Effective Reversal of Moderate Rocuronium- or Vecuronium-induced Neuromuscular Block with Sugammadex, a Selective Relaxant Binding Agent

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Background: Sugammadex rapidly reverses rocuronium-induced neuromuscular block. This study explored the dose–response relation of sugammadex given as a reversal agent at reappearance of the second muscle twitch after rocuronium- and vecuronium-induced block. A secondary objective was to investigate the safety of single doses of sugammadex.

Methods: In this two-center, phase II, dose-finding study, 80 patients (age ≥ 18 yr, American Society of Anesthesiologists physical status I or II, surgery ≥ 60 min requiring muscle relaxation for intubation) were randomly assigned to receive rocuronium (0.60 mg/kg) or vecuronium (0.10 mg/kg). Sugammadex or placebo was administered at reappearance of the second muscle twitch. The primary efficacy endpoint was time from starting sugammadex administration until recovery of the train-of-four ratio to 0.9.

Results: Compared with placebo, sugammadex produced dose-dependent decreases in mean time to recovery for all train-of-four ratios in the rocuronium and vecuronium groups. The mean time for recovery of the train-of-four ratio to 0.9 in the rocuronium group was 31.8 min after placebo compared with 3.7 and 1.1 min after 0.5 and 4.0 mg/kg sugammadex, respectively. The mean time for recovery of the train-of-four ratio to 0.9 in the vecuronium group was 48.8 min after placebo, compared with 2.5 and 1.4 min after 1.0 and 8.0 mg/kg sugammadex, respectively. Sugammadex was well tolerated.

Conclusion: Sugammadex rapidly reversed rocuronium- or vecuronium-induced neuromuscular block at reappearance of the second muscle twitch and was well tolerated. A dose–response relation was observed with sugammadex for reversal of both rocuronium- and vecuronium-induced neuromuscular block.

NEUROMUSCULAR blocking agents (NMBA) are widely used to induce muscle relaxation in anesthetized patients undergoing surgery. However, patients receiving NMBA may be at risk of residual block, a key contributing factor for the development of postoperative pulmonary complications and increased postoperative morbidity and mortality.

There are several ways to reduce the risk of developing residual block when using NMBA. One approach is to wait for spontaneous recovery of neuromuscular block combined with clinical evaluation of recovery of neuromuscular function. However, clinical tests such as leg lift, head lift, or hand grip are not useful in helping the anesthesiologist to determine whether the patient has undergone adequate neuromuscular recovery at the end of surgery. Such a clinical evaluation is not always accurate in predicting neuromuscular recovery and does not easily provide an objective evaluation of neuromuscular function. For example, a recent study found that 12% of patients who had a good response to clinical tests were still at risk for residual block. Many anesthesiologists still rely on clinical judgment and seldom use objective monitoring of neuromuscular block. However, monitoring of neuromuscular function determines whether antagonism of residual block is actually required and has been shown to be the only way to reduce the incidence of residual paralysis.

The risk of developing residual block can also be reduced by acceleration of recovery through a systematic pharmacologic reversal of the neuromuscular block. A recent study reported that patients in whom neuromuscular block was not reversed were at a higher risk of adverse outcomes than those who received reversal agents. However, anticholinesterases, such as neostigmine and edrophonium—the most commonly used reversal agents—can cause adverse cholinergic events, including cardiovascular and gastrointestinal problems, and are not effective when administered during profound block. There is thus a clear need for new reversal agents with a rapid onset of action and an improved efficacy and safety profile.

Sugammadex is a novel β-cyclodextrin and the first of a new class of selective relaxant binding agents. It was designed to rapidly encapsulate steroidal NMBA, most specifically rocuronium, thus preventing them from acting at acetylcholine receptors. In vivo studies have shown that sugammadex rapidly reverses rocuronium-induced neuromuscular block, including profound block.

Because it has been shown that sugammadex rapidly reverses neuromuscular block, it was expected that it would also be effective in reversing the neuromuscular...
block induced by the similar pharmacologic compound vecuronium. This expectation was based on affinity testing and the high potency of vecuronium (meaning that fewer molecules of vecuronium would need to be encapsulated to reverse its effect); this was subsequently confirmed in animal studies.16

This phase II study investigated the dose–response relation of sugammadex administered as a reversal agent at reappearance of the second muscle twitch (T2) in response to train-of-four stimulation after administration of either vecuronium (0.10 mg/kg) or rocuronium (0.60 mg/kg). The secondary aim was to evaluate the safety of single doses of sugammadex.

Materials and Methods

Study Design and Patient Selection

This study was a two-center, partially randomized, safety assessor–blinded, phase II dose-finding study conducted between March 2003 and September 2004 at two centers in Belgium (Aalst and Liege). The independent ethics committee at each trial center (Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium, and CHR de la Citadelle, Liege, Belgium) approved the study, and written informed consent was obtained from each patient before enrollment. The study was conducted in accordance with the current revision of the Declaration of Helsinki, International Conference on Harmonisation guidelines, and Good Clinical Practice.

Patients eligible for inclusion were aged ≥18 yr with American Society of Anesthesiologists physical status of I or II and scheduled to undergo surgery of at least 60 min duration that required general anesthesia and muscle relaxation only for intubation. Exclusion criteria were as follows: anatomical malformations expected to result in a difficult intubation; known or suspected neuromuscular disorders and/or significant hepatic or renal dysfunction; known or suspected personal or family history of malignant hyperthermia; known or suspected allergy to narcotics, muscle relaxants, or any other medication used during general anesthesia; and administration of any medication known to interfere with NMBA (such as anticonvulsants, aminoglycosides, and magnesium-containing medications). In addition, women of childbearing age not using an acceptable method of birth control and those who were breastfeeding or pregnant were not eligible for the study.

Study Procedures

All patients were premedicated with 2.5 mg oral lorazepam 1 h before induction. After 3 min of preoxygenation, anesthesia was induced with a target-controlled infusion of propofol (target 3 μg/ml, induction time 3 min) and 0.2 μg·kg\(^{-1}\)·min\(^{-1}\) remifentanil. As soon as the eyelid reflex was lost, assisted ventilation with 100% oxygen by facemask was started. After administration of the appropriate bolus dose of NMBA, the patient was intubated as soon as the first response to the train-of-four stimulus (T1) decreased to below 10%. Normocapnic ventilation was established with a Fabius GS ventilator (Dräger Medical AG & Co., Lübeck, Germany). Anesthesia was maintained with 40% oxygen in air, propofol target-controlled infusion, and 0.1–0.5 μg·kg\(^{-1}\)·min\(^{-1}\) remifentanil. Remifentanil administration was guided by the patient’s hemodynamics and was changed in steps of 0.1 μg·kg\(^{-1}\)·min\(^{-1}\) in response to variations in systolic blood pressure of 20 mmHg or greater. Routine monitoring included electrocardiography, pulse oximetry, and noninvasive blood pressure monitoring. Temperature was monitored at the esophagus. Intraoperative temperature management was facilitated by radiant heat provided by a thermal ceiling.

Neuromuscular transmission was monitored by the acceleromyographic response of the adductor pollicis muscle to repetitive train-of-four stimulation of the ulnar nerve every 15 s, using surface electrodes (TOF-Watch® SX; Organon Ireland Ltd., Dublin, Ireland). The monitored arm was immobilized on an armboard. Stabilization was achieved with a 5-s, 50-Hz tetanic stimulation. One minute after this tetanic stimulation, the fingers were fixated and completely immobilized, except for the thumb. After repetitive train-of-four stimulation for at least 3 min, calibration occurred by pressing the CAL button. After calibration, the TOF-Watch® SX was switched to the repetitive train-of-four stimulation again, which lasted until the end of anesthesia. NMBA was not to be administered until at least 3 min after calibration, to check for correct setup, including supramaximal stimulation (current < 60 mA). The normalized T1/T1 ratio (ratio of the amplitude of the fourth response [T1] over the first response [T1] to train-of-four stimulation) was determined by dividing the T1/T1 ratio by the mean of 8 baseline T1/T1 ratios which were observed after calibration of the TOF-Watch® SX during an interval of 2 min before administration of the NMBA. Neuromuscular data were collected on a personal computer by means of the TOF-Watch® SX Monitoring Program.

Patients were treated in parallel treatment groups and randomly assigned to rocuronium (Esmeron®; NV Organon, Oss, The Netherlands) or vecuronium (Norcuron®; NV Organon). There was no randomization for sugammadex, but instead, a “step-up/step-down” design was used. The rocuronium and vecuronium dose groups were enrolled in five sequential blocks. Each patient received a single intravenous bolus intubation dose of rocuronium (0.60 mg/kg) or vecuronium (0.10 mg/kg). After completion of initial enrollment of 40 patients, i.e., 20 patients receiving rocuronium and 20 patients receiving vecuronium, a prespecified interim analysis was performed. The aim was to explore whether sufficient subjects were enrolled to get conclusive results from the
dose–response analysis. Based on the outcome of this evaluation, it was decided to enroll an additional 40 subjects: 20 for the rocuronium group and 20 for the vecuronium group.

Because historic data on the reversal of vecuronium-induced neuromuscular block by sugammadex were not available, sugammadex doses were chosen in an exploratory way. At the reappearance of T2, sugammadex (1.0 mg/kg) was administered as a single bolus injection to patients in the first rocuronium and vecuronium groups. The dose of sugammadex administered in each subsequent dose group was determined after evaluation of the primary endpoint in the previous dose group(s). The doses were selected in such a way that at least two doses of sugammadex would result in a recovery time on the slope of the exponential curve and at least two sugammadex doses would result in a recovery time on the plateau of the dose–response curve. A dose resulting in a mean recovery time of less than 3 min was considered to be a plateau dose, whereas a dose resulting in a mean recovery time of 3 min or greater was considered to be located at the slope of the exponential curve. The 3-min cutoff value was based on historic data available from previous clinical studies. In this way, the dose–response relation could be determined over a range from placebo (spontaneous recovery) to recovery on the plateau of the dose–response curve. The 3-min evolution of sugammadex would result in a recovery time on the plateau of the exponential curve and at least two sugammadex doses would result in a recovery time on the plateau of the dose–response curve. A dose resulting in a mean recovery time of less than 3 min was considered to be a plateau dose, whereas a dose resulting in a mean recovery time of 3 min or greater was considered to be located at the slope of the exponential curve. The 3-min cutoff value was based on historic data available from previous clinical studies. In this way, the dose–response relation could be determined over a range from placebo (spontaneous recovery) to recovery on the plateau of the dose–response curve (fastest recovery possible).

Neuromuscular monitoring using the TOF Watch® SX was started before administration of the NMBA and continued until recovery from anesthesia to a T4/T1 ratio of 0.9. If a train-of-four ratio of 0.9 or greater was not achieved, no correction was made, and “missing data” was documented instead. In addition, oxygen saturation, respiratory frequency, and clinical evidence of residual curarization were monitored for at least 60 min after recovery of the T4/T1 ratio to 0.9. Safety variables, such as (serious) adverse events ([S]AEs), reported by the conscious patient, the investigator, or both, were evaluated by a safety assessor. AEs were monitored by questioning and/or monitoring patients throughout the intral period and follow-up period.

**Efficacy Variables**

The primary study endpoint was the time from the start of administration of sugammadex or placebo to recovery of the T4/T1 ratio to 0.9 after rocuronium- or vecuronium-induced neuromuscular block. Secondary endpoints were the times from the start of administration of sugammadex or placebo to recovery of the T4/T1 ratio to 0.8 and 0.7 after rocuronium- or vecuronium-induced neuromuscular block.

**Statistical Analysis**

Recovery from neuromuscular block induced by rocuronium (0.60 mg/kg) or vecuronium (0.10 mg/kg) was studied in the intent-to-treat population (i.e., all randomized patients who received a dose of trial medication and who had at least one efficacy assessment) and in the per-protocol population (i.e., all treated patients without any major protocol violations). Safety data were studied in all patients who received a dose of sugammadex or placebo.

Separate sugammadex dose–response relations were estimated from the available data for each NMBA. For exploring the relation between the dose of sugammadex and recovery from neuromuscular block (T4/T1 ratio to 0.9), the following exponential model was used:

Estimated time to recovery of the T4/T1 ratio to 0.9 (dose) = \( A + B \cdot \exp(-c \cdot \text{dose}) \),

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 increasing dose of sugammadex.

Weighted nonlinear regression was used to fit the parameters of the exponential model to the recovery times. Weighting factors were used, as applicable: \((1/\text{var})/(\sum(1/\text{var}))\), where var is the variance of the recovery times at dose i, and \((1/\text{SD})/(\sum(1/\text{SD}))\), where SD is the SD of the recovery times at dose i.

Data for the primary endpoint were summarized separately by dose group for each NMBA.

**Results**

**Baseline Characteristics**

Forty patients were enrolled initially, and another 40 were enrolled after the interim analysis. In total, 80 patients were randomly assigned to receive either rocuronium (\( n = 4 \) each in the placebo and 3.0-mg/kg sugammadex groups and \( n = 8 \) each in the 0.5-, 1.0-, 2.0-, and 4.0-mg/kg sugammadex groups) or vecuronium (\( n = 4 \) each in the placebo and 8.0-mg/kg sugammadex groups and \( n = 8 \) each in the 0.5-, 1.0-, 2.0-, and 4.0-mg/kg sugammadex groups). Of these, 79 were treated and had at least one efficacy assessment (intent-to-treat population); 1 patient in the rocuronium group randomized to placebo was withdrawn from the study because he or she was not in the supine position and neuromuscular monitoring could not take place. Four additional patients were excluded because of major protocol violations; 2 subjects in the rocuronium group (1.0 and 3.0 mg/kg sugammadex) had sugammadex administered too late, and 2 subjects in the vecuronium group (0.5 and 4.0 mg/kg sugammadex) had an unreliable time course of action data; the per-protocol population therefore comprised 75 patients.

Patient baseline characteristics were generally similar across the two treatment groups (table 1). Differences in

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Efficacy

Sugammadex produced dose-dependent decreases in mean time to recovery for all $T_4/T_1$ ratios in the rocuronium and vecuronium groups. A summary of the times from the start of administration of sugammadex to recovery of the $T_4/T_1$ ratio to 0.9, 0.8, and 0.7 in the per-protocol populations in both groups is presented in table 2.

Sugammadex dose-dependently decreased the time from the start of administration to recovery of the $T_4/T_1$ ratio to 0.9 in both the rocuronium (fig. 1) and vecuronium groups (fig. 2). The mean time for recovery of the $T_4/T_1$ ratio to 0.9 in the rocuronium group was 31.8 min after placebo (i.e., spontaneous recovery) compared with 3.7 min after 0.5 mg/kg sugammadex and 1.1 min after 4.0 mg/kg sugammadex (table 2). The mean time for recovery of the $T_4/T_1$ ratio to 0.9 in the vecuronium group was 48.8 min after placebo compared with 2.5 min after 1.0 mg/kg sugammadex and 1.4 min after 8.0 mg/kg sugammadex.

Results for the intent-to-treat group (not shown) were comparable with those in the per-protocol population.

Safety and Tolerability

Sugammadex was generally well tolerated. In the rocuronium group, 25 of 39 patients (64%) reported at least one AE, 2 patients in the placebo group and 23 patients in the sugammadex dose groups (0.5, 1.0, 2.0, and 4.0 mg/kg, all $n = 5$; 3.0 mg/kg, $n = 3$). However, only one of these AEs was considered by the investigator to be possibly related to the study drug. This was an episode of tachycardia in the 4.0-mg/kg sugammadex group, which developed 1 min after the start of administration of sugammadex and was of moderate intensity; the patient recovered from this episode within 1 min. In the vecuronium group, 20 of 40 patients (50%) reported at least one AE, 2 patients in the placebo group and 18 patients in the sugammadex dose groups (0.5 and 8.0 mg/kg, both $n = 3$; 1.0 and 2.0 mg/kg, both $n = 5$; 4.0 mg/kg, $n = 2$). Three of these AEs were considered by the investigator to be at least possibly treatment related: Prolonged awakening from anesthesia (recovery from anesthesia was 5 min longer than expected by the investigator; 2.0 mg/kg sugammadex) and erythema reported after the trial period (8.0 mg/kg sugammadex) were considered possibly treatment related, and abdominal discomfort (0.5 mg/kg sugammadex) was considered definitely related.

Table 1. Summary of Baseline Characteristics: Intent-to-treat Population

<table>
<thead>
<tr>
<th>NMBA Group</th>
<th>Placebo</th>
<th>Sugammadex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocuronium (0.60 mg/kg), n</td>
<td>3</td>
<td>0.5 mg/kg</td>
</tr>
<tr>
<td>Mean age (SD), yr</td>
<td>52 (5)</td>
<td>0.8 mg/kg</td>
</tr>
<tr>
<td>Male:female, n</td>
<td>0:3</td>
<td>1.0 mg/kg</td>
</tr>
<tr>
<td>Mean weight (SD), kg</td>
<td>77 (6)</td>
<td>2.0 mg/kg</td>
</tr>
<tr>
<td>ASA physical status I:II, n</td>
<td>4:2</td>
<td>3.0 mg/kg</td>
</tr>
<tr>
<td>Vecuronium (0.10 mg/kg), n</td>
<td>4</td>
<td>4.0 mg/kg</td>
</tr>
<tr>
<td>Mean age (SD), yr</td>
<td>54 (13)</td>
<td>8.0 mg/kg</td>
</tr>
<tr>
<td>Male:female, n</td>
<td>1:3</td>
<td>—</td>
</tr>
<tr>
<td>Mean weight (SD), kg</td>
<td>62 (15)</td>
<td>—</td>
</tr>
<tr>
<td>ASA physical status I:II, n</td>
<td>2:2</td>
<td>—</td>
</tr>
</tbody>
</table>

ASA = American Society of Anesthesiologists; NMBA = neuromuscular blocking agent.

Table 2. Summary of Mean (SD) Recovery Times (in Minutes) for the $T_4/T_1$ Ratios after Sugammadex Administration: Per-protocol Population

<table>
<thead>
<tr>
<th>NMBA Group</th>
<th>Placebo</th>
<th>Sugammadex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocuronium (0.60 mg/kg), n</td>
<td>3</td>
<td>0.5 mg/kg</td>
</tr>
<tr>
<td>$T_4/T_1$ ratio to 0.9</td>
<td>31.8 (21.0)*</td>
<td>3.7 (1.0)</td>
</tr>
<tr>
<td>$T_4/T_1$ ratio to 0.8</td>
<td>28.8 (17.5)*</td>
<td>2.7 (0.5)</td>
</tr>
<tr>
<td>$T_4/T_1$ ratio to 0.7</td>
<td>21.8 (12.9)*</td>
<td>2.3 (0.5)</td>
</tr>
<tr>
<td>Vecuronium (0.10 mg/kg), n</td>
<td>4</td>
<td>1.0 mg/kg</td>
</tr>
<tr>
<td>$T_4/T_1$ ratio to 0.9</td>
<td>48.8 (27.9)</td>
<td>7.7 (2.6)</td>
</tr>
<tr>
<td>$T_4/T_1$ ratio to 0.8</td>
<td>44.8 (28.2)</td>
<td>5.3 (1.8)</td>
</tr>
<tr>
<td>$T_4/T_1$ ratio to 0.7</td>
<td>33.7 (16.7)</td>
<td>3.7 (1.0)</td>
</tr>
</tbody>
</table>

*S* Data for one subject excluded because of a minor protocol violation; neostigmine administered before recovery of the $T_4/T_1$ ratio to 0.7. † Data for one subject excluded because of a minor protocol violation; cisatracurium administered before recovery of the $T_4/T_1$ ratio to 0.8.

NMBA = neuromuscular blocking agent; $T_4/T_1$ ratio = ratio of the fourth response to the first response during the train-of-four stimulation.
In the rocuronium group, four SAEs were observed: hematoma (4.0 mg/kg sugammadex), perforation of the small intestine (1.0 and 2.0 mg/kg sugammadex), and hemorrhage at the incision site (0.5 mg/kg sugammadex). All four SAEs were considered not to be treatment related. In the vecuronium group, the two observed SAEs, namely constipation and muscle hemorrhage (1.0 mg/kg sugammadex), were considered not to be treatment related.

There was no apparent relation between the sugammadex dose and the incidence of AEs, and there were no discontinuations due to AEs in either group. In addition, no residual neuromuscular block was observed except for in one patient who received the lowest dose of sugammadex (0.5 mg/kg) after vecuronium. The value of the train-of-four ratio initially increased to 0.9 and then subsequently decreased to just below 0.8 in this one patient, although there were no clinical signs of residual block.

Discussion

This two-center, partially randomized, safety assessor-blinded, phase II dose-finding study showed that, compared with placebo, sugammadex given as a reversal agent at the reappearance of T2 was effective in reversing neuromuscular block induced by either rocuronium (0.60 mg/kg) or vecuronium (0.10 mg/kg) in patients with an American Society of Anesthesiologists physical status of I or II. Cholinesterase inhibitors are only effective in reversing neuromuscular block if given when partial spontaneous recovery has already occurred.17

The present study showed that sugammadex was effective as a reversal agent for both rocuronium- and vecuronium-induced block when given at such a depth of block i.e., the reappearance of T2.18

A dose–response relation was found for both rocuronium and vecuronium. After administration of 0.6 mg/kg rocuronium, varying doses of sugammadex were administered when the train-of-four count had returned to two detectable responses. After rocuronium-induced neuromuscular block, the mean time to recovery of the train-of-four ratio to 0.9 was 1.1 min with 4.0 mg/kg sugammadex; this was similarly fast (1.5 min) after vecuronium-induced block was antagonized at reappearance of T2 with 4.0 mg/kg sugammadex. It should also be noted that, based on the data obtained in the current study, a sugammadex dose of 0.5 mg/kg is considered to be suboptimal for efficacy.

The safety data indicate that sugammadex was safe and well tolerated when used to reverse the neuromuscular block induced either by rocuronium or by vecuronium. Four of the AEs that occurred during the trial in the rocuronium and vecuronium groups were considered not to be treatment related.

Although our study only included a small number of patients, our results are in agreement with previous studies, which have shown that sugammadex is safe and effective in rapidly reversing rocuronium-induced neuromuscular block10,13–15 even when profound.11,12 This study also demonstrates that sugammadex showed similar efficacy when used to reverse the effects of vecuronium-induced neuromuscular block. Indeed, this is the first report of the use of sugammadex for reversal of vecuronium-induced neuromuscular block in patients.

Conclusions

A dose–response relation was observed with sugammadex for reversal of both rocuronium- and vecuronium-induced neuromuscular block. Sugammadex was safe
and well tolerated, and no evidence of recurarization was observed in any patient.

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References