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Reversal of Profound Neuromuscular Block by Sugammadex Administered Three Minutes after Rocuronium

A Comparison with Spontaneous Recovery from Succinylcholine

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Background: **Rocuronium in intubation doses provides similar intubation conditions as succinylcholine, but has a longer duration of action. This study compared time to sugammadex reversal of profound rocuronium-induced neuromuscular block with time to spontaneous recovery from succinylcholine.**

Methods: **One hundred and fifteen adult American Society of Anesthesiologists Class I-II surgical patients were randomized to this multicenter, safety-assessor–blinded, parallel group, active-controlled, Phase IIIa trial. Anesthesia was induced and maintained with propofol and an opioid. Neuromuscular transmission was blocked and tracheal intubation facilitated with 1.2 mg/kg rocuronium or 1 mg/kg succinylcholine. Sugammadex (16 mg/kg) was administered 3 min after rocuronium administration. Neuromuscular function was monitored by acceleromyography. The primary efficacy endpoint was the time from the start of relaxant administration to recovery of the first train-of-four twitch (T_1) to 10%.**

Results: **One hundred and ten patients received study treatment. Mean times to recovery of T_1 to 10% and T_1 to 90% were significantly faster in the rocuronium-sugammadex group (4.4 and 6.2 min, respectively), as compared with the succinylcholine group (7.1 and 10.9 min, respectively; all $P < 0.001$). Timed from sugammadex administration, the mean time to recovery of T_1 to 10%, T_1 to 90%, and the train-of-four (T_4/T_1) ratio to 0.9 was 1.2, 2.9, and 2.2 min, respectively. Reoccurrence of the block was not observed. There were no serious adverse events related to study treatments.**

Conclusion: **Reversal of profound high-dose rocuronium-induced neuromuscular block (1.2 mg/kg) with 16 mg/kg sugammadex was significantly faster than spontaneous recovery from 1 mg/kg succinylcholine.**

SUCCINYLCHOLINE is a depolarizing neuromuscular blocking agent (NMBA) used for short-term muscle relaxation, most often first-line to facilitate tracheal intubation. Because of its fast onset and short duration of action, it has considerable use in emergency situations where a neuromuscular block must be induced and the airway secured quickly to protect against aspiration of gastric contents.[1–3] A short duration of action is essential in cases of a difficult airway where the patient cannot be intubated or ventilated and rapid restoration of spontaneous respiration is crucial.[2,4]

Succinylcholine has the shortest duration of action of all currently available NMBAs.[5] At 1 mg/kg it typically provides a complete block in approximately 1 min and recovery in 6 to 9 min (first train-of-four twitch [T_1] to 10%) or 10 to 13 min (T_1 to 90%).[6–8] Succinylcholine is associated with a variety of adverse events and contraindications.[9–15] Unfortunately, decades of efforts to develop a new nondepolarizing NMBA both safer and shorter-acting than succinylcholine have failed.[16]

The nondepolarizing NMBA rocuronium is also indicated to facilitate tracheal intubation during routine and rapid-sequence intubation, especially where succinylcholine is contraindicated.** Succinylcholine (1 mg/kg) reliably provides excellent to acceptable intubating conditions, as compared with 0.6 to 0.7 mg/kg rocuronium, although no significant differences have been observed between 1 mg/kg succinylcholine 0.9 to 1.2 mg/kg rocuronium.[2] Rocuronium (0.6 to 1.2 mg/kg) typically completes a neuromuscular block in < 2 min, as compared with < 1 min on average for 1 mg/kg succinylcholine.[17] However, higher doses of rocuronium have a long duration of action; this is inappropriate in situations where rapid recovery of neuromuscular function is required.[17] In addition, anticholinesterases readily expedite recovery from nondepolarizing block but are ineffective for the reversal of a profound block, and present a significant side effect profile.[12,18]

A plausible new approach to both rapid onset and rapid recovery of neuromuscular block might involve blocking with high-dose rocuronium and reversal using high-dose

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** Zemuron (rocuronium bromide) SmPC, July 5, 2006. Available at: http://www.zemuron.com/authfiles/images/476_109852.pdf. Accessed April 1, 2008.

sugammadex. Studies in surgical patients have shown that 0.5 to 16 mg/kg sugammadex provides well-tolerated and dose-dependent rapid reversal of shallow[19–22] and profound[23–25] rocuronium-induced neuromuscular block.

Evidence suggests that sugammadex will be efficacious against high-dose rocuronium soon after the onset of neuromuscular block, with time to reversal of block at least comparable with spontaneous recovery from succinylcholine, but this requires confirmation.[25,26] In this study, the efficacy and safety of 16 mg/kg sugammadex given 3 min after 1.2 mg/kg rocuronium for reversal of profound neuromuscular block was compared with that of spontaneous recovery from 1 mg/kg succinylcholine-induced block.

Materials and Methods

This multicenter, randomized, safety-assessor–blinded, parallel-group, active-controlled Phase IIIa trial, known as the Spectrum study, was conducted in 11 centers: 9 in the United States and 2 in Canada. The study protocol was approved by the Institutional Review Committee for each center and was conducted in accordance with the Declaration of Helsinki (current revision), the International Conference on Harmonization guidelines, Good Clinical Practice, and current regulatory requirements. Written informed consent was obtained from all participating patients. Eligible patients enrolled into the trial were assigned a subject allocation number and randomized to a treatment. Patients were recruited by investigators and/or their staff.

Patients

Patients aged 18 to 65 yr, American Society of Anesthesiologists Class I or II, were eligible if they had a body mass index < 30 kg/m^2, were scheduled to undergo an elective surgical procedure under general anesthesia in the supine position requiring a short duration of neuromuscular relaxation for which rocuronium or succinylcholine was indicated, and required tracheal intubation. Exclusion criteria included ischemic heart disease or a history of myocardial infarction within the last year; a (family) history of malignant hyperthermia; significant renal dysfunction; known or suspected neuromuscular disorders; allergies to narcotics, muscle relaxants, midazolam, anesthetics, or other medications used during general anesthesia; and patients where difficult intubation was expected upon physical examination. Female patients who were pregnant, breast-feeding, or of childbearing potential and not using adequate contraception (pregnancy test performed to exclude pregnancy) were excluded. Patients receiving medication known to interfere with neuromuscular function (*e.g.,* aminoglycosides, anticonvulsants, or magnesium) were also excluded, as were any participants in a previous sugammadex trial or any other trial not approved by the sponsor within 30 days before entering this trial.

Study Design

The trial comprised a screening period of up to 7 days before treatment, a perianesthetic period (randomization to postanesthetic period), and a postanesthetic period comprising a postoperative visit by a safety assessor ($\geq$ 10 h after study drug administration), and a follow-up surveillance up to 7 days after surgery. Adverse events (AEs) and serious AEs were monitored during the postoperative visit and at follow-up by the blinded assessor, who did not perform randomization nor prepare or administer trial medication.

Patients were premedicated with intravenous midazolam, up to 2 mg as needed, upon arrival at the operating room. Noninvasive automatic monitoring of arterial blood pressure, oxygen saturation, and electrocardiography were applied.

Anesthesia was induced and maintained with an intravenous opioid and propofol and other agents/medications at a concentration/dose range according to clinical need and local practice. No inhalational anesthetic was used during the neuromuscular monitoring period. Upon induction, patients received either 1.2 mg/kg rocuronium or 1 mg/kg succinylcholine, administered within 10 s as a single bolus into a fast-running intravenous infusion. At 1 min, the endotracheal tube was inserted. Sugammadex (16 mg/kg) was administered 3 min after the start of rocuronium administration, also as a bolus within 10 s into a fast-running intravenous infusion. Patients receiving succinylcholine were allowed to recover spontaneously. After surgery, patients were allowed to recover from anesthesia and transferred to the postoperative recovery room.

Neuromuscular monitoring was performed using the TOF-Watch SX (Schering-Plough, Dublin, Ireland). The ulnar nerve was supramaximally stimulated near the wrist with square pulses of 0.2 ms duration, delivered as train-of-four pulses of 2 Hz, at intervals of 15 s. The resulting contractions of the adductor pollicis muscle were quantified acceleromyographically (TOFMON 1.2, Schering-Plough, Oss, The Netherlands). Stabilization, calibration, and baseline responses were recorded upon anesthesia induction, and neuromuscular monitoring was continued until the end of anesthesia, or at least until recovery of the T_4/T_1 ratio to 0.9. The final T_1 value was calculated as the mean of three consecutive T_1 values after T_1 had reached a plateau, when there was no or little further increase in its amplitude.

Patients were assessed for reoccurrence of neuromuscular block (decrease in T_4/T_1 to < 0.8 in the rocuronium-sugammadex group). Patients were also assessed for clinical signs of muscle weakness before transfer to and discharge from the recovery room. Central body temperature was maintained at $\geq$ 35°C, and skin temperature at the monitoring site at $\geq$ 32°C. Pulse oximetry and respiratory rate monitoring were continued for $\geq$ 60 min in the recovery room.

Efficacy Variables

The primary efficacy variable was time from the start of administration of rocuronium or succinylcholine to recovery of T_1 to 10% of the baseline value. Additional efficacy variables included time from start of administration of rocuronium or succinylcholine to recovery of T_1 to 90%, and standard clinical signs of anesthetic and neuromuscular recovery before transfer to and discharge from the recovery room. Time from start of sugammadex administration to recovery of T_4/T_1 to 0.7, 0.8, and 0.9 was also recorded.

Safety Assessment

An AE was defined as any untoward medical occurrence in a patient receiving a pharmaceutical product. A serious AE was defined as any AE that at any dose resulted in death, was life-threatening, required prolonged hospitalization, or resulted in persistent disability. AEs were categorized using MedDRA version 9.1 (International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland).

Physical examination was performed at preoperative screening and postoperative visits. Blood pressure and heart rate were recorded at regular intervals throughout. Three 10-ml blood samples were collected per patient for biochemistry and hematology assessment; just before relaxant administration, 4 to 6 h after administration, and at the postoperative visit (at least 10 h after relaxant administration). Urine samples were collected before surgery and at the postanesthetic visit for subsequent urinalysis.

Statistical Analysis

A sample size of 55 patients per treatment group was predetermined to provide 90% power to detect a between-group difference in time to $T_1 = 10\%$ of > 1 min, assuming up to 5% dropout from the intent-to-treat population (all patients randomized based on treatment intent, with ≥ 1 postbaseline efficacy assessment) and uniformity among study sites.

The primary efficacy analysis (intent-to-treat population) included imputation of missing recovery times. For imputation of missing times from the start of relaxant administration to recovery of T_1 to 10% and T_1 to 90%, a conservative approach towards sugammadex was applied. In the case of a missing recovery time in the rocuronium-sugammadex group (for example, time from administration of rocuronium to recovery of T_1 to 90%), the 95th percentile of the available times to T_1 90% in the sugammadex group was imputed for the missing recovery time. For a missing recovery time in the succinylcholine group (for example, time from administration of succinylcholine to recovery of T_1 to 90%), the 5th percentile of the available times to $T_1 = 90\%$ in the succinylcholine group was imputed. The same procedure was applied for imputation of missing times from relaxant administration to recovery of T_1 to 10%. Times to $T_1 = 10\%$ and $T_1 = 90\%$ were compared using two-way analysis of variance. *P* values, estimated between-group differences and the corresponding two-sided 95% CIs were calculated.

Results

The trial was conducted between February and August 2006. Overall, 115 patients were enrolled and randomized (rocuronium-sugammadex, n = 57; succinylcholine, n = 58); 5 patients withdrew before administration of the study drug (n = 2 and n = 3, respectively) and were excluded. The intent-to-treat population thus comprised 110 patients, 55 in each group (fig. 1). However, three patients received medication inconsistent with randomization; one patient in the rocuronium-sugammadex group received succinylcholine, while two patients in the succinylcholine group received rocuronium-sugammadex. Based on actual treatment received, the treated population comprised 56 patients in the rocuronium-sugammadex group and 54 in the succinylcholine group. All treated patients had ≥ 1 postbaseline efficacy value. The opioid used most was fentanyl. The rocuronium-sugammadex and succinylcholine groups were generally comparable regarding baseline characteristics. Patients were of respective mean ages 42 yr (rocuronium-sugammadex) and 41 yr (succinylcholine) (range, 18 to 65 yr), body mass index was 25 kg/m^2 in each group, and most patients were female (59 and 57%), of American Society of Anesthesiologists Class II (59 and 69%), and Caucasian (73 and 83%). Demographic variables were consistent across participating medical centers.

Efficacy

Mean (SD) time to recovery of T_1 to 10% from the start of NMBA administration was significantly faster for rocuronium-sugammadex (1.2 mg/kg rocuronium; 16 mg/kg sugammadex), as compared with 1 mg/kg succinylcholine (4.4 [0.7] *vs.*. 7.1 [1.6] min, $P < 0.001$), with a treatment difference of −2.7 min (95% CI, −3.1 to −2.2 min). Mean (SD) time to recovery of T_1 to 90% was also significantly faster with rocuronium-sugammadex (6.2 [1.8] min), as compared with succinylcholine (10.9 [2.4] min, $P < 0.001$), with a treatment difference of −4.6 min (95% CI, −5.5 to −3.8 min). These data include imputed values (three patients); findings were similar without imputed cases. Similar trends were apparent for median time to recovery of T_1 to 10% and 90% (table 1). Timed from rocuronium administration, mean (SD) time to recovery of T_4/T_1 to 0.7, 0.8, and 0.9 was 4.4 (0.7), 4.6 (1.1), and 5.4 (2.2) min, respectively.

Timed from sugammadex administration, 3.1 (0.2) min after rocuronium, mean (SD) time to recovery of T_1 to 10% was 1.2 (0.5) min, and to 90% was 2.9 (1.7) min.

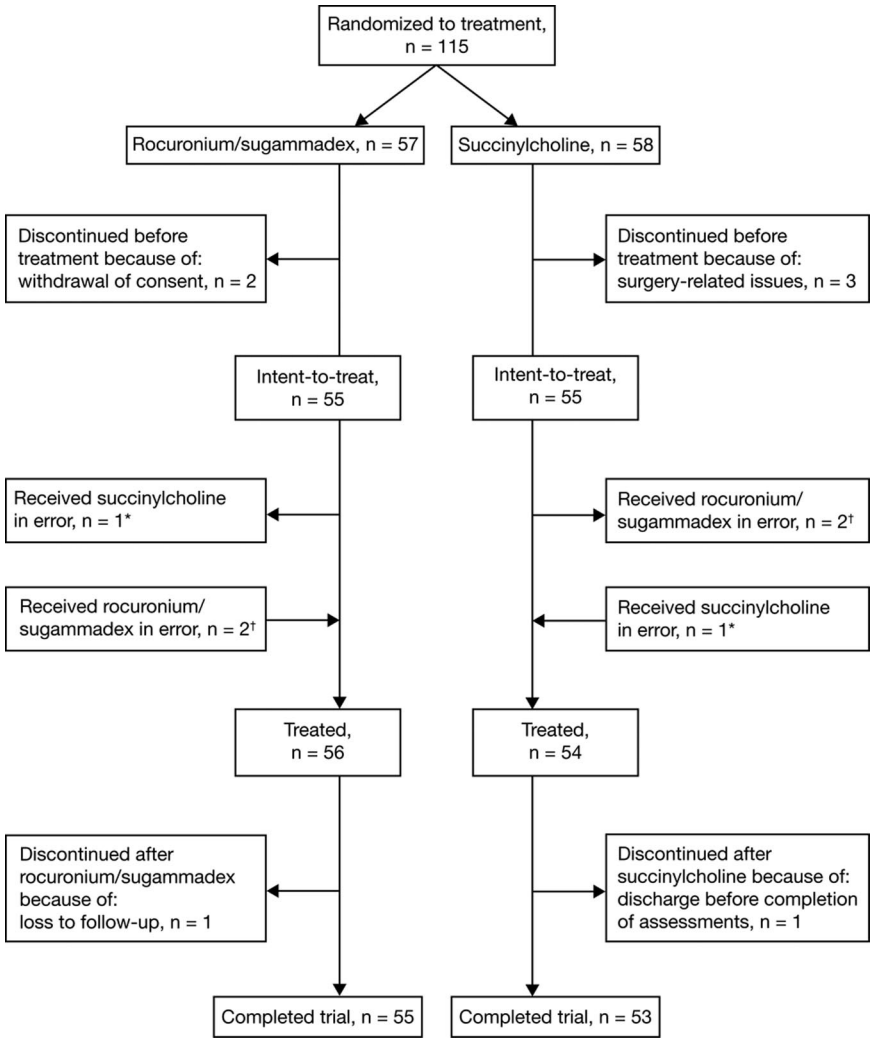

Fig. 1. Patient flow through the study. * According to the randomization schedule, this patient should have received rocuronium-sugammadex, but in error received succinylcholine. The patient was included in the succinylcholine-treated population, but in the intent-to-treat population for rocuronium-sugammadex. † According to the randomization schedule, these two patients should have received succinylcholine, but in error received rocuronium-sugammadex. They were included in the rocuronium-sugammadex–treated population, but in the intent-to-treat population for succinylcholine.

Mean (SD) time to recovery of T_4/T_1 to 0.7, 0.8, and 0.9 was 1.3 (0.6), 1.5 (1.1), and 2.2 (2.2) min, respectively. Overall, 87% of patients (47 of 54) showed recovery of the T_4/T_1 to 0.9 by 3 min, 52% between 1 to 2 min, and 13% within 1 min after sugammadex administration.

Table 1. Time (min) from Start of Administration of Neuromuscular Blocking Agent to Recovery of T_1 to 10% and T_1 to 90%

	Treatment Group	
	Rocuronium + Sugammadex* (n = 55)	Succinylcholine Only (n = 55)
Recovery to T_1 10% (primary endpoint)		
Mean (SD)	4.4 (0.7)	7.1 (1.6)†
Median	4.2	7.1
Min–max	3.5–7.7	3.8–10.5
Recovery to T_1 90%		
Mean (SD)	6.2 (1.8)	10.9 (2.4)†
Median	5.7	10.7
Min–max	4.2–13.6	5.0–16.2

* Protocol-specified sugammadex administration at 3 min after the start of rocuronium administration (mean [SD] 3.1 [0.2]; range 2.7 to 4.2 min). † $P <$ 0.001 between treatment groups.

Clinical signs of recovery were comparable between treatment groups. Before transfer to the recovery room, approximately 50% of patients in both groups were awake and oriented; this increased to > 90% at discharge from the recovery room. No patient exhibited clinical signs of muscle weakness after extubation.

Safety

Both treatments were well tolerated. Overall, 93% of patients in the rocuronium-sugammadex group and 94% of patients in the succinylcholine group had ≥ 1 AE. The most common AEs, respectively, in these groups were procedural pain (57.1 *vs.* 48.1%), and nausea (28.6 *vs.* 37.0%) (table 2). One patient in the succinylcholine group experienced a serious AE (pelvic hematoma). There were no deaths or difficult intubations.

There were no clinically meaningful differences between treatment groups in laboratory parameters, physical findings, or vital signs; and no interaction of sugammadex with any compound other than rocuronium was observed.

Table 2. Number of Patients with at Least One Adverse Event Regardless of Relationship to Study Drug*

	Rocuronium + Sugammadex, n = 56 (%)	Succinylcholine Only, n = 54 (%)
Procedural pain	32 (57.1)	26 (48.1)
Nausea	16 (28.6)	20 (37.0)
Vomiting	9 (16.1)	8 (14.8)
Procedural hypotension	7 (12.5)	13 (24.1)
Procedural hypertension	7 (12.5)	7 (13.0)
Headache	8 (14.3)	2 (3.7)
Chills	6 (10.7)	7 (13.0)
Pain in extremity	6 (10.7)	7 (13.0)
Incision site complication	5 (8.9)	7 (13.0)
Arthralgia	3 (5.4)	6 (11.1)

* Medical Dictionary for Regulatory Activities preferred terms, ≥ 10% incidence (treated population).

Discussion

As the primary endpoint, we used recovery of T_1 to 10% (instead of T_4/T_1) for its simplicity, its common usefulness between depolarizing and nondepolarizing relaxants, and because the T_4/T_1 ratio has uncertain meaning regarding a single dose of succinylcholine.[9] The observed times to spontaneous recovery of T_1 to 10% and to 90% from succinylcholine-induced block are consistent with previous reports for the same dose of succinylcholine (1 mg/kg).[27,28] While lower doses of succinylcholine may also provide adequate conditions for intubation,[28–30] higher doses are reported to provide excellent intubation conditions.[30] Although our study may be limited by the fact that the rocuronium-sugammadex group was compared against only one dose of succinylcholine (1 mg/kg), this dose of succinylcholine is the most commonly used dose for rapid-sequence induction[30] and was thus considered appropriate for this study.

At the doses tested, our findings show that with sugammadex, the mean times to recovery from profound rocuronium-induced neuromuscular block were 4.4 min (T_1 to 10%) and 6.2 min (T_1 to 90%), significantly shorter than the respective times to spontaneous recovery from succinylcholine-induced block (7.1 and 10.9 min). These times represent a saving of 2.7 and 4.6 min, respectively, for T_1 to reach 10% and 90%, favoring sugammadex-induced reversal. While a weakness in our study is the fact that three patients received the incorrect drug in error (one received succinylcholine and two received rocuronium-sugammadex), these random errors had no impact on the overall efficacy findings. If measured from the start of sugammadex administration, the reversal times became even shorter, 1.2 and 2.9 min, respectively.

The timing of sugammadex administration in this study, *i.e.*, 3 min after rocuronium administration, was selected to imitate a real-life situation in which two attempts to intubate have failed. A factor that could potentially enhance treatment differences relates to normal practice, where the intubation dose is very likely less than 1.2 mg/kg of rocuronium.

Rocuronium is currently indicated in approximately 25% of rapid-sequence induction cases in the emergency department.[31,32] Our results suggest that sugammadex may have considerable use in such a setting.

In conclusion, reversal of profound high-dose rocuronium-induced neuromuscular block (1.2 mg/kg) with sugammadex (16 mg/kg) was significantly faster than spontaneous recovery from succinylcholine (1 mg/kg). Sugammadex reversal of rocuronium may be useful should unexpected need for immediate restoration of neuromuscular function arise.

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