

Severe Perioperative Anaphylaxis Due to Allergy to the Sugammadex-Rocuronium Complex

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Perioperative anaphylaxis is a life-threatening hypersensitivity reaction developing during surgery. Many drugs have been involved in these allergic reactions, being the most frequently responsible the neuromuscular blocking drugs (NMBD) [1].

We present a 71-year-old woman with no relevant previous medical history. A vascular surgery for varicose veins in left lower limb under general anaesthesia was carried out. Propofol, fentanyl, levofloran, rocuronium and lidocaine were administered during the procedure with no complications. When surgery had finished, sugammadex was used for reversing neuromuscular blockade, as well as acetaminophen and dexketoprofen for analgesia. Severe symptoms suggesting an anaphylactic shock developed immediately, evolving to a cardiopulmonary arrest. Cardiopulmonary resuscitation and symptomatic treatment were applied, with a full recovery in a few minutes. Serum tryptase level was 55.9 µg/L during this reaction, and 67.9 µg/L two hours later.

An informed consent was obtained before starting the study 30 days after this episode. First, negative results were obtained in specific IgE levels for suxamethonium, chlorhexidine and latex (ImmunoCAP™. Thermo Fisher Scientific). At the same time, basal serum tryptase level was 8 µg/L. Then, prick-tests with latex and chlorhexidine were performed, showing negative results. Prick- tests (PT) and intradermal-tests (IDR) with commercially available involved drugs[2] were also negative: propofol (PT at 10 mg/ml, and IDR at 1 mg/ml), fentanyl (PT 0.05 mg/ml, IDR 0.005 mg/ml), and

lidocaine (PT 10 mg/ml, IDR 1 mg/ml). Skin-tests with separated sugammadex and rocuronium were carried out according to Garvey et al.: sugammadex (PT 100 mg/ml; IDR 10 mg/ml), and rocuronium (PT 10 mg/ml; IDR 0.05 mg/ml), with negative results [3].

Then, we performed skin tests with a mixture of sugammadex and rocuronium (SR-M): 1 cc of sugammadex (100 mg/ml) with 1 cc of rocuronium (10 mg/ml) using a 1:1 dilution, as previously described [4]. PT with our SR-M showed a clearly positive result in immediate reading (15 mins, 5x5 mm wheal). This mixture concentration was tested in 5 healthy individuals, and also in 5 patients previously exposed to sugammadex and rocuronium, with negative results in all of them.

Basophil activation test (BAT) was carried out with separated sugammadex (100 mg/ml) and rocuronium (10 mg/ml), showing negative results. Meanwhile, BAT with SR-M (1:1) was positive, with a stimulated-basophil rate, expressing CD63, of 56.2%. Information about BAT results are shown in Supplemental Figure S1

Oral challenge-tests with acetaminophen, dexketoprofen and fentanyl were performed in the One Day Care Unit, showing negative results. Challenge-test with propofol was not carried out due to safety reasons.

Allergic reactions to aminosteroidal NMBD are well known, and the tertiary and quaternary ammonium groups present in its molecule seem to be the epitopes recognized by IgE antibodies [5]. Muscle relaxation induced by the aminosteroidal NMBD is specifically reversed with sugammadex, a γ -cyclodextrin derivative with a truncated cone-like shape and a hydrophobic cavity that encapsulates the steroid backbone of NMBD with high affinity. Interestingly, sugammadex has been used in the

treatment of rocuronium anaphylaxis, based on its ability to encapsulate the NMBD, improving patient recovery [6].

Allergy to sugammadex has been previously reported, with positive skin-tests suggesting an IgE-mediated mechanism, and with an anaphylaxis incidence varying from 1:300 to 1:2000. In fact, sugammadex is the most common cause of perioperative anaphylaxis in Japan (28.3%), probably in relation with its higher use in this country [7].

Meanwhile, only very few cases of allergy to the SR-M, confirmed by either *in vivo* or *in vitro* tests, but with negative results to both drugs when tested separately, has been previously reported [4,5,8,9]. In this line, our case showed exclusively positive results with the SR-M, both in skin-tests and BAT, and thus it can be included within this selective group of allergic reactions to a drug complex neoantigen. It has been proposed that the new epitope could be located at the union of the pyrrolidinium quaternary ammonium group of rocuronium, with the thio (2-carboxyethyl) sodium group of sugammadex [7]. It seems that the positively charged ammonium ion of NMBD could distort the sugammadex structure, giving rise to a shape change, and these new structural features would be recognised by IgE. Since the sugammadex cone is rigid, these shape perturbations are likely to involve the carboxy-ethyl side-chains attached via a sulphur atom to the primary rim [10].

In conclusion, and according to our experience, when a perioperative allergic reaction happens during the awakening, our advice is to perform skin-tests not only with sugammadex and rocuronium separately, but also with a mixture of both of them, when skin-test results are negative for the separated drugs. In such cases, not testing the drug mixture would lead to a false result, with an unacceptable high risk of severe reactions in subsequent surgical procedures. Further studies to check if other aminosteroidal

NMBD could induce similar selective allergic reactions must be performed.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Previous presentations

These data have been previously communicated as a poster presentation in the EAACI Digital Congress 2020.

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