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Clinical Investigation

CLINICAL INVESTIGATION

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

K. C. Min[1,*], P. Bondiskey[1], V. Schulz[1], T. Woo[1], C. Assaid[1], W. Yu[2], T. Reynders[3], R. Declercq[3], J. McCrea[1], J. Dennie[1], F. Adkinson[4], G. Shepherd[5] and D. E. Gutstein[1]

[1]Merck & Co., Inc., Kenilworth, NJ, USA, [2]Merck Sharp & Dohme, Beijing, China, [3]Merck Sharp & Dohme, Brussels, Belgium, [4]Johns Hopkins Asthma & Allergy Center, Baltimore, MD, USA and [5]Weill Cornell Medical College, New York, NY, USA

*Corresponding author. E-mail: kwan-hong.chris.min@merck.com

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

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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 $\geq$19 and $\leq$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 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