

Hypersensitivity incidence after sugammadex administration in healthy subjects: a randomised controlled trial

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Abstract

Background: We evaluated the incidence of hypersensitivity or anaphylaxis after repeated single-dose sugammadex administration in non-anaesthetised adults.

Methods: In this multicentre, double-blind study (NCT02028065), healthy volunteer subjects were randomised (2:2:1 ratio) to one of three groups to receive three repeated intravenous injections of sugammadex 4 or 16 mg kg⁻¹, or placebo, separated by a ~5 week intervals. Targeted hypersensitivity assessments were performed 0.5, 4, and 24 h post-dosing, and hypersensitivity signs/symptoms were referred to a blinded independent Adjudication Committee. Anaphylaxis was determined per Sampson (Criterion 1). The primary endpoint was the proportion with confirmed hypersensitivity.

Results: Of 375 evaluable subjects, 25 had confirmed hypersensitivity [sugammadex 4 mg kg⁻¹: 10/151 (6.6%); sugammadex 16 mg kg⁻¹: 14/148 (9.5%); placebo: 1/76 (1.3%)]. The differences in incidence rates vs placebo were 5.3% (95% confidence interval: -0.9, 10.7) for sugammadex 4 mg kg⁻¹ and 8.1% (1.7, 14.2) for 16 mg kg⁻¹. Incidence was similar across sugammadex doses and dosing occasions, including in subjects with reactions to previous doses. Three subjects (16 mg kg⁻¹ group) required antihistamines/corticosteroids and discontinued the study, per protocol; symptoms resolved and no subject required epinephrine. One subject with anaphylaxis after the first 16 mg kg⁻¹ dose recovered completely post-treatment. There were no clinically relevant anti-sugammadex antibody or tryptase findings.

Conclusions: Hypersensitivity in response to sugammadex administration can occur in healthy subjects without history of previous sugammadex exposure. Hypersensitivity incidence was similar across sugammadex doses and numerically

higher than placebo, with no evidence of sensitisation with repeated administration. Hypersensitivity is unlikely to be mediated through sugammadex-specific immunoglobulin G- or E-mediated mast cell stimulation in healthy volunteers. **Clinical trial registration:** NCT02028065.

Keywords: anaphylaxis; hypersensitivity; sugammadex; neuromuscular block

Editor's key points

- The incidence and severity of hypersensitivity in response to sugammadex are not known.
- Healthy volunteers received repeated injections of either sugammadex 4 or 16 mg kg⁻¹, or placebo, separated by a ~5 week interval, and the presence or absence of hypersensitivity was assessed.
- Hypersensitivity in response to sugammadex administration can occur in healthy subjects without a history of previous sugammadex exposure.

Sugammadex, a cyclodextrin derivative, provides rapid reversal of moderate or deep rocuronium- or vecuronium-induced neuromuscular block at doses of 2 and 4 mg kg⁻¹, respectively.^{1–6} At a dose of 16 mg kg⁻¹, sugammadex is also effective for the reversal of blockade 3 min after an intubating dose of rocuronium 1.2 mg kg⁻¹ when there is an immediate need to reverse the neuromuscular block.⁷ Sugammadex received approval from the US Food and Drug Administration in December 2015, and is currently marketed for use in >70 countries worldwide. Sugammadex is generally well tolerated, but a low incidence of hypersensitivity has been observed in clinical studies^{8,9}; hypersensitivity and anaphylaxis events have also been reported post-marketing.^{10–17} Therefore, a previous repeat-dose placebo-controlled study was conducted in 448 healthy, non-anaesthetised subjects (ClinicalTrials.gov identifier NCT00988065; sponsor protocol number P06042). Hypersensitivity was adjudicated in seven (4.7%), one (0.7%), and zero (0.0%) subjects receiving sugammadex 16 and 4 mg kg⁻¹, and placebo, respectively. There was one case of anaphylaxis in the sugammadex 16 mg kg⁻¹ treatment group adjudicated using the Sampson criteria.¹⁸ However, protocol deviations were identified after study completion, some of which may have compromised the study blinding, which could introduce bias in the assessment of incidence of hypersensitivity and anaphylaxis.

Therefore, the current study was conducted to characterise further the potential risk of hypersensitivity and anaphylaxis after initial and repeat exposures to sugammadex in healthy, non-anaesthetised adult subjects. The exploratory objectives included measurement of concentrations of anti-sugammadex-specific immunoglobulin (Ig) G and IgE antibodies, and mast-cell tryptase concentrations.

Methods

Study design and subjects

This randomised, double-blind placebo-controlled study (protocol MK-8616-101; NCT02028065) was conducted at four study centres in the USA and two in Belgium. Subjects aged 18–55 yr, with BMI ≥19 and ≤32 kg m⁻², and judged to be in good health, based on medical history, physical examination,

vital-sign measurements, ECG, and capillary-refill-time measurements, were enrolled. The exclusion criteria are summarised in Supplementary methods. The study was conducted in accordance with principles of Good Clinical Practice, and was approved by the appropriate institutional review boards and regulatory agencies. Written informed consent was obtained from all participating subjects.

The subjects were randomised in a 2:2:1 ratio, using a computer-generated allocation schedule, to receive three repeat i.v. bolus injections of sugammadex 4 mg kg⁻¹, sugammadex 16 mg kg⁻¹, or placebo (normal saline), with an approximate 5 week period between each dose, to allow potential sensitisation to develop. Each i.v. bolus injection was administered in approximately 10 s to match closely clinical practice.

Hypersensitivity assessment

Hypersensitivity was defined as objectively reproducible symptoms and signs of allergic disease initiated by exposure to a defined stimulus at a dose tolerated by non-hypersensitive persons.

Targeted hypersensitivity assessments were performed at 0.5, 4, and 24 h after dosing. The assessment included elicitation of symptoms and examination of the subject, covering neurological, pulmonary, cardiovascular, gastrointestinal, and dermatological domains (Supplementary methods). The assessment was performed by a blinded investigator not involved in the preparation or administration of the study drug. To ensure subject safety, a physician with expertise in airway management was available to treat the subject if severe hypersensitivity symptoms were to occur during the first 4 h after dosing. Hypersensitivity signs or symptoms in the first 24 h after dosing were referred to a blinded independent Clinical Adjudication Committee for evaluation by allergy and anaesthesia experts (Table 1).

The Sampson criteria are generally accepted as the best definition of anaphylaxis, and were developed via a large collaborative group, including the National Institute of Allergy and Infectious Diseases.¹⁸ Sampson Criterion 1 is defined as 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, and swollen lips–tongue–uvula), and at least one of the following: (i) respiratory compromise [e.g. dyspnoea, wheezing/bronchospasm, stridor, reduced peak expiratory flow (PEF), and hypoxaemia], and (ii) reduced BP or associated symptoms of end-organ dysfunction [e.g. hypotonia (collapse), syncope, and incontinence]. Criterion 1 is limited to reactions, in which the affected subject is not known to be allergic to the potential allergen. Cases of potential hypersensitivity referred to the Clinical Adjudication Committee were classified as anaphylaxis if Sampson Criterion 1 was met.

Subjects with potential hypersensitivity remained confined to the study centre for monitoring until the investigator

Table 1 Hypersensitivity symptoms resulting in referral to the expert Adjudication Committee. PEF, peak expiratory flow; SBP, systolic blood pressure; SPO₂, oxygen saturation

Generalised urticaria
Localised injection site urticaria
Generalised angioedema
Localised angioedema
Generalised pruritus with skin rash
Generalised pruritus without skin rash
Generalised prickle sensation
Generalised erythema
Red and itchy eyes
Hypotension (reduction >30% compared with pre-dose baseline or SBP <12 kPa)
Clinical diagnosis of uncompensated shock, indicated by the combination of at least three of the following:
• Tachycardia (pulse ≥ 100)
• Capillary refill time >3 s
• Reduced central pulse volume
• Decreased or loss of consciousness
Collapse (hypotonia)
Syncope
Incontinence
Bilateral wheeze (bronchospasm)
Stridor
Upper-airway swelling (lip, tongue, throat, uvula, or larynx)
Persistent dry cough
Hoarse voice
Difficulty breathing
Sensation of throat closure
Sneezing, rhinorrhoea
Respiratory distress, two or more of the following:
• Tachypnoea (>30 min ⁻¹)
• Recession
• Cyanosis
• Increased use of accessory respiratory muscles (sternocleidomastoid, intercostals, etc.)
• Grunting
• Decrease of SPO ₂ on room air $\geq 5\%$ (absolute) from baseline
• PEF <70% of baseline
Diarrhoea
Abdominal pain
Nausea
Vomiting
Mast-cell tryptase elevation > upper normal limit

considered it safe for them to leave. Resuscitative equipment and rescue treatments were available at each study centre. Subjects with hypersensitivity-related adverse events of severe intensity or requiring treatment, those with serious adverse events (related or not to hypersensitivity or anaphylaxis), and those with anaphylaxis were discontinued. Subjects referred to the Adjudication Committee for potential

hypersensitivity were allowed to continue if (i) there was no hypotension, (ii) all symptoms of hypersensitivity were rated as mild or moderate, and (iii) a blinded independent external expert with expertise in treatment of hypersensitivity review of the case recommended that it was safe for the subject to proceed to further dosing periods.

Adverse events were recorded throughout the study. Other safety assessments included physical examination, vital signs, ECG, oxygen saturation, PEF, and laboratory assessments.

The primary endpoint was the proportion of subjects with confirmed hypersensitivity symptoms for each sugammadex and placebo dose. The key secondary endpoint was the proportion of subjects with confirmed anaphylaxis.

Anti-sugammadex antibodies

The presence of anti-sugammadex antibodies was measured as an exploratory endpoint in blood samples obtained in all subjects with potential hypersensitivity and in a subset of control subjects who had received sugammadex, but did not have any hypersensitivity findings, using a three-step tiered anti-drug assay and IgG/IgE isotyping assay. An electrochemiluminescence-based screening assay was used to detect anti-sugammadex antibodies (detection limit: 0.28 ng ml⁻¹). A confirmatory assay was performed, with positive samples consequently subjected to an IgG/IgE isotyping assay to detect sugammadex-specific IgG or IgE (detection limit: 143 ng ml⁻¹ for IgG; not determined for IgE).

Tryptase

Tryptase is a mast-cell constituent, and elevations of tryptase concentrations are an indication of mast-cell degranulation.¹⁹ Tryptase was measured as a pre-specified exploratory endpoint, with samples collected pre-dose and at 3 h post-dose for all subjects. Tryptase concentrations in subjects with anaphylaxis peak at 15–120 min and with a half-life of 1.5–2.5 h.¹⁹ A tryptase analysis was performed using ImmunoCAPTM (Phadia, Uppsala, Sweden). The assay had a detection limit of 1.0 ng ml⁻¹ (upper 95th percentile for basal concentrations of serum tryptase in healthy subjects is 11.4 ng ml⁻¹). Measurements of tryptase concentrations were performed in subjects with potential hypersensitivity; the proportions of subjects with post-dose tryptase concentrations >11 ng ml⁻¹ and of those with an increase of ≥ 3 ng ml⁻¹ from the pre-dose value were assessed.

Statistical analyses

It was estimated that a total of 150 subjects in each of the sugammadex 4 and 16 mg kg⁻¹ groups and 75 subjects in the placebo group would allow estimation of confirmed hypersensitivity amongst subjects receiving sugammadex with a 95% confidence interval (CI) with a half-width between 1.2 and 4.2 percentage points, depending upon the observed incidence. This was based on the assumptions that there would be 150 evaluable subjects for each sugammadex dose group, and of an underlying event rate of up to 6% in the sugammadex high-dose group, based on the results from the prior study P06042.

Hypersensitivity analyses were performed by estimating the incidence and 95% CI (Clopper–Pearson)²² of confirmed hypersensitivity in each treatment group, and estimating the difference in incidence and 95% CI (Miettinen and Nurminen method)²³ between each sugammadex dose group and placebo. All safety analyses were performed using the all-subjects-as-treated population, which consisted of all

randomised subjects who received at least one dose of study treatment. Subjects were included in the group corresponding to the treatment they actually received.

Results

The study was conducted from January to July 2014. In total, 382 subjects were randomised, 375 received treatment (sugammadex 4 mg kg⁻¹: n=151; 16 mg kg⁻¹: n=148; and placebo: n=76) and 334 (89.1%) completed the study and received all three doses of the assigned treatment (Supplementary Fig. S1). The overall mean (range) age was 38 (19–56) yr, BMI was 26.3 (18.7–32.0) kg m⁻², and 53% of the subjects were female. The patient and baseline characteristics were similar between the treatment groups (Table 2).

Hypersensitivity

Overall, 94 subjects with a total of 137 adverse events potentially consistent with hypersensitivity based on the targeted hypersensitivity assessments were referred to the Clinical Adjudication Committee. Of these, 25 subjects were identified with

adjudicated hypersensitivity after receiving at least one dose of study medication: 10 (6.6%; 95% CI: 3.2–11.8) and 14 (9.5%; 95% CI: 5.3–15.4) subjects receiving sugammadex 4 and 16 mg kg⁻¹, respectively, and one (1.3%; 95% CI: 0.0–7.1) randomised to placebo (Table 3). In 13 subjects, the onset of the first hypersensitivity symptoms occurred within 10 min after the dose administration. All subjects but one had symptoms that began within 1 h of the dose administration. One subject had delayed mild hypersensitivity symptoms 22 h post-dose. In total, 43 adjudicated hypersensitivity events were experienced by these 25 subjects. The incidence of confirmed hypersensitivity was similar across sugammadex dose groups and dosing occasions (Figs 1 and 2). A summary of adverse events experienced by those with confirmed hypersensitivity is shown in Table 4.

Overall, 39/43 (91%) hypersensitivity events were of mild severity; three were moderate and one was considered severe (these four events occurred in the 16 mg kg⁻¹ group) (Fig. 1). There was no clear evidence of an increase in the incidence or severity of hypersensitivity with repeated administration of sugammadex. In the 24 sugammadex subjects with hypersensitivity, 21 received all three doses: 11 subjects had an event on more than one occasion, with three in the 4 mg kg⁻¹

Table 2 Subject characteristics (all-subjects-as-treated population)

n (%)	Sugammadex 4 mg kg ⁻¹ (n=151)	Sugammadex 16 mg kg ⁻¹ (n=148)	Placebo (n=76)
Sex			
Male	68 (45.0)	68 (45.9)	41 (53.9)
Female	83 (55.0)	80 (54.1)	35 (46.1)
Age (yr)			
Mean (range)	39 (19–55)	38 (20–55)	38 (21–56)
BMI (kg m ⁻²)			
Mean (SD)	26.3 (3.3)	26.5 (3.3)	26.2 (3.3)
Race			
American Indian/Alaska Native	2 (1.3)	0 (0.0)	1 (1.3)
Black/African American	17 (11.3)	16 (10.8)	9 (11.8)
Multiple	1 (0.7)	2 (1.4)	1 (1.3)
Native Hawaiian/Pacific Islander	1 (0.7)	1 (0.7)	0 (0.0)
White	130 (86.1)	129 (87.2)	65 (85.5)

Table 3 Subjects with confirmed hypersensitivity* or anaphylaxis according to Sampson (Criterion 1). CI, confidence interval; N/A, not available. *By independent Adjudication Committee. n[†]=number of subjects receiving dose; m[‡]=number of subjects with confirmed hypersensitivity/anaphylaxis according to Sampson (Criterion 1). Note that a subject could have events on more than one dosing occasion

	Sugammadex 4 mg kg ⁻¹ (n=151)		Sugammadex 16 mg kg ⁻¹ (n=148)		Placebo (n=76)	
	n [†]	m [‡] (%)	n [†]	m [‡] (%)	n [†]	m [‡] (%)
Confirmed hypersensitivity*						
First dose	151	6 (4.0)	148	8 (5.4)	76	0 (0)
Second dose	140	7 (5.0)	138	8 (5.8)	69	0 (0)
Third dose	136	4 (2.9)	134	9 (6.7)	64	1 (1.6)
After any dose	151	10 (6.6)	148	14 (9.5)	76	1 (1.3)
Estimated difference vs placebo (95% CI)	5.3 (–0.9, 10.7)		8.1 (1.7, 14.2)		N/A	
Anaphylaxis according to Sampson (Criterion 1)						
First dose	151	0 (0)	148	1 (0.7)	76	0 (0)
Second dose	140	0 (0)	138	0 (0)	69	0 (0)
Third dose	136	0 (0)	134	0 (0)	64	0 (0)
After any dose	151	0 (0)	148	1 (0.7)	76	0 (0)
Estimated difference vs placebo (95% CI)	0.0 (–4.8, 2.5)		0.7 (–4.2, 3.7)		N/A	

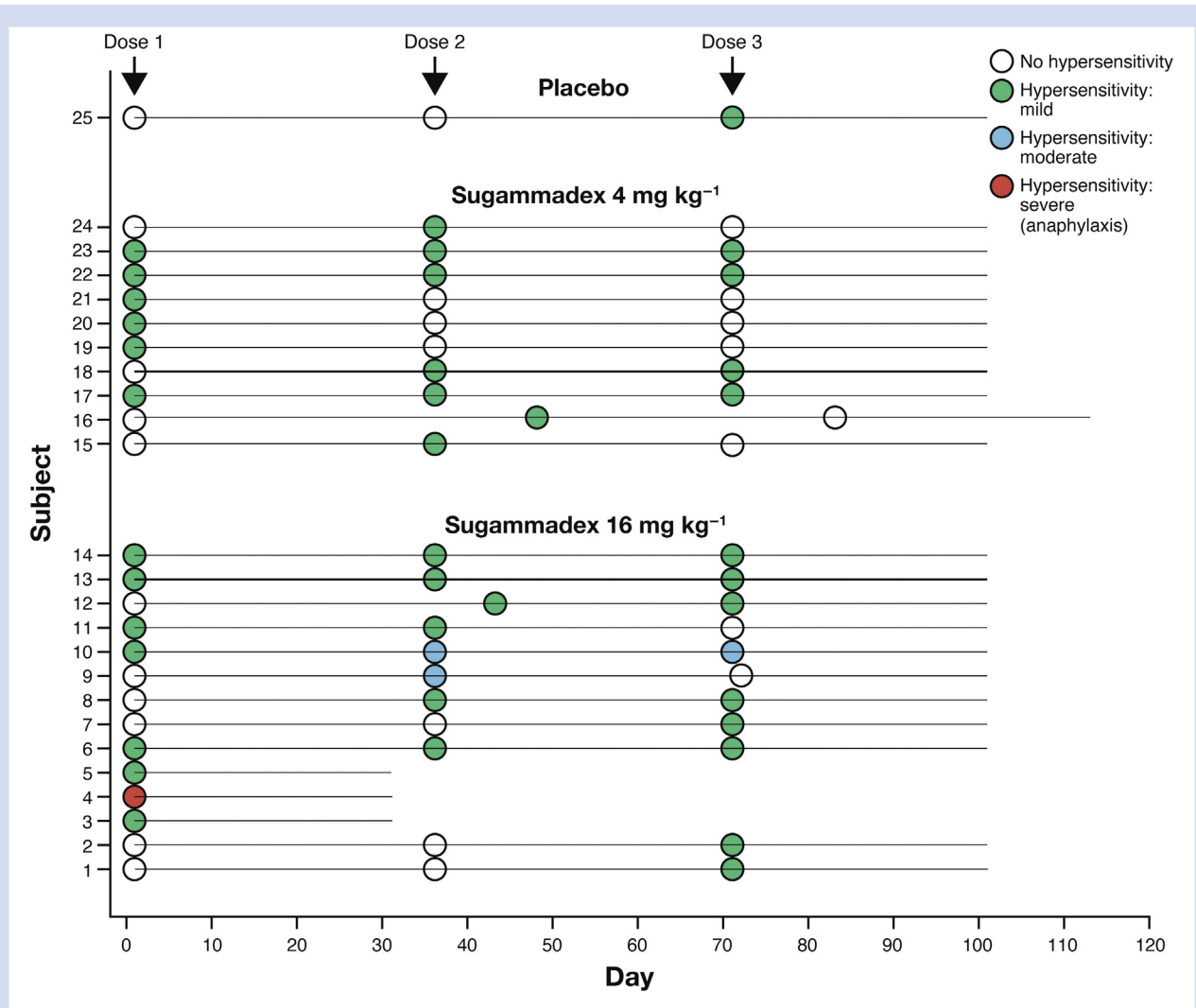


Fig 1. Time course of confirmed hypersensitivity events for each subject by treatment group, showing time point(s) and repeated occurrence of confirmed hypersensitivity, and duration of study participation. Horizontal lines represent the treatment period from first to last dosing occasion plus the 30 day follow-up period.

group and four in the 16 mg kg⁻¹ group having an event after all three doses (Fig. 1). The remaining 3 of 24 subjects (all from the 16 mg kg⁻¹ group) required treatment for hypersensitivity symptoms and were discontinued from the study, per the pre-specified protocol requirements, after the first dose. The symptoms of all three subjects rapidly improved after treatment with antihistamines/corticosteroids, and resolved completely within 22 h after symptom onset. No subject required treatment with epinephrine.

Anaphylaxis was confirmed in one of these three subjects (Table 3; Fig. 1). This subject had an onset of initial symptoms immediately after the dose administration: mild sneezing, nasal congestion, conjunctival oedema, moderate urticaria, and swelling of the uvula, and a decrease in PEF 30% below baseline. Most symptoms resolved within 3 h of treatment with antihistamine and corticosteroid, with conjunctival oedema resolving 9 h after the dose administration; the subject recovered completely without sequelae. The subject did not experience hypotension.

There was a numerically higher incidence of adverse events in the sugammadex 4 and 16 mg kg⁻¹ groups vs placebo (62.3% and 66.2% vs 47.4%, respectively). The most frequent adverse events within each treatment group are shown in Supplementary Table S1. Dysgeusia exhibited a clear dose-response relationship, with 11 (7.3%) and 47 (31.8%) subjects in the sugammadex 4 and 16 mg kg⁻¹ groups, respectively, experiencing dysgeusia, and three (3.9%) in the placebo group.

The percentage of subjects with serious adverse events was similar between groups [1.3% (2/151) and 0.7% (1/148) in the sugammadex 4 and 16 mg kg⁻¹ groups, respectively, vs 2.6% (2/76) in the placebo group]. The serious adverse events were moderate appendicitis (sugammadex 4 mg kg⁻¹ group); moderate intervertebral disc protrusion (sugammadex 4 mg kg⁻¹ group); self-limited adverse events of dysgeusia, feeling hot, and headache in setting of overdose (sugammadex 16 mg kg⁻¹ group reported as serious adverse events according to the sponsor's convention); moderate brain contusion (placebo group); and severe appendicitis (placebo). All but the adverse

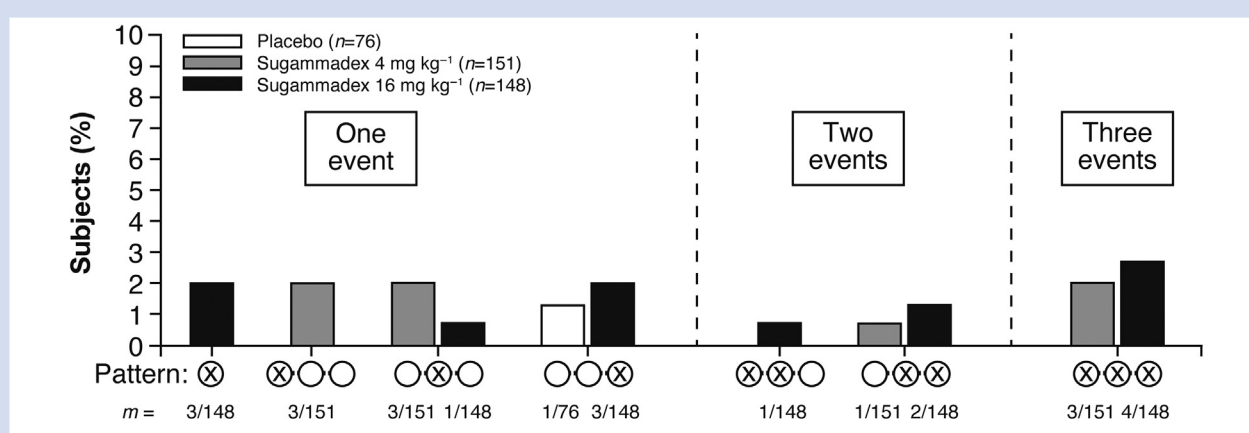


Fig 2. Patterns of confirmed hypersensitivity by treatment group. O=dose administered; X=confirmed hypersensitivity at a certain dosing occasion. n=number of subjects receiving dose; m=number of subjects with confirmed hypersensitivity. Three subjects had a hypersensitivity event on the first dosing occasion and were withdrawn.

events in the setting of overdose were considered unrelated to the study drug by the investigator. Further details are provided in [Supplementary materials](#).

No clinically relevant changes were observed in any of the vital signs, PEF, oxygen saturation by pulse oximetry, laboratory, ECG, or other routine safety parameters in the sugammadex groups relative to the placebo group.

Anti-sugammadex antibodies

Of the 25 subjects with confirmed hypersensitivity, two were positive for anti-sugammadex IgG. One subject with adjudicated hypersensitivity on each dosing occasion had positive IgG at baseline (before receiving sugammadex), but was negative before the second and third doses, and at the follow-up visit. The second subject was negative at baseline, but positive before the second and third doses, and at the follow-up visit; this subject had an adjudicated hypersensitivity event after the second dose, but not the third. None of the subjects with adjudicated hypersensitivity were positive for anti-sugammadex IgE.

Of the 69 subjects who were referred to the Clinical Adjudication Committee but whose events were not confirmed as hypersensitivity reactions, none had anti-sugammadex IgG or IgE at any evaluated time point. Furthermore, of the 91 control subjects (who were not referred to the Clinical Adjudication Committee), none had anti-sugammadex IgG or IgE at any evaluated time point.

Overall, these findings suggest a low likelihood of developing IgE or IgG antibodies to sugammadex with repeated administration, and that antibodies to sugammadex are not associated with confirmed hypersensitivity.

Tryptase

The upper limit of the normal range of tryptase in healthy subjects is 11.4 ng mL⁻¹. There were no subjects with adjudicated hypersensitivity with tryptase concentrations >11 ng mL⁻¹, either pre- or post-dose. One subject had a ≥3 ng mL⁻¹ tryptase increase post-dose relative to pre-dose with the second dose of sugammadex. This subject also had adjudicated hypersensitivity reactions after the first and third

doses, but did not have elevations of tryptase in those periods of tryptase ≥3 ng mL⁻¹.

Discussion

After repeated administration in healthy volunteers, sugammadex was associated with a numerically higher incidence of hypersensitivity than placebo at both 4 and 16 mg kg⁻¹; the incidence of hypersensitivity was similar across sugammadex doses and dosing occasions. Most hypersensitivity events occurred within minutes after the sugammadex administration. In three events occurring in the 148 subjects in the sugammadex 16 mg kg⁻¹ group, treatment was required with antihistamines and corticosteroids. There was no pattern of an increase in the severity of hypersensitivity reactions in the subjects who experienced hypersensitivity on more than one occasion. Thus, there was no evidence for the development of sensitisation to sugammadex in this study.

Overall, there were no cases of anaphylaxis in the 151 subjects who received sugammadex 4 mg kg⁻¹, the highest recommended dose for routine reversal in clinical practice. There was one case of anaphylaxis in the 148 subjects receiving sugammadex 16 mg kg⁻¹, which required treatment with antihistamines and corticosteroids. In a surgical setting, the dose of 16 mg kg⁻¹ is recommended only in emergency situations, when urgent reversal of neuromuscular block is required to restore spontaneous respiration and an airway cannot be established. It is unclear, however, whether the incidence of anaphylaxis is dose related, and thus, the observed incidence of anaphylaxis in this study with the administration of sugammadex to conscious, non-anaesthetised healthy subjects is 1 in 199, or 3.3%.

In contrast to the results of this study, no confirmed cases of anaphylaxis were observed in 3230 exposures to sugammadex during the Phases 2 and 3 sugammadex clinical development programme, which consisted almost entirely of sugammadex 2 or 4 mg kg⁻¹ doses, administered in surgical patients. There were nine sugammadex-treated patients (0.3%) with confirmed hypersensitivity in this clinical trial database. There have been a number of published reports of suspected hypersensitivity after sugammadex administration

Table 4 Summary of adverse events up to 24 h after dosing in subjects with confirmed hypersensitivity ($n=25$). Subjects could have more than one adverse event in each category

n (%)	Sugammadex 4 mg kg ⁻¹	Sugammadex 16 mg kg ⁻¹	Placebo
Subjects in population	10	14	1
Eye disorders	2 (20.0)	4 (28.6)	0 (0.0)
Conjunctival hyperaemia	0 (0.0)	1 (7.1)	0 (0.0)
Conjunctival oedema	0 (0.0)	1 (7.1)	0 (0.0)
Eye pruritus	1 (10.0)	2 (14.3)	0 (0.0)
Eye swelling	0 (0.0)	1 (7.1)	0 (0.0)
Eyelid oedema	0 (0.0)	1 (7.1)	0 (0.0)
Lacrimation increased	0 (0.0)	1 (7.1)	0 (0.0)
Ocular hyperaemia	0 (0.0)	1 (7.1)	0 (0.0)
Visual impairment	1 (10.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	1 (10.0)	6 (42.9)	0 (0.0)
Dry mouth	0 (0.0)	2 (14.3)	0 (0.0)
Enlarged uvula	0 (0.0)	1 (7.1)	0 (0.0)
Nausea	1 (10.0)	4 (28.6)	0 (0.0)
Vomiting	1 (10.0)	1 (7.1)	0 (0.0)
General disorders and administration site conditions	1 (10.0)	4 (28.6)	0 (0.0)
Catheter site haematoma	0 (0.0)	1 (7.1)	0 (0.0)
Catheter site pain	0 (0.0)	1 (7.1)	0 (0.0)
Chills	0 (0.0)	1 (7.1)	0 (0.0)
Feeling hot	0 (0.0)	1 (7.1)	0 (0.0)
Peripheral oedema	0 (0.0)	1 (7.1)	0 (0.0)
Vessel puncture site pain	1 (10.0)	0 (0.0)	0 (0.0)
Infections and infestations	1 (10.0)	1 (7.1)	0 (0.0)
Pustular rash	0 (0.0)	1 (7.1)	0 (0.0)
Rhinitis	1 (10.0)	0 (0.0)	0 (0.0)
Nervous-system disorders	2 (20.0)	5 (35.7)	0 (0.0)
Burning sensation	0 (0.0)	1 (7.1)	0 (0.0)
Dizziness	1 (10.0)	1 (7.1)	0 (0.0)
Dysgeusia	0 (0.0)	4 (28.6)	0 (0.0)
Headache	1 (10.0)	1 (7.1)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	2 (20.0)	7 (50.0)	0 (0.0)
Nasal congestion	0 (0.0)	2 (14.3)	0 (0.0)
Nasal discomfort	0 (0.0)	1 (7.1)	0 (0.0)
Pharyngeal oedema	0 (0.0)	2 (14.3)	0 (0.0)
Rhinorrhoea	1 (10.0)	0 (0.0)	0 (0.0)
Sneezing	1 (10.0)	4 (28.6)	0 (0.0)
Throat irritation	1 (10.0)	1 (7.1)	0 (0.0)
Upper-airway cough syndrome	1 (10.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	8 (80.0)	12 (85.7)	1 (100.0)
Dry skin	0 (0.0)	1 (7.1)	0 (0.0)
Erythema	1 (10.0)	4 (28.6)	0 (0.0)
Mechanical urticaria	1 (10.0)	0 (0.0)	0 (0.0)
Pruritus	7 (70.0)	7 (50.0)	0 (0.0)
Erythematous rash	0 (0.0)	2 (14.3)	1 (100.0)
Papular rash	0 (0.0)	1 (7.1)	0 (0.0)
Urticaria	6 (60.0)	10 (71.4)	0 (0.0)
Vascular disorders	0 (0.0)	1 (7.1)	0 (0.0)
Flushing	0 (0.0)	1 (7.1)	0 (0.0)

in surgical patients,^{10–16,20} although the incidence appears to be lower than that observed in this study of conscious, non-anaesthetised subjects. This may be due in part to increased detection rates of hypersensitivity signs and symptoms in awake vs anaesthetised subjects. Additionally, the intensive targeted hypersensitivity assessment used in the protocol of the current study is also likely to result in increased finding and reporting of relevant symptoms.

The mast-cell tryptase assay is considered a valuable test to detect the degranulation of mast cells with anaphylaxis.²¹ In the present study, there was limited evidence of mast-cell degranulation based on the exploratory tryptase biomarker assays, with one subject having a slight increase in tryptase from baseline, but within the upper limit of the normal range, which may be expected given the mildness of the observed hypersensitivity

reactions, with none of the subjects experiencing haemodynamic compromise. Furthermore, no anti-sugammadex IgE antibodies were detected in subjects with adjudicated hypersensitivity, suggesting that repeated exposure to sugammadex may not lead to the development of anti-sugammadex IgE antibodies that could result in IgE-mediated mast-cell degranulation. There was no consistent evidence that subjects exposed to sugammadex develop anti-sugammadex IgG antibodies in this study. Therefore, based on an evaluation of serum tryptase concentrations and assays for anti-sugammadex antibodies, it is unlikely that hypersensitivity to sugammadex observed in this study is mediated through sugammadex-specific IgG- or IgE-mediated stimulation of mast cells.

Patient characteristics, such as race and ethnicity, may play a role in predisposition to hypersensitivity reactions.¹⁹

Subject characteristics were balanced across groups. No subgroup analyses were conducted to assess the impact of race or ethnicity on potential hypersensitivity to sugammadex, as the low incidence of hypersensitivity cases in this study limited the utility of the investigation of subgroups. Another study limitation is that the anti-sugammadex antibody results rely on an *in vitro* assay, and because of lack of any reference antibody for IgE, the sensitivity of the assay for IgE antibodies could not be quantified. Finally, skin testing was not conducted as part of this study, as the previous study of hypersensitivity of sugammadex with repeated dosing in healthy subjects indicated that skin testing of subjects with hypersensitivity was generally negative.

Based on this evaluation in healthy subjects, the present study indicates that hypersensitivity, including anaphylaxis, can occur after the administration of sugammadex in subjects who have not previously been exposed to sugammadex. The reporting of anaphylaxis in post-marketing and in the broader clinical programme of surgical patients indicates that the incidence in the surgical population may be lower than was observed in this study of non-anaesthetised healthy subjects. Regardless of this potential discrepancy, clinicians should be aware of the possibility of hypersensitivity with the administration of sugammadex. Sugammadex should not be administered to patients with known hypersensitivity to sugammadex. Practitioners should observe patients for potential hypersensitivity reactions for an appropriate period of time after the administration.

Authors' contributions

Study conception and design: K.C.M., P.B., V.S., T.W., C.A., W.Y., T.R., R.D., J.D., F.A., D.E.G.

Data generation: K.C.M., P.B., V.S., W.Y., T.R., R.D., J.M., J.D., G.S.

Analysis and interpretation of data: K.C.M., P.B., V.S., C.A., W.Y., J.M., F.A., G.S., D.E.G.

Manuscript preparation: all authors.

Manuscript review for important intellectual content: all authors.

Final approval: all authors.

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.

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analysis, and interpretation of data; and data checking of information provided in the manuscript. However, the ultimate responsibility for opinions, conclusions, and data interpretation lies with the authors.

Declarations of interest

K.C.M., P.B., V.S., T.W., C.A., and J.M. are employees of Merck Sharp & Dohme (MSD), a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, all of whom may own stock options in the company. W.Y. was an employee of MSD, China at the time the study was conducted. T.R. and R.D. are employees of MSD, Belgium. J.D. and D.E.G. were employees of MSD at the time the study was conducted. F.A. is a consultant for Merck & Co., and was Chair of the study's Adjudication Committee. G.S. was a member of the Adjudication Committee.

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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.2018.05.056>.

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			title page
	1a	Identification as a randomised trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	3-4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5-6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6-8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	6

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	9
	13b	For each group, losses and exclusions after randomisation, together with reasons	Fig 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	20
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	9
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9-10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	22-24
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13-15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	13-15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13-15
Other information			
Registration	23	Registration number and name of trial registry	5
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Supplementary Materials

Supplementary Methods.

Exclusion criteria

Subjects were excluded if they had a history of clinically significant disease, prior exposure to sugammadex, multiple and/or severe allergies, or chronic urticarial oedema or angioedema; had undergone major surgery or donated or lost one unit of blood within 4 weeks prior to the study screening visit; had received immunotherapy within the past year; were unable to refrain from use of any medication for the duration of the study (with exception of paracetamol/acetaminophen, and hormonal contraceptives or hormonal replacement therapy); consumed excessive amounts of caffeine or alcohol; had a history of drug abuse; or if the investigator was concerned for any reason about the safe participation of the subject in the study.

Targeted hypersensitivity assessment

*To be performed only by blinded principal investigator or MD designate who has **NOT** been involved in preparation of study drug or in administering study drug by IV bolus. The following assessment is designed to elicit potential Hypersensitivity Signs or Symptoms. All abnormal findings should be noted. All AEs that have arisen since either the previous hypersensitivity Assessment or since administration of study drug should be noted, and a corresponding entry should be entered into the AE log for any clinically significant finding, regardless of severity. For AEs that started prior to study drug administration, findings should only be noted if there is a clear change in severity or quality in the nature of the AE. The prompts for elicited adverse events are not intended to be used verbatim, but may be adapted to the appropriate language and understanding of the subject.*

After completion of the Targeted HS Assessment, please note:

- ☐ No signs or symptoms present
- ☐ Presence

Dermatologic evaluation

- Ask about pruritus/itching, any prickle sensation (e.g., Do you have any feelings on your skin?)
- Assess for rash (patients should be in a gown that allows for assessment of skin on trunk)
 - presence of generalized urticaria (hives) or localized urticaria, or urticaria at injection site
 - presence of erythema
 - if present, describe characteristics of rash
 - Colour
 - Size, shape and number of lesions
 - Arrangement of rash
 - Distribution of rash (facial, truncal, asymmetrical or bilaterally symmetrical, related to injection site) and percent of body surface involved
- Assess for presence of angioedema, generalized or localized

Pulmonary evaluation

- Ask about difficulty breathing (e.g., Has there been any change in your breathing?)
- Perform auscultation of lung fields and assess for presence of wheezing or rhonchi
- Assess for presence of tachypnoea, stridor, increased use of accessory muscles, recession, grunting, cyanosis or dry cough
- Examine PEF measurements for decrease to <70% of baseline
- Examine SPO₂ measurements for decrease ≥5% (absolute) from baseline on room air

HEENT evaluation

- Ask about sensation of tongue swelling, throat swelling, and nose symptoms (e.g., Do you have any symptoms in your mouth, throat or nose?)
- Evaluate for presence of upper airway swelling (lip, tongue or uvula), sneezing, rhinorrhoea, and of redness and/or itching of eyes

GI evaluation

- Ask about nausea, vomiting, abdominal pain, diarrhoea

Cardiovascular evaluation

- Assess for hypotension
 - Resting* SBP reduction >30% compared to pre-dose baseline; OR
 - Resting* SBP <90 mmHg

- Assess for tachycardia
- Resting* HR ≥ 100 bpm
- Assess for capillary refill time > 3 s
- Assess for reduced central pulse volume

Neurologic evaluation

- Assess for decreased level of consciousness
- Assess for incidence of incontinence

Narrative: If there is a finding of a Symptom or Sign of Hypersensitivity, a narrative to describe the AE(s) should be provided. This narrative should supplement the information contained in the AE log, providing information about the sequence of events relative to the administration of study drug, and to provide further information about the evolution of AE(s) such as change over time of the AE(s).

AE, adverse event; GI, gastrointestinal; HR, heart rate; HEENT, head, eye, ear, nose and throat; PEF, peak expiratory flow; SBP, systolic blood pressure; SPO₂, oxygen saturation

*Resting for at least 5 min quietly

Supplementary Results

Subjects with serious AEs.

The serious AEs in the sugammadex 4 mg kg⁻¹ group were moderate appendicitis (considered unrelated to study drug by the investigator and from which the subject fully recovered after a laparoscopic appendectomy) and moderate intervertebral disc protrusion (considered unrelated to study drug by the investigator and from which the subject was recovering without complication at the time of follow-up), experienced by one subject each.

An overdose occurred in one subject allocated to sugammadex 16 mg kg⁻¹ but who received 27 mg kg⁻¹ due to a calculation error. The subject experienced dysgeusia, feeling hot, and headache following the first dosing occasion, which were reported as serious AEs according to the sponsor's reporting convention of reporting any AEs following overdose as serious. All symptoms resolved and the subject completed the three dosing periods. Of note, the AEs experienced by this subject were all rated as mild by the investigator.

Moderate brain contusion and severe appendicitis were experienced by one subject each in the placebo group and resulted in study discontinuation for both subjects. Both serious AEs were considered unrelated to the study drug by the investigator and had resolved at the follow-up examination.

Supplementary Table 1. Subjects with non-serious adverse events (incidence >5% in one or more treatment groups; all-subjects-as-treated population)

<i>n</i> (%)	Sugammadex 4 mg kg ⁻¹ (<i>n</i> =151)	Sugammadex 16 mg kg ⁻¹ (<i>n</i> =148)	Placebo (<i>n</i> =76)
Dysgeusia	11 (7.3)	47 (31.8)	3 (3.9)
Headache	29 (19.2)	30 (20.3)	10 (13.2)
Nausea	16 (10.6)	20 (13.5)	4 (5.3)
Urticaria	6 (4.0)	10 (6.8)	0 (0.0)
Pruritis	11 (7.3)	8 (5.4)	1 (1.3)
Oropharyngeal pain	2 (1.3)	3 (2.0)	4 (5.3)

Supplementary Figure 1. Disposition of subjects

