Sugammadex Provides Faster Reversal of Vecuronium-Induced Neuromuscular Blockade Compared with Neostigmine: A Multicenter, Randomized, Controlled Trial

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BACKGROUND: Sugammadex, a specifically designed γ-cyclodextrin, is a selective relaxant binding drug that rapidly reverses rocuronium-induced and, to a lesser extent, vecuronium-induced neuromuscular blockade. In this study, we compared the efficacy of sugammadex and neostigmine for the reversal of vecuronium-induced neuromuscular blockade in patients scheduled for elective surgery.

METHODS: Patients aged ≥18 yr, ASA Class I–III, and scheduled for a surgical procedure under sevoflurane/opioid anesthesia received an intubating dose of vecuronium (0.1 mg/kg) and maintenance doses of 0.02–0.03 mg/kg at reappearance of the second twitch (T_2) of train-of-four (TOF) if required. Neuromuscular blockade was monitored using acceleromyography (TOF-Watch® SX, Schering-Plough Ireland, Dublin, Ireland). At end of surgery, at reappearance of T_2 after the last dose of vecuronium, patients were randomized to receive either sugammadex (2 mg/kg) or neostigmine (50 μg/kg) plus glycopyrrolate (10 μg/kg) IV. The primary efficacy end-point was time from start of administration of sugammadex or neostigmine to recovery of TOF ratio to 0.9.

RESULTS: The geometric mean time to recovery of the TOF ratio to 0.9 was significantly faster with sugammadex compared with neostigmine (2.7 min [95% confidence interval {CI}]: 2.2–3.3) versus 17.9 min [95% CI: 13.1–24.3], respectively; $P < 0.0001$). The mean recovery times to a TOF ratio of 0.8 and 0.7 were also significantly shorter with sugammadex. No serious adverse events or unexpected side effects were reported with either drug.

CONCLUSION: Sugammadex provided significantly faster reversal of vecuronium-induced neuromuscular blockade compared with neostigmine.

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Although neuromuscular blocking drugs (NMBDs) are used extensively for facilitating surgical procedures and tracheal intubation during anesthesia, concerns have been raised about the risks of postoperative residual neuromuscular blockade, which may be associated with airway obstruction, pulmonary complications, hypoxia, and increased mortality.[1–3] Rapid and complete reversal of neuromuscular blockade at the end of surgery is therefore mandatory.

Acetylcholinesterase inhibitors, such as neostigmine and edrophonium, are used for the reversal of nondepolarizing neuromuscular blockade, but they carry a risk of unwanted effects, such as bradycardia, hypotension, bronchoconstriction, hypersalivation, and possibly nausea and vomiting.[4,5] Anticholinergic drugs, such as atropine or glycopyrrolate, are therefore coadministered to counteract these adverse effects but they may also cause their own side effects, such as tachycardia, blurred vision, sedation, and possibly mild confusion, and should be used with care in the elderly[6] and in patients with cardiovascular disease. Because of these limitations, there is a need

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The design and conduct of the study, as well as analysis of the study data and opinions, conclusions, and interpretation of the data, were the responsibility of the authors.

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for new reversal drugs with an improved tolerability profile.

Sugammadex, a water-soluble, modified γ-cyclodextrin, is a novel drug developed specifically for the rapid reversal of neuromuscular blockade induced by the steroidal NMBD rocuronium. Sugammadex acts by encapsulating unbound rocuronium and, to a lesser extent, also vecuronium molecules, and reducing the free NMBD fraction at the neuromuscular junction.[7,8] Studies in surgical patients have demonstrated that sugammadex rapidly and effectively reverses rocuronium-induced neuromuscular blockade.[9–12] The effects of vecuronium, a compound very similar to rocuronium, can also be reversed by sugammadex.[11,13,14] However, only few patients[11] have received the recommended dose of 2 mg/kg sugammadex after vecuronium so far, and clearly more data are needed for the above combination because this NMBD is (still) used widely around the world.

The present two-armed study was designed to compare the efficacy and side effects of sugammadex versus neostigmine, the current standard reversal drug, for rocuronium- or vecuronium-induced neuromuscular blockade in patients scheduled for elective surgery under sevoflurane anesthesia. Because only insufficient amounts of data are available for sugammadex reversal of rocuronium,* this paper focuses on the vecuronium arm of the study. Sevoflurane anesthesia was chosen because it is an inhaled drug widely used in clinical practice.

The primary objective of this study was to compare recovery from vecuronium-induced neuromuscular blockade with sugammadex to that with neostigmine, and the secondary objective was to evaluate the side effects of a single dose of sugammadex 2 mg/kg or neostigmine 50 μg/kg (plus glycopyrrolate) in adult patients.

METHODS

Study Design and Patient Selection

This was a multicenter, randomized, active control, safety assessor-blinded trial conducted at 13 sites in Austria, Belgium, Germany, Italy, Spain, Sweden, and the United Kingdom between November 2005 and March 2006. The trial protocol was approved by the Independent Ethics Committee of each center and conducted according to the revised Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and applicable regulatory requirements. The trial has been registered on clinicaltrials.gov (identifier NCT00451217).

Patients were eligible for entry into the trial after giving written informed consent if they were aged ≥18 yr, ASA Class I–III, and scheduled for a surgical procedure under general anesthesia in a supine position requiring tracheal intubation. Exclusion criteria included anticipation of a difficult airway, known or suspected neuromuscular disorders, significant renal dysfunction, known or suspected family history of malignant hyperthermia, and allergies to narcotics, muscle relaxants, or other medication used during general anesthesia. Patients receiving medication at a dose and/or timepoint likely to interfere with NMBDs and in whom the use of neostigmine and/or glycopyrrolate could be contraindicated were also excluded, as were those who had already participated in a previous sugammadex trial. Female patients who were pregnant, breast feeding, or of child-bearing age using only hormonal contraception or no means of birth control were also excluded.

Randomization schedules were prepared by Schering-Plough. The randomization codes were entered into a central randomization system that was part of a secured trial website, during the set up of this system. All enrolled patients were allocated a subject number in sequential order of their enrollment into the trial and received a treatment code using the central randomization system.

Study Procedures

An IV cannula was inserted into a vein of the forearm for the administration of anesthetic drugs, vecuronium, and sugammadex or neostigmine. A second IV cannula was inserted into the opposite arm for blood sampling (safety analysis) at predefined timepoints during and after anesthesia. Standard monitoring consisted of electrocardiogram, noninvasive arterial blood pressure measurements, and pulse oximetry, as well as end-tidal CO_2 and sevoflurane measurements.

Anesthesia was induced with an IV opioid (choice was left to the discretion of the investigator) and IV propofol, and maintained using sevoflurane at 1–2 minimum alveolar anesthetic concentration (MAC) end-tidal and opioids, according to each patient's need. After induction of anesthesia but before administration of vecuronium, monitoring of neuromuscular activity was started using acceleromyography (TOF-Watch® SX, Schering-Plough Ireland, Dublin, Ireland) at the adductor pollicis muscle. Repetitive train-of-four (TOF) stimulation was applied at the ulnar nerve at the wrist every 15 s until the end of anesthesia, or at least until recovery of the TOF ratio to 0.9. Stabilization and calibration of the TOF-Watch SX were performed according to good clinical research practice in pharmacodynamic studies of NMBD.[15] During that time (3–10 min) patients' lungs were ventilated via face mask with oxygen/air at normocapnia. Neuromuscular data were collected via a transducer fixed to the top of the thumb using the TOF-Watch SX Monitoring Program. After set-up and stabilization of the TOF-Watch SX, a single bolus dose of IV vecuronium

*Some data from the rocuronium arm of the study have been presented. Blobner M, Eriksson L, Scholz J, Hillebrand H, Pompei L. Sugammadex (2.0 mg/kg) significantly faster reverses shallow rocuronium-induced neuromuscular blockade compared with neostigmine (50 mcg/kg). Eur J Anaesthesiol 2007;24(suppl 39):125.

0.1 mg/kg was administered within 10 s into a fast-running infusion, and tracheal intubation was performed after onset of complete blockade. Maintenance doses of vecuronium (0.02–0.03 mg/kg) could be administered as needed at reappearance of the second twitch (T_2) of the TOF (as indicated by the TOF-Watch SX) if clinically required.

At reappearance of T_2 after the last dose of vecuronium, either sugammadex 2 mg/kg (the recommended dose for reversal of shallow vecuronium) or neostigmine 50 μg/kg[16] (to a maximum of 5 mg) plus glycopyrrolate 10 μg/kg were administered in a randomized order as an IV bolus within 10 s. The sevoflurane concentration at the time of reversal was maintained at <1.5 of MAC (0.3–2.8 vol % end-tidal) until recovery of the TOF ratio to 0.9. Sevoflurane was discontinued before tracheal extubation, which was only performed on recovery of the TOF ratio to 0.9. Immediately after tracheal extubation, patients' levels of consciousness were assessed; i.e., whether they were awake and orientated, 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 were performed. These evaluations were repeated every 15 min thereafter until the first head-lift test was achieved. Neuromuscular monitoring was stopped when TOF 0.9 was reached or continued until the end of surgery, depending on the length of the procedure and the preference of the anesthesiologist in charge.

Central body temperature was maintained at ≥35°C. Heart rate and noninvasive arterial blood pressure measurements were performed continuously and recorded at stable anesthesia, just before administration of vecuronium, at 2, 5, 10, and 30 min after administration of sugammadex or neostigmine and at the postanesthetic visit.

Postanesthetic oxygen saturation and respiratory rate were monitored as part of clinical routine for a minimum of 60 min in the recovery room. Three 10 mL blood samples were collected for safety analysis just before administration of vecuronium, at 4–6 h after administration of sugammadex or neostigmine and at the postanesthetic visit. Urine samples were collected for urinalysis on the day before surgery or just before leaving for the operating room and at the postanesthetic visit, and a physical examination was performed during the 7 days before surgery and at the postanesthetic visit.

Efficacy Variables

The primary efficacy variable was the time from the start of administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.9. Secondary efficacy variables included the time from the start of administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.7, time to recovery of the TOF ratio to 0.8, and assessments of clinical signs of recovery (level of consciousness, 5-s head-lift test, and general muscle weakness) before transfer to the recovery room after tracheal extubation and before discharge from the recovery room.

Safety Assessments

Safety assessments included pretreatment events (from signing informed consent until administration of sugammadex or neostigmine), serious trial procedure-related events (up to 7 days postdose), and vital signs (heart rate and arterial blood pressure) at screening, prevecuronium, presugammadex, or neostigmine and at 2, 5, 10, and 30 min postdose, and at the postanesthetic visit. Blood samples were assessed for abnormalities in routine biochemistry. Urinalysis included analysis of microalbumin, β_2-microglobulin, and *N*-acetyl glucosaminidase levels.

Adverse events and serious adverse events were recorded from the time of administration of sugammadex or neostigmine up to 7 days postdose, and any clinically significant changes on physical examination between the first assessment and the postanesthetic assessment were recorded. Clinical signs of possible residual paralysis or reoccurrence of neuromuscular block were also recorded.

Statistics

Efficacy analyses were performed using data from the intent-to-treat (ITT) population, which consisted of all randomized subjects who received sugammadex or neostigmine and had at least one efficacy measurement. Time from the start of administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.7, 0.8, and 0.9 was analyzed using a two-way analysis of variance model in which treatment group and trial site were the factors of the model. Because it was expected that the variance of recovery times after administration of sugammadex and neostigmine would differ, the analysis of variance was applied to logarithm-transformed recovery times.[17,18]† Two-sided statistical testing was done at a significance level of 5%.

A separate analysis was also performed in which missing recovery times were imputed using a conservative approach toward sugammadex. It was considered 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 (Appendix).

Because the recovery times in both groups followed a skewed distribution, and because large observations have a major influence on the arithmetic mean, this summary measure is prone to sampling error.[19] However, the geometric mean is robust against large observations arising from data with skewed distribution and was warranted in the current study.[19] Therefore, the

†When data are log-transformed and statistically analyzed in this way, the *P* values obtained in the analysis are related to comparison of the two geometric means, answering the question: is the ratio of the two geometric means different from one (alternative hypothesis) or not (null hypothesis)?

recovery times from administration of sugammadex or neostigmine to a TOF ratio of 0.7, 0.8, or 0.9 were summarized using the geometric mean (calculated by taking the logarithm of each subject's recovery time to TOF 0.7, 0.8, or 0.9, then calculating the arithmetic mean of the logarithm-transformed data, and finally transforming back into the original time scale by taking the antilogarithm). Data were also summarized using median and range values.

RESULTS

Baseline Characteristics

One hundred patients were enrolled in the study, of which 51 were randomized to the sugammadex group and 49 to the neostigmine group. Three subjects in the sugammadex group and four in the neostigmine group did not receive the study drug. Reasons for discontinuation in the sugammadex group were refusal of surgical procedure ($n = 1$) and TOF-Watch SX problems ($n = 2$). In the neostigmine group, patients were discontinued because of unavailability of site staff to perform the protocol ($n = 1$), randomization failure ($n = 1$), surgeon's withdrawal of consent for operating room time for the research team ($n = 1$), and a TOF-Watch SX problem ($n = 1$). Hence, 48 subjects in the sugammadex group and 45 in the neostigmine group were treated (representing the all-subjects-treated population). All treated patients had at least one efficacy measurement and therefore the all-subjects-treated population was equivalent to the ITT population. The treatment groups had similar baseline characteristics (Table 1).

Table 1. Baseline Characteristics (All-Subjects-Treated Population)

	Sugammadex ($n = 48$)	Neostigmine ($n = 45$)
Age (yr), mean (SD)	49 (16)	50 (15)
Weight (kg), mean (SD)	81 (19)	76 (13)
Height (cm), mean (SD)	173 (11)	170 (11)
Gender (M/F), *n* (%)	26/22 (54/46)	21/24 (47/53)
ASA Class, *n* (%)		
I	18 (38)	17 (38)
II	27 (56)	25 (56)
III	3 (6)	3 (7)

Efficacy

In the ITT population, the time from start of administration of study drug to recovery of the TOF ratio to 0.9 was estimated to be 6.6 times faster with sugammadex compared with neostigmine (95% confidence interval [CI]: 4.7–9.3). Geometric mean times (95% CI) to recovery of the TOF ratio to 0.9 were 2.7 (2.2–3.3) min after sugammadex and 17.9 (13.1–24.3) min after neostigmine ($P < 0.0001$) (Table 2). The 95th percentile of the time to recovery of the TOF ratio to 0.9 was 6.95 min in the sugammadex group and 76.15 min in the neostigmine group.

In addition, the mean times to recovery of the TOF ratio to 0.7 and 0.8 were also significantly faster with sugammadex compared with neostigmine (Table 2). The 95th percentile of the time to recovery of the TOF ratio to 0.8 was 3.7 min in the sugammadex group and 41.4 min in the neostigmine group. A comparison of results for this dataset (termed the completed cases dataset), which includes only those patients providing times to TOF ratios of 0.9, 0.8, or 0.7, was made with results for an imputed data analysis dataset (times to TOF 0.9, 0.8, or 0.7 were imputed for those patients with missing values) and shows virtually no difference between the two approaches (Table 3).

Figure 1 shows the neuromuscular recovery profile for two patients after administration of sugammadex and neostigmine. Figure 2 shows the percentage of patients who had achieved a TOF ratio of 0.9 over the course of the study. In the sugammadex group, monitoring was stopped in a median (range) of 17 (1–105) min after TOF >0.9 was attained, and 13 patients (28%) were monitored for >30 min. In the neostigmine group, the TOF recordings were stopped in a median (range) of 5 (1–177) min (five subjects [11%] for >30 min) after the last TOF evaluation. Eight patients in the neostigmine group failed to achieve a TOF ratio of 0.9 during the monitoring period. Three other neostigmine patients and two sugammadex patients are not included in Figure 2 because the time to a TOF ratio of 0.9 was not available (neuromuscular monitoring was stopped prematurely 30 min after administration of study drug in one patient in the neostigmine group) or considered unreliable ($n = 2$ in both groups). Two patients receiving sugammadex had unexpectedly long recovery times to a TOF ratio of 0.9 (20 and 64 min) but were within the normal range for time to recovery to a TOF ratio of 0.8 (4.3 and 3.7 min, respectively). Before and after reversal, the sevoflurane concentrations were similar between the two groups.

Of those subjects randomized to receive sugammadex for reversal of vecuronium-induced neuromuscular blockade, and who provided evaluable data for the time to recovery to TOF 0.9 ($n = 46$), 27 received only an intubating dose and 19 received an intubating dose plus one or more maintenance doses (range, 1–15 maintenance doses). Of the evaluable patients in the neostigmine group ($n = 34$), 27 patients received only an intubating dose of vecuronium and 7 received one or more maintenance doses (range, 1–4 maintenance doses). Geometric mean time to recovery of the TOF ratio to 0.9 after administration of sugammadex was slightly shorter in patients who received an intubating dose of vecuronium only, compared with those who received at least one maintenance dose of vecuronium, whereas recovery of the TOF ratio to 0.9 after neostigmine was considerably shorter in those who received an intubating dose only (Table 4). As no comparison of the recovery times after maintenance doses was planned in the protocol, only descriptive information can be given in the above-mentioned table.

Table 2. Time (min) from Start of Administration of Sugammadex or Neostigmine to Recovery of the Train-of-Four (TOF) Ratio to 0.9, 0.8, and 0.7 (Intent-to-Treat Population)

	Sugammadex	Neostigmine	*P*
Recovery of TOF ratio to 0.9			
N	46[a]	34[b]	< 0.0001
Geometric mean	2.7	17.9	
Median (range)	2.1 (1.2–64.2)	21.9 (2.9–76.2)	
Recovery of TOF ratio to 0.8			
N	46[a]	42[c]	< 0.0001
Geometric mean	1.9	10.8	
Median (range)	1.7 (1.0–4.3)	13.6 (2.2–59.1)	
Recovery of TOF ratio to 0.7			
N	46[a]	43[d]	< 0.0001
Geometric mean	1.6	6.4	
Median (range)	1.4 (0.7–3.4)	5.2 (1.9–54.3)	

[a] Data excluded from two patients as TOF data to 0.9, 0.8, and 0.7 were considered unreliable because of unstable TOF baseline.

[b] Data excluded from 11 patients because TOF data to 0.9 were missing (8 patients failed to achieve a TOF ratio of 0.9, 1 patient did not have a recovery time measured for TOF to 0.9, and in 2 patients the TOF data to 0.9 were considered unreliable because of unstable TOF baseline).

[c] Data excluded from three patients as TOF data to 0.8 were either missing (two patients) or considered unreliable because of unstable TOF baseline (one patient).

[d] Data excluded from two patients as TOF data to 0.7 were either missing (one patient) or considered unreliable because of unstable TOF baseline (one patient).

Table 3. Time (min) from Start of Administration of Sugammadex or Neostigmine to Recovery of the Train-of-Four (TOF) Ratio to 0.9, 0.8, and 0.7 in Completed Cases and Imputed Data (Intent-to-Treat Population)

Recovery of TOF ratio to	Analysis using	Sugammadex Geometric mean	Neostigmine Geometric mean	Estimated treatment effect[a] (95% CI)
0.9	Completed cases	2.7 ($n = 46$)	17.9 ($n = 34$)	6.6 (4.7, 9.3)
	Imputed data	2.8 ($n = 48$)	16.8 ($n = 45$)	6.7 (5.0, 9.1)
0.8	Completed cases	1.9 ($n = 46$)	10.8 ($n = 42$)	5.9 (4.4, 8.0)
	Imputed data	2.0 ($n = 48$)	10.2 ($n = 45$)	5.4 (4.0, 7.2)
0.7	Completed cases	1.6 ($n = 46$)	6.4 ($n = 43$)	4.2 (3.1, 5.6)
	Imputed data	1.6 ($n = 48$)	6.1 ($n = 45$)	3.9 (2.9, 5.2)

CI = confidence interval.

[a] Treatment effect is defined here as the ratio of the geometric mean recovery time after neostigmine over the geometric mean recovery time after sugammadex. Estimate for treatment effect is obtained from analysis of variance on log-transformed data.

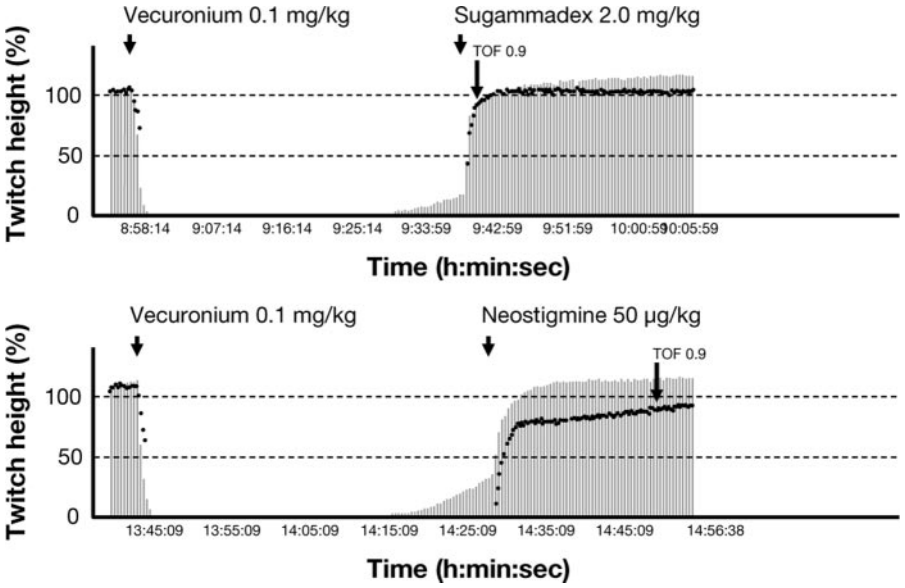

Figure 1. Examples of recovery profiles for vecuronium 0.1 mg/kg after administration of sugammadex 2.0 mg/kg or neostigmine 50 μg/kg at reappearance of second twitch (T_2). Bars represent first twitch (T_1) values (twitch height %) and dots the train-of-four (TOF [T_4/T_1]) ratio. TOF 0.9 arrow represents the time to attain a TOF ratio of 0.9 after administration of sugammadex and neostigmine, $P < 0.0001$ (for the difference between the geometric means for the two groups).

In terms of clinical signs of recovery, 29 of 48 patients (60.4%) in the sugammadex group and 26 of 45 patients (57.8%) in the neostigmine group were awake and oriented before transfer to the recovery room, and all except 7 patients in each group were cooperative. Only one patient in the sugammadex group and six in the neostigmine group were unable to perform the 5-s head lift before transfer to the recovery room, and general muscle weakness was reported in four and six patients in each group, respectively. Before discharge from the recovery room, the clinical signs of recovery were similar in

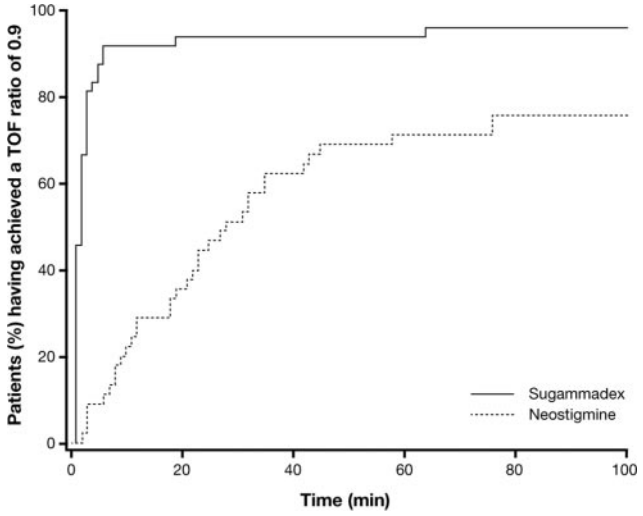

Figure 2. Percentage of patients having achieved a train-of-four (TOF) ratio to 0.9 after reversal of vecuronium-induced neuromuscular blockade with sugammadex or neostigmine (intent-to-treat population). Patients with missing data are not included. Time to TOF ratio of 0.9 = the time from start of administration of sugammadex or neostigmine to TOF ratio of 0.9.

both groups. Except for one subject in the neostigmine group, who was arousable with minimal stimulation, all patients were awake and oriented, cooperative, and able to perform the 5-s head lift, and none had general muscle weakness.

Safety

There were no serious adverse events or serious trial procedure-related events in this study. No patients discontinued from the trial because of an adverse event. Seventeen patients experienced one or more adverse events that were considered by the investigator to be possibly, probably, or definitely related to study drug: 7 (14.6%) in the sugammadex group and 10 (22.2%) in the neostigmine group.

Drug-related adverse events occurring in each group are summarized in Table 5. All of these were mild or moderate in nature except for two events in the neostigmine group that were classified by the investigator as severe: one case of prolonged neuromuscular blockade and one sleeping disorder. None of the drug-related events was reported as a serious adverse event.

Overall, there were no marked differences in routine laboratory variables between the sugammadex and neostigmine groups.

Mean values for systolic and diastolic blood pressure and heart rate from the screening visit to the postanesthetic visit were similar in both treatment groups. Higher mean diastolic blood pressure at 2 min postdose with neostigmine (64 vs 59 mm Hg) and a faster heart rate with neostigmine at 2 min (74 vs 61 bpm) and 5 min postdose (70 vs 62 bpm) compared with sugammadex were observed (Figs. 3 and 4). Central body temperature was maintained at ≥35°C in all patients except one in the neostigmine group and two in the sugammadex group. As the temperature deviations were only minor and for short periods, these were not considered to have an effect on recovery in these patients.

There was no clinical evidence of reoccurrence of neuromuscular block or residual neuromuscular blockade in either group.

DISCUSSION

The results of this randomized, actively controlled study demonstrate that sugammadex achieves reversal of vecuronium-induced neuromuscular blockade significantly more rapidly than neostigmine. The (geometric) mean times to achieve a TOF ratio of 0.9 with sugammadex and neostigmine were 2.7 and 17.9 min, respectively, resulting in a reversal time that was almost seven times faster with sugammadex compared with neostigmine.

The results presented are for completed cases only; that is, patients for whom recovery times to the respective TOF ratio of 0.7, 0.8, or 0.9 were available. Another analysis was also done in which missing recovery times were imputed using a conservative approach for sugammadex and a best-case scenario for neostigmine. There was no statistical difference between the completed cases analysis reported here and the imputed data analysis.

The geometric mean time to reversal of neuromuscular blockade (TOF of 0.9) with sugammadex 2.0

Table 4. Time (min) from Start of Administration of Sugammadex or Neostigmine to Recovery of the Train-of Four (TOF) Ratio to 0.9 for Patients Who Received an Intubating Dose Only and Those Who Received at Least One Maintenance Dose of Vecuronium (Exploratory Analysis of the Intent-to-Treat Population)

	Sugammadex group		Neostigmine group	
	Intubating dose only	Intubating dose and maintenance dose	Intubating dose only	Intubating dose and maintenance dose
Recovery of TOF ratio to 0.9				
N	27[a]	19[a]	27[b]	7[b]
Geometric mean	2.3	3.5	15.9	28.0
Median (range)	1.9 (1.2–64.2)	3.4 (1.7–19.8)	18.9 (2.9–76.2)	35.7 (6.2–76.2)

[a] Data excluded from one patient in each group of the sugammadex cohort ($n = 48$) because TOF data to 0.9 were considered unreliable.

[b] Data excluded from five patients in the intubating dose only group and six patients in the intubating plus maintenance doses group of the neostigmine cohort ($n = 45$) either because the time to recovery data were unavailable or because the TOF data to 0.9 were considered unreliable.

Table 5. Incidence (Number [%] of Patients) of Drug-Related[a] Adverse Events (All-Subjects-Treated Population)

	Sugammadex ($n = 48$)	Neostigmine ($n = 45$)
Chills	2 (4.2)	0 (0)
Nausea	2 (4.2)	2 (4.4)
Procedural hypertension	2 (4.2)	1 (2.2)
Vomiting	2 (4.2)	0 (0)
Vertigo	1 (2.1)	0 (0)
Headache	1 (2.1)	0 (0)
Retching	1 (2.1)	0 (0)
Airway complication of anesthesia	1 (2.1)	0 (0)
Postprocedural nausea	1 (2.1)	0 (0)
Hot flush	1 (2.1)	0 (0)
Body temperature increased	1 (2.1)	0 (0)
Procedural complication (i.e., increased/ decreased heart rate)	0 (0)	4 (8.9)
Dry mouth	0 (0)	4 (8.9)
Neuromuscular blockade prolonged	0 (0)	2 (4.4)
Supraventricular extrasystoles	0 (0)	1 (2.2)
Ventricular extrasystoles	0 (0)	1 (2.2)
Sleep disorder	0 (0)	1 (2.2)
Erythema	0 (0)	1 (2.2)
γ-Glutamyltransferase increased	0 (0)	1 (2.2)
Heart rate increased	0 (0)	1 (2.2)

[a] Considered by the investigator to be possibly, probably, or definitely related to study drug.

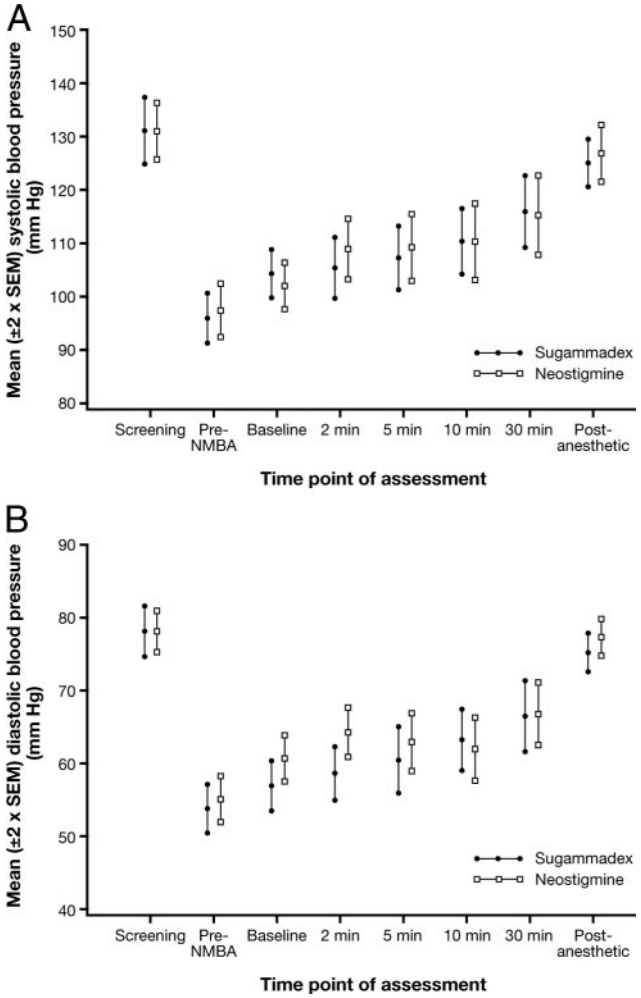

Figure 3. Mean systolic (A) and diastolic (B) blood pressure rate before (at screening, preneuromuscular blocking agent [NMBA], and baseline) and after administration (at timepoints shown) of sugammadex or neostigmine (all-subjects-treated population). SEM = standard error of the mean.

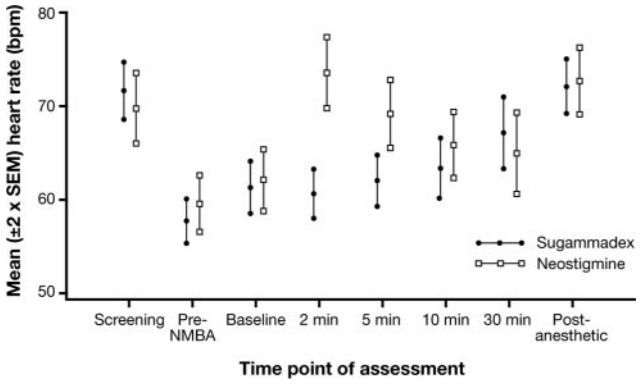

Figure 4. Mean heart rate before (at screening, preneuromuscular blocking agent [NMBA], and baseline) and after administration (at timepoints shown) of sugammadex or neostigmine (all-subjects-treated population). SEM = standard error of the mean.

mg/kg in this study was in line with the results observed previously in a dose-finding study, in which sugammadex 2.0 mg/kg administered at reappearance of T_2 was found to reverse neuromuscular blockade at a mean time of 2.3 min, after administration of the same dose of vecuronium (0.1 mg/kg) under anesthesia with a target-controlled infusion of propofol.[11] These results suggest that after vecuronium-induced neuromuscular blockade time to recovery from sugammadex administration to a TOF ratio of 0.9 is in the range of 2–3 min. In comparison, even faster recovery times, in the range of 1–2 min, have been observed for reversal of rocuronium-induced blockade with sugammadex.[9–12]

Recovery to a TOF ratio of at least 0.9 is now considered to be the "gold standard" for neuromuscular recovery after administration of NMBD.[15,19,20] For this reason, time to achieve a TOF ratio of 0.9 was selected as the primary efficacy end-point in this study. Although the use of acceleromyography is more prone to artifacts than mechanomyography, it is widely accepted for research.[15] As it is easier to use in the clinical setting, neuromuscular monitoring was performed with acceleromyography in this study, in accordance with previous sugammadex trials.

Neostigmine should only be administered when some signs of recovery from neuromuscular block occur[15,16] and therefore reappearance of T_2 (measured by the TOF-Watch SX) was chosen. This approach might enable transfer of the data obtained in this study into clinical practice. Many clinicians unfortunately still only use a peripheral nerve stimulator for monitoring of neuromuscular function and reappearance of the T_2 can

also be determined with nonquantitative monitoring devices.

Residual neuromuscular blockade may be observed in patients in the recovery room after surgery and has been shown to be associated with significant morbidity.[1,3,21,22] In one study, residual blockade defined as a TOF ratio <0.9 was reported on arrival in the recovery room in 45% of patients administered a single intubating dose of an intermediate acting NMBD without reversal, and 16% of patients had a TOF ratio as low as <0.7.[22] There was no clinical evidence of residual neuromuscular blockade in our study after reversal with either sugammadex or neostigmine. Eight patients in the neostigmine group failed to achieve a TOF of ≥0.9; sevoflurane was discontinued in these patients either because recovery took too long or surgery was finished and tracheal extubation was performed before a TOF ratio of 0.9 (and occasionally 0.8) was reached. This prolonged recovery and early tracheal extubation may be associated with a possible risk of residual paralysis. However, even after early reversal of high-dose rocuronium (1.2 mg/kg) with sugammadex, adequate TOF values were sustained,[23] with no evidence of reparalysis. Failure to achieve a TOF of ≥0.9 in some neostigmine patients in the current study may have been related to the use of sevoflurane, which has been shown to enhance the effect of NMBDs[24] and to delay reversal of neuromuscular blockade with neostigmine.[25] In contrast, all patients in the sugammadex group achieved a TOF of ≥0.9, although two patients did have unexpectedly long recovery times (20 and 64 min). A possible effect of hypothermia could be excluded because central core temperature and skin temperature above the thenar muscle remained above 35°C and 33°C, respectively. Whether this was a prolonged recovery from neuromuscular blockade or the effect of sevoflurane is unknown. Both patients recovered clinically. Previous results suggest that sevoflurane does not have an effect on the action of sugammadex when administered for reversal at T_2.[12] For one of the patients with outlying recovery times, time to achieve a TOF of ≥0.9 on three consecutive TOF stimulations was prolonged, although the TOF ratio returned to 0.7 and 0.8 after 2.2 and 3.7 min, respectively. TOF recovery was defined by the first of three consecutive TOF values. The first TOF ≥0.9 was reached at 8.7 min; the curve then varied between TOF 0.79 and 0.93 with three consecutive TOF values of ≥0.9 being reached after only 64 min. For the other patient, the TOF ratio returned to 0.7 and 0.8 after 2.3 and 4.3 min, respectively, but a plateau TOF ratio of 0.85–0.87 was observed for 10 min. Thus, the 95th percentile of the time to recovery of the TOF ratio to 0.8 was only 3.7 min in the sugammadex group, much shorter than the 95th percentile of the time to recovery of the TOF ratio to 0.9 of 6.95 min. In contrast, the 95th percentile of the time to recovery of the TOF ratio to 0.8 was 41.4 min in the neostigmine group. Although the use of sevoflurane may have influenced the recovery time as it enhances the effect of NMBDs, it was selected because it is an inhaled drug frequently used in clinical practice. Sevoflurane concentrations administered during recovery were in the same range (and always below 1.5 MAC) in both groups.

Table 4 shows that the geometric mean recovery time to TOF ratio of 0.9 for patients who received an intubating dose of vecuronium is only slightly shorter compared with patients who also received one or more maintenance doses. Because of the small number of patients who received maintenance doses, no statistical analysis was planned or performed. There was no apparent correlation between recovery time and number of maintenance doses administered. The only patient who received 15 maintenance doses of vecuronium followed by sugammadex recovered in 1.7 min, one of the fastest recovery times in the sugammadex group. Also, in the case of neostigmine, the recovery time to TOF ratio of 0.9 did not increase with an increasing number of maintenance doses.

The incidence and profile of drug-related adverse events was generally low and similar in the sugammadex and neostigmine groups, and there were no reports of serious adverse events. Overall, the incidence of drug-related adverse events was slightly higher in the neostigmine group compared with the sugammadex group (22.2% vs 14.6% of patients), and this was largely accounted for by a higher incidence of dry mouth (four cases) and procedural complications of mild-to-moderate intensity (one case of bradycardia and three cases of increased heart rate). The similar tolerability profile of sugammadex and neostigmine reported in this study was unexpected given the fact that, in contrast to neostigmine, sugammadex does not affect cholinergic transmission and is therefore unlikely to cause cholinergic side effects.[26] However, it should be noted that this study was not specifically designed to evaluate any differences between sugammadex and neostigmine in terms of cardiovascular or other side effects and therefore no comparative statistics were applied here.

Evaluation of changes in vital signs during the study do suggest, however, that sugammadex may be associated with fewer hemodynamic effects compared with neostigmine. Although the course for mean systolic blood pressure was similar in both groups, the increase in mean diastolic blood pressure at 2 min postdose was higher with neostigmine compared with sugammadex, as was the increase in mean heart rate at 2 and 5 min postdose.

In conclusion, the results of this study show that under sevoflurane anesthesia sugammadex is significantly more effective than neostigmine for recovery from neuromuscular blockade induced by vecuronium.

APPENDIX

Method for Imputation of Missing Recovery Times

In cases where times from the start of administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.7, 0.8, and 0.9 were missing, values were imputed using a conservative approach for sugammadex. Thus, relatively long recovery times were imputed for sugammadex subjects and relatively short recovery times were imputed for neostigmine subjects with missing recovery times.

Cases Where Times to TOF Ratio of 0.9 were Missing

If the time to recovery of the TOF ratio of 0.8 was available, then imputation of the time to a TOF ratio of 0.9 was performed as follows:

- Sugammadex group: for all subjects who were randomized to receive sugammadex and had times to recovery of the TOF ratio to 0.8 and 0.9, the difference between these two recovery times was determined. The 95th percentile (representing a long time interval for recovery from TOF 0.8 to 0.9) of these differences was calculated and then added to the time to recovery of the TOF ratio to 0.8.
- Neostigmine group: the same procedure as for sugammadex subjects with missing times was performed but only subjects randomized to receive neostigmine were used, the 5th percentile (representing a short time interval for recovery from TOF 0.8 to 0.9) 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 were also missing but the time to the TOF ratio of 0.7 was available, then imputation of the time to a TOF ratio of 0.9 was performed as follows:
- Sugammadex group: for all subjects who were randomized to sugammadex and had times to recovery of the TOF ratio to 0.7 and 0.9 available, the difference between these two recovery times was determined. The 95th percentile of these differences was calculated and then added to the time to recovery of the TOF ratio to 0.7.
- Neostigmine group: the same procedure as for sugammadex subjects was performed, but only subjects randomized to receive neostigmine were used, 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 sugammadex-treated patients where the times to recovery of the TOF ratio to 0.9, 0.8, and 0.7 were unavailable, the imputed time for recovery to a TOF ratio of 0.9 was the 95th percentile of the time to recovery of the TOF ratio to 0.9 observed in all subjects randomized to receive sugammadex. Similarly, for all neostigmine-treated patients where the time to recovery of the TOF ratio to 0.9, 0.8, and 0.7 was unavailable, the imputed time for recovery to a TOF ratio of 0.9 was the 5th percentile of the time to recovery of the TOF ratio to 0.9 observed in all subjects randomized to receive neostigmine.

Cases Where Times to TOF Ratio of 0.8 were Missing

Imputation of missing times from the start of administration of study drug to recovery of the TOF ratio to 0.8 followed a corresponding procedure to that used for missing times to a TOF ratio of 0.9: 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.

Cases Where Times to TOF Ratio of 0.7 were Missing

The 95th percentile observed time for subjects randomized to sugammadex and 5th percentile observed time for subjects randomized to neostigmine were imputed for subjects in whom the time to recovery of the TOF ratio to 0.7 was unavailable.

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