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Diagnosis and Management of Rocuronium-induced Perioperative Anaphylaxis

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Abstract: Introduction - Perioperative anaphylaxis is a hypersensitivity reaction that occurs after exposure to drugs used for anaesthesia 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 anaesthesia, was scheduled for elective coronary 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 performed during the same hospitalization. After recovery, he was sent for a prick skin test and intradermal test, where sensitivity to rocuronium and insensitivity to the anaesthetics used were determined. Two months later, he developed an acute myocardial infarction. Chronic total occlusive percutaneous coronary intervention was attempted, but without optimal results, so the patient was prepared for elective surgery. Due to potential further complications during anaesthesia, the medical team decided to send him for a skin allergy test for neuromuscular blocking agents. The only neuromuscular relaxant available was Cisatracurium, and it was tested for sensitivity by intradermal test. The intradermal test showed insensitivity to Cisatracurium and Suxamethonium chloride. Conclusion - Early recognition and management of anaphylaxis is based on clinical presentation. The diagnosis by in-vivo and in-vitro tests is useful to determine the cause of anaphylactic reaction and safe alternatives for future anaesthesia.

Keywords: Rocuronium, Anaphylaxis, Perioperative Period, Drug Hypersensitivity, Anesthesia, Signs and Symptoms, Skin Tests, Cisatracurium

1. Introduction

Anaphylaxis is a severe, systemic hypersensitivity reaction that occurs suddenly after exposure to a provoking agent and may cause death [1]. Perioperative anaphylaxis is the result of drugs or substances used for anesthesia and surgery. Neuromuscular blocking agents and antibiotics are the most common triggers. Early recognition and management of the anaphylaxis are crucial. Still, anaphylaxis is usually unrecognized and managed improperly. Diagnosis and management are difficult because reactions occur promptly and suddenly. Skin tests with in-vitro tests remain the measure for detection of suspected agent, pathophysiological mechanism, safe alternatives, and include contact of the mast cells of patients who experience anaphylaxis to the suspected immune trigger. The aim of this case report was to describe clinical presentation and management of perioperative anaphylaxis as well as approach for the accurate diagnosis of the causative drug.

2. Case Report

A 71-old – male (weight 70 kg and body mass index 22, 36), American Society of Anesthesiologist physical status Class IV, was scheduled for elective coronary artery bypass graft surgery. He had a history allergic reaction during anaesthesia 11 months before in our hospital when he was scheduled for the same surgery. The patient`s anaesthesia record from the previous surgery showed that he received 5 mg Bisoprolol and 0, 25 mg/kg Midazolam preoperatively. General anaesthesia was induced with 80 mg Lidocaine, 50 mcg Sufentanil, 2 mg Midazolam, 60 mg Propofol and 70 mg

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 haemodynamically 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 haemodynamically stable. He did not require any inotropes and after 3 hours he was extubated with satisfactory blood gas analyses. 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 circumflexus artery and ramus intermedius artery.

He was sent for prick skin test and intradermal test after 10 weeks to an Allergy and Immunology Clinic. It was found that he was not sensitive to Lidocaine, Bupivacaine, Atropine, Neostigmine, Fentanyl, Midazolam, Propofol, Midarine, Meropenem, and Metronidazole. The patient was a diabetic on combined therapy with Insulin and oral hypoglycemic drugs, but was also taking oral medications for hypertension (Bisoprolol, Ramipril, Trimetazidine, Furosemide, Spironolactone) and hyperlipoproteinemia (Rosuvastatine). The medical history revealed that the patient underwent tonsillectomy and inguinal hernia repair on right side, 30 and 20 years ago, respectively. However, there were no records on the type of anaesthesia he had received. There was no history of any drug allergy, but he reported edema of the face after consuming products that contain propolis and edema of mouth after a bee sting. One month after the skin test was performed the patient developed acute myocardial infarction of the anterior wall and was hospitalized. During that hospitalization, coronary angiography procedure showed triple vessel coronary artery disease. Optimized results with chronic total occlusion percutaneous coronary intervention could not be achieved, so coronary bypass surgery was recommended. Because of persisting symptoms after myocardial infarction (chest pain, fatigue, dizziness, syncope) the patient was prepared for surgery. He was sent to 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 reaction 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 allergologist`s recommendation, he was received 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 in syringes and equipment required for resuscitation was kept ready. The premedication included intravenous Methylprednisolone 40 mg, 1 intramuscular Chloropiramine 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 mg 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 haemodynamically stabile. After Protamine 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 in Intensive Care Unit where he maintained haemodynamically stable. After 3 hours he was extubated with satisfactory blood gas analyses. 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 anaesthesia procedures.

3. Discussion

Perioperative anaphylaxis is defined as a life-threatening hypersensitivity reaction which may be a result of non-allergic or allergic reaction [2]. The incidence of perioperative anaphylaxis varies from one in 18600 to one in 353 with geographical variability [3].

Neuromuscular blocking agents and antibiotics are the most common triggers and usually occur after induction of anaesthesia. Rocuronium is the most common cause of perioperative anaphylaxis compared to other neuromuscular blocking agents [3, 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 [3, 5]. The diagnosis of perioperative anaphylaxis is usually made by clinical sings, their manifestation, and the time appearance after drug administration. Clinical presentation can range from mild symptoms to serious illness and mortality. Skin manifestations of perioperative anaphylaxis are often present.

Unexpected perioperative hypotension, bradycardia, asystole and bronchospasm can also occur [6].

Ring and Messmer classification is used to describe

clinical severity of perioperative anaphylaxis. Grades I and II include skin or mucosal signs and vary from mild to moderate signs from several organ systems. Grades III and IV are life-threating and include sings from one or multiple organ systems and circulatory or/and respiratory arrest [7].

A patient with clinically suspected anaphylaxis should have allergy test. The aim of investigation is to detect a suspected drug, find safe alternative and provide safe future anaesthesia. Complete medical data, including relevant timelines and information about used drugs are essential. They include the anaesthetic 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 has both high sensitivity and high specifity and can be performed safely. In-vitro tests provide an opportunity to make accurate diagnosis of perioperative anaphylaxis and identification of the triggering agent. When the culprit agent is identified and substance test is positive, it is recommended to examine cross-sensitivity, with possibility that multiple culprits contributed to reaction. In-vitro diagnostic tests and their performance 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 anaphylactic reaction occurred. That helped identification of rocuronium as triggering agent and provide safe alternatives. The skin tests for neuromuscular blocking agents have a sensitivity 94-97% in patients with history of anaphylaxis [9]. Negative predictive values are limited, and such studies need further diagnostic evaluation such as controlled drug provocations test. Drug provocation tests have not been recommended in the investigation in high-risk patients (Steven-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms). In patients with life-threatening anaphylaxis, drug provocation testing has not been recommended after negative skin test and the risk-benefit ratio should be estimated [8, 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" [11]. The aim of in-vitro tests performed in acute phase of the anaphylaxis is estimation of mast cell and 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 in the right time, kinetics of peak tryptase and histamine has short half-life and comparison with basal levels is needed [12]. 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 by using a solid- phase immunoassay [11]. Because of limited drug-specific IgE testing, most of them have not been completely validated. In regard to neuromuscular blocking agents, it was proved that the diagnosis should not be based on quantification and isolation of serum immunoglobulin E (IgE) [13]. Basophil activation tests are useful to measure involvement of basophils, regardless of the activation pathway and display specificity (>90%) and sensitivity rates up to 92% for neuromuscular blocking agents [14]. In-vitro cellular tests are used to determine cellular proliferative response in lymphocyte transformation tests, measurements of T lymphocytes (T-cell) reactions, production of cytokines or cytotoxicity. Cell stimulation with suspected drug leads to cytokine release (interleukin-4, interleukin-5, interferon gamma-INF γ) or cytotoxic markers (granzyme B, granulysin) and it can be identified by using enzyme-linked immune absorbent spot (ELIspot), enzyme-linked immune absorbent assay (ELISA) or bead assay/flow cytometry. In patients with drug-suspected anaphylaxis, different in-vitro test which measure and estimate inflammatory mediators in effector cells increase the mean sensitivity and specifity [15]. In-vitro tests along with additional tests are usually performed for evaluation of the association between culprit drug and an observed clinical reaction. They can be additional tests 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 [11, 16, 17].

4. Conclusion

Perioperative anaphylaxis is an unexpected and unpredictable critical event primarily associated with neuromuscular blocking agents and antibiotics. Our experience suggest that rate of anaphylaxis to rocuronium is rising in proportion to usage of the drug. In patients with neuromuscular blocking agents anaphylaxis, alternative anaesthetic approach that does not demand the use of muscle relaxant medications should be observed. If the surgical procedure requires muscle relaxation, the anaesthesiologist should estimate risk-benefit ratio. In patients who have experienced an allergic reaction to medication, it is necessary to perform in-vivo and in-vitro tests to determine the etiology of the reaction and their results must be correlated with patient`s medical history. When the responsible medication is identified, the administration of the causative agent should be avoided and safe alternatives should be used. Early recognition of clinical signs of anaphylaxis and providing the proper treatment is essential. In our patient, 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 clinical diagnosis of anaphylaxis.

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