

## Safety and tolerability of single intravenous doses of sugammadex administered simultaneously with rocuronium or vecuronium in healthy volunteers

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**Background.** Sugammadex rapidly reverses rocuronium- and vecuronium-induced neuromuscular block. To investigate the effect of combination of sugammadex and rocuronium or vecuronium on QT interval, it would be preferable to avoid the interference of anaesthesia. Therefore, this pilot study was performed to investigate the safety, tolerability, and plasma pharmacokinetics of single i.v. doses of sugammadex administered simultaneously with rocuronium or vecuronium to anaesthetized and non-anaesthetized healthy volunteers.

**Methods.** In this phase I study, 12 subjects were anaesthetized with propofol/remifentanyl and received sugammadex 16, 20, or 32 mg kg<sup>-1</sup> combined with rocuronium 1.2 mg kg<sup>-1</sup> or vecuronium 0.1 mg kg<sup>-1</sup>; four subjects were not anaesthetized and received sugammadex 32 mg kg<sup>-1</sup> with rocuronium 1.2 mg kg<sup>-1</sup> or vecuronium 0.1 mg kg<sup>-1</sup> (n=2 per treatment). Neuromuscular function was assessed by TOF-Watch<sup>®</sup> SX monitoring in anaesthetized subjects and by clinical tests in non-anaesthetized volunteers. Sugammadex, rocuronium, and vecuronium plasma concentrations were measured at several time points.

**Results.** No serious adverse events (AEs) were reported. Fourteen subjects reported 23 AEs after study drug administration. Episodes of mild headache, tiredness, cold feeling (application site), dry mouth, oral discomfort, nausea, increased aspartate aminotransferase and  $\gamma$ -glutamyl-transferase levels, and moderate injection site irritation were considered as possibly related to the study drug. The ECG and vital signs showed no clinically relevant changes. Rocuronium/vecuronium plasma concentrations declined faster than those of sugammadex.

**Conclusions.** Single-dose administration of sugammadex 16, 20, or 32 mg kg<sup>-1</sup> in combination with rocuronium 1.2 mg kg<sup>-1</sup> or vecuronium 0.1 mg kg<sup>-1</sup> was well tolerated with no clinical evidence of residual neuromuscular block, confirming that these combinations can safely be administered simultaneously to non-anaesthetized subjects. Rocuronium and vecuronium plasma concentrations decreased faster than those of sugammadex, reducing the theoretical risk of neuromuscular block developing over time.

*Br J Anaesth* 2008; **100**: 373–9

**Keywords:** antagonists neuromuscular block, sugammadex; neuromuscular blockade, rocuronium, vecuronium; pharmacokinetics, sugammadex, rocuronium, vecuronium; safety, drug, sugammadex, rocuronium, vecuronium

Accepted for publication: November 22, 2007

Sugammadex is a novel, modified,  $\gamma$ -cyclodextrin that encapsulates steroidal non-depolarizing neuromuscular blocking agents (NMBAs) such as rocuronium and vecuronium, thereby reversing neuromuscular block.<sup>1</sup> Although anti-muscarinic agents such as atropine or glycopyrrolate

are administered concomitantly with reversal agents such as neostigmine, edrophonium, and pyridostigmine, a drawback is the occurrence of cardiovascular effects, because acetylcholine persists longer in the synaptic cleft.<sup>2 3</sup> Because of its mode of action, sugammadex is not

associated with the cardiovascular side-effects associated with stimulation of muscarinic receptors.<sup>4</sup> Sugammadex is an effective and well-tolerated agent for the reversal of neuromuscular block.<sup>4–11</sup>

Many drugs used in anaesthesia may prolong the QT interval of the ECG. QTc prolongation may cause the development of cardiac arrhythmias, including torsade de pointes, which can degenerate into ventricular fibrillation, leading to sudden death. Therefore, a thorough QT study is required for any new clinical agent.<sup>12</sup> Sugammadex will always be administered after rocuronium or vecuronium in clinical practice; therefore, it is necessary to establish the effect on QTc of the combination of sugammadex with rocuronium or vecuronium. In order to avoid interference of anaesthetic agents or other concomitant medication such a study is to be performed in non-anaesthetized healthy volunteers. Before this can be safely performed in a large number of subjects, a smaller pilot study is necessary.

The primary objective of this study was to investigate the safety and tolerability of single i.v. doses of sugammadex administered simultaneously with rocuronium or vecuronium, first in anaesthetized and then in non-anaesthetized healthy volunteers. The secondary objective was to investigate the plasma pharmacokinetic profiles of sugammadex, rocuronium, and vecuronium. It was considered important to evaluate whether the molar ratios for sugammadex/rocuronium and sugammadex/vecuronium remain approximately the same after concomitant administration of the drugs.

## Methods

This was a single-centre, phase I, open-label study with three consecutive sugammadex treatment groups (I, II, and III). Healthy male and female volunteers aged 18–45 yr and with a BMI of 18–30 kg m<sup>-2</sup> were eligible for study entry if they fulfilled the following inclusion criteria: were in a good, age-appropriate healthy condition as established by medical history, physical examination, ECG, and results of biochemistry, haematology, and urinalysis testing in the 3 weeks before administration of study drugs; were normotensive (diastolic arterial pressure <90 mm Hg and systolic arterial pressure <140 mm Hg) and had a heart rate within the range 50–90 beats min<sup>-1</sup> at screening. Pregnant or breast-feeding women, female subjects of childbearing potential not using a reliable method of birth control, subjects with a history of difficult intubation or for whom a difficult intubation was expected, and those with a (family) history of malignant hyperthermia or who were known or suspected to have an allergy to neuromuscular blocking agents or other drugs used during general anaesthesia were excluded from the study. Additional exclusion criteria were: a history of, or ongoing abuse of, drugs or alcohol; positive hepatitis A, B, or C test results; positive test results on HIV serology; positive drug or alcohol screen. The ingestion of any drugs other than those

specified in the protocol, and intake of alcohol, food and drink containing caffeine and other methylxanthines, or strenuous physical exercise were not allowed in the 24–48 h before administration of the study drugs and until after collection of the last blood sample for pharmacokinetic analysis. Smoking was prohibited during the entire period of institutionalization.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice and applicable regulatory requirements. The ethics committee at the Onze Lieve Vrouw Clinic, Aalst, Belgium, approved the study, and written informed consent was obtained from each subject.

## Treatment and study procedures

Group I subjects ( $n=6$ ) were anaesthetized and received sugammadex 16, 20, or 32 mg kg<sup>-1</sup> in combination with rocuronium 1.2 mg kg<sup>-1</sup>, with two subjects assigned to each sugammadex dose. The higher doses were administered before the lower doses. The second subject of each treatment group received sugammadex at least 2 h after the first subject. Sugammadex 20 mg kg<sup>-1</sup> was only administered if there was no evidence of neuromuscular block or any other major safety concerns in the sugammadex 32 mg kg<sup>-1</sup> group. Evidence of neuromuscular block was concluded if three consecutive, normalized  $T_4/T_1$  ratios (15 s apart) were <0.9, with a consistent decrease in  $T_1$ – $T_4$ . Similarly, sugammadex 16 mg kg<sup>-1</sup> was only administered if there was no evidence of neuromuscular block or any other major safety concerns in the sugammadex 20 mg kg<sup>-1</sup> group. After completion of the Group I administration schedule, Group II treatment, comprising decreasing doses of sugammadex (32, 20, or 16 mg kg<sup>-1</sup>) in combination with vecuronium 0.1 mg kg<sup>-1</sup>, was administered to anaesthetized subjects ( $n=6$ ) using the same procedure as for Group I. The Group III treatment schedule ( $n=4$ ) was initiated after completion of Group II treatment. In Group III, subjects received sugammadex 32 mg kg<sup>-1</sup> in combination with either rocuronium 1.2 mg kg<sup>-1</sup> or vecuronium 0.1 mg kg<sup>-1</sup> without anaesthesia, provided this was considered safe based on the safety results of Groups I and II. Although subjects in Group III were not anaesthetized, they were treated in the same operating room setting as subjects in Groups I and II and remained under observation for at least 2 h after dosing.

Subjects in Groups I and II were pre-oxygenated with oxygen 100% for 5 min. Anaesthesia was induced with i.v. remifentanyl (GlaxoSmithKline, Genval, Belgium) 0.15–0.25 µg kg<sup>-1</sup> min<sup>-1</sup> and propofol (Astra-Zeneca, Destelbergen, Belgium) 3–4 µg ml<sup>-1</sup> target-controlled infusion (Diprifusor<sup>TM</sup>, Astra-Zeneca) until loss of eyelash reflex. Hartmann's solution (B. Braun Melsungen AG, Melsungen, Germany) was also administered i.v. at a rate of 1 ml kg<sup>-1</sup> h<sup>-1</sup> to compensate for fasting and to allow

the administration of rescue medication, if required. A laryngeal mask airway was inserted and subjects were ventilated to normocapnia with an air-oxygen mixture. Maintenance of anaesthesia was with remifentanyl and propofol infusion. The dose of remifentanyl was guided by patient haemodynamics and was changed in steps of  $0.1 \mu\text{g kg}^{-1} \text{ min}^{-1}$  in response to variations in systolic arterial pressure of 20 mm Hg.

For subjects in all groups (I, II, and III), a twincath multilumen peripheral catheter (Arrow International Inc., Reading, PA, USA) was inserted in the opposite forearm to that used for the administration of propofol and remifentanyl. This catheter allowed administration of sugammadex and rocuronium or vecuronium by two separate, distinct, non-communicating lumens, thus preventing drug mixing within the catheter. Sugammadex and rocuronium or vecuronium were administered simultaneously at the specified doses, over a fixed time period of 4 min using an infusion pump.

Because of the possibility of neuromuscular block occurring, laryngeal mask airway ventilation and anaesthesia were continued for a minimum of 120 min after the administration of study medication; propofol and remifentanyl were stopped, provided that TOF values were  $>0.9$  during the previous 10 min. Neuromuscular monitoring was stopped at recovery from anaesthesia; assessment of post-anaesthetic recovery was conducted by the anaesthetist.

### *Safety assessments*

In Groups I and II, neuromuscular function was monitored by acceleromyography using the TOF-Watch<sup>®</sup> SX (Organon Ireland Ltd, Dublin, Ireland) with repetitive TOF nerve stimulation applied every 15 s to the ulnar nerve. This was started after the induction of anaesthesia but before the administration of sugammadex and rocuronium or vecuronium, and was continued until recovery from anaesthesia. Stabilization and calibration of the TOF-Watch<sup>®</sup> SX was undertaken in the operating theatre after the induction of anaesthesia. Neuromuscular data were collected using the TOF-Watch<sup>®</sup> SX Monitoring Programme. Before administration of study drugs to the non-anaesthetized subjects in Group III, a baseline clinical evaluation of neuromuscular function was performed. This comprised an evaluation of: ability to smile, swallow and speak; appearance of general weakness; sustained head-lift for 5 s; leg lift; hand grip; and sustained tongue depressor test. After drug administration, these tests were repeated every 2 min during the first 10 min, every 5 min during the next 10 min, and thereafter every 15 min until transfer to the recovery ward, where the clinical tests were repeated on arrival and before discharge.

All subjects were continuously monitored for 8 h after drug administration by clinical staff and any adverse

events (AEs) or serious AEs (SAEs), including clinical evidence of neuromuscular block, were recorded by the investigator. AEs were complaints or symptoms which were either new or that had increased in intensity. An SAE was defined as any untoward medical occurrence that at any dose: resulted in death; was life-threatening; required in-patient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity or in a congenital anomaly/birth defect. Pulse oximetry was monitored before induction of anaesthesia and for 8 h after dosing. Blood and urine samples were collected for safety analysis (haematology, biochemistry, and urinalysis) at screening, at pre-dose, at 6 h after dosing on day 1, and at follow-up (at least 3 days after dosing). Arterial pressure and heart rate were measured at screening, admission, pre-dose at stable anaesthesia, at 5, 10, and 30 min after drug administration and at follow-up. Safety ECGs (12-lead) were performed at screening and follow-up, and cardiac monitoring was started before the administration of study drug on day 1 and stopped approximately 4 h after dosing.

### *Pharmacokinetic assessments*

A total of six 5 ml blood samples were collected from each subject, before drug administration and at 30 min and 1, 2, 4, and 8 h post-dose, for the determination of sugammadex, rocuronium, and vecuronium plasma concentrations. Drug plasma concentrations were determined by the Department of Clinical Pharmacology and Kinetics, N.V. Organon, The Netherlands, using validated liquid chromatographic assay methods with mass spectrometric detection.<sup>13</sup> The lower limits of quantification were 2, 6 ng ml<sup>-1</sup>, and  $0.1 \mu\text{g ml}^{-1}$  for rocuronium, vecuronium, and sugammadex, respectively.

The assays were carried out in full compliance with Good Laboratory Practice regulations. The assay methods used to determine the drug plasma concentrations did not discriminate between complexed (sugammadex–rocuronium or –vecuronium complexes) and non-complexed sugammadex and rocuronium or vecuronium because the complexes dissociate on the liquid chromatography column.<sup>13</sup> Thus, the concentrations in plasma reported in this study pertain to total plasma sugammadex, rocuronium, and vecuronium. The molar ratios for sugammadex/rocuronium and sugammadex/vecuronium, defined as the plasma concentration of sugammadex on a molar basis divided by the plasma concentration of either rocuronium or vecuronium, on a molar basis, were determined.

No statistical tests were planned; therefore, no sample size calculations were performed. Two subjects per group/treatment combination were considered sufficient to conclude that it is safe to simultaneously administer sugammadex  $32 \text{ mg kg}^{-1}$  and rocuronium  $1.2 \text{ mg kg}^{-1}$  or vecuronium  $0.1 \text{ mg kg}^{-1}$  to a large group of

non-anaesthetized subjects, on the condition that no relevant safety and tolerability problems were observed.

## Results

Sixteen subjects (10 males and six females, age 18–43 yr) were enrolled in the study (Group I,  $n=6$ ; Group II,  $n=6$ ; Group III,  $n=4$ ). There were no premature discontinuations from the study and all subjects completed the trial according to the protocol (Table 1).

No SAEs occurred during this trial and none of the subjects discontinued the trial because of an AE. All but two subjects experienced at least one AE after study drug administration (in total 23 AEs); however, most of the AEs were mild or moderate in nature and all resolved by the end of the study. One severe AE, severe tiredness for 1 h, was reported in a subject in Group I, 3 h after administration of sugammadex 20 mg kg<sup>-1</sup> and rocuronium 1.2 mg kg<sup>-1</sup>; however, the relation of the AE to the study drug was considered unlikely by the investigator. Four male and two female subjects reported nine AEs which were at least possibly related to the study drug (Table 2). With the exception of moderate injection site irritation, all drug-related AEs were of mild intensity, and with the exception of mild nausea, which occurred on day 3, they all developed on day 1. More than half of the AEs reported were in Group III.

There was no evidence of neuromuscular block in Group I and II subjects before, during, or after dosing. In Group III, neuromuscular function tests showed no abnormalities. With one exception, there were no abnormalities in oxygen saturation. In one subject, oxygen saturation monitoring was stopped 2 h earlier than planned because the subject wanted to sleep. The oxygen saturation of this subject was always 99%.

No abnormal physical examination findings were observed at screening or during the study period. There were no markedly abnormal vital signs during the trial, except for a 10 min period of moderate hypotension in a Group II female subject which occurred 25 min after administration of sugammadex 16 mg kg<sup>-1</sup> and vecuronium 0.1 mg kg<sup>-1</sup>. The investigator considered it unlikely that this event was related to the study drug, but rather a consequence of a deep level of anaesthesia.

**Table 1** Baseline characteristics [values are expressed as mean (range) or mean (SD)]. BMI, body mass index; SD, standard deviation

	Group I ( $n=6$ )	Group II ( $n=6$ )	Group III ( $n=4$ )
Age (yr)	27.3 (24–38)	28.7 (18–43)	28.3 (21–37)
Male:female ( $n$ )	4:2	3:3	3:1
Weight (kg)	70.7 (10.6)	72.1 (17.0)	77.5 (5.4)
Height (cm)	175 (9.3)	176 (11.3)	178 (8.8)
BMI (kg m <sup>-2</sup> )	23.1 (3.2)	23.1 (3.1)	24.5 (0.8)

**Table 2** Adverse events judged as at least possibly related to administration of sugammadex

Adverse event	Subject number	Sugammadex dose group	Intensity
Headache	1	Group I; sugammadex 32 mg kg <sup>-1</sup> and rocuronium 1.2 mg kg <sup>-1</sup>	Mild
Nausea	5	Group I; sugammadex 16 mg kg <sup>-1</sup> and rocuronium 1.2 mg kg <sup>-1</sup>	Mild
Increased aspartate aminotransferase	9	Group II; sugammadex 20 mg kg <sup>-1</sup> and vecuronium 0.1 mg kg <sup>-1</sup>	Mild
Increased $\gamma$ -glutamyltransferase	9	Group II; sugammadex 20 mg kg <sup>-1</sup> and vecuronium 0.1 mg kg <sup>-1</sup>	Mild
Injection site irritation	13	Group III; sugammadex 32 mg kg <sup>-1</sup> and rocuronium 1.2 mg kg <sup>-1</sup>	Moderate
Tiredness	13	Group III; sugammadex 32 mg kg <sup>-1</sup> and rocuronium 1.2 mg kg <sup>-1</sup>	Mild
Cold feeling at application site	15	Group III; sugammadex 32 mg kg <sup>-1</sup> and vecuronium 0.1 mg kg <sup>-1</sup>	Mild
Dry mouth	15	Group III; sugammadex 32 mg kg <sup>-1</sup> and vecuronium 0.1 mg kg <sup>-1</sup>	Mild
Oral discomfort	16	Group III; sugammadex 32 mg kg <sup>-1</sup> and vecuronium 0.1 mg kg <sup>-1</sup>	Mild

Individual relevant changes in heart rate from pre-dose to 30 min after dosing were not observed, except for a subject with a decrease in heart rate from 64 beats min<sup>-1</sup> pre-dose to 49 beats min<sup>-1</sup> 5 min after administration of sugammadex 16 mg kg<sup>-1</sup> with vecuronium 0.1 mg kg<sup>-1</sup>; however, at 10 and 30 min after dosing, the heart rate was within the normal range (50 and 62 beats min<sup>-1</sup>, respectively). None of the other subjects showed markedly abnormal heart rate values. All ECGs were normal, with the exception of one which showed a left axis deviation at follow-up, 7 days after administration of sugammadex 20 mg kg<sup>-1</sup> with vecuronium 0.1 mg kg<sup>-1</sup>; however, this was considered as clinically insignificant. Individual relevant changes in biochemistry parameters were only observed in one subject (Group II). In this subject, clinically significant increases in aspartate aminotransferase (ASAT) and  $\gamma$ -glutamyltransferase ( $\gamma$ -GT) levels were reported 6 h after administration of sugammadex 20 mg kg<sup>-1</sup> with vecuronium 0.1 mg kg<sup>-1</sup>; these increases were considered to be possibly related to study drug and reported as mild AEs. At screening and pre-dose, values for these two measures were within the normal range (ASAT: 10–37 U litre<sup>-1</sup>;  $\gamma$ -GT: 10–66 U litre<sup>-1</sup>). On day 1, ASAT levels increased from 21 U litre<sup>-1</sup> pre-dose to 54 U litre<sup>-1</sup> post-dose but were within the normal range at an additional assessment on day 2 (26 U litre<sup>-1</sup>).  $\gamma$ -GT increased from 22 U litre<sup>-1</sup> pre-dose to 73 U litre<sup>-1</sup> post-dose on day 1 but was again within the normal range on day 2 (63 U litre<sup>-1</sup>).



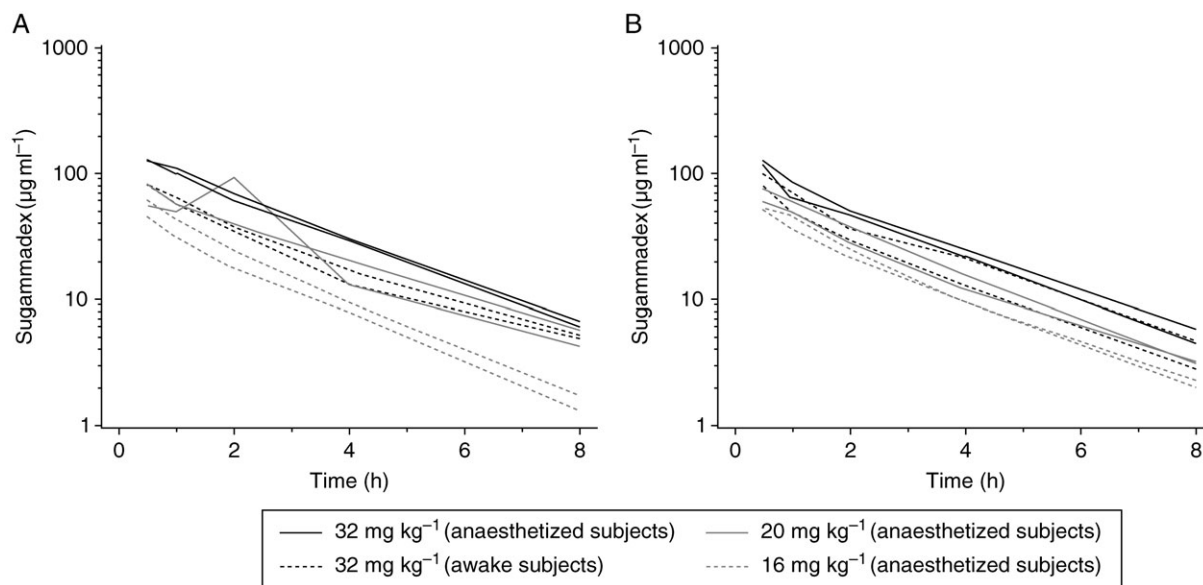
### Pharmacokinetics

The plasma concentrations of rocuronium and vecuronium appeared to decrease more rapidly with time than the plasma concentrations of sugammadex (Figs 1 and 2). This was reflected in an increase in the molar ratios for sugammadex/rocuronium and sugammadex/vecuronium with time in all subjects. The molar ratio of sugammadex/vecuronium showed a steeper increase than the molar ratio sugammadex/

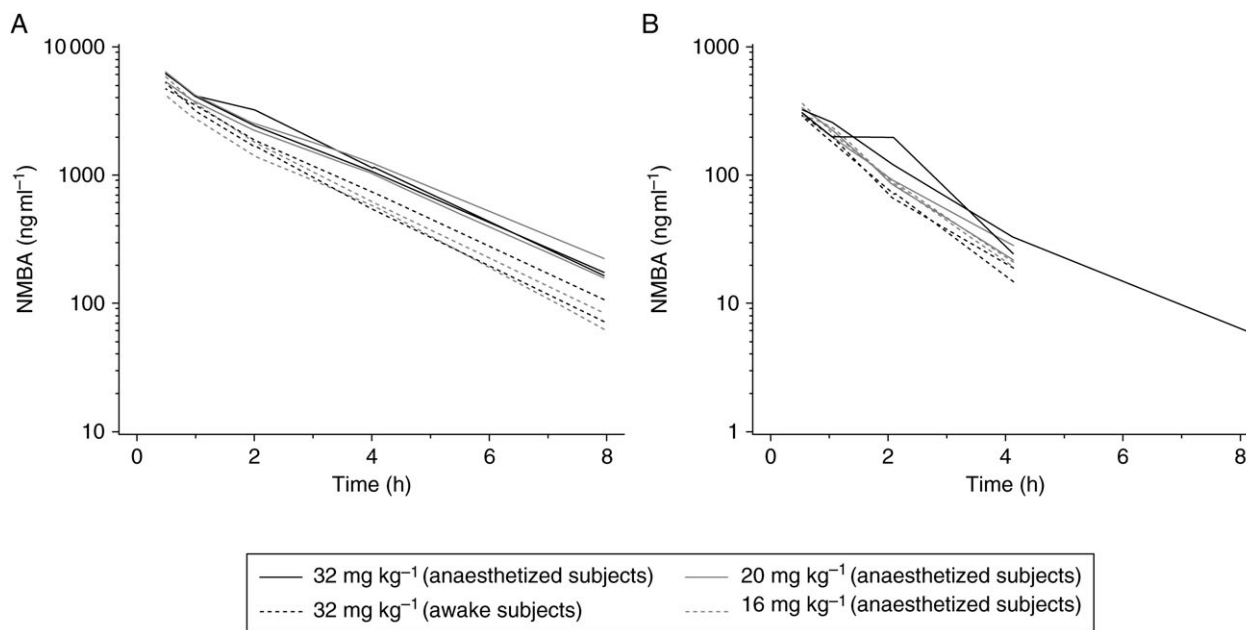
rocuronium, indicating that the vecuronium concentration decreased more rapidly than the rocuronium concentration (Fig. 3).

### Discussion

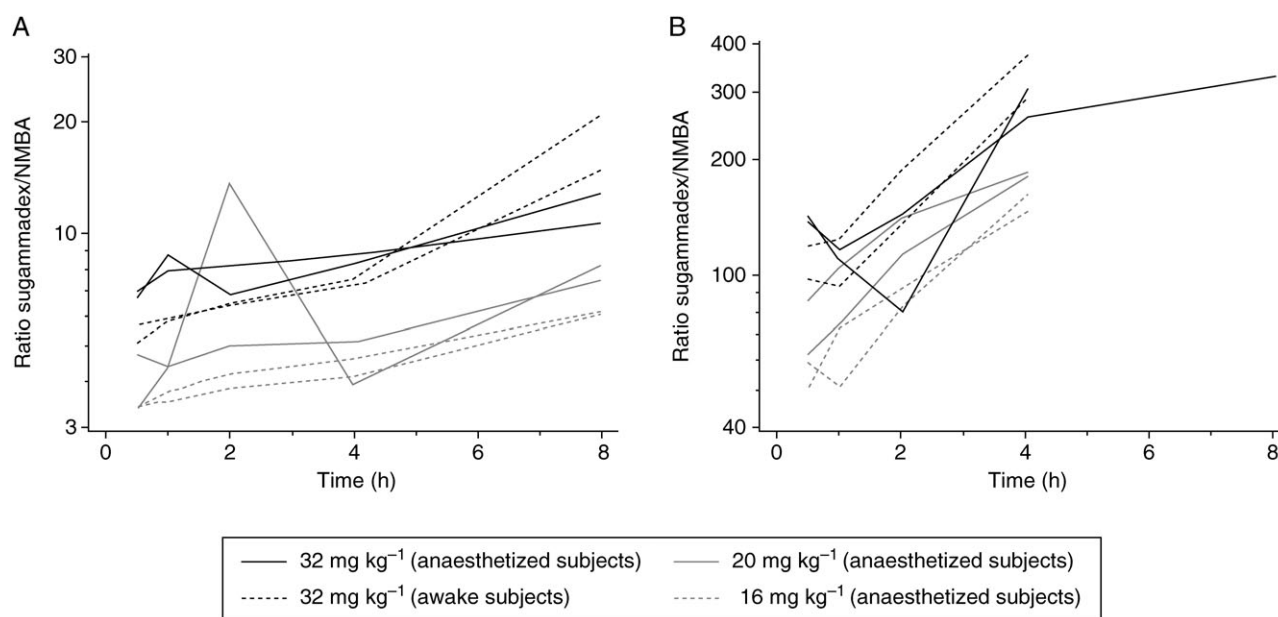
In our study, single i.v. doses of sugammadex up to  $32 \text{ mg kg}^{-1}$ , given simultaneously with rocuronium or vecuronium, were well tolerated and associated with minimal



**Fig 1** Semi log plots of plasma concentrations of sugammadex vs time after simultaneous administration with rocuronium  $1.2 \text{ mg kg}^{-1}$  (A) or vecuronium  $0.1 \text{ mg kg}^{-1}$  (B).



**Fig 2** Semi log plots of plasma concentrations of rocuronium  $1.2 \text{ mg kg}^{-1}$  (A) or vecuronium  $0.1 \text{ mg kg}^{-1}$  (B) vs time after simultaneous administration with sugammadex. NMBA, neuromuscular blocking agent.



**Fig 3** Molar ratios (ratio of concentrations in moles) of sugammadex/rocuronium (A) and sugammadex/vecuronium (B) vs time after simultaneous administration. NMBA, neuromuscular blocking agent.

side-effects in 16 human volunteers. In anaesthetized subjects, the sugammadex dose was reduced from 32 to 20 mg kg<sup>-1</sup> and then to 16 mg kg<sup>-1</sup>. Importantly, no signs of neuromuscular block were observed even with relatively low sugammadex/rocuronium and sugammadex/vecuronium molar concentration ratios. As mixing of sugammadex with rocuronium or vecuronium occurred in the vein, this procedure precluded the development of symptoms of rocuronium- or vecuronium-induced neuromuscular block. Furthermore, no major safety or tolerability issues were observed in the subjects who received sugammadex 32 mg kg<sup>-1</sup> with rocuronium 1.2 mg kg<sup>-1</sup> or sugammadex 32 mg kg<sup>-1</sup> with vecuronium 0.1 mg kg<sup>-1</sup> without anaesthesia.

This phase I study was conducted as a precursor to a large thorough QTc study designed to investigate the effect of sugammadex in combination with rocuronium or vecuronium on the QTc interval in a large group of healthy volunteers without anaesthesia. In this subsequent study, sugammadex will be administered at a supra-therapeutic dose of 32 mg kg<sup>-1</sup>. Selection of this dose is based on the ICH guidelines for the conduct of studies to assess the potential of a drug to cause QT interval prolongation.<sup>12</sup> Selection of the 32 mg kg<sup>-1</sup> dose is also based on the fact that sugammadex is not metabolized, is excreted via the kidneys<sup>5</sup> and that the only drugs likely to affect exposure to sugammadex would be those that interfere with the glomerular filtration and renal elimination rate. The findings from the present study suggest that it would be safe to administer sugammadex 32 mg kg<sup>-1</sup> in combination with rocuronium 1.2 mg kg<sup>-1</sup> or vecuronium 0.1 mg kg<sup>-1</sup> without anaesthesia to volunteers in a QTc study.

A rocuronium dose of 1.2 mg kg<sup>-1</sup> was selected for our phase I pilot study because this is the highest dose used in clinical practice and which is recommended for and used in practice for rapid sequence induction. As a consequence, the concentrations of rocuronium and sugammadex evaluated in combination were the highest that could potentially be achieved in the patient population. In clinical practice, combination concentrations would be lower because sugammadex would be administered at a time point at which part of the rocuronium dose has already been cleared. The molar ratio of sugammadex 32 mg kg<sup>-1</sup> and rocuronium 1.2 mg kg<sup>-1</sup> would be 8:1, which is expected to be safe based on results from animal studies (unpublished data; N.V. Organon, The Netherlands).

An analogous approach was used to select the dose of vecuronium (0.1 mg kg<sup>-1</sup>) to be used in our study and again, in clinical practice, combination concentrations would be lower. The molar ratio of sugammadex 32 mg kg<sup>-1</sup> and vecuronium 0.1 mg kg<sup>-1</sup> would be 102:1; a higher molar ratio is needed for vecuronium because of the six- to 12-fold higher potency of vecuronium relative to rocuronium and because it has a three-fold lower affinity for sugammadex. The free acid of sugammadex (active entity) has a molecular weight (MW) of 2002. Rocuronium bromide has a MW of 610, and vecuronium bromide has a MW of 638. Thus, if rocuronium is administered at a dose of 1.2 mg kg<sup>-1</sup>, an equimolar dose of sugammadex would be 3.9 mg kg<sup>-1</sup> (a ratio of 3.3:1).

After simultaneous administration of sugammadex with rocuronium or vecuronium, NMBA plasma concentrations appeared to decline consistently faster than those of sugammadex and the ratio of sugammadex:NMBA showed a consistent increase over time in all subjects (Fig. 3). If

sugammadex persists longer in plasma than rocuronium or vecuronium, recurarization is unlikely. The molar ratio increased more steeply for vecuronium than for rocuronium. For both NMBAs, there was one apparent outlying ratio value. In each case, this was caused by one outlying concentration value for either sugammadex or vecuronium. No explanation could be found for these outlying concentrations. The faster elimination of vecuronium compared with rocuronium is in agreement with the fact that vecuronium has a shorter half-life than rocuronium.

In conclusion, single-dose administration of sugammadex 16, 20, or 32 mg kg<sup>-1</sup> in combination with rocuronium 1.2 mg kg<sup>-1</sup> or vecuronium 0.1 mg kg<sup>-1</sup> was well tolerated with no clinical evidence of neuromuscular block, confirming that these combinations can be safely administered simultaneously to non-anaesthetized subjects. Rocuronium and vecuronium plasma concentrations decreased faster than those of sugammadex, further reducing the theoretical risk of neuromuscular block developing over time.

## Acknowledgements

Editorial assistance was provided by Julie Adkins (BPharm, MSc) at Prime Medica Ltd (Knutsford, Cheshire, UK) during the preparation of this paper, supported by N.V. Organon. The design and conduct of the study, as well as analysis of the study data and opinions, conclusions, and interpretation of the data, were the responsibility of the authors. P.J.D.K., P.A.M.P., and J.M.W.S. are employees of N.V. Organon, Oss, The Netherlands.

## Funding

Financial support was provided by: N.V. Organon, Oss, The Netherlands.

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