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Reversal of Profound, High-dose Rocuronium–induced Neuromuscular Blockade by Sugammadex at Two Different Time Points

An International, Multicenter, Randomized, Dose-finding, Safety Assessor–blinded, Phase II Trial

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Background: **Sugammadex (Org 25969), a novel, selective relaxant binding agent, was specifically designed to rapidly reverse rocuronium-induced neuromuscular blockade. The efficacy and safety of sugammadex for the reversal of profound, high-dose rocuronium-induced neuromuscular blockade was evaluated.**

Methods: **A total of 176 adult patients were randomly assigned to receive sugammadex (2, 4, 8, 12, or 16 mg/kg) or placebo at 3 or 15 min after high-dose rocuronium (1.0 or 1.2 mg/kg) during propofol anesthesia. The primary endpoint was time to recovery of the train-of-four ratio to 0.9. Neuromuscular monitoring was performed using acceleromyography.**

Results: **Sugammadex administered 3 or 15 min after injection of 1 mg/kg rocuronium decreased the median recovery time of the train-of-four ratio to 0.9 in a dose-dependent manner from 111.1 min and 91.0 min (placebo) to 1.6 min and 0.9 min (16 mg/kg sugammadex), respectively. After 1.2 mg/kg rocuronium, sugammadex decreased time to recovery of train-of-four from 124.3 min (3-min group) and 94.2 min (15-min group) to 1.3 min and 1.9 min with 16 mg/kg sugammadex, respectively. There was no clinical evidence of reoccurrence of neuromuscular blockade or residual neuromuscular blockade. Exploratory analysis revealed that prolongation of the corrected QT interval considered as possibly related to sugammadex occurred in one patient. Another two patients developed markedly abnormal arterial blood pressure after sugammadex that lasted approximately 15 min.**

Conclusion: **Sugammadex provides a rapid and dose-dependent reversal of profound neuromuscular blockade induced by high-dose rocuronium (1.0 or 1.2 mg/kg) in adult surgical patients.**

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SUGAMMADEX (Org 25969; NV Organon, a part of Schering-Plough Corporation, Oss, The Netherlands), a modified γ-cyclodextrin, is a novel, fast-acting, selective relaxant binding agent that was specifically designed to rapidly reverse rocuronium-induced neuromuscular blockade. Cyclodextrins are cyclic oligosaccharides, well known for their ability to encapsulate lipophilic guest molecules.[1] Sugammadex was designed to have an optimal affinity for rocuronium, and its lipophilic interior was tailored to fully encapsulate the hydrophobic steroid skeleton of rocuronium.[1] Thus, the sugammadex-rocuronium interaction reduces the amount of free rocuronium in the plasma and leads to a shift of rocuronium from the tissue compartment into the plasma, dramatically reducing the level of free rocuronium at the neuromuscular junction.[2]

In a preliminary study in 10 healthy volunteers, it was shown that a profound neuromuscular blockade can be fully reversed within 2 min when sugammadex is given 3 min after administration of rocuronium (0.6 mg/kg).[3] However, these findings do not allow definition of a dose–response relation for sugammadex when given to patients paralyzed by high-dose rocuronium (1.0 or 1.2 mg/kg). Furthermore, it is not known whether sugammadex can also reverse neuromuscular blockade after administration of high-dose rocuronium (1.0 or 1.2 mg/kg) at an early stage. High-dose rocuronium has been recommended by some authors as an effective alternative to succinylcholine for rapid-sequence intubation.[4–6] However, the use of such a large dose of rocuronium must always be balanced against its consequences, a prolonged duration of action that may put the patient at risk.[7–9]

The main objective of this study was to evaluate the dose–response relation of sugammadex given for reversal of intense, profound neuromuscular blockade in-

duced by high-dose rocuronium (1.0 or 1.2 mg/kg). A dose of 1.0 mg/kg rocuronium is the highest dose registered in Europe, and 1.2 mg/kg rocuronium is the highest dose registered in the United States. In addition, with an exploratory intention, we investigated the safety profile and tolerability of sugammadex.

Materials and Methods

Study Design and Patient Selection

A total of 176 patients were planned to participate in this international, multicenter, randomized, safety assessor–blinded, placebo-controlled, parallel, dose-finding, phase II trial conducted in six centers (Medical University of Innsbruck, Austria; University Hospital of Reutlingen, Germany; University Hospital of Münster, Germany; University Hospital Copenhagen, Denmark; University Clinics Essen, Germany; and University Hospital Herlev, Denmark). The study was approved by the relevant ethics committee of each center, and all patients were required to give written informed consent. Patients were included in the study if they had an American Society of Anesthesiologists (ASA) class of I–III, were aged 18 yr or older, and had an expected duration of surgery of at least 120 min in the supine position. Patients were excluded if they were expected to have a difficult airway; were known or suspected to have neuromuscular disorders impairing neuromuscular function and/or impaired renal function; had a (family) history of malignant hyperthermia; had any allergies to narcotics, muscle relaxants, or other drugs that may be given during anesthesia; or were receiving drugs that might interfere with neuromuscular blocking agents. Women who were pregnant, breast-feeding, or of childbearing age using pharmacologic contraceptives were also excluded from participation in the study.

Sugammadex (2, 4, 8, 12, or 16 mg/kg) or placebo was administered at two different time points: at 3 or 15 min after administration of 1.0 or 1.2 mg/kg rocuronium. In total, 24 different treatment groups were investigated (table 1).

Randomization was performed using a central randomization system, which was part of a secured trial Web site. The central randomization system was used to assign a randomization number and treatment code to each patient, which provided details of the rocuronium dose to be administered, the time point of administration, and the dose of sugammadex or placebo.

Table 1. Trial Plan of the Study Showing the Number of Subjects per Dose of Rocuronium and per Time Point of Administration

		1.0 mg/kg Rocuronium		1.2 mg/kg Rocuronium	
Dose Group	Treatment	3 min	15 min	3 min	15 min
1	Placebo	5	3	5	3
2	2 mg/kg sugammadex	11	5	11	5
3	4 mg/kg sugammadex	11	5	11	5
4	8 mg/kg sugammadex	11	5	11	5
5	12 mg/kg sugammadex	11	5	11	5
6	16 mg/kg sugammadex	11	5	11	5

Anesthesia and Neuromuscular Monitoring

Before induction of anesthesia, a preanesthetic 12-lead electrocardiogram was recorded. An intravenous cannula was then inserted into a vein in the forearm for the administration of anesthetic drugs, rocuronium, and sugammadex or placebo. Anesthesia was induced with an intravenous opioid (selected by the anesthetist) and intravenous propofol and was maintained by a continuous infusion of propofol, oxygen in air, and further doses of opioid, according to the needs of the patient.

Neuromuscular function of the adductor pollicis was monitored on the contralateral arm using the TOF-Watch® SX acceleromyograph (Organon Ireland Ltd., a part of Schering-Plough Corporation, Dublin, Ireland) according to the guidelines for Good Clinical Research Practice in pharmacodynamic studies.[10] After degreasing the skin, two pediatric surface electrodes (Neotrode®; ConMed, New York, NY) were placed above the ulnar nerve at the wrist. A 50-Hz tetanic stimulation was applied for 5 s and followed after 1 min by train-of-four (TOF) simulation every 15 s. When the response to TOF stimulation was stable, calibration and supramaximal stimulation were assured by the in-built calibration function. Rocuronium was administered when the baseline recording had been stable for at least 2 min. Data were collected continuously and transferred to a laptop computer using the TOF-Watch® SX monitoring program. Neuromuscular monitoring was continued until the end of surgery, at least until recovery of the TOF ratio to 0.9 and for a minimum of 30 min after the administration of sugammadex to evaluate reoccurrence of neuromuscular blockade.

After induction of anesthesia and attainment of a stable baseline TOF recording, the patients received an intubating dose of 1.0 or 1.2 mg/kg rocuronium according to the randomization schedule. Two minutes after rocuronium administration, another 12-lead electrocardiogram was recorded. At 3 or 15 min after the administration of rocuronium, patients received the single bolus of sugammadex (2, 4, 8, 12, or 16 mg/kg) or placebo according to the randomization. Additional 12-lead electrocardiograms were recorded 2 and 30 min after the start of sugammadex or placebo administration and at the end of anesthesia in the recovery room. Oxygen saturation and breath frequency were monitored for at least 60 min after recovery of the TOF ratio to 0.9. Patients were monitored for clinical evidence of residual neuromuscular blockade (*e.g.*, respiratory problems or a decrease in the TOF ratio) or reoccurrence of blockade from admin-

istration of sugammadex or placebo until 60 min after recovery of the TOF ratio to 0.9.

Safety Assessments

A physical examination, including a general system review, was performed up to 7 days before surgery. Vital signs (heart rate and blood pressure) were assessed at baseline, 2, 10, and 30 min after the administration of sugammadex or placebo, and at the postanesthetic visit ($\geq$ 10 h after administration of sugammadex or placebo).

The physician involved with the safety assessments was blinded to the treatment. A postanesthetic visit was performed 10–24 h after sugammadex administration and involved a physical examination, assessment of vital signs, and an interview about any problems or changes in physical status. On the seventh postoperative day, the safety assessor contacted the patients again to inquire about their physical status.

All electrocardiograms were evaluated by the investigators and sent electronically to an independent cardiologist (Covance Central Diagnostics Inc., Reno, NV), who was blinded to the treatment. The cardiologist interpreted the electrocardiograms according to Food and Drug Administration requirements. Corrected QT interval (QTc) (Bazett) prolongations greater than 500 ms or individual changes greater than 60 ms relative to the preanesthetic (control) electrocardiogram were to be reported as serious adverse events (AEs).

All AEs were reported. An AE was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of sugammadex or placebo, whether or not considered related to sugammadex or placebo. The relation of any AE to sugammadex was reported by the investigator as not related, unlikely, possibly, probably, or definitely related, and the intensity of the AE was reported as mild, moderate, or severe.

Efficacy Variables

The primary efficacy variable was the time from the start of administration of sugammadex or placebo to recovery of the TOF ratio to 0.9. Secondary efficacy variables included time from the start of administration of sugammadex or placebo to recovery of the TOF ratio to 0.7. The endpoints were defined as the first of three consecutive values equal to or above the given TOF ratio (*i.e.*, $\geq$ 0.70, $\geq$ 0.80, and $\geq$ 0.90). The incidence of reoccurrence of neuromuscular blockade after sugammadex or placebo administration was also included as an additional efficacy parameter. Reoccurrence of neuromuscular blockade was defined as a decrease in the TOF ratio to less than 0.80 for three consecutive measurements within 30 min of achieving sufficient recovery to a TOF ratio of 0.9 first. Residual neuromuscular blockade was defined as a final TOF ratio of less than 0.9.

Statistical Analysis

The proposed sample size of 11 patients per dose group (5 for placebo) for administration of sugammadex 3 min after administration of rocuronium (1.0 and 1.2 mg/kg) and 5 patients per dose group (3 for placebo) for administration of sugammadex 15 min after administration of rocuronium (1.0 and 1.2 mg/kg) was based on simulations using the results (means and SDs of recovery times of TOF ratio to 0.9) of a previous study by Sparr *et al.*[11] (additional information is available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org). Although in our study higher doses of rocuronium and sugammadex were given, it was reasonable to assume that the variation in recovery times would be comparable with that reported previously by Sparr *et al.*[11]

Analysis of the efficacy variables was performed if a patient met the following criteria: randomized, received treatment, and had at least one postbaseline efficacy assessment without any major protocol violations.

Data on the primary efficacy variable were analyzed to explore the relation between the dose of sugammadex and the time from start of administration to recovery of the TOF ratio to 0.9. The software used for analysis was SAS version 8.2 (SAS Institute Inc., Cary, NC) under Windows XP (Microsoft Corporation, Redmond, WA). Weighted nonlinear regression with SAS nonlinear procedure was used to fit the parameters of an exponential model to the observed data. An α error of less than 0.05 was considered significant for all calculations. Additional information is available on the ANESTHESIOLOGY Web site at http://www.anesthesiology.org.

This analysis was performed separately for each dose of rocuronium and for each time point of administration of sugammadex. The secondary efficacy variables were analyzed in the same way; for other data, descriptive statistics were used.

The safety analysis was performed on the all-subjects-treated group, which comprised all randomized patients who received sugammadex or placebo. The safety part of this study was performed with an exploratory intention, and no statistical tests were performed to compare differences between groups. For safety data, descriptive statistics are presented.

Results

Of the 176 patients planned for study enrollment, 2 patients were not randomized because of technical problems with the Web-based randomization system, and 1 patient was excluded before administration of sugammadex because of technical problems with the TOF-Watch® SX. Therefore, a total of 173 patients were randomized and treated and included in the all-subjects-treated group.

Two patients did not have a valid time to recovery to TOF 0.9, and four patients were excluded subsequently.

Table 2. Baseline Characteristics (All-subjects-treated Group)

n	173
Age, mean ± SD, yr	50 ± 16
Weight, mean ± SD, kg	77 ± 15
Height, mean ± SD, cm	172 ± 10
Male/female, n/n	93/80
ASA physical status, n (%)	
I	66 (38)
II	88 (51)
III	19 (11)

ASA = American Society of Anesthesiologists.

Reasons for these exclusions were administration of the incorrect sugammadex dose (8 mg/kg instead of 4 mg/kg, n = 2) and incorrect timing of sugammadex administration, and/or administration of an incorrect rocuronium dose (n = 2). Although the two patients given the wrong sugammadex dose were excluded from the efficacy analysis, they were transferred and analyzed in the 8-mg/kg group for the safety analysis.

Groups did not differ clinically significantly regarding age, weight, height, sex, and ASA physical status distribution. Their mean (± SD) age was 50 ± 16 yr, their mean (± SD) weight was 77 ± 15 kg, and their mean (± SD) height was 172 ± 10 cm. The minority of the subjects were female (93 males and 80 females). Sixty-six of 173 subjects were classified as ASA physical status I, 88 as ASA physical status II, and 19 as ASA physical status III (table 2).

Efficacy

All administered doses of sugammadex resulted in a marked reduction in time to recovery of the TOF ratio to 0.9 compared with placebo. A clear dose–response relation for time to recovery of the TOF ratio to 0.9 was observed for sugammadex when administered 3 and 15 min after 1.0 and 1.2 mg/kg rocuronium. When administered 3 min after 1.0 and 1.2 mg/kg rocuronium, respectively, the median times to recovery of the TOF ratio to 0.9 decreased from 111.1 and 124.3 min with placebo to 1.9 min or less with higher doses of sugammadex (12 or 16 mg/kg) (tables 3 and 4). When each sugammadex dose group was considered along with each time point of administration and rocuronium dose group, times to recovery of the TOF ratio to 0.9 were similar, with the exception of the 2.0-mg/kg sugammadex group (tables 3–6). When 2.0 mg/kg sugammadex was administered at 15 min for the reversal of neuromuscular blockade induced by 1.0 mg/kg rocuronium, the median time to recovery was considerably faster than after administration at 3 min or after a higher dose (1.2 mg/kg) of rocuronium (9.0 *vs.* 34.4–63.3 min) (tables 3–6). Doses of 8.0 mg/kg sugammadex or higher administered 3 min after 1.0 or 1.2 mg/kg rocuronium provided recovery to TOF ratio of 0.9 within 3.2 min. The mean recovery times for these doses ranged from 1.3 to 3.2 min, with corresponding largest upper limit of the 95% confidence interval below 4 min (tables 3 and 4). When administered 15 min after rocuronium, the doses of 8.0 or 12 mg/kg sugammadex reached recovery to a TOF ratio of 0.9 within 2.3 min. The mean recovery times for these doses ranged from 1.8 to 2.3 min, with corresponding largest upper limit of the 95% confidence interval below 3.2 min (tables 5 and 6).

For all four fits (figs. 1–4), the parameters of the nonlinear regression (*i.e.*, a, b, and c) were statistically significantly different from zero ($P < 0.05$), indicating that sugammadex was efficacious. When sugammadex was administered 3 min after 1.0 mg/kg rocuronium, the exponential model adequately described the relation between the dose of sugammadex and the time to recovery of the TOF ratio to 0.9 for all sugammadex doses except for the 2.0-mg/kg dose, for which the model underestimated the mean recovery time (fig. 1). When sugammadex was administered 15 min after 1.0 mg/kg rocuronium, the curve did not adequately fit the recovery times

Table 3. Recovery Times after an Initial Bolus Dose of 1.0 mg/kg Rocuronium, with Sugammadex or Placebo Given 3 min after Rocuronium

		Sugammadex Dose				
	Placebo	2 mg/kg	4 mg/kg	8 mg/kg	12 mg/kg	16 mg/kg
Recovery to TOF 0.7, min						
n	5	11	11	11	11	10
Mean (SD)	91.6 (27.4)	36.4 (17.2)	4.6 (1.4)	1.6 (0.7)	1.1 (0.1)	1.3 (0.5)
Median	86.8	30.4	4.2	1.4	1.1	1.1
Min–max	54.2–119.9	18.8–74.8	2.6–7.1	0.8–3.3	1.0–1.4	0.7–2.6
Recovery to TOF 0.9, min						
n	5	11	11	11	11	10
Mean (SD)	108.4 (31.2)	44.7 (22.2)	6.9 (2.9)	2.4 (1.2)	2.4 (2.1)	1.8 (1.1)
95% CI for the mean	[70; 147]	[30; 60]	[5.0; 8.9]	[1.6; 3.2]	[1.0; 3.8]	[1.0; 2.6]
Median	111.1	34.4	6.8	2.2	1.4	1.6
Min–max	63.7–144.8	23.3–94.3	3.4–11.9	1.3–4.8	1.0–7.1	0.9–4.8

Times were recorded when train-of-four (TOF) ratios of 0.7 and 0.9 were reached (n = 59).

CI = confidence interval.

Table 4. Recovery Times after an Initial Bolus Dose of 1.2 mg/kg Rocuronium, with Sugammadex or Placebo Given 3 min after Rocuronium

		Sugammadex Dose				
	Placebo	2 mg/kg	4 mg/kg	8 mg/kg	12 mg/kg	16 mg/kg
Recovery to TOF 0.7, min						
n	5	10	8	11	10	11
Mean (SD)	122.9 (36.2)	54.4 (17.3)	7.5 (2.8)	2.4 (0.9)	1.6 (0.8)	1.2 (0.2)
Median	107.5	53.5	7.4	2.6	1.3	1.3
Min–max	81.3–173.1	33.6–92.5	2.8–11.5	0.8–4.0	1.0–3.6	0.8–1.5
Recovery to TOF 0.9, min						
n	4	9	8	11	10	11
Mean (SD)	123.0 (28.5)	65.7 (24.6)	13.8 (7.6)	3.2 (1.0)	2.1 (0.9)	1.3 (0.4)
95% CI for the mean	[78; 168]	[47; 85]	[7.4; 20.2]	[2.6; 3.9]	[1.5; 2.7]	[1.0; 1.6]
Median	124.3	63.3	11.3	3.6	1.9	1.3
Min–max	87.3–156.1	36.3–117.2	5.3–28.5	1.5–4.7	1.2–4.1	0.8–2.3

Times were recorded when train-of-four (TOF) ratios of 0.7 and 0.9 were reached (n = 55/53).

CI = confidence interval.

for the first part of the curve (0–2 mg/kg) (fig. 2) because of extensive variation in the recovery times for the placebo group (58–233 min) and small variation for the 2.0-mg/kg sugammadex dose group (6.8–9.6 min). Nevertheless, the fit of the exponential part of the curve, from a sugammadex dose of 4.0–16.0 mg/kg, was good. When sugammadex was administered 3 min after 1.2 mg/kg rocuronium, the exponential model adequately described the relation, apart from the 2.0- and 12.0-mg/kg doses, for which the model slightly underestimated the mean recovery time (fig. 3). The fit of the mean recovery times was good for all sugammadex doses in the 1.2-mg/kg rocuronium 15-min group (fig. 4), although there was one outlier in the 16.0-mg/kg dose group who had a value that was higher than the estimated average recovery time for that dose group. This patient only achieved a TOF ratio of 0.9 after 16.6 min (according to the requirement of three consecutive TOF values ≥ 0.9) but achieved a TOF ratio of 0.8 within 2.1 min and a first TOF ratio of 0.9, 15 s later; however, the patient did not sustain a TOF ratio of 0.9 for three consecutive TOF stimulations until 16.6 min later. Nevertheless, there was a tendency toward a greater SD in the groups where sugammadex was administered 3 min after rocuronium (figs. 1 and 3). The convergence measure according to Bates and Watts was met and amounted to 8.747E-6, 2.265E-6, 7.432E-6, and 8.874E-7 for figures 1–4, respectively.

In all except two patients, neuromuscular monitoring was continued for 30–120 min after sugammadex administration. There was no clinical evidence of residual neuromuscular blockade or reoccurrence of neuromuscular blockade in any patient.

Safety

At least one AE was reported in 97 of 157 patients (62.0%) in the sugammadex groups and in 13 of 16 patients (81.2%) in the placebo group. The incidences of subjects with AEs in the dose groups do not indicate a dose–response relation: AEs were reported in 16 of 31 patients (52%) in the 2-mg/kg sugammadex group, and in 21 of 29 patients (72%), 17 of 34 patients (50%), 20 of

Table 5. Recovery Times after an Initial Bolus Dose of 1.0 mg/kg Rocuronium, with Sugammadex or Placebo Given 15 min after Rocuronium

		Sugammadex Dose				
	Placebo	2 mg/kg	4 mg/kg	8 mg/kg	12 mg/kg	16 mg/kg
Recovery to TOF 0.7, min						
n	3	5	4	5	5	5
Mean (SD)	81.7 (34.2)	5.3 (0.8)	3.3 (1.6)	1.3 (0.2)	1.3 (0.4)	0.9 (0.1)
Median	79.3	5.3	3.1	1.3	1.2	0.9
Min–max	48.8–117.1	4.6–6.4	1.6–5.3	1.0–1.4	0.9–1.8	0.8–1.2
Recovery to TOF 0.9, min						
n	3	5	4	5	5	5
Mean (SD)	127.4 (92.8)	8.5 (1.1)	5.5 (3.1)	1.9 (0.6)	1.8 (0.9)	0.9 (0.1)
95% CI for the mean	[−103; 358]	[7.1; 9.9]	[0.5; 10.5]	[1.2; 2.5]	[0.7; 2.9]	[0.8; 1.1]
Median	91.0	9.0	5.4	1.8	1.9	0.9
Min–max	58.3–232.8	6.8–9.6	1.8–9.3	1.0–2.4	0.9–2.9	0.8–1.2

Times were recorded when train-of-four (TOF) ratios of 0.7 and 0.9 were reached (n = 27).

CI = confidence interval.

Table 6. Recovery Times after an Initial bolus Dose of 1.2 mg/kg Rocuronium, with Sugammadex or Placebo Given 15 min after Rocuronium

		Sugammadex Dose				
	Placebo	2 mg/kg	4 mg/kg	8 mg/kg	12 mg/kg	16 mg/kg
Recovery to TOF 0.7, min						
n	3	5	5	5	5	5
Mean (SD)	111.4 (53.0)	24.2 (13.0)	3.1 (0.9)	1.6 (0.4)	1.7 (1.0)	1.2 (0.6)
Median	81.6	29.9	3.6	1.4	1.3	0.9
Min–max	79.8–172.6	4.3–35.5	1.9–3.9	1.3–2.2	0.8–3.3	0.8–2.1
Recovery to TOF 0.9, min						
n	3	5	5	5	5	5
Mean (SD)	139.6 (79.9)	42.2 (29.3)	6.0 (2.5)	2.3 (0.3)	1.8 (1.2)	4.7 (6.7)
95% CI for the mean	[−59; 338]	[5.8; 79]	[2.9; 9.0]	[2.0; 2.7]	[0.3; 3.2]	[−3.6; 13.6]
Median	94.2	41.9	5.6	2.2	1.3	1.9
Min–max	92.8–231.9	7.3–86.5	2.6–9.2	2.1–2.8	0.8–3.8	0.9–16.6

Recovery times were recorded when train-of-four (TOF) ratios of 0.7 and 0.9 were reached (n = 28).

CI = confidence interval.

32 patients (63%), and 23 of 31 patients (74%) in the 4-, 8-, 12-, and 16.0-mg/kg sugammadex groups, respectively. None of the subjects discontinued from the trial because of an AE or a serious AE. The majority of these AEs were classified as mild or moderate in intensity. Table 7 summarizes the most important AEs. The most frequently observed AEs after administration of sugammadex were anesthetic complications (18.5%), including signs characteristic of insufficient depth of anesthesia (*e.g.*, sucking, grimacing, moving, and coughing on the tube), nausea (15.3%), vomiting (11.5%), and pain (13.3%).

Twenty-two of 157 patients (14%) in the sugammadex group had at least one AE that was considered by the investigator to be possibly, probably, or definitely drug related; however, the incidence of subjects with drug-related AEs in the dose groups do not indicate a dose–response relation. The most common drug-related AEs were nausea (n = 6), vomiting (n = 6), and anesthetic complications (n = 6). All but three patients (with nausea/vomiting and QTc prolongation) had recovered from their drug-related AE at the postanesthetic visit. No patients in the placebo group experienced a drug-related AE.

Twelve patients (sugammadex n = 11, placebo n = 1) experienced a serious AE. In nine patients, this was associated with a prolongation of the QTc interval (four cases in the 16-mg/kg sugammadex group); this was considered by the investigator to be possibly related to sugammadex in one patient (4 mg/kg sugammadex). The other serious AEs included two cases of postprocedural bleeding (16 mg/kg sugammadex and placebo) and one case of asystole (4.0 mg/kg sugammadex), which were not considered to be related to sugammadex or placebo. The patient who presented with an asystole was a 61-yr-old man who underwent endoscopic sinus surgery. Rocuronium, 1.2 mg/kg, had been given, and 4 mg/kg sugammadex was given 15 min later. No electrocardiographic abnormalities had occurred before surgery began. Sixty-five minutes after sugammadex injection, immediately after the endoscope was introduced into the patient's maxillary sinus, the patient developed a brief asys-

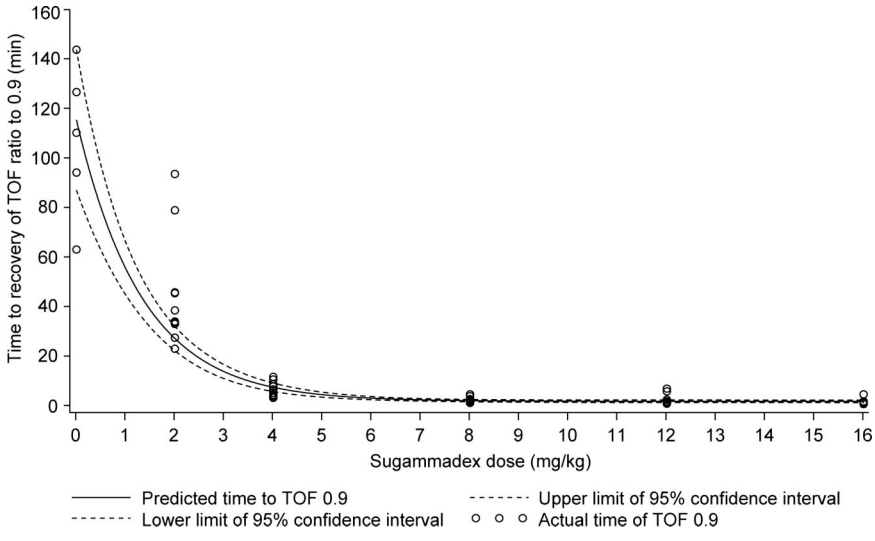

Fig. 1. Estimated dose–response relation between the time from start of administration of sugammadex to recovery of the train-of-four (TOF) ratio to 0.9 and the dose of sugammadex. Sugammadex was administered 3 min after administration of 1.0 mg/kg rocuronium, n = 59.

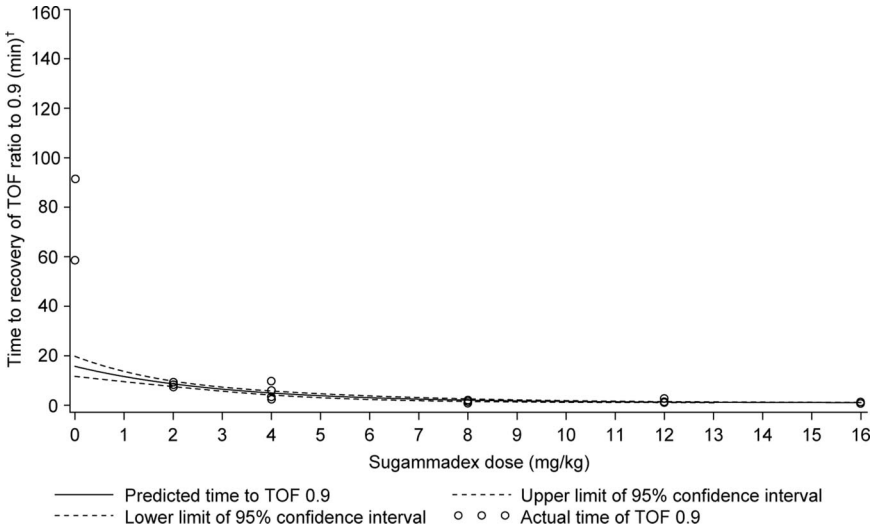

Fig. 2. Estimated dose–response relation between the time from start of administration of sugammadex to recovery of the train-of-four (TOF) ratio to 0.9 and the dose of sugammadex. Sugammadex was administered 15 min after administration of 1.0 mg/kg rocuronium, n = 27. † One recovery time (232.8 min) in the placebo group was outside the time axis range.

tole, which in turn resolved immediately after the endoscope was withdrawn and the surgical assistant removed his elbow from the patient's face. Surgery was completed without any further events after 0.5 mg atropine had been given intravenously. Therefore, asystole was most likely due to a trigeminocardiac reflex, a well-recognized phenomenon that occurs during manipulations at the sensory branches of the maxillary and mandibular divisions of the trigeminal nerve.[12] Two cases of markedly abnormal high systolic and/or diastolic blood pressure values 2 min after administration of 12 mg/kg sugammadex, which lasted approximately 15 min, were reported as AEs. In general, systolic and diastolic blood pressure and heart rate values were much lower during anesthesia compared with pretrial values, and postanesthetic values were nearly normalized compared with pretrial values.

Discussion

Our study shows that sugammadex provides rapid and dose-dependent reversal of profound neuromuscular blockade induced by high-dose rocuronium (1.0 or 1.2 mg/kg) in adult surgical patients.

All sugammadex studies published to date[3,11,13,14] have shown a dose–response relation for time from the start of administration of sugammadex to recovery of the TOF ratio to 0.9. The dose–response relation observed between rocuronium and sugammadex compares favorably with that reported previously in studies conducted by Gijsenbergh *et al.*[3] and Sparr *et al.*,[11] which evaluated the dose–response relation of sugammadex administered for the early reversal (at 3 min) of profound rocuronium (0.6 mg/kg)–induced blockade. Gijsenbergh *et al.*[3] reported that a plateau effect for the time to recovery of the TOF ratio to 0.9 was reached with sugammadex doses of 4.0, 6.0, and 8.0 mg/kg, with recovery times between 1.0 and 3.3 min, which favorably correlates with the findings of our study. Sparr *et al.*[11] investigated the efficacy of sugammadex (1–8 mg/kg) administered at three time points (3, 5, or 15 min) after rocuronium (0.6 mg/kg). The speed of recovery in this study was also dose dependent, and the reversal was sustained without

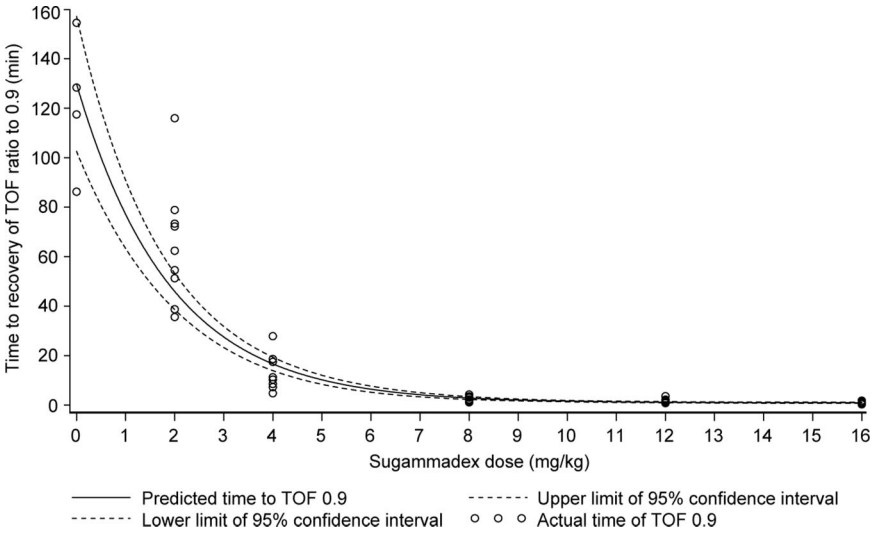

Fig. 3. Estimated dose–response relation between the time from start of administration of sugammadex to recovery of the train-of-four (TOF) ratio to 0.9 and the dose of sugammadex. Sugammadex was administered 3 min after administration of 1.2 mg/kg rocuronium, n = 53.

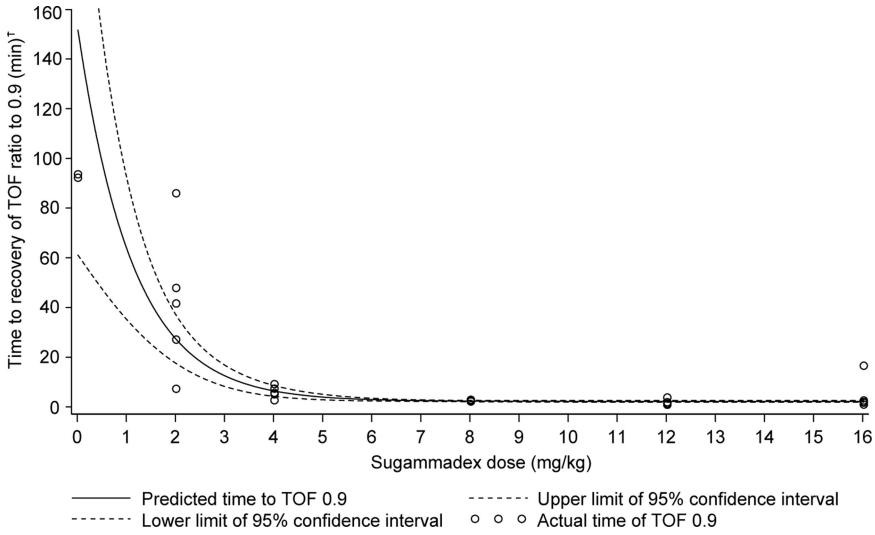

Fig. 4. Estimated dose–response relation between the time from start of administration of sugammadex to recovery of the train-of-four (TOF) ratio to 0.9 and the dose of sugammadex. Sugammadex was administered 15 min after administration of 1.2 mg/kg rocuronium, n = 28. † One recovery time (231.9 min) in the placebo group was outside the time axis range.

any signs of reoccurrence of neuromuscular blockade, which is in accord with our findings. Sparr *et al.* reported differences in the mean time to recovery of the TOF ratio to 0.9 dependent on both the sugammadex dose and the time of its administration. In contrast, in our study, no differences were observed when the same sugammadex dose was administered at different time points, except for the lowest doses applied (2.0 and 4.0 mg/kg). This difference to the data of Sparr *et al.* and those of our study can likely be attributed to the higher rocuronium dose applied in our study, such that sugammadex doses less than 8 mg/kg administered at 3 or 15 min did not sufficiently reverse neuromuscular blockade in 3 min or less. Groudine *et al.*[13] reported dose-dependent, effective reversal of profound rocuronium-induced neuromuscular blockade when sugammadex was administered at 1–2 posttetanic counts. In contrast to our observations, a plateau effect was reported already with sugammadex doses of 4 mg/kg or greater, whereas in our study 8 mg/kg was required until a plateau of recovery time was achieved. This difference can likely be explained by elimination of rocuronium at the time of sugammadex administration, given at partial recovery of neuromuscular transmission (at 1–2 posttetanic counts) in the study of Groudine *et al.*[13]

High-dose rocuronium almost meets the onset time of succinylcholine,[15–17] and it already has a place as a valuable alternative in the rapid-sequence setup[4,6,17–19] when succinylcholine is contraindicated. However, at high doses, the duration of action of rocuronium is unacceptably long, and there is currently no acceptable method of reversing profound rocuronium-induced blockade. Because anticholinesterases are unable to reverse profound neuromuscular blockade,[18] the current data suggest that the time course of action of the combination of rocuronium (1.2 mg/kg) and early administration of sugammadex (16 mg/kg) could potentially challenge the spontaneous recovery times of succinylcholine (1.0 mg/kg).[20] However, clearly patients undergoing a rapid-sequence induction will need to be studied in a rigorous fashion before final conclusions can be drawn.

The number of AEs in this study was relatively high, 110 of 173 patients (64.0%), but seems to support the quality of this investigation. Nevertheless, drug-related AEs were reported in 22 of 157 patients receiving sugammadex (14.0%) but in none of the patients receiving placebo (0 of 16). All drug-related AEs reported in the sugammadex group occurred mainly perioperatively and included nausea and vomiting and spontaneous movements such as grimacing, moving, coughing, bucking, and sucking on the tube. These effects were of mild or moderate intensity only, and the incidence of these effects in our study (18.4%) was similar to those observed in the study of Sparr *et al.*[11] (20.4%). Exploratory analysis revealed that prolongation of the QTc interval occurred in nine patients after sugammadex and was considered as possibly related to sugammadex in a single patient. In accord, Sparr *et al.*[11] reported slightly higher QTc values after sugammadex, but these changes were considered rarely significant, and a relation between dose of sugammadex and QTc prolongation was not observed, as it was not in our study. In a recently presented QT/QTc study in volunteers, de Kam *et al.*[21] were not able to show an association between sugammadex doses up to 32 mg/kg and QT/QTc prolongation using standard criteria for quantification of QT/QTc.

While the side effects of sugammadex were of mild to moderate intensity, we also know that side effects from any new drug that becomes clinically available are not usually detected until several thousand patient exposures have occurred.[22] In our study, two patients developed markedly abnormal arterial blood pressure after sugammadex that lasted approximately 15 min. Although it is unclear why the blood pressure was increased in these two individuals, possible explanations

Table 7. Incidence of Serious Adverse Events and Most Important Adverse Events for the Sugammadex and Placebo Groups (All-subjects-treated Group)

	Placebo	Sugammadex
Number of investigated patients	16	157
Investigations		
Corrected QT interval prolongation (serious AE)	0	9 (5.7%)
Cardiac disorders		
Cardiac arrest (serious AE)	0	1 (0.6%)
Bradycardia	0	3 (1.9%)
Procedural complications		
Postoperative bleeding	1 (6.3%) [serious AE]	2 (1.3%) [1 serious AE]
Anesthetic complications (intraoperative cough/ movements)	0	29 (18.5%)
Airway complication (bucking)	0	1 (0.6%)
Hypotension	2 (12.5%)	9 (5.7%)
Hypertension	0	3 (1.9%)
Postprocedural pain	0	4 (2.5%)
Delayed recovery from anesthesia	0	1 (0.6%)
Gastrointestinal disorders		
Nausea	3 (18.8%)	24 (15.3%)
Vomiting	5 (31.3%)	18 (11.5%)
General disorders and administration site disorders		
Pain	1 (6.3%)	21 (13.3%)
Musculoskeletal disorders		
Muscular weakness	0	1 (0.6%)
Nervous system disorders		
Headache	1 (6.3%)	3 (1.9%)
Dizziness	0	1 (0.6%)
Vertigo	0	4 (2.5%)
Respiratory system disorders		
Cough	1 (6.3%)	0
Hiccups	0	1 (0.6%)
Renal system disorders		
Oliguria	0	3 (1.9%)
Vascular disorders		
Hypotension	1 (6.3%)	6 (3.8%)
Hypertension	3 (18.8%)	8 (5.1%)

AE = adverse event.

include a reversal agent–evoked decrease in depth of anesthesia, a mechanism that may also be involved in mediating the observed motor responses in the sugammadex group. In fact, a sustained reversal agent–induced arousal reaction has been reported for neostigmine during anesthesia.[23,24] Further studies will help to further define its safety profile, and studies including Bispectral Index/entropy monitoring will show whether sugammadex can evoke an arousal reaction and/or unmask an inappropriately "light" level of anesthesia.

Conclusion

A clear dose–response relation was found for sugammadex and time to recovery of the TOF ratio to 0.9 for both time points of administration (3 and 15 min) and both doses of rocuronium (1.0 and 1.2 mg/kg). Sugammadex at 8 mg/kg consistently resulted in a TOF ratio of 0.9 or greater within a median value of 3.6 min or less. Increasing the sugammadex dose up to 16 mg/kg resulted in even faster reversal times (median 1.3 and 1.6 min) and less individual subject variability. No signs of reoccurrence of neuromuscular blockade were observed in any patient in the different sugammadex dose groups. We conclude that chemical encapsulation of rocuronium by sugammadex allows rapid and predictable reversal of profound neuromuscular blockade induced by high-dose rocuronium.

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