Reversal of Rocuronium-induced Neuromuscular Block by the Selective Relaxant Binding Agent Sugammadex

A Dose-finding and Safety Study

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Background: Sugammadex (Org 25969) forms a complex with steroidal neuromuscular blocking agents, thereby reversing neuromuscular block. This study investigated the dose–response relation, safety, and pharmacokinetics of sugammadex to reverse rocuronium-induced block.

Methods: Twenty-seven male surgical patients aged 18–64 yr were randomly assigned to receive placebo or sugammadex (0.5, 1.0, 2.0, 3.0, or 4.0 mg/kg) for reversal of 0.6 mg/kg rocuronium–induced neuromuscular block. Anesthesia was induced and maintained using intravenous fentanyl and propofol. Neuromuscular function was assessed using acceleromyography. Sugammadex or placebo was administered at reappearance of T_2 of the train-of-four. The primary efficacy variable was the time required for recovery to a train-of-four ratio of 0.9.

Results: Sugammadex decreased median recovery time in a dose-dependent manner from 21.0 min in the placebo group to 1.1 min in the group receiving 4.0 mg/kg sugammadex. Doses of sugammadex of 2.0 mg/kg or greater reversed rocuronium-induced neuromuscular block within 3 min. A median of 59–77% of sugammadex was excreted unchanged in the urine within 16 h, mostly in the first 8 h. Sugammadex increased the proportion of the rocuronium dose excreted unchanged in the urine (from a median of 19% in the placebo group to 53% in the 4.0-mg/kg group within 16 h). Sugammadex was safe and well tolerated. No evidence of recurarization was observed in any patient.

Conclusion: At doses of 2.0 mg/kg or greater, sugammadex safely reversed 0.6 mg/kg rocuronium–induced neuromuscular block in a dose-dependent manner. Sugammadex enhanced renal excretion of rocuronium and was excreted unchanged by the kidneys.

POSTOPERATIVE residual curarization is of clinical concern.[1–4] It has been associated with an impairment of the respiratory response to hypoxemia,[5–7] dysfunction of the pharynx and upper esophagus resulting in a possible increased risk of aspiration,[8,9] and an increased risk of postoperative pulmonary complications.[10] Residual block has been reported to occur in 16–64% of patients after a single intubating dose of an intermediate-acting nondepolarizing neuromuscular blocking agent (NMBA).[2–4] In a study of patients undergoing long procedures requiring continuous infusion, residual block was present in all but 5 of the 30 patients.[11] Reversal of neuromuscular block is therefore recommended to accelerate patient recovery in all patients who are not monitored objectively and in those who are monitored objectively and show signs of weakness.[12,13]

Currently, the main agents available for reversal of neuromuscular block are cholinesterase inhibitors. However, there are a number of limitations with these agents: Reversal may not be completely achieved, and patients treated with a cholinesterase inhibitor may still have residual block in the recovery room.[14] Because the action of cholinesterase inhibitors is indirect, they are only effective in reversing neuromuscular block if given when partial spontaneous recovery has already occurred,[15,16] and there is no reliable method of reversing profound neuromuscular blockade.[17] Cholinesterase inhibitors are also associated with a relatively high incidence of cholinergic side effects, including bradycardia, hypotension, salivation, bronchoconstriction, vomiting, and others. In one study, 50% of patients had adverse cardiovascular effects after neostigmine.[18] Muscarinic antagonists such as atropine or glycopyrronium are given concomitantly to reduce these effects but may result in tachycardia.[19] Therefore, there is a need for a new reversal agent with rapid onset of action, efficacy against profound blockade, and an improved safety profile.

Drug-specific cyclodextrins offer a radically new mechanism of reversal, by directly removing the NMBA from the neuromuscular junction rather than by indirectly increasing the activity of the cholinergic system,[17] and represent potentially a great advance in the field. Sugammadex (Org 25969; NV Organon, Oss, The Netherlands) is a modified γ-cyclodextrin designed to form an inactive complex with steroidal NMBAs such as rocuronium (fig. 1).[20–22] The cavity depth of the sugammadex molecule is optimal for encapsulating the four hydrophobic steroidal rings of rocuronium, and this is complemented by the formation of an electrostatic interaction between the positively charged quaternary nitrogen of rocuronium and the negatively charged carboxyl groups

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This article is accompanied by an Editorial View. Please see: Kopman AF: Sugammadex: A revolutionary approach to neuromuscular antagonism. ANESTHESIOLOGY 2006; 104:631–3.
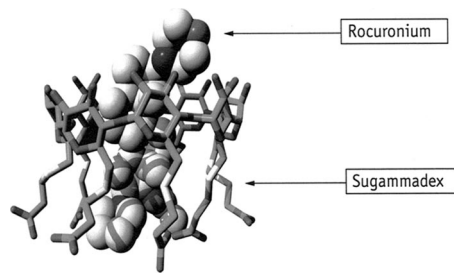

Fig. 1. Complex formation of sugammadex and rocuronium.

of sugammadex.[20] Sugammadex rapidly encapsulates steroidal NMBAs, thus preventing the relaxant from acting on the acetylcholine receptor and theoretically reducing its effective plasma concentration to zero. Reversal of block occurs rapidly and completely as the NMBA diffuses from the neuromuscular junction back into the plasma; in theory, all degrees of block could be reversed. Although sugammadex can form complexes with nonsteroidal drugs such as atropine and verapamil and with non-NMB steroidal drugs such as cortisone and hydrocortisone, their affinities to sugammadex are greater than 120- to 700-fold less than that of the steroidal NMBA rocuronium.[17] This can be attributed to the size of the cavity of the sugammadex molecule and its structural complementarity with rocuronium's rigid hydrophobic steroid skeleton.[17] Sugammadex is also biologically inactive, showing a lack of effect on animal tissue *in vitro*.[17] In recent studies, sugammadex was shown to rapidly reverse rocuronium-induced neuromuscular block *in vitro* and *in vivo*.[17,21] In a phase I study in healthy volunteers, sugammadex reversed rocuronium-induced neuromuscular block within 3 min, and results showed that the sugammadex–rocuronium complex was eliminated unchanged in the urine.[23]

The current phase II study investigated the dose–response relation, safety, and pharmacokinetics of sugammadex given at the reappearance of the second twitch (T_2) in response to train-of-four (TOF) stimulation to reverse rocuronium-induced neuromuscular block in surgical patients.

Materials and Methods

Study Design and Patient Selection

This randomized, placebo-controlled, safety assessor-blinded trial was conducted at two centers in Denmark. Male patients aged 18–64 yr, with physical status classed as I or II according to the American Society of Anesthesiologists classification system, were eligible for inclusion if they were scheduled to undergo surgery in which anesthesia was anticipated to last for 60 min or longer, without requiring muscle relaxation other than for intubation. Patients with any of the following characteristics were excluded: anatomical malformations expected to

produce a difficult intubation; known or suspected neuromuscular disorders and/or significant hepatic or renal dysfunction; known or suspected history or family history of malignant hyperthermia; known or suspected allergy to narcotics, muscle relaxants, or other medication used during general anesthesia; receiving medication known to interfere with NMBAs (such as anticonvulsants, aminoglycosides, and magnesium [Mg^{2+}]). Patients could only participate in the study once, and patients who had participated in another clinical trial (not preapproved by Organon NV) within the previous 30 days were excluded. The protocol was approved by the regional Ethics Committee in Copenhagen County, Denmark. All patients gave written informed consent according to the Declaration of Helsinki.

Study Procedures

Patients were preoxygenated for 3 min, and anesthesia was induced with an intravenous bolus dose of fentanyl (1–3 μg/kg), followed by intravenous propofol (1.5–2.5 mg/kg). Anesthesia was maintained by a continuous intravenous infusion of propofol, air–oxygen mixture, and increments of fentanyl as needed. All patients received 0.6 mg/kg rocuronium as a single rapid intravenous bolus over 10 s, and their tracheas were intubated 60–90 s later. No additional NMBA was given. Neuromuscular function was monitored using the TOF Watch® SX (NV Organon) and TOF nerve stimulation. The guidelines for good clinical research practice in pharmacodynamic studies of NMBAs were followed.[24] The ulnar nerve was stimulated through surface electrodes, and the adductor pollicis muscle response was measured. When the T_2 of the TOF reappeared, patients received a randomized, single, intravenous bolus dose of placebo or sugammadex at a dose of 0.5, 1.0, 2.0, 3.0, or 4.0 mg/kg, given over 30 s. Anesthesia was maintained until the end of surgery (a minimum of 60 min after administration of sugammadex or placebo) and at least until the TOF ratio had recovered to 0.9. No other reversal agent was used. Neuromuscular monitoring (TOF ratio) was continued until the end of surgery (a minimum of 60 min after administration of sugammadex or placebo) to check for signs of recurarization. In the event of recurarization, monitoring was to be continued until the TOF ratio had returned to 0.9. Clinical evidence of recurarization or residual curarization (*e.g.*, respiratory problems, respiratory rate, oxygen saturation) was to be recorded from administration of placebo or sugammadex until 60 min after extubation.

Urine and blood samples (9 ml) were collected for safety assessment before administration of rocuronium and at 20 min (blood only) and at 4–6 h (blood and urine) after administration of sugammadex or placebo. The assessments included blood biochemistry and hematology analyses (*e.g.*, hematocrit, blood cell counts, creatinine, blood urea, fasting glucose) and urine chemistry

(*e.g.*, pH, protein, glucose, blood, ketones). Pharmacokinetic assessments were also conducted to determine the plasma concentration and percentage of administered dose excreted in the urine over 24 h for sugammadex and rocuronium. A total of six blood samples (5 ml) were collected for pharmacokinetic analysis at the following time points: immediately before administration of rocuronium, immediately before administration of sugammadex or placebo (at reappearance of T_2), at 2 min after administration of sugammadex or placebo, at recovery of the TOF ratio to 0.9 or between 2 and 20 min after administration of sugammadex or placebo, and at 20 min and 4–6 h after administration of sugammadex and placebo. If a TOF of 0.9 was reached within 2 min, the 2-min sample and the TOF 0.9 sample overlapped. Urine was collected for a 24-h pharmacokinetic analysis from patients participating at the site at the Copenhagen University Hospital, Rigshospitalet, divided into collection intervals of 0–4, 4–8, 8–12, 12–16, and 16–24 h.

Sugammadex and rocuronium concentrations in plasma and urine were determined in the Department of Clinical Pharmacology and Kinetics, NV Organon, using validated liquid chromatographic assay methods with mass spectrometric detection (NV Organon). Assay validation was performed according to the Food and Drug Administration Guidance for the industry on Bioanalytical Method validation.[25] The assays were conducted in compliance with Good Laboratory Practice regulations. The limits of quantitation for the assays were as follows: sugammadex, 0.1 μg/ml (plasma) and 5 μg/ml (urine); rocuronium, 2 ng/ml (plasma) and 50 ng/ml (urine). The intraassay and interassay coefficients of variation (both plasma and urine) were within 1.6–5.6% and 3.0–7.3%, respectively, for sugammadex and within 2.5–11.2% and 4.1–14.5%, respectively, for rocuronium. The assay methods did not differentiate between the sugammadex–rocuronium complex and free sugammadex and rocuronium, because the complex dissociates on the liquid chromatography column.[26]

Blood pressure and heart rate were recorded at the screening visit, just before administration of rocuronium (at stable anesthesia), at 2, 10, and 30 min after administration of sugammadex or placebo and at the posttrial visit. Values outside the following ranges were considered to be markedly abnormal values: heart rate $\leq$ 50 beats/min or $\geq$ 120 beats/min (change from baseline $\geq$ 15 beats/min), systolic blood pressure $\leq$ 90 mmHg or $\geq$ 160 mmHg (change from baseline $\geq$ 20 mmHg), diastolic blood pressure $\leq$ 45 mmHg or $\geq$ 95 mmHg (change from baseline $\geq$ 15 mmHg). A postanesthetic visit was conducted at least 10 h after the administration of sugammadex or placebo, at which vital signs were recorded, a physical examination was performed, and blood and urine samples were taken for safety analysis.

On the seventh day after the operation, patients were contacted and asked about their well-being.

Adverse events (AEs) were recorded during the trial and at the postanesthetic visit and were graded as mild (no interference with functioning), moderate (no significant interference with functioning), and severe (significant interference with functioning). A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in death or persistent/significant disability, was life threatening, required an in-patient hospital stay or prolongation of an existing hospital stay, or was a congenital abnormality or birth defect. SAEs were recorded up to the seventh-day follow-up call. The assessor carrying out subjective safety assessments was blind to the reversal medication administered.

Efficacy Variables

The primary efficacy variable was the time from the start of administration of sugammadex or placebo to the recovery of the TOF ratio to 0.9. Secondary efficacy variables were the time from the start of administration of sugammadex or placebo to the recovery of the TOF ratio to 0.8 and 0.7.

Statistical Analysis

The intent-to-treat population consisted of all subjects who received a dose of sugammadex or placebo and had at least one postbaseline efficacy measurement. The per-protocol population consisted of those members of the intent-to-treat group who had no major protocol violation. The safety population consisted of all subjects who received a dose of sugammadex or placebo. For the pharmacokinetic analysis, data were analyzed from all subjects who received a dose of sugammadex or placebo and provided at least one measurable sugammadex or rocuronium sample for which the related dosing and sampling times were documented according to the protocol, as well as those with no protocol violations that may have interfered with pharmacokinetics.

Data on the primary efficacy variable were analyzed to explore the relation between the dose of sugammadex and the time from start of administration of sugammadex to recovery of the TOF ratio to 0.9. Weighted nonlinear regression was used to fit the parameters of an exponential model to the observed data: mean time to recovery of TOF to 0.9 (dose) = a + b.exp (c.dose), where a represents the fastest achievable recovery time for the average subject, b represents the difference in time between mean spontaneous recovery and mean recovery after an infinitely large dose of sugammadex, and c represents the extent of the reduction in recovery time with sugammadex. The secondary efficacy variables were analyzed in the same way. Other data were analyzed using descriptive statistics.

Table 1. Time from Start of Administration of Sugammadex or Placebo at Reappearance of T_2 to Recovery of the TOF Ratio to 0.9, 0.8, and 0.7: Per-Protocol Population

	Placebo	Sugammadex Dose Group				
		0.5 mg/kg	1.0 mg/kg	2.0 mg/kg	3.0 mg/kg	4.0 mg/kg
TOF 0.9						
n	4	5	4	3	5	3
Median	21.0	4.3	3.3*	1.3	1.2	1.1
Range (min–max)	(15.0–35.4)	(1.3–8.5)	(1.4–4.9)	(0.9–1.7)	(0.7–3.2)	(1.0–1.4)
TOF 0.8						
n	3	5	5	3	5	3
Median	15.8*	3.7	1.7	1.1	1.2	1.1
Range (min–max)	(13.0–16.7)	(1.1–7.5)	(1.1–2.6)	(0.9–1.5)	(0.7–2.4)	(0.7–1.1)
TOF 0.7						
n	4	5	5	3	5	3
Median	14.8	2.8	1.4	0.9	1.0	0.9
Range (min–max)	(11.5–26.4)	(1.1–5.7)	(1.1–1.8)	(0.8–1.5)	(0.7–2.2)	(0.7–1.1)

Values are reported in minutes.

* Data for one subject excluded.

TOF = train-of-four.

Results

Demographics

A total of 27 male patients were given sugammadex or placebo (29 subjects were randomized, but two dropped out before sugammadex or placebo was administered). There were five patients each in the placebo and 0.5, 1.0, and 3.0 mg/kg sugammadex groups and four and three patients, respectively, in the 2.0 and 4.0 mg/kg sugammadex groups. There was no significant difference in demographic characteristics between the six groups of patients. Mean (SD) age, weight, and height were 40 (13) yr, 80 (12) kg, and 178 (8) cm, respectively. Of the 27 patients, 25 were white and 2 were Asian. Twenty-two patients had an American Society of Anesthesiologists physical status of I, and five had an American Society of Anesthesiologists physical status of II. All 27 patients treated completed the trial and were included in the intent-to-treat population, safety population, and pharmacokinetic population. Two patients (one in the placebo group and one in the 2.0 mg/kg group) had a major protocol violation. The data from these two patients were therefore excluded from the per-protocol analysis. One patient (in the 1.0-mg/kg group) had a minor protocol violation. The TOF ratio to recovery to 0.9 of this patient was excluded from the per-protocol analysis.

Efficacy

Sugammadex produced a dose-dependent reduction in the time taken for the TOF ratio to recover to 0.9 (table 1). Median recovery time decreased from 21.0 min (placebo; spontaneous recovery) to 1.1 min in the group receiving 4.0 mg/kg sugammadex. The estimated dose–response relation and associated 95% confidence intervals are shown for the per-protocol population in figure 2. The estimated dose–response curve adequately fitted
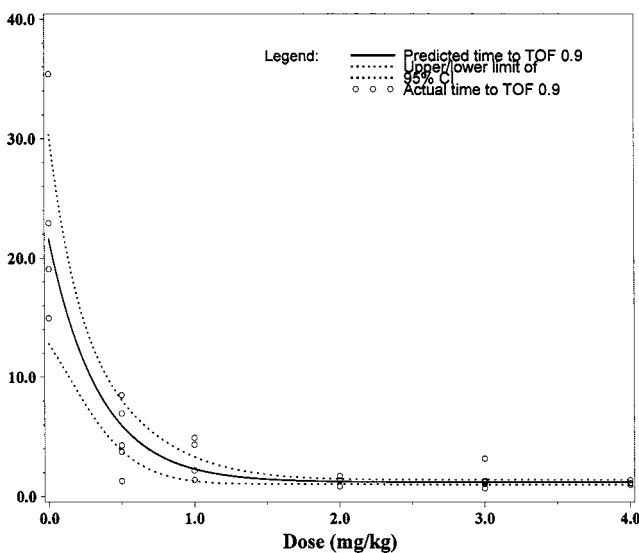
Fig. 2. Estimated mean dose–response relation for the time from administration of sugammadex to recovery of the train-of-four (TOF) ratio to 0.9, including 95% confidence intervals (CIs) (per-protocol population).
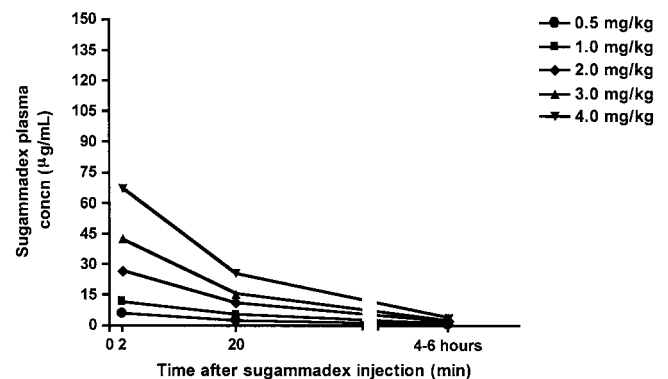
Fig. 3. Median plasma concentrations of sugammadex *versus* time after administration of sugammadex (0.5, 1.0, 2.0, 3.0, or 4.0 mg/kg).
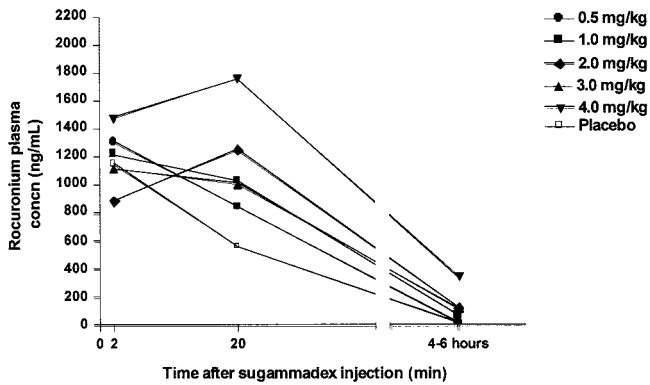
Fig. 4. Median plasma concentrations of rocuronium (sum of free and sugammadex bound) *versus* time after administration of sugammadex (0.5, 1.0, 2.0, 3.0, or 4.0 mg/kg) or placebo.

the observed data on time to recovery over the dose range studied (fig. 2) and showed a statistically significant dose–response effect. Sugammadex also shortened the times required for the TOF ratio to recover to 0.7 and 0.8 in a dose-dependent manner (table 1).

Pharmacokinetics

Figures 3 and 4 show the median plasma concentrations of sugammadex and rocuronium (sum of free and sugammadex bound). In the placebo group, the rocuronium plasma concentration declined with time after dosing. However, rocuronium plasma concentrations at 20 min after administration of sugammadex (all doses) were increased compared with those at the corresponding time point in the placebo group and were still increased at 4–6 h in the highest sugammadex dose groups (2.0, 3.0, and 4.0 mg/kg) compared with placebo.

Tables 2 and 3 show the median cumulative percentage of the sugammadex and rocuronium doses excreted in the urine over 24 h. A median of 59–77% of sugammadex was excreted unchanged in the urine within

16 h. In patients receiving rocuronium alone, a median of 19% of the rocuronium dose was excreted in the urine at 16 h. Administration of sugammadex increased this percentage, reaching 53% in the 4.0-mg/kg dose group at 16 h. The apparent decline in cumulative excretion in the 16- to 24-h period is an artifact due to the small number of patients per dose group and a decrease in the number of patients who provided urine samples in the 16- to 24-h collection period.

Safety

In total, 22 of the 27 patients (82%) experienced at least one AE, and 12 of the 22 patients (55%) experienced at least one AE that was considered possibly, probably, or definitely related to treatment (table 4). Three patients had AEs that were categorized as severe, and one patient (in the 3.0-mg/kg dose group) experienced an SAE. This patient experienced hypotension, beginning 10 min after administration of sugammadex and lasting for 5 min. Blood pressure changed from 120/80 mmHg at baseline (*i.e.*, just before administration of rocuronium) to 102/60 mmHg at 2 min and 61/30 mmHg at 10 min after administration. At 30 min, blood pressure had returned to 96/48 mmHg. The maximum intensity of the event was considered to be moderate and was categorized as possibly related to sugammadex. However, the chronology of the symptoms suggested a relation with the injection of propofol and/or fentanyl, both of which were injected 2–5 min before the event. The patient was treated with four doses of ephedrine and plasma expander and recovered fully.

The most frequently occurring AEs that were considered possibly, probably, or definitely related to treatment were coughing (n = 3; 2.0-, 3.0-, and 4.0-mg/kg dose groups), movements (n = 3; 0.5-, 2.0-, and 3.0-mg/kg dose groups), and hypotension (n = 2; 2.0- and

Table 2. Urinary Excretion of Sugammadex

Collection Interval	Sugammadex Dose Group				
	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg	3.0 mg/kg	4.0 mg/kg
0–4 h, n	4	3	2	3	3
	36.8	42.7	42.0	52.9	20.5
	(0–51.9)	(22.6–43.1)	(34.9–49.0)	(50.0–87.3)	(0–32.3)
4–8 h, n	3	2	2	3	3
	71.5	53.3	67.2	66.7	71.7
	(62.6–79.2)	(27.1–79.4)	(45.0–89.3)	(62.0–89.9)	(36.7–86.4)
8–12 h, n	3	2	2	3	3
	73.8	58.1	73.5	69.4	72.2
	(66.0–83.7)	(28.6–87.5)	(49.7–97.4)	(68.0–92.5)	(38.9–92.2)
12–16 h, n	3	2	2	3	3
	76.3	59.1	76.5	71.3	72.4
	(69.8–93.1)	(28.6–89.5)	(50.7–102)	(69.3–93.8)	(39.5–94.6)
16–24 h, n	2	2	1	2	1
	75.4	60.1	52.1	70.7	39.9
	(70.7–80.2)	(29.6–90.6)	—	(69.9–71.5)	—

The cumulative amount excreted is given as percentage of dose. Medians and ranges are given.

Table 3. Urinary Excretion of Rocuronium (Sum of Free and Sugammadex Bound)

Collection Interval	Placebo	Sugammadex Dose Group				
		0.5 mg/kg	1.0 mg/kg	2.0 mg/kg	3.0 mg/kg	4.0 mg/kg
0–4 h, n	4	4	3	2	3	3
	17.8	17.9	28.5	30.9	41.1	12.6
	(0–24.7)	(0–26.0)	(22.8–36.8)	(28.9–32.9)	(40.8–54.5)	(0–25.9)
4–8 h, n	4	3	2	2	3	3
	18.3	26.7	36.0	40.1	47.0	50.8
	(0.36–28.3)	(21.5–29.7)	(33.6–38.4)	(35.8–44.5)	(46.3–55.2)	(16.8–53.3)
8–12 h, n	4	3	2	2	3	3
	18.8	26.9	37.4	41.3	47.1	53.0
	(0.95–29.7)	(21.9–30.1)	(34.5–40.3)	(36.6–45.9)	(46.9–56.1)	(17.1–53.5)
12–16 h, n	4	3	2	2	3	3
	19.1	27.0	37.5	41.7	48.9	53.4
	(1.14–30.2)	(22.2–30.3)	(34.6–40.3)	(36.7–46.6)	(47.2–56.8)	(17.2–53.7)
16–24 h, n	3	2	2	1	2	1
	20.4	28.8	37.5	36.9	48.2	17.5
	(18.3–30.7)	(27.2–30.4)	(34.7–40.3)	—	(47.3–49.0)	—

The cumulative amount excreted is given as percentage of the dose. Medians and ranges are given.

3.0-mg/kg dose groups) shortly after the injection of sugammadex. In one patient, the hypotension was classified as severe and started 17 min after administration of sugammadex and lasted for 5 min with a reduction in blood pressure to 60/27 mmHg. Blood pressure was 100/50 mmHg at baseline and 103/53 and 74/36 mmHg at 2 and 10 min, respectively. At 30 min, the blood pressure returned to 111/74 mmHg. As described previously, the other case of hypotension was classified as an SAE. Postoperatively, six patients had abnormal urine (0.5 [n = 2], 1.0 [n = 1], 3.0 [n = 1], and 4.0 mg/kg [n = 2]), two patients vomited (3.0 mg/kg), one patient reported malaise and sensation of changed temperature (2.0 mg/kg), one reported vertigo and nausea (3.0 mg/kg), one reported rhinitis (3.0 mg/kg), and one reported parosmia (3.0 mg/kg). Five of the six patients with abnormal urine had abnormal levels of *N*-acetyl-glucosaminidase; in four of five patients, the abnormal value had resolved by the time of the posttrial assessment, and in the fifth patient, the abnormal value occurred only at the posttrial assessment. The last patient (4.0 mg/kg) with abnormal urine postoperatively had a slightly increased urine albumin value in the 4- to 6-h postdose urine sample. The value was normal in the posttrial sample. The changes that occurred in the urinalysis variables were reported in the placebo group as well as in the active treatment groups and were not considered to be clinically relevant.

No clinically relevant changes occurred in hematology or biochemistry laboratory values. Overall, the changes observed in urinalysis parameters were not considered clinically relevant. Also, no clinically relevant changes from baseline were observed in physical examinations. No AEs related to vital signs were considered treatment related, except in the two patients (described previously) who experienced hypotension after administration of 2.0 and 3.0 mg/kg sugammadex; both events resolved completely.

No recurarization was observed in any patient. There were no deaths, and no patient discontinued the trial because of an AE.

Discussion

The main finding of this study was that sugammadex, administered at reappearance of the T_2 of TOF stimulation, reversed 0.6 mg/kg rocuronium–induced neuromuscular block in a dose-dependent manner. In the absence of sugammadex, spontaneous recovery of the TOF ratio to 0.9 took a median time of 21.0 min. At doses

Table 4. Adverse Events by Dose Group: Safety Population (n = 27)

	Placebo (n = 5)	Sugammadex Dose Groups				
		0.5 mg/kg (n = 5)	1.0 mg/kg (n = 5)	2.0 mg/kg (n = 4)	3.0 mg/kg (n = 5)	4.0 mg/kg (n = 3)
Patients with AEs, n	4	4	3	3	5	3
Patients with drug-related AEs,* n	0	3	1	2	4	2
Patients with severe AEs, n	0	1	0	1	1	0
Patients with SAEs, n	0	0	0	0	1	0

* Considered to be possibly, probably, or definitely related to treatment.

AE = adverse event; SAE = serious adverse event.

of sugammadex at or above 2.0 mg/kg, recovery occurred within 3 min, and the dose–response relation estimated from the observed data indicated that the dose–response curve reached a plateau at around this dose. Because of the small sample size, median values have been presented to reduce the effect that possible outliers may have on mean values.

Because the study was designed to determine the dose–response relation of sugammadex, it did not include an anticholinesterase control group. A further aim of the study was to establish a suitable dose for use in phase III studies, thereby enabling the future conduct of trials with the aim of demonstrating the superiority of sugammadex *versus* anticholinesterases.

The current study thus shows that sugammadex was effective when given at the normal time for administration of cholinesterase inhibitors.[15] Also, no evidence of recurarization was observed in any patient. Because sugammadex has a direct mechanism of action, it should, in theory, be capable of reversing deeper levels of neuromuscular block. Evidence from studies in rhesus monkeys supports the possibility of profound block reversal.[27] Results were also positive in a study composed of healthy male volunteers who received 0.6 mg/kg rocuronium, with recovery of the TOF to 0.9 within 2 min after administration of 8 mg/kg sugammadex.[23] Clinical applications of sugammadex may therefore include use in both shallow as well as profound neuromuscular block with the potential prospect of sustained neuromuscular recovery. The lack of any residual curarization with sugammadex may be an important advance in anesthetic practice, providing the potential to reduce morbidity in the postanesthetic phase.

Pharmacokinetic evaluations showed that the administration of sugammadex increased the plasma concentration of rocuronium, compared with that in patients who received rocuronium alone. These findings are consistent with those of a previous study showing an increase in rocuronium plasma concentrations and increased renal excretion of rocuronium with increasing doses of sugammadex in healthy volunteers.[23] The majority (up to 77%) of the dose of sugammadex was excreted unchanged in the urine, and administration of sugammadex also increased the proportion of the rocuronium dose that was excreted unchanged in the urine. In patients receiving rocuronium alone, 19% of the rocuronium dose was recovered in urine collected for 16 h after administration. This is similar to results reported from previous studies, in which 12–22% of the rocuronium dose was excreted in urine in the 12 h after dosing.[28] and 14–18% recovered in the 24 h after dosing.[23,29] In contrast, administration of sugammadex (4.0 mg/kg) in the current study increased the proportion of the rocuronium dose excreted in urine collected up to 16 h to 53%. An ongoing clinical study is currently investigating the efficacy and safety of sugammadex in patients with

renal impairment. In animal studies, in the absence of renal function, administration of sugammadex produced fast, effective, and complete reversal of rocuronium-induced block.[30]

These pharmacokinetic results are consistent with the rapid formation of a complex between rocuronium and sugammadex, which is distributed in the central (plasma) compartment and extracellular fluid and is excreted unchanged in the urine. When sugammadex is administered, it rapidly encapsulates free rocuronium molecules in the plasma. This increases the diffusion gradient for free rocuronium from the tissue compartment to the plasma compartment, thereby withdrawing rocuronium from the tissue compartment and reversing its effect at the neuromuscular junction. As they enter the plasma, these free rocuronium molecules form complexes with more sugammadex, thus maintaining the diffusion gradient until either all the rocuronium is held in sugammadex–rocuronium complexes in the plasma or until all the sugammadex molecules are saturated. The assay method cannot differentiate between free and complex forms of rocuronium and sugammadex, so the movement of rocuronium from the tissue compartment to form sugammadex–rocuronium complexes in the plasma appears as an increase in total plasma rocuronium concentration. The increase in the proportion of the rocuronium dose recovered in the urine after administration of sugammadex is consistent with urinary excretion of the unchanged sugammadex–rocuronium complex.

The safety data from the current study indicate that sugammadex was well tolerated. Coughing was observed in three patients, and movement during anesthesia occurred in three patients. These effects may have been due to sudden reversal of neuromuscular block after administration of sugammadex combined with a surgical stimulus at a time of insufficient depth of anesthesia. All patients recovered without clinical consequences. Hypotension, considered to be at least possibly related to treatment, was observed in two patients, and in one patient, it was considered an SAE. The hypotension may have been related to administration of propofol and fentanyl, rather than to sugammadex, because hypotension is a known AE with both of these agents. Both cases of hypotension resolved within 5 min, and both patients recovered with no adverse consequences.

In conclusion, we found that sugammadex administered at the reappearance of T_2 dose-dependently reversed 0.6 mg/kg rocuronium–induced neuromuscular block within 3 min at doses at or above 2.0 mg/kg. Up to 77% of sugammadex was excreted unchanged by the kidneys within 16 h, and administration of sugammadex enhanced renal excretion of rocuronium. Sugammadex was safe and well tolerated, and no evidence of recurarization was observed in any patient.

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