchospasm³ (patient history of asthma)</td>
</tr>
</tbody>
</table>
Appendix A - Key

Adverse events Key:

*found in placebo group

1. Definitely related to study drug
2. Probably related to study drug
3. Possibly related to study drug
4. Not related to study drug

Abbreviations:

Abd-abdominal
AE-adverse effect
GA-general anesthesia
N: NMBM-necromuscular blocking agent
N2O-nitrous oxide
N&V-nausea and vomiting
PK-pharmacokinetic
prop-propofol
remifent-remifentanyl
RCT-randomized controlled trial
roc-rocuronium
SAE-serious adverse effect
SCh-succinylcholine

Definitions:

TOF-Train of four mode using peripheral nerve monitor (twitch monitor)
T2-Two twitches out of four using a TOF monitor (shallow block)
PTC-Post tetanic count (1-8), 1-2 = profound, deep block.
0.9 TOF-The product of the ratio of the fourth twitch strength compared to the first twitch strength when using a TOF monitor. Represents a 90% return of the fourth twitch strength to baseline.

"Full reversal"- End target of 0.9 TOF ratio
## Appendix B

**Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)**

<table>
<thead>
<tr>
<th>Level</th>
<th>Therapy/Prevention, Aetiology/Harm</th>
<th>Prognosis</th>
<th>Diagnosis</th>
<th>Differential diagnosis/symptom prevalence study</th>
<th>Economic and decision analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>SR (with homogeneity*) of RCTs</td>
<td>SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations</td>
<td>SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres</td>
<td>SR (with homogeneity*) of prospective cohort studies</td>
<td>SR (with homogeneity*) of Level 1 economic studies</td>
</tr>
<tr>
<td>1b</td>
<td>Individual RCT (with narrow Confidence Interval‡)</td>
<td>Individual inception cohort study with &gt; 80% follow-up; CDR† validated in a single population</td>
<td>Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre</td>
<td>Prospective cohort study with good follow-up****</td>
<td>Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses</td>
</tr>
<tr>
<td>1c</td>
<td>All or none§</td>
<td>All or none case-series</td>
<td>Absolute SpPins and SnNouts††</td>
<td>All or none case-series</td>
<td>Absolute better-value or worse-value analyses ††††</td>
</tr>
<tr>
<td>2a</td>
<td>SR (with homogeneity*) of cohort studies</td>
<td>SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs</td>
<td>SR (with homogeneity*) of Level &gt;2 diagnostic studies</td>
<td>SR (with homogeneity*) of 2b and better studies</td>
<td>SR (with homogeneity*) of Level &gt;2 economic studies</td>
</tr>
<tr>
<td>2b</td>
<td>Individual cohort study (including low quality RCT; e.g., &lt;80% follow-up)</td>
<td>Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split-sample§§ only</td>
<td>Exploratory** cohort study with good†††reference standards; CDR† after derivation, or validated only on split-sample§§ or databases</td>
<td>Retrospective cohort study, or poor follow-up</td>
<td>Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses</td>
</tr>
<tr>
<td>2c</td>
<td>&quot;Outcomes&quot; Research; Ecological studies</td>
<td>&quot;Outcomes&quot; Research</td>
<td>Ecological studies</td>
<td>Audit or outcomes research</td>
<td>Ecological studies</td>
</tr>
<tr>
<td>3a</td>
<td>SR (with homogeneity*) of case-control studies</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
<td>SR (with homogeneity*) of 3b and better studies</td>
</tr>
<tr>
<td>3b</td>
<td>Individual Case-Control Study</td>
<td>Non-consecutive study; or without consistently applied reference standards</td>
<td>Non-consecutive cohort study, or very limited population</td>
<td>Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.</td>
<td>Non-consecutive cohort study, or very limited population</td>
</tr>
<tr>
<td>4</td>
<td>Case-series (and poor quality cohort and case-control studies§§)</td>
<td>Case-series (and poor quality prognostic cohort studies***</td>
<td>Case-control study, poor or non-independent reference standard</td>
<td>Case-series or superseded reference standards</td>
<td>Analysis with no sensitivity analysis</td>
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<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or &quot;first principles&quot;</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or &quot;first principles&quot;</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or &quot;first principles&quot;</td>
<td>Expert opinion without explicit critical appraisal, or based on economic theory or &quot;first principles&quot;</td>
<td>Expert opinion without explicit critical appraisal, or based on economic theory or &quot;first principles&quot;</td>
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</table>
Notes
Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because of:
- EITHER a single result with a wide Confidence Interval (such that, for example, an ARR in an RCT is not statistically significant but whose confidence intervals fail to exclude clinically important benefit or harm)
- OR a Systematic Review with troublesome (and statistically significant) heterogeneity.
- Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

* By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.

† Clinical Decision Rule. (These are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category.)

‡ See note #2 for advice on how to understand, rate and use trials or other studies with wide confidence intervals.

§ Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.

$$ By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.

$$§§ Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.

†† An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.

‡‡ Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.

††† Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.

†††† Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.

*** By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.

**** Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (eg 1-6 months acute, 1-5 years chronic)

Grades of Recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>consistent level 1 studies</td>
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<tr>
<td>B</td>
<td>consistent level 2 or 3 studies or extrapolations from level 1 studies</td>
</tr>
<tr>
<td>C</td>
<td>level 4 studies or extrapolations from level 2 or 3 studies</td>
</tr>
<tr>
<td>D</td>
<td>level 5 evidence or troublingly inconsistent or inconclusive studies of any level</td>
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</table>

"Extrapolations" are where data is used in a situation which has potentially clinically important differences than the original study situation.