

Reversal of Profound Rocuronium-induced Blockade with Sugammadex

A Randomized Comparison with Neostigmine

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Background: Traditionally, reversal of nondepolarizing neuromuscular blocking agents was achieved using acetylcholinesterase inhibitors, but these are unable to adequately reverse profound blockade. Sugammadex is a novel reversal agent, reversing the effects of rocuronium by encapsulation. This study assessed the efficacy and safety of sugammadex *versus* neostigmine for reversal of profound rocuronium-induced neuromuscular blockade.

Methods: This phase III, randomized study enrolled surgical patients, aged 18 yr or older with American Society of Anesthesiologists physical status I–IV. Patients were randomized to receive sugammadex (4.0 mg/kg) or neostigmine (70 µg/kg) plus glycopyrrolate (14 µg/kg). Anesthetized patients received an intubating dose of rocuronium (0.6 mg/kg), with maintenance doses (0.15 mg/kg) as required. Neuromuscular monitoring was performed by acceleromyography. Sugammadex or neostigmine was administered at reappearance of 1–2 posttetanic counts (profound neuromuscular blockade). The primary efficacy parameter was the time from sugammadex or neostigmine–glycopyrrolate administration to return of the train-of-four ratio to 0.9.

Results: In the intent-to-treat population (n = 37 in each group), geometric mean time to recovery to a train-of-four ratio of 0.9 with sugammadex was 2.9 min *versus* 50.4 min with neostigmine–glycopyrrolate (P < 0.0001) (median, 2.7 min *vs.* 49.0 min). Most sugammadex patients (97%) recovered to a train-of-four ratio of 0.9 within 5 min after administration. In contrast, most neostigmine patients (73%) recovered between 30 and 60 min after administration, with 23% requiring more than 60 min to recover to a train-of-four ratio of 0.9.

Conclusions: Recovery from profound rocuronium-induced neuromuscular blockade was significantly faster with sugammadex *versus* with neostigmine, suggesting that sugammadex has a unique ability to rapidly reverse profound rocuronium neuromuscular blockade.

REVERSAL of nondepolarizing neuromuscular blocking agents (NMBAs) such as rocuronium and vecuronium traditionally has been achieved by using acetylcholinesterase inhibitors.¹ However, these agents cannot adequately reverse profound neuromuscular blockade.^{2,3} Acetylcholinesterase inhibitors suppress the enzymatic breakdown of acetylcholine, allowing it to accumulate and displace the NMBA molecules from the binding sites on the nicotinic receptors. If the NMBA concentration is very high, the increase in acetylcholine concentration is insufficient to displace enough NMBA molecules to reverse neuromuscular blockade.⁴

Rapid, complete, and reliable reversal of neuromuscular blockade is desirable to improve patient comfort and safety. To achieve this goal, there is general agreement that return to a train-of-four (TOF) ratio of 0.9 or greater should be achieved at the end of surgery before tracheal extubation. Despite intraoperative use of nerve stimulation to gauge depth of blockade and adequacy of reversal with acetylcholinesterase inhibitors, many patients do not achieve adequate neuromuscular recovery before tracheal extubation in the early postoperative period.⁵ The occurrence of postoperative residual neuromuscular blockade in the recovery room may result in airway obstruction, pulmonary complications,⁶ and other significant morbidity.^{5,7,8}

The administration of acetylcholinesterase inhibitors (e.g., neostigmine, edrophonium) can lead to cardiovascular, gastrointestinal, and respiratory adverse events (AEs) through undesired stimulation of muscarinic receptors,^{9,10} resulting in the need for coadministration of muscarinic antagonists such as glycopyrrolate or atropine. These agents may themselves induce AEs such as tachycardia, blurred vision, and sedation.¹¹

There is, therefore, a need for a reversal agent that can rapidly reverse neuromuscular blockade, regardless of the depth of block. Sugammadex, a modified γ -cyclodextrin, is a selective relaxant-binding agent. Sugammadex achieves rapid reversal of muscle relaxation by forming a tight complex with unbound steroidal NMBA molecules, thereby preventing their action at the neuromuscular junction.^{12,13} Dose-finding studies have shown that sugammadex rapidly and effectively reverses rocuronium-induced neuromuscular blockade, including profound blockade.^{14–21}

The aim of this phase III study was to compare the efficacy and safety of sugammadex *versus* neostigmine plus glycopyrrolate for reversal of profound rocuronium-

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or vecuronium-induced blockade. This article focuses on the rocuronium arms of the study. The findings of the vecuronium study arms have been reported separately.²²

Materials and Methods

This phase III, multicenter, randomized, parallel-group, safety assessor-blinded study, known as the Signal study (NCT00473694), was conducted at eight sites in the United States. The study protocol was approved by institutional review boards of each center, and the study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Guideline for Good Clinical Practice, and current regulatory requirements. Patients were assigned a subject allocation number in sequential order of their enrollment and were randomly assigned to a treatment group, according to a randomization schedule card prepared in advance by Schering-Plough (Roseland, New Jersey).

Patients were included if they were aged 18 yr or older with American Society of Anesthesiologists physical status I-IV and were scheduled to undergo elective surgery during general anesthesia in the supine position, using rocuronium for tracheal intubation and maintenance of neuromuscular blockade. Patients were excluded if they were expected to have a difficult airway or were known or suspected to have neuromuscular disorders that might impair neuromuscular blockade; significant renal dysfunction; a (family) history of malignant hyperthermia; or allergy to narcotics, muscle relaxants, or other medications used during anesthesia. Patients receiving medication at a dose and/or time known to interfere with NMBAs (e.g., antibiotics, anticonvulsants, magnesium salts); those in whom the use of neostigmine and/or glycopyrrolate was contraindicated; female patients who were pregnant, breast-feeding, or of child-bearing age and not using reliable birth control; and patients who had already participated in another clinical trial within 30 days of entering this study were also excluded. All patients gave written informed consent before enrollment.

Anesthesia

An intravenous cannula was inserted into a forearm vein for routine anesthetic and study drug administration. Another intravenous cannula was inserted into the opposite arm for blood sampling for safety analysis. Anesthesia was induced with an intravenous opioid and propofol and was maintained with an intravenous opioid and sevoflurane. The recommended sevoflurane concentration was less than 1.5 times the age-adjusted minimum alveolar concentration at the time of sugammadex or neostigmine administration. All other anesthetic practices were consistent with routine practices at the trial centers. The anesthetic agents and doses used were

adjusted to provide optimal patient care as determined by the anesthesiologist caring for the patient. Ventilatory support and anesthesia were appropriately maintained until recovery of neuromuscular function to a TOF ratio of 0.9 and until the patient was judged by the anesthesiologist to be ready for tracheal extubation and transfer to the postanesthesia care unit.

Neuromuscular Monitoring

Neuromuscular function was monitored using the TOF-Watch[®] SX acceleromyograph (Schering-Plough, Swords, Co., Dublin, Ireland) at the adductor pollicis muscle, starting after induction of anesthesia (before rocuronium administration) and continuing at least until recovery of the TOF ratio to 0.9. Stabilization and calibration of the acceleromyograph were performed in the operating room. After induction of anesthesia but before administration of the intubating dose of rocuronium, neuromuscular transmission monitoring was measured continually with the TOF-Watch[®] SX version 1.6 and the TOF-Watch[®] SX monitoring program version 2.1. Repetitive TOF stimulation was applied every 15 s at the ulnar nerve. Neuromuscular data were collected *via* a transducer fixed to the thumb. TOF-Watch[®] SX calibration was performed 5 min after a 5-s, 50-Hz tetanic stimulation, and this was preceded by a 1-min repetitive TOF stimulation. After calibration, a 3- to 4-min repetitive TOF stimulation was required before administration of rocuronium. This tetanic preconditioning reduced the evoked mechanical response of the muscle and thereby shortened the time required to achieve baseline stability. Central body temperature was maintained at 35°C or greater. In addition, peripheral body temperature was measured continuously by a thermistor at the thenar eminence of the palm and maintained at 32°C or greater during neuromuscular transmission monitoring. To reduce variability between study centers, the study sponsor provided practical guidance on setup, operation, maintenance, and troubleshooting of the TOF-Watch[®] SX.

Before surgical incision, patients received 0.6 mg/kg rocuronium followed by tracheal intubation, with maintenance doses of 0.15 mg/kg rocuronium as required to maintain surgical paralysis. After the T₁ response had disappeared on the TOF stimulation mode, posttetanic count (PTC) stimulation was started; the TOF-Watch[®] SX delivered a 5-s, 50-Hz tetanic stimulation. After a 3-s pause, stimulations were performed at a frequency of 1 Hz for 15 s. The TOF-Watch[®] SX automatically prevented the use of the PTC button for 2 min after a previous successful operation of PTC. When judged clinically appropriate by the anesthesiologist caring for the patient, spontaneous recovery was allowed to progress until the reappearance of 1-2 PTCs. Then, a single dose of 4.0 mg/kg sugammadex or 70 µg/kg neostigmine (total dose ≤ 5.0 mg) plus 14 µg/kg glycopyrrolate (total dose ≤ 1.0 mg) was administered. All drugs (rocu-

nium, sugammadex, and neostigmine plus glycopyrrolate) were administered over 10 s into a fast-running intravenous cannula using a three-way stopcock. Patients received only rocuronium for muscle relaxation and only a single dose of either neostigmine or sugammadex for neuromuscular reversal.

Starting before transfer to the recovery room (after tracheal extubation), patients were assessed every 15 min for clinical signs of neuromuscular recovery until discharge from the recovery room. This included an assessment of the patient's level of consciousness (awake and oriented, arousable with minimal stimulation, or responsive only to tactile stimulation). For patients considered cooperative, a 5-s head lift test and a check for general muscle weakness (using a rating scale of 1 [extreme impairment] to 9 [close to no impairment]) were performed. Patients were monitored for clinical evidence of residual neuromuscular blockade or reoccurrence of neuromuscular blockade (respiratory problems or, as measured only up to the point a patient awakened, a significant decrease in the TOF ratio to < 0.8) in the postoperative period until discharge. Respiratory rate and pulse oximetry were monitored for 60 min or more after recovery of the TOF ratio to 0.9.

Efficacy Endpoints

The primary efficacy parameter was time from start of sugammadex or neostigmine administration until recovery of the TOF ratio to 0.9. Secondary efficacy variables included time from sugammadex or neostigmine administration to recovery of the TOF ratio to 0.7 and 0.8, and clinical signs of recovery.

Safety Assessments

A blinded safety assessor (who was not involved in randomization of the patients or in the preparation or administration of trial medication, or allowed in the operating room during surgery) performed a physical examination before surgery and during the postanesthetic visit (day after surgery and ≥ 10 h after sugammadex or neostigmine administration). Vital signs (blood pressure and heart rate measured noninvasively in the supine position) were recorded at regular intervals during the study, including before surgery; at 2, 5, 10, and 30 min after sugammadex or neostigmine administration; and at the postanesthetic visit.

Blood samples were collected before administration of rocuronium, 4–6 h after administration of sugammadex or neostigmine, and at the postanesthetic visit for assessments of blood counts and biochemistry. Urine samples, collected up to 24 h preoperatively and at the postanesthetic visit, were assessed for standard urinalysis. All laboratory testing was performed centrally by BARC USA (Lake Success, NY).

The blinded safety assessor also monitored all patients for AEs, including serious AEs (SAEs) on the day after

surgery and at follow-up, 7 days after surgery. All AEs and SAEs were coded using MedDRA[®] (International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland) version 9.1. Serious trial procedure-related events and medical-device reporting events also were recorded. AEs were defined as drug related if the investigator considered them to be definitely, probably, or possibly related to the study drug.

Statistical Analysis

The primary efficacy analysis was based on the intent-to-treat population, comprising all randomized subjects who had received sugammadex or neostigmine and had at least one efficacy assessment. In case of missing data, imputed data were used for the efficacy analysis. For imputation of missing times from the start of administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.7, 0.8, and 0.9, a conservative approach for sugammadex was applied. (See appendix 1 for the method for imputation of missing recovery times.)

A two-way analysis of variance model with treatment group, center, and treatment-by-center interaction terms was used to analyze time from sugammadex or neostigmine administration to recovery of the TOF ratio to 0.7, 0.8, and 0.9. It was expected that the variance of recovery times after administration of sugammadex and neostigmine would differ; therefore, the analysis of variance was applied to logarithm-transformed values.^{23,24} A *P* value of 0.05 or less was considered statistically significant. When log-transformed data are statistically analyzed in this way, the *P* values derived from this analysis are related to the comparison of the two geometric means, *i.e.*, is the ratio of the two geometric means different from one (alternative hypothesis) or not (null hypothesis)?

The recovery times in both groups followed a skewed distribution, and because large observations are known to have a major influence on the arithmetic mean, this summary measure is prone to sampling error.²⁵ In contrast, the geometric mean is robust against large observations arising from data with a skewed distribution and is justified in the current study.²⁵ The recovery times from administration of sugammadex or neostigmine to a TOF ratio of 0.7, 0.8, or 0.9 were, therefore, summarized using the geometric mean, with corresponding two-sided 95% confidence intervals, as well as the median with interquartile and overall ranges. The geometric mean was calculated by first taking the logarithm of each recovery time (to TOF 0.7, 0.8, or 0.9), then calculating the arithmetic mean of the logarithm-transformed data, and finally transforming the mean back to the original time scale by taking the antilogarithm. For categorical variables, frequency counts and percentages were presented.

An all-subjects-treated group was used for the safety analysis, comprising all randomized subjects who received a dose of study medication.

To achieve 95% power to detect a difference of 5 min or greater between treatment groups, and assuming an SD of 1.5 min in the sugammadex and 7.0 min in the neostigmine group, 30 patients were needed per group. Assuming that 5% of patients might be excluded from the intent-to-treat population, a sample size of 32 patients/group was required.

An interim analysis of the primary efficacy variable was planned when 10 patients from each group had completed the study and provided data. Statistical evaluation of the primary efficacy variable was conducted using validated data for the intent-to-treat population, using imputed data in the case of missing values. The Hwang-Shih-de Cani method was used; the interim analysis was conducted at a significance level of 0.0025 (one-sided).²⁶ The results of the interim analysis were assessed by a Data and Safety Monitoring Board, who were to make a recommendation to stop the neostigmine arm early if there were marked differences in efficacy between treat-

ment arms. Enrollment continued into both groups during the data analysis and deliberations of the Data and Safety Monitoring Board.

Results

The trial was conducted between November 2005 and November 2006. Eighty-eight patients were randomized in the rocuronium arm of the study, 48 to sugammadex and 40 to neostigmine (fig. 1). The number of patients randomized at each center is shown in appendix 2. After interim analysis, and recommendation by the Data and Safety Monitoring Board, the neostigmine group was discontinued because of marked differences in efficacy between treatments, although by this time 40 patients had already been randomized into the neostigmine group.

Fourteen patients (sugammadex, $n = 11$; neostigmine, $n = 3$) discontinued the study (fig. 1). Thirteen of these

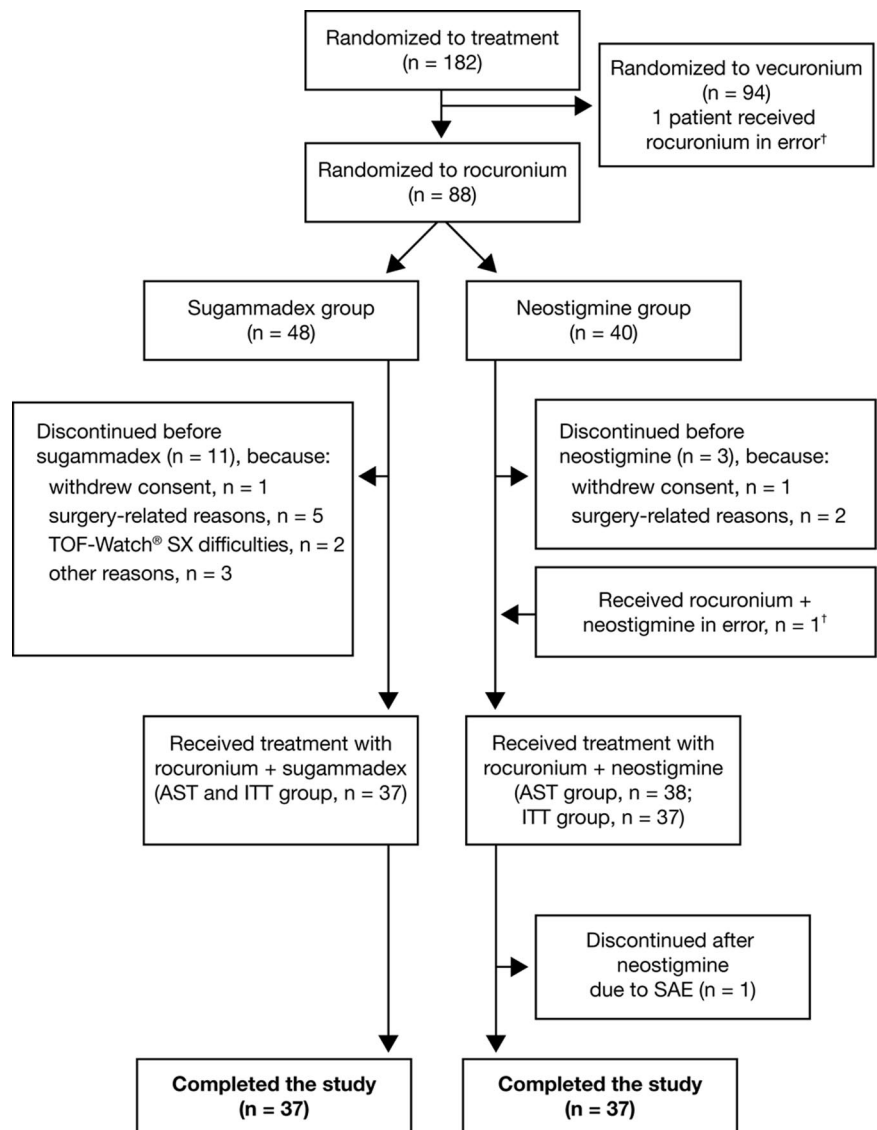


Fig. 1. Patient disposition of those randomized to the rocuronium arm of the study (patients treated with vecuronium are not described in this article). † According to the randomization schedule, this patient should have received vecuronium plus sugammadex. She was included in the all-subjects-treated (AST) population here as treated with rocuronium plus neostigmine but not the intent-to-treat (ITT) population. SAE = serious adverse event; TOF = train-of-four.

Table 1. Baseline Characteristics (All-subjects-treated Population, n = 75)

	Sugammadex, n = 37	Neostigmine, n = 38
Sex, n (%)		
Male	16 (43)	17 (45)
Female	21 (57)	21 (55)
Age, mean (SD), yr	52 (14)	54 (11)
Weight, mean (SD), kg	90 (32)	85 (23)
Height, mean (SD), cm	170 (10)	169 (10)
Race, n (%)		
Asian	0	3 (8)
Black (of African heritage)	3 (8)	1 (3)
White/Caucasian	32 (86)	34 (89)
Other	2 (5)	0
ASA physical status, n (%)		
I	3 (8)	3 (8)
II	25 (68)	30 (79)
III	9 (24)	5 (13)
IV	0	0

ASA = American Society of Anesthesiologists.

discontinued before receiving rocuronium or study drug, primarily for surgery-related reasons; one patient in the sugammadex group discontinued after receiving rocuronium prematurely. Patients who discontinued before receiving study drug were not included in the all-subjects-treated or intent-to-treat populations of the study. One patient randomized to the vecuronium-sugammadex arm received rocuronium-neostigmine and was included in the rocuronium-neostigmine all-subjects-treated group here; however, because treatment was not given according to randomization, this patient was excluded from the intent-to-treat group. Therefore, the all-subjects-treated group comprised 75 patients (sugammadex, n = 37; neostigmine, n = 38) and the intent-to-treat group comprised 74 patients (n = 37 in each group; fig. 1).

Treatment groups were generally comparable with respect to baseline characteristics (table 1). The median (range) age was 51 (19–85) yr in the sugammadex group and 54 (30–73) yr in the neostigmine group. Most patients were American Society of Anesthesiologists physical status II and none were American Society of Anesthesiologists physical status IV.

The median (range) intubating dose of rocuronium was 0.6 (0.56–0.64) mg/kg in the sugammadex group and 0.6 (0.57–0.61) mg/kg in the neostigmine group. Two sugammadex patients and three neostigmine patients did not receive maintenance doses of rocuronium. In those patients receiving maintenance doses of rocuronium, a median of 4 (range, 1–12) maintenance doses were given in the sugammadex group and a median of 2 (range, 1–7) were given in the neostigmine group. The median maintenance dose of rocuronium was 0.15 (0.12–0.18) mg/kg in the sugammadex group and 0.15 (0.07–0.16) mg/kg in the neostigmine group. Some patients (n = 8 in the sugammadex group and n = 3 in the

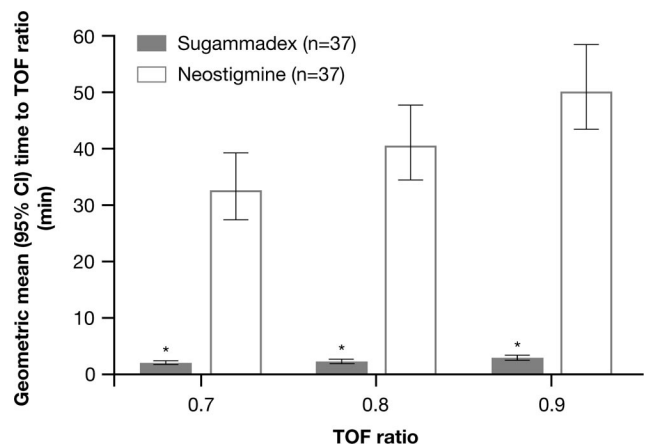


Fig. 2. Time from start of administration of sugammadex or neostigmine to recovery of the train-of-four (TOF) ratio to 0.7, 0.8, and 0.9 (intent-to-treat population, imputed data, n = 74). * $P < 0.0001$ versus neostigmine. CI = confidence interval.

neostigmine group) received study drug in the 3, 4, or 5 PTC range after the last dose of rocuronium.

Efficacy Results

One sugammadex-treated patient and 15 neostigmine-treated patients had missing times for recovery of the TOF ratio to 0.9, because a TOF ratio of 0.9 was not reached during the observation period. In addition, the time to recovery of the TOF ratio to 0.9 was considered unreliable in six sugammadex patients (as determined by the Central Independent Adjudication Committee due to errors with the TOF-Watch[®] SX). Using imputed data (both groups n = 37), geometric mean time from start of administration of study drug to recovery of TOF ratio to 0.9 was significantly ($P < 0.0001$) faster in the sugammadex group than in the neostigmine group (fig. 2). The median (range [interquartile range]) time to recovery of the TOF ratio to 0.9 was 2.7 (1.2–16.1 [2.1–4.1]) min in the sugammadex group versus 49.0 (13.3–145.7 [35.7–65.6]) min in the neostigmine group.

The faster time to recovery in the sugammadex group is also represented in figure 3, which compares the percentage of patients reaching a TOF ratio of 0.9 in each of the groups versus time after administration of sugammadex or neostigmine. Based on patients with data available (sugammadex group, n = 30; neostigmine group, n = 22), most sugammadex patients (70%) recovered within 3 min of administration of study drug, and all except one recovered within 5 min. The remaining sugammadex patient had a time from sugammadex administration to a TOF ratio of 0.9 of 16.1 min. In contrast, most neostigmine patients (73%) recovered 30–60 min after administration, with 23% taking more than 60 min to achieve a TOF ratio of 0.9.

Likewise, geometric mean times from start of administration of study drug to recovery of TOF ratio to 0.7 and 0.8 were significantly ($P < 0.0001$) faster in the sugammadex group than in the neostigmine group (fig. 2). The

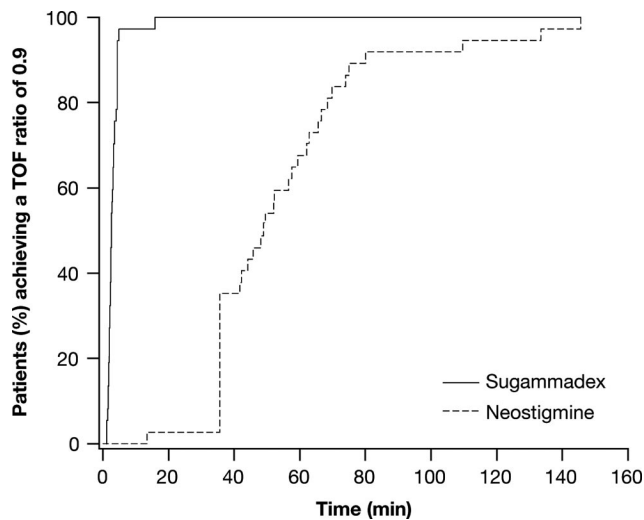


Fig. 3. Time to recovery of the train-of-four (TOF) ratio to 0.9 from profound rocuronium-induced neuromuscular blockade after administration of sugammadex or neostigmine (intent-to-treat population, imputed data, n = 74).

median (range [interquartile range]) times to recovery of the TOF ratio to 0.7 and 0.8 with sugammadex were 1.8 (1.0–7.8 [1.4–3.1]) and 2.3 (1.1–10.1 [1.6–3.3]) min, respectively, and those with neostigmine were 32.1 (9.3–123.2 [19.0–47.8]) and 40.9 (11.3–143.7 [26.3–56.1]) min, respectively.

After tracheal extubation and before transfer to the recovery room, 26 (70%) of 37 sugammadex patients and 20 (59%) of 34 neostigmine patients who had assessments were awake and oriented. Apart from 3 sugammadex patients and 5 neostigmine patients, all patients were cooperative, and most cooperative patients could perform the 5-s head lift test (33 of 34 sugammadex patients; 28 of 30 neostigmine patients) and had no signs of general muscle weakness (31 of 34 sugammadex patients; 25 of 30 neostigmine patients).

Before discharge from the recovery room, clinical signs of recovery were similar in both groups. Apart from one neostigmine patient, all were awake and oriented. All patients in both groups were cooperative and could perform the 5-s head lift. Two sugammadex and three neostigmine patients had signs of mild muscle weakness before discharge from the recovery room (graded as recovery of strength to ≥ 7 out of 10 on the general muscle weakness scale). All of these patients had contributing factors that may increase the likelihood of postoperative weakness (concomitant medications, decrease in potassium levels, and/or postoperative pain).

Safety Results

Adverse events were reported in 36 (97.3%) of 37 sugammadex patients and 37 (97.4%) of 38 neostigmine patients. The most frequently reported AEs are summarized in table 2 and included procedural pain, nausea, and incision-site complications. SAEs were reported for

Table 2. Adverse Events Occurring in at Least 10% of Patients in Either Treatment Group, Regardless of Relation to Study Drug (All-Subjects-treated Population, n = 75)

Adverse Event	Sugammadex, n = 37	Neostigmine, n = 38
Procedural pain	26 (70.3)	29 (76.3)
Nausea	14 (37.8)	19 (50.0)
Incision site complication	9 (24.3)	8 (21.1)
Postprocedural nausea	7 (18.9)	5 (13.2)
Vomiting	5 (13.5)	7 (18.4)
Flatulence	6 (16.2)	2 (5.3)
Procedural complication	2 (5.4)*	6 (15.8)†
Insomnia	5 (13.5)	4 (10.5)
Dizziness	0	5 (13.2)
Muscular weakness	4 (10.8)	3 (7.9)
Headache	3 (8.1)	4 (10.5)
Pharyngolaryngeal pain	3 (8.1)	4 (10.5)
Pruritus	3 (8.1)	4 (10.5)

* Both cases of mild tachycardia. † Includes five cases of tachycardia (four mild and one moderate) and one case of mild sinus bradycardia.

two patients in the sugammadex group (postoperative infection and postoperative ileus) and three patients in the neostigmine group (nausea/pain/dyspnea, gastric perforation/procedural complication, and postoperative ileus). No SAE was considered study drug related. Only one patient (neostigmine group) discontinued from the study because of two SAEs (gastric perforation/procedural complication) and subsequently recovered. There were no deaths, serious trial procedure-related events, or medical-device reporting events during the trial.

Ten sugammadex-treated patients (27.0%) and 12 neostigmine-treated patients (31.6%) experienced AEs that were considered to be definitely, probably, or possibly related to study drug. Drug-related AEs in the sugammadex group were muscle weakness (n = 3), nausea (n = 2), vomiting (n = 2), postprocedural nausea (n = 2), and one case each of procedural hypertension, postprocedural complication, increased blood creatine phosphokinase, increased body temperature, headache, pruritus, and paresthesia. Drug-related AEs in the neostigmine group were nausea (n = 5), muscle weakness (n = 3), procedural complications (n = 3), vomiting (n = 2), postprocedural nausea (n = 2), and one case each of chest discomfort, incision-site complication, procedural hypertension, dizziness, restlessness, decreased blood total protein, hyperhidrosis, and pruritus. No patient discontinued because of a drug-related AE. All patients with muscle weakness listed as an AE could perform the 5-s head-lift test during the initial assessment of clinical signs of recovery, and all but one patient, in whom the TOF trace was considered to be unreliable, were able to reach a TOF ratio of 0.9. Moreover, in all patients, there were other contributing factors: one sugammadex patient received furosemide postoperatively; one sugammadex patient received furosemide and had a decrease in potassium levels despite receiving potassium chloride preoperatively; and two sugammadex patients and all

three neostigmine patients had postoperative pain, which may result in a feeling of weakness.

There were few differences between the sugammadex and neostigmine groups with respect to urinalysis or changes in hematology and biochemistry parameters during the study. In both treatment groups, mean leukocyte and neutrophil counts were increased at the 4- to 6-h and postanesthetic assessments. There were no other clinically meaningful changes in laboratory values. There were no clinically relevant changes in physical examination findings or blood pressure in either group.

Mean heart rate was increased compared with baseline at 2, 5, and 10 min after administration of neostigmine-glycopyrrolate, but not after sugammadex administration. However, there was no clinically significant difference between the two treatment groups with respect to percentage of patients with abnormal heart rate values (defined as heart rate ≤ 50 or ≥ 120 beats/min, and representing a decrease or an increase of at least 15 beats/min from baseline) at any assessment. No patient showed any evidence of residual neuromuscular blockade or reoccurrence of neuromuscular blockade either clinically (respiratory problems) or according to study neuromuscular transmission guidelines (significant decrease in the TOF ratio to < 0.8) measured up to the point when the patient awakened.

Discussion

In this study, 4 mg/kg sugammadex produced a significantly more rapid recovery from profound rocuronium-induced neuromuscular blockade when administered at 1-2 PTCs than neostigmine did. It is well known that acetylcholinesterase inhibitors provide only slow recovery when given during profound blockade,^{2,3} and our study confirms the ineffectiveness of neostigmine in this setting. Importantly, this is the first comparative study to demonstrate that rapid reversal of profound blockade is possible. Reversal of profound rocuronium-induced neuromuscular blockade (recovery of TOF ratio to 0.9) was achieved within a geometric mean of 2.9 min in the sugammadex group *versus* 50.4 min in the neostigmine (70 $\mu\text{g}/\text{kg}$) plus glycopyrrolate (14 $\mu\text{g}/\text{kg}$) group. This equates to a reversal time with sugammadex that is approximately 47 min or 17-fold faster than that achieved with neostigmine.

Importantly, 97% of sugammadex-treated patients had recovered to a TOF ratio of 0.9 within 5 min of administration of the reversal agent. In contrast, 73% of neostigmine-treated patients did not recover until 30-60 min, and a large proportion (23%) did not recover to a TOF ratio of 0.9 until more than 60 min after neostigmine administration. The ability of sugammadex to rapidly reverse profound rocuronium blockade is likely to have important clinical implications, proving particularly

useful during prolonged surgery in patients who require maintenance of deep neuromuscular blockade throughout the procedure, and would also be beneficial when surgery ends prematurely.²⁷

In this study, we addressed the issue of patients with missing recovery times, either because a TOF ratio of 0.9 was not reached during the monitoring period or because the TOF trace data were considered to be unreliable, by using an imputation technique. This technique provided a recovery time for the 7 patients in the sugammadex group and 15 patients in the neostigmine group with a missing time to a TOF ratio of 0.7, 0.8, and/or 0.9 using a worst-case scenario for sugammadex-treated patients and a best-case scenario for neostigmine-treated patients. The geometric mean time to recovery of the TOF ratio to 0.9 using only the collected data were 2.6 min in the sugammadex group ($n = 30$) compared with 56.0 min in the neostigmine group ($n = 22$), similar to the results of the more conservative imputed data analysis (2.9 *vs.* 50.4 min, respectively).

The dose of sugammadex used in our study (4 mg/kg) was based on phase II dose-ranging studies,¹⁶⁻¹⁸ and the doses of neostigmine and glycopyrrolate were the standard recommended doses. The findings of the current study are consistent with those from previous phase II studies showing that sugammadex provides fast and safe recovery from rocuronium-induced neuromuscular blockade,^{14-17,19,20} including profound blockade.¹⁸ The geometric mean time to achieve a TOF ratio of 0.9 with 4.0 mg/kg sugammadex in the current study (2.9 min) was comparable with the recovery time reported previously in a randomized, dose-finding study evaluating sugammadex for the reversal of profound rocuronium-induced blockade.¹⁸ In that study,¹⁸ mean recovery times (TOF ratio of 0.9) of 3.3 and 1.9 min were reported after the administration of 4.0 mg/kg sugammadex at 1-2 PTCs in patients who had received rocuronium at 0.6 or 1.2 mg/kg, respectively.

Our study also supports findings of a study by Sacan *et al.*²⁸ in which sugammadex provided more rapid reversal of moderately profound rocuronium-induced blockade compared with neostigmine and edrophonium. In that study, empirical reversal of rocuronium-induced blockade (to a TOF ratio of 0.9) at least 15 min after administration of the last dose of rocuronium was approximately 10-fold faster with 4 mg/kg sugammadex compared with neostigmine plus glycopyrrolate (mean, 1.8 *vs.* 17.4 min).²⁸ As expected, dose-finding studies evaluating 4 mg/kg sugammadex for reversal of shallow rocuronium-induced blockade (administration at reappearance of second twitch) have reported recovery times even faster (1.1-1.4 min) than those reported here.^{16,17,20}

Of the various techniques available for monitoring recovery, acceleromyography (together with clinical tests) was chosen in the current study as it provides an easy-to-use, objective assessment of the level of neuromuscu-

lar blockade.²⁹ It had also been the method of monitoring used in other studies on sugammadex,^{14–21} which allowed us to compare the results of the current study with those of other published studies. It has been suggested that the evidence for the clinical use of acceleromyography is good and that this technique is less cumbersome than mechanomyography and electromyography.³⁰ There is general agreement that a TOF ratio of 0.9 or greater should be achieved before tracheal extubation.^{5,31,32} Although recent studies suggest that a TOF ratio of 0.9 may not represent complete recovery of neuromuscular function when measured by acceleromyography,^{33,34} no patients included in a sugammadex trial to date who have achieved a TOF ratio of 0.9 using this technique have shown signs or symptoms of residual neuromuscular blockade. To improve the reliability of detecting residual neuromuscular blockade, the device was calibrated at baseline, as has been recommended in recent publications.^{32,34}

Sugammadex was well tolerated in the 37 patients who received this treatment, and its safety profile was at least comparable with that of neostigmine in the current study. Only two SAEs were reported in the sugammadex group (postoperative infection and ileus), and neither was considered related to sugammadex.

Studies have shown that in clinical practice, patients' tracheas are often extubated before complete recovery has occurred,^{35,36} leaving the patients at risk of associated postoperative complications.⁵ Residual neuromuscular blockade, which is an important cause of NMBA-associated morbidity in surgical patients,⁷ was not reported in any patients in our study. This is to be expected because patients' tracheas were not extubated until a TOF ratio of 0.9 was achieved, even though this took more than 60 min in 23% of the patients receiving neostigmine. In addition, reoccurrence of blockade was not observed in any patient in the study. Although TOF monitoring was stopped after the patient awakened because spontaneous movements precluded the collection of any further useful data, we continued to monitor the patient for signs of respiratory problems for at least 1 h after a TOF ratio of 0.9 was achieved.

Conclusions

This study demonstrates that profound neuromuscular blockade, defined as the presence of 1–2 PTCs, can be rapidly and reliably reversed by sugammadex in patients categorized as American Society of Anesthesiologists physical status I–III. Sugammadex is the first agent that permits rapid reversal of such a profound level of rocuronium-induced neuromuscular blockade. The finding that sugammadex provides a more rapid reversal of profound rocuronium-induced neuromuscular blockade than neostigmine suggests that sugammadex is a promising alternative to conventional reversal agents.

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Appendix 1: Method for Imputation of Missing Recovery Times

For imputation of missing times from the start of administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.7, 0.8, and 0.9, a conservative approach toward sugammadex was applied. This approach was considered to be conservative because relatively long recovery times were imputed for sugammadex subjects with missing recovery times and relatively short recovery times were imputed for neostigmine subjects. The method for imputation depended on availability of previous times to TOF ratios of 0.8 and 0.7.

- If, for a given subject, the time from the start of administration of study drug (sugammadex or neostigmine) to recovery of the TOF ratio to 0.9 was missing but the time to the TOF ratio of 0.8 was available, imputation of the time to a TOF ratio of 0.9 was performed as follows:
 - Sugammadex group: For all subjects randomized to receive sugammadex and with times to recovery of the TOF ratio to 0.8 and 0.9 available, the difference in time between these two recovery times was determined. The 95th percentile of these differences was calculated and added to the time to recovery of the TOF ratio to 0.8.
 - Neostigmine group: The same procedure as for sugammadex was performed, but only subjects randomized to receive neostigmine were used, and the 5th percentile of the differences in time

to recovery of the TOF ratio to 0.8 and 0.9 was calculated and added to the time to recovery of the TOF ratio to 0.8.

- If, for a given subject, the times from the start of administration of study drug to recovery of the TOF ratio to 0.8 and 0.9 were missing but the time to the TOF ratio of 0.7 was available, imputation of the time to a TOF ratio of 0.9 was performed as follows:
 - Sugammadex group: For all subjects randomized to sugammadex and with times to recovery of the TOF ratio to 0.7 and 0.9 available, the difference in time between these two recovery times was determined. The 95th percentile of these differences was calculated and added to the time to recovery of the TOF ratio to 0.7.
 - Neostigmine group: The same procedure was used as for sugammadex, but only subjects randomized to receive neostigmine were used, and the 5th percentile of the differences in time to recovery of the TOF ratio to 0.7 and 0.9 was calculated and added to the time to recovery of the TOF ratio to 0.7.
- For all subjects with missing times to recovery of the TOF ratio to 0.9, 0.8, and 0.7 in the sugammadex group, the 95th percentile of the time to recovery of the TOF ratio to 0.9 observed in all subjects randomized to receive sugammadex was imputed to give the time for recovery to a TOF ratio of 0.9. Similarly, for all patients with missing times to recovery of the TOF ratio to 0.9, 0.8, and 0.7 in the neostigmine group, the 5th percentile of the time to recovery of the TOF ratio to 0.9 observed in all subjects randomized to receive neostigmine was imputed for the recovery time to a TOF ratio of 0.9.

A corresponding procedure was followed for imputation of missing times from the start of administration of study drug to recovery of the TOF ratio to 0.8. For imputation of missing times, the 95th percentile (sugammadex) or 5th percentile (neostigmine) of the differences in time between recovery of the TOF ratio to 0.7 and 0.8 was used.

For imputation of missing times for the TOF ratio of 0.7, the 95th percentile observed time for subjects randomized to sugammadex and 5th percentile observed time for subjects randomized to neostigmine were imputed.

Appendix 2: Number of Patients Randomized at Each Center

Stanford University Medical Center, Stanford, California—14 patients randomized to the rocuronium arm and received treatment with either sugammadex or neostigmine; Saddleback Memorial Medical Center, Laguna Hills, California—15 patients randomized to the rocuronium arm; The State University of New York at Stony Brook, Health Sciences Center, Stony Brook, New York—5 patients randomized to the rocuronium arm; Duke University Medical Center, Durham, North Carolina—9 patients randomized to the rocuronium arm; Mayo Clinic, St. Luke's Hospital, Jacksonville, Florida—8 patients randomized to the rocuronium arm; University of California, San Francisco, Moffitt/Long Hospitals and Mount Zion Hospital, San Francisco, California—13 patients randomized to the rocuronium arm; Vanderbilt University Medical Center, Nashville, Tennessee—14 patients randomized to the rocuronium arm; Advocate Illinois Masonic Medical Center, Chicago, Illinois—10 patients randomized to the rocuronium arm.