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Early Reversal of Profound Rocuronium-induced Neuromuscular Blockade by Sugammadex in a Randomized Multicenter Study

Efficacy, Safety, and Pharmacokinetics

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Background: **Sugammadex reverses the neuromuscular blocking effects of rocuronium by chemical encapsulation. The efficacy, safety, and pharmacokinetics of sugammadex for reversal of profound rocuronium-induced neuromuscular blockade were evaluated.**

Methods: **Ninety-eight male adult patients were randomly assigned to receive sugammadex (1, 2, 4, 6, or 8 mg/kg) or placebo at 3, 5, or 15 min after 0.6 mg/kg rocuronium. Patients were anesthetized with propofol and fentanyl. The primary endpoint of the study was the time to achieve a recovery of train-of-four ratio to 0.9. Neuromuscular blockade was measured using acceleromyography. Concentrations of rocuronium and sugammadex were determined in venous blood and urine samples. A population pharmacokinetic model using NONMEM (GloboMax LLC, Hanover, MD) was applied.**

Results: **The mean time to recovery of the train-of-four ratio to 0.9 after dosing at 3, 5, and 15 min decreased from 52.1, 51.7, and 35.6 min, respectively, after administration of placebo to 1.8, 1.5, and 1.4 min, respectively, after 8 mg/kg sugammadex. Sugammadex was safe and well tolerated. However, 20.4% of patients showed signs of inadequate anesthesia after its administration. The median cumulative excretion of rocuronium in the urine over 24 h was 26% in the placebo group and increased to 58–74% after 4–8 mg/kg sugammadex. The mean plasma clearances of sugammadex and rocuronium were 0.084 and 0.26 l/min, respectively.**

Conclusions: **In male subjects, sugammadex safely reversed profound neuromuscular blockade induced by 0.6 mg/kg rocuronium in a dose-dependent manner. Sugammadex enhanced the renal excretion of rocuronium, and its clearance is approximately one third that of rocuronium.**

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THE duration of action of all currently available nondepolarizing muscle relaxants is too long if an anesthesiologist is faced with a short case or an unexpected cannot-intubate, cannot-ventilate scenario. Early or "escape" reversal using neostigmine was shown to be partially effective with rapacuronium but not with rocuronium.[1–3] The inability of cholinesterase inhibitors to reverse a profound nondepolarizing blockade may be one important reason for the unrelenting persistence of succinylcholine in current anesthetic practice, in particular for its two principal indications, relaxation for rapid-sequence induction and ultrashort procedures.

An ideal reversal agent should, among other things, facilitate rapid and complete reversal of any level of neuromuscular blockade (NMB), even profound blockade, at any time, and should be devoid of muscarinic effects. To fulfil these criteria, a new concept for the reversal of NMB has been developed, *i.e.*, inactivation through complex formation. Various cyclodextrins were synthesized and tested for their ability to reverse steroidal muscle relaxants such as rocuronium. Sugammadex, a water-soluble, modified γ cyclodextrin, was selected for clinical development.[4,5] In animal models, intravenous administration of sugammadex rapidly reverses rocuronium-induced NMB by encapsulating the unbound rocuronium molecules, thereby enhancing the transfer of rocuronium from the effect compartment (the neuromuscular junction).[6] In addition, sugammadex enhances the renal excretion of rocuronium.[7] In a phase I study in 29 male volunteers, sugammadex was both well tolerated and effective in reversing NMB induced by rocuronium.[7]

The current phase II dose-finding study was performed to investigate further the efficacy and safety of sugammadex, attempting reversal of NMB under more demanding conditions, *i.e.*, at 3, 5, or 15 min after an intubating dose of 0.6 mg/kg rocuronium. Pharmacokinetic evaluations were performed simultaneously to determine the effect of sugammadex on rocuronium plasma concentrations, and the urinary excretion of sugammadex and rocuronium.

Materials and Methods

Study Design and Patient Selection

This multicenter, randomized, assessor-blinded, placebo-controlled, dose-finding, phase II clinical trial was

conducted at three European university hospitals: University Medical Center Groningen, The Netherlands; University Hospital of Antwerp, Belgium; and the Medical University Innsbruck, Austria, during the period December 2002 to June 2003. The protocol was approved by the independent Medical Ethics Committee for each center, and all patients gave written informed consent. The study was conducted in compliance with the current revision of the Declaration of Helsinki, the International Conference on Harmonisation guidelines, Good Clinical Practice, and current regulatory recommendations.

The primary objective of the study was to explore the dose–response relation of sugammadex given as a reversal agent at 3, 5, and 15 min after administration of 0.6 mg/kg rocuronium. Secondary objectives were to evaluate the safety, pharmacokinetic profile, and pharmacokinetic–pharmacodynamic relation of single doses of sugammadex.

Male patients aged between 18 and 64 yr, with American Society of Anesthesiologists physical status I or II, scheduled to undergo elective surgery lasting at least 75 min, and requiring muscle relaxation only to facilitate tracheal intubation, were eligible for inclusion in the study. Patients were excluded from the study if a difficult intubation was anticipated; if they had a neuromuscular disorder, a history of malignant hyperthermia, hepatic or renal dysfunction, or suspected allergy to medication used during general anesthesia; or if they were receiving medication known to interfere with muscle relaxants.

Anesthesia

After arrival in the operating room, the patient was connected to the monitoring equipment, which consisted of an electrocardiographic monitor, a noninvasive blood pressure monitor, and a pulse oximeter. An intravenous cannula was inserted, and infusion with a crystalloid solution was initiated. After preoxygenation, anesthesia was induced intravenously with fentanyl (1.5–3 μg/kg) and propofol (2–3 mg/kg) and maintained with a continuous infusion of propofol and intermittent administration of fentanyl as needed. After induction of anesthesia, the patient was ventilated by mask with oxygen-enriched air. On reaching stable anesthesia, baseline hemodynamic values and a 12-lead electrocardiogram were obtained. A second intravenous cannula was then inserted in the opposite arm, and a blank sample was taken for safety and pharmacokinetic analysis. Thereafter, rocuronium (0.6 mg/kg Esmeron®; NV Organon, Oss, The Netherlands) was administered intravenously as a single rapid bolus dose within 10 s, followed 1.5–2 min later by intubation. Three, 5, or 15 min after administration of rocuronium, a single intravenous bolus dose of sugammadex (1, 2, 4, 6, or 8 mg/kg) or placebo was administered within 30 s, according to the randomization scheme. Anesthesia was continued for at least 60 min after the administration of sugammadex or placebo and until recovery of the train-of-four (TOF) ratio to 0.9.

Neuromuscular Monitoring

The ulnar nerve was stimulated through surface electrodes (four pulses of 0.2 ms duration, delivered at a frequency of 2 Hz, every 15 s) and the adductor pollicis neuromuscular response was monitored with the TOF-Watch® SX acceleromyograph (Organon Ltd., Dublin, Ireland). All neuromuscular monitoring data were transferred to a personal computer using a fiber-optic cable (TOF-Link®), and saved using TOF-Watch® SX Monitor software (Organon Ltd.).

After induction of anesthesia and prior to calibration of the TOF-Watch® SX unit, a 5-s, 50-Hz supramaximal tetanic stimulus was administered at the ulnar nerve.[8] Thereafter, the acceleromyograph was calibrated using the implemented TOF-Watch® SX calibration mode 2. The control value of the twitch was determined using the supramaximal stimulation current, and the TOF ratio, measured just before injection of the neuromuscular blocking agent, was recorded as the control value. Skin temperature over the adductor pollicis muscle was maintained above 32°C by wrapping the arm in cotton wool and using forced-air warming blankets.

Neuromuscular monitoring was continued for at least 60 min after the administration of sugammadex or placebo. The time from the end of study drug administration until recovery of the TOF to a ratio of 0.7, 0.8, and 0.9 was assessed. In the event of residual curarization or recurarization, the time and value of the lowest TOF ratio and the time taken for the TOF ratio to reach 0.9 were recorded. In patients scheduled to receive the study drug or placebo 15 min after rocuronium, a second TOF-Watch® SX was affixed to the opposite arm and calibrated to allow a single posttetanic count measurement just before administration of sugammadex or placebo.

Pharmacokinetic Analysis

In total, six venous blood samples were collected from each patient at specified time points, and the actual time of blood withdrawal was recorded. The first sample (blank) was taken after induction of anesthesia and just before administration of rocuronium. Second and third samples were taken at 2 min before and 2 min after administration of sugammadex or placebo, respectively. A fourth sample was taken 4, 7, or 10 min after administration of sugammadex or placebo, depending on the trial site. Finally, the fifth and sixth samples were drawn at 20 min and between 4 and 6 h, respectively, after sugammadex or placebo.

Urine samples were obtained from patients at only one of the trial sites (Antwerp, Belgium), for determination of rocuronium and sugammadex concentrations. A blank urine sample was collected before anesthesia, after

which urine was collected at 0- to 4-, 4- to 8-, 8- to 12-, 12- to 16-, and 16- to 24-h intervals after administration of sugammadex or placebo. The actual sampling periods and volumes were recorded.

Sugammadex and rocuronium concentrations in plasma and urine were determined in the Department of Clinical Pharmacology and Kinetics, NV Organon, Oss, The Netherlands, 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.[9] The assays were conducted in compliance with Good Laboratory Practice regulations. The limits of quantitation for the assays were as follows: 0.1 μg/ml (plasma) and 5 μg/ml (urine) sugammadex; 2 ng/ml (plasma) and 50 ng/ml (urine) rocuronium. 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.[10]

A population-based pharmacokinetic model was developed from previous studies by a stepwise, nonlinear, mixed-effects modeling approach using NONMEM (version V, release 1; Globomax LLC, Hanover, MD) and has been described elsewhere in detail (data on file, Organon NV, Oss, The Netherlands). Briefly, a pharmacokinetic model for rocuronium was developed initially, using data from patients receiving rocuronium alone. Next, a pharmacokinetic model was developed for sugammadex and its interaction with rocuronium, using data from patients receiving both compounds. The interaction between rocuronium and sugammadex was modeled as a dynamic interaction, taking into account the rates of association of rocuronium to and dissociation from the sugammadex–rocuronium complex. The equilibrium dissociation constant of the complex was assumed to be equal to the value determined from *in vitro* experiments (K_d 0.1 μM). The dissociation rate constant of the complex was assumed to be a physicochemical parameter that was the same in each patient, and was fixed as the value estimated during the pharmacokinetic modeling process (K_2 0.00216 min^{-1}). The hysteresis between the venous and arterial concentration was modeled by an additional compartment for the venous plasma concentration with a first-order rate constant, and was fixed as the value estimated during the pharmacokinetic modeling process (k_{vo} 0.531 min^{-1}). It was assumed that the pharmacokinetics of the rocuronium–sugammadex complex were similar to those of sugammadex alone.

Safety

All adverse events (AEs), including signs of residual curarization or recurarization and electrocardiographic abnormalities, were recorded, whether or not considered related to the drug under investigation. Urine and blood samples were taken for safety assessment before administration of rocuronium, at 20 min (blood only) and 4–6 h after administration of sugammadex or placebo, and at the posttrial visit (12–24 h after surgery). Twelve-lead electrocardiographic recordings were made for determination of PR, QRS, QT, and QTc intervals, U and T waves, and heart rate at stable anesthesia just before administration of rocuronium and 2 and 30 min after administration of sugammadex or placebo. The data were transferred electronically and interpreted by a cardiologist who was blinded to the study medication. Clinical chemistry evaluation included haptoglobin to detect possible hemolysis. Urinalysis included *N*-acetyl-β-D-glucosaminidase, microalbumin, and β_2-microglobulin as sensitive markers of potential renal tubular and glomerular damage.

Statistical Analysis

The proposed sample size of 99 patients was mainly determined by practical reasons and to enable completion of the trial within a reasonable time frame. It also allowed exploration of the neuromuscular recovery after different doses of sugammadex, at different time points of administration after rocuronium. The intent-to-treat population consisted of all subjects who received at least one dose of sugammadex or placebo and had at least one postbaseline efficacy measurement. The per-protocol (PP) population consisted of those subjects from the intent-to-treat group who had no major protocol violation. The safety population comprised all subjects who received a dose of sugammadex or placebo.

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 the time from the start of administration of sugammadex or placebo to recovery of the TOF ratio to 0.7 and 0.8.

The relation between the dose of sugammadex and the time from start of administration of sugammadex or placebo to TOF ratio 0.9 was described by the following equation:

$$T_{TOF\,0.9}(\text{dose}) = a + b \cdot e^{-c \cdot \text{dose}},$$

where $T_{TOF\,0.9}$ is the mean time to recovery of the TOF ratio to 0.9 for each dose, and

- a estimates the fastest achievable recovery time for the average subject;
- b estimates the difference in time between the mean spontaneous recovery and the mean recovery following an infinitely large dose of sugammadex; and

Table 1. Demographics and Baseline Characteristics by Dose Group (All Subjects Treated Group)

Parameter	Placebo	Sugammadex Dose Group, mg/kg				
		1.0	2.0	4.0	6.0	8.0
n	10	18	16	18	18	18
Age, yr	41 (21–63)	40 (19–57)	39 (19–62)	41 (26–60)	36 (22–59)	37 (20–63)
Weight, kg	85 (12)	80 (9)	82 (8)	83 (11)	84 (16)	78 (12)
Height, cm	181 (8)	179 (7)	177 (5)	181 (9)	179 (9)	182 (7)
ASA physical status I:II	8:2	14:4	11:5	15:3	15:3	14:4
Creatinine clearance, ml/min*	164 (120–231)	142 (74–187)	137 (100–176)	138 (95–203)	163 (93–295)	137 (85–163)

Data are presented as number, mean (range), or mean (SD).

* Predose.

ASA = American Society of Anesthesiologists.

- c estimates the degree of reduction in recovery time with dose of sugammadex: the larger the c parameter is, the steeper the curve is with respect to the decrease in recovery time in the first part of the dose–response curve.

The parameters a, b, and c were estimated by weighted nonlinear regression analysis, using the reciprocal of the variance of $T_{TOF\ 0.9}$ as a weighting factor. This analysis was performed for each time point of administration of sugammadex separately.

The paired *t* test was used for within-subject comparisons of the electrocardiographic data (QTc intervals and heart rate), and analysis of variance was used to compare the dose groups. Linear regression analysis was used to explore the possible relation between sugammadex dose and QTc intervals and heart rate. Analysis of covariance was used to investigate the effect of sugammadex dose and time point of administration on selected laboratory variables, using the baseline value as a covariable. Data are presented as mean (SD) unless stated otherwise.

Results

Patients

A total of 99 male white patients were enrolled in the study and randomized, and 98 patients were included in the intent-to-treat population and safety populations; one patient who discontinued from the trial before receiving study medication was excluded from the intent-to-treat population. In 4 subjects, noncompliance with the protocol was observed that might have affected the primary and secondary endpoints; therefore the PP population comprised 94 patients. No statistically significant differences were observed between the treatment groups in terms of baseline characteristics (table 1). The median (range) induction doses of propofol and fentanyl were 2.4 (1.7–3.1) mg/kg and 2.7 (0.6–4.7) μg/kg, respectively. The median (range) skin temperature over the adductor pollicis muscle was 34.4°C (32.5°–37.5°C) at 1 h after administration of both sugammadex and placebo.

Efficacy

Results for the intent-to-treat population differed from those for the PP population. This was mainly due to the fact that one patient who was randomly assigned to the 2.0 mg/kg sugammadex group received placebo instead. Time to recovery of the TOF ratio to 0.9 for this patient was 46.8 min, which is approximately nine times longer than the mean recovery time in the 2.0 mg/kg sugammadex group. Including this result in the fit of the dose–response curve would introduce a high variability around the curve. Efficacy results are therefore presented for the PP population only.

The mean time to recovery of the TOF ratio to 0.9, after dosing at 3, 5, and 15 min, decreased from 52.1, 51.7, and 35.6 min, respectively, after administration of placebo to 1.8, 1.5, and 1.4 min, respectively, after 8 mg/kg sugammadex in the PP population (table 2). The estimated dose–response relation and associated 95% confidence intervals between recovery of the T_4/T_1 ratio to 0.9 and the dose of sugammadex for the 3-, 5-, and 15-min groups (PP population) are shown in figures 1A–C. In the group receiving sugammadex or placebo 15 min after rocuronium, 8 of 31 patients had already recovered to one or two twitches of the TOF, whereas in the remaining 23 patients, the number of posttetanic counts reached a median [range] value of 1 [0–15] 1 min before reversal was attempted. When sugammadex was administered at 15 min, the exponential model adequately described the relation between the dose of sugammadex and the time to recovery of the TOF ratio to 0.9. When administered at 3 and 5 min, the dose–response curve underestimated the recovery time to TOF 0.9 for the 1 mg/kg dose but adequately estimated the recovery times for higher doses of sugammadex. For all time points of administration of sugammadex, there was a statistically significant ($P < 0.05$) decrease in the mean recovery time to TOF 0.9 with increasing doses of sugammadex.

In one subject treated with 4 mg/kg sugammadex in the 3-min group, the time to recovery of TOF ratio to 0.9 was considerably longer (24.6 min) than the mean time

Table 2. Time Interval (Minutes) from Administration of Sugammadex or Placebo to a Train-of-four Ratio of 0.7, 0.8, and 0.9 for the Various Time and Dose Groups (Per-protocol Population)

		Placebo	Sugammadex Dose Group, mg/kg				
Time of Administration of Sugammadex or Placebo	Time to Train-of-four Ratio	(n = 3)	1.0 (n = 6)	2.0 (n = 6)	4.0 (n = 6)	6.0 (n = 6)	8.0 (n = 6)
3 min	0.7	46.0 (8.0)	17.8 (8.8)	4.1 (1.3)*	2.1 (0.5)	1.3 (0.5)†	1.2 (0.3)†
	0.8	48.2 (8.0)	20.0 (10.7)	4.5 (1.5)*	2.3 (0.6)	1.6 (0.5)†	1.2 (0.4)†
	0.9	52.1 (8.8)	22.7 (11.6)	4.9 (1.3)*	6.3 (9.0)	1.9 (0.6)†	1.8 (0.9)†
5 min	0.7	45.2 (7.8)	22.8 (5.9)	4.8 (1.3)	1.8 (0.7)	1.4 (0.5)	1.1 (0.3)
	0.8	46.8 (8.4)	24.8 (5.7)	6.4 (3.1)	2.0 (0.7)	1.7 (0.7)	1.1 (0.3)
	0.9	51.7 (13.1)	27.4 (6.4)	8.9 (7.8)	2.3 (0.7)	2.1 (0.9)	1.5 (0.6)
15 min	0.7	31.2 (6.6)	4.7 (1.3)	2.2 (0.6)	1.2 (0.3)‡	1.1 (0.5)	1.1 (0.1)
	0.8	33.4 (8.1)	5.5 (1.4)	2.4 (0.7)	1.3 (0.5)‡	1.2 (0.5)	1.2 (0.2)
	0.9	35.6 (9.1)	6.5 (1.7)	2.7 (0.7)	2.1 (1.2)	2.1 (2.0)	1.4 (0.2)

Data are presented as mean (SD).

* n = 3. † n = 5. ‡ n = 5 because one patient (in the 4.0 mg/kg group) had a minor protocol violation: Times to recovery train-of-four ratios to 0.7 and 0.8 were considered to be unreliable.

in the 2 mg/kg dose group (fig. 1A). In contrast, the times to TOF ratio 0.7 and 0.8 in this subject were 2.7 and 3.4 min, respectively. This explains the large SD in the time to TOF ratio 0.9 in the 4.0 mg/kg dose group (table 2). Another outlying recovery time of TOF ratio to 0.9 was observed in the 2 mg/kg dose group administered at 5 min after rocuronium (fig. 1B). Sugammadex also shortened the times to recovery of the TOF ratio to 0.7 and 0.8 in a dose-dependent manner (table 2). No signs of recurarization were observed in the 60 min of TOF monitoring after administration of sugammadex or during the stay in the postoperative recovery unit.

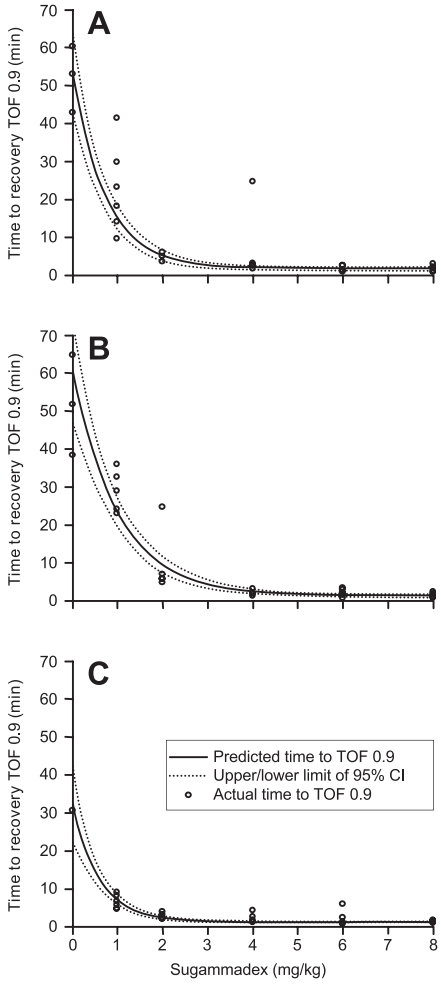

Fig. 1. Estimated dose–response relation between the recovery of the train-of-four (TOF) ratio to 0.9 and the dose of sugammadex, administered 3 min (*A*), 5 min (*B*), and 15 min (*C*) after 0.6 mg/kg rocuronium, with 95% confidence intervals (CIs). Actual data are indicated by *open dots* (per-protocol population).

Pharmacokinetics

No plasma samples were taken from one of the 99 patients, and the rocuronium dosing information was not known in another. These data were therefore excluded from the pharmacokinetic analysis. In total, 475 rocuronium plasma samples and 344 sugammadex plasma samples from 97 patients were used for the pharmacokinetic analysis. Individual pharmacokinetic parameters for rocuronium (97 patients) and sugammadex (87 patients) were obtained by *post hoc* analysis of the plasma concentration–time data, using the pharmacokinetic model developed previously.

Figures 2A–D show four representative examples of the plasma concentration profiles of rocuronium and sugammadex. After administration of sugammadex, the total plasma concentration of rocuronium (free and bound combined) increased slightly in the 1 mg/kg (fig. 2B) and 2 mg/kg dose groups and more pronouncedly in the 6 and 8 mg/kg dose groups (fig. 2D), compared with the placebo group (fig. 2A). The concentration of free rocuronium, as calculated using the pharmacokinetic model, decreased more rapidly in the higher sugammadex dose groups (figs. 2C and D) compared with the lower sugammadex dose groups (fig. 2B).

The median cumulative excretion of rocuronium in the urine over 24 h was 26% in the placebo group, 30% for 1 mg/kg sugammadex, 33% for 2 mg/kg sugammadex, and 58–74% after sugammadex doses of 4 mg/kg

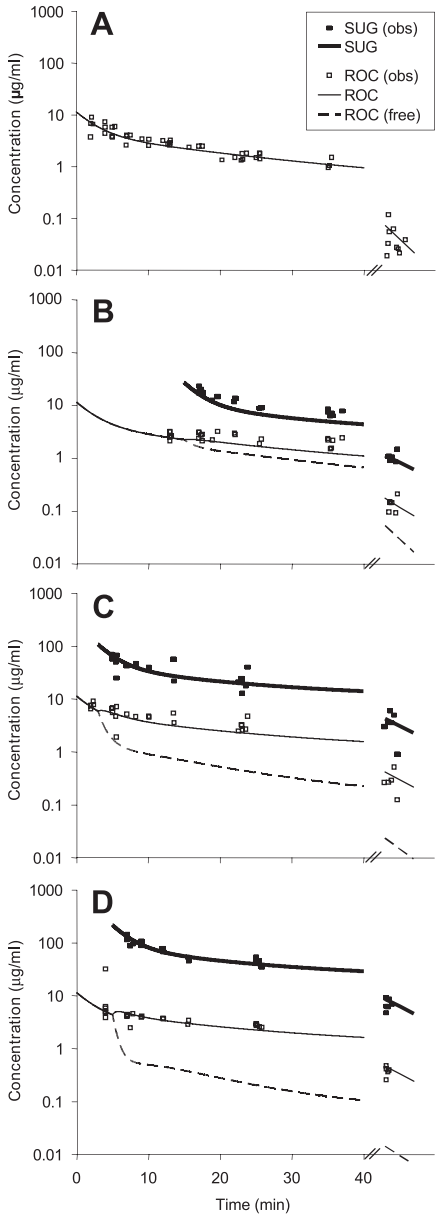

Fig. 2. Plasma concentration–time profiles of rocuronium and sugammadex, after administration of 0.6 mg/kg rocuronium followed by sugammadex placebo (*A*), 1 mg/kg sugammadex administered after 15 min (*B*), 4 mg/kg sugammadex administered after 3 min (*C*), 8 mg/kg sugammadex administered after 5 min (*D*). The *open* and *closed symbols* represent the observed (obs) plasma concentrations of all patients in the dose group for rocuronium (ROC) and sugammadex (SUG), respectively. The *normal* and *thick lines* represent the plasma concentration profiles according to the pharmacokinetic model for rocuronium and sugammadex, respectively. The *dashed line* is the calculated plasma concentration of free rocuronium (ROC (free)). The *right part of the graph* represents the time period between 4 and 6 h after administration.

and higher. The mean cumulative percentage of sugammadex excreted in the urine up to 24 h varied between 48% and 86%. There was no relation between the dose of sugammadex administered and the percentage of the dose excreted in the urine. The pharmacokinetic parameters for rocuronium and sugammadex, obtained from the *post hoc* analysis, are shown in table 3. The major difference in the pharmacokinetics of rocuronium and sugammadex is the clearance, which is approximately three times higher for rocuronium.

Table 3. Pharmacokinetic Parameters of Rocuronium (97 Patients) and Sugammadex (87 Patients)

Parameter	Rocuronium	Sugammadex
CL, l/min	0.26 (23)	0.084 (22)
V_1, l	3.7 (32)	2.6 (29)
CL_{12}, l/min	0.58 (12)	0.43*
V_2, l	3.4 (18)	2.3 (12)
CL_{13}, l/min	0.13 (23)	0.21*
V_3, l	7.6 (15)	8.9*
$t_{½}$, min	69 (18)	136 (17)

Data are the geometric means of the *post hoc* individual values (coefficient of variation).

* *Post hoc* value the same for each patient.

CL = clearance; CL_{12} = intercompartmental clearance 1–2; CL_{13} = intercompartmental clearance 1–3; $t_{½}$ = terminal elimination half-life; V_1 = volume of distribution of the central compartment; V_2 = volume of distribution of the first peripheral compartment; V_3 = volume of distribution of the second peripheral compartment.

Safety

The majority of the AEs were classified as mild or moderate in intensity. Among the most frequently reported AEs were signs characteristic of insufficient depth of anesthesia such as an increase in Bispectral Index (Bispectral Index monitoring was not specified in the protocol, but applied in several patients), sucking, grimacing, moving, and coughing on the tube, which were reported in 18 of 88 patients (20.4%) receiving sugammadex (table 4).

No clinically relevant changes were reported for heart rate or blood pressure (systolic and diastolic) for an interval of 30 min after administration of sugammadex compared with predrug control values. Electrocardiographic analysis generally showed slightly higher QTc values after sugammadex compared with placebo, but these differences were rarely significant, and a relation between dose and QTc prolongation was not found. Abnormal or pathologic electrocardiographic waves were not observed.

Table 4. Signs of Light Plane of Anesthesia Observed in 18 of 88 Patients Given Sugammadex

	Sugammadex Dose Group, mg/kg					
	1.0	2.0	4.0	6.0	8.0	Total
Grimacing	1	0	0	0	0	1
Sucking	1	1	0	0	0	2
Increase in BIS value	1	1	0	1	1	4
Movement	1	1	0	2	3	7
Coughing	3	1	1	1	4	10

One single patient can have more than one sign.

BIS = Bispectral Index.

Urinalysis revealed AEs in 10 patients, of whom 4 showed abnormal values for microalbumin (1 patient each in the 1, 2, 4, and 6 mg/kg sugammadex dose groups), 2 showed abnormal values for *N*-acetyl-glucosaminidase (1 patient each in the 1 and 4 mg/kg dose groups), and 3 showed abnormal values for β_2-microglobulin (2 patients in the 1 mg/kg dose group and 1 in the 2 mg/kg dose group). Most of these AEs were considered mild by the investigators, and any relation to sugammadex dose and time point of administration was excluded. One patient (6.0 mg/kg dose group) had a serum creatinine level above the normal range on the day after surgery (an increase from 89.3 μM before administration of rocuronium to 161.8 μM the day after surgery), which had returned to normal (95.5 μM) when remeasured in an unscheduled blood sample 20 days after surgery.

At least one AE was reported in 42 of 88 patients (48%) in the sugammadex group and in 2 of 10 patients (20%) in the placebo group. For 16 of 98 subjects (16%), one or more AEs were considered to be possibly related to sugammadex. No dose–response relation was observed with respect to the incidence of drug-related AEs. Drug-related AEs were reported in 5 of 18 patients (28%) in the 1.0 mg/kg sugammadex group, 3 of 16 patients (19%) in the 2.0 mg/kg sugammadex group, 1 of 18 patients (6%) in the 4.0 mg/kg sugammadex group, 3 of 18 patients (17%) in the 6.0 mg/kg sugammadex group, and 4 of 18 patients (22%) in the 8.0 mg/kg sugammadex group. None of the subjects discontinued the trial because of an AE, and no serious AEs occurred. With respect to the 3-, 5-, and 15-min time groups, the numbers of patients with AEs considered possibly related to sugammadex were 9, 1, and 6, respectively.

Discussion

The selective relaxant binding agent sugammadex was developed to reverse rocuronium-induced NMB.[5] This phase II study showed that sugammadex was well tolerated and reversed profound NMB when given as early as 3, 5, or 15 min after an intubating dose of rocuronium (0.6 mg/kg). The speed of recovery was dose dependent, and the reversal was sustained without any signs of recurarization. The mean time to recovery of the TOF ratio to 0.9 was less than 3 min at sugammadex doses of 6.0 mg/kg or greater in the 3-min group, at sugammadex doses of 4.0 mg/kg or greater in the 5-min group, and at sugammadex doses of 2.0 mg/kg or greater in the 15-min group.

The ability of sugammadex to rapidly reverse profound rocuronium-induced blockade has been demonstrated in animal experiments,[5,6,11] as well as in studies in human volunteers[7] and patients.[12,13] The rapid sugammadex-induced recovery times after NMB induced by rocuronium are comparable with the spontaneous recovery times with succinylcholine. In addition, the interindividual variability in the response to effective doses of sugammadex (2–8 mg/kg in the present study) seems small. The mechanism of reversal of rocuronium by sugammadex (physicochemical binding) seems in agreement with the observed lack of important interindividual variability in recovery times.[7] In contrast, there is a considerable variation in the spontaneous recovery time from succinylcholine. Roy *et al.*[14] reported a mean time to 50% T_1 recovery of 10.2 min (range, 7.8–16.8 min) after administration of 1 mg/kg succinylcholine to patients undergoing surgery. Even after a lower dose of succinylcholine (0.6 mg/kg), the time to 90% T_1 recovery may be too long (5.5–10.5 min) to shorten the period of apnea below the safe level in all subjects in the case of an unexpected difficult airway.[15,16] Although rocuronium is a commonly accepted alternative to succinylcholine to facilitate tracheal intubation during rapid-sequence induction, its long duration of action is considered the major drawback in this context.[17] However, the ability of sugammadex to reverse even a profound rocuronium-induced NMB may allow anesthesiologists to control the time course of rocuronium to a previously unknown extent. A comparison of rocuronium/sugammadex with succinylcholine, which was not undertaken in this study, should be conducted in the future.

Another important issue in the reversal of nondepolarizing muscle relaxants is the well-known unwanted effects of cholinesterase inhibitors and anticholinergic drugs. Because sugammadex acts by specific binding to free rocuronium, and not at the nicotinic acetylcholine receptor of the muscle end plate nor by influencing the release and metabolism of acetylcholine, unwanted cardiovascular and pulmonary effects are not anticipated and have not been observed so far.[7,18] A secondary objective of this study was to assess the safety of sugammadex. Patients were followed up for 7 days after anesthesia. Overall, sugammadex was well tolerated. In particular, there were minimal effects on heart rate and blood pressure after sugammadex administration. Electrocardiographic analysis showed slightly higher QTc values after sugammadex than after placebo, but the changes were rarely significant, and no relation between the dose of sugammadex and QTc prolongation was found.

The most striking AEs related to the administration of sugammadex were signs characteristic of insufficient depth of anesthesia, such as an increase in Bispectral Index, grimacing, moving, sucking on the tube, and coughing. Vasella *et al.*[19] have shown that neostigmine alters the depth of propofol–remifentanil anesthesia and enhances recovery as assessed by Bispectral Index and middle-latency auditory evoked potentials. In accordance with the muscle spindle theory, these authors speculated that the reversal of NMB by neostigmine

leads to a sustained cerebral arousal reaction during anesthesia.[19,20] This mechanism, in combination with a light plane of anesthesia at the time of administration of sugammadex and some kind of stimulation, may be considered the trigger for the observed motor responses in the current study. Theoretically, the anesthetic state might also be changed due to capture of fentanyl and/or propofol by sugammadex. This mechanism, however, is unlikely, because the affinity of sugammadex for narcotics and intravenous anesthetics is negligibly small (data on file, Organon NV). In five patients given sugammadex, abnormal values for microalbumin, *N*-acetyl-glucosaminidase, and/or β_2-microglobulin were found. However, there was no relation between these abnormal laboratory values and the dose of sugammadex.

In accordance with the only published phase I study[7] and all other phase II studies with sugammadex,[11–13,18,21] acceleromyography was used in this study for the objective monitoring of neuromuscular function. Although it is common to recommend the use of mechanomyography in phase I and II studies of new compounds,[22] mechanomyographic monitors are no longer being manufactured. There is convincing evidence that acceleromyography tends to overestimate the extent of recovery after the use of nondepolarizing muscle relaxants. The average displayed acceleromyographic TOF ratio usually exceeds the simultaneously measured mechanomyographic or electromyographic value by 0.05–0.15.[23,24] It has been suggested that acceleromyography can be used with confidence for neuromuscular monitoring provided a TOF ratio of 0.9 or more is used to denote adequate recovery.[23–25] One limitation of the current study is lack of documentation of core temperature. However, patients were actively warmed with forced-air warming blankets starting just before the induction of anesthesia and maintained throughout surgery. It is therefore likely that patients were—with exception of a mild initial redistribution hypothermia—normothermic during the study period.[26]

The plasma concentrations of rocuronium and sugammadex were measured at several time points, *i.e.*, immediately before administration of sugammadex and at 2, 10, and 20 min and 4–6 h after sugammadex administration. This sampling schedule allowed an estimation of the individual pharmacokinetic parameters of rocuronium and sugammadex, using the Bayesian *post hoc* procedure and the pharmacokinetic population model of both compounds derived from previous studies. From this pharmacokinetic analysis, we determined the unbound and total plasma concentration–time profiles of rocuronium and sugammadex to allow a better understanding of the time course of action of sugammadex (fig. 2). The main difference in the pharmacokinetic profile of sugammadex and rocuronium is that the clearance of sugammadex is approximately three times lower than that of rocuronium. Similar findings were reported by Gijsenbergh *et al.*[7] in a phase I study in human volunteers. In that study, the plasma clearance of rocuronium decreased by a factor of greater than 2 when administration of rocuronium was followed by a sugammadex dose of 2.0 mg/kg or greater. Rocuronium is cleared in unchanged form primarily by the liver, is excreted into the bile, and is eventually excreted with the feces, with a contribution of renal excretion of 26% of the dose.[27]

In our study, the renal excretion of rocuronium was enhanced by sugammadex. In agreement with the results of Gijsenbergh *et al.*,[7] the mean percentage of the dose of sugammadex excreted in the urine up to 24 h varied between 48% and 86% in our study. The mean clearance values for sugammadex in this study and the volunteer study of Gijsenbergh *et al.*[7] were 84 and 93 ml/min, respectively, and the clearance of sugammadex in our study is 38% less than the average creatinine clearance of 136 ml/min. This suggests that filtration of sugammadex is lower than glomerular filtration due to plasma protein binding, or that sugammadex is partly reabsorbed from the lumen of the tubulus.

Assuming that the pharmacokinetic profile of the rocuronium–sugammadex complex is similar to that of sugammadex, the lower clearance of sugammadex compared with rocuronium implies that the elimination of rocuronium is retarded by the administration of sugammadex. In the absence of sugammadex, rocuronium is eliminated mainly by excretion into bile and feces. In the presence of sugammadex, however, urinary excretion of the rocuronium–sugammadex complex is the major route of elimination of rocuronium. The biliary excretion route is not available for the rocuronium–sugammadex complex; therefore, the total clearance of rocuronium in the presence of sugammadex is lower than in the absence of sugammadex. Indeed, the plasma concentration of total rocuronium (free and complexed drug combined) decreases less rapidly after administration of sugammadex. However, as indicated by the rapid recovery from NMB, the plasma concentration of free rocuronium decreases rapidly after administration of sugammadex. Interestingly, shortly after administration of sugammadex, the total plasma concentration of rocuronium increases. This can be explained by redistribution of free rocuronium from the peripheral compartments back to plasma as a result of the decreased free plasma concentration. Redistributed free rocuronium is largely encapsulated by sugammadex, thus increasing the total rocuronium concentration.

In conclusion, this study in male subjects shows that sugammadex is effective in reversing profound NMB induced by 0.6 mg/kg rocuronium, and it is well tolerated up to doses of 8 mg/kg. However, in 20.4% of patients, signs of inadequate anesthesia became evident after reversal. No signs of recurarization were observed after sugammadex. There is a clear dose–response rela-

tion upon administration of sugammadex at 3, 5, or 15 min after 0.6 mg/kg rocuronium. Early reversal of rocuronium (at 3 and 5 min) to a TOF ratio of 0.9 is achieved within 2–3 min after sugammadex doses of 6 and 8 mg/kg, respectively. Sugammadex enhanced the renal excretion of rocuronium and its clearance is approximately one third that of rocuronium. In view of the potential of sugammadex to reverse even a profound NMB, and its favorable safety profile, this agent may fulfill the criteria of an ideal reversal agent for rocuronium.

Bart A. Ploeger, Pharm.D., Ph.D. (LAP&P Consultants, Leiden, The Netherlands), developed the pharmacokinetic–pharmacodynamic interaction model for sugammadex and rocuronium and performed the pharmacokinetic *post hoc* analysis. Editorial assistance was provided by Julie Adkins, B.Pharm., M.Sc. (Principal Medical Writer, Prime Medica, Knutsford, Cheshire, United Kingdom).

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