Reversal of Neuromuscular Blockade with Sugammadex at the Reappearance of Four Twitches to Train-of-four Stimulation

Adrienn Pongrácz, M.D.,* Szilárd Szatmári, M.D., Ph.D.,† Réka Nemes, M.D.,† Béla Fülesdi, M.D., Ph.D., D.Sci.,‡ Edömér Tassonyi, M.D., Ph.D., D.Sci.§

ABSTRACT

Background: Doses of sugammadex required to reverse deep, moderate, and shallow rocuronium-induced neuromuscular blockade have been established. However, no adequate doses for the reversal of reappearance of four twitches of train-of-four (TOF) stimulation (threshold TOF-count-four) have been established.

Methods: This single-center, randomized, controlled, double-blind, four-groups parallel-arm study included 80 patients undergoing general anesthesia with propofol, sevoflurane, fentanyl, and rocuronium. Neuromuscular monitoring was performed with calibrated acceleromyography. Once rocuronium-induced neuromuscular blockade recovered spontaneously to threshold TOF-count-four, patients randomly received 0.5, 1.0, 2.0 mg/kg of sugammadex or 0.05 mg/kg of neostigmine. The time between study drug injection and reversal of TOF ratios to 1.0 was measured. Rapid reversal (≤2.0 min average, upper limit of 5.0 min) was the primary endpoint and slower reversal (≤5.0 min average, upper limit of 10 min) was the secondary endpoint of the study.

Results: Sugammadex, in doses of 1.0 and 2.0 mg/kg, reversed threshold TOF-count-four to TOF ratios of 1.0 in 2.1 ± 0.8 min (mean ± SD) and 1.8 ± 0.9 min, respectively. Sugammadex, 0.5 mg/kg, induced a similar degree of reversal in 4.1 ± 1.9 min ($P < 0.001$ *vs.* 1.0 and 2.0 mg/kg). Neostigmine, 0.05 mg/kg, reversed TOF ratios to 1.0 in 8.5 ± 3.5 min ($P < 0.001$ *vs.* sugammadex groups).

Conclusion: Sugammadex, 1.0 mg/kg, rapidly and effectively reverses rocuronium-induced block that has recovered spontaneously to a threshold TOF-count-four. A dose of 0.5 mg/kg was equally effective, but satisfactory antagonism took as long as 8 min to take place.

What We Already Know about This Topic

- Sugammadex is a modified γ-cyclodextrin that reverses the neuromuscular (NM) blockade produced by rocuronium by encapsulating it, making it unavailable to interact with the nicotinic acetylcholine receptor at the NM junction
- Sugammadex doses of 2.0–16 mg/kg can reverse moderate to profound rocuronium-induced NM blockade within 2–5 min

What This Article Tells Us That Is New

- Residual rocuronium-induced NM blockade at the reappearance of the fourth twitch in response to train-of-four stimulation can be reversed within 5 min by 1.0 and 2.0 mg/kg of sugammadex
- A sugammadex dose of 0.5 mg/kg can reverse such residual NM blockade in less than 10 min

ACCUMULATING evidence indicates that residual postoperative neuromuscular block (RPONB) may cause potentially dangerous respiratory complications and thereby compromise patient safety.[1,2] Neostigmine, an acetylcholinesterase inhibitor, has been used to reverse residual neuromuscular (NM) blockade before extubation of the trachea, to prevent RPONB. However, neostigmine may induce side effects, its onset of action is relatively slow, and it is not efficacious in deep block.[2–4] Sugammadex, a γ-cyclodextrin compound, is a new reversal agent, a specific encapsulator of steroidal muscle relaxants, such as rocuronium and vecuronium.[5] Unlike neostigmine, sugammadex is efficacious in reversing profound (no responses to either train-of-four [TOF] or posttetanic count stimulation) or deep (posttetanic count of 1 or 2) rocuronium neuromuscular block (NMB) in doses of 16 and 4 mg/kg, respectively.[4,6] We also know the dose of sugammadex required for the reversal of moderate block of TOF-count-two (TOFC-2; 2.0 mg/kg).[7] However, there is no information on how to proceed on

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* Staff Anesthesiologist, † Resident, ‡ Professor and Head, § Titular Professor, Department of Anesthesiology and Intensive Care, University of Debrecen, Debrecen, Hungary.

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Address correspondence to Dr. Fülesdi: Department of Anesthesiology and Intensive Care, University of Debrecen, Hungary, H-4032, Debrecen, Nagyerdei krt. 98. fulesdi@dote.hu. Anesthesiology 2013; 119:36-42

the reappearance of the fourth twitch of TOF stimulation (threshold TOF-count-four [TOFC-4]). This level of blockade can be detected by visual or tactile means, using a simple nerve stimulator, not requiring objective monitoring, and it gives the clinician an appropriate information on which to base dosage decisions.[8] Sugammadex is very efficient in reversing any depth of rocuronium NMB within 2–5 min depending on the dose.[9] Because the encapsulation of rocuronium by sugammadex is a one-to-one molecular interaction, theoretically the shallower the depth of block, the lower the dose requirement of sugammadex.[5] Therefore, we hypothesized that the doses lower than 2.0 mg/kg would produce rapid and adequate reversal once spontaneous recovery to a threshold TOFC-4 was achieved.

The aim of the study was to determine the time required for 0.5, 1.0, and 2.0 mg/kg of sugammadex to reverse a threshold TOFC-4 level block to a TOF ratio of 1.0. Rapid reversal (≤2.0 min average, upper limit of 5.0 min) was the primary endpoint and slower reversal (≤5.0 min average, upper limit of 10 min) was the secondary endpoint of the study. We compared these times with the times required for the control treatment of 0.05 mg/kg of neostigmine to similarly reverse a threshold TOFC-4 degree blockade.

Materials and Methods

Study Design and Patient Allocation

This single-center, randomized, controlled, double-blind, four-groups parallel-arm study was approved by the ethics committee of the medical faculty of the University of Debrecen, Hungary, and the National Institute of Pharmaceutics (Országos Gyógyszerészeti Intézet, Budapest, Hungary). The study is classified as EudraCT Number: 2011-001683-22.

The investigation was conducted at the University Hospital of Debrecen, Hungary, between 2011 and 2012 April. The service of anesthesiology recruited 80 patients, who then gave their written informed consent to participate. Subjects were allocated in a 1:1 ratio to the four-study groups. Inclusion criteria were as follows aged 18–65 yr, body mass index 18.5–25.0 kg/m^2, American Society of Anesthesiologists physical status I–III, and scheduled for elective surgery with an expected duration of more than 50 min under general anesthesia with intubation of the trachea. Patients who had participated in another clinical trial within 1 month were not included. Patients with suspected difficult airway, bronchial asthma, chronic obstructive pulmonary disease, known NM disease, suspected malignant hyperthermia, hepatic or renal dysfunction, glaucoma, allergy to the medication that used in this trial, taking medicaments that might influence the effect of NMB agents, pregnant, or breastfeeding state were not included.

Patients randomly received 0.5, 1.0, and 2.0 mg/kg of sugammadex or 0.05 mg/kg of neostigmine in a mixture with 0.015 mg/kg of atropine. To ensure the equal numbers of patients per group, permuted-block randomization was used.[10] Numbers of one to four were prepared 20 times each and placed into an envelope, each number identifying one of the four study groups. In the operating room, a different anesthesiologist prepared the study drug in an unlabeled syringe according to the randomization and injected it upon the request of the blinded anesthesiologist who was responsible for the patient.

Procedure

Patients were received 7.5 mg of midazolam orally 1 h before the induction of anesthesia. On arrival at the operating room, an intravenous cannula was inserted in a forearm vein on the opposite side of the acceleromyography. Noninvasive blood pressure, electrocardiogram, and oxygen saturation monitoring were performed. Anesthesia was induced with intravenous propofol (1.5–2.5 mg/kg) and fentanyl (2 μg/kg) and maintained with inhaled sevoflurane (1.1–1.8 vol%) in air–oxygen mixture and intravenous fentanyl according to clinical need. Patients' lungs were artificially ventilated by face mask until intubation of the trachea to maintain an oxygen saturation of more than 96%, to obtain stable end-expiratory sevoflurane concentration, and to ensure normocapnia. Body temperature was maintained at 36.0°C or higher.

NM monitoring was carried out according to the international consensus guidelines,[11] monitoring the adductor pollicis muscle in response to ulnar nerve stimulation using the TOF-Watch-SX® device (Organon Teknika B.V., Boxtel, Holland). The piezoelectric probe of the acceleromyograph was attached to the tip of the thumb together with a hand adapter to ensure preload and stabilize the movement of the thumb. The forearm was immobilized, and surface skin electrodes were placed over the ulnar nerve proximal to the wrist. A TOF mode of stimulation was started and repeated every 15 s for 3 min followed by a 5-s tetanic train of 50 Hz. Two minutes later, automatic calibration (CAL-2 mode to set out supramaximal current intensity and calibration of the device) was carried out, and TOF stimulation (supramaximal square wave stimuli of 0.2 ms duration at 2 Hz frequency) was continued until the signal was stable. If the signal was not stable, the calibration was repeated. The TOF stimulation was applied at 15-s intervals until the end of the study. The responses to the four stimuli (TOFC of 1–4) and the ratio of the fourth to the first twitch responses of a TOF complex (TOF ratio) were displayed by the device and were recorded (displayed or nonnormalized TOF ratios). Skin temperature was measured at the site of NM measurements and maintained above 32.0°C. After stabilization of the acceleromyographic recording, 0.6 mg/kg of rocuronium was injected. The trachea was intubated when the TOFC was 0. During surgery, 0.1–0.15 mg/kg of rocuronium was injected as needed when the TOFC exceeded 1.

At the end of the surgery, spontaneous recovery from the NMB was allowed. The study medication was injected when the fourth twitch of TOF returned (threshold TOFC-4) at three consecutive TOF measurements.[12] Reversal of the

displayed TOF ratio to 1.0 was considered as efficacy endpoint of the study.[13] The time intervals between the start of injection of the study drug and the reversal of TOF ratios to 1.0 were recorded. To ensure satisfactory reversal of the NM blockade, displayed TOF ratios at recovery were divided by control TOF ratios measured before the administration of rocuronium ("normalization") because control acceleromyographic TOF ratios usually exceed 1.0. Satisfactory recovery has been defined as normalized TOF ratios of 0.9 or more.[12] TOF ratios before injection of the study drugs were also normalized.

NM monitoring was continued after the reversal of TOF ratios to 1.0 until the end of surgery (there was no more need for relaxation) for an average of 16 min (10–50 min), then the administration of sevoflurane was stopped and the patient's trachea was extubated once the patient was awake. If the TOF ratio did not reach 1.0 within 15 min, 2.0 mg/kg of sugammadex (rescue treatment) was injected to prevent RPONB. If the TOF ratio returned below 0.9, recurrent block was recorded.

After extubation of the trachea, patients were kept in the recovery room for at least 60 min under close surveillance for recurrence of any sign of muscle weakness or critical respiratory or circulatory events. Oxygen saturation, respiratory rate, heart rate, and noninvasive blood pressure were monitored. After discharge from the recovery room, the patients were followed for 24 h to detect late adverse events.

Data Management and Statistical Analysis

Calculation of sample size was carried out assuming that the usual time for recovery is 500 s with an SD of 200 s in patients treated with neostigmine, and that 0.5 mg/kg of sugammadex decreases the time of recovery to 300 s. Using a Type I error rate (α) of 0.05, n of 10 in the treatment group would be needed to reach a power of 0.8 and n of 15 would result in a power of 0.95. As we assumed that dropouts might happen, we included 20 patients in each group.

Recovery from rocuronium-induced threshold TOFC-4 NMB was studied in the per-protocol population. We calculated normalized TOF values at antagonism and at recovery. We analyzed data by using parametric statistical tests only when the assumptions of these tests were met by the data. Otherwise, we used nonparametric statistics or log-transformed the data to comply with the parametric assumptions. We tested the normality of response variables using the Kolmogorov–Smirnov test and the equality of variances using Levene test. The time of the reversal of TOF ratios was measured in seconds, converted to minutes, and was log-transformed ($\log_{10}$) to achieve the equality of variances for use in parametric statistical tests. We first analyzed whether patients' characteristics and treatment factors, which could have influenced the results, differed among experimental groups (untransformed data and Kruskal–Wallis tests) and then we analyzed the times of recovery (log-transformed data and ANOVA). We used Tukey honestly significant difference procedure for the *post hoc* comparison of means among experimental groups.

For the analysis of primary and secondary outcome variables (rapid reversal and slower reversal), we selected the patients in categories according to the predetermined criteria. Rapid reversal *versus* not rapid reversal was compared between the sugammadex groups (pooled data) and the control group (neostigmine), using relative risk calculations. In addition, we compared the incidence of rapid and slower reversal in patients who received sugammadex (pooled data), using the odds ratio calculation.

In all statistical analyses, we used SPSS version 17.0 for Windows (IBM Corporation, Armonk, NY). Two-tailed probabilities ($\alpha = 0.05$) are reported in the text.

Results

In total, the study drugs were injected in 80 patients. Five patients were excluded. In four patients, the TOF ratio did not reach 1.0 within 15 min after the injection of neostigmine, and therefore 2 mg/kg of sugammadex was given as a rescue medication to prevent RPONB. In one patient (0.5-mg/kg sugammadex group), the study drug was injected at a TOF ratio of 0.6 (minor protocol violation). With the five patients excluded from the final efficacy analysis, 75 patients were finally analyzed for TOF recovery.

The four experimental groups did not differ in any of the factors that could have influenced the results (sex, age, body mass index, and American Society of Anesthesiologists physical status score) or in treatment (total rocuronium dose, time from last rocuronium dose to antagonism, concentrations of sevoflurane at induction and at antagonism, and TOF ratios at antagonism and at recovery; $P > 0.085$; tables 1–3).

The times of reversal to nonnormalized TOF ratios of 1.0 (normalized TOF ratios 0.98–1.0) after injection of 0.5, 1.0, and 2.0 mg/kg of sugammadex were (mean ± SD) 4.1 ± 1.9, 2.1 ± 0.8, and 1.8 ± 0.9 min, respectively. The time of reversal to nonnormalized TOF ratios of 1.0 (normalized TOF ratio 1.0) after the injection of 0.05 mg/kg of neostigmine was 8.5 ± 3.5 min (table 3). The times of reversal differed significantly among the four experimental groups ($P < 0.001$). Patients who received 1.0 or 2.0 mg/kg of sugammadex recovered significantly faster from the threshold TOFC-4 NMB than with sugammadex 0.5 mg/kg or with neostigmine 0.05 mg/kg ($P < 0.001$; table 3). The difference in times of recovery between sugammadex of 0.5 mg/kg and neostigmine of 0.05 mg/kg was also significant ($P < 0.001$). There was no significant difference in times of recovery between 1.0 and 2.0 mg/kg of sugammadex (table 3; $P = 0.581$).

The incidence of rapid reversal (primary endpoint) after sugammadex treatment was higher than that after neostigmine treatment ($P = 0.022$). The incidence of rapid reversal after sugammadex treatment was higher than the incidence of slower reversal (secondary endpoint; table 4; $P < 0001$).

Table 1. Baseline Characteristics of Patients in the Four Experimental Groups

Patients' Data	Sugammadex 0.5 mg/kg	Sugammadex 1.0 mg/kg	Sugammadex 2.0 mg/kg	Neostigmine 0.05 mg/kg
Sex (M/F)	8/11	6/14	6/14	3/13
Age, yr				
Mean (±SD)	45.79 (±11.73)	46.35 (±12.60)	47.55 (±10.93)	44.63 (±10.83)
95% CI	40.52–51.06	40.43–52.17	42.33–52.67	39.69–50.31
Median (range)	48 (20–63)	48 (26–65)	51 (26–62)	46 (24–62)
BMI, kg/m^2				
Mean (±SD)	24.0 (±1.5)	24.4 (±1.1)	23.7 (±1.6)	23.2 (±2.0)
95% CI	23.33–24.70	23.81–24.88	22.94–24.46	22.22–24.16
Median (range)	25 (20–25)	25 (22–25)	24 (20–25)	24 (19–25)
ASA class				
I	3	4	6	8
II	14	16	14	7
III	2	0	0	1
N	19	20	20	16

$P > 0.085$ among the four groups.

ASA = American Society of Anesthesiologists; BMI = body mass index; F = female; M = male; N = number of patients.

No recurrent NMB or postoperative critical respiratory or circulatory events occurred in our patients.

Discussion

In the current study, we investigated the efficacy of 0.5, 1.0, and 2.0 mg/kg of sugammadex for antagonism of rocuronium-induced threshold TOFC-4 NMB. At present, there is no information on which dose of sugammadex will provide adequate antagonism of TOFC-4 degree of blockade, and therefore, the administration of 2.0 mg/kg is recommended by the manufacturer, similarly to the reversal of a TOFC-2 block.‖

We preselected 0.5 and 1.0 mg/kg of sugammadex as intermediate doses between 0.25 and 2.0 mg/kg. Recently, Schaller *et al.*[14] demonstrated that 0.25 mg/kg of sugammadex was able to reverse a TOF ratio of 0.5 to 0.9 in an average time of 1.7 min. Based on this information, we hypothesized that the doses lower than 2.0 mg/kg would produce rapid and adequate recovery once spontaneous recovery to a threshold TOFC-4 was achieved. To cover the dose gap between 0.5 and 2.0 mg/kg, a dose of 1.0 mg/kg of sugammadex was also studied. The 2.0 mg/kg dose was included as the lowest recommended dose by the manufacturer. We did not include a placebo group because the efficacy of sugammadex to accelerate the recovery from a rocuronium-induced block is already well documented.

Instead of placebo, we included 0.05 mg/kg of neostigmine, regarded as a fully effective dose for antagonism. We estimated that the comparison of neostigmine with sugammadex for the reversal of a threshold TOFC-4 rocuronium-induced blockade might provide clinically relevant information.

‖ European Medicines Agency: EPAR Bridion summary for the public. Available at: http://www.emea.europa.eu. © European Medicines Agency. Accessed April 21, 2012, EMEA/H/C/885.

We have arbitrarily defined rapid reversal (≤2.0 min average, upper limit of 5.0 min) and slower reversal (≤5.0 min average, upper limit of 10 min) as primary and secondary study endpoints, to depict the rapidity and flexibility of sugammadex for antagonism. This is in agreement with published data because 2.0 min were introduced during the dose-finding studies for sugammadex.[7,15] For a less than 5.0 min average recovery time with an upper limit of 10 min, we considered the data of Schaller *et al.*,[14] who found this time sufficient for the reversal of a TOF ratio of 0.5 to a ratio of 0.9 by 0.1 mg/kg of sugammadex.

For the measurement of NM transmission, we applied the TOF-Watch-SX® acceleromyography device according to the international guidelines.[11] To detect residual paralysis reliably with this method, recovery of nonnormalized TOF ratio of 0.9 is considered insufficient, and a threshold of 1.0 is now recommended to confirm adequate recovery from NMB.[13] Therefore, the efficacy endpoint in this study was set to a nonnormalized TOF ratio of 1.0, which is different from previously published trials.[14,16,17] However, it does not apply to normalized TOF values where the threshold TOF ratio to exclude clinically significant residual paralysis was set at 0.9.[12] In the current study, patients who exhibited nonnormalized TOF ratios of 1.0 also met the criteria of normalized TOF ratios for adequate reversal of 0.9 or more (table 3).

For maintaining anesthesia, 1.1–1.8 vol% concentrations of sevoflurane were used in low-flow mode according to clinical requirement. Since sevoflurane potentiates the effect of NMB agents, similar end-expiratory concentrations were ensured during the induction of and the recovery from NMB in individual patients to avoid bias by variation of the effect of sevoflurane.

The time of recovery after injection of 1.0 mg/kg of sugammadex was 2.1 ± 0.8 min, thus 1.0 mg/kg of sugammadex

Table 2. Rocuronium and Sevoflurane Treatment

Parameters	Sugammadex 0.5 mg/kg	Sugammadex 1.0 mg/kg	Sugammadex 2.0 mg/kg	Neostigmine 0.05 mg/kg
Total rocuronium doses, mg/kg				
Mean (±SD)	0.75 (±0.24)	0.64 (±0.07)	0.77 (±0.22)	0.77 (±0.18)
95% CI	0.64–0.87	0.61–0.68	0.66–0.87	0.67–0.86
Median (range)	0.63 (0.59–1.30)	0.60 (0.55–0.83)	0.69 (0.59–1.38)	0.73 (0.59–1.18)
Time from last rocuronium dose to antagonism, min				
Mean (±SD)	46.55 (±22.75)	53.71 (±16.66)	43.72 (±14.13)	39.82 (±19.43)
95% CI	35.58–57.51	45.91–61.51	37.11–50.34	29.47–50.18
Median (range)	49.0 (5.6–89.4)	55.0 (17.0–80.0)	46.3 (16.0–66.1)	40.2 (9.3–69.0)
Sevoflurane concentrations at antagonism, %				
Mean (±SD)	1.18 (±0.23)	1.19 (±0.27)	1.27 (±0.38)	1.08 (±0.23)
95% CI	1.08–1.32	1.06–1.32	1.08–1.45	0.96–1.21
Median (range)	1.2 (0.8–1.6)	1.2 (0.8–1.8)	1.2 (0.8–2.4)	1.15 (0.8–1.6)
N	19	20	20	16

$P > 0.085$ among the four groups.
N = number of patients.

fulfilled the criterion of rapid reversal and can be regarded as an adequate dose for rapid antagonism of a threshold TOFC-4 rocuronium blockade. Indeed, all but one patient who received 1.0 mg/kg of sugammadex met the primary endpoint of the study (table 4). Several investigators have found time slightly more than 2.0 min average (2.3 and 3.3 min) for the reversal of TOFC-2 blocks to 0.9 TOF ratios when using 1.0 mg/kg of sugammadex.[7,15] This difference can be well explained by the fact that the block was deeper (TOFC-2) in their studies than in ours (threshold TOFC-4).

The time of recovery after injection of 0.5 mg/kg of sugammadex was 4.1 ± 1.9 min (mean ± SD). This time corresponds to our criterion of slower recovery, which was fulfilled in 84% of patients who received 0.5 mg/kg of sugammadex, and may be regarded as adequate from a clinical perspective. In addition, 16% of patients in the 0.5-mg/kg sugammadex group exhibited rapid reversal. These results can be compared with published data by Sorgenfrei *et al.*,[7] who found 4.3 min (1.3–8.5 min) necessary to reach a TOF ratio of 0.9 when antagonizing a TOFC-2 rocuronium block

Table 3. TOF Ratios at Antagonism and Recovery and Time Intervals of Recovery

Parameters	Sugammadex 0.5 mg/kg	Sugammadex 1.0 mg/kg	Sugammadex 2.0 mg/kg	Neostigmine 0.05 mg/kg
Normalized TOF ratios at antagonism				
Median	0.09	0.10	0.09	0.10
Range	0.00–0.23	0.00–0.33	0.00–0.16	0.00–0.34
95% CI	0.06–0.12	0.04–0.13	0.05–0.10	0.04–0.14
Nonnormalized TOF ratios at recovery				
Median	1.00	1.01	1.00	1.00
Range	1.00–1.04	1.00–1.09	1.00–1.09	1.00–1.10
95% CI	1.00–1.02	1.01–1.03	1.00–1.02	1.00–1.03
Normalized TOF ratios at recovery				
Median	0.98	1.00	1.00	1.00
Range	0.90–1.01	0.90–1.03	0.91–1.03	0.92–1.07
95% CI	0.96–0.99	0.97–1.00	0.97–1.00	0.98–1.01
Time intervals of recovery, min				
Mean ± SD	4.1 ± 1.9*	2.1 ± 0.8	1.8 ± 0.9#	8.5 ± 3.5**
95% CI	3.2–5.0	1.7–2.5	1.4–2.3	6.7–10.4
Median (range)	3.5 (1.7–8.0)	1.9 (1.2–4.5)	1.7 (0.8–4.7)	8.7 (2.7–15.0)
N	19	20	20	16

*$P < 0.001$ *vs.* 1.0, 2.0 mg/kg sugammadex and neostigmine groups; **$P < 0.001$ *vs.* 0.5, 1.0, and 2.0 mg/kg sugammadex groups; $P = 0.085$ for TOF ratios among the four groups; #$P = 0.581$ for sugammadex 1.0 *vs.* 2.0 mg/kg.
N = number of patients; TOF = train-of-four.

Table 4. Primary and Secondary Outcome Variables

Treatment Group	Rapid Reversal ≤2.0-min average	Slower Reversal ≤5.0-min average	Reversal >5-min average	N
Sugammadex, 0.5 mg/kg	3*#	16#	0	19
Sugammadex, 1.0 mg/kg	19*#	1#	0	20
Sugammadex, 2.0 mg/kg	20*#	0#	0	20
Neostigmine, 0.05 mg/kg	0*	6	10	16

* $P = 0.022$ for rapid reversal; pooled data of sugammadex *vs*. neostigmine (relative risk, 24.08; 95% CI, 1.56–3.46); #$P < 0.0001$ for rapid *vs.* slower reversal with sugammadex (pooled data; odds ratio, 6.1; 95% CI, 2.75–13.5).
N = number of patients.

with 0.5 mg/kg of sugammadex, or by Suy *et al.*,[15] who measured 3.7 min to obtain a comparable effect.

It should be noted that our results apply only to rocuronium and may not be valid for vecuronium. To our knowledge, the reversal with sugammadex of a threshold TOFC-4 vecuronium-induced NMB has not been studied.

Neostigmine performed poorly compared with sugammadex, and needed twice as long as 0.5 mg/kg of sugammadex for the reversal of threshold TOFC-4 to TOF ratio of 1.0. Consequently, the secondary efficacy endpoint of the study was fulfilled only in 37.5% of the patients treated with neostigmine. In addition, four patients who received neostigmine did not recover completely after 15 min and had to be treated with sugammadex according to the study protocol. These patients were excluded from the final analysis. If the observations had gone on for some additional time, then the upper extreme recovery intervals for neostigmine would have been even longer. Terminating the observation of recovery at 15 min undoubtedly made neostigmine look better than it is.

Kirkegaard *et al.*[18] also observed that it was not possible to achieve complete recovery with neostigmine in all patients. Furthermore, it was demonstrated that continued administration of sevoflurane resulted a delay in attaining adequate antagonism of rocuronium-induced NMB by neostigmine.[19] Unlike in the case of neostigmine, prolongation of the effect of sugammadex by sevoflurane compared with propofol was not observed.[20]

To identify threshold TOFC-4 NMB, we applied quantitative NM monitoring. Although we had a visual control on the appearance of four twitches, we did not compare quantitatively objective monitoring with perception of TOF count and fade by tactile or visual means. Furthermore, the TOF-Watch-SX® did not calculate the TOF ratio when T1 was below 20% of the control. In this case, we considered the TOF ratio zero.[12] Zero values were not excluded from the calculation of average TOF ratios surrounding the threshold TOFC-4 level of block, because our criterion for antagonism was the spontaneous reappearance of four twitches and not a predetermined TOF ratio. However, this may have resulted in lower TOF ratios in our study (0.1) than reported by other investigators (0.14).[21]

To exclude recurrence of muscle paralysis, we continued objective NM monitoring for 10–50 min following the reversal of TOF ratios to 1.0. Recurrent block (TOF ratio <0.9) did not occur in our patients. This is consistent with the finding of Murphy *et al.*,[22] who demonstrated that patients who exhibited TOF ratios more than 0.8 when their tracheas were extubated had no residual blockade (TOF ratio of <0.85) in the postanesthesia care unit.

Nevertheless, RPONB remains a relevant and frequent phenomenon, its occurrence ranges between 4 and 50% in the postanesthesia care unit depending on the diagnostic criteria, the type of NMB agent, and the administration of a reversal agent.[1,2] RPONB may be associated with postoperative complications such as hypoxia, weakness, pulmonary aspiration of gastric content, and respiratory failure. The prevention of these complications by adequate antagonism may improve patients' safety and decrease mortality rate.[23] Our results confirm the findings of Kirkegaard *et al.*[18] that neostigmine cannot promptly and reliably reverse nondepolarizing NMB at a threshold TOFC-4. We have demonstrated that, unlike neostigmine, reduced doses of sugammadex are efficient in antagonism of rocuronium-induced threshold TOFC-4 NMB.

The acquisition price of sugammadex, however, may preclude its wide-spread adoption and administration, especially because low-dose sugammadex confers no economic advantage based on the current packaging of a single use vial of 200 mg. If we wish to significantly decrease the incidence of RPONB, then neostigmine is not the answer and sugammadex may be indicated.

The availability of lower total milligram vials (*e.g.*,100 and 25 mg) with a proportionally reduced price would be of benefit not only for the health care system, but also for the manufacturer by encouraging the more wide-spread use of sugammadex.

In conclusion, residual NM blockade of threshold TOFC-4 frequently occurs at the end of anesthesia and surgery. To prevent RPONB, it is necessary to reverse any residual paralysis before extubation of the trachea. We have demonstrated that, unlike neostigmine, 1.0 mg/kg of sugammadex rapidly reverses rocuronium-induced threshold TOFC-4 NMB, and 0.5 mg/kg of sugammadex reverses a similar block within 8.0 min.

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