THE CASE REPORTS

Institute of Cardiovascular Diseases of Vojvodina, Sremska Kamenica

Summary

Introduction. Perioperative anaphylaxis is a hypersensitivity reaction that occurs after exposure to drugs used for anesthesia during a surgical procedure. The most common triggers are neuromuscular blocking agents and antibiotics. Case Report. A 71-old man, with a history of anaphylaxis during previous anesthesia, was scheduled for elective surgery. The clinical signs included skin rash, swelling of the upper part of the body with angioedema of the eyelids and lips, without bronchospasm. Based on the assumption that rocuronium was the most likely causative agent, percutaneous coronary intervention was attempted, but without optimal results, so the patient was prepared for elective coronary surgery. The most common triggers are neuromuscular blocking agents and antibiotics. Neuromuscular blocking agents and antibiotics are the most common triggers. Skin tests and in-vitro tests remain the gold standard for detection of suspected agent, pathophysiological mechanism, safe alternatives, and involve exposure of the skin mast cells of patients who experience anaphylaxis to the suspected allergen. The aim of this case report was to describe early diagnosis and management of perioperative anaphylaxis.
**Case Report**

A 71-old male (weight 70 kg and body mass index 22/36), American Society of Anesthesiologists physical status Class IV, was scheduled for elective coronary artery bypass graft surgery. He had a history of allergic reaction during anesthesia 11 months before in our hospital when he was scheduled for the same surgery. The patient’s anesthesia record from the previous surgery showed that he received 5 mg Bisoprolol and 0.25 mg/kg Midazolam preoperatively. General anesthesia was induced with 80 mg Lidocaine, 50 mcg Sufentanil, 2 mg Midazolam, 60 mcg Propofol and 70 mcg Rocuronium. After the medications were given, he developed skin rash and edema on his head, neck and chest. With possible diagnosis of anaphylaxis, Methylprednisolone 1 mg/kg was given intravenously. Bronchospasm after tracheal intubation was not recorded and he remained hemodynamically stable. After tracheal intubation, angioedema of eyelids and mouth occurred, and another dose of Methylprednisolone 1 mg/kg was given together with Chloropyramine 40 mg intravenously with continuous infusion of diluted Adrenaline 0.1 mcg/kg/min. He responded to the treatment and the swelling of the face and body decreased gradually. The surgery was suspended and he remained orotracheally intubated and transferred to the Intensive Care Unit where he remained hemodynamically stable. He did not require any inotropes and after 3 hours he was extubated with satisfactory blood gas analysis. He was transferred to the ward the next morning. After 4 days, percutaneous coronary intervention was performed successfully and stents were placed in the ramus circumflex artery and ramus intermedium artery.

He was sent for prick skin test and intradermal test after 10 weeks to an Allergy and Immunology Clinic where examination on neuromuscular blocking agents was performed and confirmed immune reaction to Rocuronium (generalized urticaria). It was strongly recommended to avoid the triggering agent and other aminosteroid neuromuscular blocking agents (Pancuronium). There were no clinical signs of early or late allergic reactions to Suxamethonium chloride and Cisatracurium, so they could be used. The patient was hospitalized for a planned surgery. The only alternate neuromuscular blocking agent available to us was Cisatracurium. According to the allergist’s recommendations, he was received intravenous Methylprednisolone 40 mg, a Levocetirizine and a Famotidine tablet the day before surgery. All precautionary measures were taken, drugs such as adrenaline, steroids and antihistamines were loaded drogwise as in syringes and equipment required for resuscitation was kept ready. The premedication included intravenous Methylprednisolone 40 mg, 1 intramuscular Chloropyramine vial, and 1 intravenous Pantoprazole vial and the patient was transferred to the operating room. The electrocardiogram, blood pressure, pulse, SpO₂, and capnography were monitored and intravenous access was established. His preoperative blood pressure was 150/74, pulse 88/min and SpO₂ was 98% on room air. The patient was preoxygenated with 100% oxygen. General anesthesia was performed with 100 mcg Fentanyl, 2 mg Midazolam, and 60 mcg Propofol. Muscle relaxation was achieved by infusion of Cisatracurium (0.2 mg/kg). After 3 minutes of ventilation, the patient was intubated and the position of orotracheal tube was checked. Anesthesia was maintained by sevoflurane 0.8 – 1.5% in 1:2 mixture of oxygen and air. Muscle relaxation was maintained with 6 supplemental bolus doses of Cisatracurium (0.03 mg/kg). Intraoperatively, patient remained hemodynamically stable. After Propamine administration, 100 mg Hydrocortisone was administered intravenously to slow down the patient’s immune system and prevent allergic reaction. The surgery lasted 180 minutes and total anesthesia 205 minutes. The patient was moved into the Intensive Care Unit where he maintained hemodynamically stable. After 3 hours he was extubated with satisfactory blood gas analysis.

The patient was moved to the ward and discharged from hospital 7 days later. He received written information about all procedures and tests that were performed, safe and unsafe drugs and anesthesia procedures.

**Discussion**

Perioperative anaphylaxis is a life-threatening immediate hypersensitivity condition which may be a result of non-allergic (immunological mechanism excluded) or allergic (immunological mecha-
nism proved or highly suspected) reaction [2]. The incidence of perioperative anaphylaxis ranges from 1 in 18,600 to 1 in 353 with geographical variability [3]. Neuromuscular blocking agents and antibiotics are the most common cause of anaphylaxis and usually occur after induction of anesthesia. Rocuronium is associated with a higher rate of anaphylaxis compared to other neuromuscular blocking agents [4]. The other triggering agents that may cause perioperative anaphylaxis are hypnotics, opioids, local anesthetics, latex, nonsteroidal anti-inflammatory drugs, disinfectants, dyes, colloids, blood products, aprotinin, and protamine sulphate [5]. The diagnosis of perioperative anaphylaxis is based on a combination of clinical signs, their severity, and the time of reaction in relation to the drugs administration. Signs and symptoms may vary from mild symptoms to life-threatening anaphylaxis. Cutaneous signs, such as urticaria and generalized erythema are often present. Unexpected perioperative hypotension, bradycardia, isolated cardiovascular collapse, cardiac arrest and bronchospasm may also be the presenting features [6]. Ring and Messmer scale is the most widely used tool to describe clinical phenotypes. Grades I and II are not life-threatening and they include skin or mucosal signs and moderate signs from several organ systems. Grades III and IV are life-threatening and include signs from one or multiple organ systems and circulatory and/or respiratory arrest [7].

A patient with clinically suspected anaphylaxis should have an allergy test. The aim of investigation is to identify a culprit drug, find a safe alternative and ensure safe future anesthesia. Complete medical data, including relevant timelines and information about used drugs are essential. They include the anesthetic record, all drug charts including time of their administration, exposure to other agents (sprays, gels, disinfectants) and details of all procedures (catheters, stents). An ideal screening test is associated with optimal sensitivity and specificity and is safe to perform. Reliable in-vitro tests offer an opportunity to improve accurate diagnosis of perioperative anaphylaxis and identification of the triggering agent. When the culprit agent is identified and substance test is positive, cross-sensitivity should be investigated, due to risk that more than one culprit contributed to reaction. The performance of in-vitro tests in diagnostic algorithm should be done before or after the skin tests, but always before drug provocation testing [8].

In our patient, skin tests were carried out for all the drugs that were given before the anaphylactic reaction occurred. That helped identification of rocuronium as a triggering agent and provide safe alternatives. The skin tests for neuromuscular blocking agents have a sensitivity of 94–97% in patients with a history of anaphylaxis [9]. Negative predictive values are limited, and such studies require additional investigations such as controlled drug provocations test. Drug provocation tests should not be performed in high-risk patients (Ste-ven-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms). In patients with life-threatening anaphylaxis, drug provocation tests after negative skin test should only be performed after balancing the risk-benefit ratio [10]. Because drug provocation tests are not frequently performed for ethical reasons, in many cases the clinical history and use of skin tests are considered the "reference test". The main goal of in-vivo tests performed in acute phase of the reaction is assessment of mast cell and/or basophil involvement and quantification of inflammatory mediators, such as tryptase, histamine, prostaglandins and leukotrienes. There are some limitations to these tests: it is difficult to perform testing at the right time, kinetics of peak tryptase and histamine has short half-life and comparison with basal levels is needed [11]. Identification of suspected drug or drugs in resolution phase of anaphylaxis can involve quantification of serum drug-specific IgE measurements and direct/indirect basophil activation tests. Serum drug-specific IgE detection is traditionally performed using a solid-phase immunosassay. Because only a few drug-specific IgE assays are available, most of them have not been thoroughly validated.

In regard to neuromuscular blocking agents, it has been shown that the diagnosis should not rely on quantification and isolation of serum immunoglobulin E (IgE) [12]. Basophil activation tests are useful to study the involvement of basophils, irrespective of the activation pathway and display specificity (> 90%) and sensitivity rates up to 92% for neuromuscular blocking agents [13]. In-vitro approaches are cellular tests including determination of the cellular proliferative response in lymphocyte transformation tests, measurements of T-cell reactions, and production of cytokines and cytotoxicity. In these tests, cells are stimulated with suspected drug and cytokine release (IL-4, IL-5, INF-γ) and cytotoxic markers (granzyme B, granzulysin) and can be detected by using ELispot, ELISA or bead assay/flow cytometry. In patients with drug-suspected anaphylaxis, using different in-vitro approaches evaluating inflammatory mediators in effector cells increases the mean sensitivity and specificity [14]. In-vitro testing is usually not performed as a test in isolation, but rather as a component of a diagnostic strategy along with additional tests for evaluation of the association between a given drug and an observed clinical reaction. They can be complementary to in-vivo testing for the identification of cross-reactivity missed by skin test or in patients in whom the in-vivo test shows negative or equivocal results [15, 16].

**Conclusion**

Perioperative anaphylaxis is an unexpected and unpredictable critical event primarily associated with neuromuscular blocking agents and antibiotics. Our experience suggests that the rate of anaphy-
laxis to rocuronium is rising in proportion to the drug usage. In patients with neuromuscular blocking agents anaphylaxis, alternative anesthetic techniques that do not require the use of muscle relaxant medications should be considered. If the surgical procedure requires muscle relaxation, the anesthesiologist should determine the balance of risks. In patients with a history of neuromuscular blocking agent-induced anaphylaxis, an antihistamine and steroid were administered as a premedication prior to surgery to reduce any immune response to medications. The surgery was safely performed, after rocuronium was identified as the causative agent of anaphylaxis, using the intradermal skin test. Patients with anaphylaxis must be informed about its cause and causative agent, signs and symptoms, and about all diagnostic measures which were performed to confirm the diagnosis of anaphylaxis.

References

1. Turner PJ, Worm M, Ansotegui IJ, El-Gamal Y, Rivas MF, Fineman S, et al. Time to revisit the definition and clinical criteria for anaphylaxis? World Allergy Organ J. 2019;12(10):100066.

2. Harper NJN, Cook TM, Garcez T, Farmer L, Floss K, Marinho S, 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(1):159-71.

3. Mertes PM, Ebo DG, Garcez T, Rose M, Sabato V, Takazawa T, et al. Comparative epidemiology of suspected perioperative hypersensitivity reactions. Br J Anaesth. 2019;123(1):e16-28.

4. Reitter M, Petitpain N, Latarche C, Cotton J, Massy N, Demaily P, et al. Fatal anaphylaxis with neuromuscular blocking agents: a risk factor and management analysis. Allergy. 2014;69(7):954-9.

5. Dewachter P, Savic L. Perioperative anaphylaxis: pathophysiology, clinical presentation, and management. BJA Educ. 2019;19(10):313-20.

6. Garvey LH. Perioperative hypersensitivity reactions: diagnosis, treatment and evaluation. Curr Treat Options Allergy. 2016;3:113-28.

7. Rose MA, Green SL, Crilly HM, Kolawole H. Perioperative anaphylaxis grading system: ‘making the grade’. Br J Anaesth. 2016;117(5):551-3.

8. Mayorga C, Celik G, Rouzaire P, Whitaker P, Bonadonna P, Rodrigues-Cernadas J, et al. In vitro tests for drug hypersensitivity reactions: an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy. 2016;71(8):1103-34.

9. Mertes PM, Moneret-Vautrin DA, Leynadier F, Laxenaire MC. Skin reactions to intradermal neuromuscular blocking agent injections: a randomized multicenter trial in healthy volunteers. Anesthesiology. 2007;107(2):245-52.

10. Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy. 2003;58(9):854-63.

11. Berroa F, Lafuente A, Javaloyes G, Ferrer M, Moncada R, Goikoetxea MJ, et al. The usefulness of plasma histamine and different tryptase cut-off points in the diagnosis of preanaesthetic hypersensitivity reactions. Clin Exp Allergy. 2014;44(2):270-7.

12. Lysen J, Uyttebroek A, Sabato V, Bridts CH, De Clerck LS, Ebo DG. Predictive value of allergy tests for neuromuscular blocking agents: tackling an unmet need. Clin Exp Allergy. 2014;44(8):1069-75.

13. Hoffmann HJ, Santos AF, Mayorga C, Nopp A, Eberlein B, Ferrer M, et al. The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease. Allergy. 2015;70(11):1393-405.

14. Porebski G, Gschwend-Zawodniak A, Pichler WJ. In vitro diagnosis of T cell-mediated drug allergy. Clin Exp Allergy. 2011;41(4):461-70.

15. Porebski G. In vitro assays in severe cutaneous adverse drug reactions: are they still research tools or diagnostic tests already? Int J Mol Sci. 2017;18(8):1737.

16. Mayorga C, Ebo DG, Lang DM, Pichler WJ, Sabato V, Park MA, et al. Controversis in drug allergy: in vitro testing. J Allergy Clin Immunol. 2018;143(1):56-65.