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

N. Kaufhold[1,‡], S. J. Schaller[1,*‡], C. G. Stäuble[1], E. Baumüller[1], K. Ulm[2], M. Blobner[1] and H. Fink[1]

[1]Klinik für Anaesthesiologie, and [2]Institut für Medizinische Statistik und Epidemiologie, Klinikum rechts der Isar, Technische Universität München, Ismaningerstraße 22, 81675 München, Germany

*Corresponding author: E-mail: s.schaller@tum.de

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

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‡ Both authors contributed equally to this work.
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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