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Severe allergic reactions following administration of Sugammadex with low tryptase levels but positive skin prick test: a case report

Teške alergijske reakcije nakon primjene Sugammadexa s niskom razinom triptaze, ali pozitivnim testom uboda kože: prikaz slučaja

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Summary

We describe here the case of a severe anaphylactic episode to Sugammadex administered to reverse neuromuscular block in a 54-year-old man who underwent lumbar discectomy under general anaesthesia. Induction to anaesthesia and the entire surgical procedure were without any peculiarities. At the end of the surgery, 200 mg of Sugammadex was administered. Three minutes later, he developed a severe anaphylactic reaction accompanied by severe bronchospasm, with high peak airway pressures, drop of pulse oxygen saturation down to 70% despite FiO2 of 1.0, moderate decrease of arterial blood pressure (lowest was 80/50 mmHg) and normal heart rate of 70/min. Also, five minutes later he developed generalized skin rash and piloerection. The patient recovered completely after initial medical treatment per guidelines for treatment of anaphylactic shock. He was extubated in the Intensivel Care Unit a few hours later. Repeated blood mastocyte tryptase levels showed only a mild increase during the acute reaction. The allergic reaction to Sugammadex was confirmed by a positive intradermal test to Sugammadex a couple months later.

Key words: anaesthesia, general; hypersensitivity; allergic reaction: anaphylaxsis; Sugammadex

Sažetak

U radu opisujemo slučaj teške anafilaktičke reakcije na Sugammadex primijenjen u svrhu reverzije neuromišićnog bloka kod pedesetčetvorogodišnjeg muškarca tijekom lumbalne discektomije u općoj anesteziji. Uvod u anesteziju i sam operacijski postupak prošli su bez osobitosti. Na kraju operacijskog zahvata bolesnik je primio 200 mg Sugammadexa. Nakon tri minute po primjeni sredstva za reverziju bloka bolesnik je razvio tešku anafilaktičku reakciju praćenu teškim bronhospazmom, visokim tlakovima u dišnome krugu, padom saturacije periferne krvi kisikom do 70%, unatoč FiO2 1,0. Također, bolesnik je razvio umjereni pad krvnog arterijskog tlaka (najniža vrijednost bila je 80/50 mmHg), uz normalnu frekvenciju srčane akcije od 70/min. Nadalje, 5 minuta nakon početne reakcije razvio je i generalizirani osip i piloerekciju. Bolesnik se ubrzo oporavio nakon početnog liječenja anafilaktičke reakcije po važećim smjernicama, te je ekstubiran u jedinici intenzivnog liječenja nekoliko sati kasnije. Laboratorijski uzorci za mastocitnu triptazu pokazali su samo blagi porast tijekom akutne reakcije. Alergijska reakcija na Sugammadex potvrđena je nekoliko mjeseci kasnije pozitivnim intradermalnim testiranjem.

Ključne riječi: anestezija, opća, preosjetljivost, alergijska reakcija, anafilaksa, Sugammadex

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Introduction

Perioperative anaphylactic reactions are rare but potentially life-threatening events. The usual culprits are neuromuscular blocking agents, intravenous anaesthetics, opioids and non-steroidal anti-inflammatory drugs. Diagnosis of anaphylaxis is based on clinical findings and elevated histamine and mastocyte tryptase levels. Anaphylactic reactions are immune mediated type I allergic reactions following the massive release of mediators from mast cells and basophils as a response to an allergen. Anaphylactoid reactions are defined as those reactions that produce the same clinical picture with anaphylaxis but are not IgE mediated, occur through a direct nonimmune-mediated release of mediators from mast cells and/or basophils or result from direct complement activation.[1] The severity of allergic reactions can vary significantly. A recent gradation by Niggemann and Beyer suggested three grades: local reaction, mild to moderate systemic reaction (no cardiovascular and/or respiratory symptoms) and severe systemic allergic reaction (anaphylaxis) with cardiovascular and/or respiratory involvement.[2]

Sugammadex is a newer neuromuscular blockade reversal agent. It acts by encapsulation of rocuronium or vecuronium molecules making them unavailable to the acetylcholine receptor at the neuromuscular junction. Sugammadex, unlike neostigmine, does not inhibit acetylcholinesterase, therefore co-administration of an antimuscarinic agent (glycopyrrolate or atropine) is not needed to prevent undesirable cholinergic effects and might have fewer adverse effects than the traditional reversal agents. Sugammadex has been approved for use in the European Union since 2008 by the European Medicines Agency (EMA). Due to concerns about its safety, the United States Food and Drug Administration (FDA) just recently approved the use of Sugammadex, which is generally considered a safe and well tolerated drug. Only a few cases of allergic reactions are described in the literature. We will describe a case of severe systemic allergic reaction to Sugammadex in a patient after lumbar spine surgery.

Informed consent was obtained from the patient.

Report

A 54-year-old man (173 cm, 92 kg, BMI 31 kg/m^2) underwent lumbar discectomy in a prone position. His medical history along with severe back pain was well controlled hypertension, high cholesterol, and asthma and with no history of allergies. His surgical history was only hernia surgery done under general anesthesia with no exposure to neuromuscular blocking agents (NMBA) nor reversal agents.

General endotracheal anesthesia was induced with 2 mg of midazolam (Midazolam, ADVANZ Pharma), 100 mcg of fentanyl (Fentanyl, hameln pharmaceuticals ltd), 200 mg of propofol (Diprivan, Aspen) and 100 mg of rocuronium (Esmeron, Merck Sharp & Dohme Limited). After the induction, the patient received dexamethasone (8 mg) and ondansetron (4 mg) for prophylaxis of postoperative nausea and vomiting, as well as tranexamic acid (1 g) for the prevention of acute blood loss during the surgery. Five milligrams of morphine were given for intraoperative pain control. Gentamicin (320 mg) and flucloxacillin (2 g) were given as prophylactic antibiotics. Sevoflurane in mixture of air and oxygen (50:50) with fresh gas flow of 1L/min was used for the maintenance of anesthesia. One hour after the induction, additional doses of fentanyl (100 mcg) and morphine were used for pain control. Also, 20 mg of rocuronium was given at the same time. Hartman's solution was given for volume replacement. During the surgery, the patient was stable without any clinical problems. At the end of the surgery 1 g of vancomycin was locally applied to the wound and the wound was closed. The patient was flipped back to supine position and 200 mg of Sugammadex was administered for the reversal of neuromuscular blockade. Three minutes after Sugammadex administration we noticed severe bronchospasm, with high peak airway pressures, drop of pulse oxygen saturation down to 70% despite FiO_2 of 1.0, moderate decrease of BP (lowest was 80/50 mmHg) and normal HR of 70/min. Also, five minutes later he developed generalized skin rash and piloerection. Immediately treatment of severe allergic reaction was started as with epinephrine 0.5 mg intramuscularly, 100 mg of hydrocortisone, 10 mg of chlorphenamine maleate and bolus of 1 L of Hartman's was immediately infused. Due to severe wheezing, we administered 250 mg of aminophylline and 2 g magnesium sulphate in slow infusion. The patient responded to the initial treatment, but because of slowly resolving of bronchospasm he was sedated and remained intubated. Mechanical ventilation was continued in the critical care unit for the next few hours. He was haemodynamically stable and needed only epinephrine nebulizers for bronchoconstriction treatment for the next few hours until it was resolved. There was no need for intravenous vasopressors. Skin rash resolved 1 hour after intramuscular epinephrine injection which was given in the operation room. The patient completely recovered and was extubated that evening. Our patient's symptoms would be Grade III-severe systemic reaction = anaphylaxis.[2]

Sugammadex was suspected as the allergic cause because no drug except Sugammadex was administrated prior to development of the symptoms.

Blood samples were taken for mastocyte tryptase levels per guidelines for intraoperative anaphylaxis. Results were as follow: 1st sample (30 minutes after Sugammadex was given) 5.43 ng/L, 2nd sample (one hour later) 6.33 ng/L, 3rd sample (six hours later) 2.18 ng/L, and 4th sample (3 days after an event) < 1.00 ng/L with normal values being below 11.5 ng/ml. Eight weeks later, allergy testing was performed. The skin Prick Test (SPT) and intradermal test (IDT) were negative for fentanyl, propofol, rocuronium, midazolam, ondansetron, dexamethasone, tranexamic acid, gentamicin and vancomycin, but the IDT was positive for Sugammadex (6 x 6 mm to 10 x 11 mm). Also, the patient tolerated the challenge to tranexamic acid with no adverse events.

Discussion

Perioperative anaphylaxis is a life-threatening condition with an estimated prevalence of 1:3,500 to 1: 20.000 procedures and a mortality rate of up to 9%.[3]

Muscle relaxants and latex allergy account for most cases of anaphylaxis during the perioperative period.[4] Symptoms may include all organ systems and present with bronchospasm and cardiovascular collapse in the most severe cases.[5] We have described severe anaphylactic reaction that occurred immediately after administration of 2.1 mg/kg of Sugammadex in a patient that underwent spinal surgery. Sugammadex was chosen due to fewer side effects and no need for anti-muscarinic agent co-administration.

Sugammadex is rapidly replacing reversal of NMBA with neostigmine, where it is available, because of its safety profile. Hypersensitivity to Sugammadex is the major concern, but fortunately hypersensitivity reactions rarely occur.[6] The US FDA postponed the approval of Sugammadex until 2015, citing concerns regarding its safety profile, including the risk of potentially life-threatening hypersensitivity reactions.[7] A recent clinical trial did not show significantly different incidence of anaphylactic reactions between Sugammadex and placebo.[8] However, there are sporadic case reports of possible anaphylactic reactions caused by Sugammadex worldwide. The incidence of anaphylactic reactions caused by Sugammadex is much lower than that of anaphylaxis associated with neuromuscular blocking agents.[8,9] Miyazaki and colleagues investigated retrospectively the incidence of potential Sugammadex-induced anaphylaxis at a single centre in Japan over a period of 3 years. They found that the overall incidence of intraoperative hypersensitivity reaction was 0.22%, and the incidence of anaphylaxis was only 0.059%.[10] In a recent clinical study, Min and al. found that subjects who received Sugammadex with general anesthesia and/or NMB had a low overall incidence of hypersensitivity, with no apparent increase in hypersensitivity or anaphylaxis with Sugammadex as compared to placebo or neostigmine.[11]

Even though our patient had not been previously exposed to Sugammadex, development of allergic reaction was possible. Allergic reactions might occur due to cross-sensitivity to other drugs, foods, or common environmental chemicals.[12] Also, our patient had a history of well controlled asthma which could increase the risk for severe allergic reaction. He developed mostly respiratory symptoms with only a mild decrease of blood pressure and normal heart rate. Prompt treatment with epinephrine and fluid loading are probable reasons for preserved cardiovascular stability. Additionally, our patient was a middle aged man who was fit and well before surgery with no cardiac symptoms and good exercise tolerance and, therefore, more capable to compensate cardiovascular changes during anaphylactic reaction. The diagnosis of anaphylaxis is based on suggestive clinical symptoms after exposure to a potential triggering agent or event. Currently, there is no reliable biological marker available to confirm the diagnosis.[13] It can be only supported by laboratory tests, such as histamine or tryptase levels. These mediators are contained in the mast cells and they are released into circulation after mast cell activation.[13] Serum tryptase concentration is the most used laboratory test to confirm anaphylaxis, still normal levels do not refuse diagnosis. Current recommendation from literature is serial measurements of tryptase levels because of higher sensitivity and specificity.[14] Despite the typical clinical picture of anaphylactic reaction, tryptase levels in our patient remained within normal range (less than 11.5 ng/mL), but still showed changes over the time. Our diagnosis is supported by decreasing of tryptase levels below 1 ng/mL three days after anaphylactic reaction (baseline level). Studies on drug-induced anaphylactic reactions suggest that milder allergic reactions may be associated with no increase in the tryptase levels.[15] Allergy tests of our patient showed positive result on intradermal test (IDT) only for Sugammadex, supporting a diagnosis of allergic reaction.

Conclusion

Clinicians must be aware that severe anaphylactic reactions can be induced by the administration of Sugammadex, even with patients with no previous exposure. Diagnosis is still based on typical clinical features, and laboratory tests are only supportive.

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