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Sugammadex and Neostigmine Dose-finding Study for Reversal of Residual Neuromuscular Block (SUNDRO-Study)

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Ich weiß, dass ich nichts weiß.

(Sokrates)

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List of Abbreviations

AE	Adverse Event
AIC	Akaike Information Criterion
ASA	American Society of Anesthesiology
COO^-	Carboxy-group
CRE	Critical Respiratory Event
ECG	Electrocardiogram
Max	Maximum
min	Minutes
Min	Minimum
mio	Million
ml	Milliliter
MRC	Medical Research Council
n.e.	not estimable
NMT	Neuro Muscular Transmission
PORC	Postoperative Residual Curarization
PTC	Post-Tetanic Count
SAE	Serious Adverse Event
smPC	Summary of Product Characteristics
SUNDRO	Sugammadex and Neostigmine Dose-finding Study for Reversal of Residual Neuromuscular Block
TOF	Train-of-Four

1 Introduction

1.1 Historical View and Safety

Over the last years there has been tremendous improvement in patient safety as regards anesthesia. This is reflected by a reduction of intraoperative mortality from approximately 1 in 10,000 in the 1980s to under 1 in 100,000 in the year 2000 (Gibbs 2005, p. 616; Hovi-Viander 1980, p. 483; Lagasse 2002, p. 1609; Lienhart 2006, p. 1087). This improvement may be credited not only to technical advances like intraoperative high-tech monitoring or ventilation machines (Auroy 2009, p. 366) as well as structured training programs, but also to pharmacological advances like short acting substances. These contributing factors to the aforementioned improvement have led to a concept of (so-called) "balanced anesthesia" (Tonner 2005, p. 475), a concept which connotes the combination of an anesthetic, an analgesic and a muscle relaxant so as to induce (and maintain) general anesthesia. The combination of different substances thereby reduces each substance's individual amount and consequently the unwanted effects otherwise implicated by these substances.

An integral element of (the concept of) balanced anesthesia are muscle relaxants. They improve intubation conditions (Mencke 2003, p. 1049; Schlaich 2000, p. 720; Sparr 1997, p. 1300) and might even contribute to depth of anesthesia (Bonhomme 2007, p. 456). During the overall improvement on patient safety it became evident that the ratio of intra- to post-operative mortality is 1 to 1000 (Fink 2007, p. 1127; Henderson 2007, p. 1103); a development which caused the researches to focus on potential unintended (and undesirable) effects of muscle relaxation. A pharmacological action of muscle relaxation, beyond its intended effect for induction of anesthesia and intraoperative surgical conditions, defined as postoperative residual curarization (PORC) (Cammu 2002, p. 129; Debaene 2003, p. 1042; Hayes 2001, p. 312; McCaul 2002, p. 766) can cause the following effects:

(1) respiratory insufficiency (Murphy 2008, p. 130),

(2) impaired upper airway function (Eikermann 2006, p. 937),

(3) increased risk of aspiration (Sundman 2000, p. 977), as well as (consecutively)

(4) the risk of postoperative pulmonary complications (Berg 1997, p. 1095).

1.2 Muscle Relaxants

Muscle relaxation improves intubation conditions, which in turn lead to reduced postoperative hoarseness and injuries of the vocal cords (Lieutaud 2003, p. 121; Masso 2006, p. 249; Mencke 2003, p. 1049). Since airway injuries are a frequent cause for claims against anesthesiologists (Cass 2004, p. 47), muscle relaxation is an imperative for modern balanced anesthesia including intubation. In addition, muscle relaxants may potentially improve surgical conditions – although there are no supporting studies available to date.

Muscle relaxants can be divided into:

1. depolarizing muscle relaxants (e.g. succinylcholine) and
2. nondepolarizing muscle relaxants
    a. benzylisoquinolones (e.g. atracurium, cisatracurium and mivacurium)
    b. aminosteroidal muscle relaxants (e.g. rocuronium, vecuronium and pancuronium) (Blobner 2009, p. 105)

Succinylcholine (structurally a di-acetylcholine molecule) mimics the effect of acetylcholine at the neuromuscular junction. It depolarizes the post-synaptic membrane, leading to an initial fasciculation. Succinylcholine is the only depolarizing muscle relaxant in clinical use. However, it has numerous unwanted effects such as life-threatening hyperkalemia, malignant hyperthermia, as well as increased intraocular, gastric, and cerebral pressure (Blobner 2009, p. 112).

Non-depolarizing muscle relaxants act by inducing a competitive blockade of the acetylcholine receptor of the neuromuscular junction, thus inhibiting any physiologic neuromuscular transmission.

The effects of muscle relaxants are evaluated by neuromuscular monitoring. Most frequently a train-of-four stimulation pattern is used. For two seconds, four 2 Hz stimuli are applied to a peripheral nerve, with the evoked muscle contraction recorded. The fourth contraction is then set into relation to the first contraction, resulting in a train-of-four ratio. Complete muscle paralysis occurs at a train-of-four ratio of zero. Recovery to a train-of-four ratio of 0.9 is considered to be sufficient functional recovery by today's standard.

1.3 Postoperative Residual Curarization (PORC)

Although textbooks suggest muscle relaxants to have a predictable duration of effect clinically, there is a wide inter-individual difference in duration of action, which leads to high rates of PORC (Maybauer 2007, p. 12). PORC is defined as a train-of-four (TOF) ratio below 0.9 and is a common but largely underestimated problem. PORC leads to respiratory insufficiency, impaired upper airway function and increased risk of aspiration, which leads to an increased incidence of postoperative pulmonary complications if not treated properly.

In 1979 Viby-Mogensen showed (Viby Mogensen 1979, p. 539) that 42% of patient admissions in the recovery room suffered from PORC (in those days defined as a TOF ratio below 0.7). Unfortunately, patient safety has not improved as regards PORC, as in 2003 60% of the patients in the recovery room still suffered PORC with a TOF ratio below 0.9 (Debaene 2003, p. 1042). Clinically, there is a high incidence of Critical Respiratory Events (CRE) in patients with PORC (Murphy 2008, p. 130). However, clinical tests per se are not sufficient to identify PORC. The only way to identify PORC and thereby effectively treat patients is by neuromuscular monitoring (Baillard 2005, p. 622). And once PORC is identified, the residual effects of muscle relaxants need to be reversed.

1.4 Reversal of Muscle Relaxants

1.4.1 Overview

Drugs used to reverse the effects of neuromuscular blocking drugs are divided into:

1. Antagonists
2. Encapsulators

1.4.2 Cholinesterase Inhibitors

Presynaptically released acetylcholine is degraded by acetylcholine esterase into acetate and choline. Both choline and acetate are transported back into the presynaptic nerve terminal and re-used to synthesize acetylcholine. Acetylcholine esterase is mostly located in the extracellular matrix of the neuromuscular junction. As a result, most of the released

acetylcholine is degraded right after its release. Inhibition of acetylcholine esterase therefore increases the concentration of acetylcholine in the neuromuscular junction. Due to the competitive mechanism of non-depolarizing muscle relaxants, an increase in acetylcholine leads to a higher possibility of the agonist to bind at the receptor location, leading to restored neuromuscular transmission. (Fink 2004, p. 573)

Two acetylcholine esterase inhibitors are currently used in Germany for reversal of neuromuscular block:

1. neostigmine
2. pyridostigmine

Physiostigmine is not used to reverse neuromuscular block, since it crosses the brain-blood-barrier. Its application is limited to act as a therapeutic agent for a central anticholinergic syndrome.

Antagonists, however, have certain limitations. After blocking all present acetylcholine esterase an additional dose of cholinesterase inhibitors will not produce a further effect (ceiling effect). Therefore, a deep neuromuscular block cannot be antagonized with acetylcholine esterase inhibitors. Secondly, acetylcholine esterase inhibitors do not selectively act at the neuromuscular junction. They also increase acetylcholine in the autonomous nervous system, leading to several side effects – in particular, bradycardia, rise in intraocular pressure, increased bowel movement, increased contraction of the gall bladder, ureter and detrusor muscle, relaxation of the bladder sphincter and increased sudoral secretion. Therefore, acetylcholine esterase inhibitors are usually combined with parasympatholytic drugs (e.g. atropine or glycopyrronium bromide) to decrease these unwanted side effects. Parasympatholytic drugs, however, exert unwanted effects of their own, such as tachycardia or dry mouth.

Neostigmine, which was used in this study, has a quaternary ammonium structure and is a peripheral acting reversible cholinesterase inhibitor. It is not lipophilic and therefore does not cross the blood brain barrier. It is poorly reabsorbed after oral intake, but is quickly distributed after intravenous application. After application, a high concentration can be measured in the liver and muscle tissue. Elimination half time after intravenous application occurs between 24 and 80 minutes, a duration which increases under impaired renal function (Blobner 2008, p. 342).

Recommended doses of neostigmine for reversal of neuromuscular block vary from 20-70 µg/kg bodyweight (Blobner 2009, p. 115). A ceiling effect is observed at approximately 60-80 µg/kg. Maximal antagonistic effect of neostigmine occurs in approximately ten minutes. The recommended combination of neostigmine with a parasympatholytic agent is 1:2.5 for atropine or 1:5 for glycopyrronium bromide. In this study, glycopyrronium bromide is used as it (in addition) does not cross the blood-brain-barrier and thus has a lower incidence for postoperative cognitive deficits compared to atropine.

1.4.3 Encapsulator Sugammadex

Sugammadex is a modified γ-cyclodextrin which has been developed to reverse rocuronium bromide-induced neuromuscular block. It has been available in Germany since October 2008. Cyclodextrins are cyclic oligosaccharide molecules, which are known for their capability to encapsulate lipohilic molecules. Cyclodextrins are divided into α-, β- and γ-cyclodextrins dependent on their assembly of six, seven or eight glucose molecules. Characteristically, they have a cylindrical form with a lipophilic cavity and a hydrophilic exterior part. Liphophilic molecules can be encapsulated in the cavity and transported to a hydrophilic environment. Sugammadex, however, is a synthetic γ-cyclodextrin where every sixth carbohydroxyl-group is replaced by a thioether-side-chain with a negatively charged carboxy-group (COO^-). This leads to a larger cavity and allows encapsulating the muscle relaxants rocuronium (and, to a lesser effective degree, vecuronium) (Bom 2009, p. 29; Welliver 2009, p. 49).

Encapsulation of rocuronium or vecuronium occurs in two phases:

1. After intravenous injection, all intravasal rocuronium/vecuronium-molecules are encapsulated and by that, pharmacologically inactivated. This results in a concentration gradient between plasma and extravasal space (including the neuromuscular junction).

2. All extravasal rocuronium/vecuronium molecules are recruited back into the bloodstream where they are immediately encapsulated and inactivated.

The binding shows a high stability based on electrostatic interaction between the positively charged azotic molecules of rocuronium/vecuronium and the negatively charged carboxy-groups of sugammadex. Van der Waals forces play a minor role in this interaction. The

association-dissociation-rate of sugammadex and rocuronium is 25,000,000 to 1 – meaning, while 25 million molecules of rocuronium are encapsulated, only one molecule dissociates from sugammadex within the same time (Bom 2009, p. 30; Welliver 2009, p. 52). The rocuronium-sugammadex complex is highly stable under alternating conditions as regards temperature or pH, and is eliminated entirely via the kidney (normally within 8 hours). Interestingly, the primary hepatic elimination of rocuronium is in this way replaced by a renal elimination (together with sugammadex). Its elimination half-life period is approximately 100 minutes, calculated at a plasma clearance equal to the glomeric filtration rate of 120 ml/min (Naguib 2007, p. 577; Sparr 2009, p. 69).

Because of the 1:1 interaction of the encapsulation, the reversal depends on adequate dosage. The following doses are recommended in the Summary of Product Characteristics when used for a reversal of rocuronium-induced block:

a. appearance of second twitch of TOF-stimulation (T2>0): 2 mg/kg
b. 1-2 post-tetanic counts after five seconds of tetanic stimulation (PTC 1-2): 4 mg/kg
c. immediate reversal of rocuronium-induced block: 16 mg/kg

Under these dosages, a TOF-ratio of 0.9 will be reached within two minutes on average (Sparr 2009, p. 70).

Compared to antagonists (like neostigmine) cyclodextrins have no intrinsic effect. Their most common side effects consist in anesthetic complications (such as grimacing or coughing against the intratracheal tube), intraoperative awareness, allergic reactions, or dysgeusia.

In pharmaco-kinetic/pharmaco-dynamic modeling, no interaction was found for 300 compounds commonly used during anesthesia. However, three drugs are identified where interaction may occur (Sparr 2009, p. 73):

1. Toremifene (an orally administered non-steroidal Selective Estrogen Receptor Modulator used for treatment of metastatic breast cancer)

2. Flucloxacillin (a narrow spectrum beta-lactam penicillin)

3. Fusidic acid (a steroidal bacteriostatic agent)

Since progesterones and estrogens show some affinity for sugammadex, clinically relevant interaction with hormonal contraceptives could not be excluded.

1.5 Aims of the Study

Previous dose finding studies were restricted to immediate reversals of 1.2 mg/kg rocuronium or to reversals of very deep (post tetanic count of 1-2) or deep (T2 > 0) rocuronium or vecuronium neuromuscular blockade. In a clinical setting, however, residual neuromuscular paralysis occurs more frequently at much lower levels, as not every anesthetized patient requires deep neuromuscular blockade for the complete surgical procedure. Unfortunately, no dose recommendation is provided for any level of neuromuscular blockade beyond T2 > 0. Since, however, rocuronium encapsulation by sugammadex is a 1:1 molecule interaction, it seems feasible that shallow neuromuscular blocks would require less sugammadex.

In addition, those studies also showed that neostigmine is not effective to reverse profound or deep neuromuscular blockade. This is due to the nature of competitive neuromuscular blocking, where – even if all acetylcholine esterase in the junction is inhibited – there is still too few of it in the neuromuscular junction to reverse a deep neuromuscular block. However, neostigmine is widely used as reversal agent of residual neuromuscular block.

The primary aim of the study was to find the doses of neostigmine and sugammadex able to reverse a residual neuromuscular block from a train-of-four ratio (TOF) of 0.5 to TOF ≥ 0.9 within two minutes on average and no more than five minutes for 95% of all patients.

The secondary goal of the study was to obtain the dose for a less accelerated reversal – meaning, five minutes on average, and the upper time limit being 10 minutes for 95% of the patient population.

2 Materials and Methods

2.1 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 ("Bundesanstalt für Arzneimittel und Medizinprodukte") of Germany. The study is listed under the acronym SUNDRO (NCT00895609 and EudraCT 2008-008239-27).

Patients were included after informed written consent. Inclusion criteria were: age between 18 and 65 years, American Society of Anesthesiology physical status (ASA) I to III, and scheduled for elective surgery under general anesthesia with rocuronium for endotracheal 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 which may interact with muscle relaxants, as well pregnant women or women who were breast feeding. In addition, patients were not included if they were included in another clinical study in the past 30 days.

Ninety-nine patients were randomly assigned to receive either sugammadex at doses of 0.0625 mg/kg, 0.125 mg/kg, 0.25 mg/kg, 0.5 mg/kg, and 1.0 mg/kg or neostigmine at doses of 5 µg/kg, 8 µg/kg, 15 µg/kg, 25 µg/kg, and 40 µg/kg in a mixture with 1 µg glycopyrrolate / 5 µg neostigmine or saline (n = 9 per dose group).

2.2 Procedure

An intravenous cannula was inserted into a forearm vein and standard anesthesia monitoring (non-invasive blood pressure, ECG 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 µg/kg) and maintained with propofol and remifentanil according to the clinical need and preference of the anesthesiologist. Patients received a laryngeal mask and were artificially ventilated to keep the arterial oxygen saturation ≥ 96% and to maintain normocapnia. Body temperature was maintained ≥ 35.0°C.

Neuromuscular monitoring was carried out according to international consensus guidelines (Fuchs-Buder 2007, p. 789), using evoked electromyography of the adductor pollicis muscle

using the NMT module in a S/5 GE Datex Light monitor (GE Datex Medical Instrumentation, Inc., Tewksbury, MA). In brief, the forearm was immobilized and surface skin electrodes were placed over the ulnar nerve proximal to the wrist. Following 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. 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_2, T_3, and T_4) related to the baseline values and the ratio of the fourth twitch response, T_4, to the first, T_1, of a TOF complex (TOF ratio). Skin temperature was measured at the site of the neuromuscular measurements and maintained ≥ 32.0°C using heating blankets.

Following three minutes of stabilization of the electromyography recording, 0.6 mg/kg rocuronium was injected. At T1 = 0 the trachea was intubated. 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 a stable TOF ≥ 0.9. 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 and 2, 5, 10, and 20 min after the injection of the study medication.

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 patients' levels of consciousness (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 seconds, perform a 5-s head lift test, a 5-s arm lift test and were asked to swallow a bolus of 20 ml plain water. Then a test for general muscle weakness was performed using the Medical Research Council (MRC) Scale: 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 & some resistance exerted by examiner, 5 - normal power. These postoperative

clinical assessments were performed by the blinded safety assessor. 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), including serious AEs (SAE). However, if there was doubt about classification the safety assessor had to decide the coding of the AE or SAE. AEs were defined as drug related if the investigator considered them to be definitely, probably or possibly related to the study drug.

2.3 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 aim was to estimate a dose of sugammadex or neostigmine to accelerate the time between start of administration of the respective study drug at TOF = 0.5 to TOF ≥ 0.9 to an average time of two min with an upper limit of five min for 95% of the patients. Secondary aim of the study were to estimate the doses of sugammadex and neostigmine for a less advanced acceleration of the reversal, i.e. an average time of five min and upper time limit of 10 min for 95% of patients.

Separate dose–response relationships were estimated from the available data for each reversal agent. To explore the relationship between the dose of sugammadex or neostigmine and recovery from neuromuscular block (TOF ratio to 0.9), several models have been tested in order to describe the data with the model that fits best. We tested mono-(Puhringer 2008, p. 188; Sorgenfrei 2006, p. 669; Sparr 2007, p. 935) and bi-exponential models with the recovery time to a TOF ratio ≥ 0.9 (Δt) in linear or logarithmic scale.

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

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

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

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

Additionally, we analyzed the data using fractional polynomials (FP) developed by Royston and Altman (Royston 1994, p. 429), consisting of one (= FP_1) or two degrees (= FP_2) :

$$FP_1:\ \Delta t(dose) = a_1 + a_2 \cdot dose^{p} \tag{5}$$

$$FP_1:\ \ln \Delta t(dose) = a_1 + a_2 \cdot dose^{p} \tag{6}$$

$$FP_2: \Delta t(dose) = \begin{cases} a_1 + a_2 \cdot dose^{p_1} + a_3 \cdot dose^{p_2} \\ a_1 + a_2 \cdot dose^{p} + a_3 \cdot dose^{p} \cdot \ln(dose) \end{cases} \tag{7}$$

$$FP_2: \ln \Delta t(dose) = \begin{cases} a_1 + a_2 \cdot dose^{p_1} + a_3 \cdot dose^{p_2} \\ a_1 + a_2 \cdot dose^{p} + a_3 \cdot dose^{p} \cdot \ln(dose) \end{cases} \tag{8}$$

Since the models are not nested they were compared by applying the adjusted R^2 (= R^2_{adj}):

$$R^2{}_{adj} = 1 - \left(1 - R^2\right) \cdot \frac{n-1}{n-r-1}$$

with R^2_{adj} the value for the fit of the model and k the number of parameters in the model excluding the intercept. The model with the largest R^2_{adj} is considered to be the best and was used for further evaluations.

3 Results

3.1 Demographics

The study drug was injected in 99 patients. With five patients, major protocol violations occurred: with one patient the neostigmine was incompletely injected due to a leaking venous cannula, with four patients electromyographic response was instable. Since these violations might have affected the primary and secondary aims, the respective data were omitted resulting in a per protocol population of 94 patients.

Groups did not differ significantly regarding age, weight, height, sex and ASA physical status: age was 42 ± 14 years, height 173 ± 10 cm, weight 76 ± 16 kg, 46 females and 53 males, 48 patients were classified as ASA physical status I, 44 as ASA II, and 7 as ASA III.

3.2 Efficacy

The median time to recover to a TOF ratio of 0.9 after injection of the study drug decreased from 19 min (placebo) to 2.0 minutes with 40 µg/kg neostigmine (table 1) and to 1.0 min with 1.0 mg/kg sugammadex (table 2). No signs of re-curarization in any patient were observed during the TOF monitoring or at the clinical testing of the patient in the recovery room.

3.2.1.1.1.1 Table 1: Time interval from administration of various doses of neostigmine or placebo at Train-of-four (TOF) Ratio of 0.5 to 0.7, 0.8, or 0.9.

*Placebo values are also presented in table 2.
Per-protocol population

	Placebo*	Neostigmine. Dose Group				
		5 µg/kg	8 µg/kg	15 µg/kg	25 µg/kg	40 µg/kg
	n = 9	n = 8	n = 8	n = 9	n = 9	n = 8
Reversal – to TOF ³ 0.7						
Median [min]	5.9	2.7	1.9	1.5	1.3	1.1
(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)
Reversal – to TOF ³ 0.8						
Median [min]	10	4.9	2.8	2.3	1.8	1.4
(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)
Reversal – to TOF ³ 0.9						
Median [min]	19	9.3	5.3	4.0	3.2	2.0
(Min - Max) [min]	(12 – 33)	(5.8 - 15)	(3.5 - 8.7)	(2.8 – 6.0)	(1.7 - 6.2)	(1.7 - 4.2)

3.2.1.1.1.2 Table 2: Time interval from administration of various doses of sugammadex or placebo at Train-of-four (TOF) Ratio of 0.5 to 0.7, 0.8, or 0.9.

*Placebo values are also presented in table 1.
Per-protocol population

	Placebo*	Sugammadex. Dose Group				
	n = 9	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
Reversal – to TOF ³ 0.7						
Median [min]	5.9	1.3	1.0	1.0	0.7	0.8
(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)
Reversal - TOF ³ 0.8						
Median [min]	10	2.5	1.2	1.0	1.0	1.0
(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)
Reversal - TOF ³ 0.9						
Median [min]	19	7.8	2.3	1.7	1.3	1.0
(Min - Max) [min]	(12 – 33)	(2.0 - 13)	(1.0 – 11)	(1.0 – 4.0)	(0.8 – 2.0)	(0.7 - 1.5)

The best fit of the relationship between the neostigmine dose and the time between administration at TOF = 0.5 to recovery of TOF ≥ 0.9 was revealed by the bi-exponential model using the time in logarithmic scale (model 4) with the highest adjusted regression coefficient $R^2 = 0.814$ (table 3). Based on this estimate, the dose of neostigmine is calculated to be 50 µg/kg for an average recovery time of two min (extrapolation) and 34 µg/kg for an upper limit of five min for the 95% patients' population (primary endpoint) or 11 µg/kg for an average recovery time of five min and 10 µg/kg for an upper limit of 10 min for 95% of patients (secondary endpoint).

Table 3: Dose estimations for neostigmine using several mathematical models.

n.e. not estimable
[ ] estimate of the value required extrapolation

Model	Δt scale	R^2	Para-meters	Adjusted R^2	Dose estimate [µg/kg] for ...			
					Mean Δt = 2 min	95% of patients Δt < 5 min	Mean Δt = 5 min	95% of patients Δt < 10 min
					(primary endpoint)		(secondary endpoint)	
mono-exponential	linear	0,805	3	0,797	n.e.	n.e.	10	14
	logarithmic	0,816		0,808	n.e.	41	10	10
bi-exponential	linear	0,807	4	0,795	[60]	n.e.	11	17
	logarithmic	0,825		**0,814**	**[50]**	**34**	**11**	**10**
fractional polynomas (1 degree)	linear	0,789	3	0,780	[60]	n.e.	14	26
	logarithmic	0,806		0,797	40	32	13	13
fractional polynomas (2 degrees)	linear	0,807	5	0,791	[130]	n.e.	11	16
	logarithmic	0,825		0,810	[70]	35	10	9

The best fit of the relationship between the sugammadex dose and the time between administration at TOF = 0.5 to recovery of TOF ≥ 0.9 was revealed by the mono-exponential model using the time in logarithmic scale (model 2) with the highest adjusted regression coefficient $R^2 = 0.820$ (table 4). Based on this estimate the dose of sugammadex is calculated

to be 200 µg/kg for an average recovery time of two min and 210 µg/kg for an upper limit of five min for 95% of patients (primary endpoint) or 80 µg/kg for an average recovery time of five min and 100 µg/kg for an upper limit of 10 min for 95% of patients (secondary endpoint).

Table 4: Dose estimations for sugammadex using several mathematical models.

n.e. not estimable;

Model	Δt scale	R^2	Para-meters	Adjusted R^2	Dose estimate [µg/kg] for ... Mean Δt = 2 min (primary endpoint)	95% of patients Δt < 5 min (primary endpoint)	Mean Δt = 5 min (secondary endpoint)	95% of patients Δt < 10 min (secondary endpoint)
mono-exponential	linear	0.813	3	0.805	200	n.e.	100	130
	logarithmic	0.827		**0.820**	**200**	**210**	**80**	**100**
bi-exponential	linear	0.813	4	0.802	230	210	100	140
	logarithmic	0.829		0.818	210	220	80	100
fractional polynomas (1 degree)	linear	0.794	3	0.786	460	n.e.	100	250
	logarithmic	0.716		0.705	280	780	25	50
fractional polynomas (2 degrees)	linear	0.813	5	0.797	280	n.e.	100	150
	logarithmic	0.831		0.817	190	190	70	100

The estimated dose-response relationship and the respective 95% confidence intervals for the recovery from a TOF 0.5 to TOF 0.9 for the per-protocol population are shown in figure 1 (neostigmine) and figure 2 (sugammadex).

Figure 1: Neostigmine bi-exponential fit

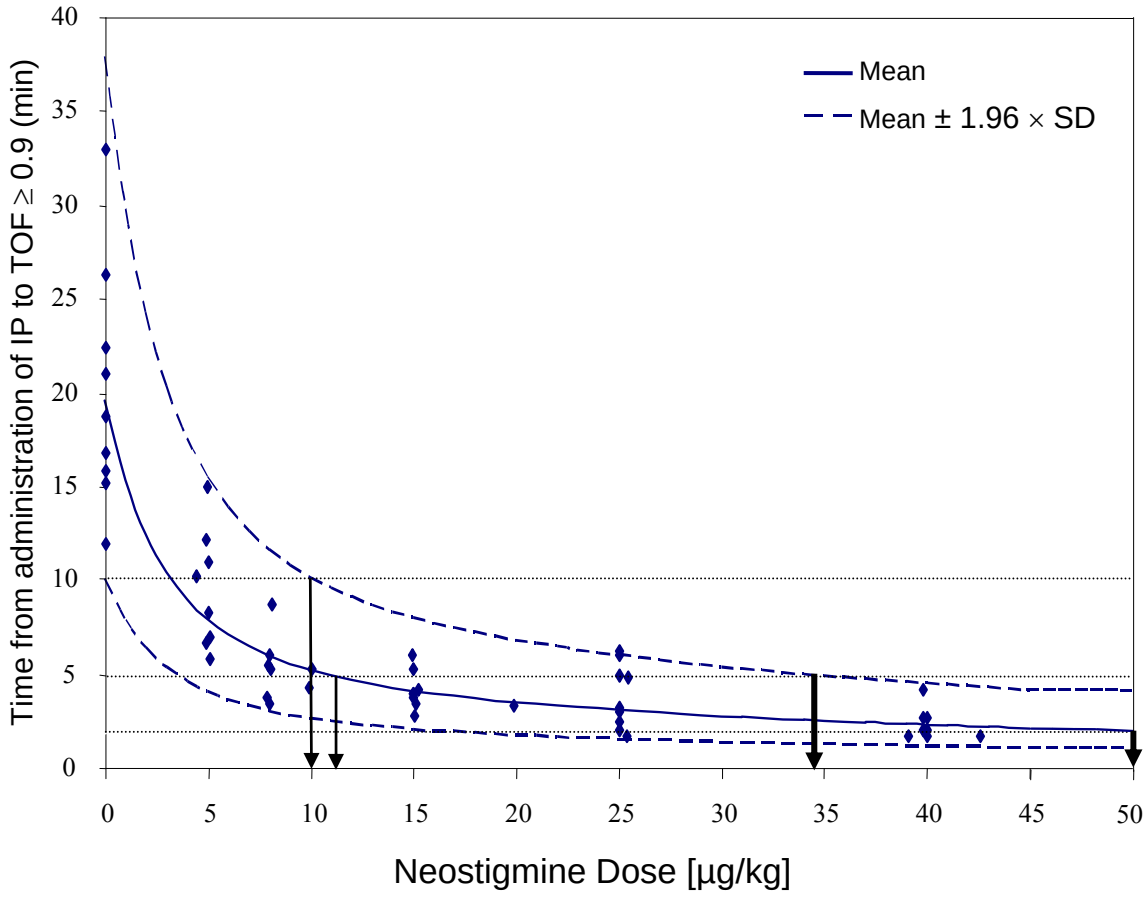
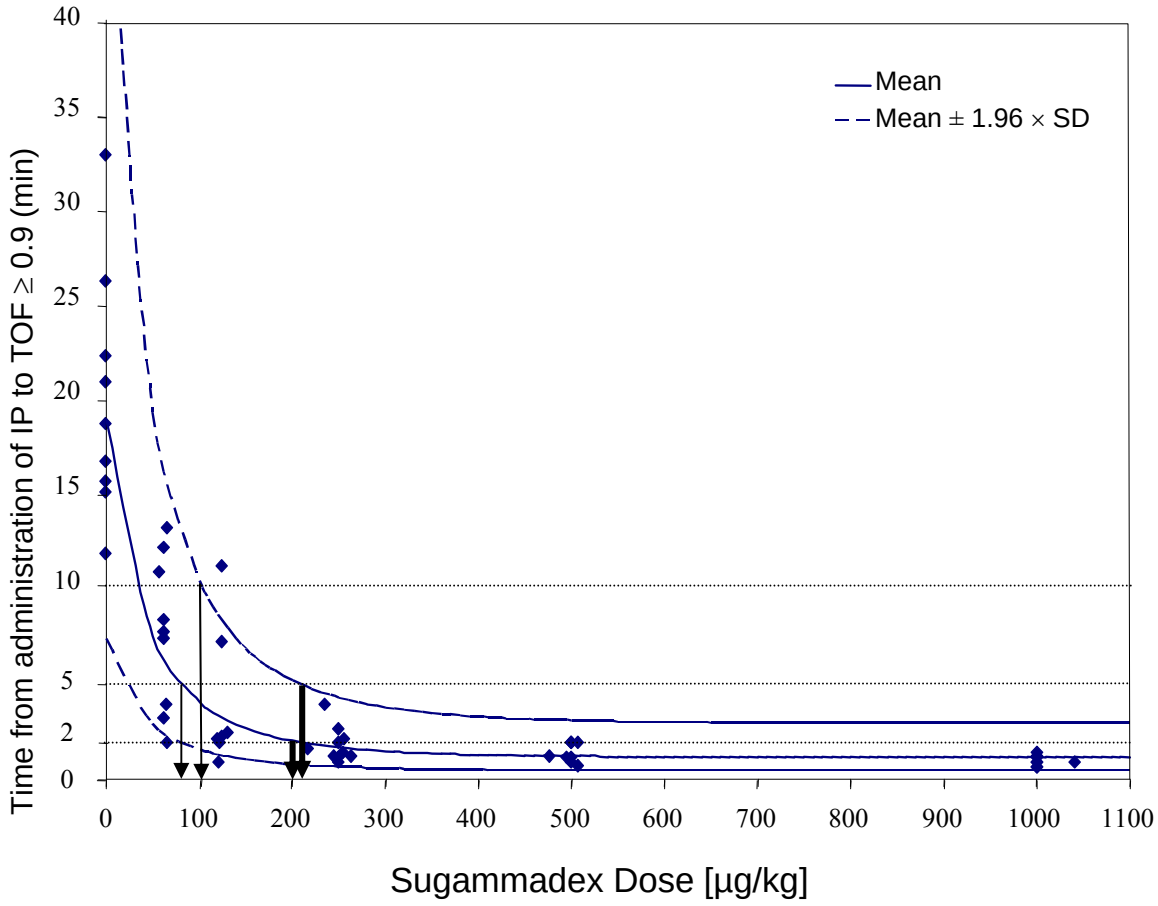


Figure 2. Sugammadex mono-exponential fit



3.3 Safety

Clinical muscle function tests and evaluation of consciousness revealed no difference between groups at any time during postoperative period in the recovery room. At arrival, 13% of the 79 cooperative patients were not able to keep the eyes open for 5s, 6% were not able to lift the head for 5s, 4% were not able to lift the arm for 5s, 13% were not able to swallow 20 ml of water without difficulties, and 46% of the cooperative patients had not reached normal muscle strength (MRC 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 adverse events were reported in 48 patients (table 5). The majority of AEs were classified as mild or moderate. The three most often observed AEs were postoperative shivering, bradycardia, and hypotension. Postoperative shivering was treated with 25-50 mg meperidine, bradycardia was treated with

0.2 mg glycopyrrolate, and hypotension with 0.5 – 2.0 ml Akrinor™ (vasopressor available in Germany consisting of theophylline, ephedrine, caffeine and norepinephrine). No dose-response relationship was observed.

Table 5: Incidence of Adverse Events for all Groups after Administration of Neostigmine, Sugammadex or Placebo.

SAE = Serious Adverse Event * $p < 0.05$ compared to sugammadex groups

	Neostigmin	Placebo	Sugammadex
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 N. ulnaris	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 (SAE)	1 (2%)	0	0
At least 1 AE	28 (64%)*	4 (44%)	16 (36%)

One patient developed acute lung failure 63 h postoperatively. This adverse event was categorized to be severe and possibly related to the study medication of 5 µg/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.

4 Discussion

Sugammadex as well as neostigmine was able to reverse a rocuronium-induced residual neuromuscular block at a TOF ratio of 0.5 in a dose-dependent manner. Best fit modeling of the dose response relationship revealed 0.21 mg/kg sugammadex and 34 µg/kg neostigmine to be able to accelerate the recovery from TOF = 0.5 to TOF ≥ 0.9 in an average of two min or, at least, in five min in 95% of all treated patients. Incidence of adverse events was significantly higher in neostigmine treated patients. It is important to note, that no patient showed any sign of recurarization following every tested dose of the two reversal agents.

Quintessentially for any dose finding study is the statistical model to calculate the requested dose. The published dose finding studies for sugammadex used a mono-exponential approach with the recovery times in linear scale (de Boer 2007, p. 239; Groudine 2007, p. 555; Puhringer 2008, p. 188; Sorgenfrei 2006, p. 667; Sparr 2007, p. 935). This approach assumes that only one process, e.g. encapsulation of rocuronium, is responsible for the recovery 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 additionally analyzed bi-exponential models with the time to recovery of the TOF ratio to 0.9 (Δt) in linear or logarithmic scale as well as fractional polynomials consisting of one, two or more degrees (Royston 1994, p. 429). Our results confirmed the notion that a logarithmic scale may improve the fitting of the models because all models using the recovery times in logarithmic scale showed higher R^2_{adj} and more homogeneous variances at each dose fulfilling one of the assumptions of any regression analysis.

The decision which model fits the observed values best was performed based on the linear least square technique and an adjustment of R^2 in order to address the different number of free variables. An alternative approach the AIC criterion proposed by Akaike has the disadvantage that only models using the same type of values for the dependent variable can be compared (Akaike 1973, p. 267).

In addition to the highest correlation coefficient, the extrapolation of the model to high doses of the reversal agents influenced our decision which model fits best. The results obtained from the sugammadex dose finding study at reappearance of T2 (Sorgenfrei 2006, p. 667) suggest the existence of a dose that is able to reverse even deeper neuromuscular blocks than

the TOF of 0.5 within an average time of two min or in five min in 95% of the patients (Jones 2008, p. 816; Sorgenfrei 2006, p. 667). Accordingly, models that cannot estimate a respective dose are in contradiction to the published data and have to be rejected; in addition, such models do not reflect the observation of the 1 mg/kg and 0.5 mg/kg sugammadex subgroups of this investigation.

The three models with the highest adjusted R^2 and an estimate for the dose according to our endpoints were the mono-exponential, the bi-exponential, and the fractional polynomial with two degrees, all using the recovery times in logarithmic scale. Based on these models the dose to reverse a residual rocuronium-induced neuromuscular block at TOF = 0.5 with sugammadex is considered to be between 0.19 mg/kg and 0.22 mg/kg, resulting in a recommendation to test 0.25 mg/kg in a comparative study with a larger number of patients, expecting a recovery time of 1.7 min with a 95% tolerance interval of 0.7 min to 4.3 min.

In this study we did not observe any clinical or monitoring related sign of residual paralysis or re-curarization. This is important to note since we have tested doses between 0.0625 and 1.0 mg/kg sugammadex. Especially in the low dose sugammadex groups, one can assume that there are not enough sugammadex molecules present to encapsulate all rocuronium molecules expected to be in the patients' body at TOF 0.5. Accordingly, we must assume that – irrespectively of the complete recovery of the TOF ratio with doses below 1.0 mg/kg sugammadex – unbound rocuronium is still available (Bom 2002, p. 265; Robertson 2005, p. 4). In other words, fast recovery is not only caused by the encapsulation with sugammadex but also by the margin of safety of the neuromuscular transmission (Paton 1967, p. 59). Therefore, neuromuscular monitoring to control the sufficient reversal effect is mandatory, even when the suggested dose of 0.25 mg/kg is used at a TOF ratio of 0.5.

Analogously rigorous claims regarding the quality of reversal cannot be postulated as regards neostigmine, as that drug has neither the potential to withdraw muscle relaxants from neuromuscular cleft (owing to its indirect and therefore limited antagonism, (Bartkowski 1987, p. 594) nor an onset of action which merits expecting a recovery time averaging below 3 min (Calvey 1979, p. 149). In accordance, only one model was able to define a dose being able to reverse the neuromuscular function within an average of two min. As a result, it seems to be more relevant to base the primary endpoint upon a recovery to TOF > 0.9 of the 95% population within five min. Although a dose recommendation influenced by this decision still meets clinical needs, it marks another difference between the two study arms.

The three models with the highest adjusted R^2 of the neostigmine dose-response relationship were the same as for sugammadex: the mono-exponential model, the bi-exponential model, and the fractional polynomial model with two degrees, using recovery times in logarithmic scale. Based on these models and the knowledge about the onset time of neostigmine, the dose to reverse a residual rocuronium-induced neuromuscular block at TOF = 0.5 is considered between 34 µg/kg and 41 µg/kg, resulting in a recommendation to test 40 µg/kg in a comparative study with a larger number of patients, expecting a recovery time of 2.4 min with a 95% tolerance interval of 1.2 min to 4.6 min.

Less advanced accelerations of neuromuscular recovery have been defined for the secondary endpoint. Since 95% of the placebo treated patients recovered within 25 min there is still an acceleration of recovery of 15 min if reversal agents shorten the recovery time to 10 min. Based on the same criteria applied at the primary endpoint, the dose recommendations for a recovery between TOF 0.5 and 0.9 within an average of five min and an upper confidence limit of 10 min were found to be 10 µg/kg neostigmine and 0.1 mg/kg sugammadex, respectively. The recommended neostigmine dose is in accordance with the recent findings of Fuchs-Buder et al. who suggested 10-20 µg/kg to be sufficient for a reversal of a shallow atracurium-induced neuromuscular block, defined at a TOF ratio of 0.4 or 0.6 (Fuchs-Buder 2010, p. 34).

This study was neither designed nor powered to address any side effect comparisons. Due to safety issues, the side effects were documented and are presented descriptively. The number of patients showing at least one side effect following the study drug was significantly lower in the summarized sugammadex groups. With the exception of the higher incidence of bradycardia (heart rate < 40 beats/min) following neostigmine there was no systematic observation. The latter, however, is a well-known cholinergic side effect, which appeared even though neostigmine was administered as a premix with glycopyrronium (ratio 1:5). Bradycardia could be controlled in every patient with an additional dose of 0.2 mg glycopyrronium.

Interestingly, postoperative shivering was observed after neostigmine or sugammadex in respectively 18% and 25 % of patients, but not in the placebo treated patient and not in the low dose subgroups of neostigmine (5 µg/kg) and sugammadex (0.0625 mg/kg). Further investigation may be meaningful to elucidate whether an effective or fast reversal of neuromuscular blocking agents increases the risk of postoperative shivering.

This study represents a third degree of incomplete recovery from rocuronium-induced neuromuscular block. Deep block defined as PTC 1-2 (Groudine 2007, p. 555), moderate block defined as reappearance response of the second twitch following train-of-four stimulation (Sorgenfrei 2006, p. 667), and residual block at TOF = 0.5 as shown in this study require decreasing doses of sugammadex in order to achieve the same result, i.e. TOF > 0.9 within approximately two min. This relationship between depth of block and sugammadex demand in conjunction with the very fast onset of its reversal effect suggests that titration of sugammadex based on quantitative neuromuscular monitoring might be possible. Additional dose finding studies, e.g. at TOF = 0.2, may help to estimate the appropriate dose at a block between reappearance of T2 and TOF 0.5. Since we were able to identify an effective neostigmine dose at TOF 0.5 below the maximum recommended 70 µg/kg, it also appears reasonable to test neostigmine at lower TOF values, addressing the question at which TOF value the ceiling effect of neostigmine becomes relevant.

In conclusion, sugammadex 0.25 mg/kg and neostigmine 40 µg/kg effectively reverse a rocuronium-induced residual neuromuscular block of TOF 0.5 in a comparable manner.

5 Abstract

Introduction: Sugammadex is very effective to rapidly reverse moderate or deep rocuronium-induced neuromuscular blockade. However, the dosage of sugammadex to reverse residual neuromuscular block at the end of surgery (a phenomenon in clinical practice more widespread than the aforementioned) is still unknown. This study therefore compares the efficacy of sugammadex and neostigmine in various doses at a train-of-four (TOF) ratio of 0.5.

Methods: After IRB approval and written informed consent, 99 patients (ASA physical status I-III) aged between 18 and 65 years were anaesthetized with propofol, remifentanil, and rocuronium. Neuromuscular monitoring was performed by calibrated electromyography. At recovery of the TOF-ratio to 0.5, patients were randomized 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 µg/kg) or saline (n = 9 per group). The time between injection of the drug under study and TOF ≥ 0.9 was measured. Several mathematical models (mono-exponential, bi-exponential, and fractional polynomial) were tested in order to describe the data with the model that best fits the data using the recovery time in logarithmic or linear scale. The effective doses were calculated by interpolation of the regression models.

Results: 0.21 mg/kg sugammadex is able to reverse a TOF ratio of 0.5 to ≥ 0.9 at an average time of two min – and within five min for 95 % of patients in the best fitting model. 34 µg/kg neostigmine is able to reverse a TOF ratio of 0.5 to ≥ 0.9 within five minutes for 95 % of patients. No re-curarization was observed.

Conclusions: Sugammadex 0.25 mg/kg and neostigmine 40 µg/kg effectively reverse a rocuronium-induced residual neuromuscular block of TOF 0.5 in a comparable manner.

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