BJA

British Journal of Anaesthesia, ■ (■): 1–10 (2018)

doi: 10.1016/j.bja.2018.05.057
Advance Access Publication Date: xxx
Clinical Investigation

CLINICAL INVESTIGATION

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.

Editorial decision: 24 May 2018; **Accepted:** 24 May 2018

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