

## **Sugammadex Induced Anaphylaxis: Two Case Reports**

Lazo Uslar C, Navarro Vives L, Miquel Marco S, Roger Reig A, Basagaña Torrento M

Allergy Section, University Hospital Germans Trias i Pujol, Badalona

### **Corresponding author**

Carlota Lazo Uslar

Allergy Section, University Hospital Germans Trias I Pujol, Crta/Del Canyet s/n.,  
Badalona 08916. Spain

Email: [carlotalazo89@gmail.com](mailto:carlotalazo89@gmail.com)

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi:  
10.18176/jiaci.0719

**Key words:** Anaphylaxis. Sugammadex. Allergy. Anesthetic.

**Palabras clave:** Anafilaxia. Sugammadex. Alergia. Anestésicos.

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 of the anesthetic procedures, while the incidence of life-threatening anaphylaxis was estimated at 1/10.000 anesthetic procedures in adults and 1/37.000 in pediatric population [1].

Sugammadex is a modified  $\gamma$ -cyclodextrin with a high capacity to bind selectively with amino steroid neuromuscular blocking agents (Rocuronium and Vecuronium) present in plasma. It favors its renal elimination, reducing the time of blockage of the nicotine receptors in the neuromuscular plate. It is used for a quick anesthetic reversal during surgery, because it is three to eight times faster than Neostigmine (commonly used reversal method) and does not have the adverse cholinergic effects [2].

We present two cases of anaphylaxis minutes after intravenous administration of sugammadex for anesthetic reversal.

Case 1: A 62-year-old, non-atopic male with a history of high blood pressure, type 2 diabetes, and stage V chronic kidney disease underwent surgery for a kidney transplant in June 2019. The anesthetic induction and operation were uneventful. However, during the anesthetic reversal the patient developed marked arterial hypotension, signs of low cardiac output and desaturation. Cardiopulmonary resuscitation maneuvers were performed for 6 minutes and after the administration of adrenaline, the haemodynamic stability was achieved. Thirty minutes before the episode he had received 2g iv metemazole, five minutes before 4mg iv ondansetron and two minutes before 200mg iv sugammadex (first time reception, confirmed by the medical history check). He was extubated 24 hours after the cardiac arrest and transferred to the hospitalization unit where he received treatment with noradrenaline for three days. He was later shown to tolerate metemazole.

Case 2: A 9-year-old girl with a history of well-controlled allergic rhinitis to house dust mites. She was admitted in July 2019 to perform an umbilical herniorrhaphy. The anesthetic induction and operation were uneventful. A dose of metemazole was administered during maintenance. At the end of the surgery, muscle relaxation was observed, showing residual blockage. Therefore, 80 mg of sugammadex were administered. Two-three minutes after intravenous administration, an absence of the pulse oximetry wave and blood pressure was observed. Ventilation through the laryngeal mask was no longer effective with severe hypoxaemia that required urgent orotracheal intubation. On physical examination, the patient had a generalized erythema. After starting treatment with an adrenaline perfusion, corticotherapy and fluid therapy resuscitation, haemodynamic stability was achieved, resulting in her successful extubation after 24 hours. She was later shown to tolerate Paracetamol and Ibuprofen.

Immunoallergic study of case 1: the patient had a positive tryptase curve, skin tests (skin prick test (SPT) to sugammadex 100 mg/ml and intradermal reaction (IDR) at 1/1000, 1/100 and 1/10 dilution) were positive at IDR 0.1mg/ml and a positive basophil

activation test to sugammadex performed as proposed for ML Sanz et al [3]. The skin tests (SPT+IDR) to ondansetron and rest of general anesthetics were all negative. As a limitation, the patient refused to test for oral tolerance to ondansetron. Table 1.

Immunoallergic study of case 2: the patient had a positive tryptase curve, skin test (skin tests (SPT) to sugammadex 100 mg/ml and IDR at 1/1000, 1/100 and 1/10 dilution) were positive at SPT 100mg/ml and a positive basophil activation test to sugammadex[3] The skin tests to metamizole and rest of general anesthetics were all negative. As a limitation, no oral tolerance test to Metamizole was performed. The patient later tolerated ibuprofen and paracetamol, as alternative NSAIDs. Table 1.

Sugammadex was approved in Europe in 2008, in Japan in 2010 and later, in 2015, in the USA because the FDA had some concerns about the risk for hypersensitivity reactions [1]. Until now, the usage of sugammadex in Europe was limited due to cost and patent, prioritizing other agents, making the hypersensitivity reactions to sugammadex rare. Since the recent expiry of the patent, there has been an increase in the use of sugammadex as a neuromuscular reversal agent during surgery.

The incidence of hypersensitivity reactions associated to sugammadex varies with geographical regions. It can be affected by gene-environmental interactions, differences in anaesthetical practice, recognition of potential hypersensitivity reactions and the amount of cyclodextrins used in the food industry in each country [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]. Later in 2019, with an epidemiological review based on a retrospective study with 15.479 patients the estimate was 0.0039% [5], and more recently in an American study with 19.821 patients, the rate of anaphylactic reactions was 0.0085% [6].

A Cochrane meta-analysis reported equal risk for adverse effects of sugammadex and neostigmine (<1%) [7], but 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 two case reports of anaphylactic shock in patients who had not previously received sugammadex. The allergy to this drug was confirmed by a positive SPT, increased levels of tryptase and a positive basophil activation test. To the best of our knowledge this is the second case report of sugammadex induced anaphylaxis in Spain since 2011 [9].

None of the patients described here, neither most of the patients included in previous studies had been exposed to sugammadex. There are many hypotheses for the mechanism of sugammadex induced anaphylaxis. One of them being the exposure to cyclodextrins (at least 4gr a day) through pharmaceutical and food industries [10]. Other theories involve complexes with rocuronium were skin test are negative when tested alone and positive when tested combined (our patient has a positive skin test to sugammadex, and a negative skin test to rocuronium, although the sugammadex-rocuronium complex was not tested).

The management of patients with a perioperative anaphylaxis requires a 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.

### Conflicts of interest

The authors declare that they have no relevant conflicts of interest.

### Funding

None.

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**Table 1. Immunoallergic study**

<b>Case 1.</b>	<b>Case 2.</b>
<b>Skin Test Sugammadex</b> Positive Intradermal reaction 0.1mg/ml	<b>Skin Test Sugammadex</b> Positive Prick test 100mg/ml
<b>Skin Test general anesthetics</b> Negative	<b>Skin Test general anesthetics</b> Negative
<b>Skin Prick Test ondansetron</b> Negative	<b>Skin Prick Test metamizole</b> Negative
<b>Basophil activation test</b> Positive	<b>Basophil activation test</b> Positive
<b>Tryptase curve</b> Positive	<b>Tryptase curve</b> Positive
<b>Immediately after reaction</b> >200 ug/l	<b>Immediately after reaction</b> 44 ug/l
<b>2 hours</b> 140 ug/l	<b>2 hours</b> 40.3 ug/l
<b>6 hours</b> 74.6 ug/l	<b>6 hours</b> 25.7 ug/l
<b>Basal (24 hours after the reaction)</b> 18.8 u/l * (9.48ug/l 6 months before reaction)	<b>Basal (24 hours after the reaction)</b> 6.55 u/l