

An Update on Sugammadex Sodium

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Sugammadex sodium is the generic drug name for the novel modified gamma cyclodextrin that terminates neuromuscular blockade induced by aminosteroidal neuromuscular blocking agents. Published phase II and phase III clinical data support preclinical and clinical phase I study findings of fast, safe, and efficacious reversal of all levels of neuromuscular blockade induced by rocuronium and vecuronium. Low levels of neuromuscular blockade induced by pancuronium have also been suc-

cessfully reversed by sugammadex. This agent does not reverse the bis-isoquinoline neuromuscular blocking agents. Special patient populations, including pediatric, elderly, cardiac, and renal-compromised subjects, have been studied in phase III. This update focuses on the most recent findings of phase II and III clinical studies.

Keywords: Clinical trials, neuromuscular blockade reversal, sugammadex.

Sugammadex sodium (Organon/Schering-Plough, Oss, The Netherlands), a modified gamma cyclodextrin (CD), has been described as a novel and revolutionary new drug that is poised to radically change the use and reversal of neuromuscular blocking agents (NMBAs). Preclinical study with animals has shown fast and effective reversal of aminosteroidal NMBAs. Phase I and II clinical studies have shown that sugammadex provides a safe, dose-dependent, fast time to reversal of neuromuscular blockade induced by the aminosteroidal NMBAs. The ability of sugammadex to reverse the effects of rocuronium is greater than that of vecuronium and much greater than with pancuronium.¹⁻²⁰ The data collected in phase III clinical study have shown similar findings of a dose-dependent, fast time to reversal of aminosteroidal NMBAs, as well as few side effects in diverse patient populations and those with coexisting disease.²¹⁻²⁸ Currently available results of clinical trials are summarized in the Table.

Phases of Clinical Trials Defined

After initial discovery of any active compound, and bench studies to assess its pharmacologic characteristics, animal testing is done. Testing a new drug in animals is undertaken to explore a drug's actions and side effects and to anticipate and minimize possible harm to humans during human clinical testing. An Investigational New Drug (IND) application to the US Food and Drug Administration (FDA) follows successful preclinical bench and animal study in the United States. An IND application must be accepted and approved by the FDA before clinical trials (studies with human subjects) may begin.

There are 4 phases of clinical trials. Phase I trials are the first administration of a new drug to healthy human subjects. There are usually very few subjects ($n < 100$), and the purpose is to assess drug action, safety, and optimal dosage ranges, and to identify possible side

effects. The Phase II trial incorporates larger numbers of subjects ($n \geq 100$) to further identify safety, efficacy, and dosage ranges. Multiple study sites may be used in phase II and phase III clinical trials. Phase III trials use a much larger number of subjects ($n \geq 1,000$) to refine the safety, efficacy, and effective dosage ranges identified in phase II trials. Additionally, phase III trials seek to identify possible interactions with other drugs, determine efficacy in different patient populations, and compare the new treatment with conventional treatments. Submission of a New Drug Application (NDA) to the FDA for marketability usually occurs after successful conclusion of phase III clinical trials. Clinical study continues after FDA licensing for commercial production. Phase IV is a postmarketing surveillance that explores long-term benefits and risks as well as the efficacy of the drug compiled from its use on a large scale ($n \geq 10,000$).

Sugammadex (previously identified as Org 25969) has followed this research path, and at the time of this update, Schering-Plough has not received NDA approval and is continuing phase III clinical study.

Dose-Finding Studies

Dose-finding studies have explored the effective doses (EDs) for not only shallow levels but also profound levels of neuromuscular blockade. A shallow level of neuromuscular blockade is defined as 2 twitches following train-of-four neuromuscular stimulation (TOF 2/4). A profound level of neuromuscular blockade is defined as no twitches on TOF stimulation and only 1 to 2 twitches following a post-tetanic count (PTC 1-2). The target end point ("full reversal") for these studies was a TOF ratio of 0.9, meaning the fourth twitch of the TOF is 90% the height or strength of the first twitch from baseline. Reversal criteria were standardized by using an accelerometry nerve stimulator (TOF-Watch, Organon Ltd, Swords, Ireland). Accelerometry allowed the objective

Source	Study phase and type	No. of subjects/ASA class/age, y	Anesthesia	Methodology	Major findings and conclusions	Adverse effects
Gijzenbergh ¹	I Safety, efficacy, PK	N = 29 Healthy males	Undisclosed	Sug (1-8 mg/kg) or placebo 3 min after roc 0.6 mg/kg	Roc plasma concentration and renal excretion increased after sug (Org 25969). Well tolerated, effective.	5 mild, 1 moderate (IV site paresthesia for 7 d). ^a No SAE.
de Kam ²	I Pilot safety study	N = 16 Healthy volunteers	Prop and remifent, or no anesthesia	Roc 1.2 mg/kg, TOF < 0.9 for 2 h, sug 16, 20, or 32 mg/kg. Vec 1 mg/kg, TOF < 0.9 for 2 h, sug 16, 20, or 32 mg/kg	Several combinations of sug and roc or vec safe, well tolerated in anesthetized and nonanesthetized volunteers.	None
de Kam and van Kuijk ³	I Safety	N = 62	Undisclosed	Sug 4 or 32 mg/kg, moxifloxacin, or placebo	Sug single IV doses 4 and 32 mg/kg not associated with QTC prolongation. Safe, well tolerated.	No SAE
Sorgenfrei ⁴	II Safety, dose-response, PK	N = 27 Age 18-64	Prop, narc	Sug 0.5-4.0 mg/kg or placebo 60 min after roc 0.6 mg/kg (1 dose)	Roc plasma concentration and renal excretion increased. Dose-dependent time to "full reversal." ^b Safe. Well tolerated.	2 hypotension, ^{a,c} 3 coughing, ^a 3 movement ^a
Suy ⁵	II Dose-finding	N = 80 ASA I-III Age ≥ 18	Prop and remifent	Roc 0.6 mg/kg; vec 0.1 mg/kg; sug 0.5-4 mg/kg (roc group), 0.5 mg-8 mg/kg (vec group); or placebo at TOF 2/4	Dose-dependent fast time to reversal. Dose-response relationship. Effectively reversed roc and vec.	6 SAE surgery-related, 1 SAE tachycardia, ^a 1 prolonged awakening, ^a 1 erythema, ^a 1 abdominal discomfort ^d
Vanacker ⁶	II Safety, efficacy	N = 42 ASA I-III Age 18-82	Sevo or prop	Sevo group; prop group; sug 2.0 mg/kg at TOF 2/4 after roc 0.6 mg/kg	Mean time to full reversal equivalent for both groups (1.8 min). Unaffected by sevo or prop. No residual paralysis.	8 QT prolongation, ^e 2 hypotension, ^{a,f} 1 bradycardia, ^a 2 N&V. No SAE.
Puehringer ⁷	II Efficacy	N = 100 ASA I-III Age 20-64	Undisclosed	Roc 0.9 mg/kg; vec 0.1 mg/kg; vec 0.1 mg/kg; sug 0.5-4 mg/kg (roc group), 0.5 mg-8 mg/kg (vec group); or placebo at TOF 2/4	Sug dose-dependent time to reversal and dose-response relationship for reversal of roc and vec.	3 SAE ^e
Shields ⁸	II Safety, efficacy, dose-response	N = 30 ASA I-III Age > 18	Prop, narc, and N ₂ O	Sug 0.5-6 mg/kg at TOF 2/4 after profound roc block for 2 h	Reversed profound and prolonged roc block. Dose-response effect. Sug 2-4 mg/kg- full reversal within 3 min. Safe and effective.	Atrial fibrillation, respiratory failure ^a
Decoopman ⁹	II Exploratory	N = 20 ASA I-II Age 20-81	Undisclosed	Sug 1.0-8 mg/kg at TOF 2/4 after pancuronium 0.1 mg/kg	Sug decreases mean recovery time of shallow pancuronium block. No dose-response relation shown. Good safety profile, well tolerated.	2 SAE ^e
Groudine ¹⁰	II Dose-finding	N = 50 ASA I-III Age ≥ 18	Prop, narc, and N ₂ O	Sug 0.5-8 mg/kg after roc 0.6 or 1.2 mg/kg and PTC 1-2	Mean time to full reversal 1.2 min with sug 8 mg/kg. Profound roc block reversed at doses ≥ 2 mg/kg. Well tolerated.	4 SAE, ^e undisclosed type
Duvaldestin ¹¹	II Dose-finding	N = 102 ASA I-III Age 21-64	Sevo	Sug 0.5-8 mg/kg at PTC 1-2 after roc 0.9 mg/kg or vec 0.1 mg/kg	Dose-response relation. Recurarization (TOF ratio > 0.9 to < 0.8) with sug 0.5-1 mg/kg.	4 SAE, ^e undisclosed type
Sparr ¹²	II Safety, efficacy, PK	N = 98 Men	Prop, narc	Sug 1-8 mg/kg or placebo at 3, 5, or 15 min after roc 0.6 mg/kg	Dose-dependent time to reversal. Sug enhanced renal excretion of roc.	Undisclosed
Khuenl-Brady ¹³	II Dose-finding	N = 87 ASA I-III	Prop, narc	Sug 2-16 mg/kg or placebo 3 or 15 min after profound	Average time to full reversal 2.5 min with sug 8 mg/kg. Dose-response	SAE: 6 QT prolongation, ^e 8 N&V, ^a 1 hypotension, ^a 1

Source	Study phase and type	No. of subjects/ASA class/age, y	Anesthesia	Methodology	Major findings and conclusions	Adverse effects
Rex ¹⁴	II Dose-finding	Age 18-80 N = 87 ASA I-III Age 18-80	Prop, narc	roc block (1.0 mg/kg) Sug 2-16 mg/kg or placebo 3 or 15 min after profound roc block; 1.2 mg/kg	relationship. Well tolerated, good safety profile. Time to full reversal < 3 min with sug 8 mg/kg. Dose-response relationship. Safe.	vertigo, ^a 1 hiccups, ^a 1 delayed awakening ^a 6 SAE: 5 undisclosed type, 1 QT prolongation ^a
de Boer ¹⁵	II Safety, dose-finding	N = 46 ASA I-II Age 18-64	Prop and remifent	Sug 2-16 mg/kg 5 min after 1.2 mg/kg roc	Dose-dependent fast time to reversal. All doses well tolerated. No recurarization.	2 movement, 1 light anesthesia, ^a 1 diarrhea. ^a No SAE.
Pavlin ¹⁶	II Efficacy, dose-response	N = 197 ASA I-III Age 18-70	TIVA, GA	Sug 4.0 mg/kg 15 min or greater after roc	Mean time to reversal 1.9 min. Effective, well tolerated.	None
Lee ¹⁷	II Safety, efficacy, comparative	N = 110 ASA I-II Age 18-65	Undisclosed	Sug 16 mg/kg 3 min after roc 1.2 mg/kg or SCh 1 mg/kg followed by spontaneous recovery	Mean time to 0.9 TOF from delivery of NMBA: roc/sug group, 4.4 min; SCh group, 7.1 min. No residual paralysis or recurarization.	8 sug group; 8 SCh group (type undisclosed)
Alvarez-Gomez ¹⁸	II Efficacy, comparative	N = 100 ASA I-III Age ≥ 18	Undisclosed	Sug 2.0 mg/kg or neo/glyco 50/10 µg/kg after vec and TOF 2/4	Median time to vec reversal faster with sug vs neo (2.1 vs 18.9 min). No residual paralysis or recurarization.	No SAE
Lemmens ¹⁹	II Efficacy, comparative	N = 84 ASA I-III Age ≥ 18	Prop, narc	Sug 2.0 mg/kg after roc or neo/glyco 50/10 µg/kg after cisatracurium. Both at TOF 2/4.	Median time to roc reversal with sug 1.9 min vs cisatracurium reversal with neo 7.2 min. No recurarization in either group.	No SAE
Flockton ²⁰	II Efficacy, safety, comparative	N = 74 ASA I-III Age ≥ 18	Prop, sevo, and narc	Sug 4.0 mg/kg or neo/glyco 70/14 µg/kg after roc and PTC 1-2	Mean time to roc reversal faster with sug vs neo (2.9 min vs 50.4 min). Good safety profile, sug reversal had less tachycardia.	No SAE
Jones ²¹	III Efficacy, safety, comparative	N = 83 ASA I-III Age ≥ 18	Prop, narc; sevo, narc	Sug 4.0 mg/kg or neo/glyco 70/14 µg/kg after vec and PTC 1-2	Mean time to vec reversal faster with sug vs neo (4.5 min vs 66.2 min). No residual paralysis or recurarization.	9 sug group, 10 neo group. No SAE in either group.
Blobner ²²	III Comparative	N = 98 ASA I-III Age ≥ 18	Undisclosed	Sug 2.0 mg/kg or neo/glyco 50/10 µg/kg after roc and TOF 2/4	Median time to reversal 1.4 min vs 17.6 for neo/glyco. No residual paralysis or recurarization.	2 SAE sug group, ^e 3 SAE neo group ^e
Sacan ²³	III Comparative	N = 60 ASA I-III	Desflurane and remifent	Sug 4.0 mg/kg or edrophonium 1 mg/kg + atropine 0.01 mg/kg, respectively or neo/glyco 70 and 10 µg/kg, respectively, after roc and TOF 2/4	Mean time and % achieved full (0.9 TOF) reversal: sug, 107 s, 100%; edrophonium, 1,044 s, 25%; neo/glyco, 331 s, 10%	Sug: 1 dry mouth, 4 nausea; edrophonium: 19 dry mouth, 3 nausea; neo/glyco: 17 dry mouth, 6 nausea, 1 vomiting
Plaud ²⁴	III Safety pediatric, adult	n = 8 infants n = 24 children n = 31 adolescents n = 28 adults ASA I-II	Prop, caudal, opioid	Sug 0.5-4.0 mg/kg after roc 0.6 mg/kg and TOF 2/4	Median time to full reversal with 2.0 and 4.0 mg/kg: infants, 0.6 and 0.7 min; children, 1.2 and 0.6 min; adolescents, 1.1 and 1.1 min; adults, 1.4 and 1.2 min. Placebo: 19-28.5 min.	SAE in 1 infant ^e and 1 child ^e

Table. Review of Literature of Sugammadex to Reverse Neuromuscular Blockade

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Source	Study phase and type	No. of subjects/ASA class/age, y	Anesthesia	Methodology	Major findings and conclusions	Adverse effects
McDonagh ²⁵	III Safety elderly	N = 150 ASA I-III Age ≥ 18	GA	Sug 2 mg/kg after roc 0.6 mg/kg and TOF 2/4	Mean time to reversal: age < 65, 2.3 min; age 65-74, 2.6 min; age > 75, 3.6 min. Reversal slightly longer for age > 65.	Hypotension, ^a tachycardia, ^a pyrexia, ^a dizziness, ^a oliguria ^a
Staals ²⁶	III Safety renal disease	N = 30 ASA II-III Age 29-81	Prop, narc	Sug 2.0 mg/kg after roc 0.6 mg/kg and TOF 2/4	Mean time to reversal 2.0 min in renal-impaired and 1.7 min in normal renal function group. Well tolerated, rapid recovery.	No SAE disclosed
Dahl ²⁷	III Safety cardiac disease—noncardiac surgery	N = 121 ASA II-IV Age 36-90	Undisclosed	Sug 2 or 4 mg/kg or placebo after roc 0.6 mg/kg and TOF 2/4	No QTc prolongation. Decrease in mean QTc noted from baseline in sug groups. Safe and effective in cardiac patients. Time to recovery faster with sug vs placebo.	2 SAE: QTc prolongation ^{a,c}
Amao ²⁸	III Safety pulmonary disease	N = 77 ASA II-III Age ≥ 18	Undisclosed	Sug 2 or 4 mg/kg after roc 0.6 mg/kg and TOF 2/4	Generally well tolerated and effective. Mean time to reversal: sug 2 mg/kg, 2.1 min; sug 4 mg/kg, 1.8 min	2 SAE: bronchospasm ^a (patient history of asthma)

Table. Review of Literature of Sugammadex to Reverse Neuromuscular Blockade

Abbreviations: AE, adverse effect; GA, general anesthesia; glyco, glycopyrrolate; IV, intravenous; NIMBA, neuromuscular blocking agent; narc, narcotics; neo, neostigmine; N₂O, nitrous oxide; N&V, nausea and vomiting; PK, pharmacokinetic; prop, propofol; PTC, post-tetanic count (1-8), 1-2 = profound, deep block; remifent, remifentanyl; roc, rocuronium; SAE, serious adverse effects; Sch, succinylcholine; sevo, sevoflurane; sug, sugammadex; TIVA, total intravenous anesthesia; TOF, train-of-four mode using peripheral nerve monitor (twitch monitor); T2, 2 twitches out of 4 using TOF monitor (shallow block); 0.9 TOF, product of ratio of fourth twitch strength compared with first twitch strength when using TOF monitor, represents 90% return of fourth twitch strength to baseline; vec, vecuronium.

- a Possibly related to study drug.
- b Full reversal indicates end target of 0.9 TOF ratio.
- c Found in placebo group.
- d Definitely related to study drug.
- e Not related to study drug.
- f Probably related to study drug.

analysis of motor function and standardized the target end point of the clinical studies. The sugammadex dose ranged from 0.5 mg/kg to 16 mg/kg. Many studies also reported safety findings, which were investigated along with the primary research goals of efficacy and dose finding.

- *Shallow Rocuronium and Vecuronium Reversal.* Low to moderate levels of neuromuscular blockade induced by rocuronium and vecuronium have consistently and effectively been reversed by sugammadex.¹⁻⁴ These findings have been supported by a recent study of 100 patients who were ASA classes I through III and aged 20 to 64 years.⁵ Rocuronium- and vecuronium-induced shallow levels of neuromuscular blockade (TOF 2/4) were effectively reversed using sugammadex doses of 1.0 to 4.0 mg/kg. The recovery times displayed a dose-dependent fast time to reversal. The mean reversal time for the 4.0 mg/kg dose of sugammadex was 1.5 minutes for rocuronium and 3 minutes for vecuronium. All doses were well tolerated.⁵ Shields et al⁸ reported the dose-related times-to-TOF ratio 0.9 from profound rocuronium-induced neuromuscular blockade reversed upon spontaneous return to TOF 2/4 (shallow neuromuscular blockade). The dose and corresponding median times (minutes:seconds) to TOF ratio 0.9 were as follows: 0.5 mg/kg (6:49), 1 mg/kg (2:42), 2 mg/kg (1:42), 4 mg/kg (1:04), 6 mg/kg (2:42). The ED was found to be 2 to 4 mg/kg for shallow block.⁸ The longer duration to reversal observed for the 6 mg/kg dose was unexplained and not found in other studies discussed in this review.

- *Shallow Pancuronium Reversal.* Despite sugammadex being found in preclinical and clinical studies to have a lower affinity for pancuronium compared with rocuronium, reversal of shallow pancuronium-induced neuromuscular blockade with sugammadex was attempted.^{9,13,29} In one study, shallow pancuronium-induced neuromuscular blockade was successfully reversed.⁹ Twenty ASA class I or II patients, aged 18 to 81 years, were administered pancuronium, 0.1 mg/kg. At the reappearance of 2 twitches on TOF, neuromuscular blockade was reversed with sugammadex doses ranging from 1.0 mg/kg to 8.0 mg/kg. With the dose of 4.0 mg/kg, the mean time-to-TOF ratio 0.9 was 2:46 minutes. Larger sugammadex doses (6 mg/kg and 8 mg/kg) achieved reversal to a TOF ratio 0.9 in less than 1.5 minutes.⁹ Only 1 dose of pancuronium was given in this study, and a degree of spontaneous recovery of neuromuscular function was present before sugammadex reversal. Additional study of pancuronium reversal needs to be conducted, including reversal after repeated doses of pancuronium and at varying depths of neuromuscular blockade. The successful reversal of shallow pancuronium-induced blockade after a single 0.1 mg/kg dose suggests another potential clinical application for sugammadex.

- *Profound Rocuronium and Vecuronium Reversal.* Doses

of 2 to 16 mg/kg of sugammadex have successfully reversed all levels of rocuronium- and vecuronium-induced neuromuscular blockade, with higher doses exhibiting faster reversal times.⁸⁻¹⁶ In a study of 50 patients (ASA classes I-III, aged ≥ 18 years) profound rocuronium-induced neuromuscular blockade was successfully reversed with sugammadex doses 2 mg/kg or greater. The lower dose of 2 mg/kg displayed a large variability in recovery times (1.8-15.2 minutes). The authors concluded that 4.0 mg/kg and 8.0 mg/kg were EDs, exhibiting a mean time of 1.2 minutes to full reversal from profound rocuronium-induced block.⁸

Similarly, others studied the ability of sugammadex to reverse profound block induced by rocuronium and vecuronium in 102 patients (ASA classes I-III, aged 21-64 years). Sugammadex doses of 0.5, 1.0, 2.0, 4.0, and 8.0 mg/kg were delivered at PTC 1 or 2. At the 2.0 mg/kg dose, the mean time to full recovery was 3.2 minutes for rocuronium and 9.1 minutes for vecuronium. The 4.0 mg/kg dose elicited a mean time to full recovery of 1.6 minutes for rocuronium and 3.3 minutes for vecuronium. With the 8.0 mg/kg dose, the mean time to full recovery was 1.1 minutes for rocuronium and 1.7 minutes for vecuronium. A dose-dependent time to full recovery was found with doses 2 mg/kg and greater.⁹

Exploration of immediate reversal of profound rocuronium-induced blockade was conducted with 98 men.¹⁰ Sugammadex at doses of 1.0 to 8.0 mg/kg was administered 3, 5, and 15 minutes after rocuronium. At those administration times, the mean recovery times were 1.8 minutes, 1.5 minutes, and 1.4 minutes, respectively, for the 8.0 mg/kg dose. The authors concluded that a dose-dependent reversal of profound rocuronium-induced blockade was safe and well tolerated.¹⁰ Additional studies also explored the effectiveness of immediate reversal of rocuronium-induced profound blockade. Rocuronium, 1.0 mg/kg, was administered and reversed with sugammadex after 3 or 15 minutes with sugammadex doses ranging from 2.0 to 16 mg/kg. The average time to full reversal was 2.5 minutes with a sugammadex dose of 8.0 mg/kg.¹¹ Similarly, rocuronium, 1.2 mg/kg, was administered and reversed after 3 or 15 minutes with sugammadex doses of 2.0 to 16 mg/kg. The 12 and 16 mg/kg doses reversed 90% of the cases within 3 minutes. A dose-dependent time to reversal was found.¹²

Unique to sugammadex is the ability to reverse both shallow and profound rocuronium-induced and vecuronium-induced neuromuscular blockade of varying durations. Dose-finding studies continue to aim for the ED for reversal of shallow and profound block as well as the dose needed to immediately (3 minutes after administration) reverse 1.2 mg/kg of rocuronium. It is apparent from the clinical studies that a sliding-scale dosage schedule will likely be recommended, with higher doses required to reverse deeper levels of blockade. The dose-

dependent fast time to reversal may allow the continuation of any level of neuromuscular blockade up to the time of surgical conclusion. Surgical closures and procedures of short duration may benefit from neuromuscular blockade that is not lessened by spontaneous recovery toward the end of surgery. A degree of spontaneous recovery of neuromuscular function is a necessary component of cholinesterase inhibitor reversal therapy, and this aspect of current practice may be changed by the introduction of sugammadex. Additionally, the ability of sugammadex to reverse rocuronium, 1.2 mg/kg, within 3 minutes also offers an alternative to succinylcholine for rapid-sequence intubations.

• *Insufficient Dosing.* Eleveld et al³⁰ described the case of a 108-kg woman (ASA class II, aged 48 years) whose neuromuscular blockade was reversed with sugammadex (0.5 mg/kg) 42 minutes after profound rocuronium (0.9 mg/kg)-induced blockade (PTC 1). The TOF ratio initially improved to 0.6. In minutes, the TOF ratio decreased to approximately 0.25 and gradually improved to 0.9 over the next 65 minutes. The authors concluded that this “muscle relaxant rebound” (recurarization) was due to an insufficient dose of sugammadex.³⁰ This scenario has occurred in phase II trials using a low sugammadex dose of 0.5 to 1.0 mg/kg.^{5,8,9,30} Others found that the low-dose (0.5 mg/kg) sugammadex initially reversed the shallow neuromuscular blockade induced by rocuronium and vecuronium to a TOF ratio of 0.9 but was followed by a decrease to a TOF ratio less than 0.8.⁵ Similarly, with profound rocuronium- and vecuronium-induced blockade, the low doses (0.5 and 1.0 mg/kg) of sugammadex initially reestablished a TOF ratio of 0.9 or greater, which subsequently decreased to under 0.8.⁹

Eleveld and colleagues³⁰ theorized that this recurarization was due to an insufficient dose of sugammadex that may have initially established a concentration gradient by binding central-compartment (plasma) rocuronium, substantially decreasing the amount of unbound rocuronium. The decreased concentration of unbound central-compartment rocuronium, then pulled peripheral-compartment rocuronium into the plasma and caused a return of motor function. The insufficient amount of sugammadex may not have been able to bind all of the additional rocuronium molecules drawn from the peripheral compartment, and these unbound rocuronium molecules may have reequilibrated with the effect compartment (nicotinic junction). This redistribution of unbound NMBAs back onto the nicotinic receptors was thought to be the cause of the recurarization (“muscle relaxant rebound”).³⁰ This explanation may apply to the recurarization found in other studies with vecuronium and rocuronium using sugammadex doses of 0.5 to 1.0 mg/kg.

Regardless of the exact mechanism of this recurarization, these findings reflect the importance of proper dosing when using sugammadex. It is important to think

of sugammadex reversal in terms of direct binding (encapsulation) termination of NMBAs effects, and the establishment of a concentration gradient that extracts the NMBAs off the nicotinic receptor and draws them into the plasma. Sufficient doses of sugammadex must be given to fully encapsulate all NMBA molecules in a 1:1 ratio. The use of neuromuscular monitoring is advised to ensure the correct dose and full reversal.³⁰

• *High Dosing.* In a 2007 report,³¹ a sugammadex dose (40.0 mg/kg), which is 10 times the desired dose of 4.0 mg/kg was inadvertently delivered by investigators to a 36-year-old man, ASA class I, 5 minutes after receiving rocuronium, 1.2 mg/kg. The error was quickly recognized, and data collection continued. Full recovery to TOF ratio 0.9 occurred in 1.31 minutes. No untoward effects were revealed apart from immediate and effective rocuronium reversal. Investigators disclosed an uneventful duration of anesthesia (150 minutes) and recovery. No adverse or serious adverse events were identified by a blinded safety assessor postoperatively, or at a 7-day follow-up. The investigators suspected that a faster reversal time could have occurred but was dependent on cardiac output or circulation time and not the encapsulation process, which is very rapid.³¹

It is likely that sugammadex will be prescribed on a sliding scale based on study findings showing that time to full reversal and degree of efficacy are dose dependent. Doses of 2 to 4 mg/kg have effectively reversed shallow neuromuscular blockade (TOF 2/4) induced by rocuronium and vecuronium. Greater doses of sugammadex are required to reverse deeper levels of blockade. Profound levels of neuromuscular blockade (PTC 1-2) induced by rocuronium and vecuronium have been effectively reversed with doses of 4 to 8 mg/kg.

Comparative Studies

• *Comparison to Succinylcholine Recovery.* Successful, immediate reversal of rocuronium prompted the question of a comparison to succinylcholine. Spontaneous enzymatic degradation of succinylcholine restores motor function within 10 minutes.³² The recovery time of succinylcholine was compared with the reversal time of rocuronium after administration of sugammadex, 16 mg/kg. In the study, 110 patients (ASA classes I-II, aged 18-65 years) were randomly assigned to receive either 1.0 mg/kg of succinylcholine or 1.2 mg/kg of rocuronium. Three minutes after rocuronium administration, sugammadex (16 mg/kg) was delivered and time to full reversal recorded. The spontaneous recovery time of succinylcholine was also recorded. The mean time to a TOF ratio 0.9 was 6.2 minutes for rocuronium and 10.9 minutes for succinylcholine. The authors concluded a faster safe reversal of rocuronium-induced block compared with spontaneous recovery from succinylcholine.¹⁷ It is important to note that the time count to recovery began im-

mediately after succinylcholine administration and not until after sugammadex delivery for rocuronium.

• **Comparison to Cholinesterase Inhibitors.** Vecuronium-induced reversal of neuromuscular blockade by sugammadex was compared with conventional reversal with cholinesterase inhibitors. Alvarez-Gomez and coworkers¹⁸ found a faster time to full reversal of shallow vecuronium block (TOF 2/4) with sugammadex (average, 2.1 minutes) vs neostigmine (average, 18.9 minutes). Profound vecuronium-induced blockade reversal by sugammadex was compared with both edrophonium and neostigmine. Eighty-three patients (ASA classes I-III, aged >18 years) received propofol, sevoflurane, opioids, and vecuronium (maintenance doses, 0.1 mg/kg) to maintain profound blockade. Sugammadex, 4.0 mg/kg, or neostigmine, 70 µg/kg, with glycopyrrolate, 14 µg/kg, was administered. The time to full recovery averaged 4.5 minutes for the sugammadex group and 66.2 minutes for the neostigmine-glycopyrrolate group. No residual curarization was found in either group. Investigators concluded that sugammadex allowed safe, efficient, and faster reversal.¹⁷

Sugammadex reversal of shallow rocuronium-induced neuromuscular blockade was compared with neostigmine reversal of shallow cisatracurium blockade. Eighty-four patients (ASA classes I-III) were randomly assigned to receive sugammadex-rocuronium or cisatracurium-neostigmine at a TOF 2/4. The mean reversal time for sugammadex was 1.51 minutes (range, 0.7-6.4 minutes) compared with 2.85 minutes (range, 4.2-28.2 minutes) for neostigmine. The time to full reversal by sugammadex was significantly faster ($P < .0001$).¹⁸ The wide range of reversal times associated with neostigmine reflected the individual variability of its competitive antagonism mechanism of action compared with the direct encapsulation mechanism by sugammadex.

Comparison of sugammadex to neostigmine for reversal of shallow levels of rocuronium blockade was conducted. Ninety-eight patients (ASA classes I-III, aged >18 years) received rocuronium. At TOF 2/4, sugammadex, 2.0 mg/kg, or neostigmine, 50 µg/kg, with glycopyrrolate, 10 µg/kg, was administered. The median time to full reversal was 1.4 minutes (range, 0.9-5.4 minutes) for sugammadex and 17.6 minutes (range, 3.7-106.9 minutes) for neostigmine. No residual paralysis or recurarization occurred in either group.²² Moderately profound and profound rocuronium-induced neuromuscular blockade reversal by sugammadex was compared with reversal by edrophonium and neostigmine. Sixty patients (ASA classes I-III) received desflurane, remifentanyl, and rocuronium. Moderately profound blockade was not clearly described in this study, but at a “similar first twitch height” sugammadex, 4.0 mg/kg; edrophonium, 1 mg/kg, with atropine, 10 µg/kg; or neostigmine, 70 µg/kg, with glycopyrrolate, 14 µg/kg, was administered. The time to

full recovery averaged 1.78 (\pm 1.1) minutes for sugammadex, 5.52 (\pm 0.45) minutes for edrophonium, and 17.44 (\pm 9.8) minutes for neostigmine.²³ Similarly, Jones found profound rocuronium-induced neuromuscular blockade (PTC 1-2) was fully reversed faster with sugammadex, 4.0 mg/kg (average, 2.9 minutes), compared with neostigmine, 70 µg/kg, with glycopyrrolate, 14 µg/kg (average, 50.4 minutes).²¹

Diverse Patient Population Studies

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

• **Pediatric.** Pediatric use of sugammadex was studied by Plaud and colleagues²⁴ in infants, children, and adolescents. Eight infants (aged 28 days to 23 months), 24 children (aged 2-11 years), and 31 adolescents received propofol anesthesia and either caudal analgesia (infants) or opioids (children and adolescents). Rocuronium, 0.6 mg/kg, was administered, and at TOF 2/4 sugammadex, 0.5 to 4.0 mg/kg, or placebo was administered. The time to full recovery ranged from 0.7 to 4.2 minutes in the infant group. The time to full recovery ranged from 0.6 to 10.9 minutes in a dose-dependent manner in the children's group, and from 0.7 to 43.5 minutes in a dose-dependent manner in the adolescent group. Higher doses (2.0-4.0 mg/kg) of sugammadex had substantially faster times to full recovery. Safety was assessed by electrocardiography, laboratory values, and documentation of adverse events. The authors concluded that safe and effective use of sugammadex was possible in infant, child, and adolescent populations.²⁴

• **Elderly.** Drug pharmacokinetics and pharmacodynamics can be altered in the elderly. McDonagh and coworkers²⁵ explored sugammadex efficacy in this patient population. A total of 150 patients were grouped by age: 48 adults (aged 18-64 years), 62 elderly (aged 65-74 years), and 40 “old elderly” (>75 years). All received 0.6 mg/kg of rocuronium and, at a return of TOF 2/4, sugammadex (2 mg/kg) was administered. The mean time to full recovery in the adult group was 2.3 minutes; elderly group, 2.6 minutes; and old elderly, 3.6 minutes. The authors concluded that there was a significant time delay for all patients over age 65 years (average, 2.9 minutes) compared with those younger than 65 (average, 2.3 minutes; $P = .022$).²⁵

• **Renal Insufficiency.** Patients with renal impairment indicated by creatinine clearance less than 30 mL/min were compared with non-renal-impaired patients who received sugammadex. All patients were anesthetized with propofol, opioids, and rocuronium (0.6 mg/kg). At TOF 2/4, sugammadex, 2.0 mg/kg, was administered and time to full recovery recorded. The mean time to full recovery was 2.0 minutes for the renal-impaired group ($n = 15$), and 1.7 minutes for the non-renal-impaired group ($n =$

15). The authors concluded that sugammadex allows for safe and effective reversal of rocuronium-induced neuromuscular blockade in both healthy and renal-impaired patients.²⁶

- **Cardiac.** A study of sugammadex reversal in 121 cardiac patients (NYHA classes II-III, ASA classes II-IV, aged 36-90 years) was conducted in a randomized, placebo-controlled, multicenter study. All patients in this study underwent noncardiac surgery with rocuronium-induced neuromuscular blockade. Baseline QTc intervals, using the Fridericia correction formula (to account for changes in heart rate), were recorded and compared with QTc intervals after sugammadex and placebo reversal. Reversal was administered at the conclusion of surgery and return of TOF 2/4 using sugammadex at either 2.0 mg/kg or 4.0 mg/kg doses, or placebo. The mean time to full recovery was 1.7, 1.4, and 34.4 minutes, respectively. Analysis of QTc intervals showed no statistically significant differences (using analysis of covariance, or ANCOVA) between the sugammadex and placebo groups. The authors reported only 2 episodes of QTc interval prolongation, 1 in the sugammadex group and 1 in the placebo group; the former case was "possibly related to study treatment."²⁷ The anesthetic agents used to induce general anesthesia in these patients was not disclosed. Inhalation volatile anesthetic agents have been implicated as a cause of QTc interval prolongation.^{33,34} Previous studies reported QTc prolongations that were "possibly related" to sugammadex.^{1,2,4,6}

Specific analysis of possible QTc prolongation by sugammadex was therefore conducted. Using criteria of the International Conference on Harmonisation (ICH-E14) guidelines,³⁵ researchers eliminated agents that may prolong QTc intervals and evaluated only sugammadex. A total of 62 volunteers were randomly assigned to receive 4.0 mg/kg or 32 mg/kg of sugammadex, 400 mg of moxifloxacin (known to cause QTc prolongation), or placebo. No significant QTc prolongation was found with the sugammadex or placebo groups. Substantial (>10 ms) QTc was found with the positive control drug moxifloxacin.²¹ Although this study is limited by a small number of patients, it appears that disclosed QTc prolongations in previous studies^{1,2,4,6} are more likely to be associated with concomitantly administered agents rather than sugammadex. This finding, in association with safe and efficacious conclusions in patients with cardiac disease, suggests sugammadex may be safely used in the presence of cardiac disease and possibly in patients with conduction defects.²⁷ The finding that sugammadex alone is unlikely to cause QTc prolongation is important to disclose.³⁵

- **Pulmonary.** The effects of sugammadex in patients with pulmonary disease were studied. Seventy-seven patients (ASA classes II-III, aged >18 years) with a known history or diagnosis of pulmonary disease received

rocuronium (0.6 mg/kg). At a TOF 2/4, sugammadex, 2.0 or 4.0 mg/kg, was administered. The mean time to full reversal was 1.8 minutes with the 2.0 mg/kg dose, and 2.1 minutes for the 4.0 mg/kg dose. Two serious episodes of bronchospasm, possibly related to sugammadex, were observed in the group receiving the 4.0 mg/kg dose. Both of these patients had a disclosed history of asthma. No alterations in respiratory rate or reoccurarization were observed in any patients. The authors concluded that sugammadex was well tolerated and effective for reversal of rocuronium-induced neuromuscular blockade in patients with pulmonary disease.²⁸

Duration of Action

Once encapsulated, rocuronium and vecuronium molecules remain unable to exert their paralytic effects. The sugammadex/NMBA inclusion complex is excreted unchanged in the urine, mirroring the glomerular filtration rate (GFR).¹ The specific duration of time that sugammadex may exert its NMBA reversal effects is determined by dose as well as GFR. Specific recommendations have not been described in the literature, but human models may be loosely based on the model proposed with rhesus monkeys. Early pharmacokinetic and pharmacodynamic studies in rhesus monkeys found that the half-life of sugammadex is 30 minutes, but the ED₉₀ of rocuronium differs between rhesus monkeys and humans, 100 µg/kg versus 300 µg/kg, respectively.³⁶ The lower ED₉₀ for rhesus monkeys allows less rocuronium molecules to produce an equipotent block with their human counterparts, and therefore fewer sugammadex molecules are needed for reversal. Lower amounts of sugammadex molecules will be cleared faster and allow quicker readministration of rocuronium or vecuronium. The time needed to pass until readministration of rocuronium or vecuronium after sugammadex has not been reported in humans but will likely be longer for higher doses of sugammadex than for lower doses.

Summary

It is intriguing to follow the progression of clinical trials with sugammadex as a new reversal drug for aminosteroidal NMBAs. Although this review is based only on available published clinical studies, the data disclosed suggest a safe and effective reversal agent that appears to be free of the side effects associated with cholinesterase inhibitors and anticholinergic drugs. Sugammadex use in pediatric and elderly populations as well as patients with coexisting diseases of cardiac, pulmonary, and renal origin have shown safe and effective reversal of rocuronium- and vecuronium-induced neuromuscular blockade. Reversal of shallow pancuronium-induced blockade has been successfully achieved, although not extensively studied. It is likely that a sliding-scale dosage schedule based on the degree of neuromuscular blockade determined by neuro-

muscular monitoring will be recommended. As described in the published dose-finding studies, higher doses of sugammadex will be needed to reverse greater depths of blockade. A much higher dose for immediate reversal of profound rocuronium-induced blockade after 1.2 mg/kg may enable safer rapid-sequence intubations when avoiding the use of succinylcholine.

It appears that sugammadex not only achieves fast and effective reversal of neuromuscular blockade but also may provide surgeons with improved surgical conditions. The ability of sugammadex to reverse all levels of rocuronium- and vecuronium-induced blockade unveils options in neuromuscular blockade management that competitive antagonism has precluded. Complete muscle laxity achieved only with profound blockade enables surgeons to operate without any of the muscular tension that may impede their procedures.³⁷ Some authors have suggested that the provision of profound blockade may have prevented negative patient outcomes during orthopedic procedures.³⁸⁻⁴¹ Improved surgical performance and outcomes may be found in the future with the expanded abilities in neuromuscular blockade management. The new management option of neuromuscular blockade of any depth and duration will require the continued use of neuromuscular monitoring to assess these varying depths. The PTC mode will likely become as standard as TOF for those desiring to achieve and maintain deeper (profound) levels of blockade that sugammadex enables.

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