Sugammadex: Pharmacology, Safety, and Associated Anesthetic Implications
LESSON OBJECTIVES
Upon completion of this lesson, the reader should be able to:
1. Identify the indication for sugammadex use in clinical anesthesia practice.
2. Describe the evolution of neuromuscular blockade in clinical anesthesia since the first report on the use of curare.
3. Explain the mechanism of action of sugammadex reversal.
4. Describe the chemical structure of sugammadex.
5. State the manufacturer’s recommended dosing of sugammadex.
7. Discuss the pharmacokinetics of sugammadex, including its primary method of elimination.
8. Discuss the drug interactions that should be considered prior to sugammadex administration.
9. Discuss the warnings and precautions related to the use of sugammadex, including the drug’s effect on coagulation.
10. Identify the minimum waiting interval for re-administration of rocuronium or vecuronium following reversal with sugammadex.

Current Reviews for Nurse Anesthetists® designates this lesson for 1 CE contact hour in Clinical pharmacology/therapeutics.

Introduction
In light of evidence supporting the reality and danger of residual neuromuscular blockade, every anesthetist has wished at times that he or she might be able to produce rapid and complete reversal of muscle relaxation without the unfortunate side effects of the anticholinesterase reversal agents. On December 17, 2015 Merck received approval from the United States Food and Drug Administration (FDA) for sugammadex (BRIDION®), the first cyclodextrin introduced into anesthesia practice. Sugammadex is indicated as a reversal agent for neuromuscular blockade induced by the aminosteroid-based, non-depolarizing agents rocuronium bromide and vecuronium bromide in adult surgical patients. This lesson will review the clinical pharmacology, safety profile, and associated anesthetic implications of sugammadex for consideration prior to adoption of the drug into the armamentarium.

Historical Perspective
“Every anesthetist has wished at times that he might be able to produce rapid and complete muscular relaxation in resistant patients under general anesthesia.”¹ With those words, Griffith and Johnson’s 1942 preliminary report on purified curare (d-tubocurarine (dTc)) introduced neuromuscular blockade into clinical anesthesia practice. Griffith and Johnson further described dTc as “a drug which will give us this kind of relaxation, temporarily and apparently quite harmlessly.”¹ Throughout the 1940s, neuromuscular blocking drugs (NMBDs) were rapidly accepted into practice. However, the inher-
ent safety hazard associated with these drugs was not fully appreciated until a decade later.

Following a decade of rapid expansion in the use of dTc, Beecher and Todd published “A Study of Deaths Associated with Anesthesia and Surgery” in 1954. An analysis of approximately 600,000 anesthetics across ten institutions demonstrated a six-fold increase in mortality in patients receiving NMBDs. The rise in mortality was attributable to a clinical knowledge deficit of a new class of pharmacologic agents and the drug’s physiological target receptors.

In an attempt to combat the associated rise in mortality related to residual neuromuscular blockade, short and intermediate acting NMBDs as well as reversal agents were introduced. Thesleff and Foldes introduced succinylcholine in the early 1950s as the first depolarizing NMBD. Succinylcholine, an ultra short-acting NMBD (duration of action < 10 minutes), was originally understood to have a relative sparing effect on respiration, a lack of unwanted side effects, and initial reports stated that the disadvantages of succinylcholine were not serious. Large-scale clinical use of the drug allowed clinicians to successfully identify succinylcholine-associated complications (i.e., hyperkalemia, cardiovascular effects, phase II block, malignant hyperthermia, increased intra-ocular pressure, myalgia, etc.). The introduction of succinylcholine may serve to caution clinicians on the importance of vigilance with the adoption of new pharmacologic agents.

**Muscle weakness with associated respiratory impairment has been observed with a TOFR up to 0.9.**

Pancuronium (the first synthetic aminosteroid-based NMBD) was introduced in 1967 by Baird and Reid and approved by the FDA in 1972. Atracurium, the first intermediate-acting NMBD (duration of action 25-50 minutes), attained FDA approval in 1983. Vecuronium, an aminosteroid-based intermediate-acting NMBD soon followed with FDA approval in 1984. Rocuronium joined the intermediate-acting aminosteroid family with FDA approval in 1994. One year later the FDA approved the use of cisatracurium, an intermediate-acting benzylisoquinolinium, which had the distinct advantage of not causing histamine release.

Reversal of NMBDs with the use of acetylcholinesterase inhibitors (e.g., neostigmine) has remained controversial since first suggested in 1945. Some anesthetists routinely administer a reversal agent while others contend that in the absence of clinically observable muscle weakness, the side effects of reversal outweigh the risk of residual neuromuscular blockade. A growing consensus of clinical studies contests the dogma that clinically undetectable residual neuromuscular blockade is of little concern to patient safety.

**Residual Neuromuscular Blockade**

**Definition**

Residual neuromuscular blockade is defined as a train of four ratio (TOFR) of less than 0.9 at the adductor pollicis muscle. The adductor pollicis muscle is the muscle of the hand used to adduct the thumb. The TOFR assesses the degree of fade between the first twitch (T1) and the fourth twitch (T4). (TOFR = the height of the fourth twitch divided by the height of the first twitch.) **Muscle weakness with associated respiratory impairment has been observed with a TOFR up to 0.9.** The clinical characteristics of residual neuromuscular blockade are “reduced upper airway tone and diameters, upper airway obstruction, pharyngeal dysfunction with impaired airway integrity, decreased upper esophageal tone with an increased risk of aspiration, impaired hypoxic ventilatory control, and unpleasant symptoms of muscle weakness.” The potential hazard to patient safety is clear, but how frequently does residual muscle weakness occur with intermediate-acting NMBDs?

**Incidence**

Naguib et al published a meta-analysis of 24 trials (3,375 patients) from 1979 to 2005. The authors identified the pooled incidence of residual neuromuscular weakness (TOFR < 0.9) in the postoperative care unit (PACU) to be remarkably high. Following intraoperative use of long-acting NMBDs, 72% of patients demonstrated residual neuromuscular blockade in the PACU. When an intermediate-acting NMBD was used, 41% of patients demonstrated residual blockade in the PACU. Several limitations challenge the anesthetist in identifying residual neuromuscular weakness prior to extubation and PACU transfer.

**Assessment**

Anesthesia providers utilize a combination of clinical tools and assessment parameters to determine a patient’s recovery and strength prior to extubation and transfer to PACU. A pre-extubation physical assessment for signs of residual muscle weakness is the most common approach for determining the adequacy of the patient’s recovery from NMBDs. Some providers utilize qualitative neuromuscular monitors in addition to physical assessment, but few employ a quantitative neuromuscular monitoring device.

Pre-extubation physical assessment for residual muscle weakness examines the patient for a regular respiratory rate, adequate tidal volumes, and signs of strength (e.g., thumbs up, hand squeeze, or head lift). These assessments have been shown to have poor sensitivity for detecting residual neuromuscular blockade. Tidal volume, for example, is shown to be well preserved despite residual neuromuscular block-
ade when an endotracheal tube is maintaining airway patency. However, as TOFR decreases, swallowing impairment, airway obstruction, and pulmonary aspiration are shown to increase markedly. Anesthesia providers routinely rely on these signs of muscle strength, but a growing body of literature has emerged demonstrating the poor reliability of such tests in identifying residual neuromuscular blockade.

Qualitative neuromuscular monitoring refers to use of the peripheral nerve stimulator for train of four (TOF) assessment. This modality is considered qualitative because its findings are subject to the provider’s interpretation. Residual neuromuscular blockade is defined as a TOFR of less than 0.9 at the adductor pollicis muscle. However, providers are unable to subjectively (visually or tactually) detect fade when the TOFR exceeds 0.4-0.6.

Quantitative neuromuscular monitoring refers to a device capable of both peripheral nerve stimulation and objective quantification (numeric valuation) of the muscle response. Clinically available quantitative monitors work via acceleromyography (AMG) to measure a muscle’s force of contraction following nerve stimulation. Murphy et al concluded, “At the present time, quantitative neuromuscular monitoring is the only method of determining whether full recovery of muscular function has occurred and reversal drugs safely avoided.” Residual neuromuscular blockade is an important patient safety consideration. To avert its occurrence, anesthetists may benefit from a drug capable of rapid and complete reversal of muscle relaxation that is devoid of adverse side effects.

**A Novel Addition to the Armamentarium**

Sugammadex (Org 25969) was introduced into clinical practice in 2008 and approved by the FDA in December 2015. Sugammadex is indicated as a selective relaxant-binding reversal agent for neuromuscular blockade induced by rocuronium and vecuronium in adult surgical patients (Table 1). Sugammadex forms a tight 1:1 complex with the amino-steroid-based NMBDs (rocuronium and vecuronium). Each sugammadex molecule encapsulates a rocuronium or vecuronium molecule and prevents the neuromuscular blocking agent from binding nicotinic cholinergic receptors. Sugammadex has a high affinity for rocuronium. The sugammadex:rocuronium association-dissociation rate is 25,000,000:1. This means the binding affinity of sugammadex for rocuronium is so high that sugammadex encapsulates rocuronium 25 million times for each instance the complex separates. The result is a rapid and reliable reversal of neuromuscular blockade.

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**The 1:1 complex prevents rocuronium from agonizing nicotinic cholinergic post junctional receptors at the neuromuscular junction.**

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**Medicinal Chemistry**

The name sugammadex is derived from the drug’s chemical structure. “Su” is representative of the drug being a sugar-based compound. “Gammadex” is derived from the drug’s gamma-cyclodextrin (γ-cyclodextrin) chemical structure. Naturally occurring cyclodextrins contain 6, 7, or 8 cyclic oligosaccharides (dextrose units) and are respectively referred to as α, β, or γ-cyclodextrins. The molecular structure of a cyclodextrin consists of a circular ring of dextrose molecules (Figure 1) viewed as a three-dimensional structure; the configuration appears as a short, hollow cone. Because sugammadex is a sugar-based, short, hollow cone, the drug is regularly referred to in the literature as a doughnut.

The doughnut has a hydrophobic (water repelling) inner core and a hydrophilic (water loving) exterior. Sugammadex is a modified γ-cyclodextrin. The naturally occurring γ-cyclodextrin molecule has an inner cavity that is 7.5 to 8.3 Å (one angstrom (Å) equals one ten-billionth of a meter) and is too small to accommodate the rocuronium molecule. Chemists modified the naturally occurring γ-cyclodextrin by adding eight side chains with polarcarboxyl (-COOH) groups to the drug’s inner core. This modification extends the inner cavity to 11 Å and allows adequate binding of rocuronium’s four steroidal rings (Figure 2).

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**Table 1. Neuromuscular Blocking Drugs**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Drug</th>
<th>Sugammadex for Reversal?</th>
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<tbody>
<tr>
<td>Non-depolarizing</td>
<td>Rocuronium</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Vecuronium</td>
<td></td>
</tr>
<tr>
<td>Amniosteroids</td>
<td>Cisatracurium</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Atracurium</td>
<td></td>
</tr>
<tr>
<td>Benzyloquinoliniums</td>
<td>Succinylcholine</td>
<td>No</td>
</tr>
<tr>
<td>Depolarizing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Succinylcholine</td>
<td></td>
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</tbody>
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The addition of negatively charged carboxyl groups also increases the inner core’s attraction to the rocuronium molecule’s positively charged quaternary nitrogen group (Figure 3). A combination of intermolecular forces including electrostatic interactions, van der Waals forces, hydrogen bonding, and hydrophobic interactions result in the formation of a tight sugammadex:rocuronium complex. The 1:1 complex prevents rocuronium from binding nicotinic cholinergic receptors at the neuromuscular junction. The hydrophilic exterior then promotes rapid and nearly complete (95%) renal excretion of the biologically inactive complex.

**Pharmacokinetics**

Pharmacokinetics describes the relationship between a drug dose and the concentration of a drug at the target effect site over time. Absorption, distribution, and elimination (metabolism and excretion) regulate the concentration of a drug in the plasma that is available to interact with target receptors. Since sugammadex is administered intravenously, absorption is bypassed.

**Distribution**

The gamma cyclodextrin molecule is highly water-soluble as a result of the doughnut’s hydrophilic outer ring. For this reason, sugammadex demonstrates a large apparent volume of distribution (11-14 liters). Neither the drug, nor the sugammadex:rocuronium complex appears to bind red blood cells or plasma proteins. The drug may collect in bone and teeth; however, non-clinical toxicology studies have yet to demonstrate a clinically significant effect of this occurrence.

**Elimination**

Sugammadex does not appear to undergo any significant metabolism in vivo (within the body). The drug is primarily (95%) renally excreted unchanged in the urine and has an elimination half-life ($t_{1/2}$) of approximately 2 hours in patients with normal renal function. Therefore, the $t_{1/2}$ of sugammadex may increase up to ten-fold in the patient with renal impairment. The drug is not recommended for use in...
patients with severe renal dysfunction, including those patients requiring dialysis. However, no dosage adjustment is required for patients with mild-to-moderate renal dysfunction. The drug’s ability to reverse rocuronium-induced neuromuscular blockade remains unchanged in patients with mild-to-moderate renal impairment. A single study in a small subset of patients with severe renal impairment requiring hemodialysis demonstrated that sugammadex and the sugammadex:rocuronium complex were removed during high-flux dialysis (modern form of dialysis utilizing dialyzers that have large pores for removing both uremic toxins and fluid). No pharmacokinetic differences have been identified to date in regard to age, sex, or race. Nevertheless, the safety and efficacy of sugammadex is yet to be established in children, and the drug is not currently recommended for use in this population.

Patients should be educated to use additional, non-hormonal contraception for one week after receiving sugammadex.

**Pharmacodynamics**

Simply stated, pharmacodynamics describes what the drug does to the body. Specifically, pharmacodynamics describes the relationship between drug dose and pharmacologic effect. The effectiveness of sugammadex as a reversal agent has been shown to increase as the dose increases. This relationship is referred to in pharmacology as dose-dependent efficacy.

Sugammadex may bind other endogenous or exogenous steroidal complexes in addition to amino-steroid-based NMBDs. For example, the use of dexamethasone as an antiemetic has been considered. Buonnano et al demonstrated that the use of dexamethasone for postoperative nausea and vomiting (PONV) prophylaxis does not interfere with sugammadex reversal of rocuronium-induced neuromuscular blockade. Hormonal contraceptives are the primary clinical concern to date. A bolus dose of sugammadex is considered to be equivalent to a single missed dose of oral contraceptive. **Patients should be educated to use additional, non-hormonal contraception for one week after receiving sugammadex.**

Sugammadex is described as biologically inactive.

**Dosing**

Manufacturer dosing recommendations are based on spontaneous recovery of the response to peripheral nerve stimulation (Table 2). The manufacturer recommends weight-base dosing based on the patient’s actual body weight. Sugammadex (BRIDION®) is supplied as a sterile, clear colorless to slightly yellow-brown aqueous solution for intravenous infusion. The concentration of available preparations is 100 mg/ml. Both 2 ml (200 mg) and 5 ml (500 mg) single dose vial preparations are available.

If the clinical setting demands rapid reversal of a recently administered dose of rocuronium (i.e., the “cannot intubate, cannot ventilate” scenario) sugammadex may be considered. The manufacturer recommends a dose of 16 mg/kg if rapid reversal of neuromuscular blockade...
is indicated approximately 3 minutes following the administration of a single injection of high dose (1.2 mg/kg) rocuronium. Sugammadex 16 mg/kg has been shown in a single study to reverse rocuronium 1.2 mg/kg to a TOFR of 0.9 within approximately 3 minutes, compared to approximately 10 minutes for spontaneous recovery from succinylcholine. However, further studies are needed to confirm the clinical efficacy of sugammadex for this indication.

Table 2.
Manufacturer Dosing Recommendations
Based on Spontaneous Recovery of Response to Nerve Stimulation

<table>
<thead>
<tr>
<th>Spontaneous Recovery of Twitch Response</th>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 PTC* &amp; 0/4 on TOF**</td>
<td>Rocuronium &amp; Vecuronium</td>
<td>4 mg/kg</td>
</tr>
<tr>
<td>2/4 on TOF**</td>
<td>Rocuronium &amp; Vecuronium</td>
<td>2 mg/kg</td>
</tr>
<tr>
<td>Clinical need to reverse neuromuscular blockade 3 minutes after administration of 1.2 mg/kg of rocuronium</td>
<td>Rocuronium ONLY</td>
<td>16 mg/kg</td>
</tr>
</tbody>
</table>

*PTC – post-tetanic count
**TOF – Train of four

If the clinical setting demands rapid reversal of a recently administered dose of rocuronium (i.e., the “cannot intubate, cannot ventilate” scenario) sugammadex may be considered.

For the reversal of rocuronium and vecuronium, the manufacturer recommends a dose of 4 mg/kg if the patient demonstrates a 1 to 2 post-tetanic count (PTC), but shows a 0 out of 4 twitch response with TOF monitoring. To assess the post-tetanic count, use a peripheral nerve stimulator to apply 50 Hz tetany stimulation for 5 seconds, allow a 3-second pause, then stimulate with 1 Hz twitch stimulation and count the total number of post-tetanic twitches or repeat the train of four. Sugammadex (4 mg/kg) reversal of rocuronium-induced neuromuscular blockade to a TOFR of 0.9 has been shown to occur 10 times faster than reversal with neostigmine (0.7 mg/kg) and endrophonium (1 mg/kg). Reversal of neuromuscular blockade with sugammadex (4 mg/kg) at a PTC of 1 to 2 has been shown to occur within 5 minutes in 97% of patients. A dose of 2 mg/kg is recommended for the reversal of rocuronium or vecuronium if the patient exhibits at least a 2 out of 4 twitch response on TOF. Sugammadex (2 mg/kg) reverses rocuronium-induced neuromuscular blockade five times faster than does neostigmine (0.5 mg/kg), approximately 2 minutes vs. approximately 9 minutes, respectively.

Warnings and Precautions
Sugammadex is described as biologically inactive and neither stimulates nor antagonizes receptors in vivo. The drug is contraindicated in patients with known hypersensitivity to sugammadex or any of its components. Anaphylaxis has been observed in 0.3% of healthy volunteers studied. Cases of marked bradycardia progressing to cardiac arrest have been reported. The manufacturer recommends close hemodynamic monitoring during and immediately following reversal with sugammadex.

Table 3
Sugammadex: Warnings and Precautions

Anaphylaxis
- Reported in 0.3% of healthy volunteers
- Observe patients for an appropriate period following administration

Marked Bradycardia
- Though rare, bradycardia progressing to cardiac arrest has been reported
- Monitor for hemodynamic changes following administration

Respiratory Function
- Even if recovery from neuromuscular blockade is complete, other drugs used in anesthesia practice may suppress respirations
- Monitor respiratory pattern following administration

Prolonged Neuromuscular Blockade
- A small number of patients have demonstrated delayed or minimal response to sugammadex administration
- Monitor ventilation and reflex activity until recovery occurs
A small number of patients have demonstrated delayed or minimal response to the administration of sugammadex; as always, monitor ventilation and reflex activity until recovery from neuromuscular blockade occurs. In one clinical trial, bronchospasm was reported as a possibly related adverse event. In this trial 77 patients with a past medical history of pulmonary complications were administered sugammadex. Two asthmatic patients demonstrated bronchospasm approximately 2 minutes after receiving sugammadex. However, no evidence has conclusively linked bronchospasm to the use of sugammadex (Table 3).

Following sugammadex administration, a minimum waiting period is required before re-administration of rocuronium or vecuronium.

Sugammadex (16 mg/kg) has been associated with up to a 25-50% prolongation in coagulation profiles for up to 1 hour in selected patients. Clinical trials to date have not demonstrated an increase in blood loss, bleeding events, or transfusion requirements related to sugammadex use. The manufacturer recommends that coagulation parameters be carefully monitored in patients with known coagulopathies, those being treated with therapeutic anticoagulation or receiving thromboprophylaxis drugs other than heparin and low molecular weight heparin, or patients receiving thromboprophylaxis drugs who then receive a dose of 16 mg/kg sugammadex.

Following sugammadex administration, a minimum waiting period is required before re-administration of rocuronium or vecuronium. Following a reversal dose of sugammadex, 4 mg/kg, should neuromuscular blockade need to be reintroduced, the onset of additional rocuronium will be significantly delayed, and the duration will be significantly abbreviated (Table 4). A nonsteroidal NMBD is recommended if neuromuscular blockade is required before the minimum recommended interval has elapsed. The manufacturer also cautions that the onset of a depolarizing neuromuscular blocker (e.g., succinylcholine) may be slower than expected.

### Summary

Evidence supporting the reality and danger of postoperative residual neuromuscular blockade encourages anesthetists to seek to ensure complete reversal of muscle relaxation. The ideal reversal agent would provide rapid and reliable reversal of neuromuscular blockade without side effects. Sugammadex (BRIDION®), the first cyclodextrin introduced into clinical anesthesia practice, is now FDA approved and can be considered for reversal of neuromuscular blockade induced by rocuronium and vecuronium in adult surgical patients. After reviewing the pharmacology, safety, and associated anesthetic implications of sugammadex, anesthetists may consider adopting this new reversal agent into their armamentarium.

### Suggested Reading


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**Tips for your Clinical Practice: Key Points**

- This novel and unique agent **encapsulates** rocuronium and vecuronium providing for rapid antagonism of neuromuscular blockade.
- The **cycloexodextrin molecular structure** that sugammadex is based on was **modified**, enlarging it so that it can accommodate rocuronium-like molecules.
- Sugammadex acts as a guest-host complex, binding the neuromuscular blocking drug, and having **no effect on acetylcholinesterase** or any other receptors.
- Sugammadex is **largely excreted in the urine** in the first 8 hours but its efficacy as an antagonist does not appear to rely on renal excretion of the guest-host complex.
- Sugammadex appears to be **biologically inactive**, has minimal association with plasma proteins, and appears to be a safe and effective antagonist to rocuronium and vecuronium.

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POST-STUDY QUESTIONS

1. Sugammadex is indicated for reversal of neuromuscular blockade induced by which neuromuscular blocking drug (NMBD)?
   - A. Cisatracurium.
   - B. Succinylcholine.
   - C. Rocuronium.
   - D. Curare.

2. Griffith and Johnson first reported on the use of purified curare in:
   - A. 1935.
   - B. 1942.
   - C. 1957.
   - D. 1963.

3. Residual neuromuscular blockade is defined as:
   - A. A train of four ratio of less than 0.9 at the adductor pollicis muscle.
   - B. A train of four ratio of less than 0.5 at the adductor pollicis muscle.
   - C. A train of four ratio of less than 0.9 at the orbicularis oculi muscle.
   - D. A train of four ratio of less than 0.5 at the orbicularis oculi muscle.

4. What is the mechanism of action of sugammadex reversal?
   - A. Antagonism of acetylcholine at muscarinic receptors.
   - B. Inhibition of acetylcholinesterase.
   - C. Potentiation of acetylcholine at the neuromuscular junction.
   - D. Encapsulation of rocuronium or vecuronium.

5. The chemical structure of sugammadex can be described as:
   - A. A modified gamma cyclodextrin.
   - B. A short, hollow cone resembling a doughnut.
   - C. A circle of dextrose molecules.
   - D. All of the above.

6. Sugammadex is primarily eliminated via:
   - A. Renal excretion.
   - B. Hepatic metabolism.
   - C. Ester hydrolysis.
   - D. Hoffman elimination.

7. Which of the following drug interactions should be considered prior to the administration of sugammadex?
   - A. The use of dexamethasone for PONV prophylaxis may interfere with the ability of sugammadex to reverse neuromuscular blockade.
   - B. A bolus dose of sugammadex is considered to be equivalent to a single missed dose of oral contraceptive.
   - C. Angiotensin receptor blockers may interfere with the ability of sugammadex to reverse neuromuscular blockade.
   - D. Patients taking 81 mg of aspirin daily should not receive sugammadex.

8. The manufacturer recommends which of the following sugammadex doses if the patient demonstrates 2 out of 4 twitches on train of four monitoring?
   - A. 1 mg/kg.
   - B. 2 mg/kg.
   - C. 4 mg/kg.
   - D. 16 mg/kg.

9. Coagulation parameters should be carefully monitored in which of the following scenarios?
   - A. Patients with known coagulopathies.
   - B. Patients being treated with therapeutic anticoagulation.
   - C. Patients receiving thromboprophylaxis drugs and who then receive a dose of 16 mg/kg sugammadex.
   - D. All of the above.

10. When reinstituting neuromuscular blockade after sugammadex reversal, what will be observed with additional rocuronium administration?
    - A. Onset accelerated, duration prolonged.
    - B. Onset accelerated, duration abbreviated.
    - C. Onset delayed, duration prolonged.
    - D. Onset delayed, duration abbreviated.