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Treatment of Anaphylaxis to Rocuronium with Sugammadex: A Case Report with Bronchospasm as the Only Symptom

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Abstract

Anaphylaxis during anaesthesia is a rare event occurring in up to 1:20,000 anaesthetics and in 33%-63% neuromuscular blocking agents are involved. Several case reports suggested the effectiveness of sugammadex in the treatment of rocuronium-induced anaphylactic shock refractory to conventional treatment. We report a case of anaphylactic reaction to rocuronium that caused isolated respiratory symptoms and showed no improvement in oxygen saturation after intravenous corticosteroids and intratracheal beta-2 agonists and that was successfully treated with sugammadex. The underlying pathophysiological mechanisms that explain the potential beneficial effect of sugammadex in this context are not completely known. We briefly review the literature regarding this topic.

Keywords: Anaphylaxis, rocuronium, sugammadex

Introduction

Some perioperative drugs induce allergic reactions (1). Other factors could be involved in a surgical patient.

The incidence of perioperative anaphylaxis ranges from 1 in 385 to 1 in 20,000 (2). The worse outcomes are mortality (3% to 9%) and severe morbidity as anoxic cerebral injury. Neuromuscular blocking agents (NMBAs) have been involved in 33% to 63% of the cases (2) and 57% to 86% during the anaesthesia induction (1, 2). In this setting, the most frequent symptoms were cardiovascular- (78.6%), skin- (66.4%) and respiratory-related symptoms. A single organ system is involved in 10% to 14% of the episodes. The main symptom used to be bronchospasm in the case of the respiratory apparatus (39.9%). Notwithstanding, severe, isolated cardiovascular collapse and severe bronchospasm are the most frequent symptoms hindering the diagnosis (1).

Sugammadex (Bridion; Merck, Madrid, Spain) is a modified gamma-cyclodextrin that irreversibly binds rocuronium molecules (1:1). It blocks or attenuates the immunological processes by binding to rocuronium in the case of rocuronium-induced anaphylaxis (3).

Case Presentation

A 36-year-old male patient weighing 66 kg with a height of 162 cm, with an American Society of Anesthesiologists physical status I and a heavy smoker required laparotomy for blunt abdominal trauma. On admission, he was haemodynamically stable with normal eco-FAST. After 2 h, haemoglobin decreased from 14 g dL^{-1} to 9 g dL^{-1}, and computed tomography showed haemoperitoneum. On arrival in the operating room, haemodynamic, respiratory and oxygenation parameters were in normal range. Non-invasive monitoring was initiated, and two large bore

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intravenous catheters were inserted. Rapid sequence induction of anaesthesia was performed with midazolam, fentanyl, propofol and rocuronium (1.2 mg kg^{-1}), with the trachea being easily intubated. Suddenly severe difficulty to both mechanical and manual ventilation was noted, and arterial oxygen desaturation develops (65%). Laryngospasm, endotracheal tube misplacement, kinking or a foreign body (by passing an orogastric tube) and pneumothorax were excluded by exploration and a subsequent portable chest X-ray. There were no other signs or symptoms that appeared. Anaphylaxis was suspected. Some improvement in ventilation was observed with intravenous corticosteroids and intratracheal beta-2 agonists, but oxygen saturation did not improve (88%-90%) with 100% oxygen. As rocuronium anaphylaxis was suspected, 280 mg sugammadex was administered. Ventilation was possible, and the symptoms completely resolved in 2 min. Patient's gross movements started, and surgery proceeded using cisatracurium and sevoflurane with no incidences. The patient was admitted to the intensive care unit for 24 h without additional events.

Blood samples were obtained >1 h after the event started. Results showed serum tryptase in the normal range, as were complement and total IgE. A late skin prick testing was positive to rocuronium and negative to latex, propofol, cisatracurium, atracurium and succinylcholine. The basophil activation test (BAT) was positive to rocuronium, rocuronium plus sugammadex and cisatracurium and negative to succinylcholine.

Several months later, the patient was operated on twice due to surgical sequelae and relaxed with cisatracurium without any adverse effect.

Discussion

Clinical aspects

Up to 75% of allergic reactions to NMBA have been reported on the first known contact with an NMBA. Structure and activity studies have established that the substituted ammonium groups are part of the allergenic determinant structure. Since compounds containing tertiary and/or quaternary ammonium groups occur widely, previous sensitisation to NMBAs has been suggested (4).

In our patient, the isolated respiratory symptoms, together with the trauma he sustained, delayed the diagnosis. In the presence of bronchospasm, a part of the cited causes, inadequate anaesthetic depth or muscle relaxation and aspiration of gastric contents or blood should be ruled out.

Biochemical investigations

The higher the levels of biomarkers, such as serum tryptase and plasma histamine, the higher the probability the symptoms are related to an immediate hypersensitivity reaction. However, normal levels do not absolutely exclude the diagnosis because of a short plasma half-life. The diagnostic accuracy increases when histamine and tryptase are combined. The histamine half-life is approximately 2-3 min, making it of no practical value. Sheldon et al. suggested to obtain several samples to improve the detection of tryptase, both because of a narrow window to detect the increase and because of haemodilution.

Detection of IgE antibodies remains a key in the diagnosis. Rouzaire et al. (5) showed that in order to detect sensitisation, specific IgE against substituted tertiary ammonium structures are more useful than IgE antibodies against individual NMBA molecules (6).

Skin prick and intradermal tests should be performed at least 4-6 weeks after the reaction occurs because of false negatives. Positive skin tests using NMBAs are highly specific and had an adequate negative predictive value (7, 8).

Cell-targeted assays include histamine release assay, BAT by flow cytometry and leukotriene release test and are considered unnecessary if skin tests or specific IgE assays are positive. BAT has a good specificity but a low sensitivity and strongly correlates with skin test (9). Provocation testing is usually not used.

In the case presented, BAT results and cisatracurium tolerance may be explained because of (1) massive degranulation and inflammatory mediators release had occurred before, (2) sensitisation to cisatracurium occurred after surgery and (3) a false positive laboratory reaction to cisatracurium. Sensitivity was 54% versus 62% of specific IgE using flow cytometry (10).

A positive result to rocuronium plus sugammadex could be explained by the presence of specific antibodies to rocuronium on the basophils' membrane that quickly activates these cells before sugammadex had any effect on rocuronium molecules. The other explanation would be that the part of the molecules of rocuronium outside the sugammadex ring triggered the in vitro reaction (11).

Literature review

The usefulness of sugammadex in the management of rocuronium-induced anaphylaxis is supported by several case reports (Appendix 1).

We speculate whether sugammadex can rapidly obtund the biomarker response (11). The quick resolution of symptoms suggests a rapid block of free drug in plasma but also sequestration of the IgE cell antibody-bound rocuronium. In

this way, the allergic cascade would be suddenly stopped, even though the antibody-bound antigen in mast cells and basophils remained unaffected. Notwithstanding, this scenario does not fit with our current understanding of allergen-induced release of the mediators in anaphylaxis (12).

Leysen et al. (13) using in vitro activation of basophils concluded that encapsulating rocuronium by sugammadex can prevent, but not stop, the activation by the NMBA, and the administration of sugammadex unlikely mitigates anaphylaxis. Clarke et al. (14) using a skin model of anaphylaxis demonstrated that sugammadex-bound rocuronium prevents triggering a type 1 hypersensitivity reaction in sensitised individuals. However, sugammadex was ineffective in modifying the course of the reaction already triggered by rocuronium.

Sugammadex was ineffective in some cases otherwise responding to epinephrine and fluid loading, whereas others suggest that recovery could have occurred after 15-20 min only with the standard treatment (15).

The causative agent of the allergic reaction is incorrectly identified at the time of the reaction in one-third of the cases. Theoretically, at the target cell, the affinity of sugammadex for rocuronium should exceed the affinity of the cell-bound IgE antibodies, and encapsulation should hide the epitope responsible for rocuronium-induced anaphylaxis (3).

The patient did not receive adrenaline prior to sugammadex treatment. Therefore, improvement cannot be explained by its actions. Improvement cannot be attributed to an increase in preload as the only manifestation was bronchospasm and, conversely, reversal of neuromuscular blockade use to worse respiratory mechanics. In our patient, the time since the reaction to sugammadex injection started was approximately 15 min.

The current guidelines recommend to administer nebulised adrenaline after the inhaled beta-2 adrenergic receptor agonists or an intravenous bolus and infusion of beta-agonist or an adrenaline infusion. Corticosteroids are second-line treatment.

Conclusion

In isolated symptoms, as severe bronchospasm that develops during anaesthesia, an anaphylactic reaction should be suspected, and immediate treatment started. A case of rocuronium-induced anaphylaxis with clinical improvement after sugammadex is presented, adding to the small body of evidence regarding this topic.

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References

1. Escolano F, Sierra P. Reacciones alérgicas durante la anestesia. Rev Esp Anestesiol Reanim 1996; 43: 17-26.
2. Berroa F, Lafuente A, Javaloyes G, Cabrera-Freitag P, de la Borbolla JM, Moncada R, et al. The incidence of perioperative hypersensitivity reactions: a single-center, prospective, cohort study. Anesth Analg 2015; 121: 117-23. **[CrossRef]**
3. Jones PM, Turkstra TP. Mitigation of rocuronium-induced anaphylaxis by sugammadex: the great unknown. Anaesthesia 2010; 65: 82-93.
4. Mertes PM, Demoly P, Malinovsky JM. Hypersensitivity reactions in the anesthesia setting/allergic reactions to anesthesics. Curr Opin Allergy Clin Immunol 2012; 12: 361-8. **[CrossRef]**
5. Rouzaire P, Proton G, Bienvenu F, Guilloux L, Benoit Y, Piriou V, et al. IgE antibody detection in the diagnosis of hypersensitivity to neuromuscular blocking agents. Acta Anaesthesiol Scand 2012; 56: 263-4. **[CrossRef]**
6. Laroche D, Chollet-Martin S, Léturgie P, Malzac L, Vergnaud MC, Neukirch C, et al. Evaluation of a new routine diagnostic test for immunoglobulin E sensitization to neuromuscular blocking agents. Anesthesiology 2011; 114: 91-7. **[CrossRef]**
7. Ramirez LF, Pereira A, Chiriac AM, Bonnet-Boyer MC, Demoly P. Negative predictive value of skin test to neuromuscular blocking agents. Allergy 2012; 67: 439-441. **[CrossRef]**
8. Leysen J, Uyttebroek A, Sabato V, Bridts CH, De Clerck LS, Ebo DG. Predictive value of allergy test for neuromuscular blocking agents: tackling an unmet need. Clin Exp Allergy 2014; 44: 1069-75. **[CrossRef]**
9. Abuaf N, Rajoely B, Ghazouani E, Levy DA, Pecquet C, Chabane H, et al. Validation of a flow cytometric assay detecting in vitro basophil activation for the diagnosis of muscle relaxant allergy. J Allergy Clin Immunol 1999; 104: 411-8. **[CrossRef]**
10. Monneret G, Benoit Y, Debard AL, Gutowski MC, Topenot I, Bienvenu J. Monitoring of basophil activation using CD 63 and CCR3 in allergy to muscle relaxant drugs. Clin Immunol 2002; 102: 192-9. **[CrossRef]**
11. Baldo BA, McDonnell NJ. Sugammadex and anaphylaxis in the operating theater. Rev Esp Anestesiol Reanim 2014; 61: 239-45. **[CrossRef]**

12. Baldo BA, McDonnell NJ, Pham NH. The cyclodextrin sugammadex and anaphylaxis to rocuronium: is rocuronium still potentially allergenic in the inclusion complex form? MiniRev Med Chem 2012; 12: 1-12.
13. Leysen J, Bridts CH, De Clerck LS, Ebo DG. Rocuronium-induced anaphylaxis is probably not mitigated by sugammadex: evidence from an in vitro experiment. Anaesthesia 2011; 66: 519-31. **[CrossRef]**
14. Clarke RC, Sadleir PHM, Platt PR. The role of sugammadex in the developement and modification of an allergic response to rocuronium: evidence from a cutaneus model. Anaesthesia 2012; 67: 266-73. **[CrossRef]**
15. Platt PR, Clarke RC, Johnson GH, Sadleir PHM. Efficacy of sugammadex in rocuronium-induced or antibiotic-induced anaphylaxis. A case-control study. Anaesthesia 2015; 70: 1264-7. **[CrossRef]**

Appendix 1. Case reports of patients with suspected anaphylactic reaction to rocuronium treated with sugammadex

Reference	Patient characteristics	Scheduled surgical procedure	Symptoms	Start of anaphylaxis	Rocuronium dose (mg)	Sugammadex dose (mg)	Other treatments, timing*	Clinical response time**, outcome
Sirieix et al. (1) (2014)	Woman 60 years old, 92 kg, prior surgeries without allergy reports	Biliopancreatic endoscopic US	Arterial hypotension	17 min	50	400	Ephedrine, crystalloid infusion, adrenaline before	Favourable
Raft et al. (2) (2012)	Woman 51 years old, 112 kg, arterial hypertension, diabetes mellitus, hypercholesterolemia, prior surgeries without allergy reports	Umbilical hernia repair	Arterial hypotension, tachycardia, oxygen desaturation, $EtCO_2$ decrease	2 min	50	2000	Adrenaline, fluid therapy before	Few seconds, favourable
Motamed et al. (3) (2012)	Woman 61 years old, 45 kg, prior surgeries without allergy reports	Bone cementoplasty	Arterial hypotension, tachycardia, EtCO2 decrease, rash, wheezing	5 min	27	18	Adrenaline before	3 min, favourable
Timbó Barbosa et al. (4) (2012)	Woman 62 years old, 72 kg, prior surgeries without allergy reports	Cranial epidural haematoma evacuation	Arterial hypotension, tachycardia, oxygen desaturation, rash	Immediate	45	700	Crystalloid infusion, adrenaline before	2 min, favourable
Badaoui et al. (5) (2012)	Woman 52 years old, 77 kg, prior surgeries without allergy reports	Laparoscopic rectal cancer surgery	Arterial hypotension, tachycardia, oxygen desaturation, $EtCO_2$ decrease, rash	2 min	50	1000	Crystalloid infusion, adrenaline before	5 min, favourable
Funell et al. (6) (2011)	Woman 47 years old, 78 kg, previous allergic reaction to cotrimoxazole (rash and swelling)	Laparoscopic cholecystectomy	Difficult ventilation, $EtCO_2$ decrease, arterial hypotension, tachycardia, rash	Immediate	50	400	Crystalloid infusion, adrenaline, hydrocortisone, chlorpheniramine before	2.5 min, favourable
McDonnell et al. (7) (2011)	Woman 33 years old, 77 kg, heavy smoker, prior surgeries without allergy reports	Diagnostic abdominal laparoscopic procedure (infertility)	Difficult ventilation, $EtCO_2$ decrease, oxygen desaturation, hypotension, tachycardia, cardiorespiratory arrest	30 s	30	500	Crystalloid infusion, adrenaline, cardiopulmonary resuscitation manoeuvres before	45 s, favourable

Appendix 1. Case reports of patients with suspected anaphylactic reaction to rocuronium treated with sugammadex (continued)

Kawano et al. (8) (2012)	Woman 62 years old, 45 kg, no prior surgeries, preoperative chemotherapy	Modified radical mastectomy	Rash, arterial hypotension	Immediate	20	200	Ephedrine, fluid therapy before	'Shortly' afterwards, favourable
This study	Man 36 years old, 66 kg, heavy smoker	Laparotomy for blunt abdominal trauma	Severe difficulty to mechanical and manual ventilation, oxygen desaturation	Immediate	80	280	Intravenous corticosteroids, intratracheal beta-2 agonists before	Completely resolved in 2 min

Start of anaphylaxis in relation to rocuronium injection. All reactions occurred during the anaesthesia induction.
*Timing means other treatment administrations in relation to sugammadex administration.
**Clinical response time means the time that elapsed from sugammadex injection to clinically deemed adequate response.
US: ultrasound; NMBA: neuromuscular blocking agent

References in Appendix

1. Sirieix D, Latreille S, Raft J. Récupération hémodynamique rapide après une injection précoce conjointe d´adrenaline et de sugammadex lors d´un choc anaphylactique au rocuronium. Ann Fr Anesth Réanim 2014; 33: 600-609 **[CrossRef]**
2. Raft J, Leclercq M, Longrois D, Meistelman C. Récupération hémodynamique et ventilatoire rapide après injection de sugammadex lors d´un choc anaphylactique au rocuronium, réfractaire au traitement conventionnel. Ann Fr Anesth Réanim 2012; 31: 158-161 **[CrossRef]**
3. Motamed C, Baguenard P, Bourgain JL. Possible mitigation of rocuronium-induced anaphylaxis after administration of sugammadex. J Anaesthesiol Clin Pharmacol 2012; 28: 1: 127-128 **[CrossRef]**
4. Timbó Barbosa F, Martins da Cunha R. Case of anaphylaxis induced by rocuronium treated with sugammadex. Rev Bras Anestesiol 2012; 62: 4: 538-542. **[CrossRef]**
5. Badaoui R, Popov I, Dupont H. Un nouveau cas de choc anaphylactique induit par le rocuronium amélioré par le sugammadex. Can J Anesth 2012; 59: 909-910. **[CrossRef]**
6. Funnell AE, Griffiths J, Hodzovic I. A further case of rocuronium-induced anaphylaxis treated with sugammadex. Br J Anaesth 2011; 107:2: 275-6. **[CrossRef]**
7. McDonnell NJ, Pavy TJG, Green LK, Platt PR. Sugammadex in the management of rocuronium-induced anaphylaxis. Br J Anaesth 2011; 106:2: 199-201 **[CrossRef]**
8. Kawano T, Tamura T, Hamaguchi M, Yatabe T, Yamashita K, Yokoyama M. Successful management of rocuronium-induced anaphylactic reactions with sugammadex: a case report. J Clin Anesth 2012; 24: 62-64. **[CrossRef]**