Non-IgE-Dependent Hypersensitivity to Rocuronium Reversed by Sugammadex: Report of Three Cases and Hypothesis on the Underlying Mechanism

David Spoerl^a Stéphanie D'Incau^b Pascale Roux-Lombard^c Thomas Harr^a
Christoph Czarnetzki^d

^aDivision of Clinical Immunology and Allergy, Department of Medical Specialties, ^bDepartment of Internal and General Medicine, ^cDivision of Laboratory Medicine, Department of Genetics and Laboratory Medicine, and ^dDivision of Anesthesiology, Geneva University Hospital, Geneva, Switzerland

Established Facts

- Rocuronium has been shown to activate the MRGPRX2 receptor on mast cells, inducing a non-IgE-mediated histamine release, which explains its potential for causing pseudoallergic reactions.
- Sugammadex has been designed to encapsulate rocuronium and specifically antagonize its pharmaceutical effects.
- There are several case reports describing the reversal of rocuronium-induced anaphylaxis by the injection of sugammadex; however, the exact pathophysiological mechanism is still unknown.

Novel Insights

- Sugammadex was successfully used in 3 patients to rapidly reverse ongoing pseudoallergic reactions.
- Sugammadex abolished the rocuronium-induced irritative skin test reaction in the 3 patients and in 3 healthy individuals, suggesting that this effect might be mediated by the inhibition of rocuronium-induced MRGPRX2 activation.

Key Words

Anaphylaxis · Anaphylactoid reaction · Rocuronium · Sugammadex · Receptor

Abstract

We present 3 cases of pseudoallergic (anaphylactoid) reactions to perioperatively administered rocuronium, which rapidly resolved after sugammadex injection. Allergological workup showed no evidence for immediate-type hypersensitivity to the drugs used for anesthesia, including rocuroni-

um. However, rocuronium induced an irritative reaction in skin tests in all 3 patients and in 3 healthy individuals. This reaction was specifically suppressed by adding sugammadex at a 1:1 molecular proportion to rocuronium before the skin tests. This observation suggests that the patients suffered from a pseudoallergic reaction, and indicates that sugammadex might act via the inhibition of non-IgE mediated MRGPRX2 (Mas-related G-protein-coupled receptor member X2)-triggered mast cell degranulation induced by rocuronium.

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T.H. and C.C. contributed equally to this work.

Introduction

Approximately 60% of perioperative hypersensitivity reactions are IgE-mediated anaphylactic reactions, whereas 40% are pseudoallergic (anaphylactoid) reactions. Neuromuscular blocking agents (NMBA) have been reported to account for the majority of IgE-mediated reactions occurring during general anesthesia [1, 2].

Quaternary and tertiary ammonium (QA) ions are thought to be the main allergenic epitopes in NMBAs. Other drugs, such as opiates, and environmental chemicals also contain QA [2–4]. This shared epitope might in part explain the cross-sensitization between different NMBAs, as seen in most patients allergic to NMBAs, and the fact that a history of previous exposure to NMBAs is only found in fewer than 50% of patients adversely reacting to NMBAs during anesthesia [5, 6].

Rocuronium bromide is a nondepolarizing NMBA. Controversies exist as to the best approach to evaluate rocuronium hypersensitivity reactions. Skin tests in healthy individuals have shown a nonirritating concentration at approximately 10^{-4} and 10^{-3} M [7]. Fifty percent of healthy individuals show a positive prick test reaction (irritative) with the undiluted drug [8] and current guidelines propose intradermal tests (IDTs) at a dilution of 1:200, i.e. 0.05 mg/ml, corresponding to approximately 10^{-4} M [9]. ImmunoCAP assays for the determination of specific IgE to rocuronium have been used in this setting (specificity 93%, sensitivity 68%) [10]. The testing of specific IgE to QA is otherwise more widely available.

Sugammadex has been specifically designed to antagonize rocuronium-induced neuromuscular blockade [11–13]. Its chemical structure is a modified γ -cyclodextrin with 8 sugar molecules forming a rigid ring with a central lipophilic cavity designed to incorporate the rocuronium molecule. Sugammadex binds at a 1:1 ratio to rocuronium with an extremely high binding affinity ($K_a = 1.8 \times 10^7 \text{ M}^{-1}$) [5]. Once enveloped with sugammadex, rocuronium is unable to bind to the acetylcholine receptor at the neuromuscular junction. Whether sugammadex is useful for antagonizing IgE-mediated or pseudoallergic reactions due to rocuronium remains a matter of debate [14].

In the following, we report 3 cases of presumed pseudoallergic reactions to rocuronium with a rapid response to sugammadex. In addition, we also propose a hypothesis about the underlying pathological mechanism of this response.

Case Reports

Case 1

A 36-year-old atopic female underwent abdominal surgery during which fentanyl, lidocaine, propofol, suxamethonium and ceftriaxone followed by repeated injections of rocuronium were given. At the end of the procedure she presented a generalized urticarial rash associated with bronchoconstriction and hypoxemia. She was treated with antihistamines, methylprednisolone and nebulized adrenaline, but her condition improved rapidly only after treatment with 400 mg i.v. of sugammadex. Tryptase was not measured during the reaction.

Skin tests for penicillin (benzylpenicilloyl octa-L-lysine, benzylpenilloate minor determinant), amoxicillin, ceftriaxone, lidocaine, procaine, fentanyl, suxamethonium, propofol, latex and chlorhexidine were negative. IDT for rocuronium at a concentration of 10 mg/ml resulted in an erythema without papule formation at the 10^{-3} and 10^{-2} dilutions, and was clearly positive at the 10^{-1} dilution, which is known to be irritative. The mixture of sugammadex and rocuronium (1:1 molecular) was negative in all the tested dilutions (mild erythema at the 10^{-1} dilution; fig. 1a). Specific IgEs for penicillin G and V, ampicillin, amoxicillin, chlorhexidine, QA, rocuronium, suxamethonium, ethylene oxide and latex were negative. A basophil activation test (BAT) with and without the addition of IL-3, measuring CD63 and CD203c expression, was negative for atracurium (concentration 1,000, 100 and 10 ng/ml; highest stimulation index 1.8), chlorhexidine (concentration 100, 10 and 1 ng/ml; highest stimulation index 2.0), rocuronium (concentration 1,000, 100 and 10 ng/ml; highest stimulation index 1.5) and the mixture of rocuronium and sugammadex (concentration 1,000, 100 and 10 ng/ml; highest stimulation index 0.9). The basal tryptase was within the normal range 6 months later.

Case 2

A 48-year-old female was scheduled for surgical resection of an unexplained left parietal cerebral mass. A few minutes after the induction with propofol and fentanyl, and injection of 40 mg of rocuronium, she developed tachycardia and a generalized urticarial rash, followed by profound hypotension (mean arterial pressure between 40 and 50 mm Hg) and metabolic acidosis without hypoxemia. An anaphylactic shock was suspected and hydrocortisone and clemastine were administered once. Despite repeated epinephrine injections and intravenous fluids the patient remained hypotensive and the surgical procedure was cancelled. Fifty-three minutes after the induction, 200 mg of sugammadex were injected, resulting in rapid hemodynamic normalization, disappearance of the urticarial rash and extubation 15 min later. A serological analysis during the anaphylactic reaction showed an elevated tryptase level of 36 $\mu\text{g/l}$ (normal value $<11.1 \mu\text{g/l}$).

Prick tests and IDTs were negative to all substances used during the procedure as well as to latex, ethylene oxide and chlorhexidine. Prick tests were positive to 10 mg/ml of pure rocuronium and negative for the 1:1 mixture of rocuronium and sugammadex. The IDT to rocuronium was positive at 10^{-2} and 10^{-1} dilution, which is presumably an irritative dose. An IDT using the 1:1 mixture of rocuronium and sugammadex was negative at dilutions of 10^{-2} and 10^{-1} (fig. 1b). Specific IgEs were negative for rocuronium, chlorhexidine, suxamethonium, QA, ethylene oxide and latex. BAT was negative for rocuronium, rocuronium and sugammadex mixture, and atracurium (with the same concentrations as in case 1; the

Fig. 1. a–c IDT with rocuronium and rocuronium mixed with sugammadex (1:1 molecular) in 3 cases of probable pseudoallergic reaction following perioperative rocuronium injection. All IDTs were considered either irritative or negative, but when sugammadex was mixed before the IDT, the reaction was attenuated.

highest stimulation index for rocuronium was 1.9, and for rocuronium and sugammadex mixture was 0.9). Basal tryptase was within the normal range.

Case 3

A 69-year-old male underwent craniotomy for a suspected glioblastoma multiforme. A few minutes after the induction with propofol and sufentanil, and injection of 50 mg of rocuronium and 40 mg of ketamine, he developed severe hypotension (mean arterial pressure between 40 and 50 mm Hg), requiring intravenous fluids and epinephrine (total dose 1.5 mg). Sixty minutes after the

first dose of rocuronium, a second dose of 20 mg was injected to facilitate transesophageal echocardiography, which did not show signs of cardiogenic shock. Forty minutes after the second dose of rocuronium, 400 mg of sugammadex were injected. The blood pressure stabilized rapidly and the patient was extubated after a second dose of 200 mg of sugammadex, injected 20 min later. The patient did not receive corticosteroids or antihistaminic drugs before extubation. Tryptase was within the normal range during the reaction and 2 h later. The surgery was subsequently postponed. Because of the necessity to rapidly perform the surgical procedure, the skin tests were performed only 3 days after the reaction when

still under corticosteroid treatment, possibly compromising their validity.

Skin tests for all the substances used during the procedure were negative. However, an IDT for rocuronium was weakly positive at a presumably irritative 10^{-1} dilution, and negative for the 1:1 rocuronium and sugammadex mixture at the same dilution (fig. 1c). No specific IgEs were found against rocuronium, chlorhexidine, suxamethonium, QA and latex. BAT was inconclusive due to a low basophil count ($<0.01\%$ of leucocytes). During the following surgical procedure, ketamine, etomidate and isoflurane were used for anesthesia and sufentanil for analgesia. NMBAs were completely avoided.

Discussion

NMBAs are well known to potentially cause anaphylactic (i.e. IgE-mediated) reactions during anesthesia. However, many reactions to NMBAs occur during the first exposure, suggesting a non-IgE-mediated pathomechanism. Under most circumstances, it is impossible to clinically distinguish an IgE-mediated allergic reaction from a pseudoallergic reaction. NMBAs have direct vasodilating effects on blood vessels. They are able to induce histamine and tryptase release from mast cells within the skin via different mechanisms that might vary depending on the compounds studied [7].

We report 3 cases of probable pseudoallergic reactions to rocuronium, which rapidly resolved after the administration of sugammadex. Tryptase was not measured in the first patient, in the second tryptase was increased during the reaction, and in the third case tryptase was within normal values, possibly due to the low sensitivity of this test [15–17]. Two patients received standard treatment for anaphylaxis, including corticosteroids, antihistaminic drugs and adrenaline, without an apparent response. One patient received only epinephrine. The rapid clinical improvement within minutes after sugammadex in the 3 patients can thus not be explained by the standard treatment for anaphylaxis.

Rocuronium hypersensitivity could not be demonstrated in the 3 patients, neither in vivo by skin tests, nor in vitro by IgE to QA, IgE to rocuronium or BAT. In case 2, the prick test was positive with pure rocuronium and the IDT was positive at a dilution of 10^{-2} . In the other 2 patients skin tests with rocuronium were only positive at a dilution of 10^{-1} . These results were probably due to an irritative reaction. Sugammadex mixed at a 1:1 ratio with rocuronium was able to neutralize the irritative effect of rocuronium in all the performed skin tests. Hypersensitivity to other drugs used during surgery in all 3 patients could not be identified by skin and specific IgE testing as well as BAT.

Recently, a mast cell-specific receptor, the human MRGPRX2 (Mas-related G-protein-coupled receptor member X2) has been reported to be involved in pseudoallergic reactions seen in patients after treatment with peptidergic drugs, including rocuronium [18]. It is possible that the high rate of anaphylactic reactions reported in NMBA-naïve patients, as well as the high percentage of cross-reactivity reported in NMBA-allergic patients (mostly based on skin test results), might in fact be due to the effects of NMBA on the MRGPRX2 receptor and, therefore, be pseudoallergic and not anaphylactic. This mechanism may also explain the irritative reaction in skin tests with NMBAs.

Whether sugammadex blocks IgE binding to rocuronium is not known [19]. Jones and Turkstra [20] first raised the possibility of using sugammadex to treat rocuronium anaphylaxis in 2010. Since this first report, many other case reports have followed [21–28]. Whether this beneficial effect is due to the inhibition of IgE-mediated activation of mast cells remains elusive. It is possible that reversal of the neuromuscular blockade by sugammadex might help in restoring adequate cardiovascular function. It is also possible that standard treatment for anaphylaxis with adrenaline and fluids, etc. might additionally improve the condition of patients suffering from rocuronium anaphylaxis [24].

In order to elucidate this issue, a BAT was performed showing that sugammadex is able to prevent basophil activation by rocuronium, provided that sugammadex and rocuronium were preincubated prior to basophil stimulation. However, sugammadex was not able to stop an ongoing activation in this test [29]. These in vitro experiments were consistent with data from skin tests in rocuronium-sensitized patients. Clarke et al. [30] showed that these patients were anergic to sugammadex-bound rocuronium and concluded that sugammadex was able to prevent rocuronium from interacting with the immune system, presuming an underlying IgE-mediated mechanism. However, sugammadex was unable to attenuate the cutaneous hypersensitivity reaction after it had been triggered by rocuronium. Taken together, these data from BAT and skin tests suggest a similar mechanism being responsible for rocuronium-induced histamine release from basophils and mast cells mediated by MRGPRX2. Nevertheless, as it is not known whether the MRGPRX2 receptor is expressed on basophils, BAT does not allow differentiating true hypersensitivity from anaphylactoid reactions.

Our observations suggest that sugammadex might be beneficial to treat pseudoallergic reactions due to ro-

Fig. 2. a–c IDT with suxamethonium, atracurium and rocuronium alone and mixed with sugammadex (1:1 molecular for rocuronium, same volume for atracurium and suxamethonium) in 3 healthy individuals. When sugammadex was mixed before the IDT, the irritative (pseudoallergic) skin reaction of rocuronium was specifically attenuated, while atracurium and suxamethonium were not affected.

curoonium, due to the likely inhibition of rocuronium-mediated MRGPRX2 activation. The rapid clinical improvement seen during anesthesia in the 3 reported patients might be explained by the high affinity of sugammadex to rocuronium, possibly inducing cleavage of MRGPRX2 receptor-bound rocuronium.

Sugammadex has been designed to specifically encapsulate rocuronium [13]. It is not expected to influence the

binding of other molecules to mast cells or IgE. Nevertheless, in order to test whether sugammadex might have an effect on pseudoallergic reactions to other compounds, we tested its effects on atracurium and suxamethonium, two NMBAs but with different chemical structures. We performed prick tests and IDTs in 3 healthy individuals who had never had one of these compounds injected. We mixed the same amount of sugammadex (Bridion®; MSD

Fig. 3. a, b Prick tests with grass pollen and mold extracts in 2 atopic individuals. Adding sugammadex to the extracts before the prick test did not alter the reaction.

AG, Luzern, Switzerland) to atracurium (Atracurium Labatec®; Labatec-Pharma SA, Meyrin, Switzerland), suxamethonium (Lysthenon®; Takeda Pharma AG, Pfäffikon, Switzerland) and rocuronium (Esmeron®; MSD AG, Luzern, Switzerland), as tested previously in our 3 patients. The prick tests with pure rocuronium, suxamethonium and atracurium were negative and sugammadex had no effects when added to these drugs before testing. The IDTs with atracurium (dilution 1:100) and suxamethonium (dilution 1:10) were positive (both irritative). Adding sugammadex before testing did not affect the test result. On the contrary, the rocuronium IDT (dilution 1:10) was positive (irritative) when tested alone, and negative when tested after mixing sugammadex in a 1:1 molar dilution (fig. 2), except in 1 healthy individual, in whom the IDT with rocuronium mixed with sugammadex (dilution 1:10) was positive, but with a smaller papule and erythema than rocuronium (dilution 1:10) alone (fig. 2a). This confirmed the specificity of sugammadex for inhibiting rocuronium-induced pseudoallergic reactions, and not other NMBA-induced pseudoallergic reactions. Moreover, in order to investigate the effects of sugammadex in classical IgE-me-

diated hypersensitivity reactions, we performed prick tests in two atopic individuals, adding sugammadex to commercial grass pollen (Allergopharma, Reinbek, Germany) and *Alternaria tenuis* mold extracts (Alyostal®; Stallergenes SA, Antony, France). Adding sugammadex did not alter the positive prick test reaction in the two atopic controls (fig. 3). These observations speak against an unspecific stabilizing effect of sugammadex on mast cells and support our hypothesis that sugammadex suppresses rocuronium-specific, non-IgE-mediated mast cell activation.

Sugammadex was recently also shown to be useful in the treatment of 2 cases of perioperative anaphylaxis due to antibiotic hypersensitivity in patients having received rocuronium. However, sugammadex was ineffective in anaphylaxis due to proven rocuronium hypersensitivity [14]. These observations do not argue against our hypothesis, and although we cannot exclude other mechanisms being involved in the rapid clinically favorable response seen in the reported patients, we suggest that sugammadex could be used to reverse pseudoallergic reactions to rocuronium, in addition to standard treatment including adrenaline.

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