Clin Drug Investig (2013) 33:545–551
DOI 10.1007/s40261-013-0095-8

ORIGINAL RESEARCH ARTICLE

Effect of Sugammadex on QT/QTc Interval Prolongation when Combined with QTc-Prolonging Sevoflurane or Propofol Anaesthesia

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Published online: 4 July 2013

Abstract

Background We evaluated the potential for QT/corrected QT (QTc) interval prolongation after sugammadex given with propofol or sevoflurane anaesthesia.

Methods This was a two-factorial, randomized, parallel-group study in 132 healthy subjects. Anaesthesia was maintained with sevoflurane or propofol. At ~20 min following sevoflurane/propofol initiation, sugammadex 4 mg/kg or placebo was administered. Neuromuscular blocking agents were not administered. Electrocardiograms were recorded regularly. The primary variable was the time-matched mean difference in the Fridericia-corrected QT interval (QTcF) change from baseline for sugammadex versus placebo when combined with propofol or sevoflurane. No relevant QTcF prolongation was concluded if the upper one-sided 95 % confidence interval (CI) was below the 10 ms margin of regulatory non-inferiority, up to 30 min post-study drug. Blood samples were taken for pharmacokinetic analysis. An exploratory analysis evaluated potential QT/QTc effects of neostigmine 50 μg/kg/glycopyrrolate 10 μg/kg in combination with propofol.

Results The estimated mean QTcF differences between sugammadex and placebo ranged from −2.4 to 0.6 ms when combined with either anaesthetic. The largest upper one-sided 95 % CI for the mean QTcF difference between sugammadex and placebo was 2 ms, occurring 2 min post-dosing. Propofol and sevoflurane resulted in mean QTcF increases exceeding 10 and 30 ms, respectively. On top of these prolongations, the effect of sugammadex was negligible at all timepoints. The mean peak sugammadex concentration was 66.5 μg/mL, with exposure similar in the sevoflurane/propofol groups. The mean QTcF changes from baseline following neostigmine/glycopyrrolate in 10 healthy subjects ranged between −1.4 and 3.6 ms.

Conclusion Sugammadex 4 mg/kg does not cause clinically relevant QTc interval prolongation versus placebo when combined with propofol or sevoflurane.

Electronic supplementary material The online version of this article (doi:10.1007/s40261-013-0095-8) contains supplementary material, which is available to authorized users.

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1 Introduction

The selective relaxant binding agent sugammadex (Bridion®; Merck Sharp & Dohme Corp., Oss, The Netherlands) is a modified γ-cyclodextrin which reverses the effects of the steroidal neuromuscular blocking agents (NMBAs) rocuronium bromide and vecuronium bromide by encapsulation [1–3]. Sugammadex has been shown to be well tolerated and to

provide complete and rapid reversal of both rocuronium bromide- and vecuronium bromide-induced moderate and deep neuromuscular blockade (NMB) [4–7], and is currently approved for use in >70 countries.

Prolongation of the QT/corrected QT (QTc) interval on the electrocardiogram (ECG) has been reported following anaesthesia with both inhalational and intravenous agents [8–10], and is particularly common following sevoflurane [11, 12]. This effect can be a concern, as QT or QTc interval prolongation may lead to an increased risk of cardiac arrhythmias, including the potentially fatal *torsades de pointes*.

It has previously been demonstrated that sugammadex is not associated with QTc prolongation of regulatory non-inferiority when administered alone [13, 14] or in combination with rocuronium bromide and vecuronium bromide [13]. For the first time, this study evaluated the potential for QT/QTc prolongation after sugammadex 4 mg/kg compared with placebo, when given in combination with propofol or sevoflurane maintenance anaesthesia in healthy subjects.

An additional, exploratory analysis was added to evaluate potential QT/QTc effects of neostigmine 50 μg/kg plus glycopyrrolate 10 μg/kg in combination with propofol in healthy subjects.

2 Methods

2.1 Main Study

The main study (sponsor protocol number P06315; the study protocol is accessible as Electronic Supplementary Material) had a two-factorial, randomized, placebo-controlled, parallel-group design, in 132 subjects, and was double-blind for administration of sugammadex versus placebo with single-blind administration of the anaesthetic agents sevoflurane or propofol. The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies.

Healthy, non-pregnant subjects aged 18–55 years with a body mass index of 18–32 kg/m^2, a normal 12-lead ECG and no family history of QT/QTc interval prolongation or any QT-prolonging risk factor at baseline were included. Premenopausal females were required to use an acceptable form of contraception. Subjects were excluded if they had a history of risk factors for *torsades de pointes* or life-threatening ventricular arrhythmia; had any surgical or medical condition that might significantly alter the absorption, distribution, metabolism or excretion of any drug; or had demonstrated allergic reactions affecting their ability to participate in the study or previous unexplained hypersensitivity reactions or anaphylaxis of any cause. All subjects were required to provide written, informed consent.

Anaesthesia was induced with an intravenous propofol target-controlled infusion of 2–6 μg/mL, using Schneider's pharmacokinetic model [15]. After pre-oxygenation with 100 % oxygen, subjects received a laryngeal mask airway and were ventilated to normocapnia with an air–oxygen mixture. Anaesthesia was maintained according to a 1:1 randomization ratio with either sevoflurane (1.5 minimum alveolar concentration) or propofol 4 μg/mL. At ~20 min following maintenance anaesthetic administration, either sugammadex 4 mg/kg or placebo was administered according to randomization (1:1). Anaesthesia was maintained up to at least 35 min after sugammadex or placebo administration.

Continuous 12-lead ECGs were recorded for 8 h; monitoring started ~2 h before induction of anaesthesia and continued until ~6 h thereafter. ECGs were extracted in triplicate at pre-defined time points: before anaesthesia induction; before the start of maintenance anaesthesia and before sugammadex or placebo administration; and at 2, 5, 15, 30 and 120 min after sugammadex or placebo administration. The extracted data were analysed by the central ECG laboratory, according to the protocol.

In the primary safety analysis, the time-matched mean differences in the change of the pre-specified primary Fridericia-corrected QT interval (QTcF) from baseline for the sugammadex group versus the placebo group were evaluated for all time points up to 30 min post-study drug administration for the two anaesthetic groups combined. The pre-defined criterion was that no clinically relevant QTcF prolongation associated with sugammadex would be concluded if the upper limit of the one-sided 95 % confidence interval (CI) for the time-matched mean difference in the QTcF change from baseline compared with placebo (on top of background propofol or sevoflurane anaesthesia) was below the margin of 10 ms, specified by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E14 guidelines, at all analysed time points up to 30 min post-study drug administration [16]. In accordance with the ICH-E14 Guidelines, similar QTc evaluations were performed using Bazett's correction (QTcB).

Additional safety evaluations included adverse events (AEs), physical examination, vital signs and clinical laboratory evaluations.

Blood samples were taken pre- and post-anaesthesia at the same time points as the scheduled ECG assessments following sugammadex or placebo administration, for pharmacokinetic analysis.

2.1.1 Statistical Analysis

A sample size of 120 subjects (30 per treatment arm) was considered sufficient to achieve a power of ≥90 % to support the primary objectives of this study. Assuming that

up to 10 % of subjects would not have evaluable ECG recordings, a total of 132 subjects were randomized and treated.

The primary QTc analysis was performed for all treated subjects who had an evaluable pre-dose ECG and at least one evaluable post-dose sugammadex/placebo ECG (the full-analysis set). The safety analysis was performed for all subjects who received sugammadex/placebo (the all-subjects-treated group).

An analysis of covariance (ANCOVA) model was used to analyse changes in the QTc interval from baseline (pre-sugammadex/placebo administration) at each time point, with the factors anaesthetic (propofol or sevoflurane), treatment (sugammadex or placebo), sex, site and baseline QTc measurement as covariates to estimate the difference between sugammadex and placebo in the change of QTcF.

As a key sensitivity analysis, the effect of sugammadex treatment was evaluated per anaesthetic separately. If the interaction term between the factor for anaesthetic and sugammadex was statistically significant at the 0.05 level for at least one of the time points, the results for sugammadex versus placebo were to be analysed via separate ANCOVAs on the propofol and sevoflurane arms. If the upper limits of the one-sided 95 % CIs for QTcF changes were <10 ms for all in-treatment assessments for both anaesthetics separately, then it would also be concluded that sugammadex when combined with propofol or sevoflurane maintenance treatment does not clinically prolong the QTc interval.

Pharmacokinetic analysis was performed for the all-subjects-pharmacokinetically evaluable (ASPE) group.

2.2 Study Extension

The exploratory extension to assess the effect of neostigmine/glycopyrrolate on the QTc interval started after randomization and treatment of the subjects in the main study, and was performed in 10 healthy subjects at one clinical site.

Anaesthesia was induced and maintained with propofol. At ~20 min following induction of anaesthesia, neostigmine 50 μg/kg plus glycopyrrolate 10 μg/kg was administered, in an open-label manner.

Summary statistics and 95 % CIs were calculated for the QTcF and QTcB changes from baseline following neostigmine administration and reported separately from the main study.

3 Results

In the main study, all 132 randomized subjects (aged 18–55 years) completed the study. The exploratory extension included five male and five female subjects between the ages of 18 and 52 years. Baseline characteristics for both parts of the study are presented in Table 1.

3.1 Main Study

3.1.1 QTc Interval

Estimated differences of time-matched changes from baseline between sugammadex and placebo ranged from −2.4 to 0.6 ms when combined with either propofol or sevoflurane anaesthesia up to 30 min after treatment (Fig. 1). The upper limit of the one-sided 95 % CI of the maximum estimated mean QTcF difference from placebo was 2.0 ms, thus well below the pre-specified 10 ms margin (Fig. 1).

Maintenance anaesthesia resulted in strong QTc interval prolongations, with mean QTcF increases exceeding 10 ms for propofol and exceeding 30 ms for sevoflurane when compared with pre-anaesthetic values (Fig. 2). QTcF rapidly returned to baseline levels in both the sugammadex and placebo groups following the discontinuation of anaesthesia from 35 min onwards (Fig. 2). On top of the QTcF prolongations induced by anaesthesia, the effect of sugammadex was negligible at all time points when considering both anaesthetics combined (Fig. 1), as well as for propofol and sevoflurane separately (Fig. 3).

The QTcB-estimated mean differences between sugammadex and placebo, and the corresponding upper one-sided 95 % CI, were similar to those for QTcF, with estimated differences between sugammadex and placebo for the time-matched change from baseline up to 30 min after administration ranging from −2.0 ms to 0.8 ms when combined with either propofol or sevoflurane anaesthesia.

There was no overall increase in the ventricular rate in the sugammadex group compared with the placebo group. The incidence of QTcF values between 450 and 480 ms was higher during maintenance anaesthesia with sevoflurane than during maintenance with propofol, but similar between the sugammadex and placebo arms, and incidental QTcF values above 480 or 500 ms were observed with sevoflurane.

3.1.2 Safety

Sugammadex was generally well tolerated, with 11 subjects in the sevoflurane group and 12 subjects in the propofol group experiencing AEs of mild intensity and only one subject experiencing an AE of moderate intensity (in the sevoflurane group). Only one AE was considered possibly related to sugammadex (dysgeusia of mild intensity, reported in the sugammadex/sevoflurane group, which occurred 17 min after sevoflurane maintenance anesthesia was stopped [and 52 min after sugammadex administration]). The most frequently reported AEs in all treatment groups

Table 1 Baseline characteristics (all-subjects-treated group)

Main study					Extension
Variable	Propofol/ sugammadex ($n = 31$)	Propofol/ placebo ($n = 33$)	Sevoflurane/ sugammadex ($n = 34$)	Sevoflurane/ placebo ($n = 34$)	Propofol/ neostigmine ($n = 10$)
Sex [*n* (%)]					
Female	16 (52)	18 (55)	18 (53)	19 (56)	5 (50)
Male	15 (48)	15 (45)	16 (47)	15 (44)	5 (50)
Race [*n* (%)]					
White	30 (97)	32 (97)	33 (97)	32 (94)	10 (100)
Non-white	1 (3)	1 (3)	1 (3)	2 (6)	0
Age [years; mean (SD)]	34.5 (10.1)	33.0 (11.3)	34.3 (10.2)	34.0 (11.7)	32.6 (10.9)
Weight [kg; mean (SD)]	70.9 (9.6)	70.9 (12.8)	71.2 (12.9)	69.8 (13.3)	63.0 (7.0)
BMI [kg/m^2; mean (SD)]	24.4 (2.9)	23.4 (2.9)	24.0 (3.0)	23.8 (2.9)	21.9 (1.4)

BMI body mass index, *SD* standard deviation

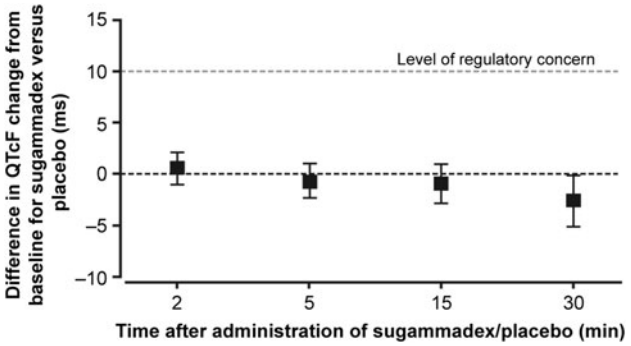

Fig. 1 Estimated mean difference (with two-sided 90 % confidence interval) between sugammadex and placebo in the time-matched Fridericia-corrected QT interval (QTcF) change from baseline (pre-sugammadex/placebo administration) [anaesthetic groups combined, $n = 132$]

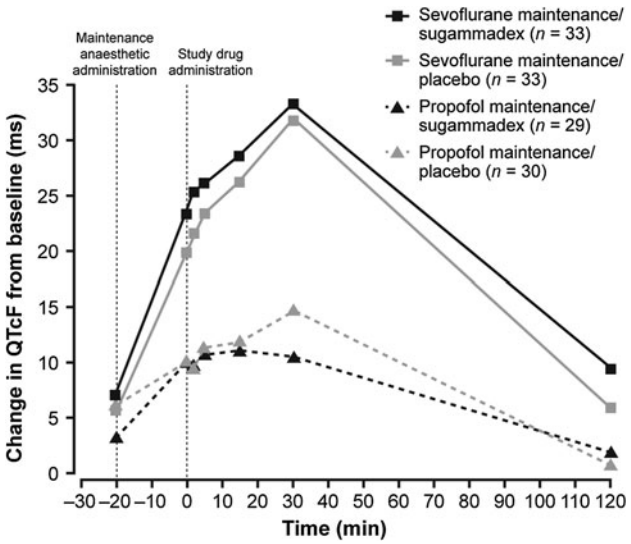

Fig. 2 Change in the Fridericia-corrected QT interval (QTcF) from baseline (pre-administration of propofol for induction) according to study drug and maintenance anaesthetic administration (patients with an electrocardiogram reading at baseline and with at least one post-baseline reading are included)

were headache and oropharyngeal pain (Table 2). There were no serious or severe AEs reported. Although some abnormally high and low values for blood chemistry, haematology and urinalysis parameters were noted, none were considered clinically relevant, with the exception of elevated triglyceride levels in one subject (receiving sevoflurane/placebo), who also had elevated triglycerides before receiving study treatment, and one case of hyperbilirubinaemia (in a subject receiving sevoflurane/sugammadex). Vital signs remained within the range observed for healthy subjects. For four subjects, an ECG or safety ECG finding was reported as an AE; these were two cases with a prolonged QTcF or QTcB interval on day 1 or day 2 (in the sevoflurane/placebo group), one with a prolonged PR interval on day 2 (in the propofol/sugammadex group) and one with a prolonged QTcB interval on day 7 (in the sevoflurane/sugammadex group), respectively. Apart from these AEs, no clinically relevant ECG findings were observed.

3.1.3 *Pharmacokinetics*

One subject from the sevoflurane/sugammadex group was excluded from the ASPE group because blood samples were unavailable at two of the specified time points. The ASPE group thus consisted of 31 subjects in the propofol/sugammadex group and 33 subjects in the sevoflurane/sugammadex group.

Plasma concentrations of sugammadex up to 2 h after dosing are shown in Fig. 4. The overall mean peak sugammadex concentration was 66.5 μg/mL (at the 2-min time

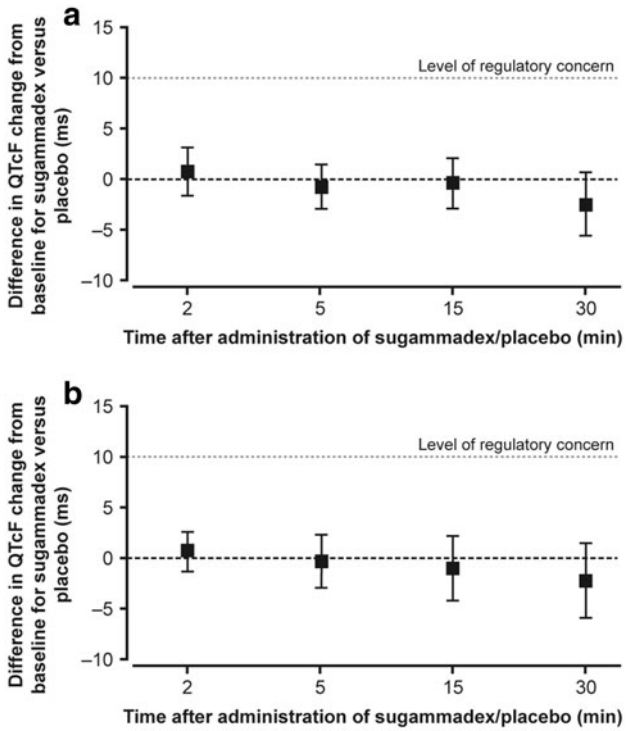

Fig. 3 Estimated mean difference (with two-sided 90 % confidence interval) between sugammadex and placebo in the Fridericia-corrected QT interval (QTcF) change from baseline (pre-study drug administration): **a** propofol group ($n = 64$); **b** sevoflurane group ($n = 68$)

point). Exposure to sugammadex was similar in the sevoflurane and propofol groups (Fig. 4).

3.2 Study Extension

Mean QTcF changes from baseline following neostigmine given on top of propofol ranged between −1.4 and 3.6 ms over 30 min post-administration, while mean QTcB prolongations ranged from 5.3 ms (30 min post-neostigmine plus glycopyrrolate) to 9.6 ms (5 min post-neostigmine plus glycopyrrolate). There was a concomitant increase in the mean ventricular rate ranging from 2.5 beats per min [bpm] (1 min post-neostigmine) to 10.7 bpm (5 min post-neostigmine plus glycopyrrolate).

AEs were reported for three subjects following neostigmine administration (one case each of headache, nasopharyngitis and oropharyngeal pain, respectively), but none were considered drug-related.

No clinically significant changes in laboratory or haematological parameters, vital signs, or local safety ECGs were observed.

4 Discussion

As sugammadex is generally administered in the presence of QTc-prolonging anaesthetics, it was considered relevant

Table 2 Subjects with any adverse event (AE) and AEs occurring in at least 5 % of subjects in any group (all-subjects-treated group)

Main study					Extension
Variable	Propofol/ sugammadex ($n = 31$)	Propofol/ placebo ($n = 33$)	Sevoflurane/ sugammadex ($n = 34$)	Sevoflurane/ placebo ($n = 34$)	Propofol/ neostigmine ($n = 10$)
Subjects with any AE [*n* (%)]	12 (39)	12 (36)	12 (35)	23 (68)	3 (30)
Headache [*n* (%)]	5 (16)	3 (9)	7 (21)	18 (53)	1 (10)
Oropharyngeal pain [*n* (%)]	4 (13)	8 (24)	5 (15)	4 (12)	1 (10)
Nausea [*n* (%)]	0	0	2 (6)	2 (6)	0
Diarrhoea [*n* (%)]	1 (3)	2 (6)	0	0	0
Nasopharyngitis [*n* (%)]	1 (3)	2 (6)	0	0	1 (10)
Electrocardiogram QT prolonged [*n* (%)]	0	0	1 (3)	2 (6)	0
Hypotension [*n* (%)]	0	1 (3)	0	2 (6)	0
Back pain [*n* (%)]	0	0	2 (6)	0	0
Somnolence [*n* (%)]	2 (6)	0	0	0	0

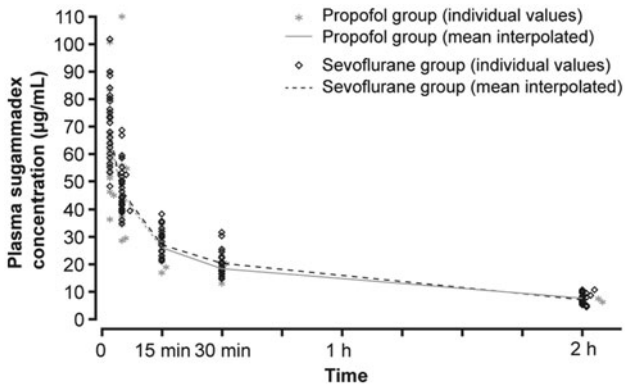

Fig. 4 Mean and individual plasma concentrations of sugammadex 4 mg/kg up to 2 h after dosing (all-subjects-pharmacokinetically evaluable group)

to evaluate the effects of sugammadex on top of anaesthetics on the QTc interval. The current study was designed to evaluate the potential interaction between sugammadex and the anaesthetics propofol and sevoflurane on the QT/QTc interval, implementing elements of the ICH-E14 guidance. The results of this study demonstrate the absence of clinically relevant QTc interval prolongation with sugammadex 4 mg/kg on top of background propofol or sevoflurane anaesthesia in healthy anaesthetized subjects. Estimated mean differences in time-matched QTcF changes from baseline between sugammadex and placebo ranged from −2.4 to 0.6 ms up to 30 min after treatment when combined with either anaesthetic. Moreover, the upper limit of the one-sided 95 % CI of the maximum estimated mean QTcF difference from placebo was 2.0 ms, lying well below the pre-specified 10 ms margin of regulatory non-inferiority [16].

The absence of relevant QT/QTc prolongation after sugammadex treatment is in agreement with two thorough QTc studies in which sugammadex was assessed without concomitant anaesthesia. In these studies, sugammadex at doses of up to 32 mg/kg alone [13, 14] or in combination with rocuronium bromide or vecuronium bromide [13] was not associated with clinically relevant QTc prolongation. Importantly, the lack of QTcF and QTcB prolongation of sugammadex when combined with propofol and sevoflurane in the current study was demonstrated in the presence of relevant QTc prolongations caused by the anaesthetics themselves (exceeding 10 and 30 ms for propofol and sevoflurane, respectively). These extensive QTc effects of propofol and sevoflurane were comparable to those reported in the literature [8–12].

While a 'real-world' clinical study setting with patients of a broad age range and with various comorbidities and concomitant medications is often desirable, a healthy volunteer setting was selected for this study so that the effects of sugammadex and the anaesthetic agents could be evaluated without potentially confounding QT/QTc prolonging factors, such as intubation, extubation, certain surgical conditions and perioperative co-administration of other drugs.

In current clinical practice, neostigmine is commonly administered for reversal of moderate NMB, in combination with atropine or glycopyrrolate to counteract any muscarinic effects. However, administration of neostigmine with glycopyrrolate has been shown to result in mean QTcB interval prolongations of up to 30 ms [17]. Additionally, the depth of NMB may impact upon the heart rate. For example, administration of neostigmine with atropine at deep levels of NMB may result in a greater increase in the heart rate than when the blockade is shallower [18]. It has been suggested, therefore, that anticholinergic drug combinations should be avoided in patients with cardiovascular disease [17, 19].

We examined the impact of neostigmine on top of propofol on QTc prolongation as an exploratory extension to the current study. The mean QTcF interval prolongations after the combination of neostigmine 50 µg/kg plus glycopyrrolate 10 µg/kg did not exceed 5 ms in the 10 healthy subjects who were investigated, and thus did not reproduce the extensive findings by Saarnivaara and Simola [17] of neostigmine on QTc prolongation. However, it must be pointed out that in the neostigmine-treated subjects in the present study, QTcB appeared to result in an overestimation of QTc effects, with mean QTcB increases of up to 10 ms observed in the presence of a mean ventricular rate increase ranging from 2.5 to 10.7 bpm. Overcorrection of the QT interval due to increases in the heart rate is not an uncommon finding when using the Bazett QT correction method [20]. A recent study evaluating ECG changes following neostigmine together with atropine also found no significant QT/QTc prolongations, although statistically significant increases in the PR interval were reported [21]. Of note, in contrast to the study extension findings with neostigmine, there was no overall increase in the ventricular rate in the sugammadex group compared with the placebo group in the present study.

Sugammadex was found to be generally well tolerated in combination with both sevoflurane and propofol, with very few differences in the type and intensity of AEs observed when compared with the placebo group.

5 Conclusions

Sugammadex 4 mg/kg did not cause clinically relevant QTc interval prolongation compared with placebo on top of background propofol or sevoflurane maintenance anaesthesia in healthy subjects. Maintenance anaesthesia with propofol or sevoflurane resulted in mean QTcF prolongations

(compared with pre-anaesthesia) exceeding 10 and 30 ms, respectively. Moreover, sugammadex was generally well tolerated in combination with sevoflurane or propofol.

The results of the exploratory part of this study suggest mean QTcF interval prolongations not exceeding 5 ms after treatment with neostigmine (50 μg/kg) plus glycopyrrolate (10 μg/kg) in healthy propofol-anaesthetized subjects.

Acknowledgments Pieter-Jan de Kam and Justin Dennie are employees of Merck Sharp & Dohme Corp. (Whitehouse Station, NJ, USA). Peter Grobara, Marjan LF Jagt-Smook and Michiel W van den Heuvel are employees of MSD (Oss, The Netherlands). Employees of Merck Sharp & Dohme Corp. and MSD may potentially own stock and/or hold stock options in the company. Pierre AM Peeters and Rob JW Berg were formerly employees of MSD. Guy Cammu has received lecture fees from MSD and research grants for funded work on sugammadex from MSD. Pierre Peeters received stocks from MSD during his time of employment by them. Steven Ramael is an employee of SGS Life Science Services (Antwerp, Belgium), and his institution received funding for the current study from MSD. Medical writing support was provided by Melanie More of Prime Medica Ltd (Knutsford, Cheshire, UK). This assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Whitehouse Station, NJ, USA). This study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Whitehouse Station, NJ, USA). Support with ECG analysis was provided by Biomedical Systems [BMS] (St Louis, MO, USA), with logistical support from BMS in Brussels, Belgium. The design and conduct of the study, as well as the analysis of the study data and opinions, conclusions, and interpretation of the data, were the responsibility of the authors.

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