A Randomized, Dose-Finding, Phase II Study of the Selective Relaxant Binding Drug, Sugammadex, Capable of Safely Reversing Profound Rocuronium-Induced Neuromuscular Block

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BACKGROUND: The reversal of a deep neuromuscular blockade remains a significant clinical problem. Sugammadex, a modified γ-cyclodextrin, encapsulates steroidal neuromuscular blocking drugs, promoting their rapid dissociation from nicotinic receptors. Sugammadex is the first drug that acts as a selective relaxant binding agent.
METHODS: We enrolled 50 patients into a Phase II dose-finding study of the efficacy and safety of sugammadex. Subjects, anesthetized with nitrous oxide and propofol, were randomized to one of two doses of rocuronium (0.6 or 1.2 mg/kg) and to one of five doses of sugammadex (0.5, 1.0, 2.0, 4.0 , or 8.0 mg/kg). Neuromuscular monitoring was performed using the TOF Watch SX® acceleromyograph. Recovery was defined as a train-of-four ratio ≥0.9. Sugammadex was administered during profound block when neuromuscular monitoring demonstrated a posttetanic count of one or two.
RESULTS: Reversal of neuromuscular block was obtained after administration of sugammadex in all but the lowest dose groups (0.5–1.0 mg/kg) where several subjects could not be adequately reversed. At the 2 mg/kg dose all patients were reversed with sugammadex, but there was significant variability (1.8–15.2 min). Patient variability decreased and speed of recovery increased in a dose-dependent manner. At the highest dose (8 mg/kg), mean recovery time was 1.2 min (range 0.8–2.1 min). No serious adverse events were reported during this trial.
CONCLUSIONS: Sugammadex was well tolerated and effective in rapidly reversing profound rocuronium-induced neuromuscular block. The mean time to recovery decreased with increasing doses. Profound rocuronium-induced neuromuscular block can be reversed successfully with sugammadex at doses ≥2 mg/kg.
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Neuromuscular blocking drugs (NMBDs) are often used to facilitate endotracheal intubation and provide skeletal muscle relaxation during surgery. At the conclusion of surgery, it is desirable that the effects of NMBDs be reversed as rapidly and completely as possible. Currently, anticholinesterases are used to reverse the effects of NMBDs. Cholinesterase inhibitors, however, are not effective if used in profound block, and may not even completely reverse a moderate block after 20 min (1). Because of their site of action, administration of anticholinesterases can result in cardiovascular and respiratory effects arising from direct cholinergic stimulation of unblocked muscarinic receptors (2,3). Muscarinic antagonists are usually administered together with anticholinesterases but also are associated with side effects relating to their function.

The ability to terminate the action of NMBDs quickly at any level of block is highly desirable. A new class of drugs, selective relaxant binding agents (SRBAs), was engineered to specifically reverse the effects of aminosteroid NMBDs (4–6). Sugammadex, the first SRBA to be tested clinically, is a modified γ-cyclodextrin (Fig. 1) that encapsulates rocuronium, forming a tightly bound complex (4). Sugammadex was recently found to be effective and well tolerated in healthy volunteers (7) and surgical patients (8) at doses up to 16.0 mg/kg. Additionally, sugammadex at doses of 2.0–4.0 mg/kg has been shown to safely reverse moderate neuromuscular block (NMB) induced by rocuronium in a dose-dependent manner in surgical patients (9,10).

In this study, we assessed the safety and efficacy of five doses of sugammadex in reversing profound rocuronium-induced NMB, defined as one or two

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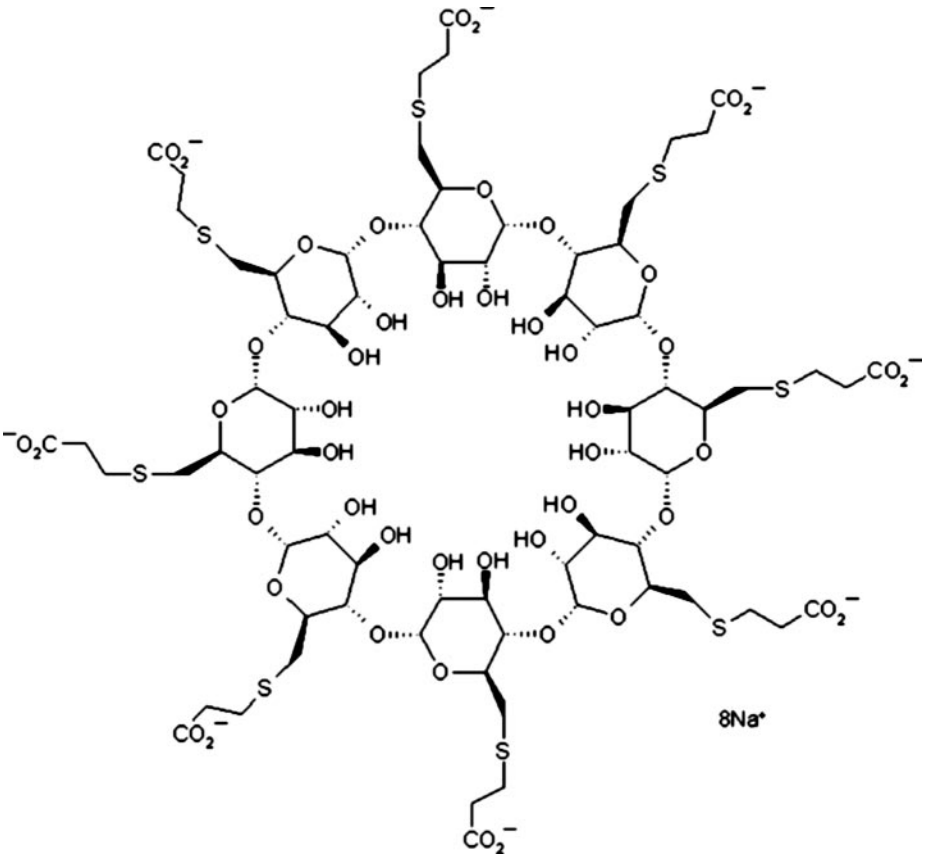

Figure 1. Chemical structure of sugammadex, a modified cyclodextrin.

posttetanic counts (PTCs), in patients undergoing elective surgery. Our primary objective was to explore the dose–response relationship of sugammadex in reversing profound rocuronium-induced NMB. Additionally, we hypothesized that the intubating dose of rocuronium (0.6 or 1.2 mg/kg) would not influence the dose of sugammadex required to reverse a NMB if reversal was attempted at the same level of profound block.

METHODS

We conducted a Phase II, randomized, assessor-blinded, parallel-group, dose-finding trial at four sites in the United States: Albany Medical Center, NY; Weill Medical Center at Cornell University/NY Presbyterian Hospital, NY; SUNY/Stony Brook Health Sciences Center, NY; and Stanford Medical Center, CA. The protocol was approved by the IRB at each participating center. Subjects were enrolled between August 2004 and May 2005, after written informed consent was obtained.

Subjects aged ≥18 yr of age, with ASA physical status I–III, scheduled to undergo an elective surgical procedure anticipated to last at least 45 min , and requiring endotracheal intubation and the use of a nondepolarizing NMBD were eligible for inclusion.

Patients were excluded from the study if they were undergoing dental or neck surgery, were expected to have intubation difficulties, had neuromuscular disorders and/or significant renal dysfunction in the opinion of the primary investigator, had a personal or family history of malignant hyperthermia, or an allergy to narcotics, muscle relaxants , or other medication used in anesthesia. Patients receiving medication known to interfere with NMBDs, such as anticonvulsants, certain antibiotics, and magnesium, were also excluded, as were female patients who were pregnant, breast-feeding, or of childbearing age not using a reliable method of contraception.

Before the surgical procedure, subjects were randomized to one of two doses of rocuronium (0.6 or 1.2 mg/kg) and to one of five doses of sugammadex (0.5, 1.0, 2.0, 4.0 , or 8.0 mg/kg). Computer randomization was performed, and subjects were assigned to a group by an investigator at each research site who was not involved in medication administration. Each patient was then assigned the next sequential number for their particular center in order of their enrollment into the clinical trial. Six patients were anticipated for each group. The proposed sample size per dose group was determined by practical reasons because there were no prior data available on sugammadex and profound NMB that could be used to perform a power analysis. A safety assessor was assigned to each subject, and this assessor was blinded to treatment group.

Anesthesia was induced with propofol (2–4 mg/kg) and maintained with nitrous oxide (50%–70%), IV

propofol (75–200 $\mu g \cdot kg^{-} \cdot min^{-}$) and opioids (fentanyl 2–5 μg/kg and/or remifentanil 0.125–1 $\mu g \cdot kg^{-} \cdot min^{-}$) titrated to desired clinical effect by the attending anesthesiologist. Neuromuscular function was monitored using the TOF-Watch® SX acceleromyograph (Organon Ireland , Dublin, Ireland). Stabilization, calibration , and baseline responses were obtained after induction of anesthesia but before the administration of rocuronium. Stabilization was performed with a 5- s, 50 -Hz tetanic stimulus. After 1 min, repetitive train-of-four (TOF) stimulation was started every 15 s for 3 min, and then , the TOF-Watch SX was calibrated followed by 3 min of baseline tracing. Calibration was considered stable if the TOF ratio during the baseline period was consistently within 10% of 100 and the postcalibration current was ≤60mA. Rocuronium 0.6 or 1.2 mg/kg was then administered, and once adequate muscle relaxation was achieved, the trachea was intubated. Maintenance doses of rocuronium 0.15 mg/kg were given if the PTC exceeded 2.

TOF stimulation was performed every 15 s. When no TOF response could be detected, the investigators performed PTC stimulation to assess depth of NMB. PTC stimulation occurred no more frequently than once every 2 min. As soon as muscle relaxation was no longer required for surgery and the TOF-Watch SX reading was 1–2 PTCs, a single IV bolus dose of sugammadex (0.5, 1.0, 2.0, 4.0 , or 8.0 mg/kg) was administered. The patient remained tracheally intubated and anesthesia was maintained for a minimum of 30 min after the administration of sugammadex to assure full recovery from the NMB (TOF ≥0.9) and to allow observation of the TOF-Watch SX for signs of muscle weakness. Other reversal drugs (e.g., neostigmine) were not administered to enrolled patients unless at least 30 min had passed and the TOF ratio remained ≤0.9. If after administration of sugammadex, renewed muscle relaxation was needed, a nonsteroidal NMBD could be administered. Standard clinical tests of muscle strength including 5-second head lift test, a tongue depressor test (11) and inquiries as to the presence of diplopia (11,12) were performed in the recovery room to assure adequate recovery from NMB.

Vital signs were recorded at pretrial screening, just before administration of rocuronium, at 2, 10, and 30 min after administration of sugammadex, and at the postanesthetic visit. Central body temperature was measured continuously in the nasopharynx or esophagus, and maintained at ≥35°C using standard techniques of heat conservation (fluid warming and warm air convection heating). Oxygen saturation and respiratory frequency were monitored for at least 400 min after recovery to a TOF ratio of 0.9.

Arterial blood pressure, pulse oximetry, and heart rate were monitored (intraoperatively and throughout the postoperative period) and 12-lead electrocardiograms (ECG) were recorded preoperatively, just before administration of rocuronium, and 2 and 30 min after sugammadex administration. Covance (Reno, NV) an independent contract research organization, collected, analyzed, and summarized the ECG data for the Biometrics Department of Organon. The ECG recording taken just before the administration of rocuronium was used as baseline and changes in the corrected QT (QTc) interval were quantified and compared with baseline data. For the evaluation of QT intervals, three established corrections were used (13,14). ECGs were also analyzed for any changes in PR, QRS, and T wave morphology.

A physician member of the study team who was blinded to the treatment groups conducted a postanesthetic visit between 10 and 24 h after administration of sugammadex. The follow-up period started at the end of the trial period and ended on the seventh postoperative day.

Venous blood samples were obtained preoperatively and at 20 min, 4–6 h, and 24 h after administration of sugammadex. Laboratory tests included a complete blood count, standard electrolytes, liver enzymes, and haptoglobin. Urine samples were also obtained immediately preoperatively and 24 h after the administration of sugammadex. In addition to standard urinalysis parameters, *N*-acetyl glucosaminidase, β2-microglobulin, and microalbumen were also assayed. All laboratory testing was done centrally by BARC USA (Lake Success, NY).

Recovery from NMB was studied in the protocol population (PP) (i.e., all patients in the intent-to-treat (ITT) population without any major protocol violations). The safety analysis was performed on the all-patients-treated population (i.e., all patients who received a dose of sugammadex).

The primary efficacy variable was the time from the start of administration of sugammadex to recovery of the TOF ratio to 0.9. Secondary efficacy variables were the time from the start of administration of sugammadex to recovery of the TOF ratio to 0.7 and 0.8. Descriptive statistics for the efficacy variables (mean, SD, median, minimum, and maximum values) were grouped by intubating dose of rocuronium and dose of sugammadex. Dose–response curves were also estimated for the primary and secondary efficacy variables. Statistical analyses were performed by the statistics department of Organon, USA. Statistical testing was performed to examine the dose relationship between primary and secondary variables and the doses of sugammadex for each rocuronium dose group. Dose–response curves relating time to recovery to a TOF ratio of 0.9 were constructed. The number of PTCs at administration of sugammadex was summarized, but no statistical analyses were performed because of small sample size. All statistical tests were two-sided with significance level of 0.05.

RESULTS

Fifty of the planned 60 patients were enrolled in the study and randomized to one of the five sugammadex dose groups. Seven patients were withdrawn from the

Table 1. Number of Patients in Each Treatment Group

	Sugammadex dose group (mg/kg)					
o:p	0.5	1.0	2.0	4.0	8.0	Total
After administration of rocuronium 0.6 mg/kg						
Randomized	6	6	6	4	6	28
Treated[a]	5	6	5	3	5	24
PP population	4	5	5	2	4	20
After administration of rocuronium 1.2 mg/kg						
Randomized	5	4	5	4	4	22
Treated	4	4	4	3	4	19
PP population	3	4	3	3	4	17

PP = per protocol population.

[a] One subject in the rocuronium 0.6 mg/kg group was randomized to sugammadex 8.0 mg/kg but received sugammadex 0.8 mg/kg and was included in the sugammadex 1.0 mg/kg dose group.

trial before sugammadex was administered for the following reasons: unable to calibrate and/or stabilize the TOF-Watch SX or obtain TOF-Watch SX readings ($n = 4$), change in surgical plan necessitating removal of the twitch monitor ($n = 2$), and patient withdrew consent ($n = 1$). Forty-three patients therefore received a dose of sugammadex (Table 1), of which one patient did not have efficacy assessments because of technical problems with the TOF-Watch SX, leaving 42 subjects in the ITT group. Five patients had major protocol violations and were excluded from the PP analysis ($n = 37$). The major protocol violations comprised the following: missing PTC data (sugammadex 2.0 mg/kg group and sugammadex 8.0 mg/kg); premature administration of neostigmine before any efficacy data obtained (sugammadex 0.5 mg/kg); administration of a magnesium containing medication (sugammadex 0.5 mg/kg), and administration of the incorrect sugammadex dose (0.8 mg/kg instead of 8.0 mg/kg). The latter patient was included in the sugammadex 1.0 mg/kg group for the safety analysis and in the 8.0 mg/kg group for the ITT analysis, but was excluded from the PP analysis.

There were no significant demographic differences between the ITT groups with regard to height, sex, weight, ASA classification, and race. Ninety-one percent of the subjects described themselves as Caucasian, 5% African American, and 5% as other.

The times from the start of administration of sugammadex to recovery of the TOF ratio to 0.9 for the PP population who attained this end point without protocol violation are summarized in Table 2. Eight of the 37 patients in the PP did not reach this end-point (Table 3). All patients eventually had complete recovery of their neuromuscular function and had their tracheas extubated postoperatively.

In both rocuronium dose groups there was a substantial decrease in time to recovery of the TOF ratio to 0.9 with increasing dose of sugammadex. For example, in the rocuronium 0.6 mg/kg group, the mean time to recovery to a TOF ratio of 0.9 after administration of sugammadex 0.5 mg/kg was 44.2 min and this decreased to 1.5 min in the sugammadex 8.0 mg/kg group. In the rocuronium 1.2 mg/kg group the mean time to recovery with sugammadex 0.5 mg/kg was 20.6 min and this was reduced to 1.0 min in the sugammadex 8.0 mg/kg group. A similar trend was observed for the secondary efficacy variables with the mean time to recovery to a TOF ratio of 0.7 and 0.8 decreasing with increasing dose of sugammadex.

On admission to the recovery room 16/24 (67%) patients in the rocuronium 0.6 mg/kg group and 11/19 (58%) in the rocuronium 1.2 mg/kg group were oriented. Of these, all but one patient (rocuronium 0.6 mg/kg group; 8.0 mg/kg of sugammadex) were able to perform a 5 s head lift. Before discharge from the recovery room, 42/43 patients (23/23 patients in the rocuronium 0.6 mg/kg group and 19/20 patients in the rocuronium 1.2 mg/kg group) successfully performed the 5 s head lift: one patient was discharged from the postanesthetic care unit (PACU) before an assessment was performed. All patients (excluding those who were edentulous) were able to hold a tongue depressor between their teeth while a blinded assessor attempted to remove it. There was no subjective evidence of diplopia or general muscle weakness in any patients when admitted to, or discharged from, the PACU.

The principal investigators identified four serious adverse events (AEs), none of which were felt by the investigators to be related to study medication or protocol. All four patients made full recoveries.

Thirty-five of the 43 patients experienced at least 1 AE during the trial, but no dose relation was seen. The most common AEs were postprocedural pain ($n = 18$ patients), nausea ($n = 14$), vomiting ($n = 6$), hypertension ($n = 5$), hypotension ($n = 4$), and brief periods of oxygen desaturation ($n = 4$).

No patient complained of weakness or diplopia during their PACU stay, no evidence of muscle weakness was seen, and no subject suffered any permanent morbidities or mortality as a result of participation in the study.

Six patients experienced AEs that were considered by the investigator to be possibly related to sugammadex. In the rocuronium 0.6 mg/kg group these included incomplete reversal of NMB (sugammadex 0.5 mg/kg), moderate dizziness (sugammadex 2.0 mg/kg), coughing on the endotracheal tube and movement during surgery (sugammadex 8.0 mg/kg) 1 min after sugammadex administration, and moderately elevated $\beta 2$ microglobinuria with a substantially elevated creatine phosphokinase (CK) (5400 U/L) at the 24-h postdose assessment in the sugammadex 8.0 mg/kg group. In the rocuronium 1.2 mg/kg group, one patient in the lowest sugammadex dose group (0.5 mg/kg) experienced incomplete reversal that was reported by the investigator as an AE. Another patient in the sugammadex 8.0 mg/kg group experienced mild bradycardia. This patient's heart rate decreased from 62 to 42 bpm 2 min after the administration of sugammadex. This was treated with 0.4 mg of glycopyrrolate and immediately responded with a rate increase to 65 bpm.

Table 2. Time from Start of Administration of Sugammadex to Recovery of the Train-of-Four (TOF) Ratio to 0.9 by Dose Group (Per-Protocol Population)

	Time to recovery of TOF ratio to 0.9 (min) Sugammadex dose group (mg/kg)				
	0.5	1.0	2.0	4.0	8.0
Rocuronium 0.6 mg/kg					
n	3	2	5	2	4
Mean ± SD	44.2 ± 34.6	19.1 ± 20.0	5.4 ± 5.7	3.3 ± 1.6	1.5 ± 0.6
Range	22.4–84.1	5.0–33.2	1.8–15.2	2.2–4.7	1.0–2.1
Rocuronium 1.2 mg/kg					
n	1	3	3	2	4
Mean ± SD	20.6 ± 0.0	11.5 ± 11.6	4.3 ± 0.5	1.9 ± 0.7	1.0 ± 0.2
Range		4.5–25.0	3.8–4.8	1.5–2.4	0.8–1.3

Table 3. Reasons Why Per Protocol Population (PP) Subjects Were Not Included in the Train-of-Four (TOF) Ratio ≥0.9 Efficacy Data

Rocuronium dose group (mg/kg)	Sugammadex dose group (mg/kg)	Reason for noninclusion
0.6	0.5	Received neostigmine more than 30 min after sugammadex dose
0.6	1.0	Received neostigmine more than 30 min after sugammadex dose
1.2	0.5	Received neostigmine more than 30 min after sugammadex dose
1.2	1.0	Received neostigmine within 30 min of sugammadex dose
0.6	1.0	Received neostigmine within 30 min of sugammadex dose
1.2	0.5	Patient awake and TOF tracing prematurely discontinued
0.6	1.0	Patient awake and TOF tracing prematurely discontinued
1.2	4.0	TOF-watch recalibrated during emergence from anesthesia

Three of the six reported AEs thought to be possibly related to sugammadex were, in fact, cases of inadequate reversal or unexpectedly quick reversal, which were expected in this dose-finding study. The remaining three AEs, dizziness, bradycardia, elevated CK and β2-microglobinuria are not infrequent effects of surgery and anesthesia and were not reported as AEs in other patients in this study.

No clinically significant laboratory abnormalities were reported in terms of hematology, biochemistry and urinalysis, apart from the patient (0.6 mg/kg rocuronium group, 8.0 mg/kg sugammadex dose group) mentioned above, who had an elevated CK level. Furthermore, no clinically significant changes for systolic and diastolic arterial blood pressure were reported. The analysis of the ECG data did not indicate an association between sugammadex dose and QTc interval.

DISCUSSION

Residual NMB after spontaneous or pharmacologic reversal of NMBDs is a recognized problem (11,15). Spontaneous recovery from most commonly used nondepolarizing NMBDs can be dose dependent and highly variable (16). Many anesthesiologists regularly administer anticholinesterases and an appropriate dose of a muscarinic cholinergic blocking drug in order to speed recovery (17). However, some return of neuromuscular function must be present before acetylcholinesterase inhibitors are effective (18), and attempts at reversing intense NMB may even prolong recovery (19).

Sugammadex is a new γ-cyclodextrin that, rather than antagonizing NMBDs at the motor end plate, binds the NMBD forming a complex that prevents the NMBD from acting at the receptors. The complex is ultimately renally excreted. Sugammadex is not a reversal drug , but rather a SRBA that was engineered to bind aminosteriod NMBDs. It forms a host-guest complex with rocuronium that binds in a 1:1 ratio.

The data presented in this study are consistent with previous studies demonstrating that sugammadex provides a fast and safe recovery from steroidal NMB (7,9,10). Previous studies indicate that sugammadex is capable of rapidly reversing moderate NMB (7), that it acts more quickly than drugs in current use, and that at doses in excess of 2 mg/kg, it is not associated with muscle weakness (9,10). Unlike other studies, however, we have shown that sugammadex can also completely reverse a profound NMB. Although the number of patients in most treatment groups was small, we found that sugammadex (4.0 and 8.0 mg/kg) reversed profound NMB induced by rocuronium in a mean time of 1.7 min. Incomplete reversal of rocuronium NMB was only seen with the two lowest doses of sugammadex. This may indicate that sugammadex at doses of 0.5–1.0 mg/kg does not reliably bind sufficient rocuronium to produce complete reversal of the NMBD.

Monkeys injected with 0.5 mg/kg of rocuronium (approximately 5 X ED_{90}) had a spontaneous 90% recovery in TOF ratio in 28 min (6). One min after this injection a 1 or 2.5 mg/kg dose of sugammadex was administered. The 1 mg/kg dose shortened recovery by only 2 min (26 min), but the 2.5 mg/kg dose lead to a 90% recovery of TOF in 8 min (6). A molecule of sugammadex ($C_{72}H_{104}O_{48}S_8Na_8$: molecular weight 2178) is approximately 3.6 times heavier than a molecule of rocuronium (molecular weight 610). This would suggest that a dose of 1.8 mg/kg of sugammadex would be required bind all the rocuronium in a 0.5 mg/kg dose. It is not surprising, then, that a 1 mg/kg dose would be largely ineffective, and that a dose only 40% above this calculated minimum could be effective but would not have a rapid onset.

In this study, using a 1:1 binding model, 0.6 mg/kg of rocuronium should be reversible with a minimum of 2.2 mg/kg of sugammadex. However, sugammadex was not given immediately after an intubating dose of rocuronium but only after minimal return of neuromuscular function documented by a PTC of one or two for both intubation groups. Therefore, a lower dose might be sufficient, depending on the individual's elimination and redistribution of rocuronium. Subsequent to sugammadex doses of 0.5 and 1 mg/kg, some patients received neostigmine because the drug failed to adequately reverse the NMB in 30 min. The 2.0 mg/kg dose always succeeded in producing a TOF ratio of ≥0.9 but there was significant variability in the time it took to achieve these results (1.8–15.2 min). As the ratio of the SRBA molecule to the amount of rocuronium available to bind is increased, a decrease in intersubject variability and faster pharmacologic onset would be expected. When the dose of sugammadex was increased to 4.0 mg/kg, both the variability of response and time to a TOF ratio of ≥0.9 decreased. Doubling the sugammadex dose to 8 mg/kg resulted in mean times to reversal decreasing by almost 50% and smaller SDs (Table 2). Figure 2 indicates that the 4.0 and the 8.0 mg/kg sugammadex doses lie on the plateau of the dose–response curve (because of the decreased patient variability in drug response at the 4 and 8 mg/kg, individual patient's values are difficult to discern).

Sorgenfrei et al. (9) and Shields et al. (10) used sugammadex to reverse NMB while monitoring TOF at the reappearance of T_2. In both studies , the plateau of the dose–response curve started at 2.0 mg/kg. This difference can be explained by the fewer molecules of rocuronium necessary for binding at a moderate level of block compared to the profound block reversed in this study. This shifting of the dose–response curve to the right is consistent with a SRBA mechanism of action. It is expected that a further shift to the right would occur should rapid reversal from a deeper NMB, PTC = 0 become necessary.

The safety data from this study indicate that sugammadex is well tolerated. However, it is worth

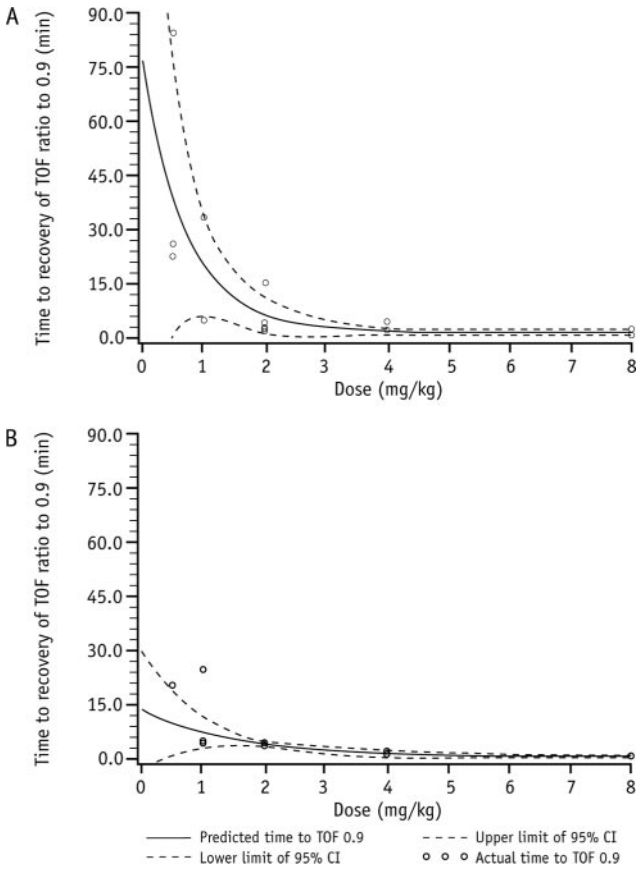

Figure 2. Estimated dose–response relation between the time from start of administration of sugammadex to recovery of the Train-of-Four (TOF) ratio to 0.9 and the dose of sugammadex, after administration of 0.6 mg/kg rocuronium (A) and 1.2 mg/kg rocuronium (B) (per protocol population).

noting that the only subject who experienced a significantly increased CK level (5400U/L) was one of nine treated in the 8 mg/kg group (Table 1). This patient was 41-yr-old and had a total abdominal hysterectomy. She went from profound NMB to full recovery in approximately 2 min. Before development of sugammadex, this rapidity of deep NMB reversal was impossible, and has not been clinically studied. There are many causes for postoperative increases of CK level (20). The investigator caring for this patient considered it possibly related to sugammadex administration. This will be an important area for further study in larger patient populations. This patient had an uneventful hospital course and had no complaints at the 7-day follow-up study visit.

There were four serious AEs reported among the patients involved in this study. None was thought to be related to the administration of sugammadex by the principal investigators. One involved a bowel injury that was recognized after the sugammadex was administered. The wound had to be reopened. As sugammadex binds both rocuronium and vecuronium (21), these drugs may not have been effective in reestablishing repeated NMB in this particular case. Sugammadex has been shown to have no significant

effect on the NMB activities of mivacurium or atracurium when used in monkeys and other species (5). The selectivity of sugammadex for aminosteroid NMBDs means that the activity of nonsteroidal NMBDs should be unaffected. This is true in some animal models (5) but has yet to be proven in humans. Fortunately, in this case the bowel repair was easy and the surgeon did not need additional muscle relaxation.

One of this study's limitations is small sample size. Unexpectedly, slow enrollment led the sponsors of this study to prematurely terminate enrollment after 50 patients were randomized. No data analysis was performed before this decision was made. Patients feared involvement in the first North American trial of a new drug, and the additional neuromuscular monitoring requirements which were part of this protocol significantly prolonged the patient's anesthetic. After induction of anesthesia the TOF-Watch SX required stabilization, calibration and baseline tracings. At a minimum, this delayed the administration of muscle relaxant and intubation for 9 min, but often much longer. The safety requirement requiring TOF-Watch SX monitoring for at least 30 min after sugammadex administration also prolonged the duration of anesthesia and discouraged subject enrollment. With the small number of patients in the PP group (37 patients) this study lacked sufficient statistical power to detect differences in the two rocuronium dosing groups. Therefore, testing to evaluate whether the response relationship is dependent on the intubating dose of rocuronium was not performed, but would be a reasonable area for further research.

Another limitation of the study is the sponsor's involvement. The involvement of sponsors will always be an issue in Phase II clinical trials because they are the source of an unapproved drug. Efforts were made to minimize bias. The statistical analysis plan was prespecified during the protocol development and was not changed after the data were collected. A third party was contracted to analyze and interpret the ECG data (Covance). This was an open-label trial and, except for the safety assessor, there was no one on the team that was blinded. All data from the TOF-Watch SX were electronically captured and analyzed by the site before forwarding it to the sponsor. Additionally, Organon's involvement in this study was fully disclosed.

Finally, this trial was limited to ASA I–III patients who were reasonably healthy and had levels of NMB that were deeper than usual clinical practice. The safety of this drug and its dosing in patients with significant comorbidities, such as renal, hepatic, and cardiac dysfunctions, were not studied. Dose–response curves could be significantly different in these populations.

In conclusion, this study demonstrates that a profound NMB defined as a PTC of I–II can be quickly and reliably reversed with sugammadex in subjects categorized as ASA class I–III. Sugammadex doses of $\leq$1.0 mg/kg did not bind sufficient rocuronium to rapidly reverse a profound NMB. Doses $\geq$2 mg/kg of sugammadex consistently resulted in a TOF ratio $\geq$0.9 in 15 min or less. Increasing the dose from this level resulted in faster reversal times and less individual subject variability. Sugammadex was well tolerated by all subjects in this study.

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ERRATUM

In the December 2006 issue, in the article by Sauter et al., "Use of Magnetic Resonance Imaging to Define the Anatomical Location Closest to All Three Cords of the Infraclavicular Brachial Plexus" (Anesth Analg 2006;103:1574–6), on page 1576, Reference 5 was incorrect. The correct Reference 5 should be:

5. Koscielniak-Nielsen ZJ, Rasmussen H, Hesselbjerg L, Nielsen TP, Gurkan Y. Infraclavicular block causes less discomfort than axillary block in ambulatory patients. Acta Anaesthesiol Scand 2005;49:1030–4.

The author apologizes for the error.