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NEUROMUSCULAR BLOCKADE (GS MURPHY, SECTION EDITOR)

Sugammadex: Clinical Pharmacokinetics and Pharmacodynamics

Jennifer Nguyen-Lee[1] · Natalie Moreland[1] · Alireza Sadoughi[1] · Reza Borna[1] · Ali Salehi[1] · Jonathan S. Jahr[1,2]

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Abstract

Purpose of Review The purpose of this chapter is to provide an evidence based understanding of the pharmacokinetics and pharmacodynamics of sugammadex.

Recent Findings Sugammadex is a c-cyclodextrin that rapidly reverses the effect of aminosteroid nondepolarizing neuromuscular blocking agents (NMBAs) rocuronium and vecuronium by forming an inactive 1:1 complex. It is only available in an intravenous form with a bioavailabilty of 100%. It does not bind to plasma proteins and is eliminated unchanged by the kidneys. The type of NMBA used and the degree of the residual neuromuscular blockade at the time of administration determine the dose of sugammadex needed and the speed of reversal. Plasma levels of exogenous compounds with similar steroidal structure, such as some hormones, hormonal contraceptives, and pheromones may also be reduced following administration of sugammadex. While the package insert does not indicate dosage adjustments in elderly patients, or those with hepatic, cardiac, pulmonary comorbidities (not approved in pediatric patients less than 18 years or patients with a creatinine clearance less than 30 ml/min), sugammadex dosing possibly should be adjusted based upon the patient's age and comorbidities, including liver or kidney failure and morbid obesity.

Summary Sugammadex has been shown to be an effective agent in reversing the effects of NMBAs with an acceptable safety and efficacy profile.

Keywords Sugammadex · Pharmacokinetics · Pharmacodynamics · Clinical therapeutics

Introduction

Sugammadex is a revolutionary drug that can reverse all levels of neuromuscular blockade (mild, moderate, and deep) following the administration of the aminosteroid muscle relaxants rocuronium and vecuronium. This novel cyclodextran molecule is the first in a new class of selective relaxant binding agents, and it acts by encapsulation of the free molecule to form a stable inactive complex. This review aims to discuss the pharmacokinetics and pharmacodynamics of sugammadex in a clinically relevant context [1].

This article is part of the Topical Collection on *Neuromuscular Blockade*

✉ Jonathan S. Jahr
j.s.jahr@ucla.edu

[1] Anesthesiology and Perioperative Medicine, David Geffen School of Medicine at UCLA, UCLA Health, Los Angeles, CA, USA

[2] David Geffen School of Medicine at UCLA, UCLA Health, 757 Westwood Plaza, Suite 3325, Los Angeles, CA 90095, USA

The pharmacokinetic principles of absorption, distribution, excretion, and elimination describe how much drug reaches the site of drug action and over what time this occurs. Simply stated, pharmacokinetics describes how the human body affects the drug. The first process, absorption, or bioavailability, refers to the fraction of drug that reaches the central compartment. This is particularly relevant for oral administration, as absorption is bypassed when drugs are administered intravenously. Distribution of the drug depends upon cardiac output, regional blood flow, capillary permeability and tissue volume; as such, drugs reach well-perfused areas such as the liver, kidney, and brain before less well-perfused tissue beds such as muscle and fat. Tissue distribution further depends upon the relative binding of each drug to plasma proteins and tissue macromolecules process also known as blood-tissue partitioning which limits the concentration of free drug. The volume of distribution is a theoretical volume that describes the extent to which a medication is present in the plasma versus the extravascular tissues. In most cases, termination of a drug effect is by excretion of the unchanged drug or excretion of metabolites [1].

The pharmacodynamic properties of a drug describe its biochemical effect on the body, or its mechanism of action. Drugs exert their effects by binding to tissue macromolecules which start the biochemical and physiological changes characteristic of the response of the drug. The interaction between the drug and receptor is defined by the principles of affinity, efficacy, and potency. The reversible binding of the drug and receptor is described as affinity. Efficacy describes the ability of the drug-receptor complex to produce a cellular response. Dose-response curves describe the observed effect of a drug as a function of the concentration of the drug in the receptor compartment. The affinity describes the reversible formation of the ligand-receptor complex. Finally, potency quantifies the relationship between the affinity and efficacy of a drug; when two drugs have an equivalent efficacy, the drug that produces this effect at a lower concentration is said to be more potent. Finally, dose-response curves are used to describe the effect of a drug as a function of its concentration [1].

This review will present previously published materials and no new data; it will be divided into the following sections: clinical pharmacodynamics—drug specificity, dose-response curve, drug-receptor interaction, potency, efficacy and affinity, pediatric, elderly, morbid obesity, renal insufficiency and liver dysfunction, bleeding and sugammadex, pharmacokinetics—absorption and distribution, excretion, metabolism, clearance, and conclusion.

Clinical Pharmacodynamics

Drug Specificity

Sugammadex is a modified c-cyclodextrin that rapidly reverses the effect of the steroidal nondepolarizing NMBAs rocuronium and vecuronium. Sugammadex forms a stable, inactive 1:1 complex with rocuronium or vecuronium; this reduces the amount of free NMBA that is available to bind to nicotinic acetylcholine receptors at the neuromuscular junction, resulting in reversal of neuromuscular blockade [2, 3].

In healthy anesthetized volunteers, a single intravenous dose of sugammadex 1–8 mg/kg rapidly reversed neuromuscular blockade induced by rocuronium 0.6 mg/kg in a dose-dependent manner [4]. The degree of residual neuromuscular blockade at the time of sugammadex administration influenced the speed of reversal of rocuronium-induced neuromuscular blockade [5]. The choice of anesthetic agent (propofol or sevoflurane) did not affect the ability of sugammadex 2 or 4 mg/kg to reverse rocuronium-induced neuromuscular block (unlike neostigmine) [6, 7].

Dose-Response Curve

The recovery of the T_4/T_1 ratio to 0.9 over the sugammadex dose range in patients who have received rocuronium or vecuronium have been studied. As parameters in the exponential part of the model were significantly different from zero, a dose–response effect could be demonstrated. From this, it was estimated that for an average patient in the rocuronium and vecuronium groups the fastest achievable time to recovery of the T_4/T_1 ratio to 0.9 was 1.4 and 3.1 min, respectively [8].

In the rocuronium group, the mean time to recovery of the T_4/T_1 ratio to 0.9 was 1.4 and 1.5 min in the sugammadex 2.0 and 4.0 mg kg^{-1} groups. In the vecuronium group, these times were 3.4 and 3.0 min, respectively. Furthermore, the estimated dose–response curve was found adequately to fit observed data for recovery of the T_4/T_1 ratio to 0.9 over the sugammadex dose range studied. Parameters in the exponential part of the model were significantly different from zero; thus demonstrating a dose–response effect. From this, it was estimated that for an average patient in the rocuronium and vecuronium groups, the fastest achievable time to recovery of the T_4/T_1 ratio to 0.9 was 1.4 and 3.1 min, respectively (see Fig. 1) [9].

Drug-Receptor Interaction

Sugammadex has high binding affinities to the neuromuscular blocking agents, rocuronium and vecuronium. Some other drugs might have some degrees of affinity to sugammadex too. Among different drugs screened for this reason, only three drugs have shown high affinity. Those are toremifene, flucloxacillin, and fusidic acid. They have potentials for displacement interactions with sugammadex. This might cause delay in recovery of the TOF ratio to 0.9 when neuromuscular agents are reversed by sugammadex [10].

For patients who receive toremifene on the day of surgery, the recovery from neuromuscular blockade and reversal by sugammadex can be delayed. The high binding affinity of toremifene for sugammadex may cause displacement of rocuronium and vecuronium from the complex [11].

Plasma levels of endogenous or exogenous compounds with steroidal structure like aminosteroid neuromuscular blocking agents may also be reduced after administration of sugammadex. This includes some hormones, hormonal contraceptives, and pheromones. An additional, non-hormonal contraceptive method or back-up method of contraception (such as condoms and spermicides) should be used for the next 7 days if an oral contraceptive containing an estrogen or progestogen is taken on the same day as sugammadex [11].

Based on studies, no clinically significant pharmacodynamic interactions with other drugs and sugammadex are expected [11].

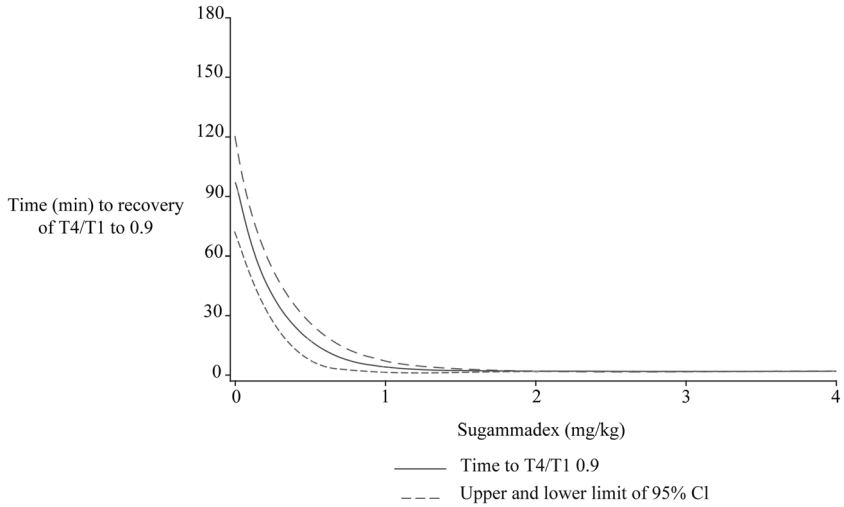

Fig. 1 Dose-response curve of sugammadex and rocuronium estimated dose-response relationship between recovery of T_4/T_1 ratio to 0.9 and the dose of sugammadex administered after rocuronium 0.9 mg kg^{-1}, with 95% confidence intervals (CI; PP subjects). Adapted from [8]

Potency, Efficacy, and Affinity

Potency

The dose of sugammadex needed for reversal of neuromuscular blockade (NMB) depends on the type of agent used and the depth of neuromuscular blockade at the time of administration. The dose administered should be able to accelerate the speed of recovery from NMB to a TOF ratio of 0.9 in an average of 3 min [12••]. The recommended doses for different stages of NMB with rocuronium are listed in Table 1.

In contrast to rocuronium, there is no dose recommendation for immediate reversal of NMB by vecuronium. Sugammadex doses required for reversing deep NMB (PTC 1–2) and moderate NMB (TOF > 2) induced by vecuronium is similar to rocuronium.

Sugammadex dosing may need to be adjusted based upon specific patient populations.

Pediatric

Sugammadex use is not approved in children in the USA and may not be administered to anyone younger than 18 years. There may be non-US use over 2 years of age and specifically for reversal of moderate NMB (TOF > 2) at a dose of 2 mg/kg [12••].

Elderly

The recovery time is prolonged from < 2 to < 4 min in this patient population but doses similar to younger adults are recommended [12••,16].

Morbid Obesity

Muscle relaxants are usually dosed based on ideal body weight in morbidly obese patients. Evidence has showed that sugammadex dosing based on ideal body weight (IBW) is insufficient to reverse deep and moderate blockade [17]. However, in a prospective observational study, Badaoui et al. concluded that a dose reduction from actual weight may be possible. Their study in morbidly obese patients undergoing sleeve gastrectomy found that time to reversal after deep neuromuscular blockade was insignificant (115 ± 69 s vs. 87 ± 40 s, $p < 0.0001$) when a 4 mg/kg dose was used based on real weight vs. ideal body weight increased by 35–50%. The authors also noted based on a subgroup analysis that there were no major adverse consequences or side effects [18•]. The results are based on non-standardized dosing and an observational study and therefore need to be confirmed in a randomized double-blinded study. Loupec et al. randomized patients to 4, 2, or 1 mg/kg ideal body weight of sugammadex for reversal of deep neuromuscular blockade (post-tetanic contractions of one to five), and found that the mean recovery time was significantly shorter ($p < 0.001$) in the high-dose group (255 (63) s) vs. the middle-dose group (429 (102) s) [19••]. This study supports the use of 4 mg/kg IBW for reversal of deep neuromuscular blockade, but continued quantitative or objective monitoring after reversal is still essential, as there was still one failed reversal in the high-dose group. Until further larger scale studies are conducted, it is recommended that dosing of sugammadex should be based upon actual body weight.

Renal Insufficiency and Liver Dysfunction

Sugammadex diverts the metabolism path of rocuronium from a hepatic to renal. Thus, the same principals for dosing can

Table 1 Sugammadex doses for an average reversal time of 3 min in a rocuronium-induced neuromuscular block

Dose	Indication	Mean time to TOF 0.9	Technique	Remarks
16 mg/kg [11]	Immediate reversal after 1.2 mg/kg rocuronium	1.5 min	AMG	Official dose recommendation
4 mg/kg [11]	Reversal of deep NMB (PTC 1 to 2)	3 min	AMG	Official dose recommendation
2 mg/kg [11]	Reversal of moderate NMB (T2 appearance)	2 min	AMG	Official dose recommendation
1 mg/kg [13]	Reversal at the appearance of 4 twitches to TOF stimulation	2 min	AMG	Data from single-center RCT
0.49 mg/kg [14••]	Reversal at TOF 0.2	0.2 min	EMG	Data from single-center RCT
0.22 mg/kg [15]	Reversal at TOF 0.5	2 min	EMG	Data from single-center RCT

PTC, post-tetanic count; *RCT*, randomized control trial; *TOF*, train of four; *AMG*, acceleromyography; *EMG*, electromyography. Adapted from [12••]

apply in this patient population [20]. Sugammadex is not recommended for patients with creatinine clearance < 30 ml/min or needing dialysis but if necessary sugammadex can be dialyzed with an appropriate dialysis filter [21]. In patients with creatinine clearance > 30 ml/min sugammadex can be safely used for the reversal of deep and moderate NMB using the recommended doses for adults. Recovery time is prolonged necessitating close neuromuscular monitoring [22].

Efficacy

Sugammadex has demonstrated superiority over neostigmine in rapidly reversing neuromuscular blockade by rocuronium (or vecuronium) in any stage. It achieves higher TOF ratio at the time of extubation and is associated with fewer incidences of postoperative residual/recurrent neuromuscular blockade [23, 24]. This could be explained by the difference in the mechanism of action of the two drugs. Sugammadex is also associated with less adverse events. Neostigmine administration has been associated with higher incidence of hypoxemia, bronchospasm, increased airway secretions, pulmonary edema/atelectasis, and reintubations [15, 25, 26]. Neostigmine negatively affects genioglossus muscle and diaphragmatic function in a dose-dependent fashion after full recovery from neuromuscular blockade increasing the risk of upper airway obstruction [27]. Sugammadex has no effect on genioglossus muscle and the diaphragm and has been shown to be safe when used in patients suffering from pulmonary disease [28].

Incidence of cardiovascular side effects like bradycardia, arrhythmias, and arterial vasodilatation is higher with neostigmine [15]. This is partly due to the vagotonic effect of neostigmine (bradycardia) and partly due to the use of antimuscarinic agents like atropine and glycopyrrolate that result in an increased sympathetic tone [29] that also can lead to a prolonged QTc. A recent study does show no direct relation between sugammadex and QTc prolongation [30]. In general, mechanism of cardiovascular side effects associated with sugammadex is unclear. Incidence of postoperative pain and postoperative nausea and vomiting are similar between the two drugs.

Affinity

Sugammadex is designed to bind with high affinity to rocuronium and with lesser affinity to vecuronium by the process of encapsulation thus forming a 1:1 complex. This mechanism of action enables sugammadex to bind to other molecules and if the affinity is high enough can displace rocuronium leading to reoccurrence of neuromuscular blockade. The affinity of rocuronium and vecuronium for sugammadex is very high as demonstrated by their association rate constant [Kass] of $1.79 \text{ X } 10^7$ mol/lit and 5.72×10^6 mol/lit, respectively. Other medications associated with anesthesia that have a high affinity to sugammadex are corticosteroids and corticosteroid like compounds with Kass $> 1.24 \times 10^5$ mol/lit. Among other agents, remifentanil, with Kass of 5×10^4 mol/lit and antibacterial agents polymixin B, fusidic acid, and flucloxacillin with Kass of $> 2.5 \times 10^4$ mol/lit. This brings up the potential of displacement and reoccurrence of the NMB.

A. Zwiers et al. [10] showed that only three drugs (toremifene, fusidic acid, and flucloxacillin) have the potential for displacement. Potential displacement depends on the affinity of the drug and the plasma concentration of the dug at the time of sugammadex administration. Kam et al. showed no clinical displacement with diclofenac or flucloxacillin [31]. Toremifene is only available in the oral form and fusidic acid reaches plasma concentrations needed for displacement after 500 mg of intravenous infusion every 8 h for 3 days, making these agents very unlikely to cause delayed recovery or reoccurrence of NMB. Pharmacokinetic-pharmacodynamic simulations show that 34% of (free) etonogestrel can be captured by sugammadex, so it is important to inform females of child-bearing age taking oral contraceptives (OCP) and receiving a bolus dose of sugammadex that it counts as a missed daily dose of the OCP. On the other hand, the plasma concentration of OCP is not high enough at the time of administration to cause delayed recovery and reoccurrence of NMB [10].

Anaphylaxis and Hypersensitivity

Anaphylaxis and serious hypersensitivity reactions have been reported in patients receiving sugammadex in clinical trials

[11]. In a randomized, double-blind, multicentre study, healthy adults received three repeat doses of sugammadex 4 mg/kg ($n = 151$), sugammadex 16 mg/kg ($n = 148$), or placebo ($n = 76$), with each dose separated by a washout period of approximately 5 weeks [32]. After any dose of study drug, hypersensitivity symptoms (e.g., nausea, pruritus, urticaria) were reported in 6.6% of sugammadex 4 mg/kg recipients, 9.5% of sugammadex 16 mg/kg recipients and 1.3% of placebo recipients.

Most hypersensitivity reactions occurred immediately after the administration of sugammadex and were mild and self-limiting. Confirmed anaphylaxis occurred in one subject following the first dose of sugammadex 16 mg/kg [32]. Anaphylaxis (characterized by dermatological symptoms such as rash, erythema, and urticaria, and hypotension) has also been reported with sugammadex in the postmarketing setting [11], with an estimated rate of adjudicated anaphylaxis alone of 0.008% and an estimated rate of adjudicated anaphylaxis and hypersensitivity combined of 0.01% [33]. Sugammadex is contraindicated in patients who have known hypersensitivity to sugammadex or any of its components [11].

Cases of marked bradycardia, including cases which have led to cardiac arrest, have been reported within minutes of administering sugammadex [11]. Patients should be closely monitored during and after reversal of neuromuscular blockade for haemodynamic changes, and anticholinergic agents should be administered in the event of clinically significant bradycardia [11].

Moderate or severe bronchospasm was reported in two of 42 patients with underlying asthma who received sugammadex 4 mg/kg. Symptoms of bronchospasm resolved in both patients within 5 min of initiating treatment [28].

Bleeding and Sugammadex

Sugammadex has been noted to cause increases in the coagulation laboratories aPTT and PT(INR) of up to 25% for up to 1 h in healthy volunteers [11]. Verified bleeding was observed in 2.9% of patients in the sugammadex group and 4.1% in the standard of care group.

The mechanism by which sugammadex causes these coagulation alterations has not been elucidated. An ex vivo study [34] demonstrated increases in PT (9.1%) and aPTT (13.1%) when sugammadex was titrated to the blood of healthy human volunteers. The titration of [sugammadex + rocuronium] to blood samples did not reveal an effect on PT or aPTT, and additional evaluations in this analysis indicated that the effect of sugammadex on these coagulation laboratories may be an in vitro artifact presumed related to binding of phospholipids used in preparation of common phospholipid-dependent assays [34].

Rahe-Meyer et al. [35] conducted a Phase III, randomized, controlled, double-blind, parallel-group study that evaluated the effects on coagulation of sugammadex 4 mg/kg compared to standard care (neostigmine or spontaneous recovery) for the reversal of rocuronium- or vecuronium-induced neuromuscular blockage (NMB) under general anesthesia. Ninety-eight percent of subjects received thromboprophylaxis, mostly (84%) low molecular weight heparin. Analyses were performed on the as-treated population of 1184 subjects (sugammadex, $n = 596$; usual care, $n = 588$). Of the usual care patients, 52% received neostigmine (with glycopyrrolate or atropine) and 48% were allowed to have spontaneous recovery from NMB [35].

The subjects with creatinine clearance [Cr Cl] < 60 mL/min had higher bleeding rates compared with subjects with Cr Cl 0 > 60 mL/min (RR 2.4; $p < 0.01$), but there was no heterogeneity based on renal status with regard to the treatment effect of sugammadex vs. usual care (interaction $p = 0.85$). In addition, no heterogeneity was noted in the effect of sugammadex in subgroups by age (< 75, 0 > 75), ASA class, or gender [34–36].

De Kam et al. [34] performed a randomized, placebo-controlled, three-period cross-over trial in eight healthy adults in the Netherlands that studied the effects of sugammadex on aPTT and PT(INR). Subjects included adults 18 to 45 years of age with BMI between 18 and 30 kg/m^2 and normal baseline values for aPTT and PT/INR. In each study period subjects were administered a single dose of (a) 16 mg/kg sugammadex, (b) 4 mg/kg sugammadex, or (c) placebo [34].

Blood samples were drawn at − 5, 2, 3, 5, 15, and 30 min and 1, 5, 12, and 72 h post-dose. The primary endpoint was the area under the curve (AUC) during the post-dose interval of 2–60 min (AUC2-60 min) for aPTT and PT(INR).

De Kam et al. [36] published an additional randomized, double-blind, placebo-controlled, four-period cross-over study to determine the effects of sugammadex on anti-Xa anticoagulant activity after pre-treatment with enoxaparin and on aPTT after pre-treatment with unfractionated heparin (UFH) in healthy adult males. First, subjects received 40 mg of enoxaparin (in Part I), 5000 units UFH (in Part 2), or placebo followed by 4 mg/kg or 16 mg/leg sugammadex, or placebo. Endpoints were anti-Xa activity and aPTT, both time-averaged from 3 to 30 min post-dose. GMRs and their two-sided 90% confidence limits were evaluated for anticoagulant plus sugammadex (4 or 16 mg/kg) vs. anticoagulant plus placebo. A clinically relevant treatment effect was made as a GMR with a 90% upper confidence limit (UCL) > 1.50. Administration of sugammadex did not meet a treatment effect for the prespecified criterion of potential clinical relevance [36].

Tas et al. [37•] conducted a randomized, controlled, prospective study evaluating the effect of sugammadex on postoperative coagulation parameters and bleeding in adults after nasal septoplasty. Subjects scheduled for septoplasty who did not take anticoagulants, had no history of bleeding disorder, and had normal complete blood count and coagulation

tests (PT, INR, aPTT) participated in the study. Fifty subjects were randomized to receive neostigmine 0.05 mg/kg plus atropine ($n = 26$) or sugammadex, 2 mg/kg (actual body weight) after surgery when two twitches were reached on TOF stimulation. Blood loss was evaluated by nasal tip dressing for 3 h postoperatively at 30 min intervals for the first hour and then every hour during the next 2 h. Postoperatively nasal tip dressings were changed and amount of blood loss on the nasal tip dressing was evaluated by a blinded surgeon. PT and aPTT were measured at 120 min after administration of sugammadex or neostigmine.

No statistically significant difference was determined between the treatment groups in change in PT ($p = 0.953$) or aPTT ($p = 0.734$) measured preoperatively and at 2 h following administration of sugammadex or neostigmine [37•].

The volume of postoperative bleeding measured by nasal tip dressings was significantly greater in the sugammadex treatment group compared for the neostigmine group in all measurement time periods ($p = 0.024$). The mean total amount of blood loss was significantly larger in the sugammadex group (4.1 mL) compared with neostigmine (2.5 mL) ($p = 0.033$) [37•].

De Kam et al. [38] performed a randomized, double-blind, placebo-controlled, four-period cross-over study in 26 healthy adult males to evaluate the effects of sugammadex and aspirin on platelet aggregation. The four treatment groups were placebo, sugammadex 4 mg/kg, and oral aspirin 75 mg plus placebo or sugammadex 4 mg/kg.

Blood samples for evaluation of platelet aggregation and aPTT were obtained 16 min before the sugammadex or placebo, and then at 3, 15, and 301 min, and 1, 3, and 6 h post-dose. Bleeding time was measured pre-dose (− 15 min), at 5 min and 6 h after study drug. Collagen-induced platelet aggregation was evaluated by impedance aggregometry between 3–30 min after administration of sugammadex/placebo. Bleeding time utilized the Ivy technique. The primary endpoint was understanding of platelet aggregation for sugammadex with aspirin compared to aspirin solo. Secondary endpoints included comparisons of aPTT (between sugammadex and aspirin and sugammadex alone or placebo) and bleeding time (sugammadex with aspirin or aspirin alone). PT/INR was deemed an exploratory endpoint. Non-inferiority margins for clinical relevance were prespecified in a literature review [38].

A mean elevation in aPTT GMR of 6% during the 30 min after sugammadex administration was noted and deemed statistically significant. PT/INR increased by 10% at 3 min post-dose for sugammadex compared to placebo and for sugammadex with aspirin vs. aspirin alone, PT/INR returned towards baseline levels after 30 min post-dose [38].

Sugammadex, in doses up to 16 mg/kg, was connected with elevations in the coagulation parameters activated partial thromboplastin time (aPTT) and prothrombin time/international normalized ration [PT(INR)] of up to 25% for up to l hour in healthy volunteers [39]. This high dose of sugammadex is uncommonly used in clinical practice, only in cases of immediate reversal.

In subjects undergoing major orthopedic surgery of the lower extremity who were also treated with heparin or low molecular weight heparin for thromboprophylaxis, elevations in a PTT and PT(INR) of 5.5 and 3.0%, respectively, were noted in the hour following sugammadex 4 mg/kg administration [36]. This study did not determine an elevated blood loss or anemia incidence with sugammadex compared to standard of care. The rate of adjudicated bleeding within 24 h was 2.9% for sugammadex and 22% for standard care. The rate of postoperative anemia was 21% for sugammadex and 22% for standard care. The mean 24-h drainage volume was 0.46 L for sugammadex and 0.48 L for standard care. The need for any postoperative transfusion was 37% for sugammadex and 39% for usual care.

In vitro experiments demonstrated additional aPTT and PT (INR) elevations for sugammadex in combination with vitamin K antagonists, unfractionated heparin low molecular weight heparinoids, rivaroxaban, and dabigatran up to around 25% and 50% at Cmax levels of sugammadex corresponding to 4 mg/kg and 16 mg/kg administrations, respectively [36].

Because of bleeding risk has been studied systematically only in limited uses such as subcutaneous heparin and low molecular weight heparin thromboprophylaxis in combination with 4 mg/kg doses of sugammadex, it is recommended that coagulation parameters be carefully monitored in patients with known coagulopathies, including patients treated with therapeutic anticoagulation, receiving thromboprophylaxis drugs other than heparin and low molecular weight heparin, or those receiving thromboprophylaxis drugs followed by a high dose of 16 mg/kg sugammadex [34].

Pharmacokinetics

Absorption and Distribution

The rigid cyclodextrin sugar molecule of sugammadex is given only in the intravenous form, and therefore the bioavailability of unchanged drug is by definition 100%. Dosing is based on the intensity of the neuromuscular blockade, varying between 2 mg/kg to 16 mg/kg of actual body weight to reverse rocuronium-induced neuromuscular blockade. After administration, sugammadex disperses throughout the extracellular volume, but because of its large size and negatively charged side chains, it is unable to enter the intracellular matrix. Subsequently, it also has very little absorption past the blood brain barrier or placenta [40]. The volume of distribution is between 11 to 14 l in adults, and sugammadex undergoes little to no plasma protein binding. At the therapeutic dosing range

of 1 to 16 mg/kg intravenous bolus, sugammadex follows a linear kinetic model [11].

After a dose of sugammadex is administered, it enters the plasma and results in a rapid encapsulation of steroidal nondepolarizing muscle relaxants, leading to an inability for rocuronium or vecuronium to bind to neuromuscular junctions. This results in a rapid reversal of neuromuscular blockade, although paradoxically, the concentration of paralytic in the plasma increases. This is due to a change in gradient between plasma and tissue concentration. As the rocuronium is bound by sugammadex, the concentration of free circulating rocuronium drops to zero in the plasma, and the free rocuronium in tissue is drawn back into circulation and available for encapsulation [41]. When studied more closely, this phenomenon of increasing central unbound rocuronium concentration immediately after sugammadex administration is also confirmed by the observation of a temporary decrease in twitch response if given small, partial reversal dosing of sugammadex. This muscle relaxation rebound is seen if insufficient sugammadex is given to ensure encapsulation of both central rocuronium as well as the peripheral rocuronium that is quickly redistributed back into central circulation [42].

Excretion

Sugammadex is a water-soluble molecule excreted almost exclusively by the kidneys and undergoes little to no metabolism [43]. After encapsulation by sugammadex, the sugammadex-rocuronium complex is also confined to the plasma and the clearance curve follows that of sugammadex alone [4]. In a study of six healthy male patients given radioactive-labeled [14••] C-sugammadex, excretion of sugammadex was rapid in patients with normal renal function as measured by urine radioactivity and liquid chromatography. Approximately 70% of the administered 4 mg/kg dose of sugammadex was cleared in the first 6 h, 92% in 24 h and 95% within 48 h [44].

In contrast, when sugammadex and rocuronium clearance was evaluated in patients with severe to end-stage renal failure, chronic kidney disease stage 4 or 5, defined as creatinine clearance < 30 ml/min, clearance was significantly reduced [45•]. Staals et al., calculated clearance in 13 patients with creatinine clearance ranging from 4.3 to 24.1 ml/min (mean 12.2 ml/min). Clearance in end-stage renal disease patients were statistically significantly decreased, showing a 17 times decrease in plasma clearance and a 16 times increase in $t_{1/2}$. Of the 13 patients with significant renal dysfunction, nine were hemodialysis dependent and no change in sugammadex plasma concentrations were observed between pre- and post-dialysis measurements in the seven patients who were dialyzed with low-flux membranes [22].

At this time, sugammadex is not recommended for use in patients with severe end-stage renal disease due to the prolonged clearance and small risk of recurarization if the sugammadex-rocuronium complex were to dissociate, although efficacy and dosing is equivalent between patients with decreased creatinine clearance and normal controls. The different methods of dialysis have an effect on the dialyzability of the sugammadex-rocuronium complex. Cammu et al. completed a small study showing one specific dialysis method that was successfully in removing sugammadex-rocuronium complexes from circulation. They used a technique called sustained low-efficiency daily dialysis using a high-flux dialysis membrane and low blood and dialysate flow [21]. High-flux hemodialysis membranes are defined as a β2-microglobulin clearance greater than 20 ml/min, and they have a larger pore size when compared to low-flux membranes [46]. There is some evidence that high-flux membranes, although having no improvement in all-cause mortality, may decrease mortality due to cardiovascular death [47•]. Hence, sugammadex could theoretically be used in dialysis-dependent patients without putting them at increased risk of adverse events concurrent with the use of particular dialysis methods.

Metabolism

Sugammadex does not bind to plasma proteins and metabolism is very limited and eliminated predominately unchanged by the kidneys. Therefore, it is important to take caution with the use in patients with impaired creatinine clearance [48].

Clearance

Given the high binding to rocuronium and the large size of the sugammadex-rocuronium complex, there is very little crossing through blood brain barrier and there have been no studies demonstrating redistribution of the complex. Also, there is no dose adjustment based upon most intrinsic factors (e.g., age, gender, BMI, and race) except severe renal impairment [45•].

In patients with renal dysfunction, several studies have been done using assays and randomized control to observe the difference.

In patients with kidney dysfunction, Staals and colleagues state that the elimination half-life was increased by a factor of 15 for sugammadex and rocuronium by a factor of 2.5 [49]. In a study of 18 subjects with moderate and severe renal impairment, clearance was decreased, and apparent terminal half-life was prolonged with increased renal dysfunction, but no adverse effects were noted with sugammadex 4 mg/kg. Thus, dose adjustments of sugammadex are not required in patients with moderate renal impairment [50•].

In patients with severe kidney dysfunction, although effective, the patients, sugammadex complexed rocuronium was

detected up to 7 days after exposure [45•]. In these patients, however, although no side effects have been seen, if necessary, sugammadex complexed rocuronium may be dialyzed [21]. Current safety experience is insufficient to support the use of sugammadex in patients with a creatinine clearance < 30 ml min^{-1} at this time but data is insufficient to support the use of sugammadex in patients with Cl < 30 mL/min.

Staals et al. presented the following study: the intent-to-treat group comprised 67 patients (renal $n = 35$; control $n = 32$) [51]. Median (95% CI) time from sugammadex to recovery to T_4/T_1 ratio 0.9 was 3.1 (2.4–4.6) and 1.9 (1.6–2.8) min for renal patients vs. controls. Estimated median (95% CI) difference between groups was 1.3 (0.6–2.4) min; thus equivalence bounds were not met. One control patient experienced acceleromyography-determined NMB recurrence (reduction in the TOF fade ratio measured with a quantitative monitor), possibly as a result of premature sugammadex (4 mg/kg) administration, with no clinical evidence of NMB recurrence observed. Rocuronium encapsulated by sugammadex was detectable in plasma at day 7 in six patients. Bioanalytical data for sugammadex were collected but could not be used for pharmacokinetics. Sugammadex 4 mg/kg provided rapid reversal of deep rocuronium-induced NMB in renal and control patients, including occasional prolonged times to recovery in renal patients as a result of underlying medical conditions. However, considering the prolonged sugammadex complexed rocuronium exposure in patients with severe renal impairment in some cases, current safety experience is insufficient to support the use of sugammadex in patients with a creatinine clearance <30 ml/min at this time.

Conclusion

This review of sugammadex clinical pharmacodynamics and pharmacokinetics has presented the current literature. As with all new medications, it is strongly urged that the package insert (PI) recommendations be strictly adhered to, and that off-label use is discouraged. With growth of the knowledge base, and increased indications are approved by regulatory bodies, as the United States Food and Drug Administration (FDA), additional information will become available that will not have been presented in this review. Additionally, while no pharmacoeconomic assessments of sugammadex have been included in this review, it is important that a careful and well thought out protocol for the use of sugammadex is created for each institution when it is approved by the Pharmacy and Therapeutics committee; strict guidelines and documentation of its indications and memorialization of pre- and post-neuromuscular monitoring should be documented on medical records, so review committees can verify that appropriate use has transpired.

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Compliance with Ethical Standards

Conflict of Interest Jennifer Nguyen-Lee declares that she has no conflict of interest.

Natalie Moreland declares that she has no conflict of interest.

Alireza Sadoughi declares that he has no conflict of interest.

Reza Borna declares that he has no conflict of interest.

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- • Of importance
- •• Of major importance

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