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Anaphylactic Reaction Case After Sugammadex Application

Ökkeş Hakan Miniksar
Ramazan Kırteke

Sugammadeks Uygulaması Sonrası Anafilaktik Reaksiyon Olgusu

ABSTRACT

Sugammadex is a synthetic gamma-cyclodextrin-derived agent that selectively encapsules non-depolarizing neuromuscular blockers (NMBAs) such as rocuronium. This case report aims to present a life-threatening anaphylactic shock that is thought to be related to sugammadex application after reversal of the neuromuscular blockade. The patient was a 59-year-old male who had a history of uncomplicated inguinal hernia repair under general anesthesia 10 years ago and had no additional disease. Endovascular coil embolization of cerebral aneurysm was planned under general anesthesia by the interventional radiology clinic. No complications related to surgery or anesthesia were observed during the operation. At the end of the operation, intravenous (IV) 200 mg sugammadex was administered to the patient. Approximately 2 minutes after extubation, the patient developed an anaphylactic reaction, which was thought to be due to sugammadex injection. The symptoms of the patient regressed with the administration of ephedrine, adrenaline and methylprednisolone. We should be aware of the fact that life-threatening anaphylactic reactions may develop after administration of sugammadex.

Keywords: *Anaphylactic reaction, sugammadex, general anaesthesia*

ÖZ

Sugammadeks, roküronyum gibi steroid yapılı nondepolarizan nöromüsküler ajanları (NMBAs) selektif olarak enkapsüle eden, sentetik gamma-siklodekstrin yapısında bir ajandır. Bu olgu sunumunun amacı, nöromüsküler blokajın geri döndürülmesi sırasında sugammadekse bağlı olduğu düşünülen, hayatı tehdit eden anaflaktik şok tablosunu sunmaktır. Hasta 10 yıl öncesine ait genel anestezi altında komplikasyonsuz inguinal herni onarımı öyküsü olan ve ek hastalığı olmayan 59 yaşında erkek idi. Girişimsel radyoloji kliniği tarafından genel anestezi altında serebral anevrizmanın endovasküler koil embolizasyonu planlandı. Operasyon esnasında cerrahi veya anesteziye bağlı herhangi bir komplikasyon gözlemlenmedi. Operasyon sonunda hastaya intravenöz (IV) 200 mg sugammadeks enjeksiyonuna uygulandı. Ekstübasyondan yaklaşık 2 dakika sonra hastada sugammadekse bağlı olduğu düşünülen anaflaktik reaksiyon gelişti. Efedrin, adrenalin ve metilprednizolon uygulanan hastanın semptomları geriledi. Sugammadeks uygulanmasından sonra hayatı tehdit eden anaflaktik reaksiyonların gelişebileceğinin farkında olmalıyız.

Anahtar kelimeler: *Anafilaktik reaksiyon, sugammadeks, genel anestezi*

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Ökkeş Hakan Miniksar
Yozgat Bozok Üniversitesi
Tıp Fakültesi, Anesteziyoloji ve
Reanimasyon Anabilim Dalı,
Yozgat, Türkiye
hminiksar@yahoo.com
ORCID: 0000-0001-5645-7729

R. Kırteke 0000-0002-6869-3048
Malatya Eğitim ve Araştırma Hastanesi, Anesteziyoloji ve Reanimasyon Kliniği, Malatya, Türkiye

INTRODUCTION

Perioperative anaphylaxis; is a systemic potentially life-threatening allergic reaction that develops acutely, and affects multiple organ systems. Although it is rare (1:3500-1:13000), its mortality rate is between 3% and 9% [1]. Patients with anaphylaxis due to the administration of more than one pharmacological agent during general anesthesia should be evaluated more comprehensively [1].

Sugammadex is a synthetic γ-cyclodextrin-derived agent that selectively encapsules NMBAs such as rocuronium. It is biologically inactive, does not bind to plasma proteins, and has been reported to be safe and well-tolerated [2]. Sugammadex has been used since April 2010 in Turkey, and to our knowledge no severe anaphylaxis was reported due to sugammadex in our country.

In this article it was aimed to present the life-threatening anaphylactic shock that is thought to be due to iv bolus administration of sugammadex during the reversal of neuromuscular blockade.

CASE

Endovascular coil embolization was planned for a 59-year-old male patient (body weight: 75 kg, height: 174 cm, ASA II) by the interventional radiology clinic for the treatment of cerebral aneurysm under general anesthesia. The patient had an uncomplicated inguinal hernia repair 10 years ago under general anesthesia and a history of smoking 20 cigarettes per day. There was no history of allergy related to medication, food, latex or other environmental factors, and he had not been exposed to sugammadex before. In the preoperative examination; laboratory findings, results of chest radiography, and electrocardiography were within normal limits. No premedication was applied.

When the patient was taken to the operating room, his arterial blood pressure was 133/80 mmHg, heart rate was 84 bpm and oxygen saturation (SpO_2) was 100%. After preoxygenation, the patient underwent anesthesia induced with 2.5 mg kg^{-1} propofol, 1.5 µg kg^{-1} fentanyl, and 0.5 mg kg^{-1} lidocaine, and was intubated after injection of 0.6 mg kg^{-1} rocuronium bromide. Right internal jugular vein catheterization and intra-arterial cannula were placed. Anesthesia was maintained with a mixture of 2% sevoflurane and 50% oxygen-air mixture. During the operation, SpO_2 was 98-100%, heart rate was 95-110 bpm, arterial blood pressure was kept in the range of 120-140 mmHg and end-tidal CO_2 ($EtCO_2$) (35-45 mmHg) was within normal range. No complications related to surgery or anesthesia were observed and the duration of the procedure was 130 minutes. Antibiotic treatment was not applied to the patient during the intraoperative period. At the end of the operation, 200 mg IV sugammadex (Bridion, 200 mg mL^{-1}, MSD) was administered to reverse the rocuronium neuromuscular block. After administration of sugammadex, the patient's muscle strength recovered and he fulfilled other criteria for extubation and was extubated. No other drugs were given at this period. About 2 minutes after extubation, the patient's heart rate decreased from 78 bpm to 38 bpm, and blood pressure decreased from 130/66 mmHg to 45/26 mmHg. Crystaloid infusion and IV 20 mg ephedrine was administered to the patient. Advanced swelling of the patient's tongue, lips, eyes, and face, as well as redness of the upper body, were observed. Spontaneous breathing and consciousness of the patient deteriorated and he was ventilated with a manual mask. Despite administration of IV 0.5 mg of atropine, ongoing bradycardia, no improvement in hemodynamic parameters was observed. This situation was considered as sugammadex- related severe anaphylactic reaction and IV 0.5 mg adrenaline, 160 mg methylprednisolone and 10 mg chlorphenoxamine hydrochloride were administered rapidly. Endotracheal intubation was planned and the patient was placed in Trendelenburg position. There was no improvement in oxygen saturation with manual mask ventilation (SpO_2:80%-75%). Spontaneous breathing of the patient improved with repeated dose of IV 0.2 mg adrenaline. Swelling on the patient's face and urticaria on his body also regressed. Heart rate increased to 140 bpm and blood pressure to 210/110 mmHg. After about 3 minutes, the patient's hemodynamic status and breathing improved. The patient was fully awake and SpO_2 increased to 95-98%. Cerebral computed tomography was taken, with no pathological finding the patient was transferred to the intensive care unit. Serum tryptase and histamine levels could not be measured with our

current laboratory facilities, skin tests could not be applied because the patient could not survive after development of cerebral vasospasm on the 3rd day of his follow-up in the intensive care unit.

Written informed consent was obtained from the patient's relatives to publish this case report.

DISCUSSION

Sugammadex is a gamma amin-steroid cyclodextrin derivative and reverses the effects of NMBAs acting through encapsulating synthetic rocuronium, used in Turkey since April 2010 [2]. This is the first case of anaphylactic shock induced by sugammadex reported from Turkey as far as we know.

The mechanism of action of sugammadex is 10 times faster than neostigmine and has lesser side effects. In a multicenter study comparing the incidence of anaphylaxis between sugammadex and neostigmine, it was stated that neostigmine may be safer than sugammadex and it may be beneficial to revise the choice of reversal agents by anesthesiologists [3]. In the same study, it was reported that six of 29962 patients (0.02%) developed anaphylaxis due to sugammadex, and no patient had anaphylaxis due to neostigmine (0/3157) [3].

The incidence of perioperative anaphylaxis in the literature is 1/6.000-1/20.000; and the mortality rate is between 3-6% [1,4]. Most of the anaphylactic reactions occur in the operating room (58%) and 3% of these occur before, and 81% of them after preoperative induction of anesthesia, 13% during and 3% after surgery [4,5]. It is difficult to determine the cause of anaphylaxis as various medications are being used during anesthesia. The most common identifiable causes of perioperative anaphylaxis have been identified as antibiotics (the most common cause in several American studies), NMBAs (the most common cause in many European studies), latex, blood products, chlorhexidine and patent blue [5-7]. Sedatives, analgesics, local anesthetics, and other drugs are less common causes [1]. Prophylactic antibiotics were used in our patient 30 minutes before surgery, NMBAs in induction of anesthesia, and opioids 30 minutes before the anaphylactic reaction. The only drug used before the development of anaphylaxis was sugammadex, which we gave 2-3 minutes before its onset.

The diagnosis of perioperative anaphylaxis is mainly mainly clinical observation [8]. The diagnostic criteria of anaphylaxis according to World Allergy Organization guidelines are: sudden onset (minutes to several hours) after skin and mucosal tissue involvement, and additionally accompanied by minimal sudden breathing problems or a sudden decrease in blood pressure [8]. In this case report; the development of skin and mucocutaneous involvement, sudden respiratory distress and progressive cardiovascular collaps 2-3 minutes after administration of sugammadex meets the criteria of anaphylaxis. It has been reported that allergic reactions due to sugammadex are more common at high clinical doses (16-96 mg kg^{-1}) [9]. However, cases of anaphylaxis related to sugammadex use at low doses (1.9-2.2-1.2 mg kg^{-1}) have been also reported [3,10]. In this case, the dose of sugammadex was 200 mg (2.6 mg kg^{-1}). In addition, in a randomized study with healthy volunteers, it was reported that hypersensitivity reactions due to sugammadex were not dose-dependent [11]. It is known that after rapid administration of the drugs as an IV bolus, side effects start faster and hypersensitivity reactions are seen more frequently [12]. This is also valid for sugammadex, and it is recommended in the instructions for use that the drug should be given as a single bolus injection over 10 seconds [13]. Another important point is that hypersensitivity reactions, including anaphylaxis, were observed in healthy volunteers who had not been exposed to sugammadex before. It has been reported in many studies that sugammadex should not be administered to patients with known hypersensitivity and that patients should be observed for hypersensitivity reactions for an appropriate period after each administration [11].

Clinical diagnosis can sometimes be supported retrospectively by documentation of high plasma tryptase or histamine levels [8]. However, their normal levels do not strictly rule out the diagnosis due to its short plasma half-life. Since the clinical features of this case were very similar to the sugammadex-induced anaphylactic shock [14,15] and occur immediately after sugammadex administration, we suspected that the causal agent may be sugammadex. Skin prick and intradermal tests are the gold standard for

the diagnosis of drug hypersensitivity and should be performed at least 4-6 weeks after the reaction due to false-negative results [14]. In addition, histamine release test and basophil activation tests have been suggested in clinical practice [3,14,16]. Serum tryptase and histamine levels could not be measured with our existing laboratory facilities and skin tests could not be performed because the patient died on the 3rd day of the follow-up.

A patient developing anaphylactic shock should be treated quickly and specifically, including IV fluid replacement and the use of cardiovascular drugs. Adrenaline is the only drug recommended as the first-line treatment in all published anaphylaxis guidelines [1,8]. However, the guidelines do not agree on the initial dose or injection route of epinephrine [6]. It has been reported in the literature that delayed adrenaline injection is associated with mortality [15]. In this case, 20 mg of ephedrine was administered priorly before adrenaline. As bradycardia persisted, IV 0.5 mg of atropine and IV 0.5 mg of adrenaline were administered. The dose of IV bolus 0.5 mg and 0.1 mg adrenaline administered to this case was higher than the initial dose recommended in the guidelines. In this case, rapid improvement of symptoms was observed after IV adrenaline administration.

CONCLUSION

Although sugammadex is an effective agent, it can cause life-threatening anaphylactic reactions within the first 5 minutes after its administration. Therefore, after sugammadex administration, patients should be carefully monitored, considering the possibility of an anaphylactic reaction that may develop until they are transferred to the recovery room.

Conflict of Interest: None
Informed Consent: None

REFERENCES

1. Hepner DL, Castells MC. Anaphylaxis During the Perioperative Period. Anesth Analg. 2003;97:1381-95. https://doi.org/10.1213/01.ANE.0000082993.84883.7D
2. Bilgi M, Demirhan A, Akkaya A, Tekelioglu U, Kocoglu H. Sugammadex associate persistant bradycardia. Int J Med Sci Public Heal. 2014;3:372. https://doi.org/10.5455/ijmsph.2013.251220131
3. Orihara M, Takazawa T, Horiuchi T, et al. Comparison of incidence of anaphylaxis between sugammadex and neostigmine: a retrospective multicentre observational study. Br J Anaesth. 2019;10:1-10. https://doi.org/10.1016/j.bja.2019.10.016
4. Hunter JM, Naguib M. Sugammadex-induced bradycardia and asystole: how great is the risk?. Br J Anaesth. 2018;121:8-12. https://doi.org/10.1016/j.bja.2018.03.003
5. Center for Drug Evaluation and Research-US Food and Administration. FDA adverse event reporting system (FAERS). https://www.fda.gov/Drugs/Information On Drugs/ucm 135151.htm; 2020 [accessed 13 March 2020]
6. Hopkins PM, Cooke PJ, Clarke RJ, et al. Consensus clinical scoring for suspected perioperative immediate hypersensitivity reactions. Br J Anaesth. 2019;123:e29-37. https://doi.org/10.1016/j.bja.2019.02.029
7. Harper NJN, Cook TM, Garcez T, et al. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). Br J Anaesth. 2018;121:159-71. https://doi.org/10.1016/j.bja.2018.04.014
8. Levy JH, Castells MC. Perioperative Anaphylaxis and the United States Perspective. Anesth Analg. 2011;113:979-81. https://doi.org/10.1213/ANE.0b013e31822d68a5
9. Pierre P, Michiel H, Emiel H, et al. Safety, Tolerability and Pharmacokinetics of Sugammadex Using Single High Doses (Up to 96 mg/kg) in Healthy Adult Subjects. 2010;30:867-74. https://doi.org/10.1007/BF03256915
10. Godai K, Hasegawa-Moriyama M, Kuniyoshi T, et al. Case report Three cases of suspected sugammadex-induced hypersensitivity reactions. British Journal of Anaesthesia. 2010;109:216-8. https://doi.org/10.1093/bja/aes137
11. Min KC, Bondiskey P, Schulz V, et al. Hypersensitivity incidence after sugammadex administration in healthy subjects: a randomised controlled trial. British Journal of Anaesthesia. 2018;121:749-57. https://doi.org/10.1016/j.bja.2018.05.056
12. Simons FER, Ebisawa M, Sanchez-Borges M, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organization Journal. 2015;8:1-16. https://doi.org/10.1186/s40413-015-0080-1
13. Information for the user. https://www.merckconnect.com/bridion/dosing-administration/; 2020 [accessed 13 August 2020]
14. Tsur A, Kalansky A. Hypersensitivity associated with sugammadex administration: a systematic review. Anaesthesia. 2014;69:1251-7. https://doi.org/10.1111/anae.12736
15. McDonnell NJ, Pavy TJG, Green LK, et al. Sugammadex in the management of rocuronium-induced anaphylaxis. Br J Anaesth. 2011;106:199-201. https://doi.org/10.1093/bja/aeq366
16. Masakazu Y, Miki D, Kiichiro N, et al. A suspected case of rocuronium-sugammadex complex induced anaphylactic shock after cesarean section. J Anesth. 2017;31:148-51. https://doi.org/10.1007/s00540-016-2280-4