Anesthesiology 2007; 107:239–44

Reversal of Rocuronium-induced (1.2 mg/kg) Profound Neuromuscular Block by Sugammadex

A Multicenter, Dose-finding and Safety Study

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Background: **Reversal of rocuronium-induced neuromuscular blockade can be accomplished by chemical encapsulation of rocuronium by sugammadex, a modified γ-cyclodextrin derivative. This study investigated the efficacy and safety of sugammadex in reversing rocuronium-induced profound neuromuscular blockade at 5 min in American Society of Anesthesiologists physical status I and II patients.**

Methods: **Forty-five American Society of Anesthesiologists physical status I and II patients (aged 18–64 yr) scheduled to undergo surgical procedures (anticipated anesthesia duration ≥ 90 min) were randomly assigned to a phase II, multicenter, assessor-blinded, placebo-controlled, parallel, dose-finding study. Anesthesia was induced and maintained with propofol and an opioid. Profound neuromuscular blockade was induced with 1.2 mg/kg rocuronium bromide. Sugammadex (2.0, 4.0, 8.0, 12.0, or 16.0 mg/kg) or placebo (0.9% saline) was then administered 5 min after the administration of rocuronium. Neuromuscular function was monitored by acceleromyography, using train-of-four nerve stimulation. Recovery time was the time from the start of administration of sugammadex or placebo, to recovery of the train-of-four ratio to 0.9. Safety assessments were performed on the day of the operation and during the postoperative and follow-up period.**

Results: **A total of 43 patients received either sugammadex or placebo. Increasing doses of sugammadex reduced the mean recovery time from 122 min (spontaneous recovery) to less than 2 min in a dose-dependent manner. Signs of recurrence of blockade were not observed. No serious adverse events related to sugammadex were reported. Two adverse events possibly related to sugammadex were reported in two patients (diarrhea and light anesthesia); however, both patients recovered without sequelae.**

Conclusions: **Sugammadex rapidly and effectively reversed profound rocuronium-induced neuromuscular blockade in humans and was well tolerated.**

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Received from the Department of Anesthesiology, Raboud University Medical Center, Nijmegen, The Netherlands. Submitted for publication December 1, 2006. Accepted for publication April 6, 2007. Supported by NV Organon, Oss, The Netherlands. Timothy J. Brennan, M.D., Ph.D., served as Handling Editor for this article. Dr. Eisenach was not involved in the decision-making process.

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STEROIDAL neuromuscular blocking agents (NMBAs), such as rocuronium, are widely used in clinical anesthesia and emergency medicine to facilitate tracheal intubation and artificial ventilation and to allow surgical access to body cavities.[1] Although the use of NMBAs has significantly reduced the incidence of laryngopharyngeal lesions due to tracheal intubation, their use is still associated with higher morbidity and mortality compared with anesthetic techniques that do not use NMBAs.[2–4] This is mainly attributable to the development of postoperative residual neuromuscular blockade, resulting in hypoventilation, airway obstruction, and hypoxia.[3,4] Reversal of neuromuscular blockade is important for the acceleration of patient recovery and prevention of postoperative residual neuromuscular blockade and may reduce the incidence of severe morbidity and mortality associated with anesthesia management.[5]

Currently, the reversal of neuromuscular blockade is achieved by the administration of acetylcholinesterase inhibitors (neostigmine, edrophonium, or pyridostigmine).[6] Importantly, cholinesterase inhibitors have a number of well-known undesirable side effects (bradycardia, bronchoconstriction, hypersalivation, abdominal cramps, and nausea and vomiting)[7] that can be counteracted by coadministration of muscarinic antagonists (atropine or glycopyrrolate).[6] However, muscarinic antagonists also have side effects (blurred vision, dry mouth, and tachycardia).[7,8] Furthermore, cholinesterase inhibitors are not capable of reversing deeper levels of neuromuscular blockade.[8,9] This can be explained by their mechanism of action. At profound neuromuscular blockade, an excess of NMBA is present at the neuromuscular junction, but the maximum increase in the amount of acetylcholine to compete with NMBA is limited, even when acetylcholinesterase is totally inhibited.

Thus, there is clearly a clinical need for a new reversal agent, with minimal side effects and the capability to reverse neuromuscular blockade effectively, independently of its depth.

Sugammadex is the first selective relaxant binding agent (SRBA) and has been designed to reverse the steroidal neuromuscular blocking drug rocuronium.[9–11] Sugammadex, per-6-(2-carboxyethylthio)-per-6-deoxy-γ-cyclodextrin sodium salt (fig. 1), is a synthetic modified γ-cyclodextrin derivative designed to bind selectively to the steroidal rocuronium molecule.[9–11] Cyclodextrins, a group of cyclic oligosaccharides, are ring-shaped mole-

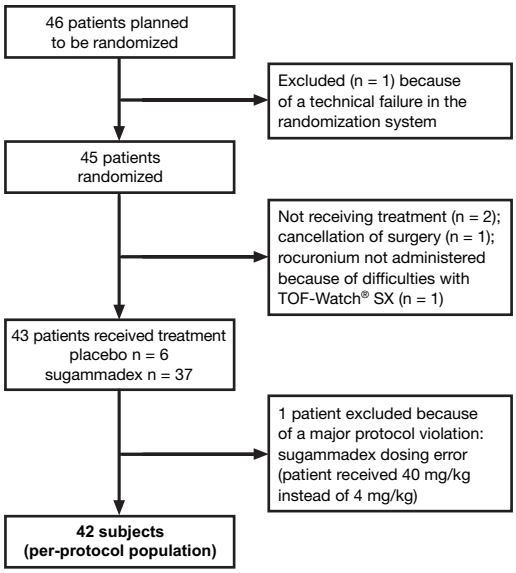

Fig. 1. Flowchart of patient disposition.

cules with lipophilic inner cavities and hydrophilic outer surfaces that form complexes by inclusion of specific guest molecules, such as steroids.[10,12] Structurally, they consist of either six (α-cyclodextrins), seven (β-cyclodextrins), or eight (γ-cyclodextrins) glucose units, and each type has its own characteristics.[12] Cyclodextrins are highly water soluble, particularly γ-cyclodextrins compared with α- and β-cyclodextrins, and are also biologically well tolerated.[10] Chemically modified cyclodextrins have been used in the clinic to increase the stability, solubility, and bioavailability of an encapsulated drug, thereby delivering the required dose of the drug to the appropriate target sites.[10] The use of a modified cyclodextrin to reverse a rocuronium-induced profound neuromuscular blockade, by removing rocuronium from the effector site, thus represents a paradigm shift from current methodology. Encapsulation of the rocuronium molecule by sugammadex results in a rapid decrease in free rocuronium in the plasma, which results in a rapid migration of rocuronium away from the synaptic cleft back into the circulation. This promotes the liberation of acetylcholine receptors, and muscle activity reappears.[10,13]

Clinical studies published thus far have investigated the effect of sugammadex doses of up to 8 mg/kg on rocuronium-induced shallow neuromuscular blockade.[14–16] Those studies on shallow blockade have shown fast and efficient reversal without the well-known undesirable side effects associated with the use of cholinesterase inhibitors.[14,15] This has been explained by the differential mechanism of action because, unlike cholinesterase inhibitors, cyclodextrin derivatives do not interfere with receptor systems, in particular the muscarinic system.

In the current study, we test the hypothesis that sugammadex can be used to reverse profound neuromuscular blockade, by administration of various doses of sugammadex at 5 min after administration of a high dose of rocuronium (1.2 mg/kg; primary objective). The secondary objective was to evaluate the safety of single doses of sugammadex up to 16 mg/kg administered to patients (American Society of Anesthesiologists physical status I and II).[17]

Materials and Methods

This multicenter, randomized, assessor-blinded and placebo-controlled, dose-finding study was conducted at four centers in The Netherlands: University Medical Centers of Nijmegen, Rotterdam, Utrecht, and Maastricht. The study was approved by the Central University Ethical Committee (University of Nijmegen) and the ethical committees of Utrecht, Rotterdam, and Maastricht, The Netherlands. Written informed consent was obtained from the participants.

Patients were sequentially enrolled and stratified between males and females. After completion of the inclusion/exclusion checklist, the investigator accessed a secure study Web site for randomization and assigned the study treatment. Before proceeding to a higher dose of sugammadex, an interim safety analysis was performed by the drug safety monitoring board, based on adverse event data and laboratory and electrocardiographic data provided by Organon. Patients were enrolled by investigators and/or their staff. The safety assessor was blinded.

Patients

Patients aged 18–64 yr (American Society of Anesthesiologists physical status I and II)[17] were eligible for inclusion in the study if they met the following inclusion criteria: scheduled to undergo a surgical procedure in the supine position with an anticipated duration of anesthesia of 90 min or greater; no anticipated difficulty with airway maintenance or intubation; no known or suspected neuromuscular disorders; no significant hepatic or renal dysfunction, malignant hyperthermia, or allergy to narcotics, NMBAs, or other medication used during anesthesia; and not receiving medication known to interfere with NMBAs. Female patients of childbearing potential not using an acceptable method of birth control (a pregnancy test was performed to exclude pregnancy) and pregnant or breast-feeding female patients were excluded from the study.

Study Design

Patients were premedicated on the morning of surgery with oral paracetamol and midazolam. On arrival in the operating room, two intravenous lines were inserted, one for the administration of anesthetics (including rocuronium and sugammadex) and the other for blood sampling. Noninvasive automatic monitoring of arterial

blood pressure, oxygen saturation, and electrocardiography were used to monitor the patients in the operating room.

Anesthesia was induced with an intravenous bolus dose of propofol and was maintained using a continuous intravenous infusion of propofol and an opioid. The opioid used most frequently was remifentanil. Patients were ventilated by mask. After induction of anesthesia, procedures for the setup, calibration, and stabilization of neuromuscular monitoring were followed in a standardized manner for each subject. Patients then received an intravenous bolus dose of 1.2 mg/kg rocuronium bromide to induce profound neuromuscular blockade. This was followed by tracheal intubation, at the time twitch suppression was 100%, and the lungs were ventilated with an oxygen-and-air mixture in a ratio of 2:3. Five minutes after administration of rocuronium, an intravenous bolus dose of sugammadex (2.0, 4.0, 8.0, 12.0, or 16.0 mg/kg) or placebo (0.9% saline) was administered. At the end of the surgical procedure, the patients were allowed to recover from anesthesia and were transferred to the postoperative recovery ward.

Neuromuscular monitoring was performed using the TOF-Watch® SX (Organon, Dublin, Ireland), by measuring the effect of stimulation of the ulnar nerve on activity of the adductor pollicis muscle. The electrodes were positioned near the wrist and the ulnar nerve. The acceleromyographic transducer was firmly placed on the ventral aspect of the top of the thumb, perpendicular to the movement of the thumb. A 5-s, 50-Hz tetanic stimulation of the ulnar nerve was given for stabilization. One minute later, the fingers were fixated and TOF stimulation was started, which continued for 2–5 min. Calibration of the TOF-watch SX® followed by using the CAL 2 sequence (Operating Manual TOF-Watch® SX; Organon, Dublin, Ireland). After calibration, repetitive TOF stimulation was started. Stimulation was supramaximal (current $<$ 60 mA) with square wave pulses of 0.2 ms in duration, delivered as train-of-four (TOF) pulses of 2 Hz, at intervals of 15 s. To check for correct setup, rocuronium was not administered until at least 3 min after calibration. Neuromuscular monitoring continued until recovery to a TOF ratio of 0.9. The data were recorded on a personal computer by means of the TOF-Watch® SX Monitoring Program (TOFMON 1.2; NV Organon, Oss, The Netherlands).

The possibility of postoperative recurrence of neuromuscular blockade or residual neuromuscular blockade was assessed by monitoring the patients' oxygen saturation, breathing pattern, and breathing frequency in the recovery ward for at least 120 min after the administration of sugammadex or placebo. Recurrence of neuromuscular blockade was defined as a relapse into a lower TOF ratio, or as deterioration in clinical signs attributed to neuromuscular blockade.

Safety Assessment

A safety assessment was performed by a blinded safety assessor, who monitored patients for adverse events, including serious adverse events, during the postoperative visit and the follow-up period. An adverse event was defined as any untoward medical occurrence in a patient administered a pharmaceutical product. A serious adverse event was defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening, required prolongation of hospitalization, or resulted in persistent disability.

Physical examination was performed at preoperative screening and postoperative visits. Measurements of blood pressure and heart rate were obtained at the screening visit, preoperatively and 24 h after administration of sugammadex or placebo. Before and at 2 and 30 min after administration of sugammadex or placebo, a 12-lead electrocardiogram was taken. The following QTc (Bazett) prolongations were to be reported as serious adverse events: individual changes $>$ 60 ms relative to baseline and absolute QTc values $>$ 500 ms.

Statistical Analysis

At the time the study protocol was written, no historic data were available on the effect of sugammadex on recovery times when administered during profound blockade. The proposed sample sizes were determined to allow exploration of neuromuscular recovery after different doses of sugammadex administered 5 min after rocuronium.

The primary efficacy variable was defined as the time from the start of the administration of sugammadex or placebo, to recovery of the TOF ratio to 0.9. Time to recovery from profound rocuronium-induced neuromuscular blockade was analyzed in the per-protocol population (*i.e.*, all treated patients without any major protocol violations). Safety data were assessed in all patients.

To explore and calculate the relation between the dose of sugammadex and the time to recovery from neuromuscular blockade to a TOF ratio of 0.9, the following exponential model was used: estimated time to recovery of the TOF ratio to 0.9 (dose) = a + b.exp{−c.dose}, where a represents the fastest achievable recovery time for the average subject, b represents the difference in time between mean spontaneous recovery and mean recovery after an infinitely large dose of sugammadex, and c represents the extent of the reduction in recovery time with sugammadex.[14,16]

Weighted nonlinear regression was used to fit the parameters of the exponential model to the recovery times. Weighting factors were used: $(1/var_i)/\Sigma(1/var_i)$, where var_i is the variance of the recovery times at dose i. A dose–response relation was calculated.

Table 1. Patient Baseline Characteristics (all Treated Patients)

		Sugammadex					
	Placebo (n = 6)	2.0 mg/kg (n = 5)	4.0 mg/kg (n = 5)	8.0 mg/kg (n = 12)	12.0 mg/kg (n = 7)	16.0 mg/kg (n = 8)	Total (n = 43)
Mean (SD) age, yr	40 (22)	44 (18)	42 (16)	44 (11)	48 (15)	33 (13)	42 (15)
Mean (SD) weight, kg	77 (11)	78 (31)	72 (8)	79 (13)	71 (12)	76 (29)	76 (18)
Mean (SD) height, cm	174 (5)	172 (13)	170 (4)	175 (9)	173 (7)	176 (12)	174 (9)
Sex, n, F/M	3/3	2/3	3/2	6/6	4/3	3/5	21/22
ASA physical status I/II, n	4/2	3/2	3/2	9/3	7/0	6/2	32/11

ASA = American Society of Anesthesiologists.

Results

The trial was conducted from November 2003 until July 2004. It was planned to enroll 46 patients in the study, but one patient could not be randomized because of a failure in the randomization system. Of the 45 patients enrolled, one patient was randomized but surgery was cancelled, and another patient did not receive any rocuronium. Forty-three patients were therefore treated with either sugammadex or placebo (fig. 1). The baseline characteristics for these patients are presented in table 1. There were no significant differences between the dose groups with respect to age, weight, height, and sex distribution. Forty-two patients were included in the per-protocol population (one patient was excluded because of a sugammadex dosing error; fig. 1).

The recovery times from neuromuscular blockade after administration of placebo or sugammadex are presented in table 2. Forty patients were analyzed for this primary efficacy variable; one patient was excluded from the analyses because the time for recovery of the TOF ratio to 0.9 was not available, and another was excluded because of a minor violation (patient received neostigmine). In the lowest sugammadex dose group (2 mg/kg), the mean time to recovery of the TOF ratio was reduced by more than 50% compared with the control group (122.1 *vs.* 56.5 min). Successive increases in the sugammadex dose to 4, 8, and 12 mg/kg decreased the mean recovery time further to 15.8, 2.8, and 1.4 min, respectively. Further increasing the dose of sugammadex to 16 mg/kg resulted in similar mean recovery times (1.9 min).

A statistically significant dose–response relation was observed between the time from start of administration of sugammadex and recovery to a TOF ratio of 0.9 (fig. 2). The estimates of the b and c variables of the model, with approximate 95% confidence intervals, were 144.3 (127.5 to 161.1) and −0.54 (−0.58 to −0.50), respectively. The mean TOF ratio after calibration and before the injection of rocuronium was 102.6% (SD = 8.6). The mean TOF ratio at the end of neuromuscular monitoring was 102.3% (SD = 7.8)

Two patients receiving sugammadex each experienced one adverse event (diarrhea and light anesthesia) that was regarded as possibly related to sugammadex. In total, three serious adverse events (all QTc prolongation) were reported, and these occurred in the 2 mg/kg (n = 1) and 12 mg/kg (n = 2) sugammadex dose groups; however, the electrocardiographic data did not indicate a relation between sugammadex administration and QTc prolongation, because there was an increase in the QTc interval between baseline and the 30-min time point for all dose groups, including placebo. None of the serious adverse events were considered related to sugammadex. All patients recovered from the serious adverse events and adverse events without sequelae. No differences were observed between the placebo and sugammadex dose groups with respect to systolic or diastolic blood pressure and heart rate. Signs of residual neuromuscular blockade and recurrence of neuromuscular blockade were not observed.

Discussion

The current study shows that, compared with spontaneous recovery, sugammadex produces rapid and effective reversal of profound rocuronium-induced neuromuscular blockade, without signs of residual or

Table 2. Summary of the Recovery Times (min) From the Start of Administration of Sugammadex or Placebo to Recovery of the TOF Ratio to 0.9 (Per-protocol Group)*

		Sugammadex				
	Placebo (n = 4)	2.0 mg/kg (n = 5)	4.0 mg/kg (n = 5)	8.0 mg/kg (n = 12)	12.0 mg/kg (n = 7)	16.0 mg/kg (n = 7)
Mean (SD)	122.1 (18.1)	56.5 (5.4)	15.8 (17.8)	2.8 (0.6)	1.4 (0.3)	1.9 (2.2)
Median	126.1	55.3	12.3	2.5	1.3	1.3
Min–max	96.8–139.4	50.5–65.1	3.3–46.6	2.2–3.7	1.0–1.9	0.7–6.9

* For one patient, the time for recovery of the train-of-four (TOF) ratio to 0.9 was not available, and for another, the time of recovery of the TOF ratio to 0.9 was excluded because of a minor violation (patient received neostigmine, a reversal agent other than sugammadex, before TOF ratio reached 0.9).

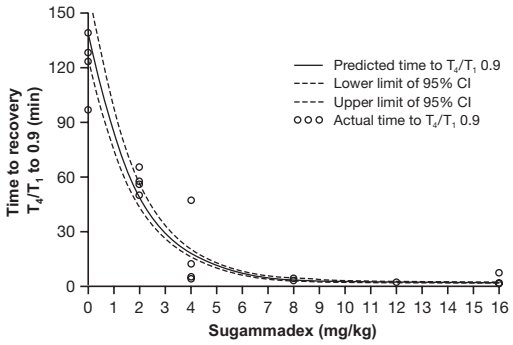

Fig. 2. Calculated dose–response relation between the time from start of administration of sugammadex and recovery of the train-of-four ratio to 0.9. CI = confidence interval.

recurrence of neuromuscular blockade. Furthermore, this reversal of neuromuscular blockade was achieved when sugammadex was administered just 5 min after administration of high-dose rocuronium (1.2 mg/kg), when plasma levels of rocuronium are still quite high after intravenous administration.[18] Increasing the dose of sugammadex up to 16 mg/kg reduced the mean recovery time to a TOF ratio of 0.9 from 122.1 min (spontaneous recovery) to less than 2 min. A clear dose–response relation between the time from start of administration of sugammadex and recovery of the TOF ratio to 0.9 was seen.

Overall, these findings demonstrate that sugammadex is effective for reversing profound neuromuscular blockade in humans. This is in contrast to the currently available cholinesterase inhibitors that are used to reverse neuromuscular blockade but are ineffective when administered during profound blockade.[9] A previous study in anesthetized rhesus monkeys showed that reversal of rocuronium-induced neuromuscular blockade was also significantly faster with sugammadex compared with a combination of neostigmine and atropine.[11] Furthermore, Kopman *et al.*[19] reported that 5 of 30 patients receiving a generally recommended dose of neostigmine (0.05 mg/kg) at a TOF count of 2 did not achieve recovery from rocuronium-induced blockade, as measured by a TOF ratio of 0.9, within 30 min of neostigmine administration. A TOF ratio of 0.9 is regarded as the cutoff point between residual paralysis and acceptable neuromuscular function.[20]

Binding of the rocuronium molecule by sugammadex is the mechanism responsible for the effective and rapid reversal of profound neuromuscular blockade induced by rocuronium. This results in a rapid decrease in the concentration of free unbound rocuronium in the plasma and subsequently at the target site, the nicotinic receptor at the motor endplate.[10,13] Rocuronium is then less available to bind to these receptors at the neuromuscular junction. This promotes the liberation of nicotinic receptors, and in turn muscle activity returns to normal. Two recent studies showed that sugammadex can reverse moderate rocuronium-induced neuromuscular blockade in surgical patients.[14,21] Recovery from shallow neuromuscular blockade after administration of a cholinesterase inhibitor results from an increase in acetylcholine in the synaptic cleft as a result of enzyme inhibition and spontaneous recovery. Administration of acetylcholinesterase inhibitors increases the half-life of acetylcholine and subsequently its concentration at the neuromuscular junction on the surface of the muscle fibers. However, there is no effect on the concentration of free NMBA, because cholinesterase inhibitors do not remove the NMBA from its site of action, like sugammadex does. As a result of this action, acetylcholinesterases are ineffective at reversing profound neuromuscular blockade induced with high-dose rocuronium as used in this study.[8,22]

Previous studies have shown that cyclodextrins are highly water soluble and do not possess intrinsic biologic activity.[12] Sugammadex has no direct or indirect action on components of cholinergic transmission (cholinesterase, nicotinic receptors, or muscarinic receptors), thus avoiding the likelihood of muscarinic side effects.[10] In the current study, significant cardiovascular changes were not observed after administration of sugammadex, indicating that in this study, the drug seems to be free of the cardiovascular effects associated with acetylcholinesterase inhibitors and/or muscarinic antagonism. This was confirmed by previous studies in rhesus monkeys and human volunteers.[15,23,24] Sugammadex–rocuronium complexes are highly hydrophilic, and it has been demonstrated that sugammadex is excreted in a rapid and dose-dependent manner in the urine,[25] resulting in complete elimination from the body.

The ability of sugammadex to reverse rocuronium-induced profound neuromuscular blockade may have major implications for routine anesthetic practice. Once sugammadex becomes commercially available, anesthesiologists will be capable of maintaining the desired depth of neuromuscular blockade at any time, thereby ensuring optimal surgical conditions. Although not directly supported by the current study, it has been speculated that sugammadex might also be used to rapidly terminate the effects of rocuronium in a dangerous and feared "cannot intubate, cannot ventilate" situation, and that it could enable rapid sequence induction by rocuronium.[26]

In conclusion, this study has shown that sugammadex can rapidly and effectively reverse profound rocuronium-induced neuromuscular blockade in humans, without apparent side effects. The mechanism by which sugammadex encapsulates rocuronium seems to be superior to currently used neuromuscular blockade reversal strategies in terms of speed, efficacy, and side effects.

Statistical analysis of the study data was performed by Wilbert G. F. van Duijnhoven, M.Sc. (NV Organon, Oss, The Netherlands), and editorial assistance was provided by Julie Adkins, B.Pharm., M.Sc. (Prime Medica, Knutsford, Cheshire, United Kingdom).

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