BJA

British Journal of Anaesthesia, 116 (2): 233–40 (2016)

doi: 10.1093/bja/aev437
Clinical Practice

CLINICAL PRACTICE

Sugammadex and neostigmine dose-finding study for reversal of residual neuromuscular block at a train-of-four ratio of 0.2 (SUNDRO20)†,#

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Abstract

Background: The aim of this dose-finding study was to evaluate the dose–response relationship of sugammadex and neostigmine to reverse a commonly observed level of incomplete recovery from rocuronium-induced neuromuscular block, that is, a train-of-four ratio (TOFR) ≥0.2.
Methods: Ninety-nine anaesthetized patients received rocuronium 0.6 mg kg^{-1} i.v. for tracheal intubation and, if necessary, incremental doses of 0.1–0.2 mg kg^{-1}. Neuromuscular monitoring was performed by calibrated electromyography. Once the TOFR recovered to 0.2, patients were randomized to receive sugammadex (0.25, 0.5, 0.75, 1.0, or 1.25 mg kg^{-1} i.v.), neostigmine (10, 25, 40, 55, or 70 μg kg^{-1} i.v.), or saline (n=9 per group). Primary and secondary end points were the doses necessary to restore neuromuscular function to a TOFR≥0.9 with an upper limit of 5 and 10 min for 95% of patients, respectively.
Results: Neostigmine was not able to fulfil the end points. Based on the best-fitting model, the sugammadex dose estimation for recovery to a TOFR≥0.9 for 95% of patients within 5 and 10 min was 0.49 and 0.26 mg kg^{-1}, respectively.
Conclusions: A residual neuromuscular block of a TOFR of 0.2 cannot be reversed reliably with neostigmine within 10 min. In the conditions studied, substantially lower doses of sugammadex than the approved dose of 2.0 mg kg^{-1} may be sufficient to reverse residual rocuronium-induced neuromuscular block at a recovery of TOFR≥0.2.
Clinical trial registration: NCT01006720.

Key words: neostigmine; neuromuscular block; quantitative neuromuscular monitoring; reversal neuromuscular block; rocuronium; sugammadex

Sugammadex rapidly restores neuromuscular transmission by encapsulating rocuronium. As a result of the one-to-one molecular binding of sugammadex and rocuronium, the dose of sugammadex necessary is dependent on the rocuronium concentration, which can be estimated clinically by neuromuscular monitoring.[1] Accordingly, dose recommendations for sugammadex are based on values obtained by neuromuscular monitoring, as follows: reversal of profound rocuronium-induced neuromuscular

† This report was previously presented, in part, at the Annual Meeting of the International Society for Anaesthetic Pharmacology, San Diego, CA, USA, on October 15, 2010.
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# This Article is accompanied by Editorial Aev448.
Accepted: November 20, 2015

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Editor's key points

- The dose is not known of sugammadex or neostigmine which reverses a commonly observed level of incomplete recovery from rocuronium-induced neuromuscular block: a train-of-four ratio (TOFR) ≥ 0.2.
- In 98 anaesthetized patients, either sugammadex (0.25-1.25 mg kg^{-1}), neostigmine (10–70-1.25 mg kg^{-1}) or saline was given to find the dose required to restore neuromuscular function to a TOFR ≥ 0.9.
- Neostigmine could not reliably reverse the effect, whereas substantially lower doses of sugammadex than the approved dose of 2.0 mg kg^{-1} would be required to reverse residual rocuronium-induced neuromuscular block.

block (i.e. no twitch response after tetanic stimulation), sugammadex 16 mg kg^{-1};[2] reversal of deep neuromuscular block (post-tetanic count >1), sugammadex 4 mg kg^{-1};[3] and reversal of moderate neuromuscular block [reappearance of the second twitch response (T2) after train-of-four (TOF) stimulation], sugammadex 2 mg kg^{-1}.[4] These doses have been proved to restore neuromuscular function in 95% of patients within 5 min.

Dose-finding studies for reversal of residual neuromuscular blocks beyond reappearance of T2 suggest the same efficacy when sugammadex 1 mg kg^{-1} is given at reappearance of the fourth twitch response (T4)[5] and sugammadex 0.22 mg kg^{-1} at a train-of-four ratio (TOFR)≥0.5.[6] However, residual neuromuscular blocks between reappearance of T4 and TOFR=0.5 are more frequent in clinical practice compared with profound or deep blocks and have not been investigated for sugammadex previously. Furthermore, the measure of depth of neuromuscular block at reappearance of T4 is unreliable, because it depends notably on the sensitivity of the measuring technique and varies to some degree.[7–9]

Effective and commonly used alternatives for reversal of weak residual neuromuscular block are cholinesterase inhibitors.[6] Yet, even the complete inhibition of acetylcholine esterase with high neostigmine doses (50–70 μg kg^{-1}) is not able to restore neuromuscular transmission effectively at reappearance of T2 and at reappearance of T4, most probably because of a ceiling effect.[4 5 10 11] The efficacy of neostigmine at a residual neuromuscular block at a TOFR≥0.2 is unknown so far.

The quality of dose finding depends substantially on the selected mathematical model. The optimal model, however, is unknown *a priori*. All sugammadex dose-finding studies have used a mono-exponential model with the recovery time on a linear scale,[12–17] without providing the reasoning behind this choice of calculation. In our previous study, however, a bi-exponential model with the time on a logarithmic scale resulted in a better fit.[6] Accordingly, we tested mono- and bi-exponential models and fractional polynomial models.[18] Given that the recovery times of all published sugammadex dose-finding studies have shown a positively skewed distribution,[6 12–17] we also plotted the recovery times on a logarithmic scale.

The aims of the present study were to find doses for neostigmine and sugammadex to reverse a residual rocuronium-induced neuromuscular block from a TOFR≥0.2 to a TOFR≥0.9. The primary study end points were the doses necessary to achieve this effect in 50% of the patients within 2 min or in 95% of the patients within 5 min. Secondary end points were the doses for a less advanced acceleration (i.e. in 50% of the patients within 5 min or in 95% of the patients within 10 min).

Methods

Study design and patient selection

This single-centre, randomized, parallel-group, double-blinded study was approved by the ethics committee of the 'Fakultät für Medizin der Technischen Universität München' (reference 2535/09) and the German Federal Institute for Drugs and Medical Devices ('Bundesanstalt für Arzneimittel und Medizinprodukte', EudraCT number 2009-013499-29) before enrolment of patients. The study is listed under the acronym SUNDRO20 (NCT01006720, registered June 12, 2009, Principal Investigator: M. Blobner).

Patients were included after providing written informed consent. Inclusion criteria were as follows: age >18 yr; ASA physical status I–III; and undergoing elective surgery under general anaesthesia with rocuronium for tracheal intubation. Patients were excluded if they were expected to have a difficult airway or had known neuromuscular disease, significant hepatic or renal dysfunction, a family history of malignant hyperthermia, known allergy to one of the drugs used in this protocol, or intake of any medication that might interact with muscle relaxants, or if they were pregnant women or women who were breast feeding. In addition, patients were excluded if they had participated in another clinical study in the past 30 days.

Ninety-nine patients were randomly assigned to receive either sugammadex at doses of 0.25, 0.5, 0.75, 1.0, and 1.25 mg kg^{-1}, neostigmine at doses of 10, 25, 40, 55, and 70 μg kg^{-1} in a mixture with 1 μg glycopyrrolate per 5 μg neostigmine, or saline (n=9 per dose group). The tested dose intervals were decided with the intention to enable interpolation of the requested doses. Accordingly, the lower limit for both drugs was chosen according to respective doses recommended at TOFR≥0.5.[6] Based on a review of studies with doses of sugammadex 1.0 mg kg^{-1} at T2[14 15 19] and calculations with pharmacological models,[20] we assumed this dose to be sufficient. To be certain, we increased by 25%, resulting in a maximal tested dose of sugammadex 1.25 mg kg^{-1}. The highest tested neostigmine dose was the maximal approved dose. The numbers one to 99 were allocated to one of the 11 groups by a computer-generated randomization list before the start of the study. Every included patient received a consecutive number. In the operating room, the unblinded study staff attending anaesthetist (H.F.), who was the only person with access to the randomization list, prepared the study drug corresponding to the randomization number in an unlabelled syringe. Upon request of the blinded anaesthetist responsible for the patient (without access to the randomization list and study medication), the unlabelled study drug was injected.

Procedure

An i.v. cannula was inserted into a forearm vein, and standard anaesthesia monitoring (non-invasive blood pressure, ECG, and oxygen saturation) was established on arrival in the operating room. Anaesthesia was induced with propofol 2–3 mg kg^{-1} i.v. and fentanyl 0.1–0.2 μg kg^{-1} i.v. and maintained with propofol and remifentanil according to clinical need and preference of the anaesthetist. Patients were initially ventilated via laryngeal mask to maintain normocapnia and keep arterial oxygen saturation ≥96%. Body temperature was maintained at ≥35.0°C.

Neuromuscular monitoring was performed according to international consensus guidelines[21] using evoked EMG of the adductor pollicis muscle using the NMT module in a S/5 GE Datex Light monitor (GE Datex Medical Instrumentation, Inc., Tewksbury, MA, USA). The raw data were saved online with Datex-Ohmeda S/5 collect 4.0 for Windows® XP on a laptop and

imported into Microsoft Excel™ (Redmond, WA, USA) for further calculations.

In brief, the forearm was immobilized, the skin was degreased, surface skin electrodes were placed over the ulnar nerve proximal to the wrist, and the respective EMG of the adductor pollicis muscle was recorded. Neuromuscular transmission and its suppression were described by parameters related to the TOF stimulation patterns [i.e. the response to the four stimulations (T1, T2, T3, and T4) as a percentage of the baseline values] and the TOFR (i.e. the ratio of the fourth twitch response, T4, to the first, T1, of a TOF complex). Skin temperature was measured at the site of the neuromuscular measurements and maintained at ≥32.0°C using heating blankets.

Before calibration, tetanic stimulation of the ulnar nerve was performed. Then, stimulation was switched to the TOF stimulation pattern (0.2 ms pulse duration, 2 Hz frequency) every 15 s. After 3 min of stable twitch response, self-calibration of the EMG monitoring was initiated to find the individual supramaximal nerve stimulation. After calibration and an additional 3 min of stable twitch response (T1/T0≥95%), rocuronium 0.6 mg kg^{-1} was injected. At maximal twitch depression, the trachea was intubated. During surgery, maintenance doses of rocuronium 0.1–0.2 mg kg^{-1} 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 TOFR of 0.2. At this point, the study medication was injected according to randomization. After a stable TOFR≥0.9 was reached, neuromuscular monitoring was continued for at least 30 min. At the end of surgery and emergence of anaesthesia, the trachea was extubated after the patient had regained consciousness. Any decrease in the TOFR below 0.8 had to be registered as reoccurrence of neuromuscular block. Heart rate and blood pressure were recorded before and 2, 5, 10, and 20 min after the injection of the study medication.

Patients were kept in the postanaesthesia care unit (PACU) for a minimum of 60 min. Oxygen saturation, respiration rate, heart rate, and blood pressure were routinely monitored. At several time points (every 15 min and before discharge from the PACU), we tested the patients clinically for neuromuscular weakness as described previously.[6] In brief, every 15 min and before discharge from the recovery room the blinded safety assessor asked the patient to open their eyes for 5 s, perform a 5 s head-lift test and a 5 s arm lift-test and asked them to swallow a bolus of 20 ml water. Then a test for general muscle weakness was performed using the Medical Research Council Scale,[22] as follows: 0, no movement; 1, flicker is perceptible in the muscle; 2, movement only if gravity is eliminated; 3, can move limb against gravity; 4, can move against gravity and some resistance exerted by examiner; and 5, normal power. A patient's participation in the study finished after discharge from the PACU to a regular ward.

Data management and statistical analysis

Recovery from rocuronium-induced neuromuscular block was studied in the per-protocol population (i.e. all treated patients without any major protocol violations). Safety data (e.g. heart rate, blood pressure, and clinical muscle function tests) were studied in all patients who received a dose of the study drug.

The aim of the study was to estimate a dose of sugammadex and neostigmine, respectively, that accelerates the time between study drug administration at a TOFR≥0.2 to a TOFR≥0.9. Primary study end points were the doses necessary to achieve this effect in 50% of the patients within 2 min or in 95% of the patients within 5 min. Secondary end points were the doses for a less advanced acceleration (i.e. in 50% of the patients within 5 min or in 95% of the patients within 10 min).

A recent guideline on how to analyse these types of dose–response relationships suggests the use of either a biological model if available or flexible models, such as fractional polynomials (FPs).[23] As biological models, we applied mono- and bi-exponential models corresponding to a one- or two-compartment system with the parameters (a_1, . . ., a_5).[12 13 15 17] The FPs developed by Royston and Altman[18] consisted of one (FP1) or two degrees (FP2) with the exponents (p, p_1, p_2) taken from a predefined set of values and parameters (a_1, a_2, a_3) . In all models, the dependent factor was the recovery time to a TOFR≥0.9 (Δt) on a linear and on a logarithmic scale.

$$\Delta t(\text{dose}) = a_1 + a_2 \cdot e^{-a_3 \cdot \text{dose}} \tag{1}$$

$$\ln \Delta t(\text{dose}) = a_1 + a_2 \cdot e^{-a_3 \cdot \text{dose}} \tag{2}$$

$$\Delta t(\text{dose}) = a_1 + a_2 \cdot e^{-a_3 \cdot \text{dose}} + a_4 \cdot e^{-a_5 \cdot \text{dose}} \tag{3}$$

$$\ln\ \Delta t(\text{dose}) = a_1 + a_2 \cdot e^{-a_3 \cdot \text{dose}} + a_4 \cdot e^{-a_5 \cdot \text{dose}} \tag{4}$$

$$\text{FP1} : \Delta t(\text{dose}) = a_1 + a_2 \cdot \text{dose}^p \tag{5}$$

$$\text{FP1} : ln\ \Delta t(\text{dose}) = a_1 + a_2 \cdot \text{dose}^p \tag{6}$$

$$\text{FP2} : \Delta t(\text{dose}) = \begin{cases} a_1 + a_2 \cdot \text{dose}^{p_1} + a_3 \cdot \text{dose}^{p_2} \\ a_1 + a_2 \cdot \text{dose}^{p_1} + a_3 \cdot \text{dose}^{p_2} \cdot \ln(\text{dose}) \end{cases} \tag{7}$$

$$\text{FP2} :\ \ln \Delta t(\text{dose}) = \begin{cases} a_1 + a_2 \cdot \text{dose}^{p_1} + a_3 \cdot \text{dose}^{p_2} \\ a_1 + a_2 \cdot \text{dose}^{p_1} + a_3 \cdot \text{dose}^{p_2} \cdot \ln(\text{dose}) \end{cases} \tag{8}$$

For comparison of the different models, we used r^2 and Akaike information criterion (AIC). The r^2 is independent of the residual sum of squares (RSS) of the dependent variable and therefore allows comparison of models using different dependent variables [i.e. Δt(dose) on a linear or logarithmic scale and Δt(dose) after neostigmine or sugammadex]. In order to adjust for the different number of parameters in the models, we compared the adjusted r^2 (r^2_{adj}), as follows:

$$r^2_{\text{adj}} = 1 - (1 - r^2) \cdot \frac{n-1}{n-k-1} \tag{9}$$

with r^2 the value for the fit of the model, k the number of parameters in the model excluding the intercept, and n the number of patients included in the analysis.

The AIC was used to decide on the best-fitting model with the lowest complexity within a given set of data, as follows:

$$\text{AIC} = n \cdot \ln\left(2\pi \cdot \frac{\text{RSS}}{n}\right) + n + 2 \cdot (k+1) \tag{10}$$

The model with the lowest AIC is considered to be the best one. Given that the AIC depends on the RSS, it can only be used to compare models with identical dependent variables.[24] Accordingly, models using Δt(dose) on a logarithmic and linear scale cannot be compared by AIC.

Sample size calculations for a reliable regression model suggest at least 10 samples per parameter.[25] We included 6×9=54 patients (samples) for each analysis (sugammadex and neostigmine), allowing up to five parameters in the model (p_i and a_i).

Statistical analysis was performed with SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 99 patients were initially enrolled after 109 had been screened (for details, see Supplementary material Fig. S1). One patient, who had received neostigmine 70 μg kg^{-1}, withdrew his written informed consent after surgery. Therefore, 98 patients were included in statistical analysis. No protocol violations occurred. Groups did not differ regarding age, weight, height, sex, and ASA physical status (Table 1).

The median time to restore neuromuscular transmission to a TOFR≥0.9 after injection of the study drug decreased from 33 min with saline to 3.3 min with neostigmine 70 μg kg^{-1} (Table 2) and to 1.5 min with sugammadex 1.25 mg kg^{-1} (Table 3). The 95% tolerance intervals and the ranges of the recovery times became smaller with higher doses.

Modelling of the dose–response relationship revealed a better correlation (higher r^2_{adj}) if it was calculated with the time between injection of the reversal agents and recovery to a TOFR≥0.9 on a logarithmic scale compared with a linear scale and if sugammadex was used for reversal (Table 4). The AIC values, however, were minimal for the mono-exponential models compared with bi-exponential models and both fractional polynomials, indicating that the higher complexity of these models was not attended by better information (Table 4).

No model could estimate a neostigmine dose fulfilling the conditions of the primary end point (i.e. TOFR≥0.9 in an average time of 2 min and in 95% of patients within 5 min). The second end point was partly met by neostigmine 37–52 μg kg^{-1} in terms of the average dose for reversal within 5 min. However, the dose allowing reversal within 10 min for 95% of patients was estimated as >70 μg kg^{-1} in seven of eight models; in particular, the best-fitting mono-exponential model did not allow estimation of a dose (Table 4 and Fig. 1C and D).

The mono-exponential model with the response variable on a logarithmic scale offered the best fit to the sugammadex data with the lowest complexity (Table 4 and Fig. 1B). Based on this model, the dose of sugammadex was estimated to be 0.66 mg kg^{-1} for an average recovery time of 2 min, whereas 0.49 mg kg^{-1} was the dose for an upper limit of 5 min for 95% of patients (primary end point). For an average recovery time of 5 min and an upper limit of 10 min for 95% of patients, the estimated dose was 0.26 mg kg^{-1} (secondary end point).

Reoccurrence of residual neuromuscular block did not appear in any of the patients during the EMG monitoring or during the clinical testing of the patient in the PACU. Clinical muscle function tests and assessment of the level of consciousness did not reveal any difference between groups at any time during the postoperative period in the PACU. None of the patients in this clinical trial experienced any serious adverse events.

Table 1 Baseline characteristics (intention-to-treat group, *n*=99)

Characteristic	Placebo	Sugammadex	Neostigmine
Age (yr; range)	19–75	22–81	19–80
Weight [kg; mean (SD)]	80 (18)	72 (15)	78 (16)
Height [cm; mean (SD)]	173 (7)	172 (9)	173 (11)
Male/female (*n*/*n*)	7/2	19/26	24/21
ASA physical status (*n*)			
I	4	23	20
II	3	19	22
III	2	3	3

Discussion

In the present study, the median time for spontaneous recovery from a TOFR=0.2 to ≥0.9 was 33 min. Dose-finding estimation

Table 2 Time from administration of various doses of neostigmine or placebo at train-of-four ratio (TOFR) of 0.2 to TOFR≥0.9. Per-protocol population. *Placebo values are also presented in Table 3. The times are given in minutes. The 95% tolerance indicates the time interval during which the recovery time of 95% of the patients can be expected after reversal with the respective dose of neostigmine. Owing to the positively skewed distribution, it is calculated with the logarithms of the recovery times but presented in a retransformed format

	Placebo*	Neostigmine dose group				
		10 μg kg^{-1}	25 μg kg^{-1}	40 μg kg^{-1}	55 μg kg^{-1}	70 μg kg^{-1}
	n=9	*n*=9	*n*=9	*n*=9	*n*=9	*n*=8
Median	33	15	6.0	4.5	4.2	3.3
95% Tolerance (minimum–maximum)	11–94 (11–68)	5.6–54 (9.5–56)	2.7–13 (3.0–11)	1.3–18 (2.0–21)	1.6–16 (2.0–8.7)	0.8–16 (1.7–19)

Table 3 Time from administration of various doses of sugammadex or placebo at train-of-four ratio (TOFR) of 0.2 to TOFR≥0.9. Per-protocol population. *Placebo values are also presented in Table 2. The times are given in minutes. The 95% tolerance indicates the time interval during which the recovery time of 95% of the patients can be expected after reversal with the respective dose of sugammadex. Owing to the positively skewed distribution, it is calculated with the logarithms of the recovery times but presented in a retransformed format

	Placebo*	Sugammadex dose group				
		0.25 mg kg^{-1}	0.50 mg kg^{-1}	0.75 mg kg^{-1}	1.00 mg kg^{-1}	1.25 mg kg^{-1}
	n=9	*n*=9	*n*=9	*n*=9	*n*=9	*n*=9
Median	33	5.2	2.5	1.7	1.8	1.5
95% Tolerance (minimum–maximum)	11–94 (11–68)	2.6–11 (3.0–8.5)	1.5–4.5 (2.0–5.0)	1.3–2.1 (1.5–2.0)	0.9–3.1 (1.0–2.3)	0.9–2.9 (1.0–2.5)

Table 4 Dose estimations for neostigmine and sugammadex using several mathematical models. Dose is not estimable (n.e.) because $\lim_{dose\to\infty}\Delta t_{50}(dose)$>2 min or $\lim_{dose\to\infty}\Delta t_{95}(dose)$>5 min (or 10 min). Models were calculated with the time between injection of neostigmine or sugammadex and a train-of-four ratio (TOFR)≥0.9 (Δt) either on a linear or on a natural logarithmic scale (ln). $\Delta t_{50/95}$, estimated time between injection of neostigmine and TOFR≥0.9 for 50/95% patients; 1-exp, mono-exponential; 2-exp, bi-exponential; FP1, fractional polynomial 1 degree; FP2, fractional polynomial 2 degrees. [a]The dose is calculated by extrapolation. [b]These models and their dose estimates are presented graphically in Fig. 1. Details of Akaike information criterion (equation 10) and r^2_{adj} (equation 9) are given in the Methods section

Reversal agent	Δt Scale	Model	r^2_{adj}	AIC	Estimated dose (μg kg^{-1})			
					$\Delta t_{50}\leq$2 min	$\Delta t_{95}\leq$5 min	$\Delta t_{50}\leq$5 min	$\Delta t_{95}\leq$10 min
					(Primary end point)		(Secondary end point)	
Neostigmine	linear	1-exp[b]	0.569	391	n.e.	n.e.	48	n.e.
		2-exp	0.562	393	n.e.	n.e.	52	n.e.
		FP1	0.568	392	n.e.	n.e.	52	n.e.
		FP2	0.569	395	n.e.	n.e.	54	n.e.
	ln	1-exp[b]	0.653	85	n.e.	n.e.	38	n.e.
		2-exp	0.647	87	n.e.	n.e.	37	n.e.
		FP1	0.648	87	n.e.	n.e.	43	69
		FP2	0.661	88	n.e.	n.e.	37	100[a]
Sugammadex	linear	1-exp[b]	0.752	274	0.59	n.e.	0.27	n.e.
		2-exp	0.747	276	0.73	n.e.	0.27	n.e.
		FP1	0.748	279	0.66	n.e.	0.38	n.e.
		FP2	0.752	278	0.64	n.e.	0.28	n.e.
	ln	1-exp[b]	0.909	76	0.66	0.49	0.26	0.26
		2-exp	0.907	78	0.64	0.48	0.27	0.26
		FP1	0.907	102	0.73	0.53	0.25	0.24
		FP2	0.908	79	0.64	0.49	0.27	0.26

using neostigmine doses ≤70 μg kg^{-1} to reverse a TOFR=0.2 within an average of 2 min was inconclusive. Even a less ambitious aim was met only to some extent; dose-finding estimates suggested that neostigmine 38 μg kg^{-1} would be effective in 50% of patients within 5 min. But even doses up to 70 μg kg^{-1} were not able to reverse 95% of patients within 10 min. In contrast, dose-finding estimates for sugammadex given at a TOFR≥0.2 suggested approximately 0.49 and 0.26 mg kg^{-1} to be effective in 95% patients within 5 and 10 min, respectively.

The basic assumption for regression models was equal variances in all dose groups. This assumption was not fulfilled using the recovery time on a linear, but on a logarithmic scale. Alternatively, equal variances could have been achieved if groups with larger variances had been excluded from the analysis. In our sugammadex study population, patients with doses <0.75 mg kg^{-1} would have had to be excluded (i.e. the estimable dose would have been ≥0.75 mg kg^{-1} by definition of a respective statistical protocol, therefore ignoring the real properties of the compound). Clinically, dose estimates based on recovery times on a linear scale tended to high values (e.g. compare published sugammadex dose-finding studies[12–17]). The very high r^2_{adj}≥0.91 of all models using the time on a logarithmic scale supported our notion that sugammadex dose-finding studies using recovery times as a dependent variable benefited from logarithmic transformation. The AIC allowed us to decide within the logarithmic models that the mono-exponential model should be used for dose recommendations.

Even complex models, however, could not overcome the inhomogeneity of the widely spreading neostigmine data. The low r^2_{adj} (0.57–0.66; Table 4) confirmed that the association between acetylcholine esterase inhibition and reversal effect at a TOFR=0.2 was low (i.e. that the individual effect variability was high). Owing to the possible desensitization of the acetylcholine receptors by high neostigmine doses,[26] we did not expect recovery times to approximate a minimum by increasing the neostigmine dose. Therefore, we questioned *a priori* the value of the exponential models. The r^2_{adj}, however, did not support our expectation of a better fit by fractional polynomials.

What do these results imply for clinicians? Neostigmine has been used to antagonize the residual effects of neuromuscular blockers for decades, with the drawback of its limited use for deep neuromuscular blocks. Owing to a ceiling effect, a certain degree of recovery has to be awaited before cholinesterase inhibition is effective in reversing neuromuscular block. It is recommended to wait until four twitches of TOF stimulation are visible.[27] However, if doses of 40–70 μg kg^{-1} are given at this point, recovery to a TOFR≥0.9 of 16 min has been reported.[10 27] In our study, we could demonstrate that after spontaneous recovery to a TOFR=0.2, neostigmine at the highest approved dose of 70 μg kg^{-1} could not reverse enough patients (≥95%) within 10 min, with a maximal time to a TOFR≥0.9 of 19 min (Table 2).

In this context, it is questionable why accelerated reversal within 10 min is intended, especially as such an ambitious objective was not considered before sugammadex was available. Most other anaesthetic agents, such as volatiles and propofol, in addition to opioids, allow emergence of anaesthesia within ~10 min. Maybe, management of neuromuscular function should not stand behind this controllability. As expected, our dose-finding study with a 10 min target could define the respective sugammadex doses. More than 20% of neostigmine-treated patients, however, will not reach TOFR ≥0.9 within 10 min; they will simply need more time.

Given the clinical target to have all patients treated in an appropriate time, we recommend sugammadex 0.5 mg kg^{-1} at TOFR≥0.2. This dose reverses to TOFR≥0.9 in more than 95% patients within 5 min. Therefore, an incremental dose of sugammadex would have enough time to treat those who are not recovered. These dose considerations, however, need a thorough effect control using quantitative neuromuscular monitoring. Especially in patients at risk of delayed recovery (e.g. because of

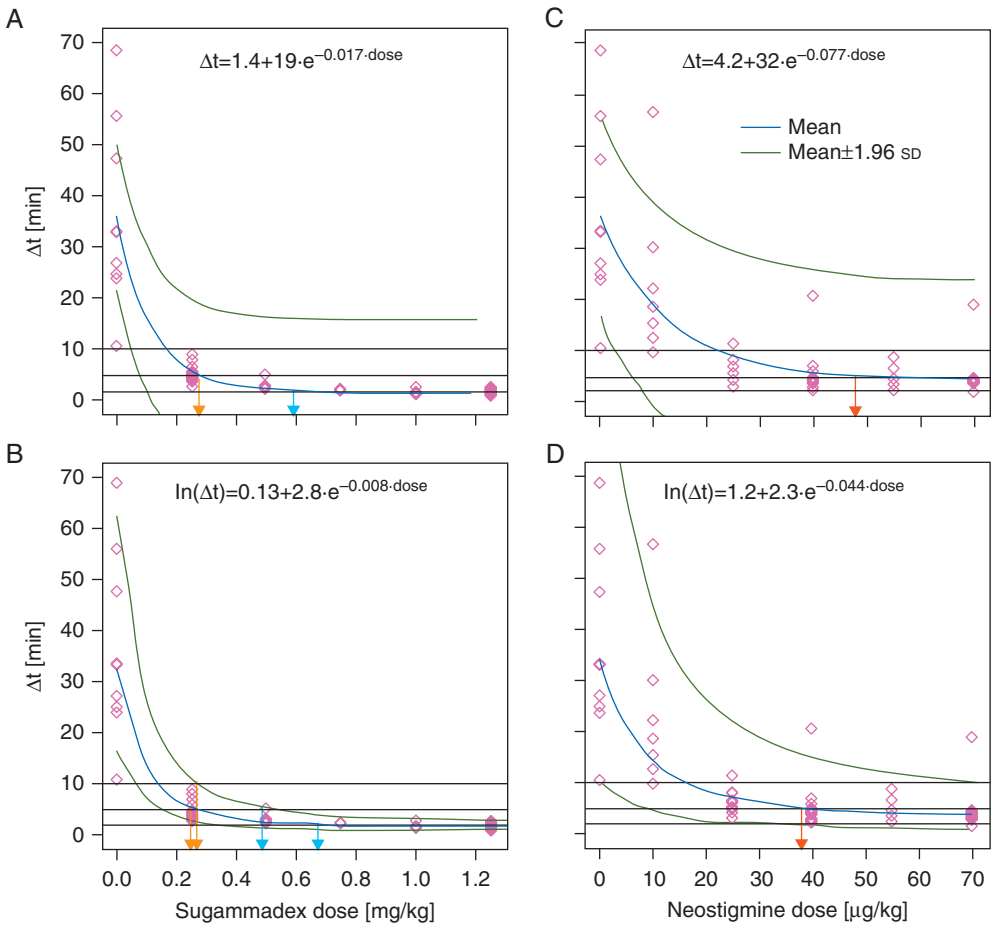

Fig 1 Sugammadex and neostigmine dose estimation with mono-exponential model: examples showing the influence of the time scale. (A–D) Mean time–dose curve with the 2.5 and 97.5% time–dose curves (mean±1.96 SD). (A and C) Recovery time on a linear scale. (B and D) The same (mono-exponential) model, with recovery time on a logarithmic scale. Arrows indicate the doses necessary to reverse a train-of-four ratio (TOFR)≥0.2 within 2 and 5 min for 50% of patients and within 5 and 10 min for 95% of patients, respectively. However, for neostigmine, only doses for 50% of patients could be estimated. Sugammadex with recovery times on a linear scale lacks estimation of doses for 95% patients. (A and C) The difficulty with linear scale models is illustrated; the upper 95% curve is too flat to allow an estimation, because in the model a_3·dose inclines to infinity, consequently $e^{-a_3 \cdot dose}$ to 0. Accordingly, the function Δt(dose)→a_1. To obtain an estimate using the mono-exponential model on a linear scale, the subjects with placebo and the low-dose groups (<0.75 mg kg^{-1}) would have to be excluded.

hypothermia, accumulated high-dose rocuronium, and liver and renal failure), the monitoring period must be expanded.

Given that many anaesthetists are still using qualitative methods to monitor neuromuscular function, it is questionable whether sugammadex 0.5 mg kg^{-1} can also be recommended for patients whose fourth twitch response has only returned according to tactile or visual observation. In the present study and in the study by Pongracz and colleagues,[5] reappearance of T4 was determined using EMG or acceleromyography. The corresponding TOFR was 0.11 (0.05–0.24 Table 5) and 0.10 (0.00–0.33), respectively. Data from studies in which reappearance of T4 was monitored by an anaesthetist's tactile sense suggest a mean TOFR of 0.14,[8] 0.17,[7] or 0.21.[9] In comparison with the data from Pongracz and colleagues[5] and our data, it may be considered that the tactile sense is less sensitive to detect reappearance of T4 than objective measurement. In a routine clinical setting, there is reason for doubt that qualitative monitoring is performed without relevant interruption, which may delay the recognition of reappearance of T4 towards higher TOFR. Even in research conditions, Kim and colleagues[7] touched the thumbs to feel the twitch responses at 2 min intervals. These considerations support the assumption that sugammadex 0.5 mg kg^{-1} may be an adequate dose to reverse a rocuronium-induced neuromuscular block at reappearance of T4 based on subjective monitoring. To override problems of missing quantitative effect control, higher doses of sugammadex were suggested at tactile reappearance of T4 (e.g. 1 mg kg^{-1} as suggested by Pongracz,[5] or simply 2 mg kg^{-1}, i.e. the dose approved at reappearance of T2).[4] This approach lacks scientific reasoning, because reversal of residual neuromuscular block with an average dose of sugammadex 2.7 mg kg^{-1} on the basis of clinical criteria still resulted in an incidence of >9% of patients with a TOFR <0.9.[28]

It is important to bear in mind that any technique for reversal has the potential for reoccurrence of neuromuscular block after a TOFR≥0.9 has been reached because of the iceberg phenomenon of neuromuscular transmission.[29] After reversal by sugammadex of a rocuronium-induced neuromuscular block, reoccurrence of TOFR <0.8 was observed when doses of 0.5–1 mg kg^{-1} were used

Table 5 Neuromuscular function at reappearance of the twitch responses (T1, T2, T4) and a train-of-four ratio (TOFR)≥0.2. Δt, time differences between different levels of reappearance of twitch responses. After repetitive doses of rocuronium, the patients' recovery started from different levels of neuromuscular block. Accordingly, a limited number of values are available at the respective levels of neuromuscular recovery from the 98 patients, as follows: [a]*n*=72; [b]*n*=91; and [c]*n*=96. Values are shown as means (SD) and ranges

Reappearance of . . .	T1	T2	T4	TOFR≥0.2
Neuromuscular function				
T1 (%)	4 (1)[a] (1–7)	16 (7)[b] (6–41)	33 (11)[c] (13–73)	58 (12) (24–87)
T4 (%)	–	–	4 (2)[c] (1–9)	12 (3) (5–20)
TOFR	–	–	0.11 (0.04)[c] (0.05–0.21)	0.21 (0.01) (0.20–0.22)
Δt (min) from reappearance of . . .				
T1 to . . .	0	10 (4)[a] (3–26)	15 (6)[a] (5–32)	21 (8)[a] (8–46)
T2 to . . .	–	0	5 (2)[b] (2–17)	11 (5)[b] (2–33)
T4 to . . .	–	–	0	6 (4)[c] (0–26)

to reverse deep neuromuscular block (post-tetanic count 1–2).[30] To ensure patients' safety regarding reoccurrence of neuromuscular block, all patients were observed after the TOFR had reached 0.9 by neuromuscular monitoring. There was no evidence for reoccurrence of neuromuscular block in any patient, most probably because of the fact that in our dose-finding study residual but not deep neuromuscular block was investigated. By all means, a prospective confirmatory trial must approve safety of any sugammadex dose before it can be recommended generally for clinical use.

In conclusion, neostigmine is not effective in reversing a TOFR from 0.2 to ≥0.9 within 10 min in 95% patients, whereas sugammadex (~0.26 mg kg^{-1}) is able to do so. Sugammadex (~0.50 mg kg^{-1}) can also rapidly (within 5 min) reverse a residual neuromuscular block at a TOFR≥0.2 in 95% patients. Given that this study was not powered for safety, it is strongly recommended that quantitative neuromuscular monitoring should be used if applying this non-labelled dose of sugammadex at TOFR≥0.2.

Authors' contributions

Study design: S.J.S., H.F., M.B.
Patient recruitment: N.K., S.J.S., C.G.S., H.F.
Data collection: N.K., S.J.S., C.G.S., H.F.
Data analysis: E.B., K.U., H.F., M.B.
Data interpretation: S.J.S., E.B., K.U., H.F., M.B.
Writing the paper: N.K., S.J.S., C.G.S., H.F., M.B.
Revising the paper: S.J.S., E.B., K.U., H.F., M.B.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Acknowledgements

We would like to thank Eberhard Kochs (Klink für Anaesthesiologie, Klinikum rechts der Isar, Technische Universität München, Munich, Germany), who also served as scientific advisor, for his unstinting support.

Declaration of interest

N.K. has received a travel grant from MSD Sharpe & Dohme.
S.J.S. holds stocks of the following companies in the health-care sector in small amounts: Bayer AG, Siemens AG, GE, Merck & Co. Inc., Rhoen-Klinikum AG, and Fresenius SE; however, these holdings did not influence any decisions regarding the study.
C.G.S. has received honoraria and a travel grant from MSD Sharpe & Dohme.
H.F. has received honoraria and travel grants from the following companies: MSD Sharp & Dohme, Essex, Baxter, Care Fusion, and GE Healthcare.
M.B. has received honoraria and travel grants from MSD Sharp & Dohme and GlaxoSmithKline.
E.B. and K.U.: none declared.

Funding

Klinik für Anaesthesiologie, Klinikum rechts der Isar der Technischen Universität München, Munich, Germany.

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Handling editor: T. Asai