

Sugammadex and Neostigmine Dose-finding Study for Reversal of Shallow Residual Neuromuscular Block

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ABSTRACT

Introduction: Sugammadex effectively and rapidly reverses deep to moderate rocuronium-induced neuromuscular block. However, the required dose of sugammadex for smaller degrees of residual block is unknown. Therefore we investigated the efficacy of sugammadex and neostigmine at a train-of-four (TOF) ratio of 0.5.

Methods: After ethics committee (Munich, Germany) approval and written informed consent were obtained, 99 patients were anesthetized with propofol, remifentanyl, and rocuronium. Neuromuscular monitoring was performed by calibrated electromyography. At recovery of the TOF ratio to 0.5, patients randomly received sugammadex (0.0625, 0.125, 0.25, 0.5, or 1.0 mg/kg), neostigmine (5, 8, 15, 25, or 40 $\mu\text{g}/\text{kg}$), or saline. The time between study drug injection, at TOF ratio of 0.5, and postoperative TOF ratio of 0.9 was measured. The dose-response relationship was analyzed with a biexponential model using the dose as the independent variable and the logarithm of the recovery time as the dependent variable. Effective doses were interpolated from regression models.

Results: Sugammadex, 0.22 mg/kg, is able to reverse a TOF ratio of 0.5 to 0.9 or higher in an average time of 2 min. Within 5 min, 95% of patients reach this TOF ratio. Neostigmine, 34 $\mu\text{g}/\text{kg}$, is able to reverse a TOF ratio of 0.5

to 0.9 or higher within 5 min. No recurarization was observed.

Conclusions: Sugammadex, 0.22 mg/kg, and neostigmine, 34 $\mu\text{g}/\text{kg}$, effectively and comparably reverse a rocuronium-induced shallow residual neuromuscular block at a TOF ratio of 0.5.

What We Already Know about This Topic

- ❖ Although sugammadex reverses profound neuromuscular block, the dose required to reverse moderate degrees of residual neuromuscular block has not been described.

What This Article Tells Us That Is New

- ❖ The dose of sugammadex required to reverse a train-of-four ratio of 0.5 residual neuromuscular block was 0.22 mg/kg, with similar characteristics to neostigmine, 34 $\mu\text{g}/\text{kg}$.

ACETYLCHOLINESTERASE inhibitors, such as neostigmine and pyridostigmine, are commonly administered to avoid postoperative residual curarization and its potential complications.^{1–3} Since 2008, sugammadex, a specific encapsulator of steroidal muscle relaxants, is available in some countries. Previous dose-finding studies were restricted to reversal of profound (no responses to either train-of-four [TOF] or posttetanic count stimulation),^{4,5} deep (posttetanic count of 1 or 2),⁶ or moderate (reappearance of the second twitch response) rocuronium neuromuscular block.⁷ In the clinical setting, however, shallow residual neuromuscular paralysis (*i.e.*, at TOF ratios between 0.4 and 0.7) is quite common.^{1,8–10} Because a specific dose recommendation is lacking, the respective dose of 2 mg/kg as a substitute for reversal of any level of neuromuscular block beyond reappearance of T_2 is suggested. Rocuronium encapsulation by sugammadex, however, is a one-to-one molecular interaction. It, therefore, would seem feasible that shallow residual neuromuscular blocks would require less sugammadex.

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The primary aim of the study was to determine the dose of neostigmine and sugammadex, which reverses a shallow residual neuromuscular block from a TOF ratio of 0.5 to a ratio of 0.9 or higher in an average of 2 min, with an upper time limit of 5 min for 95% of patients. A secondary (and perhaps more clinically relevant) endpoint of the study was the dose for a slower reversal (*i.e.*, an average time of 5 min with an upper time limit of 10 min for 95% of patients).

Materials and Methods

Study Design and Patient Selection

This single center, randomized, parallel-group, double-blinded study was approved by the ethics committee of the medical faculty of the Technische Universität München and the Federal Institute for Drugs and Medical Devices of Germany (Bundesanstalt für Arzneimittel und Medizinprodukte). The study is listed under the acronym SUNDRO (NCT00895609, EudraCT 2008-008239-27).

Patients were included after informed written consent was obtained. Inclusion criteria were: aged 18–65 yr, American Society of Anesthesiology physical status I to III, and scheduled for elective surgery under general anesthesia with rocuronium for tracheal intubation. Patients were excluded if they were expected to have a difficult airway, known neuromuscular disease, significant hepatic or renal dysfunction, family history of malignant hyperthermia, known allergy to one of the drugs used in this protocol, intake of any medication that might interact with muscle relaxants, pregnant, or breastfeeding. In addition, patients were not included if they had participated in another clinical study in the past 30 days.

Ninety-nine patients were randomly assigned to receive either sugammadex (0.0625, 0.125, 0.25, 0.5, or 1.0 mg/kg) or neostigmine (5, 8, 15, 25, or 40 $\mu\text{g}/\text{kg}$) in a mixture with 1 μg glycopyrrolate/5 μg neostigmine or saline. There were nine patients per study group by dose. The numbers 1–99 were allocated to one of the 11 groups by a computer-generated randomization list before the start of the study. Every patient included in the study received a consecutive number. In the operating room, an additional anesthesiologist prepared the study drug according to the patient number on the randomization list in an unlabeled syringe. Upon request of the blinded anesthesiologist responsible for the patient, the study drug was injected.

Procedure

An intravenous cannula was inserted into a forearm vein and standard anesthesia monitoring (noninvasive blood pressure, electrocardiogram, and oxygen saturation) established on arrival in the operating room. Anesthesia was induced with propofol (2–3 mg/kg) and fentanyl (0.1–0.2 $\mu\text{g}/\text{kg}$) and maintained with propofol and remifentanyl according to clinical need and anesthesiologist preference. Patients received a laryngeal mask and were artificially ventilated to keep arterial oxygen saturation at 96% or higher and to maintain normocapnia. Body temperature was maintained at 35.0°C or higher.

Neuromuscular monitoring was carried out according to international consensus guidelines,¹¹ using evoked electromyography of the adductor pollicis muscle using the neuromuscular transmission module in a S/5 GE Datex Light monitor (GE Datex Medical Instrumentation, Inc., Tewksbury, MA). Using electromyography avoids a common problem seen with acceleromyography (*i.e.*, TOF ratios above 1.0). In brief, the forearm was immobilized and surface skin electrodes were placed over the ulnar nerve proximal to the wrist. Before calibration, tetanic stimulation of the ulnar nerve was performed. Then, stimulation was switched to TOF mode (70-mA current; 0.2-ms pulse duration, 2 Hz frequency) every 12 s. After at least 3 min of stable twitch responses, calibration of the system was performed automatically to find individual supramaximal stimulation. After this calibration, the ulnar nerve was stimulated with supramaximal TOF stimulation at 15-s intervals and the evoked electromyogram of the adductor pollicis muscle was recorded. However, recalibration was performed if stimulation was not stable for at least 3 min postcalibration. Neuromuscular transmission and its suppression were described by parameters related to the TOF stimulation patterns (*i.e.*, the response to the four stimulations [T_1 – T_4] related to baseline values and the ratio of the fourth to first twitch response of a TOF complex [TOF ratio]). Skin temperature was measured at the site of the neuromuscular measurements and maintained at 32.0°C or higher using heating blankets.

After 3 min of stabilization of the electromyography recording, 0.6 mg/kg rocuronium was injected. The trachea was intubated when T_1 was 0. During surgery, maintenance doses of 0.1–0.2 mg/kg rocuronium were injected according to clinical need.

When the surgical procedure did not require further neuromuscular block, spontaneous recovery from the neuromuscular block was allowed to a TOF ratio of 0.5. At this point, the study medication was injected according to the randomization. Neuromuscular monitoring was continued until the end of the surgical procedure, and at least 10 min after the TOF ratio reached 0.9 at least. At the end of surgery and emergence of anesthesia, the awake patient was extubated. Any decrease in the TOF ratio below 0.8 had to be recorded as reoccurrence of neuromuscular block. Heart rate and blood pressure were recorded before the injection of the study medication and then 2, 5, 10, and 20 min afterward.

Patients were kept in the recovery room for a minimum of 60 min. Oxygen saturation, respiration rate, heart rate, and blood pressure were routinely monitored. Any signs of reoccurrence of muscle weakness were recorded. Therefore at several time points (every 15 min and before discharge from the recovery room), the consciousness level (*i.e.*, awake and oriented, arousable with minimal stimulation, or responsive only to tactile stimulation) were assessed. Cooperative patients were asked to open their eyes for 5 s, perform a 5-s head lift test, a 5-s arm lift test and were asked to swallow 20-ml bolus of plain water. Then a test for general muscle weakness was performed using the Medical Research Council Scale¹²:

0 = no movement, 1 = flicker is perceptible in the muscle, 2 = movement only if gravity eliminated, 3 = can move limb against gravity, 4 = can move against gravity and some resistance exerted by examiner, 5 = normal power. The blinded safety assessor performed these postoperative clinical assessments. The study was finished for a patient after discharge from the recovery room to the regular ward.

The anesthesiologist of the patient and the safety assessor also monitored all patients for adverse events (AE). However, if there was doubt about AE classification or severity, the safety assessor decided AE coding. AEs were defined as drug related if the investigator considered them to be definitely, probably, or possibly related to the study drug.

Data Management and Statistical Analysis

Recovery from neuromuscular block induced by rocuronium was studied in the per-protocol population (*i.e.*, all treated patients without any major protocol violations). Safety data were studied in all patients who received a dose of the study drug.

The primary study endpoint was to estimate a dose of sugammadex or neostigmine to accelerate the time between start of administration of the respective study drug at a TOF ratio of 0.5 to a TOF ratio of at least 0.9 in an average of 2 min, with an upper limit of 5 min for 95% of patients. Secondary endpoints of the study were the doses of sugammadex and neostigmine for a slower acceleration of the reversal (*i.e.*, an average time of 5 min with an upper limit of 10 min for 95% of patients).

To explore the relationship between sugammadex *vs.* neostigmine dosing and recovery time (TOF ratio of 0.5 to a TOF ratio of at least 0.9), a biexponential model was used with the logarithm of the recovery time as dependent variable. We tested several other models including the monoexponential model as well as fractional polynomials. Statistical analysis was performed with SAS software, version 9.1 (SAS Institute Inc., Cary, NC).

Results

The study drug was injected in 99 patients. In five patients, major protocol violations occurred: in one patient, neostigmine was incompletely injected as a result of a leaking venous cannula; four patients, electromyographic response was unstable (one each in 5, 8, and 40 $\mu\text{g}/\text{kg}$ neostigmine groups; two patients in 0.125 mg/kg sugammadex group). Because these violations might have affected primary and secondary endpoints, respective patient data were omitted, resulting in a per-protocol population of 94 patients. Groups did not differ significantly regarding sex, age, weight, height, and American Society of Anesthesiology physical status (table 1).

The median time to recover to a TOF ratio of at least 0.9 after injection of the study drug decreased from 19 min (placebo) to 2 min with 40 $\mu\text{g}/\text{kg}$ neostigmine (table 2) and 1 min with 1.0 mg/kg sugammadex (table 3). No signs of recurarization in any patient were observed during TOF

Table 1. Intention-to-treat Group Baseline Characteristics (N = 99)

Demographic Variable	Mean \pm SD
Sex, No.	—
Men	53
Women	46
Age, yr	42 \pm 14
Height, cm	173 \pm 10
Weight, kg	76 \pm 16
American Society of Anesthesiologists physical status, No.	
I	48
II	44
III	7

Data are presented as mean \pm SD unless otherwise indicated.

monitoring or at the clinical testing of the patient in the recovery room. The mean \pm SD time between administration of the study drug and extubation was comparable between the pooled sugammadex group (57 \pm 54 min) and the pooled neostigmine group (63 \pm 42 min).

Based on the biexponential model, neostigmine dosing is calculated to be 50 $\mu\text{g}/\text{kg}$ for an average recovery time of 2 min (extrapolation); 34 $\mu\text{g}/\text{kg}$ for an upper limit of 5 min for 95% of patients (primary endpoint); 11 $\mu\text{g}/\text{kg}$ for an average recovery time of 5 min; and 10 $\mu\text{g}/\text{kg}$ for an upper limit of 10 min for 95% of patients (secondary endpoint). Sugammadex dosing is calculated to be 0.21 mg/kg for an average recovery time of 2 min; 0.22 mg/kg for an upper limit of 5 min for 95% of patients (primary endpoint); 0.08 mg/kg for an average recovery time of 5 min; and 0.1 mg/kg for an upper limit of 10 min for 95% of patients (secondary endpoint). The estimated dose-response relationship and the respective 95% CI for recovery from a TOF ratio 0.5 to at least 0.9 for the per-protocol population are shown in figure 1 (sugammadex) and figure 2 (neostigmine).

Clinical muscle function tests and evaluation of consciousness revealed no difference between groups at any time during the postoperative period in the recovery room. At arrival, 13% of the 79 cooperative patients were not able to keep their eyes open for 5 s; 6% were not able to lift the head for 5 s; 4% were not able to lift the arm for 5 s; 13% were not able to swallow 20 ml of water without difficulties; and 46% had not reached normal muscle strength (Medical Research Council scale). After 60 min in the recovery room, all patients were cooperative and did not show any clinical sign of muscle weakness.

After administration of study medication, one or more AEs were reported in 48 patients (table 4). The majority of AEs were classified as mild or moderate. The three most frequently observed AEs were postoperative shivering, bradycardia, and hypotension. Postoperative shivering was treated with 25–50 mg meperidine; bradycardia, 0.2 mg glycopyrrolate; hypotension, 0.5–2.0 ml Akrinor™ (AWD Pharma GmbH & Co. KG, Radebeul, Germany; vasopressor consisting of theophylline,

Table 2. Placebo versus Neostigmine by Dose, Time, and Train-of-four (TOF) Ratio

TOF Reversal	Placebo — (n = 9)	Neostigmine Groups by Dose (N = 51)				
		5 $\mu\text{g}/\text{kg}$ (n = 8)	8 $\mu\text{g}/\text{kg}$ (n = 8)	15 $\mu\text{g}/\text{kg}$ (n = 9)	25 $\mu\text{g}/\text{kg}$ (n = 9)	40 $\mu\text{g}/\text{kg}$ (n = 8)
≥ 0.7	—	—	—	—	—	—
Median [min]	5.9	2.7	1.9	1.5	1.3	1.1
Range (min–max) [min]	(3.5–9.8)	(1.8–3.5)	(1.5–2.3)	(1.2–2.5)	(1.0–2.3)	(0.7–1.5)
≥ 0.8	—	—	—	—	—	—
Median [min]	10	4.9	2.8	2.3	1.8	1.4
Range (min–max) [min]	(7.2–16)	(3.3–6.0)	(2.5–3.3)	(1.7–3.7)	(1.2–3.2)	(1.2–2)
≥ 0.9	—	—	—	—	—	—
Median [min]	19	9.3	5.3	4.0	3.2	2.0
Range (min–max) [min]	(12–33)	(5.8–15)	(3.5–8.7)	(2.8–6.0)	(1.7–6.2)	(1.7–4.2)

A per-protocol population (*i.e.*, all treated patients without any major protocol violations) was used. Placebo values also presented in table 3.

ephedrine, caffeine, and norepinephrine). No dose-response relationship was observed.

One patient developed acute lung failure 63 h postoperatively. This AE was categorized as severe and possibly related to the study medication of 5 $\mu\text{g}/\text{kg}$ neostigmine. The patient was known to have a restrictive lung disorder (vital capacity of 1.9 l; *i.e.*, 35% of normal) after bleomycine chemotherapy. None of the patients discontinued the study because of a (serious) AE.

Discussion

Sugammadex as well as neostigmine is able to reverse a rocuronium-induced shallow residual neuromuscular block at a

TOF ratio of 0.5 in a dose-dependent manner. Best fit modeling of the dose-response relationship revealed that 0.22 mg/kg sugammadex and 34 $\mu\text{g}/\text{kg}$ neostigmine accelerates recovery from a TOF ratio of 0.5 to a TOF ratio of at least 0.9 in an average of 2 min but within 5 min for 95% of all treated patients. Incidence of AEs was significantly higher in neostigmine-treated patients. It is important to note, however, that no patients showed signs of recurarization after any tested dose of the two reversal agents.

Published dose-finding studies for sugammadex used a monoexponential approach with recovery times in linear scale.^{4–7,13} This approach assumes that only one process (*e.g.*, encapsulation of rocuronium) is responsible for recov-

Table 3. Placebo versus Sugammadex by Dose, Time, and Train-of-four (TOF) Ratio

TOF Reversal	Placebo — (n = 9)	Sugammadex Groups by Dose (N = 43)				
		0.06 mg/kg (n = 9)	0.12 mg/kg (n = 7)	0.25 mg/kg (n = 9)	0.5 mg/kg (n = 9)	1.0 mg/kg (n = 9)
≥ 0.7	—	—	—	—	—	—
Median [min]	5.9	1.3	1.0	1.0	0.7	0.8
Range (min–max) [min]	(3.5–9.8)	(0.8–2.8)	(0.7–1.7)	(0.7–1.7)	(0.7–1.0)	(0.7–1.0)
≥ 0.8	—	—	—	—	—	—
Median [min]	10	2.5	1.2	1.0	1.0	1.0
Range (min–max) [min]	(7.2–16)	(1.0–4.7)	(0.7–3.0)	(1.0–2.0)	(0.7–1.2)	(0.7–1.3)
≥ 0.9	—	—	—	—	—	—
Median [min]	19	7.8	2.3	1.7	1.3	1.0
Range (min–max) [min]	(12–33)	(2.0–13)	(1.0–11)	(1.0–4.0)	(0.8–2.0)	(0.7–1.5)

A per-protocol population (*i.e.*, all treated patients without any major protocol violations) was used. Placebo values also presented in table 2.

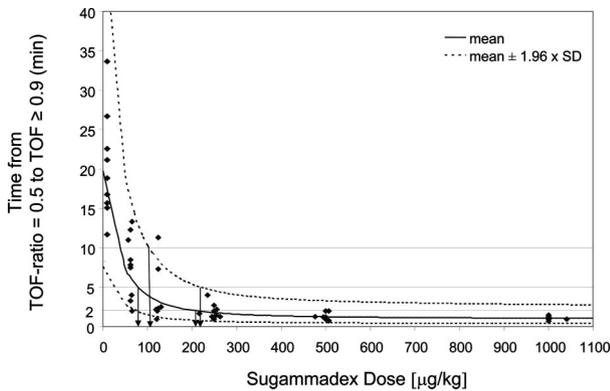


Fig. 1. Estimated mean dose-response relation for the time between administration of sugammadex, by dosing level, at a train-of-four (TOF) ratio of 0.5 to a recovery ratio of 0.9. The graph shows the results from the biexponential fitting calculated with the sugammadex dose in linear scale and time interval in logarithmic scale. The *arrows* indicate respective dosing levels necessary for recovery within mean time indicated for 95% of patients. Data are presented as mean (*solid line*) and mean $\pm 1.96 \times$ SD (*dashed line*).

ery kinetics and, in addition, that this process follows linear characteristics. Before ruling out alternative mathematical relations, this assumption cannot be transferred to the data of our study—especially for the much more complex-acting neostigmine reversal groups. Therefore, we analyzed a biexponential model with the time to recovery of the TOF ratio at 0.9 (Δt) in linear or in logarithmic scale as well as fractional polynomials consisting of one or more degrees.

Based on the best fitting model (biexponential), the dose to reverse a shallow residual rocuronium-induced neuromuscular block at a TOF ratio of 0.5 with sugammadex is 0.22 mg/kg. We recommend testing sugammadex, 0.25 mg/kg, in a comparative study with a larger cohort and an expected

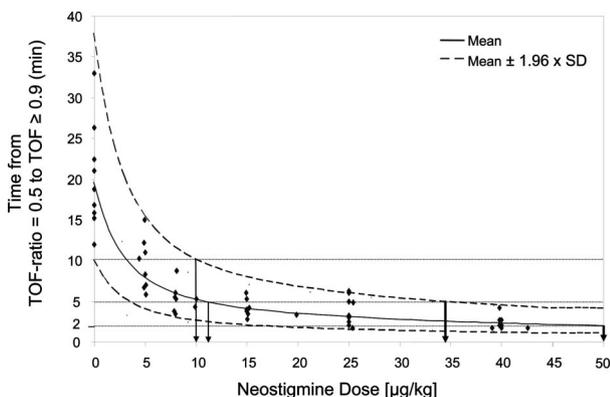


Fig. 2. Estimated mean dose-response relation for the time between administration of neostigmine, by dosing level, at a train-of-four (TOF) ratio of 0.5 to a recovery ratio of 0.9. The graph shows the results from the biexponential fitting calculated with the neostigmine dose in linear scale and time interval in logarithmic scale. The *arrows* indicate the respective dosing levels necessary for recovery within mean time indicated for 95% of patients. Data are presented as mean (*solid line*) and mean $\pm 1.96 \times$ SD (*dashed line*).

recovery time of 1.7 min with a 95% tolerance interval of 0.7–4.3 min.

In this study, we did not observe any clinical or monitoring-related sign of residual paralysis or recurarization. This observation is important as we tested doses between 0.0625–1.0 mg/kg sugammadex. Especially in the low dose sugammadex groups, one can assume that there were not enough sugammadex molecules present to encapsulate all rocuronium molecules expected in patients' bodies at a TOF ratio of 0.5. Accordingly, we must assume that, irrespective of complete TOF ratio recovery with doses below 1.0 mg/kg sugammadex, unbound rocuronium is still available.^{14,15}

In other words, fast recovery is not only caused by sugammadex encapsulation but by the margin of safety in neuromuscular transmission.¹⁶ Therefore, quantitative neuromuscular monitoring to control a sufficient reversal effect is mandatory, even when the suggested dose of 0.25 mg/kg sugammadex is used at a TOF ratio of 0.5.

Such rigorous claims regarding quality of reversal cannot be postulated for neostigmine, because this drug has neither the potential to withdraw muscle relaxants from neuromuscular cleft because of its indirect and therefore limited antagonism¹⁷ nor an onset of action that allows us to expect an average recovery time below 3 min.¹⁸ In accordance, only one model was able to define a dosing level able to reverse neuromuscular function within an average of 2 min. Accordingly, it seems more relevant to base the primary endpoint on a recovery to a TOF ratio of at least 0.9 for the 95% population within 5 min. Although a dosing recommendation influenced by this decision still meets clinical needs, it marks another difference between the two arms of the study.

Based on the biexponential model and knowledge about the onset time of neostigmine, the dose required to reverse a shallow residual rocuronium-induced neuromuscular block at a TOF ratio of 0.5 is 34 μ g/kg. Therefore, we recommend testing 40 μ g/kg neostigmine in a comparative study with a larger cohort and an expected recovery time of 2.4 min with a 95% tolerance interval of 1.2–4.6 min. However, when applying this dose, one has to take into account that neostigmine reversal depends on the anesthetic technique used; recovery times are significantly faster under total intravenous anesthesia compared with volatile anesthesia.^{19,20}

The primary endpoint of this study (2 min median; 5 min in 95% of patients) was introduced during the dose-finding studies for sugammadex.^{4–7} To allow for comparison between the studies, we chose the same endpoint. Although the endpoint seems arbitrary, it is ideal to depict the rapid-reversal properties of sugammadex. We defined a slower acceleration of neuromuscular recovery for the secondary endpoint. Although also arbitrary, it corresponds to that recently published in a study on neostigmine reversal by Fuchs-Buder.²¹ Because 95% of placebo-treated patients recovered within 25 min, there is still an advantage of 15 min if reversal agents shorten the recovery time to 10 min. Based on the same criteria applied for the primary endpoint, dose recommendations are 10 μ g/kg neostigmine and 0.1 mg/kg sugamma-

Table 4. Adverse Events Comparison among Study Groups (N of adverse events = 103)

Adverse Event	Neostigmine (n = 51)	Placebo (n = 9)	Sugammadex (n = 43)
Hypertension	1 (2)	0	1 (2)
Bradycardia	12 (27)*	0	1 (2)
Hypoglycemia	0	1 (11)	0
Hypokalemia	1 (2)	1 (11)	0
Hypocalcemia	1 (2)	1 (11)	1 (2)
Hypotension	3 (7)	4 (44)	5 (11)
Desaturation < 90%	3 (7)	0	0
Paresthesia <i>nervus ulnaris</i>	0	1 (11)	0
Postoperative nausea and vomiting	0	2 (22)	2 (5)
Postoperative shivering	11 (25)	0	8 (18)
Tachycardia	2 (5)	0	1 (2)
Anesthetic complications (intraoperative cough/movement)	1 (2)	0	1 (2)
Acute lung failure (serious AE)	1 (2)	0	0
At least 1 AE	28 (64)*	4 (44)	16 (36)

All data are presented as No. (%).

* $P < 0.05$, compared to pooled sugammadex group.

AE = adverse event.

dex for a recovery from a TOF ratio of 0.5 to a ratio of at least 0.9 in an average of 5 min, with an upper confidence limit of 10 min. The recommended neostigmine dose is in accord with the recent findings of Fuchs-Buder *et al.*²¹ who suggested 10–20 $\mu\text{g}/\text{kg}$ as sufficient for reversal of shallow atracurium-induced neuromuscular block, which was defined at a TOF ratio of 0.4 or 0.6.

This study was neither designed nor powered to address any AE comparison. Because of safety issues, AEs were documented and are presented descriptively. The number of patients showing at least one AE after study drug administration was significantly lower in the pooled sugammadex group. With the exception of the higher incidence of bradycardia (heart rate lower than 40 beats/min) after neostigmine, there was no systematic observation. The latter, however, is a well-known cholinergic AE, which appeared even though neostigmine was administered as a pre-mix with glycopyrrolate (ratio 1:5). Bradycardia could be controlled in every patient with an additional dose of 0.2 mg glycopyrrolate.

This study depicts a fourth degree of incomplete recovery from a rocuronium-induced neuromuscular block: profound neuromuscular block (*i.e.*, immediately after injection of rocuronium),^{5,13} deep block defined as posttetanic count of 1–2,⁶ moderate block defined as reappearance of the second twitch after TOF stimulation,⁷ and now in this study, shallow residual block at a TOF ratio of 0.5. Different degrees of neuromuscular block require decreasing doses of sugammadex to achieve the same result (*i.e.*, a TOF ratio of 0.9 or higher within approximately 2 min). The relationship between depth of block and sugammadex dose, in conjunction with the fast onset of its reversal effect, suggest that sugammadex titration based on quantitative neuromuscular monitoring might be possible. Additional dose finding studies (*e.g.*, at a TOF ratio of 0.2) may help to start with the appropriate dose at a block between reappearance of T_2 and a TOF

ratio of 0.5. As we were able to identify an effective neostigmine dose at a TOF ratio of 0.5, below the maximum recommended 70 $\mu\text{g}/\text{kg}$, it also appears reasonable to test neostigmine at lower TOF values to determine the value at which the ceiling effect of neostigmine becomes relevant.

This study was performed with a scientific goal. Nevertheless, any study must be judged alongside its potential to affect clinical practice, which depends on an acceptable cost-effectiveness balance. Neostigmine is available in 0.5-mg vials for less than 0.5 € and as a pre-mix-vial with 2.5 mg neostigmine/0.5 mg glycopyrrolate for 1.5–4.5 €, depending on the respective distributor and country. The smallest vial of sugammadex is currently available for 78 € and is not recommended for multiple use. Based on efficacy to reverse a TOF ratio of 0.5 in a 70-kg patient, the costs are still 78 € with sugammadex (even though only 16 mg were used) but roughly 3 € with neostigmine. A reduction in price, but even more important in vial size, would have the potential to allow anesthesiologists to treat their patients' shallow residual neuromuscular block with sugammadex economically.

In conclusion, sugammadex, 0.22 mg/kg, and neostigmine, 34 $\mu\text{g}/\text{kg}$, effectively reverse a rocuronium-induced shallow residual neuromuscular block at a TOF ratio of 0.5 to a ratio of 0.9 or higher within 5 min in 95% of patients in a comparable manner. Higher doses of sugammadex increase the reliability of the reversal acceleration and allow reversal of deeper blocks, a result that could not be demonstrated for neostigmine.

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