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Sugammadex hypersensitivity and underlying mechanisms: a randomised study of healthy non-anaesthetised volunteers

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Abstract

Background: We investigated potential for hypersensitivity reactions after repeated sugammadex administration and explored the mechanism of hypersensitivity.

Methods: In this double-blind, placebo-controlled study (NCT00988065), 448 healthy volunteers were randomised to one of three arms to receive three repeat i.v. administrations of either sugammadex 4 mg kg^{-1}, 16 mg kg^{-1}, or placebo. Primary endpoint was percentage of subjects with hypersensitivity (assessed by an independent adjudication committee). Secondary endpoint of anaphylaxis was classified per Sampson and Brighton criteria. Exploratory endpoints included skin testing, serum tryptase, anti-sugammadex antibodies [immunoglobulin (Ig) E/IgG], and other immunologic parameters.

Results: Hypersensitivity was adjudicated for 1/148 (0.7%), 7/150 (4.7%), and 0/150 (0.0%) subjects after sugammadex 4 mg kg^{-1}, 16 mg kg^{-1}, and placebo, respectively. After sugammadex 16 mg kg^{-1}, one subject met Sampson criterion 1 and Brighton level 1 (highest certainty) anaphylaxis criteria; two met Brighton level 2 criteria. After database lock it was determined that certain protocol deviations could have introduced bias in the reporting of hypersensitivity signs/symptoms in a subject subset. Objective laboratory investigations indicated that potential underlying hypersensitivity mechanisms were unlikely to have been activated; the results suggest that most of the observed hypersensitivity reactions were unlikely IgE/IgG-mediated.

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Conclusion: Dose-dependent hypersensitivity or anaphylaxis reactions to sugammadex were observed when administered without prior neuromuscular blocking agent. Laboratory investigations do not suggest prevalent allergen-specific IgE/IgG-mediated immunologic hypersensitivity. Because it could not be fully excluded that estimates of hypersensitivity/anaphylaxis incidence were unbiased, an additional study was conducted to characterise the potential for hypersensitivity reactions and is described in a companion report.
Clinical trial registration: http://www.clinicaltrials.gov NCT00988065; Protocol number P06042.

Keywords: anaphylaxis; hypersensitivity; sugammadex

Editor's key points

- Hypersensitivity in response to sugammadex administration can occur, but it is not known whether or not the incidence is dose-dependent.
- In a double-blind, placebo-controlled study, 448 healthy volunteers were randomised to receive three repeat i.v. administrations of either sugammadex 4 mg kg^{-1}, 16 mg kg^{-1}, or placebo.
- Hypersensitivity or anaphylaxis reactions to sugammadex were dose-dependent when sugammadex was administered without previous administration of a neuromuscular blocking agent.

Drug hypersensitivity is an uncommon, often unpredictable, and potentially serious medical problem in the operating room. With concomitant administration of multiple drugs, the culprit may be difficult to identify. Furthermore, presentation is highly variable, and mechanisms behind drug hypersensitivity can be allergic or non-allergic.

Sugammadex is a cyclodextrin derivative approved for reversal of neuromuscular block (NMB) induced by rocuronium or vecuronium. Safety data collected from more than 50 clinical studies including more than 600 healthy volunteers and 3000 surgical patients, together with reports from general use, indicate that sugammadex is generally well tolerated.[1,2] However, a low incidence of suspected hypersensitivity has been observed in studies on non-anaesthetised healthy volunteers and surgical patients.[3,4] The events in these studies were reported as not severe nor serious, and were self-limiting. Hypersensitivity events and rare reports of anaphylaxis/anaphylactic shock have been reported in clinical, post-market use; these were generally manageable in the operating room,[5–12] with rates conservatively estimated as comparable with background incidence in the perioperative setting.

Therefore, this study was conducted to better understand specific signs/symptoms of hypersensitivity in the absence of potentially confounding factors present under operating room conditions during surgery and to inform on the potential of sugammadex to induce hypersensitivity at different doses [4 mg kg^{-1} (highest routine reversal dose) or 16 mg kg^{-1} (recommended dose for immediate reversal in emergency situations)] and with sequential exposure, relative to placebo. The underlying mechanism of any hypersensitivity reaction was further explored.

Methods

Study design

This randomised, double-blind, parallel-group, placebo-controlled, multicentre study (Protocol number P06042; ClinicalTrials.gov identifier: NCT00988065) was conducted in healthy volunteers at four centres in Germany, the Netherlands, the UK, and the USA between August 24, 2009 and April 13, 2010 (Supplementary Material, Fig. S1). Written informed consent was obtained from all participating subjects. The study was conducted in accordance with principles of Good Clinical Practice and approved by appropriate institutional review boards and regulatory agencies.

All subjects received single-blind placebo on Day 1. Subjects without suspect hypersensitivity signs/symptoms were randomised 1:1:1 on Day 8 according to a computer-generated randomisation schedule (prepared for each clinical site separately, with each subject assigned a unique randomised number) to treatment with sugammadex 4 mg kg^{-1}, 16 mg kg^{-1}, or placebo (normal saline). Subjects received three repeat double-blind i.v. bolus administrations (one injection per dose period) of their assigned treatment during Weeks 1, 5, and 11. A follow-up visit was scheduled 1 week later (Week 12). Administrations were spaced $\geq$4 weeks apart to allow sufficient time for sensitisation to occur should the hypersensitivity signs/symptoms be secondary to sugammadex-induced immunoglobulin (Ig)E-mediated hypersensitivity reactions. Blinding was to be maintained by covering syringes so that the light colour difference between sugammadex and placebo was not revealed; the investigator evaluating adverse events was not to be involved in study drug administration.

Study subjects

Non-pregnant, non-breastfeeding healthy subjects aged 18–55 yr were included. Exclusion criteria are listed in Supplementary Material.

Hypersensitivity/anaphylaxis adjudication

Suspected hypersensitivity signs/symptoms were systematically scored by the investigator based on a pre-determined list, which could be extended as needed (Supplementary Material, Table S1), and submitted to an independent blinded external Adjudication Committee (AC). The AC assessed whether the constellation of signs/symptoms could be classified as hypersensitivity while blinded to subject, visit number, and treatment. If a hypersensitivity reaction was confirmed, the AC

assessed whether it fulfilled anaphylaxis criteria as described by Sampson and colleagues[13] criterion 1, by the Brighton Collaboration Anaphylaxis Working Group,[14] or both (Table 1). The Sampson criteria for anaphylaxis were determined by a meeting of the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network; these criteria are generally accepted as the definition of anaphylaxis. The Sampson criterion 1 is limited to reactions in which the affected subject is not known to be allergic to the potential allergen.[13] The Brighton Collaboration Anaphylaxis Working Group also defined anaphylaxis, taking the approach of using a list of defined terms of major and minor criteria with a scoring system and three levels of diagnostic certainty with a focus on analysis of patient records, with level 1 representing the highest level of anaphylaxis certainty. Both methods were used in this study to ensure all potential cases of anaphylaxis would be identified.

Safety endpoints

The primary safety endpoint was the number/percentage of subjects with adjudicated hypersensitivity signs/symptoms for each study drug administration. The key secondary endpoint was the number/percentage of subjects with adjudicated anaphylaxis according to Sampson criteria (Table 1). Other safety parameters included number/percentage of subjects by level of certainty of anaphylaxis according to Brighton criteria, and changes over time in frequency/severity of adjudicated hypersensitivity symptoms by study drug administration. All subjects were admitted to Phase 1 research units for monitoring during the study. Investigators were trained in recognising and recording hypersensitivity signs/symptoms and instructed on how to act in the event of severe hypersensitivity signs/symptoms. To ensure subject safety, full resuscitative equipment and rescue treatment, including epinephrine and antihistamine, were available at each participating study centre during the trial. Additional safety assessments included repeated assessment of vital signs, ECGs, adverse events (including hypersensitivity symptoms), physical examination, haematology, and blood chemistry examinations, including tryptase. An external Data Safety Monitoring Committee reviewed data, monitoring subject safety during the conduct of the study.

Post-study review of protocol deviations

After database lock and study completion, it was determined that certain protocol deviations could have introduced bias

Table 1 Scoring of anaphylaxis according to the Sampson[13] and Brighton criteria.[14] For the purposes of adjudication, sugammadex was not considered a known or likely allergen for a healthy subject and categories 2 and 3 of the Sampson definition of anaphylaxis (not shown in table) were not considered applicable according to the Adjudication Committee. PEF, peak expiratory flow

Sampson criteria

Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g. generalised hives, pruritus or flushing, swollen lips/tongue/uvula) **and at least one of the following:**

Respiratory compromise (e.g. dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

Reduced BP or associated symptoms of end-organ dysfunction [e.g. hypotonia (collapse), syncope, incontinence]

Major Brighton criteria		**Minor Brighton criteria**	
Dermatologic or mucosal	Generalised urticaria (hives) or generalised erythema Angioedema, localised or generalised Generalised pruritus with skin rash	Dermatologic or mucosal	Generalised pruritus without skin rash Generalised prickle sensation Localised injection site urticaria Red and itchy eyes
Cardiovascular	Hypotension Clinical diagnosis of uncompensated shock, indicated by the combination of at least three of the following: – tachycardia – capillary refill time >3 s – reduced central pulse volume – decreased or loss of consciousness	Cardiovascular	Reduced peripheral circulation as indicated by the combination of at least two of: – tachycardia – capillary refill time of >3 s without hypotension – decreased level of consciousness
Respiratory	Bilateral wheeze (bronchospasm) Stridor Upper airway swelling (lip, tongue, throat, uvula, or larynx) Respiratory distress – 2 or more of the following: – tachypnoea – recession – cyanosis – increased use of accessory respiratory muscles (sternocleidomastoid, intercostals, etc.) – grunting	Respiratory	Persistent dry cough Hoarse voice Difficulty breathing without wheeze or stridor Sensation of throat closure Sneezing, rhinorrhoea
		Gastrointestinal	Diarrhoea Abdominal pain Nausea Vomiting
		Laboratory	Mast cell tryptase elevation > upper normal limit

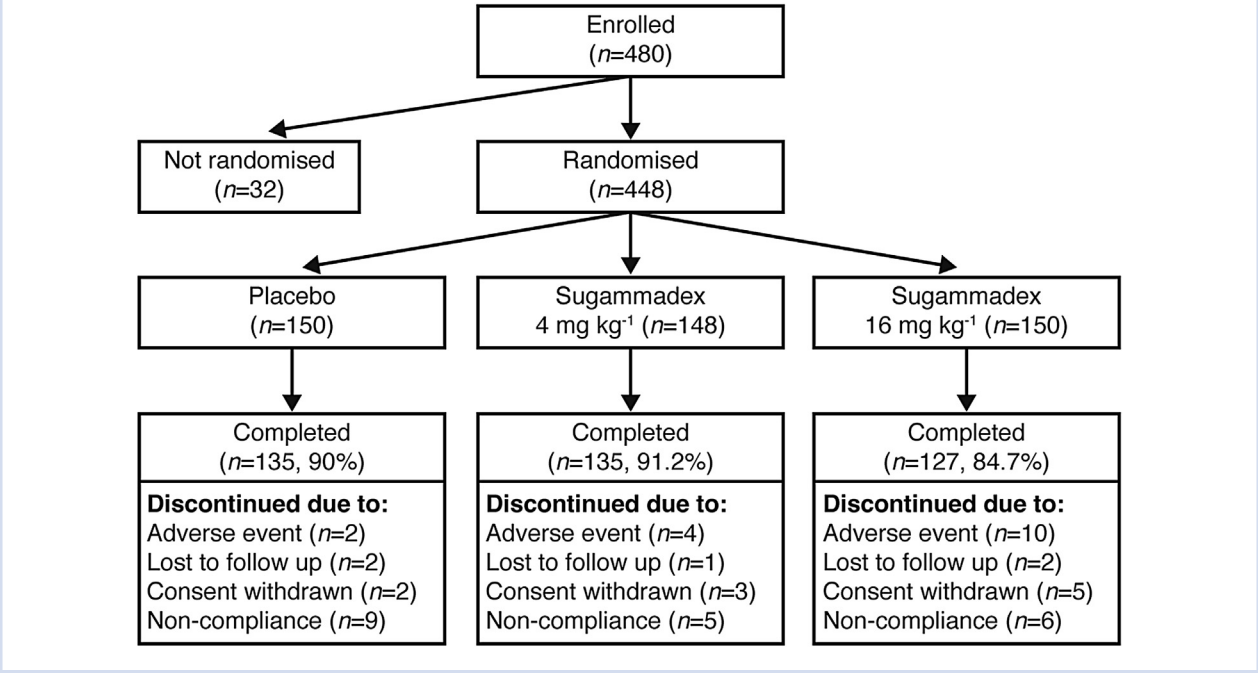

Fig 1. Disposition of subjects. Of 10 subjects who discontinued treatment after experiencing suspected hypersensitivity signs/symptoms, seven were from the sugammadex 16 mg kg^{-1} group (six of the seven subjects had adjudicated hypersensitivity), two were from the sugammadex 4 mg kg^{-1} group (neither of these two subjects had adjudicated hypersensitivity), and one was from the placebo group (this subject did not have adjudicated hypersensitivity).

into the reporting of hypersensitivity signs/symptoms in a subset of subjects. Subsequently, an extensive review of documentation was undertaken at all study sites revealing that most of the protocol deviations mainly involved documentation issues and were generally assessed as likely to have little impact upon the primary study results. However, there were deviations which had the potential to affect blinding of safety assessors and thereby introduce bias in the collection of hypersensitivity signs, symptoms, or both in a subset of subjects: (i) at one site with 129 subjects, some staff members who assisted the pharmacist with the preparation of blinded medication doses also interacted with subjects in the acquisition of vital signs and adverse events; (ii) for 199 subjects, the safety assessor was not different from the person administering the study drug, although the study drug was administered using a masked syringe. These deviations were unlikely to affect the objectively measured exploratory biomarkers in the identified cases of hypersensitivity.

Given the number of cases involved, an additional dedicated hypersensitivity study was conducted (www.clinicaltrials.gov NCT02028065), described in an accompanying manuscript, to characterise the incidence and potential for sugammadex to induce hypersensitivity reaction.

Exploratory mechanistic research

Tryptase

Tryptase concentrations were measured in subjects with suspected hypersensitivity to help assess mast cell response and activation. Blood sampling was performed before dosing and 1 h after administration of study drug, at screening and the follow-up visit. For subjects with suspected hypersensitivity signs/symptoms, additional blood samples were collected 3, 6, and 24 h after onset of suspected event. Tryptase was measured by the Phadia UniCAP assay (Phadia AB, Uppsala, Sweden) (reference values for healthy subjects: geometric mean of 3.8 μg l^{-1} and upper 95th percentile of 11.4 μg l^{-1}). Quest Diagnostics (San Juan Capistrano, CA, USA) was used as the central laboratory.

Anti-sugammadex antibodies

A sugammadex-specific antibody assay was developed (Supplementary Material, Methods). Samples were collected before each administration of study drug and 24 h, 14 days, and 28 days after onset of signs/symptoms. Samples were centrally analysed for subjects with adjudicated hypersensitivity, and for a subset of 94 subjects without suspected hypersensitivity signs/symptoms.

Skin testing

Skin-prick testing (SPT) and intradermal testing (IDT) were performed in triplicate for subjects with adjudicated hypersensitivity signs/symptoms. Skin reactivity was assessed using negative (saline) and positive (histamine) controls. For SPT, ascending concentrations of 0.1, 1, 10, and 100 mg ml^{-1} sugammadex were applied. IDT used ascending concentrations of 0.01, 0.1, 1, and 10 mg ml^{-1} sugammadex; IDT was administered to subjects with no response to sugammadex SPT. Skin tests were performed approximately 4–6 weeks after sugammadex exposure. The first 175 subjects without

hypersensitivity signs/symptoms were skin tested after the first administration. Further details are provided in Supplementary Materials, Methods.

Basophil histamine release

Basophil histamine release testing was performed by RefLab ApS (Copenhagen, Denmark), as previously described (Supplementary Material, Methods),[15] for subjects with adjudicated hypersensitivity and an equal number of age-, sex-, and clinical site-matched subjects without adjudicated hypersensitivity.

Additional exploratory mechanistic endpoints

Blood samples for additional assessment of potential hypersensitivity mechanisms were obtained pre-dose, 2 and 10 min, and 1, 3, and 6 h after dosing of study medication for all subjects and additionally 24 h, 14 days, and 28 days after onset of signs/symptoms of hypersensitivity (Supplementary Material, Methods).

Statistical analysis

A sample size of 450 randomised subjects (150 per treatment arm) was considered sufficient to obtain an indication of the number/percentage of subjects with adjudicated hypersensitivity/anaphylaxis symptoms, resulting in half-width of 95% confidence interval (CI) for a single group of 2.2–4.8% if the empirical percentages of subjects with hypersensitivity symptoms were between 2% and 10%.

Analysis was performed for the all-subjects-treated group, which comprised all subjects who were randomised and subsequently received blinded study medication. For the primary and key secondary safety endpoints, the percentage (95% CI) of subjects with adjudicated hypersensitivity symptoms was calculated by treatment group. For each of the two sugammadex doses, the difference *vs* placebo in overall incidence of subjects with adjudicated hypersensitivity symptoms was also calculated together with the two-sided 95% CI using the method of Miettinen and Nurminen.[16] For other safety parameters, data were summarised using descriptive statistics.

Results

Patient disposition and baseline characteristics

In total, 480 subjects received single-blind placebo on Day 1 (Fig. 1); 448 were randomised. Baseline characteristics were similar between groups (Table 2). Overall, 397 (89%) randomised subjects received their three scheduled administrations of study drug and completed the Week 12 follow-up visit. More subjects in the sugammadex 16 mg kg^{-1} treatment group discontinued because of adverse events compared with those in the placebo and sugammadex 4 mg kg^{-1} treatment groups.

Hypersensitivity analysis

Placebo treatment group

No subject in the placebo group had adjudicated hypersensitivity.

Sugammadex 4 mg kg^{-1} treatment group

Hypersensitivity was adjudicated for one (0.7%) subject who experienced moderate, mild-to-moderate, and no hypersensitivity symptoms after the first, second, and third administration, respectively (Fig. 2a). All observed signs appeared within 10 min of sugammadex administration and resolved within 5 h without treatment. Compared with placebo, the mean (95% CI) difference in rate of subjects with adjudicated hypersensitivity after sugammadex 4 mg kg^{-1} was 0.7% (−1.8, 3.7%).

Table 2 Summary of patient and baseline characteristics within and across treatment groups. SD, standard deviation

Characteristic		Treatment group			Total (*n*=448)
		Placebo (*n*=150)	Sugammadex 4 mg kg^{-1} (*n*=148)	Sugammadex 16 mg kg^{-1} (*n*=150)	
Age (yr)	*n*	150	148	150	448
	Mean (SD)	33.8 (10.8)	34.4 (10.6)	33.2 (10.2)	33.8 (10.5)
	Median	32.0	33.0	30.5	32.0
	Range	18–55	18–55	18–58	18–58
BMI (kg m^{-2})	*n*	150	147	150	447
	Mean (SD)	25.08 (3.43)	24.44 (3.20)	24.93 (3.41)	24.82 (3.35)
	Median	24.65	24.00	24.40	24.30
	Range	19.0–32.4	19.4–31.8	18.6–31.9	18.6–32.4
Sex, *n* (%)	Female	75 (50)	70 (47)	73 (49)	218 (49)
	Male	75 (50)	78 (53)	77 (51)	230 (51)
Race, *n* (%)	Asian	4 (3)	4 (3)	2 (1)	10 (2)
	Black/African American	6 (4)	9 (6)	10 (7)	25 (6)
	White	135 (90)	133 (90)	133 (89)	401 (90)
	Multiracial	5 (3)	2 (1)	5 (3)	12 (3)
Ethnicity, *n* (%)	Hispanic or Latino	46 (31)	42 (28)	47 (31)	135 (30)
	Not Hispanic or Latino	104 (69)	106 (72)	103 (69)	313 (70)

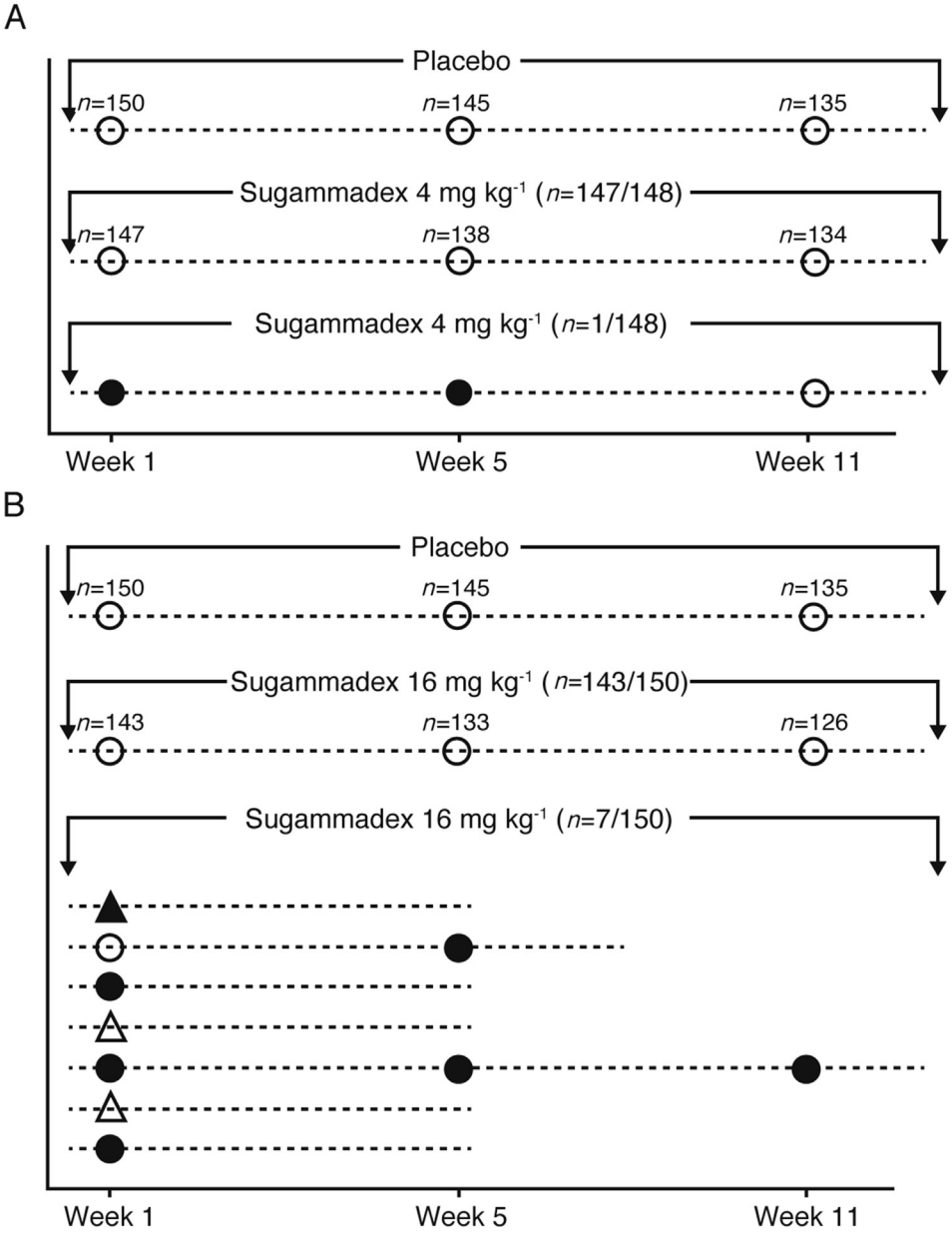

Fig 2. Occurrence of adjudicated hypersensitivity events and timing of events after treatment with (A) sugammadex 4 mg kg^{-1} and (B) sugammadex 16 mg kg^{-1}. Subjects with no adjudicated hypersensitivity or anaphylaxis are presented first. Each subject with hypersensitivity, anaphylaxis, or both is then represented by a separate horizontal line. ○: no hypersensitivity; ●: adjudicated hypersensitivity with no evidence of anaphylaxis; △: adjudicated hypersensitivity and anaphylaxis according to Brighton (level 2) criteria only; ▲: adjudicated hypersensitivity and anaphylaxis according to both Sampson and Brighton (level 1) criteria.

Sugammadex 16·mg kg^{-1} treatment group

Hypersensitivity was adjudicated for seven (4.7%) subjects (Fig. 2b), all of whom experienced dermatological symptoms, and with four experiencing hypersensitivity signs/symptoms related to other organ classes. Most of the observed signs appeared within 5 min after sugammadex 16 mg kg^{-1} administration, were of mild/moderate intensity, and resolved within 5 h without treatment. Compared with placebo, the mean (95% CI) difference in rate of subjects with adjudicated hypersensitivity was 4.7% (2.1, 9.3%).

Six of the seven subjects experienced hypersensitivity after the first sugammadex administration; one subject proceeded to receive a second and third administration of sugammadex 16 mg kg^{-1}, and mild hypersensitivity symptoms occurred after each administration. The seventh subject had adjudicated hypersensitivity after the second administration, and discontinued treatment thereafter (Fig. 2b).

One subject, a 55-yr-old white female, had hypersensitivity symptoms which met the Sampson criteria[13] (key secondary endpoint) for anaphylaxis, according to the AC, and the secondary Level 1 Brighton criteria[14] (i.e. highest certainty). This event occurred within minutes after the first sugammadex 16 mg kg^{-1} administration. Symptoms included severe non-pruritic generalised urticaria, severe flushing, moderate tachycardia (HR 149 beats min^{-1} 3 min post-administration, *vs* median 82 beats min^{-1} pre-administration), hypotension (67/42 mm Hg at 18 min post-administration, *vs* median 113/77 mm Hg pre-administration), severe nausea with vomiting, mild muscle spasms of the back, and mild numbness of the lips. S.C. epinephrine was administered 10 min after sugammadex and diphenhydramine was administered 8 min later for persistent hypotension. Nineteen minutes after the initial sugammadex administration, BP returned to normal (116/72 mm Hg). All other hypersensitivity signs/symptoms resolved the same day, although the subject continued to have mild, intermittent headaches, which resolved after 6 weeks without treatment, and were considered unrelated to sugammadex.

Two subjects had one event each after the first administration of sugammadex 16 mg kg^{-1} adjudicated as meeting the Brighton criteria for anaphylaxis with lower certainty (i.e. level 2); neither met the Sampson criteria for anaphylaxis. The underlying hypersensitivity symptoms were mild (dysgeusia, persistent dry cough, generalised urticaria) for one and moderate (flushing, sneezing, rhinorrhoea, generalised urticaria, ronchi) for the other; they resolved without treatment.

Compared with placebo, the mean (95% CI) difference in subjects meeting Sampson criteria for anaphylaxis was 0.7% (−1.8, 3.7%), and meeting the Brighton criteria of combined level 1 or 2 diagnostic certainty was 2.0% (−0.5, 5.7%) after sugammadex 16 mg kg^{-1}.

Adverse events

Treatment-related adverse events were reported in nine (6.0%), 16 (10.8%), and 56 (37.3%) subjects in the placebo, sugammadex 4 mg kg^{-1}, and 16 mg kg^{-1} treatment groups, respectively. Adverse events of reported severe intensity were reported in one (0.7%), one (0.7%), and four (2.7%) patients in the placebo, sugammadex 4 mg kg^{-1}, and 16 mg kg^{-1} groups, respectively.

Mechanistic analysis

Anti-sugammadex antibodies

Of the eight subjects with adjudicated hypersensitivity, two showed reactivity in the anti-sugammadex screening and confirmatory assay. Both subjects tested negative in the specific anti-sugammadex IgG and IgE assays (Supplementary Material, Results).

Of 94 control subjects (without hypersensitivity signs/symptoms), five (5.3%) had positive screening and confirmatory assays for pre-administration samples (sugammadex, n=2; placebo, n=3). While four subjects tested negative for anti-sugammadex IgG and IgE, one subject tested positive for anti-sugammadex IgG in samples obtained on Days 1, 7 (pre-sugammadex administration), 35, and 77, and negative for IgE. This subject did not show any clinical signs/symptoms of hypersensitivity, and had no prior sugammadex exposure.

Skin testing

Upon testing, seven of the eight subjects with adjudicated hypersensitivity met the pre-defined criteria for the positive and negative controls for SPT; all had negative SPT to all sugammadex concentrations.

Five of the eight subjects met the pre-defined criteria for positive and negative controls for IDT; one subject (who experienced anaphylaxis according to both the Sampson and Brighton criteria in the sugammadex 16 mg kg^{-1} group) had a positive IDT in triplicate at the maximum test concentration of 10 mg ml^{-1} only.

Both the SPT and IDT results in the 161 subjects without adjudicated hypersensitivity and with skin-test results showed high specificity (>99%); only one subject receiving sugammadex 4 mg kg^{-1} had a positive SPT (sugammadex dilutions 1 mg ml^{-1} and 0.1 mg ml^{-1}) and one subject in the placebo group had a positive IDT (sugammadex dilutions 0.1 mg ml^{-1} and 0.01 mg ml^{-1}).

Additional hypersensitivity mechanistic empirical analysis

No meaningful differences between subjects with and without adjudicated hypersensitivity were observed in additional mechanistic tests (Table 3).

Discussion

This study suggests a risk of hypersensitivity reactions (including anaphylaxis) with sugammadex in conscious healthy volunteers who have not been anaesthetised or administered a neuromuscular blocking agent. After sugammadex 4 mg kg^{-1}, the highest recommended dose for routine reversal of neuromuscular block, one subject experienced adjudicated hypersensitivity, and there were no cases of adjudicated anaphylaxis. Seven subjects experienced adjudicated hypersensitivity with sugammadex 16 mg kg^{-1}, a dose recommended only for potentially life-threatening emergency situations during which rapid reversal of neuromuscular block is deemed necessary. Most of the adjudicated hypersensitivity signs/symptoms reported in this study started within 5 min of sugammadex administration, were of mild-to-moderate intensity, and resolved without medical intervention. The incidence of hypersensitivity reactions did not increase after repeated sugammadex exposure with doses administered at least 4 weeks apart, a regimen selected to optimise priming of the immune system. After administration of the 16 mg kg^{-1} dose, one subject met the predefined primary endpoint for anaphylaxis (Sampson criteria[13]); this subject responded well to medical management. Two other subjects met criteria (Brighton, level 2) for anaphylaxis after sugammadex 16 mg kg^{-1}; their symptoms resolved without treatment.

Subsequent to database lock and study completion, review of study source data from all sites revealed multiple protocol deviations. For a subset of subjects, those protocol deviations may have introduced bias in reporting of hypersensitivity signs/symptoms. As a result, the primary and secondary endpoints of incidences of hypersensitivity and anaphylaxis confirmed by adjudication may not accurately reflect the true incidences. A second dedicated study to characterise the potential for sugammadex to induce hypersensitivity reactions in healthy volunteers was conducted (study P101; www.clinicaltrials.gov NCT02028065).

Table 3 Summary of mechanistic hypersensitivity research (subjects [*n*=8] with adjudicated hypersensitivity only). *Basophil histamine release testing was performed in three parts: using the subject's washed white blood cells (WBCs) containing intact basophils; using the subject's washed WBCs containing IgE-stripped basophils; and using donor (from blood bank) washed WBCs containing intact basophils treated with sera from these same subjects (passive sensitisation). IDT, intradermal test; IgE, immunoglobulin type E; IgG, immunoglobulin type G; SPT, skin prick test

Mechanistic test/research	Sugammadex 4 mg kg^{-1} (*n*=1)	Sugammadex 16 mg kg^{-1} (*n*=7)
Skin testing (in triplicate)		
SPT	Negative	All negative
IDT	Negative	One positive result at sugammadex 10 mg ml^{-1} (maximum test concentration) for one subject with anaphylaxis
Serum tryptase concentrations	Within normal range and no meaningful increments after challenge	All within normal range and no meaningful increments after challenge
Basophil histamine tests*	No relevant histamine release after sugammadex by IgE-intact, IgE-stripped, and sensitised donor basophils	No relevant histamine release after sugammadex by IgE-intact, IgE-stripped, and sensitised donor basophils
Anti-sugammadex IgE/IgG assay	Anti-sugammadex IgE/IgG tests negative	All anti-sugammadex IgE/IgG tests negative
Relevant differences between hypersensitivity cases and controls in:		
Susceptibility factors	None	None
Contact activation	None	None
Complement activation	None	None
Neutrophil/cytokine activation	None	None

Biomarker analyses conducted in this study were based on quantitative, objective measures in identified hypersensitivity cases. These are unlikely to have been affected by the identified protocol deviations and are considered informative regarding the underlying mechanism(s), especially as clinical manifestations may be more severe in patients with documented immunologic hypersensitivity reactions than in subjects presenting with a non-immunologic reaction.[17,18] In this study, no sugammadex-specific IgE antibodies were found in the serum of any subject with adjudicated hypersensitivity, or in the subset of (*n*=94) subjects tested without hypersensitivity, despite repeated sugammadex exposure.

Skin testing, a method presumed to assess allergen-specific IgE mediated degranulation of mast cells, is the present 'gold standard' widely used in the diagnosis of IgE-mediated allergy.[18,19] Results must be interpreted in clinical context and ideally with a well-characterised non-irritant extract.[20] There are no large studies determining non-irritant concentrations of sugammadex in the literature.[21] In the current study, 159 of 161 subjects without adjudicated hypersensitivity and seven of the eight subjects with adjudicated hypersensitivity had negative SPT results. One subject (of five with adjudicated hypersensitivity and adequate responses to IDT controls) had a positive IDT result at the maximum concentration of 10 mg ml^{-1} only. Interestingly, this subject was classified with anaphylaxis (Sampson and Brighton criteria), after sugammadex 16 mg kg^{-1}. However, this single positive IDT may not reflect an IgE response, as the subject tested negative for serum anti-sugammadex IgE/IgG antibodies. Moreover, basophil histamine release and tryptase values were within normal limits without significant increase from baseline and it is possible that a concentration as high as 10 mg ml^{-1} may have a direct local effect. Results of mechanistic testing in this individual, together with the overall low frequency of positive skin-testing, further support the absence of drug-specific IgE antibodies in subjects with adjudicated hypersensitivity. Hence, skin-testing did not appear to be of significant value in the diagnosis or prediction of most hypersensitivity to sugammadex in this study. Serological data reported here concur with studies in rabbits, indicating very weak immunogenicity (Merck & Co., Inc., Kenilworth, NJ, USA, data on file).

Assessment of tryptase concentrations can be helpful in evaluating underlying mechanisms of hypersensitivity signs/symptoms.[22–26] All subjects with adjudicated hypersensitivity had tryptase values within the normal range, with no relevant changes from baseline observed post-sugammadex, even in the single subject with anaphylaxis. These results are in line with an anaphylactic case report,[5] and the follow-up dedicated sugammadex hypersensitivity study (P101; www.clinicaltrials.gov NCT02028065).

No significant histamine release was observed post-challenge by basophils isolated from subjects with adjudicated hypersensitivity. Results from a broader exploratory evaluation of biomarkers to assess contact and complement activation, neutrophil activation, and levels of inflammatory cytokines do not suggest a role for these processes or mediators in the hypersensitivity signs/symptoms after sugammadex administration.

In the wider sugammadex clinical development programme, suspected cases of hypersensitivity after administration of high doses of sugammadex (above those approved for immediate reversal of neuromuscular block in an emergency situation, i.e. exceeding 16 mg kg^{-1}) have been observed; all cases were self-limiting and did not require treatment.[4] Tryptase concentrations and skin testing were performed on one patient who experienced paraesthesia in the skin of hands and face, blurred vision of moderate intensity, dysgeusia, nausea, tachycardia, and stomach discomfort after sugammadex infusion of 8.4 mg kg^{-1} of a 32 mg kg^{-1} dose; skin

flushing and an abdominal erythematous rash subsequently occurred.[4] Elevated tryptase concentrations were seen at 1 and 3 h post-dose, and positive IDT results at a 1:1000 dilution of sugammadex 100 mg ml^{-1}.[4] However, no IgE antibodies could be detected in blood samples from this patient collected approximately 1.5 yr after sugammadex exposure. In addition, there have been occasional case reports of hypersensitivity and anaphylaxis at lower doses of sugammadex (1.8–3.3 mg kg^{-1}).[5–12] Positive skin test reactions were observed in some of these cases, with variable tryptase and histamine concentration results. In general, onset of symptoms occurred within 5 min of sugammadex administration.

The exploratory mechanistic research of hypersensitivity reactions detected in this study neither support an IgE/IgG-mediated immunologic hypersensitivity mechanism nor affirm direct basophil/mast cell degranulation or mechanisms related to contact/complement activation or acute inflammation. Skin-testing or measuring serum anti-sugammadex antibodies appear unlikely to identify individuals at risk for anaphylaxis. Regardless of the exact underlying mechanism, physicians should monitor for hypersensitivity symptoms after sugammadex administration and be prepared to treat with standard measures for hypersensitivity in the perioperative setting, where sugammadex is intended for use.

Authors' contributions

Participated in the conception and design of the study: P.J.d.K., H.N., S.G., M.Y., J.B., C.K., N.F.A., C.C., J.H.L., D.J.v.d.D., E.L.G.M.v.H., F.C.M.v.M., D.G., T.W., P.A.M.P.
Participated in data generation: P.J.d.K., H.N., M.Y., J.B., C.K., C.C., P.S.S., T.W.
Participated in the analysis, interpretation, or both of the data: P.J.d.K., H.N., S.G., M.Y., D.E.W.-H., C.K., J.B., N.F.A., C.C., P.S.S., J.H.L., D.J.v.d.D., E.L.G.M.v.H., F.C.M.v.M., T.W., P.A.M.P., K.C.M.
Were involved in the preparation of the manuscript, reviewed the manuscript for important intellectual content, and provided final approval of the version to be published: all authors.
Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bja.2018.05.057.

Declarations of interest

D.G., K.C.M., and T.W. are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. P.J.d.K., H.N., M.Y., D.E.W.-H., C.C., and S.G. were employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. at the time the study was conducted. E.L.G.M.v.H, D.J.v.d.D., P.A.M.P., and F.C.M.v.M. were employees of MSD, Oss, The Netherlands at the time the study was conducted. Employees or former employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. may own stock and/or stock options in the company. J.B. and C.K. received a grant to perform laboratory methods. N.F.A. was a consultant for Merck & Co., Inc. and Chair of the Adjudication Committee for the study.

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