Sugammadex-Induced Anaphylaxis: 2 Case Reports

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The incidence of perioperative hypersensitivity reactions according to a recent epidemiological review has been estimated to be in the range of 1/18 600 to 1/353 anesthetic procedures, while the incidence of life-threatening anaphylaxis was estimated at 1/10 000 anesthetic procedures in adults and 1/37 000 in children [1].

Sugammadex is a modified γ-cyclodextrin with a high capacity to bind selectively to aminosteroid neuromuscular blocking agents in plasma (rocuronium and vecuronium). It is eliminated via the kidneys, thus reducing the time of blockade of the nicotine receptors in the endplate. It is used for quick anesthetic reversal during surgery because it is 3 to 8 times faster than neostigmine (commonly used reversal agent) and does not have adverse cholinergic effects [2].

We present 2 cases of anaphylaxis that occurred minutes after intravenous administration of sugammadex for reversal of anesthesia.

The first patient was a 62-year-old, nonatopic man with a history of high blood pressure, type 2 diabetes, and stage V chronic kidney disease who underwent a kidney transplant in June 2019. Induction of anesthesia and surgery were uneventful. However, during reversal, the patient developed marked arterial hypotension, signs of low cardiac output, and desaturation. Cardiopulmonary resuscitation maneuvers were performed for 6 minutes, with hemodynamic stability being achieved after administration of adrenaline. He had received metamizole 2 g IV at 30 minutes before the episode, ondansetron 4 mg IV at 5 minutes before, and sugammadex 200 mg IV at 2 minutes before. The clinical history revealed that this was the first time he had received sugammadex. He was extubated 24 hours after the cardiac arrest and transferred to the hospitalization unit, where he received treatment with noradrenaline for 3 days. He was later shown to tolerate metamizole.

The second patient was a 9-year-old girl with a history of well-controlled allergic rhinitis to house dust mites. She was admitted in July 2019 for umbilical herniorrhaphy. Induction of anesthesia and surgery were uneventful. A dose of metamizole was administered during maintenance. Muscle relaxation was observed at the end of surgery, with residual blockade. Therefore, 80 mg of sugammadex was administered. No pulse oximetry wave or blood pressure was observed 2-3 minutes

after intravenous administration. In addition, ventilation through the laryngeal mask was no longer effective, with severe hypoxemia requiring urgent orotracheal intubation. Physical examination revealed generalized erythema. Hemodynamic stability was achieved after administration of adrenaline, corticosteroid therapy, and fluid therapy–based resuscitation. The patient was extubated successfully 24 hours later and tolerated paracetamol and ibuprofen.

In the case of the first patient, the immunoallergic study revealed a positive tryptase curve, positive skin test results at 0.1 mg/mL (skin prick test [(SPT)] to sugammadex 100 mg/mL and intradermal tests [(IDT)] at dilutions of 1/1000, 1/100, and 1/10), and the basophil activation test to sugammadex performed as per Sanz et al [3] was positive. The skin tests (SPT+IDT) to ondansetron and the remaining general anesthetics were all negative. The patient refused oral challenge with ondansetron (Table).

In the case of the second patient, the immunoallergy study revealed that she had a positive tryptase curve, positive skin test results (SPT) to sugammadex 100 mg/mL and IDT at dilutions of 1/1000, 1/100, and 1/10, with a positive basophil activation test result to sugammadex [3]. The results of skin tests to metamizole and the remaining general anesthetics were all negative. Oral tolerance to metamizole was not assessed. The patient later tolerated ibuprofen and paracetamol as alternative nonsteroidal anti-inflammatory drugs (Table).

Sugammadex was approved in Europe in 2008 and in Japan in 2010. It was not approved in the USA until 2015, because the United States Food and Drug Administration had some concerns about the risk of hypersensitivity reactions [1]. Use of sugammadex in Europe to date has been limited owing to cost and patent restrictions, with priority given to other agents, thus making hypersensitivity reactions to sugammadex rare. Since the recent expiry of the patent, sugammadex is increasingly used as a neuromuscular reversal agent during surgery.

Table. Immunoallergic Study

Patient 1	Patient 2
Skin test sugammadex Positive intradermal reaction 0.1 mg/mL	Skin test sugammadex Positive prick test 100 mg/mL
Skin prick test general anesthetics Negative	Skin prick test general anesthetics Negative
Skin prick test ondansetron Negative	Skin prick test metamizole Negative
Basophil activation test Positive	Basophil activation test Positive
Tryptase curve Positive	Tryptase curve Positive
Immediately after reaction >200 µg/L	Immediately after reaction 44 µg/L
2 h 140 µg/L	2 h 40.3 µg/L
6 h 74.6 µg/L	6 h 25.7 µg/L
Basal tryptase (24 h after the reaction) 18.8 µg/L *(9.48 µg/L 6 months before reaction)	Basal tryptase (24 h after the reaction) 6.55 µg/L

The incidence of hypersensitivity reactions associated with sugammadex varies with geographical region. Incidence can be affected by gene–environment interactions, differences in anesthetic practice, recognition of potential hypersensitivity reactions, and the amount of cyclodextrins used in the food industry in different countries [1].

With the introduction of sugammadex in Japan in 2010, the Japanese Society of Anesthesiologists reported an incidence of hypersensitivity reactions of 0.0029% [4]. A subsequent epidemiological review in 2019 based on a retrospective study of 15 479 patients revealed the incidence to be 0.0039% [5]. More recently, an American study of 19 821 patients showed the rate of anaphylactic reactions to be 0.0085% [6].

A Cochrane meta-analysis reported equal risk for adverse effects of sugammadex and neostigmine (<1%) [7], although in a recent Japanese study, it was suggested that neostigmine might be a safer option than sugammadex when assessing only the incidence of anaphylaxis [8].

We present 2 case reports of anaphylactic shock in patients who had not previously received sugammadex. Allergy to this drug was confirmed by a positive SPT result, increased levels of tryptase, and a positive basophil activation test result. To our knowledge, this is the second case report of sugammadex-induced anaphylaxis in Spain since 2011 [9].

Consistent with the studies mentioned above, neither of the patients described here had been exposed to sugammadex. The many hypotheses for the mechanism of sugammadex-induced anaphylaxis include exposure to cyclodextrins (at least 4 g/d) through drugs and food [10]. Other theories involve rocuronium-containing complexes where skin test results are negative when the drug is tested alone and positive when combined (in the cases we report, the skin test result was positive for sugammmadex and negative for rocuronium, although the sugammadex-rocuronium complex was not tested).

The management of patients with a perioperative anaphylaxis requires close collaboration between the anesthesia, surgical, and allergy teams. We believe that with current epidemiological data and the position of health authorities on sugammadex, this selective relaxant binding agent should be included in the study of perioperative anaphylaxis.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Mertes PM, Ebo DG, Garcez T, Rose M, Sabato V, Takazawa T, et al. Comparative epidemiology of suspected perioperative hypersensitivity reactions. Br J Anaesth. 2019;123(1):e16-e28.
2. Honing G, Martini CH, Bom A, Van Velzen M, Niesters M, Aarts L, et al. Safety of sugammadex for reversal of neuromuscular block. Expert Opin Drug Saf. 2019;18(10):883-91.
3. Sanz ML, Maselli JP, Gamboa PM, García-Avilés C, Oehling A, Diéguez I. Flow Cytometric Cellular Allergen Stimulation Test. A Review. J Invest Allergol Clin Immunol. 2002;12(3):143-54.
4. Takazawa T, Mitsuhata H, Mertes PM. Sugammadex and rocuronium-induced anaphylaxis. J Anesth. 2016;30(2):290-7.
5. Miyazaki Y, Sunaga H, Kida K, Hobo S, Inoue N, Muto M, et al. Incidence of Anaphylaxis Associated With Sugammadex. Anesth Analg. 2018;126(5):1505-08.
6. Burbridge MA. Incidence of Anaphylaxis to Sugammadex in a Single-Center Cohort of 19,821 Patients. Anesth Analg. 2021;132(1):93-7.
7. Hristovska AM, Duch P, Allingstrup M, Afshari A. Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults. Cochrane Database Syst Rev. 2017;8(8):CD012763.
8. Orihara M, Takazawa T, Horiuchi T, Sakamoto S, Nagumo K, Tomita Y, et al. Comparison of incidence of anaphylaxis between sugammadex and neostigmine: a retrospective multicentre observational study. Br J Anaesth. 2020;124(2):154-63.
9. Soria A, Motamed C, Gaouar H, Chemam S, Amsler E, Francés C. Severe Reaction Following Sugammadex Injection: Hypersensitivity? J Invest Allergol Clin Immunol. 2012;22(5):372-92.
10. Fenyvesi É, Vikmon M, Szente L. Cyclodextrins in Food Technology and Human Nutrition: Benefits and Limitations. Crit Rev Food Sci Nutr. 2016;56(12):1981-2004.

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