Sugammadex Reversal of Rocuronium-Induced Neuromuscular Blockade: A Comparison with Neostigmine–Glycopyrrolate and Edrophonium–Atropine

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BACKGROUND: Sugammadex is a modified γ cyclodextrin compound, which encapsulates rocuronium to provide for a rapid reversal of residual neuromuscular blockade. We tested the hypothesis that sugammadex would provide for a more rapid reversal of a moderately profound residual rocuronium-induced blockade than the commonly used cholinesterase inhibitors, edrophonium and neostigmine.
METHODS: Sixty patients undergoing elective surgery procedures with a standardized desflurane–remifentanil–rocuronium anesthetic technique received either sugammadex, 4 mg/kg IV ($n = 20$), edrophonium, 1 mg/kg IV and atropine, 10 μg/kg IV ($n = 20$), or neostigmine, 70 μg/kg IV and glycopyrrolate, 14 μg/kg IV ($n = 20$) for reversal of neuromuscular blockade at 15 min or longer after the last dose of rocuronium using acceleromyography to record the train-of-four (TOF) responses. Mean arterial blood pressure and heart rate values were recorded immediately before and for 30 min after reversal drug administration. Side effects were noted at discharge from the postanesthesia care unit.
RESULTS: The three groups were similar with respect to their demographic characteristics and total dosages of rocuronium prior to administering the study medication. Although the initial twitch heights (T_1) at the time of reversal were similar in all three groups, the time to achieve TOF ratios of 0.7 and 0.9 were significantly shorter with sugammadex (71 ± 25 and 107 ± 61 s) than edrophonium (202 ± 171 and 331 ± 27 s) or neostigmine (625 ± 341 and 1044 ± 590 s). All patients in the sugammadex group achieved a TOF ratio of 0.9 ≤5 min after reversal administration compared with none and 5% in the edrophonium and neostigmine groups, respectively. Heart rate values at 2 and 5 min after reversal were significantly higher in the neostigmine-glycopyrrolate group compared with that in sugammadex. Finally, the incidence of dry mouth was significantly reduced in the sugammadex group (5% vs 85% and 95% in the neostigmine and edrophonium groups, respectively).
CONCLUSION: Sugammadex, 4 mg/kg IV, more rapidly and effectively reversed residual neuromuscular blockade when compared with neostigmine (70 μg/kg IV) and edrophonium (1 mg/kg IV). Use of sugammadex was associated with less frequent dry mouth than that with the currently used reversal drug combinations.
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The cholinesterase inhibitors, neostigmine and edrophonium, are commonly used to reverse the residual effects of nondepolarizing neuromuscular blocking drugs at the end of surgery. Although cholinesterase inhibitors are generally considered to be safe and effective for reversing residual blockade when administered in combination with muscarinic antagonists, there are a number of limitations to their use (e.g., incomplete reversal from "deep" residual blockade, tachycardia, bradycardia, dry mouth, emesis) (1,2). Therefore, there is a need for a reversal drug with a rapid onset of action, efficacy irrespective of the degree of residual neuromuscular blockade, and an improved side-effect profile (3).

Recent reports have described the use of drug-specific cyclodextrins to reverse rocuronium-induced neuromuscular block (4–6). In a preliminary dose-ranging study by Sorgenfrei et al. (6), sugammadex (Organon USA, Inc, Roseland, NJ), at doses of 2 mg/kg and larger, decreased median recovery time to achieve a train-of-four (TOF) response of 0.9 from 21 min to 1.1–1.3 min. However, this initial placebo-controlled study did not compare sugammadex with either of the two standard cholinesterase inhibitors.

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Therefore, we performed an open-label, prospective, parallel study to compare reversal of rocuronium-induced neuromuscular blockade with sugammadex to neostigmine–glycopyrrolate and edrophonium–atropine when administered under standardized balanced anesthetic conditions. We hypothesized that sugammadex would be associated with a significantly more rapid achievement of a TOF ratio of 0.9 compared with the standard neuromuscular reversal drugs. The secondary objective of the study was to compare the incidences of intra- and postoperative side effects.

METHODS

After obtaining IRB approval at the University of Texas Southwestern Medical Center and Zale Lipshy University Hospital in Dallas, 60 consenting ASA physical status I–III patients undergoing elective surgical procedures requiring tracheal intubation were enrolled in this open, parallel study design. The patients who preferred not to receive an investigational drug (sugammadex) were randomly assigned to one of the two anticholinesterase groups. Patients with a history of a difficult tracheal intubation, a Mallampati score of III or IV, allergic reactions to opioid analgesics, muscle relaxants, or other medications commonly used during general anesthesia, a positive pregnancy test (or breast feeding), or a family history of malignant hyperthermia were excluded from participating in this study.

All patients were premedicated with midazolam, 20 μg/kg IV, and fentanyl, 0.5 μg/kg IV, at 30–45 min and 5–10 min before induction of anesthesia, respectively. On arrival in the operating room, routine monitors were applied for recording heart rate (HR), mean arterial blood pressure (MAP), and oxygen saturation values. After administration of oxygen, anesthesia was induced with propofol, 2–2.5 mg/kg IV, and maintained with desflurane 4–6% end-tidal, in a 1:1 oxygen:air mixture, in combination with a remifentanil infusion, 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ IV. The end-tidal concentration of desflurane (4 ± 1%) was not changed during the assessment of the reversal drugs. Ventilation was controlled to maintain the end-tidal CO_2 values between 30 and 35 mm Hg. Nasopharyngeal temperatures were maintained between 35–37°C, and the skin surface temperature of the monitored extremity was maintained >32°C, using forced air warming.

The neuromuscular function of the adductor pollicis muscle was monitored using the TOF-Watch®SX acceleromyograph (Organon Ireland Ltd. Co., Dublin, Ireland). The TOF tracing was stabilized after induction of anesthesia by administering 1 min of repetitive TOF stimulation followed by a 5-s, 50-Hz tetanic stimulation, and then another 3–4 min period of repetitive TOF stimulation. The CAL 2 mode was used to determine the supramaximal threshold and to calibrate the transducer of the acceleromyograph. TOF stimulation at the predetermined supramaximal threshold (at a pulse width of 200 μs and a frequency of 2 Hz) was repeated every 15 s, and these data were transferred in real-time via an interface to a laptop computer in the operating room.

After induction of anesthesia and calibration of the TOF-Watch®SX, each subject received a standardized dose of rocuronium, 0.6 mg/kg IV, to facilitate tracheal intubation. Additional bolus doses of rocuronium, 0.15 μg/kg, were administered upon reappearance of the second twitch in a TOF to maintain the neuromuscular block during surgery. The reversal drugs were administered at least 15 min after the last dose of rocuronium during steady-state anesthetic conditions. Patients received either IV neostigmine (70 μg/kg) with glycopyrrolate (14 μg/kg), edrophonium (1 mg/kg) with atropine (10 μg/kg), or sugammadex (4 mg/kg) alone according to an open-parallel study design. Maintenance anesthetic drugs and neuromuscular monitoring were continued for a period of 30 min after administering the reversal drugs. Noninvasive MAP and HR measurements were obtained immediately before the administration of the reversal drugs ("baseline") and subsequently at 2, 5, 10, and 30 min intervals after administration of the reversal drugs. Before the discontinuation of the anesthetics and extubation of the trachea, all patients were required to manifest a sustained tetanic response to ulnar nerve stimulation using a standard neuromuscular stimulator. Extubation times after discontinuation of the maintenance anesthetic drugs were not recorded because the reversal drugs were given at variable times before the end of surgery.

Clinical signs of recovery were assessed at 1 min intervals after extubation including level of consciousness (i.e., 3 = awake and oriented, 2 = arousable with minimal stimulation, 1 = responsive only to tactile stimulation). Orientation was also assessed at 1 min intervals after regaining consciousness by asking their name, the hospital, and the day of the week. Upon regaining orientation, a clinical assessment of muscle strength was performed using 1) 5-s head lift test, and 2) by asking the patient if they were experiencing general muscle weakness (using a 10-point verbal rating scale from 0 = none to 9 = extremely impaired). Adverse events (e.g., cardiac arrhythmias, inability to extubate the trachea upon regaining consciousness, dizziness, headaches, dry mouth, nausea and vomiting) were recorded by a blinded observer in the operating room and upon discharge from the postanesthesia care unit.

The power analysis used a simulation to estimate the number of subjects per group ($n = 20$) needed to be able to state with 97.5% confidence that 75% or more of the patients would return to TOF ratio of 0.9 within 5 min after receiving sugammadex, compared with 25% or less of the patients receiving either of the two cholinesterase inhibitors (6,7). In a preliminary study involving sugammadex, the median (range) time to recovery of the T_4/T_1 (TOF) ratio to 0.9 was 1.1

Table 1. Patient Demographic Characteristics, Anesthesia Time, Total Rocuronium Dosage, Time to Administration of the Study Drug after the Last Dose of Rocuronium, and "Baseline" Twitch Heights in the 3 Reversal Groups[a]

	Edrophonium ($n = 20$)	Neostigmine ($n = 20$)	Sugammadex ($n = 20$)
Age (yr)	63 ± 12	60 ± 14	60 ± 10
Weight (kg)	86 ± 17	92 ± 27	93 ± 33
Height (cm)	164 ± 10	165 ± 7	165 ± 7
Gender (male/female)	8/12	12/8	14/6
Anesthesia time (min)	134 ± 90	147 ± 92	143 ± 77
Total rocuronium dosage (mg)	73 ± 30	79 ± 26	73 ± 22
Time to administering reversal after last bolus of rocuronium (min)	40 ± 16	35 ± 18	41 ± 19
Initial twitch height in TOF when reversal drug was administered (%)	12 ± 8	12 ± 14	6 ± 7

TOF = train-of-four.

[a] Values are expressed as means ± SD.

Table 2. The Times from Reversal Administration to Achieve a Train-of-Four (TOF) Ratio of 0.7, 0.8, and 0.9, as well as the Percentage of Patients who Achieved a TOF of 0.9 in ≤2 min and ≤5 min in the 3 Reversal Groups

	Edrophonium ($n = 20$)	Neostigmine ($n = 20$)	Sugammadex ($n = 20$)
Initial TOF ratio after reversal administered (%)[a]	30 ± 14*	16 ± 7*	73 ± 16
Time to achieve TOF ratio (s)[a]			
0.7	202 ± 171*	625 ± 341*	71 ± 25
0.8	248 ± 132*	990 ± 456*	79 ± 33
0.9	331 ± 27*	1044 ± 590*	107 ± 61
No. of patients achieved TOF ratio			
0.7	7	9	20
0.8	5	5	20
0.9	2	5	20
No. of patients achieved TOF ratio of 0.9			
≤2 min	0 (0%)*	0 (0%)*	15 (75%)
≤5 min	0 (0%)*	1 (5%)*	20 (100%)

[a] Values are expressed as means ± SD.

* $P < 0.05$ when compared with sugammadex group.

min (1.0–1.4 min) when a 4.0 mg/kg IV a dose of sugammadex was administered 15 min after an intubating dose of rocuronium (6). Demographic data, neuromuscular function, and hemodynamic differences among three groups were evaluated using analysis of variance with Scheffé's test. To evaluate changes over time, repeated measures of analysis of variance were used. The χ^2 test was used to evaluate differences in the numbers of events (e.g., side effects). Data were expressed as mean values ± SD or median values (ranges). Statistically significant differences were present when the P value was <0.05.

RESULTS

A total of 64 patients consented to participate in this study. However, four patients were eliminated because of our inability to obtain a stable baseline TOF tracing before administering rocuronium. There were no significant demographic differences among the three reversal groups (Table 1). The duration of anesthesia, the total dosage of neuromuscular relaxant (rocuronium), and the time to administration of the reversal drug after the last dose of rocuronium were not different in the three groups.

At the time the reversal drugs were administered, the height of the first twitch (T_1) was similar in all three reversal groups (Table 2). However, the times to achieve a TOF ratio of 0.7, 0.8, and 0.9 were prolonged in the edrophonium and neostigmine groups (versus sugammadex), $P < 0.05$. Only seven and nine patients in the edrophonium and neostigmine groups, respectively, achieved a TOF ratio of 0.7 during the 30-min observation period. (Fig. 1) All 20 sugammadex-treated patients achieved a TOF ratio of 0.9 in ≤5 min compared with none and one in the edrophonium and neostigmine groups, respectively. In fact, only 10% ($n = 2$) and 25% ($n = 5$) of the patients in the edrophonium and neostigmine groups, respectively, achieved this end-point during the 30-min study period.

Compared to sugammadex, use of neostigmine-glycopyrrolate, for reversal was associated with significantly higher HR values at 2 and 5 min after reversal drug administration (Table 3). In addition, sugammadex was associated with significantly less dry mouth in the postanesthesia care unit (Table 4). Upon emergence from anesthesia, assessment of general muscle weakness revealed that one patient in the sugammadex group experienced general muscle weakness (with a score of 3 on

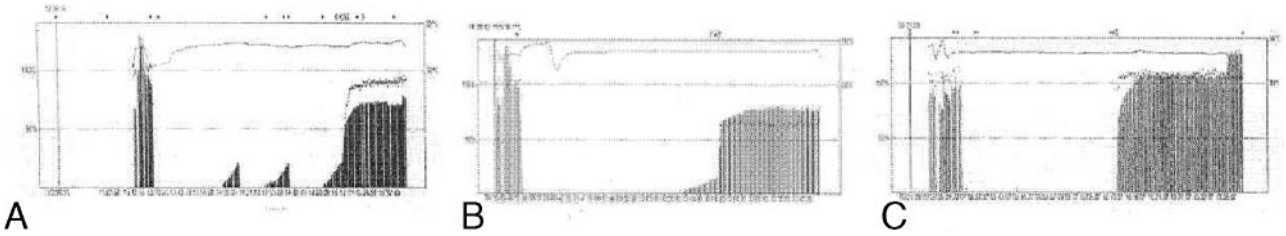

Figure 1. Sample serial train-of-four (TOF) tracings from a patient receiving rocuronium for neuromuscular relaxation during surgery followed by reversal with either r (A) neostigmine (70 μg/kg IV), (B) edrophonium (1 mg/kg IV), or (C) sugammadex (4 mg/kg IV).

Table 3. Heart Rate and Mean Arterial Blood Pressure Values Immediately Before ("Baseline") and After Administering the Reversal Medication for the 3 Reversal Groups

	Edrophonium (n = 20)	Neostigmine (n = 20)	Sugammadex (n = 20)
Heart rate (bpm)[a]			
Baseline	61 ± 14	67 ± 13	64 ± 14
+2 min	63 ± 15	75 ± 12*	62 ± 15
+5 min	63 ± 15	75 ± 8*	63 ± 17
+10 min	69 ± 19	73 ± 8	66 ± 14
Change in HR (%)			
At 2 min	+2	+13*	−2
At 5 min	+2	+16*	−1
At 10 min	−4	+11	+3
Mean arterial blood pressure (mm Hg)[a]			
Baseline	70 ± 14	74 ± 11	66 ± 10
+2 min	73 ± 18	80 ± 14	68 ± 13
+5 min	75 ± 15	77 ± 10	68 ± 12
+10 min	81 ± 19	76 ± 12	69 ± 12
Change in MAP (%)			
At 2 min	+3	+7	+3
At 5 min	+5	+3	+1
At 10 min	+8	+2	+4

[a] Values are means ± SD.

$P < 0.05$ when compared with sugammadex group.

the 10-point scale) compared with two and four patients in the edrophonium and neostigmine groups, respectively. Moreover, the ability of patients to perform a 5-s head lift did not differ significantly among the three groups (Table 4).

DISCUSSION

Compared to the standard cholinesterase-inhibiting drugs, neostigmine and edrophonium, sugammadex was associated with a more rapid and complete reversal from a moderately profound rocuronium-induced neuromuscular block under general anesthesia with a standardized "balanced" anesthetic technique. The use of sugammadex also obviated the need for the anticholinergic drugs glycopyrrolate and atropine. These comparative data suggest that when steroid-based, nondepolarizing neuromuscular blocking drugs such as rocuronium (and vecuronium) are used to facilitate tracheal intubation for short surgery procedures, use of sugammadex may provide for a more rapid and complete reversal of residual blockade at the end of surgery. Clearly, additional prospective, randomized, comparative reversal studies are needed in the ambulatory surgery setting.

The present study confirms and extends the recent observation by Sorgenfrei et al. (6), suggesting that sugammadex, administered to reverse a moderately profound rocuronium-induced neuromuscular block, allowed return of the TOF ratio to 0.9 within 5 min. Although the previous dose-ranging study included only three patients at the dose we studied, our findings suggest that there is a remarkable degree of consistency in the responses of patients to this novel reversal drug.

In contrast to the preliminary dose-ranging study by Sorgenfrei et al. (6), we found no evidence of a hypotensive effect due to sugammadex when it was administered under steady-state anesthetic conditions. In fact, the MAP and HR values remained stable during the entire post–reversal observation period. Although only 20 patients were studied, this new reversal drug appears to be free of any clinically significant side effects. The failure to demonstrate a reduction in the incidence of postoperative nausea and vomiting (PONV) with sugammadex compared with the use of the standard cholinesterase inhibitors (8,9) may be related to the small group sizes (n = 20), and the fact that all subjects remained in the hospital

Table 4. Clinical Assessment of Muscle Strength in the Operating Room, and Side Effects Reported by the Patients in the Postanesthesia Recovery Unit (PACU) in the 3 Reversal Groups

	Edrophonium ($n = 20$)	Neostigmine ($n = 20$)	Sugammadex ($n = 20$)
Initial muscle strength assessment			
Time after extubation (min)[a]	1 ± 1	3 ± 2	1 ± 1
Performed 5-sec head lift (n, %)	19 (95%)	18 (90%)	20 (100%)
Felt muscle weakness (n, %)	2 (10%)	4 (20%)	1 (5%)
General muscle weakness score[b]	0 (0–6)	0 (0–6)	0 (0–3)
Side effects in PACU			
Dry mouth	19*	17*	1
Mild	6	10	0
Moderate	7	3	1
Severe	6	4	0
Nausea	3	6	4
Vomiting	0	1	0
Drowsiness	0	0	0
Dizziness	0	0	0

[a] Values are means ± SD.

[b] Muscle weakness assessment: 0 = no impairment to 9 = severe impairment; values indicate medians and ranges given in parentheses.

* $P < 0.05$ when compared with sugammadex group.

overnight. Most studies suggesting an increase in symptoms of PONV after administration of anticholinesterases were performed in patients undergoing ambulatory surgery (10,11). Given the low incidence of PONV in this urologic surgery population, this study was clearly "under-powered" to demonstrate a difference among the three groups with respect to PONV.

Analogous to the earlier findings of Kopman et al. (7), only 5 of the 20 patients receiving neostigmine for reversal of rocuronium at a similar degree of neuromuscular blockade in our study were able to achieve a TOF ratio of 0.9 within 30 min. In contrast to an earlier comparative study by Naguib et al. (12), we found that edrophonium had a more rapid early reversal of rocuronium-induced blockade than neostigmine (e.g., average time to a TOF ratio of 0.6 was 186 ± 155 vs 505 ± 331 s, data not reported). However, both of these reversal times were significantly longer than for sugammadex to achieve a TOF ratio of 0.6 (71 ± 25 s). We would speculate that the availability of sugammadex for reversal of residual neuromuscular blockade would allow anesthesiologists to be more comfortable in using the intermediate-acting nondepolarizing muscle relaxant rocuronium for short ambulatory procedures.

According to Epemolu et al. (13), modified γ-cyclodextrins like sugammadex form tightly bound 1:1 complexes with aminosteroid-based muscle relaxants and function as chelating (encapsulating) drugs. The ability of sugammadex to encapsulate rocuronium initially increases the plasma concentration of rocuronium, thereby reducing the number of rocuronium molecules at the neuromuscular junction (i.e., effect site) resulting in a rapid reversal of residual neuromuscular blockade. As suggested in the recent editorial by Kopman (14), sugammadex seems "to provide practitioners with the ability to rapidly and completely reverse profound nondepolarizing neuromuscular blockade produced by steroid-based muscle relaxants." However, the extent to which sugammadex will replace the currently used combinations of anticholinesterases and muscarinic blocking drugs will probably depend, in large part, on pharmacoeconomic considerations, as well as on the comparative effects of these reversal drugs at less profound levels of residual neuromuscular blockade.

Because this study protocol was designed to evaluate the use of sugammadex (*versus* conventional anticholinergic drugs) for the reversal of moderately profound ("deep") neuromuscular blockade, these findings may not be reflective of the difference among these reversal drugs when the patient has recovered 2–4 twitches in a TOF at the end of surgery. Therefore, this study could be criticized for being designed to favor the investigational new drug. Future clinical studies are clearly needed comparing sugammadex to the anticholinesterase drugs when administered after recovery of 2–3 twitches in the TOF.

The major perceived deficiency in the present study relates to the fact that this was an open-parallel study design rather than a more conventional prospectively randomized study design. Unfortunately, the investigational drug status of sugammadex and the Organon protocol requirements precluded us from performing this clinical investigation in a traditional prospectively, randomized, double-blind fashion. Because the neuromuscular measurements were performed using objective "quantifiable" end points (i.e., acceleromyography data captured in real-time on a laptop computer) under identical anesthetic conditions, the reported findings represent a valid comparison of the three reversal drugs. Furthermore, the postoperative assessments were performed in blinded fashion.

A second criticism of the study relates to the seemingly arbitrarily chosen dose of sugammadex for reversal. However, we used the dose (4 mg/kg IV) which was recommended based on the recently published dose-ranging study (6). The dosages of the

anticholinesterase and anticholinergic drugs used in this study were the standard recommended doses; however, higher doses of the anticholinesterases may have been more appropriate, given the degree of residual blockade at the time of reversal.

It is also important to point out that the reversal drugs were administered during general anesthesia with desflurane, a low-solubility volatile anesthetic which has well-known depressant effects at the neuromuscular junction. Desflurane was used in combination with remifentanil to facilitate a rapid emergence from anesthesia (15) and to allow for the early clinical assessment of the patients' muscle strength. It is not known if reversal of rocuronium-induced neuromuscular blockade with sugammadex would be different when propofol is used for maintenance of anesthesia rather than a volatile anesthetic.

In summary, this study confirms the ability of sugammadex to rapidly reverse a moderately profound rocuronium-induced neuromuscular blockade without untoward side effects. More importantly, these preliminary comparative data suggest distinctive advantages over the currently used cholinesterase inhibitors with respect to the speed and completeness of the reversal process, and reduced symptoms of dry mouth after surgery.

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