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Thesis

THE SAFETY AND NECESSITY OF SUGAMMADEX IN NEUROMUSCULAR BLOCKADE REVERSAL

by

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THE SAFETY AND NECESSITY OF SUGAMMADEX IN NEUROMUSCULAR
BLOCKADE REVERSAL

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ABSTRACT

Sugammadex, a gamma cyclodextrin discovered in 2007, provides a safe and effective alternative to drugs currently used in surgery by anesthesiologists. A problem in the current practice of anesthesia is the use of Succinylcholine, a neuromuscular blocking agent used for the cessation of the patient’s skeletal muscle movement. Succinylcholine is used due to its unique fast onset and short duration, ideal for short procedures, difficult intubation scenarios, and rapid sequence intubation. However, it is used cautiously due to several risks such as causing myalgia, hyperkalemia, fasciculations, and increasing intracranial, intragastric, and intraocular pressure.

Sugammadex provides a safer alternative to Succinylcholine because it allows immediate reversal of a neuromuscular blockade through a different mechanism, which does not lead to harmful adverse effects. Sugammadex works by encapsulating its target muscle relaxant, Rocuronium. Rocuronium is a relatively safer drug than Succinylcholine with a similar time of onset, but a very long duration of action. Since Sugammadex is able to immediately reverse the effects of Rocuronium, this combination of Rocuronium and Sugammadex
provides the same desired effect as Succinylcholine but without the harmful side effects.

The current most widely used reversal agent for muscle relaxation is Neostigmine. The problems with Neostigmine are that it can lead to residual paralysis and recurarisation if under dosed. It also produces unwanted cholinergic side effects that lead to cardiovascular instability. Due to this, the medical community is in need for a better reversal agent that can both quickly and completely reverse muscle paralysis without the need to manage unwanted side effects. Sugammadex is able to address both the problems of Succinylcholine and Neostigmine.

Studies have shown Sugammadex to provide a faster, safer, and more predictable reversal of Rocuronium – induced neuromuscular blockade than Neostigmine. Sugammadex has shown to also achieve faster recovery from Rocuronium – induced muscle paralysis than the fast spontaneous recovery of Succinylcholine. With no serious adverse effects observed in these studies, the data supports the use of Sugammadex and its potential to replace the current standards of practice with Succinylcholine and Neostigmine. Furthermore, high dosage of Sugammadex has shown to be capable of immediately reversing profound neuromuscular blockades, an ability that no reversal drug currently in the market possesses. This enables the anesthesiologist to provide optimal muscle relaxation for the surgeon throughout the operation without the concern of being unable to reverse the patient in a timely manner.
Studies on multiple patient population groups do not show any serious adverse effects are linked to using Sugammadex. There have been incidences of drug induced QTc prolongation in cardiac patients, but its cause was not determined to be related solely with Sugammadex. Sugammadex has shown to be the safer reversal agent compared to Neostigmine in cardiac, pulmonary, and renal patients.

One problem that prevents the routine use of Sugammadex is its cost. The cost is significantly higher than Neostigmine. This cost is justified, however, due to staff costs saved from a faster patient recovery and shorter stay in the hospital. Therefore, while Sugammadex is definitely warranted over Succinylcholine due to its safety profile, its use over Neostigmine is dependent on each healthcare facility. While Sugammadex is currently under review by the Food and Drug Administration, it will evolve the practice of anesthesia if allowed into the United States market.
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## ABBREVIATIONS

<table>
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<tr>
<td>ACh</td>
<td>Acetylcholine</td>
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<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
</tr>
<tr>
<td>C</td>
<td>Celsius</td>
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<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<td>CYP</td>
<td>Cytochrome P450</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>IND</td>
<td>Investigational New Drug</td>
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<tr>
<td>Ka</td>
<td>Acid dissociation constant</td>
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<td>Kg</td>
<td>Kilogram</td>
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<tr>
<td>L</td>
<td>Liter</td>
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<tr>
<td>mEq</td>
<td>Milliequivalent</td>
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<td>mg</td>
<td>Milligram</td>
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<tr>
<td>mmHg</td>
<td>Millimeter of mercury</td>
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<tr>
<td>NMBA</td>
<td>Neuromuscular blocking agent</td>
</tr>
<tr>
<td>OR</td>
<td>Operating Room</td>
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<tr>
<td>PACU</td>
<td>Post Anesthesia Care Unit</td>
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<tr>
<td>QTc</td>
<td>Q – T Interval corrected for heart rate</td>
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<td>TOF</td>
<td>Train of four</td>
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Introduction

The practice of anesthesia originated in ancient times, and is a specialty undergoing constant evolution especially in the mid-nineteenth century. Ancient civilizations had long used coco leaves, opium poppy, mandrake root, and alcohol as anesthetics in order to allow surgeons to operate in tolerable conditions regarding their patients. Due to advances in the pharmaceutical industry and a better understanding of human physiology, various drugs are now administered to achieve the desired conditions for the surgeon. Prior to these advancements in the past decade, modern surgery was hampered not only by poor understanding of pathology, anatomy, and aseptic technique, but it also lacked reliable and safe anesthetics and anesthetic technique. The practice of anesthesia evolved first with development of inhalation anesthesia affecting the entire autonomic nervous system of the body. This was followed by anesthetics, which have effects locally or at a specific region of the body by targeting local conduction of nerves cells or segments of the spinal tract. Finally, pharmaceutical companies have now developed a wide spectrum of safe intravenous anesthetics with various durations, times of onset, and mechanisms of action that accommodate various scenarios of the patient and surgical procedure.

Anesthetizing a patient for preparation of surgery can be categorized as either achieving conscious sedation, regional anesthesia, or unconscious sedation, with the latter termed as general anesthesia. Conscious sedation the
anesthetic technique utilized as a standard for minor procedures such as colonoscopies, surgeries on the extremities, and other minimally invasive operations. Regional anesthesia involves blockage of pain to a specific portion of the body in either a conscious or unconscious patient, and it is the standard for parturition since only the midsection is required for anesthetizing without compromising the mother’s airway and memory of the event. General anesthesia is the main form of anesthetic technique used to provide the optimum conditions for the surgeon in general, cardiothoracic, neurosurgery, plastic, genitourinary, ophthalmic, otorhinolaryngologic, orthopedic, trauma, and pediatric surgery.

General anesthesia involves the cessation of the patient’s memory and anxiety, consciousness, pain sensation, and skeletal muscle activity. Amnesia, sedation, analgesia, and paralysis are achieved by benzodiazepines, hypnotics, analgesics, and skeletal muscle relaxants, respectively (Morgan, 2006). Furthermore, total control of the patient’s autonomous nervous system is given to the anesthetist by manipulating patient’s cardiovascular functions with intravenous medications targeting the body’s alpha and beta receptors, as well as specific ion channels in the heart and vasculature. Once the patient is under general anesthesia, the anesthetist will then be able to perform intubation in order to maintain a patent airway, as well as controlling the oxygenation, ventilation, and concentration of inhalational anesthetics that the patient receives.
The cessation of skeletal muscle movement in general anesthesia is achieved by administering a neuromuscular blocking agent. The anesthetic drugs currently used for muscle paralysis and reversal of paralysis have many adverse effects and limitations. Currently, there is still a need for a fast, effective, and relatively safe drug to provide immediate paralysis and recovery of a patient’s muscles for the various clinical scenarios that the surgeon or anesthesiologist must face from patient to patient.

Neuromuscular blocking agents, for the paralysis of skeletal muscle, are indicated for various purposes in the surgical setting. When intubating a patient, they are necessary for relaxing the vocal chords in order to gain access to the trachea and for intubating the patient without the hindrance of coughing and gagging reflexes. During surgery, they are necessary for the cessation of motor reflexes and decreasing skeletal muscle tone, so that the surgeon is able to operate and manipulate the patient’s anatomy without movement or resistance. Neuromuscular blocking agents work by targeting the ACh receptors on the motor end plate in the neuromuscular junction. Similar to ACh, all neuromuscular blocking agents are quaternary ammonium compounds, where their positively charged nitrogen exhibits great affinity to the nicotinic ACh receptors. Since these agents are not metabolized by the enzyme acetylcholinesterase, they remain on the ACh receptors and prevent ACh from binding to the receptor. As a result, the normal response of ACh induced sodium ion channel opening, end-
plate potential generation, and action potential transmission for skeletal muscle
depolarization is prevented (Morgan, 2006).

The two most widely used neuromuscular blocking agents are
Succinylcholine and Rocuronium. While both agents prevent ACh induced
skeletal muscle depolarization, they are in two separate categories involving
different mechanisms of action, times of onset, durations, advantages, and
disadvantages. Rocuronium Bromide is a non-depolarizing muscle relaxant.
Non-depolarizing muscle relaxants bind to the ACh receptor, but are incapable of
inducing a conformational change of the receptor that is necessary for opening of
the calcium ion channels. Due to its characteristics of preventing conformational
change of the receptor, neuromuscular blockade occurs even when only one
alpha subunit is blocked and the other alpha subunit is bound to ACh (Naguib, et
al., 2007). Rocuronium is administered intravenously as a concentration of
10mg/mL and with a patient dose of 0.8 mg/kg in order to achieve sufficient
paralysis for intubation. Its onset of action is 90 seconds and its duration of
action ranges from 35 to 75 minutes depending on the time it takes for
Rocuronium to diffuse away from the neuromuscular junction and also the ability
of the body to metabolize it within the plasma and liver by pseudocholinesterase,
a non-specific cholinesterase found in the plasma and liver but not at the
neuromuscular junction (Morgan, 2006).

Succinylcholine is a depolarizing muscle relaxant, and it is the only
available drug that falls in this other category of muscle relaxants. It is unique
because it resembles ACh very closely, and it is therefore able to bind the ACh receptor and generate a muscle action potential. Unlike ACh however, this drug is not metabolized by acetylcholinesterase, and it does not rapidly diffuse away from the synaptic cleft. This results in a prolonged motor end-plate depolarization without allowing repolarization of the end-plate as long as it remains concentrated in the synaptic cleft and continues to bind ACh receptors. Since the lower gate opening of the sodium ion channels on the end-plate is time limited, it will eventually close and cannot reopen until repolarization occurs. An action potential cannot be regenerated because the constant binding of this depolarizing muscle relaxant prevents repolarization, and ACh continues to be competitively inhibited by it. Consequently, the observed effect is an initial period of muscle fasciculation, or muscle twitches, followed by a period of muscle paralysis.

Succinylcholine is administered intravenously as a concentration of 20 mg/mL at a patient dose of 1 mg/kg for intubation. Its onset of action is 30 seconds and its duration of action ranges from 2 to 3 minutes depending on the normal body’s pseudocholinesterase concentration and ability when the drug diffuses away from the synaptic cleft and enters circulation (Morgan, 2006). Although Succinylcholine is a relatively safe drug, it has many potential complications.

The first risk of using Succinylcholine is its effects on the cardiovascular system due to its close resemblance to ACh. In addition to affecting the
cholinergic receptors at the neuromuscular junction, Succinylcholine stimulates all ACh receptors in the body. As a result of stimulating the nicotinic receptors in the parasympathetic, sympathetic ganglia and the muscarinic receptors in the SA node of the heart, the blood pressure, heart rate, heart contractility, and circulating catecholamine levels will all increase at high doses of the drug. Low doses of Succinylcholine, however, can produce negative chronotropic and inotropic effects, which makes the pediatric patient highly susceptible to bradycardia (Weisberg, et al., 2008). To circumnavigate this unwarranted effect, intravenous atropine is normally given prophylactically to children. The anticholinergic effects of atropine causes an increase in heart rate, which negates the negative chronotropic effects of Succinylcholine. If bradycardia is left untreated, arrhythmias such as nodal bradycardia and ventricular ectopy have been reported in the past (Weisberg, 2008; Ramamoorthy, et al., 2011).

The second risk of using Succinylcholine is its effects from the initial muscle contracts that are triggered from its depolarizing effects. The visible motor contractions, called fasciculations, can lead to an increased incidence of post-operative myalgia. Myalgia, or muscle pain, is thought to be due to the initial unsynchronized muscle contractions. When this event is observed, myoglobinemia and increased serum creatine kinase levels can be detected, which indicates occurrence of rhabdomyolysis, or muscle wasting. Prophylactically, the practice of administering NSAIDS peri-operatively has shown to reduce the incidence and severity of myalgias. Other muscular
complications observed following the administering of Succinylcholine include masseter rigidity. Transient increases in muscle tone of the masseter muscles make opening the mouth for laryngoscopy and intubation extremely difficult (Weisberg, 2008).

The third and most common risk of using Succinylcholine is inducing hyperkalemia to the patient. In a normal patient, potassium is released from the skeletal muscle cells during the drug-induced depolarizations resulting in an elevation of serum potassium levels by 0.5 mEq/L. Since normal potassium levels of patients range from 3.5 – 5.3 mEq/L, this elevation would be insignificant in patients. However, this can be life-threatening in patients with burn injury, massive trauma, neuropathies such as Guillain-Barre syndrome and Parkinson’s Disease, and myopathies such as Duchenne’s muscular dystrophy (Ramamoorthy, et al., 2011). Particularly in denervation injuries such as severe burns and massive trauma, the body expresses immature isoforms of the ACh receptor inside and outside of the neuromuscular junction, called extra-junctional receptors. As a result of administering Succinylcholine and its binding to these receptors, wide depolarization and extensive potassium release will occur. The expression of extra-junctional receptors appear after 48 hours of burn and trauma patients, and Succinylcholine is therefore contra-indicated in these patients if admitted to the hospital over 2 days of the incident.

As a result of severe hyperkalemia, defined as a potassium serum level over 7.0 mEq/L, the anesthetized patient may exhibit paresthesia and muscle
weakness leading to flaccid paralysis, metabolic acidosis, and cardiac arrhythmias. Cardiac complications arise due to depolarization of its cell membrane, slowing of ventricular conduction, and shortening of action potential duration by effects of hyperkalemia. In order of their appearance in an untreated patient, ECG will show peaked T waves, QRS complex widening, loss of the P wave, ventricular fibrillation, and finally asystole leading to cardiac arrest. The anesthetist must be vigilant in order to detect initial signs of hyperkalemia in highly susceptible patients, following the administration of Succinylcholine, by monitoring ECG trends and obtaining a Chem 7 from the serum if needed. Treating mild to moderate hyperkalemia with administering calcium, insulin with glucose, bicarbonate, or epinephrine is necessary to prevent the effects of severe hyperkalemia (Weisberg, 2008).

The fourth risk of administering Succinylcholine to a patient is its effects of elevating intra-ocular, intra-gastric, and intra-cranial pressure. The extra-ocular muscles of the eye are different from other striated muscles due to having multiple motor end-plates on each cell for minute and precise movements. Prolonged membrane depolarization and contraction of these muscles after administering Succinylcholine will transiently raise intraocular pressure and compromise a patient with an eye injury. Due to this, patients with glaucoma and patients undergoing eye surgery are both contra-indications to using this drug (Morgan, 2006).
The increase in intra-gastric pressure is due to abdominal wall muscle fasciculations. However, there is no high risk of gastric reflux and pulmonary aspiration due to an increase in the tone of the lower esophageal sphincter as well. Succinylcholine is therefore contra-indicated in patients with Scleroderma due to esophageal dysmotility and incompetence of the lower esophageal sphincter, which is found in all types of Scleroderma. Lastly, elevated intra-cranial pressure is due to increased cerebral blood flow after giving the drug. While the effects are also transient and mild, the drug is contra-indicated in patients with a closed-head injury for this reason (Morgan, 2006).

The fifth and final risk of administering Succinylcholine is both the rarest and most fatal. Succinylcholine and inhalational anesthetics both are triggering agents for Malignant Hyperthermia. In 80% of reported cases, both Succinylcholine and an inhalational anesthetic were used. Since inhalational anesthetics are almost always used in surgeries with general anesthesia, Malignant Hyperthermia is always a concern in the back of most anesthetists' minds when choosing to use Succinylcholine over a non-depolarizing muscle relaxant such as Rocuronium. Malignant Hyperthermia is a rare myopathy characterized by an acute hyper-metabolic state which can present either during or hours after general anesthesia.

The anesthetist must watch for its initial signs of masseter muscle rigidity, tachycardia, increased carbon dioxide production, and tachypnea. While two or more of these signs greatly increases the likelihood of its occurrence, it is definite
when there are signs of hypertension, metabolic acidosis, arrhythmias, rhabdomyolysis, and hyperthermia characterized by an increase of up to 1°C of core body temperature every 5 minutes. The uncontrolled release of intracellular calcium from sarcoplasmic reticulum removes the inhibition of troponin, leading to intense muscle contractions and wasting. As muscle breaks down, potassium efflux from muscle cells causes hyperkalemia. The increases of carbon dioxide indicate a hyper-metabolic state that will lead to severe lactic acidosis and hyperthermia. In the 1970s when there was no treatment protocol, this event had a mortality rate of over 80%. However, current aggressive treatment protocols with the immediate use of the intravenous drug Dantrolene, ventilation with 100% oxygen, ice packs, cooling blankets, iced saline lavage, and/or cold dialysis have lowered the risk of death to 5-30%. The osmotic diuretic Mannitol is also given to prevent acute renal failure from myoglobinuria if the patient survives. Other complications after surviving an episode of Malignant Hyperthermia include disseminated intravascular coagulation, cerebral edema with seizures, and acute hepatic failure (Morgan, 2006).

With all these risks of using Succinylcholine, it is nevertheless the only muscle relaxing agent with the fast onset time of 30 seconds combined with a short duration of 2 to 3 minutes. The fastest onset time for a non-depolarizing muscle relaxant is 60 – 90 seconds with Rocuronium, but the high dose that is required to achieve close to 60 seconds will result in a long duration of action up to 75 minutes. The shortest acting non-depolarizing muscle relaxing agent
available clinically is Mivacurium, with a duration ranging from around 10 minutes in children, 20 minutes in adults, and 30 minutes in elderly. However, the anesthetist must wait an average of 2 minutes for the onset of Mivacurium to reach conditions suitable for intubation. In these comparisons, it is apparent that the unique qualities of Succinylcholine make it ideal for patients that are characterized with full stomachs or with difficult airways, where a fast and short acting muscle relaxant is desired.

Normally before most elective surgeries, patients are required to stop eating and drinking 8 hours and 2 hours before the time of surgery, respectively. When these patients arrive in the operating room, they are considered to have an empty stomach and routine surgery is allowed to commence. This is because when consciousness is lost after induction of general anesthesia, a patient without an empty stomach may regurgitate gastric material, which may become aspirated into the lungs and cause severe inflammation to the lung tissue. This is called aspiration pneumonitis, and it is often fatal if either the gastric contents have a pH acidity less than 2.5 or if the aspirated gastric contents exceed 25 mL (Morgan, 2006).

The regurgitation occurs due to a shift of the pressure gradient at the esophagogastric junction. The lower esophageal sphincter normally maintains a tone where its closing pressure exceeds the intra-gastric pressure. When the conscious level is depressed in the anesthetized patient, the tone of the sphincter will decrease, and regurgitation will occur if intra-gastric pressures exceed the
closing pressure of the sphincter. The risk of regurgitation is even greater if the
intra-gastric pressure is further increased by presence of food or liquid, obesity,
intra-abdominal swelling, hiatal hernia, 3rd trimester pregnancy, and the lithotomy
position where the supine patient’s legs are raised. Pregnancy increases the risk
of regurgitation even further because the hormonal changes in the female patient
causes a decrease in the efficiency of the sphincter. Some anesthetic drugs also
decrease the tone of the sphincter such as opioids, which are commonly used for
analgesia and pain management in almost all surgeries. This is why a morbidly
obese patient, a pregnant patient, and a patient undergoing emergency surgery
are all considered full stomach. In these scenarios, the anesthetist must utilize
rapid sequence induction, where Succinylcholine is often used for its fast onset.

Rapid sequence induction involves taking every precaution to prevent
regurgitation and limiting the time between when a patient is anesthetized and
when the patient’s airway is secured and protected via intubation. A variety of
laryngoscopes and endotracheal tubes are prepared in advance, and a smaller
tube is often used first to maximize the chances of an easy intubation. Normally,
the patient is given positive pressure ventilation using the bag and facemask
after inducing unconsciousness to ensure that the anesthetist is able to ventilate
the patient before administering the muscle relaxant and eliminating the patient’s
ability to spontaneously breathe. However, delivering positive pressure is contra-
indicated in the full stomach patient. Therefore, the muscle relaxant is
administered immediately after the induction agent, an anesthetic used to put the
patient to sleep. The patient, as a result, will be immediately ready for intubation when unconscious and when the lower esophageal sphincter becomes depressed. Since most induction agents such as Propofol and Ketamine have an onset time of under 40 seconds, Succinylcholine is commonly used due to having a similar time of onset. The time between induction and intubation must be minimized because in addition to risks of regurgitation, the induced patient is also unable to breathe spontaneously. The anesthetist is unable to deliver positive pressure ventilation via facemask during this time because the pressure will travel down both the trachea and esophagus, potentially triggering regurgitation. Therefore if Rocuronium is used for intubation, there will be around 60 seconds of inactivity where the patient is asleep and unable to breathe spontaneously, and the anesthetist is unable to intubate until Rocuronium relaxes the vocal chords.

The most common usage of Succinylcholine by anesthetists is for intubating the difficult airway patient. A patient is considered to have a difficult airway if the conventionally trained anesthetist experiences difficulty with facemask ventilation, difficulty with tracheal intubation, or both. Difficulty with intubation commonly involves being unable to visualize any portion of the vocal chords resulting in a failed tracheal intubation, where the endotracheal tube is accidentally placed into the esophagus instead of the trachea.

The risk of a difficult airway patient is often determined from the patient’s medical history and a physical examination by the Anesthesiologist before the
surgery. Common conditions associated with difficult airways include anatomical hindrances, anatomical restrictions, and obesity. Hindrances include tumors in the airway such as Cystic Hygroma, hemangioma, and hematoma. Infections lead to hindrances such as submandibular abscess, peritonsillar abscess, and epiglottitis. Anatomic variations such as micrognathia, prognathia, and prominent upper incisors will also cause hindrances (Morgan, 2006). Foreign bodies lodged in the airway will also cause hindrances. Obesity, short and thick necks, and large tongues are the most common determinants of a difficult airway because a likely history of sleep apnea will prove to be an issue when delivering oxygen through the bag and facemask or when the patient attempts to breathe spontaneously.

When the anesthesiologist attempts to intubate the difficult airway, the difficult airway algorithm is used, implemented by the American Society of Anesthesiology. The algorithm tells the anesthesiologist to re-oxygenate the patient with a bag and facemask after a failed intubation before the next few attempts. After multiple failures, the anesthesiologist must consider advanced techniques of intubation including the use of a glidescope, light wand, laryngeal mask airway, or fiberoptic intubation depending on the anesthesiologist’s preference and expertise. When failure ensues, the anesthesiologist should allow the induction agent and muscle relaxing agent to wear off, and intubate the patient when awake. If awake intubation fails or if at any time the anesthesiologist is unable to oxygenate the patient with the facemask, a common
risk for patients with sleep apnea, the anesthesiologist must proceed with an emergency intubation, which involves invasive procedures such as a tracheotomy.

A patient is informed after the pre-operative examination that he/she has a difficult airway and if needed, the anesthesiologist must intubate the patient consciously sedated or in the worst case scenario, a tracheotomy. The benefits of the awake patient is that the patient maintains his/her own airway and the tongue does not fall back and impede the airflow and visualization in the oropharynx as much as an unconscious patient. This eliminates both the time limitations and visual hindrances that the anesthesiologist would face when intubating a patient after induction.

The advantage of Succinylcholine for intubating a difficult airway patient is its short duration of effect of 2 to 3 minutes. This allows the anesthesiologist the option to decide if the patient should be re-administered with Succinylcholine for further intubation attempts or if the patient needs to awaken and breathe spontaneously. The latter option is often the case when the anesthesiologist has difficulty with oxygenating the induced patient with the bag and facemask due to the anatomical obstructions aforementioned. The disadvantage of Rocuronium or the short acting Mivacurium is their duration of over 10 minutes. This makes Succinylcholine superior over the non-depolarizing muscle relaxants because its duration falls under the time of safe apnea.
The time of safe apnea is the time it takes for the pre-oxygenated apneic patient to fall under 90% oxygen saturation on the pulse oximeter. According to the oxygen-hemoglobin saturation curve, 90% oxyhemoglobin saturation indicates a 70 mmHg partial pressure of oxygen in the arterial blood. As the partial pressure of oxygen continues to decrease in the apneic patient, the saturation of oxyhemoglobin begins to exponentially decrease after this point due to the sigmoidal nature of the curve. At any time this occurs to the un-intubated patient, the anesthesiologist must aggressively establish an airway for oxygenation, which includes the use of oral and nasal airway tools, laryngeal mask airways, or performing tracheotomy in the cyanotic patient.

According to a study on how obesity affects the time of safe apnea, results indicate that compared to the average time of 6.1 minutes in normal patients, the time it took an obese apneic patient to fall to 90% saturation was 4.1 minutes and 2.7 minutes in a morbidly obese apneic patient (Gaszynski, et al., 2011). This is largely due to the increased metabolic oxygen demand and substantially decreased functional residual capacity of the obese patient. The Succinylcholine is therefore considered a double-edged sword due to being the only clinically safe product in the market able to quickly paralyze and un-paralyze the patient, but listed with several contra-indications and risks of use.

The practice of Anesthesiology had once again evolved with the discovery of the drug Sugammadex at the Newhouse research site in Scotland in 2008. Sugammadex is an agent used for the reversal of neuromuscular blockade by
the muscle relaxing agent Rocuronium. This is possible because of its modified
gamma cyclodextrin chemical structure, which is able to exert a chelating action
that effectively encapsulates and binds the aminosteroid non-depolarizing muscle
relaxants, Rocuronium, Vecuronium, and Pancuronium. This effectively
eliminates their ability to bind nicotinic receptors. Selectively binding and
terminating the effects of a muscle relaxing agent is an advancement to our
current standards of practice because muscle relaxant reversal is currently
achieved indirectly by means of inhibiting acetylcholinesterase (Duvaldestin, et
al., 2010).

When an operation is nearing completion and the surgeon begins to
suture, the anesthesiologist begins protocols for extubation and awakening the
patient. As a criterion before extubating the endotracheal tube, the anesthetist
must allow the patient to spontaneously breathe via the endotracheal tube by
means of reversing the effects of the long acting non-depolarizing muscle
relaxants. This is done by administering either Neostigmine or Edrophonium,
intravenous agents for inhibiting acetylcholinesterase. By selectively binding to
acetylcholinesterase, these agents indirectly increase the amount of
acetylcholine available in the neuromuscular junction. Since non-depolarizing
muscle relaxants work by direct inhibition of acetylcholine, the level of inhibition
decreases as a result of increasing the available substrate.

There are two disadvantages with using these two anticholinesterase
agents. Firstly, they do not exclusively act at the neuromuscular junction, but
rather at all cholinergic receptor sites. This includes the entire parasympathetic nervous system and parts of the sympathetic nervous system, specifically the sympathetic ganglions, adrenal medulla, and sweat glands. A generalized overabundance of acetylcholine will desirably activate the nicotinic receptors in skeletal muscle, but it will also activate the muscarinic receptors in the end-organ effector cells of bronchial smooth muscle, salivary glands, and the sinoatrial node of the heart (Illman, et al., 2010). As a result, muscle relaxant reversal will be accompanied by a vagal-like bradycardia that can progress to sinus arrest, bronchospasms, increased respiratory tract secretions, and undesired effects in the gastrointestinal tract including intestinal spasms, nausea, vomiting, and fecal incontinence. The standard of anesthetic practice is currently to administer an anti-muscarinic agent such as Glycopyrrolate or Atropine, in order to negate the marked increases in muscarinic receptor activation caused by Neostigmine or Edrophonium. These agents bind to and competitively inhibit muscarinic receptors, in order to mask the muscarinic effects of increasing acetylcholine on the sympathetic and parasympathetic autonomous nervous systems, without affecting its effect at the neuromuscular junction.

The second drawback of anticholinesterase agents is that the required dose depends on the degree of neuromuscular blockage due to the relationship of substrate and inhibitor concentration in competitive inhibition. Moreover, no amount of cholinesterase inhibitor can immediately reverse a complete neuromuscular block. This translates to time that the anesthetist must wait to
pass, normally 10 to 20 minutes, before administering this type of muscle
relaxant reversal agent (Illman, et al., 2010). The appropriate time to administer
these reversal agents is determined by frequent use of a peripheral nerve
stimulator. An elicited muscle twitch or tetanus indicates a muscle blockage
between 75 – 95%, which is suitable for reversal. In emergency or difficult
airway scenarios, where the anesthetist is unable to intubate or oxygenate the
patient, the time needed for effective reversal and return to spontaneous
breathing greatly exceeds the time of safe apnea (Sorensen, et al., 2012).

Sugammadex is unique because it is the first drug that can provide
reversal of a profound neuromuscular block, and it can provide an immediate
reversal when required. Unlike Neostigmine and Edrophonium, this is
accomplished without inhibiting acetylcholinesterase. Therefore, the cost and
labor of administering a muscarinic receptor antagonist, Atropine or
Glycopyrrolate, to negate an unwarranted decrease in heart rate are also
avoided. Sugammadex has a concentration of 100 mg/mL, and it has a varying
recommended patient dose depending on the level of neuromuscular blockade
from Rocuronium, Vecuronium, or Pancuronium.

The presence of an induced twitch or tetanus with the nerve stimulator
indicates shallow blockade, and this only requires a dose of 2.0 mg/kg for
complete reversal. This is also when the conventional muscle relaxant reversal
agents are used, after a period of 10 to 30 minutes following the administration of
the muscle relaxant depending on the patient and the drug used. In a profound
neuromuscular blockade, there are no twitches or sustained tetanus observed. However, the patient will exhibit 1 to 2 post-tetanic twitches. These are twitches that are induced after delivering 5 seconds of sustained nerve stimulation. The absence of tetanus and appearance of post-tetanic twitches indicate a profound neuromuscular blockade, and our conventional muscle relaxant reversal agents are unable to reverse (Mirakhur, 2009). However, Sugammadex is capable of reversing this profound neuromuscular blockade at a recommended dose of 4.0 mg/kg. Lastly, Sugammadex is able to provide immediate reversal of Rocuronium due to its high affinity for Rocuronium compared to Vecuronium and Pancuronium. After 3 minutes of administering Rocuronium, Sugammadex is capable of a complete reversal at a recommended dose of 16.0 mg/kg (Naguib, et al., 2007). Aside from Rocuronium, there is currently no data to support the use of Sugammadex for immediate reversal following Vecuronium or Pancuronium induced blockades.
Specific Aims

This review will address a problem in the medical field, specifically in the field of Anesthesiology, which impacts all patients undergoing surgery with anesthesia, as well as licensed providers of anesthesia. I undertook this study because of my background in pharmaceutical sciences and clinical training in anesthesia. Having performed countless intubations and administrations of Succinylcholine in my clinical experiences, I understand how important Sugammadex will be for the patient and provider. Sugammadex is currently approved for use in Europe, United Kingdoms, and Australia. Therefore, I am interested in performing a complete analysis of this drug, and whether or not it should be implemented in the United States.

This review will present all aspects of the drug Sugammadex including its chemical structure and composition, mechanism of action, pharmacokinetics, pharmacodynamics, safety profile, and cost-benefit analysis. In addition, published studies and case reports on the effects of Sugammadex on specific patient groups and specific surgical procedures will also be presented. I will determine both advantages and disadvantages of using Sugammadex, as well as determining whether it should replace any currently used anesthetics involved in neuromuscular blockade. My hypothesis is that Sugammadex is much safer to use than Succinylcholine, but due to high costs, it will not replace our conventional muscle relaxant reversal agents as the standard for routine use.
Presentation of Published Data

Sugammadex is a modified gamma cyclodextrin, a cyclic oligosaccharide composed of dextrose units. The gamma form has 8 dextrose subunits, a hydrophobic interior, and a hydrophilic exterior. By modifying every 6th carbon hydroxyl group with substitution of a carboxyl thioether linkage, the hydrophilic peripheral gains three advantages. Firstly, due to the negatively charge on the modified groups, Sugammadex will bind electrostatically to the positively charged ammonium groups of aminosteroidal neuromuscular relaxing agents with great affinity. Secondly, the longer tail of these modified peripheral groups allows greater surface area where these electrostatic interactions can occur. This allows the molecule to completely encapsulate the substrate. Lastly, the added negatively charged carboxyl groups increase the aqueous solubility of the molecule (Adam, et al., 2012).

The mechanism of action of Sugammadex reversal of Rocuronium and other aminosteroidal neuromuscular relaxing agents is by means of encapsulation and mass diffusion of the substrate from the neuromuscular junctions to the plasma. Early studies by Bom and colleagues showed the encapsulation process to be due to thermodynamic attractions at a one-to-one binding ratio. These attractions include electrostatic interactions, hydrogen bonding, hydrophobic interactions, and Van Der Waals interactions. The lipophilic cavity, where the aminosteroidal substrates become trapped in, is in close contact of all four steroidal rings of the substrate. In addition, the carboxyl
group’s attraction for Rocuronium’s tertiary ammonium results in higher affinity compared to other aminosteroidal neuromuscular relaxing agents (Bom, et al., 2002).

Encapsulation occurs mainly in the plasma, and it has two effects on Rocuronium. First, it prevents the encapsulated Rocuronium to diffuse into the neuromuscular junction and bind to the nicotinic receptors. Second, it causes a drastic decrease in concentration of unbound Rocuronium in the plasma. This causes a diffusion of Rocuronium down its concentration gradient away from the neuromuscular junction. Any molecules bound to nicotinic receptors are also rapidly drawn away and encapsulated in the plasma (Baldo, et al., 2011). This results in a rapid reversal of any depth of neuromuscular blockade.

Sugammadex is selective for steroidal neuromuscular relaxing agents only. Evidently, non-steroidal agents such as Succinylcholine and Cisatracurium both have a Ka value that is 1000 times less than the steroidal agents. The Ka value, measured in millions per one molarity, for Rocuronium, Vecuronium, and Pancuronium are 25.0, 10.0, and 2.6, respectively (Duvaldestin, et al., 2010). Therefore, Rocuronium will be the main neuromuscular relaxing agent for discussion because it is both the most selective for Sugammadex and it is the most clinically used compared to other steroidal neuromuscular relaxing agents.

Following the initial discovery of Sugammadex and assessment on animals, an Investigational New Drug application (IND) is submitted to the Food and Drug Administration (FDA). Once approved, clinical trials begin and proceed
in four phases. Phase I of clinical trials are studies performed on healthy human individuals, usually a sample size under 100, to assess the therapeutic effect, potency, dosage ranges, and identify possible side effects. Phase II trials continues to assess these drug characteristics, but there are multiple studies performed with sample sizes over 100 human participants each. Phase III trials use a sample size over 1000 subjects to further refine these drug parameters. In addition, these studies try to find potential drug-drug interactions, drug efficacy in different patient populations, and effectiveness compared to conventional treatments. Once the FDA approves the findings of Phase III trials, the drug is normally submitted to the FDA for marketability. Phase IV is the post marketing surveillance of the drug to explore its long term benefits and risks when used on a large scale. The sample size of these studies is generally over 10,000 subjects.

The approval of IND submission of Sugammadex occurred in 2004 after initial testing on animals showed successful results in its ability to reverse NMBA effects. Gijsenbergh and his colleagues were the first to perform Phase I studies of Sugammadex. 29 healthy male volunteers received either Sugammadex or a placebo, and the time and level of reversal from Rocuronium induced paralysis were recorded. Results showed that reversal occurred after 1 minute following Sugammadex administration at a dose of 8.0 mg/kg, compared to 52 minutes with the placebo. It was concluded that Sugammadex was both safe and effective in these individuals (Gijsenbergh, et al., 2005). A similar study also
came to this conclusion when Sugammadex provided complete reversal of Rocuronium or Vecuronium induced muscle paralysis in 16 individuals (Cammu, et al., 2008).

Phase II and III clinical trials were conducted to find dosage and safety margins of Sugammadex in both shallow and profound neuromuscular blockage. While Phase II studies concentrated on dose-finding and safety, Phase III also included comparative studies, where Sugammadex was cross analyzed with conventional reversal agents such as Neostigmine and Edrophonium. The level of neuromuscular block and the degree of reversal are measured by performing a train-of-four using a nerve stimulator. The train-of-four stimulation is a series of nerve stimulations, where the number and intensity of muscle twitch responses are recorded. A shallow block is defined as 2 twitches out of 4, and a profound block is defined as no twitches out of 4, but the presence of 1 to 2 post-tetanic twitches (Naguib, et al., 2007). On the other hand, a full reversal of neuromuscular blockade is defined as the presence of all 4 twitches with the 4th twitch being at least 90% the magnitude of the 1st twitch. This is due to the fact that a continuous decrease in twitch magnitude is still indicative of some level of block despite the presence of all four twitches.

The inclusion criteria of patients for Phase II and III trials were adult patients, with written consent, undergoing general anesthesia requiring neuromuscular blocking agents for surgical procedures in the supine position. These patients ranged from ASA class I to II, II or IV depending on the study.
The ASA ranking is the standard for anesthesiologists in determining how healthy a patient is for surgery and general anesthesia. The exclusion criteria for Phase II and III trials were patients with neuromuscular disorders, pregnancy, significant renal dysfunction, history of malignant hypothermia, allergies to any of the drugs used in general anesthesia, and medications currently taken that are known to interfere with neuromuscular relaxing agents.

Multiple Phase II studies were conducted on the safety and efficacy of Sugammadex in reversal of various steroidal neuromuscular blocking agents. In several studies of Rocuronium-induced blockade, Sugammadex have been shown to be dose-dependent when determining the time until complete reversal. In a study by Shields et al. (2006), Sugammadex was administered to 30 patients ranked ASA I to III at different doses ranging between 0.5 – 6.0 mg/kg after 2 hours or greater following the delivery of low dose Rocuronium. Sugammadex effectively reversed each patient within 2 minutes. Another study showed a similar mean time of reversal. Pavlin and colleagues exhibited a mean reversal time of 1.9 minutes when administering Sugammadex to 87 ASA I-III patients, and they were able to achieve full reversal after 15 minutes of low dose delivery of Rocuronium by using a Sugammadex dose of 4.0 mg/kg (Pavlin, White, Viegas, Minkowitz, & Hudson, 2007).

Sugammadex reversal of a profound blockade by high dosage of Rocuronium was also studied. In a phase II trial conducted at multiple international centers, Sugammadex was delivered either 3 or 15 minutes after a
Rocuronium dose of either 1.0 or 1.2 mg/kg in 176 ASA I-III patients. With a Sugammadex dose of 8.0 mg/kg, the average time of full reversal was under 3 minutes for both doses of Rocuronium and at both times after Rocuronium administration (Khuenl-Brady, Rex Sielenkamper, & Puhringer, 2005). These trials conclude that Sugammadex was able to completely reverse both shallow and profound Rocuronium-induced blockades in a rapid, dose-dependent manner.

Two notable comparative studies performed by the FDA also confirmed the ability of Sugammadex to reverse both shallow and profound blockade. Trial 19.4.301 sponsored by Schering-Plough in 2005 aimed to reverse shallow Rocuronium or Vecuronium induced neuromuscular blockade with a 2.0 mg/kg dose of Sugammadex compared to the traditional 50 mcg/kg of Neostigmine. Trial 19.4.302 aimed to reverse profound blockade by Rocuronium or Vecuronium with a 4.0 mg/kg dose of Sugammadex compared to the 70 mcg/kg of Neostigmine. Sugammadex achieved full reversal at significantly faster times than Neostigmine in both trials with no events of residual paralysis or reoccurrence of blockade during recovery in PACU. In Trial 19.4.301, patients fully recovered from Vecuronium – induced neuromuscular blockade in 1.4 minutes with Sugammadex, but full recovery from after Neostigmine administration required 17.6 minutes. Similarly, patients fully recovered from Vecuronium – induced blockade in 2.1 minutes with Sugammadex, as opposed to an 18.9 minute recovery time with Neostigmine. In Trial 19.4.302,
Sugammadex reversed profound blockade from Rocuronium and Vecuronium in 2.7 and 3.3 minutes, respectively. Neostigmine, on the other hand, required roughly 50 minutes for full recovery in both two groups (Boer, et al., 2007).

Following the publications of these studies, additional studies further explored the effectiveness of Sugammadex’s ability of immediate reversal of profound blockades following Rocuronium administration. Groudine and colleagues conducted a study to measure the recovery times in 98 male adults when using 8.0 mg/kg doses of Sugammadex at either 3, 5, or 15 minutes after Rocuronium was administered. The mean recovery times were 1.8 minutes, 1.5 minutes, and 1.4 minutes, respectively, and they concluded the reversal was safe and well tolerated (Groudine, Soto, Lien, Drover, & Roberts, 2007). A similar study by Sparr and his colleagues measured the recovery times of Sugammadex when the dose administered was dependent on the level of blockade measured by the nerve stimulator. A Sugammadex dose ranging from 2.0 – 16 mg/kg was administered either after 3 or 15 minutes of administering Rocuronium at 1.0 - 1.2 mg/kg. Results show that doses of 2 – 16 mg/kg of Sugammadex successfully reversed all neuromuscular blockades. Furthermore, higher doses of Sugammadex showed to reverse at faster times. Administering Sugammadex at doses of 12 – 16 mg/kg reversed profound blockades in 90% of the patients within 3 minutes (Sparr, et al., 2007). These studies conclude that not only does higher doses of Sugammadex reverse faster, higher doses are required in order to reverse deeper levels of blockade. This was confirmed in instances where
insufficient dosages of Sugammadex resulted in recurarization, which is the
reoccurrence of the muscle relaxant due to insufficient reversal.

Several studies have reported recurarization in their studies where a low
dose of Sugammadex was used. A 48 year old ASA - II female weighing 108 kg
was given 0.5 mg/kg of Sugammadex 42 minutes after a 0.9 mg/kg dose of
Rocuronium was given. The nerve stimulator showed a Post-tetanic count of 1,
which indicated a profound blockade. Within minutes of administering
Sugammadex, the blockade deepened indicated by a TOF ratio of 0.25 on the
nerve stimulator, but the reversal gradually improved to a TOF ratio of 0.9 over
the next 65 minutes (Eleveld, Kuizenga, Proost, & Wierda, 2007). Other studies
using low doses ranging from 0.5 – 1.0 mg/kg of Sugammadex have also
reported events of insufficient dosage. Minutes after administering
Sugammadex, reversal was initially achieved with a TOF ratio of 0.9, but was
followed by a subsequent decrease in the TOF ratio to under 0.8, indicating an
inadequate reversal (Suy, et al., 2007; Groudine, et al., 2007).

According to Eleveld and colleagues (2007), this recurarization from an
insufficient dose of Sugammadex may have been due to the redistribution of
Rocuronium between the central plasma compartment, peripheral compartments,
and nicotinic junction. The initial dose of Sugammadex binds plasma
Rocuronium, drastically decreases the amount of unbound Rocuronium causing
a return of motor function, and establishes a gradient between central and
peripheral compartments. The low concentration of unbound Rocuronium in the
central compartment then pulls the unbound Rocuronium from the peripheral compartments into the plasma. Due to an insufficient dose of Sugammadex, there is not enough to bind all of the additional Rocuronium molecules, which results in Rocuronium re-equilibrating with the nicotinic junctions, also known as the effect compartment. Eleveld reminds us that the correct dose of Sugammadex is when it encapsulates all neuromuscular blocking molecules in a 1:1 ratio, and the use of a neuromuscular monitoring is advised to assure adequate reversal (Eleveld, et al., 2007).

At the other extreme, there has been one report in a study, where Sugammadex was accidentally given at a dose 10 times over the desired dose of 4 mg/kg. Although this error was immediately known, the patient was carefully monitored and the data collection continued. The surgery was uneventful, and adequate reversal with a TOF ratio of 0.9 was achieved in 1.3 minutes without any adverse effects as determined by a blinded safety assessor in the PACU and at a 7 day follow-up (Molina, de Boer, Klimekl, Heerina, & Klein, 2007).

Comparison to Cholinesterase Inhibitor Reversal

There have been multiple comparative studies during stage III clinical trials to the current standards of anesthesia. Before Sugammadex, the cholinesterase inhibitors, Neostigmine and Edrophonium, were the standards for reversal of neuromuscular relaxing agents. A study by Blobner and colleagues compared the effectiveness of Sugammadex to Neostigmine in the reversal of shallow blockades by Rocuronium. Ninety eight ASA Class I – III patients over
the age of 18 were randomized to receive either 2.0 mg/kg of Sugammadex or 50 mcg/kg of Neostigmine along with 10 mcg/kg of Glycopyrrolate. Sugammadex and Neostigmine were both administered at conventional times in the surgery, near the end of the operation after two of the four muscle twitches were observed with the nerve stimulator. The median times to full reversal for Sugammadex and Neostigmine were 1.4 minutes and 17.6 minutes, respectively. With no residual paralysis or re-curarization observed, Sugammadex showed to safely provide significantly faster reversals of shallow Rocuronium induced muscle blockades compared to Neostigmine (Blobner, et al., 2007)

Similar studies were performed by Sacan and Flockton in 2007. Sacan and colleagues randomized sixty ASA Class I – III patients to receive either Sugammadex, Neostigmine or Edrophonium in patients with moderately profound neuromuscular blockade from Rocuronium. While Sacan does not clearly describe a moderately profound state, the reversal agents were administered after observing one of the four twitches with the nerve stimulator. This is also the earliest time that Neostigmine and Edrophonium can be administered, as only Sugammadex is capable of reversal when no twitches are observed. A Sugammadex dose for moderate muscle blockade, 4.0 mg/kg, was used and compared with standard dose ranges of Neostigmine (70 mcg/kg), Glycopyrrolate (14 mcg/kg), Edrophonium (1 mg/kg), and Atropine (10 mcg/kg). The mean time of full reversal and recovery for Sugammadex, Neostigmine, and Edrophonium were 1.78 minutes, 17.44 minutes, and 5.52 minutes, respectively
Sacan, et al., 2007). Sugammadex was shown to significantly achieve faster reversal of Rocuronium induced muscle blockades compared to both Neostigmine and Edrophonium. Comparatively, Flockton achieved similar results favoring Sugammadex. In his study, reversing profound Rocuronium induced muscle blockade with Sugammadex 4.0 mg/kg was compared with using Neostigmine 70 mcg/kg and Glycopyrrolate 14 mcg/kg. The mean times of recovery for Sugammadex and Neostigmine were 2.9 minutes and 50.4 minutes, respectively (Flockton, 2008).

Other comparative studies began using various neuromuscular relaxing agents other than Rocuronium. Lemmens and colleagues compared the recovery times of Sugammadex on shallow Rocuronium blockade with the recovery times of Neostigmine on shallow Cis-Atracurium blockade. Cis-Atracurium is a non-depolarizing neuromuscular blocking agent similar to Rocuronium, but it has the shortest acting profile of all in this category. Eighty-four ASA Class – I – III adult patients were randomized to receive either Rocuronium or Cis-Atracurium for muscle paralysis. After muscle paralysis was not needed, the patients received either Sugammadex or Neostigmine after two twitches out of four were observed with the nerve stimulator. The mean times for full reversal by Sugammadex and Neostigmine were 1.9 minutes and 9.0 minutes, respectively (Lemmens, et al., 2007). Although recovery with Cis-Atracurium by Neostigmine was faster than studies with Rocuronium, as
expected, Sugammadex still showed to be significantly faster in achieving full reversal.

The final two comparative studies involved comparing Sugammadex and Neostigmine on the reversal of shallow and profound blockade from Vecuronium, yet another non-depolarizing neuromuscular blocking agent. Its duration of action falls between Rocuronium and Cis-Atracurium, and it is able to be reversed by Sugammadex but at a lower efficiency than Rocuronium. Reversal of shallow Vecuronium blockade was studied by Alvarez-Gomez. His study concluded that Sugammadex achieved significantly faster full reversal than Neostigmine with mean times of 2.1 minutes and 18.9 minutes, respectively (Alvarez-Gomez, 2007). In another study Jones and colleagues recorded the full reversal times of eighty three ASA Class I – III adult patients randomized to receive either Sugammadex or Neostigmine for the reversal of profound Vecuronium induced blockade. The mean times to full reversal for Sugammadex and Neostigmine were 4.5 minutes and 66.2 minutes, respectively (Jones, et al., 2007).

There are two things that can be drawn from these comparative studies of Sugammadex to Neostigmine. Sugammadex has shown to be significantly faster at fully reversing the paralyzed patient despite which muscle relaxant or conventional cholinesterase inhibitor was used for comparison (p<0.000). With no residual paralysis or re-curarization, it can be concluded that Sugammadex is both a safe and more effective alternative. When observing the range of reversal
times for mean calculation, Neostigmine showed to have a much larger range compared to Sugammadex. In Lemmens’ study (2007), recovery times for Neostigmine ranged from 4.2 to 28.2 minutes, while Sugammadex ranged from 0.7 to 6.4 minutes. In Blobner’s study (2007), Neostigmine ranged from 3.7 to 106.9 minutes, while Sugammadex ranged from 0.9 to 5.4 minutes. In Sacan’s study (2007), the mean recovery time for Neostigmine was 17.44 (± 9.8) minutes, while mean recovery time for Sugammadex was 1.78 (± 1.1) minutes. This shows that from person to person, Sugammadex is more consistent in its encapsulation mechanism of action, while the wide range for Neostigmine reflects how its competitive antagonism mechanism of action variably affects each individual.

Comparison to Succinylcholine Recovery

The immediate reversal of Rocuronium with Sugammadex had made it the subject for comparison with Succinylcholine in multiple studies. As previously mentioned, Succinylcholine has the shortest duration of action of all the NMBAs currently available. At a dose of 1 mg/kg, it achieves complete neuromuscular blockade in 1 minute, and it achieves adequate return of motor functions with a TOF ratio of 0.9 in 10 – 13 minutes. Three studies will be presented to show the recovery times of Rocuronium and Sugammadex compared to Succinylcholine in general elective surgery, surgeries requiring rapid sequence induction, and in electro convulsive therapy.
In a study by Lee and colleagues (2009), one hundred and fifteen ASA Class I – II patients between the ages of 18 and 65 received either 1.0 mg/kg of Succinylcholine or 1.2 mg/kg of Rocuronium and 16 mg/kg of Sugammadex for neuromuscular relaxation in their elective surgical procedures. Sugammadex was administered 3 minutes after Rocuronium administration, and the spontaneous muscle recovery times of each blinded patient groups were recorded. The mean times of recovery to a TOF ratio of 0.1 and 0.9 for patients given Succinylcholine were 7.1 and 10.9 minutes, respectively. Meanwhile, the mean times of patients given Sugammadex were 4.4 and 6.2 minutes, respectively. Sugammadex was shown to provide significantly faster recovery times compared to Succinylcholine (Lee, 2007). Lee further concluded that since Rocuronium is currently indicated in roughly 25% of cases requiring rapid sequence induction, Sugammadex would be more effective in achieving immediate restoration of muscle functions.

As previously described, rapid sequence induction of a patient is an anesthetic technique to quickly intubate the patient after unconsciously sedating them. This is often used in the pregnant patient, patients with increased risk of pulmonary aspiration of gastric contents, and in the emergency setting where we cannot confirm if a patient undergoing surgery has an empty or full stomach. Succinylcholine is currently the standard for this procedure since if the event of an unanticipated difficult airway arises, the patient will be able to recover from
muscle relaxation and breathe spontaneously shortly after Succinylcholine administration.

In a study by Sorensen and colleagues, 61 patients undergoing general elective surgery that required rapid sequence induction were randomized to either receive 1 mg/kg of Succinylcholine or 1 mg/kg of Rocuronium with 16 mg/kg of Sugammadex immediately given upon verification of proper placement of the endotracheal tube. The time of full recovery and patient’s return to breathing spontaneously was recorded for both groups. The median time from tracheal intubation to spontaneous ventilation was 6.8 minutes for patients receiving Succinylcholine, and the median time was 3.6 minutes for patients receiving Rocuronium and Sugammadex. Sorensen concluded that patients receiving Sugammadex resulted in a significantly earlier re-establishment of spontaneous ventilation than patients with Succinylcholine (Sorensen, 2012). While the recovery time to a TOF ratio of 0.9 was also recorded, it is noteworthy to emphasize the recovery time of spontaneous ventilation because it is more clinically important especially in this scenario.

The final comparative study with Succinylcholine is a case report of a 69 year old woman undergoing electro convulsive therapy. Ever since the introduction of this procedure in the 1950s, Succinylcholine has remained as the most common neuromuscular relaxing agent used for temporary paralysis required by this short procedure. However, studies have shown Succinylcholine to be unsafe in patients susceptible to malignant hypothermia and neuroleptic
malignant syndrome. In this case report, Succinylcholine was contra-indicated due to a patient history of neuroleptic malignant syndrome, Parkinson’s disease, rheumatoid arthritis, celiac disease, and hypertension. Ramamoorthy and colleagues administered 1 mg/kg of Rocuronium and 16 mg/kg of Sugammadex 5 minutes afterwards. Muscle relaxation with Rocuronium achieved the prevention of violent muscle contractions during the shock therapy, and recovery times for TOF ratio to 0.9 and recovery time to spontaneous breathing were 2 minutes and 3 minutes, respectively. The patient was stable throughout the procedure, and Sugammadex was concluded to be both an effective and safe alternative when Succinylcholine is contra-indicated in the patient (Ramamoorthy, 2011).

Trials on Patient Specific Populations

All Phase III clinical studies presented up until now have had similar exclusion criteria, specifically the exclusion of age extremes, pregnancy, and patient history of heart disease, lung disease, renal disease, or neuromuscular disorders. The following Phase III clinical trials study the effectiveness of Sugammadex on these various patient populations, as well as recording possible alterations in outcome due to changes in normal physiology.

Pediatric

Pediatric patients differ from adult patients in many ways physiologically, and this affects the pharmacokinetics and pharmacodynamics of drugs. Rocuronium, for example, has shown to have a greater potency and shorter
duration in infants and children than in adults. Residual paralysis has also shown to occur more frequently in children than adults (Plaud, 2009). The first study of Sugammadex on infants, children, and adolescents compared to adults was performed by Plaud and his colleagues in 2009. His aim was to simply determine the dose–response relationship of Sugammadex, as well as its safety.

Eight infants, 24 children, and 31 adolescents were given Propofol for induction and either opioids or regional anesthesia for analgesia. Rocuronium at a dose of 0.6 mg/kg was given to all patients, and either Sugammadex or a placebo was given when two out of four twitches were observed by the nerve stimulator. The dose of Sugammadex or placebo varied from 0.5–4.0 mg/kg in each age group. The time until full recovery, defined by a TOF ratio of 0.9, was recorded, while documenting any signs of inadequate reversal (TOF < 0.9) or reoccurrence of the blockade, defined as a TOF ratio declining from 0.9 to 0.8 and below. Other safety assessments were employed by use of electrocardiography, laboratory values, and notation of adverse events.

The time from Rocuronium administration to appearance of two of four twitches was shorter for infants, adolescents, and children than for adults, as expected, with their median times being 28.0, 20.5, 25.3, and 32.4 minutes, respectively. The median times to full recovery after Sugammadex were 0.6–3.7 minutes in infants, 0.6–3.7 minutes in children, 1.1–4.6 minutes in adolescents, and 1.2–4.2 minutes in adults. This range is dose-dependent with
shorter times associating with a high Sugammadex dose of 4.0 mg/kg, and longer times associating with a low dose of 0.5 mg/kg. The placebo group had a median recovery time of 21.0, 19.0, 23.4, and 28.5 minutes in infants, children, adolescents, and adults, respectively. Plaud’s findings were consistent with previous phase II studies, that a dose of 2.0 mg/kg or greater would reverse the patient in a median time of less than 2 minutes. The authors concluded that Sugammadex overall was effective and well tolerated in each pediatric age group. Since it is much harder to recruits pediatric patients to studies, no firm conclusions can be drawn on its safety due to their small sample sizes (Plaud, et al., 2009).

Geriatric

Similar to the pediatric patient, a drug’s efficacy and metabolism may all become altered in an elderly patient. Changes in their receptor sensitivity, impairment of physiological functions in organs, and presence of chronic diseases all affect the pharmacokinetics and pharmacodynamics of drugs. Several neuromuscular blocking agents including Rocuronium, for example, all have an increased time of onset and increased duration of action in the elderly. An increased time of onset may be due to decreased cardiac functions resulting in longer times for a drug to reach their effector site. An increased duration of action may be due to decreased ability to metabolize and excrete the drug, characteristics of an impaired liver or kidney that often accompanies aging.
The first study on the elderly population was performed by McDonagh and colleagues (2007). They explored the efficacy and safety of Sugammadex on 150 patients. Forty eight adults (age 48 – 64 years), Sixty two elderly (age 65 – 74 years), and forty old elderly (age >75 years) all received 2.0 mg/kg Sugammadex after observing two of four twitches following the administration of 0.6 mg/kg Rocuronium. The mean time to full recovery in the adult, elderly, and old elderly groups was 2.3, 2.6, and 3.6 minutes, respectively (McDonagh, et al., 2007).

McDonagh concluded the adult group had a significantly faster recovery time compared to the two elderly groups. Factors contributing to this, as previously stated, are slow cardiovascular circulation, altered receptor expression at the neuromuscular junction, and also altered perfusion of Rocuronium between compartments. Despite a slower recovery, the times obtained were still significantly faster to studies comparing Sugammadex 2.0 mg/kg with Neostigmine 50 mcg/kg (Jones, et al., 2007). Since Neostigmine has shown in a past study to have decreased potency in reversal of blockades in patients older than 70 years compared to adults, Sugammadex proves to be an effective and well tolerated alternative.

Cardiac

A study on 121 cardiac patients was conducted by Dahl and colleagues (2007). These cardiac patients were between ages of 36 – 90 years, ranked ASA Class II – IV, and underwent non-cardiac surgery using Rocuronium
induced blockade. Sugammadex 2.0 mg/kg, 4.0 mg/kg, or a placebo was given after two of four twitches, and the time to full recovery was recorded along with any adverse events by means of vigilant electrocardiograph monitoring. The mean recovery time for groups receiving 2.0 mg/kg, 4.0 mg/kg, and placebo was 1.7, 1.4, and 34.4 minutes, respectively. While Sugammadex proved to safely and effectively reverse the blockade, two patient cases involved episodes of QTc interval prolongation, one in the Sugammadex group and one in the placebo group (Dahl, et al., 2007). The inhalational anesthetics, used for the prolonged induction of the patient throughout the case, were not disclosed. Inhalational anesthetics have shown in past studies to cause QTc prolongation (Schmeling, et al., 1991; Kleinsasser, et al., 2000). However, there had also been studies previously stating possible association of Sugammadex with QTc prolongations (Gijsenbergh, et al., 2005; Vanacker, et al., 2006; Sorgenfei et al., 2006).

Due to potentially finding a possible adverse effect of Sugammadex, de Kam and his colleagues (2007) performed a study on 62 volunteers by eliminating all agents that may prolong QTc intervals, while evaluating only Sugammadex and comparing the drug to Moxifloxacin, a known drug to cause QTc prolongation. The 62 volunteers were randomized to receive either 4.0 mg/kg or 32 mg/kg Sugammadex with or without Rocuronium or Vecuronium, 400 mg of Moxifloxacin, or placebo. No significant QTc prolongation was observed with the placebo and Sugammadex with or without co-administration of Rocuronium or Vecuronium. Significant QTc prolongation with Moxifloxacin was
observed as expected. De Kam concluded that previous studies with Sugammadex resulting in QTc interval prolongations are most likely due to other agents used or due to cardiac diseases, particularly defects in conduction (Kam, et al., 2007).

Pulmonary

Effects and safety of Sugammadex were studied on patients with history of pulmonary disease by Amao and colleagues in 2007. Seventy-seven adult patients undergoing general surgery (ASA class II – III), all with known history or recently diagnosed with pulmonary disease, were given Rocuronium 0.6 mg/kg and Sugammadex 2.0 mg/kg or 4.0 mg/kg after two of four twitches were observed. As expected, the mean recovery time to a TOF ratio of 0.9 for both the group that received 2.0 mg/kg and 4.0 mg/kg was 2.1 and 1.8 minutes, respectively. Regarding the safety of Sugammadex on pulmonary patients, Amao concluded that Sugammadex was well tolerated and effective in its reversal of blockade with no alterations in respiratory rate or incidence of recurarization in any of the patients (Amao, et al., 2007).

There were, however, two incidences of serious bronchospasm episodes in two patients who had a history of asthma. Since patients with asthma or other pre-existing lung diseases are highly susceptible to pulmonary complications during intubation and extubation, bronchospasms being most common, it cannot be concluded that Sugammadex was the sole cause of these incidences. Amao noted that while one patient suffered from bronchospasm following extubation,
the other patient had a bronchospasm episode before extubation and 55 minutes after receiving Sugammadex. While this suggests possible connection with Sugammadex, Amao also states that Desflurane was the inhalation agent used in each of these two cases. Desflurane, unlike Sevoflurane or Nitrous Oxide, is a noxious agent that is known to irritate the airway. Amao advises physicians to be prepared for bronchospasms in patients with underlying lung disease even though Sugammadex was shown to be effective and well tolerated (Amao, et al., 2007).

The effects of Sugammadex on bronchial smooth muscles, the muscles involved in bronchospasm, were later studied by Yoshioka and colleagues in 2012 in order to determine from Amao’s study if Sugammadex was involved in the cases where bronchospasm had occurred. The left main bronchus was extracted from male Wistar rats by thoracotomy under anesthesia. Through measuring of the isometric contraction of the circular smooth muscle of the bronchus, the baseline tension and ACH induced contraction were examined before and after the tissues were bathed in a solution containing Sugammadex sodium. Yoshioka’s results showed that Sugammadex did not induce bronchia smooth muscle contraction since there were no changes to the baseline tension when administered. Furthermore, its effects did not augment or dampen the bronchial smooth muscle contraction response when induced with ACh (Yoshioka, et al., 2012).
However, there are three possibilities that require further study. First, the rats used were healthy, while the patients in Amao’s study were asthmatic. It is unknown whether Sugammadex has an effect when the bronchial smooth muscles are hyperresponsive, as with asthmatic patients. Secondly, while Sugammadex itself did not cause any contractions in the rats, it is possible that the Sugammadex-Rocuronium chelated complex may have triggered a response. Since Rocuronium was not involved in this study, this possibility was not explored. Lastly, alternate factors that lead to in vivo bronchospasm such as cholinergic nerve stimulation and mast cell activation were not explored. It is still possible that Sugammadex or its complex with Rocuronium is involved in augmenting these pathways.

Renal Insufficiency

Patients with renal insufficiency and end stage renal disease experience longer durations from drugs. This is due to the fact that while the liver metabolizes the drug, its metabolites may still have an active effect depending on the drug (Staals, et al., 2008). Therefore, its effects are not truly ceased until the active metabolite is excreted by the kidney. While some neuromuscular blocking agents like Cisatracurium are eliminated in the plasma by Hoffman degradation, other neuromuscular blocking agents such as Rocuronium and Pancuronium are excreted by the kidney. Therefore, prolonged blockades are often reported in patients with renal failure (Craig, et al., 2008, Cammu, et al., 2012).
Since Sugammadex and its complex with Rocuronium are also cleared by the kidneys, Staals and his colleagues studies its safety and efficacy in patients with normal and severe renal diseases. 54 patients with normal renal function and 61 patients with impaired renal function, characterized by a creatinine clearance under 30 mL/minute, were given Propofol for induction, opioids for analgesia, Rocuronium 0.6 mg/kg for muscle paralysis, and Sugammadex for reversal after two of four twitches were observed. Times to full recovery with a TOF ratio of 0.9 were recorded, and possible adverse events were assessed.

Analysis of the plasma concentration was also conducted to assess the pharmacokinetics of Sugammadex and Rocuronium in patients with end stage renal failure. Plasma concentrations of Sugammadex in these patients revealed that its clearance was 17 times slower than patients with normal renal function, and its terminal half-life increased by 16 fold. Furthermore, due to their abnormal physiology, their volume of distribution was greater by 20%, which ultimately means Sugammadex exposure was prolonged by 16 fold. Its complex with Rocuronium also remained in the plasma for a longer time period. Regardless of this data, the mean time to full recovery for patients with normal renal function and patients with impaired renal function was 1.7 and 2.0 minutes, respectively. Staals concluded that although patients with normal renal function had a significantly faster time of recovery, Sugammadex still provided safe and effective reversal of Rocuronium induced blockade in both these patient groups with no events of recurarization (Staals, et al., 2007).
Liver Dysfunction

Neuromuscular blocking agents such as Rocuronium are known to have a prolonged effect in patients with impaired liver function. While Rocuronium is excreted by the kidney as previously stated, its primary method of elimination is through the liver by carrier-mediated transport and cytochrome P450 mediated metabolism, specifically the CYP3A4 enzyme (Craig, et al., 2008). While there has not been any animal studies or clinical trials on patients with liver disease, data from Schering-Plough’s simulation in hepatic impairment suggest that a Sugammadex dose of 2.0 mg/kg and 4.0 mg/kg given when two of four twitches are observed would result in a 2.55 minutes and 4.12 minutes longer recovery time, respectively, compared to patients with normal liver function. A dose of 16 mg/kg showed little difference between normal and impaired liver function (Craig, et al., 2009). These results show that time to full recovery with Sugammadex is still faster than using Neostigmine.

In 2012, two case reports by Carron and Batistaki were published regarding the safety and effectiveness of Sugammadex as an alternative to Neostigmine in patients with liver diseases. The first case report, published by Batistaki and colleagues, documents the effects of Sugammadex on three ASA Class III patients with liver dysfunction undergoing transjugular intrahepatic portosystem shunts. Two of the patients had Budd-Chiari syndrome, and the third patient had hepatitis C induced liver cirrhosis. 2.0 mg/kg Sugammadex was given, when four twitches were observed, to reverse Rocuronium administered at
1.0 - 1.2 mg/kg. The time from administering Sugammadex until a TOF ratio of 0.9 ranged from 98 – 540 seconds among the three patients. Adverse effects and recurarization were not observed (Batistaki, et al., 2012). These results were consistent with Schering-Plough's simulated pharmacodynamics model, suggesting that a 2.0 mg/kg dose of Sugammadex would result in a 2.55 minute longer reversal time compared to a reversal time of 2.8 minutes in patients with normal liver function (Batistaki, et al., 2012).

The second case report was published by Carron and colleagues (2012). Carron opted to use Sugammadex in a morbidly obese patient diagnosed with non-alcoholic steatohepatitis undergoing a laparoscopic sleeve gastrectomy. Due to a potential difficult airway, risks of aspiration, and underlying liver disease, Carron was concerned that Neostigmine would fail to fully reverse the Rocuronium induced blockade within 10 minutes. After an uneventful procedure lasting 60 minutes, there was still no twitch observed by the nerve stimulator. Rocuronium’s effect was drastically prolonged, and two of four twitches were not observed until 120 minutes after the intubating dose of Rocuronium was administered (a single bolus of 0.6 mg/kg). Neostigmine at 70 mcg/kg and Atropine at 15 mcg/kg were given to reverse the blockade, but the TOF ratio was still only 0.18 after 30 minutes. Sugammadex was ultimately decided upon. Four minutes after a dose of 2.0 mg/kg. The TOF ratio increased from 0.18 to 1.0. The author concluded that Sugammadex was advantageous over Neostigmine in
morbidly obese patients with liver disease due to effective and timely reversal (Carron, et al., 2012).

Neuromuscular Disorder

Neuromuscular disorders increase the risk of perioperative respiratory and cardiovascular complications due to underlying pathology that lead to muscle weakness, pulmonary insufficiency, and progressive paralysis. When treated with a neuromuscular blocking agent, recurarization and residual paralysis is a major concern in the post-operative period. In the past 2 years, two case reports and one clinical study have published the effects of Sugammadex on patients with myotonic dystrophy, spinal muscular atrophy, and myasthenia gravis.

Stewart and colleagues published a case report in 2012 on two patients receiving Sugammadex for reversal of Rocuronium induced blockade. Both patients required a rapid intubation to protect the airway due to possible complications from their neuromuscular disorder. Rocuronium and Sugammadex were used due to the fact that Succinylcholine was contra-indicated in these patients. The first patient was diagnosed with myotonic dystrophy upon arrival for elective surgery. Sugammadex at 2.7 mg/kg was given to reverse Rocuronium induced blockade upon observing two of four twitches. Time of recovery to a TOF ratio of 0.9 was 5 minutes, and no signs of recurarization was observed afterwards (Stewart, et al., 2012).

The second patient was diagnosed with spinal muscular atrophy and consequent COPD. Sugammadex at 4.0 mg/kg was given 17 minutes after
Rocuronium administration, where no twitches were observed. The recovery time of this profound blockade was 2.8 minutes, and no signs of recurarization or residual paralysis were observed afterwards. The author concluded that reversal of Rocuronium by Sugammadex was safe, rapid, and without recurarization (Stewart, et al., 2012).

The second case report documents Pickard and colleagues as they administer Rocuronium and Sugammadex to a 14 month old boy with myotonic dystrophy scheduled for multiple surgeries requiring muscle relaxation. Succinylcholine and Neostigmine are both contra-indicated in this case. Succinylcholine provokes generalized myotonic contractures, resulting in a difficult time providing positive pressure ventilation if the chest wall muscles become rigid. Neostigmine and other anticholinesterases have a potential to trigger myotonic episodes, as well as worsening a neuromuscular block.

These agents were avoided, and Sugammadex at 5mg/kg was given to reverse profound Rocuronium blockade, characterized by the absence of any twitches even after 57 minutes of Rocuronium administration. After 26 seconds, TOF ratio was 0.96, but over the next few minutes the ratio had fallen to 0.6. Sugammadex at a dose of 5 mg/kg was re-administered, and after 13 seconds the TOF ratio remained stable at 0.86. The author concluded that an insufficient dose was given initially resulting in recurarization, but overall Sugammadex was advantageous in this scenario where a fast and safe agent was needed to reverse a profound block (Pickard, et al., 2013).
The final publication is by Sungur Ulke and colleagues (2013), documenting the use of Sugammadex in ten patients with myasthenia gravis undergoing thymectomy. As with all neuromuscular disorders, the anesthesiologist is challenged with the question of using or not using neuromuscular blockers and anticholinergics, as well as the appropriate dosage if used. Therefore, even though the use of Rocuronium is controversial, the study aimed to evaluate if Sugammadex was useful in treatment approaches involving Rocuronium. The ten patients were given 2.0 mg/kg Sugammadex, and carefully monitored to require re-dosing or not. The initial dose of 2.0 mg/kg of Sugammadex was enough to sufficiently reverse all ten patients, with a mean time to full reversal ranging from 35 to 240 seconds. None of the patient needed assisted mechanical ventilation due to respiratory failure or myasthenic crisis. The author concluded that Rocuronium and Sugammadex is a safe and effective alternative for myasthenic patients who require muscle paralysis during surgery (Ulke, et al., 2013).

Adverse Effects

There have only been a few adverse effects that have been documented during the clinical trial phase. While no one were serious adverse effects, they included: hypotension, coughing, movement, nausea, vomiting, dry mouth, abnormal taste and smell, sensation of changed temperature, erythema, tachycardia, bradycardia, pyrexia, abnormal n-acetyl-glucosaminidase levels in the urine, and QT interval prolongation (Gijsenbergh, et al., 2005; Sorgenfrei, et
al., 2006; Shields, et al., 2006; Dahl, et al., 2007). As previously discussed, a study later showed that Sugammadex doses up to 32 mg/kg was not the cause of QT interval prolongation (de Kam, et al., 2007). Even in one study where over dosage occurred by administration of 40 mg/kg rather than 4 mg/kg, effective reversal of Rocuronium was noted without any adverse effects.

However, the Food and Drug Administration have reviewed the documented adverse effects, and were concerned that as a whole, these effects represented anaphylactic/anaphylactoid reactions. This resulted in a letter issued to Schering-Plough Pharmaceutical in July of 2008 stating their unapproval. While clinical studies resumed the addressing of this issue, it is noteworthy to mention that ever since the European regulatory commission approved Sugammadex for use in August 2008, no adverse outcomes have been published since its incorporation in clinical practice.

Discussion

Clinical Assessment

Results collected from these randomized trials indicate that Sugammadex is more effective than Neostigmine for reversal of neuromuscular blockade. This was indicated by monitoring the TOF ratio and comparing the time needed to reach full reversal. Patients reversed with Sugammadex had a narrower range of recovery times, making its time of effect more predictable than Neostigmine. Results from other trials have shown Sugammadex to be both safe and effective in reversal of moderate to profound neuromuscular blockades induced by
Rocuronium or Vecuronium. This ability is dose-dependent and unique to Sugammadex.

These three characteristics of Sugammadex allow the anesthetist to continue a neuromuscular blockade of any level in a patient up until the time of a surgical conclusion without the worry of being unable to reverse a patient’s neuromuscular blockade. Surgical procedures that require profound neuromuscular blockade throughout the procedure will benefit from Sugammadex. This includes diagnostic imaging, spine surgery, and procedures requiring the immobility of the head. The inability of Neostigmine to reverse profound blockade equates to several common clinical obstacles.

Firstly, profound blockades require extra time after surgical completion in order to wait for a blockade to fall to a level adequate for reversal. To prevent these prolongations, anesthetists often taper or discontinue the neuromuscular blocking agent towards the end of the procedure. This allows the blockade to fall to an adequate level for reversal around the same time the surgeon is finished, but this causes risks of patient movement. Secondly, a surgeon may request deeper levels of muscle paralysis, but the anesthetist would often be reluctant due to the increasing difficulty to reverse especially nearing the end of a surgery.

Lastly, it is possible that a patient may cough on the endotracheal tube or exhibit movement of the diaphragm despite careful neuromuscular monitoring of the anesthetist. This is due to the fact that the muscles of the larynx and the diaphragm are more resistant to the effects of neuromuscular blocking agents
than muscles in the rest of the body (Caldwell, et al., 2009). If the adductor pollicis or orbicularis oculi, two muscles targeted and monitored by the nerve stimulator, both appear to show absence of twitch, coughing and attempts of spontaneous breathing may still occur. These clinical situations would cease to exist if a larger dose of Rocuronium can be given periodically to achieve constant profound blockade without fear of the inability to reverse in a timely manner. Sugammadex administered at 16 mg/kg, 3 minutes following Rocuronium administration, has shown to provide faster recovery than the spontaneous recovery from Succinylcholine. While Succinylcholine is the only neuromuscular blocking agent that can provide muscle paralysis under 1 minute and recovery under 10 minutes, it has undesired effects and it is contraindicated in several scenarios previously mentioned. The safer drug, Rocuronium, in combination with Sugammadex provides the alternative that is needed in the medical community for procedures requiring short onset and duration of muscle paralysis. Cases requiring rapid sequence induction, difficult intubation cases, and extremely short procedures all benefit greatly from having a safer alternative to Succinylcholine.

Trials on specialized groups with coexisting diseases have shown effective and safe results from Sugammadex administration. Sugammadex has currently shown no serious adverse effects associated with its administration. Its side effect profile is low compared to the two current reversal agents on the market, Neostigmine and Edrophonium. As discussed, anti-muscarinic agents
such as Atropine or Glycopyrrolate are co-administered due to the hemodynamic instability associated with these two drugs. However, studies have shown that even with co-administration of anti-muscarinic drugs, Neostigmine can still result in severe bradycardia and provoked coronary artery vasospasms in patients with autonomic dysfunction (Caldwell, et al., 2009). Furthermore, anti-muscarinic drugs do not always perfectly balance the effects of anticholinesterase reversal agents. This results in cases where heart rate significantly changes with conventional reversal protocols (de Kam, et al., 2010). Some anesthetists, as a result, would completely omit the pharmacological reversal of neuromuscular blocking agents in cardiac patients in order to avoid an imbalance in oxygen supply and demand in the heart. Since Sugammadex has no effects on heart rate and blood pressure, it would greatly benefit patients with coronary artery disease or with other compromises in the heart.

Patients with acute or chronic pulmonary diseases in obstructive or restrictive nature will benefit from Sugammadex due to a faster and more effective reversal of muscles associated with breathing and airway. Inadequate reversals may lead to a feeling of shortness of breath or difficulty in breathing. Ineffective reversal of pharyngeal muscle tone compromises the airway, which is especially detrimental to patients with obesity and obstructive sleep apnea.

Economic Assessment

Sugammadex is purchased by clinical institutions as the brand name Bridion, manufactured by Organon/Schering-Plough USA. Ten vials, each
containing 5 mL of 100 mg/mL Sugammadex, costs roughly $2014.04 (Chambers, 2010). A single use of Sugammadex at a dose of 4 mg/kg would cost roughly $112.79 for a 70kg patient. For comparison, Neostigmine (1 mg/mL) is available as a generic, costing $1.99 for a 5 mL vial depending on the manufacturer. A single vial is sufficient for the reversal of a patient. Due to this dramatic price difference, cost-effectiveness studies have been conducted to assess whether its high cost is justified by the decreased time in the OR and PACU, enabled by the effectiveness of Sugammadex. This would determine if it is feasible to implement Sugammadex for routine use or for special circumstances.

Paton and colleagues (2010) assessed the cost-effectiveness of Sugammadex by studying the outcomes of patients administered with either Rocuronium or Vecuronium, and reversed with either Sugammadex or Neostigmine with Glycopyrrolate. The total cost of each case was determined, and the length of stay in the OR and in recovery was recorded. The rates of serious adverse effects and the rates of a reoccurring or residual blockade between the two anesthetic strategies were calculated. Since any reduction in recovery time by using Sugammadex represents resources saved by the facility, the total cost per minute of the staff was determined. The estimated total staff cost associated with the recovery period in a British facility is £4.44 per minute. Therefore, if inadequate reversal, recurarization, or serious adverse effects occur in the PACU, each additional hour of stay equates to a cost of £19.61 for the
institution. Under these assumptions, Paton assessed the data from comparative studies of Sugammadex and Neostigmine. In studies conducted by Blobner et al, and Jones et al, patients with moderate to profound neuromuscular blockade showed a 23.37 and 24.24 minute decrease in recovery time when using Sugammadex to reverse Rocuronium and Vecuronium, respectively (Paton, et al., 2010). With roughly £106.56 saved, Sugammadex becomes cost-effective in this scenario.

When assessing the cost and benefit of using Sugammadex over Succinylcholine in a rapid sequence induction or difficult airway scenario, Sugammadex is assumed to result in a reduced risk of morbidity and mortality. The dangers of Succinylcholine and the faster recovery times with Sugammadex from the presented literature support this assumption. While it is unlikely that decreasing patient deaths and unfavorable outcomes would result in significant savings in cost for an institution, it will be up to each individual institution to decide if the safety benefits outweigh its cost.

Conclusion

This study on the necessity, safety, and effectiveness of Sugammadex in our current healthcare practices is based on published clinical studies from both the clinical trial phase and from its implementation in the United Kingdom. The data suggests that Sugammadex is both a safe and effective agent for the reversal of Rocuronium and Vecuronium induced neuromuscular blockade. There appears to be no serious adverse effects associated with its use, unlike
drugs such as cholinesterase inhibitors, anti-muscarinic drugs, and Succinylcholine. Its use in the pediatric patients, elderly patients, and patients with co-existing cardiac, pulmonary, hepatic, renal, and neuromuscular diseases appear to be safe and effective. Sugammadex is dose-dependent, and it is up to the anesthetist to provide both adequate dosing and careful monitoring to ensure the complete reversal of a neuromuscular blockade. While overdosing appears to be safe, inadequate dosing results in the recurrence of a blockade.

With proper use, Sugammadex addresses the need for a safe and effective reversal agent for patients, who will not safely tolerate Glycopyrrolate, Atropine, and Succinylcholine. With Sugammadex, we are no longer forced to administer Succinylcholine in rapid sequence induction and difficult airway scenarios. With Sugammadex, anesthetists will no longer feel reluctant to provide the surgeon with a profound neuromuscular blockade due to the difficulty in reversing the patient in a timely manner at the end of surgery. The improved surgical conditions and predictability of Sugammadex will benefit both the surgeon and anesthetist.

Future Plans

Due to the high cost of Sugammadex, it is not cost effective to implement Sugammadex as a drug for routine use. It is, however, recommended that Sugammadex should be used for the reversal of profound blockades induced by Rocuronium or Vecuronium due the reduced staff cost from a shorter patient stay in recovery. It is also recommended over conventional drugs if a patient’s
hemodynamic, pulmonary, or parasympathetic stability is desired. While its routine use over Succinylcholine will always be beneficial, it is ultimately up to each institution to decide if the reduced risk of morbidity and mortality justifies its cost.

If Sugammadex becomes available for us in the United States, further study must ensure its safety in various patient profiles. Healthcare providers must revisit proper patient monitoring to ensure an adequate dosage of Sugammadex had been given to the patient. Reversing a profound blockade will be a novelty in our current practice, and anesthetists will need proper training to avoid inadequate reversal and recurarization. There are potential benefits of Sugammadex that may provide different ways of managing the anesthetic care of the patient. This includes its safety profile, increased predictability of reversal, and shorter recovery resulting in better use of the staff’s time and resources. These areas are the least explored in the current literature, and will probably require its adoption in clinical practice before all potential benefits of Sugammadex can be realized.

Further research in Sugammadex include, but not limited, to collecting data on its effects to better predict a patient’s recovery and potential adverse effects associated with the patient’s medical history. Effectiveness, cost, and mortality rates from replacing Succinylcholine for rapid sequence induction can be further evaluated. Pediatric and obstetric use of Sugammadex can be further investigated. Finally, research on using Sugammadex in combination with
various anesthetics and analgesics will ultimately help the optimization of multiple anesthetic approaches. This will help tailor the anesthetic management to each patient and surgeon's needs.
REFERENCES


Pühringer, F. K., Rex, C., Sielenkämper, A. W., Claudius, C., Larsen, P. B.,


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Education

Boston University School of Medicine. Boston, MA 2011-2014
Masters of Arts in Medical Sciences
Cumulative GPA: 3.8

Nova Southeastern University. Fort Lauderdale, FL 2009-2011
Anesthesiologist Assistant Program.
Cumulative GPA: 3.4

Purdue University. West Lafayette, IN 2004-2009
Bachelors of Science in Pharmaceutical Sciences.
Cumulative GPA: 3.2

High School Diploma.

Clinical Experience

Memorial West Same Day Surgery Center.
Pembroke Pines, FL June – August 2010
-Complete case management (IV insertion, pre-op, induction, intra-op, emergence, PACU) for all cases under supervision of anesthesiologist.
  D&C, TAH, Digits and wrists, ENT, Colonoscopies, Plastic, Pediatric, Orthopedic, Bariatric, and Urologic cases.
-Proficient with performing intubation, Bier Blocks, and several approaches to MAC & TIVA.
-Assisted in femoral, interscalene, axillary, and retrobulbar nerve blocks.

Veterans Affairs Medical Center. West Palm, FL February – April 2010
-Placed all patient IVs for beginning cases of the morning.
-Independently managed several types of cases under anesthesiologist supervision.
TURP/BT, Pacemakers, Lap chole, Hernia repairs, Total Hips/Knees/Shoulders, Spine fusions, Thoracotomies, Lobectomies, Colonoscopies.
- Proficient with LMAs and with difficult intubations using glidescope and Miller blade.
- Attempted a spinal insertion and DLT intubation.
- Assisted in an awake fiberoptic nasal intubation.

Healthcare Work Experience
Walgreens Pharmacy. Boston, MA. December 2012 – August 2013
Pharmacy Technician
- Process prescriptions through insurance, dispense and sell medication to customer.
- Make and receive calls to and from insurance, doctors, customers, and other pharmacies.
- Maintain adequate stock of drugs and supplies on shelves and in drug dispensing machine.

Operation Room Attendant
- Disinfect, dispose, restock, and prepare supplies and equipment in between surgical cases.
- Provide moving, positioning and preparation help to doctors and nurses.
- Answer calls for patient transportation and retrieving blood from the blood bank.

Pharmacy Technician
- Process prescriptions through insurance, dispense and sell medication to customer.
- Make and receive calls to and from insurance, doctors, customers, and other pharmacies.
- Maintain adequate stock of drugs and supplies on shelves and in drug dispensing machine.

South Cove Community Health Center. Boston, MA 2001-2002
Staff Peer Leader
- Organized outreach and workshops on AIDS and HIV in the Chinatown community.
- Delivered presentations and facilitated discussion among small groups.
Healthcare Volunteer Experience

Boston Medical Center. Boston, MA
Pharmacy Technician
- Dispensed & restocked drugs and prepared IVs.
- Prepared and checked for expiration on medicine in anesthesia kits.
- Delivered drugs to the Pixis nursing stations on several floors.

Summer 2007

New England Baptist Hospital. Boston, MA.
Anesthesia Tech Assistant
- Cleaned and prepared supplies and machine/equipment during turnover.
- Shadowed anesthesia and physicians.

July 2005

Hebrew Rehabilitation Center. Boston, MA
Elderly Assistant
- Transported patients in wheelchairs around and outside the complex to daily activities.
- Assisted in transporting patients between bed and wheelchair.

Summer 2004

Publications
Skin Avulsion Injuries with Use of Adhesive Surgical Drapes 2012
- Article accepted and published in Journal of Knee Surgery

Presentations
Patient Positioning and Associated Complications. 2010
- Paper presented in the Anesthesiologist Assistant program at Nova Southeastern University.

Certifications
- PALS, 2010

Awards
- Dean’s List & Honors at Purdue University 2004 & 2006

Activities
Lambda Phi Epsilon, Purdue University. 2004-2008
- President (2007-2008)