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

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Perioperative anaphylaxis is a life-threatening hypersensitivity reaction that can develop during surgery. Of the many drugs involved in these allergic reactions, neuromuscular blocking drugs (NMBDs) are the most frequent type [1].

We report the case of a 71-year-old woman with no relevant previous medical history who underwent vascular surgery with general anesthesia for varicose veins in her lower left leg. Propofol, fentanyl, sevoflurane, rocuronium, and lidocaine were administered during the procedure, with no complications. When surgery had finished, sugammadex was used to reverse neuromuscular blockade, and the patient was given acetaminophen and dextetopofen for analgesia. Severe symptoms suggesting anaphylactic shock developed immediately and progressed to cardiopulmonary arrest. Cardiopulmonary resuscitation and symptomatic treatment were applied, with a full recovery after a few minutes. Her serum tryptase level was 55.9 µg/L during this reaction and 67.9 µg/L 2 hours later.

The patient's informed consent was obtained before starting the study 30 days after the episode. Negative results were obtained (specific IgE levels) for suxamethonium, chlorhexidine, and latex (ImmunoCAP, Thermo Fisher Scientific). The basal serum tryptase level was 8 µg/L. Prick tests with latex and chlorhexidine yielded negative results. Prick tests (PT) and intradermal tests (IDT) with commercially available formulations of the involved drugs [2] were also negative: propofol (PT at 10 mg/mL, and IDT at 1 mg/mL), fentanyl (PT at 0.05 mg/mL, IDT at 0.005 mg/mL), and lidocaine (PT at 10 mg/mL, IDT at 1 mg/mL). Skin tests with sugammadex and rocuronium separately were carried out according to Garvey et al [3], with negative results for both sugammadex (PT at 100 mg/mL; IDT at 10 mg/mL) and rocuronium (PT at 10 mg/mL; IDT at 0.05 mg/mL).

We then 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]) at a 1:1 dilution, as previously described [4]. PT with our SR-M showed a clearly positive result in the immediate reading (15 minutes, 5×5 mm). Testing of this concentration in 5 healthy individuals and in 5 patients previously exposed to sugammadex and rocuronium yielded negative results.

A basophil activation test (BAT) carried out with sugammadex (100 mg/mL) and rocuronium (10 mg/mL) separately also yielded negative results. Meanwhile, the result of a BAT with SR-M (1:1) was positive, with a stimulated-basophil rate, expressing CD63 (56.2%). The BAT results are shown in Supplemental Figure S1.

Oral challenge tests with acetaminophen, dexketoprofen, and fentanyl performed in the outpatient clinic yielded negative results. Challenge testing with propofol was not carried out owing to safety concerns.

Allergic reactions to aminosteroid NMBDs are well known, and the tertiary and quaternary ammonium groups present in the molecule seem to be the epitopes recognized by IgE antibodies [5]. The muscle relaxation induced by aminosteroid NMBDs is reversed specifically with sugammadex, a γ -cyclodextrin derivative with a truncated cone-like shape and a hydrophobic cavity that encapsulates the steroid backbone of the NMBD with high affinity. Interestingly, based on its ability to encapsulate the NMBD, sugammadex has been used to treat anaphylaxis to rocuronium, thus improving patient recovery [6].

Allergy to sugammadex has been reported, with positive skin-tests suggesting an IgE-mediated mechanism and with an incidence varying from 1:300 to 1:2000. In fact, sugammadex is the most common cause of perioperative anaphylaxis in Japan (28.3%), probably because it is widely used there [7].

Meanwhile, there have been very few reports of allergy to SR-M, confirmed by either in vivo or in vitro tests, but with negative results to both drugs when tested separately [4,5,8,9]. In this sense, the case we report yielded exclusively positive results with SR-M, both in skin tests and in the BAT, and can therefore 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 NMBDs could distort the sugammadex structure, giving rise to a shape change. In addition, these new structural features would be recognized by IgE. Since the sugammadex cone is rigid, the shape perturbations are likely to involve the carboxy-ethyl side chains attached via a sulfur atom to the primary rim [10].

In conclusion, and according to our experience, when a perioperative allergic reaction happens during awakening, our advice is to perform skin tests not only with sugammadex and rocuronium separately, but also with a mixture of both, as skin test results could prove negative for the drugs when analyzed separately. In such cases, not testing the drug mixture would lead to a false result, with an unacceptably high risk of severe reactions in subsequent surgical procedures. Further studies must be performed to determine whether other aminosteroid NMBDs could induce similar selective allergic reactions.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentation

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