Case Report

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Suspected Anaphylactic Reaction Prior to Induction of Anesthesia

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Although uncommon, anaphylactic reactions during surgery are very dangerous and can result in serious morbidity. Various anesthetics can trigger anaphylactic reactions, and incidents with cephalosporin antibiotics are on the rise. In the case presented, an 84-year-old woman scheduled for calcaneus fracture surgery, was injected with cefbuperazone as a prophylactic antibiotic. On the way to the operating room, before induction of anesthesia, the patient lost consciousness and showed signs of hypoxemia, and anaphylactic reaction, which included hypotension, bronchospasm, and rash. Five hours after immediate intubation and fluid resuscitation, the patient was extubated and transferred to the general ward. Eight weeks later, the skin prick test confirmed a positive reaction to cefbuperazone.

Key Words: Anaphylactic reaction, Anesthesia, Cefbuperazone

INTRODUCTION

Anaphylactic reaction is a life-threatening systemic hypersensitivity reaction. It has been reported that serious problems during general anesthesia occur in 0.4% of patients [1]. It may be difficult to detect anaphylactic reactions during anesthesia because various medications are administered in short periods of time, and transient interactions between drugs may take place. There have been many reports on anaphylactic reactions due to propofol or muscle relaxants during anesthesia induction [2]. In contrast, cases on anaphylactic reactions before induction are rare, but in the absence of adequate monitoring and immediate treatment, can be fatal to the patients. We report life-threatening conditions in a patient due to a severe anaphylactic reaction during transfer to the operating room before induction of anesthesia.

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CASE REPORT

An 84-year-old woman, 148 cm in height and 61 kg in weight was scheduled for open reduction and internal fixation due to left calcaneous fracture with dislocation. She had been taking hypertension medication for five years but had no previous history of asthma, allergic rhinitis, or atopic dermatitis. However, one year ago she was treated with conservative management after experiencing dizziness and general weakness following injection of an unknown drug. She had no other significant past medical history. She received no premedication other than tridol, which was administered for pain control a day before the surgery. The patient arrived at the operating room with no premedication. Her blood pressure, heart rate, and temperature were 130/80 mmHg, 68 beat/min, 36.8°C, respectively. After a negative intradermal skin test (2 mg/mL in normal saline with cefbuperazone (Tomiporan®), 1 g of cefbuperazone (Tomiporan®)

was injected before transfer to the operating room. Fifteen minutes later in the surgical waiting room, the patient had slight difficulty in breathing but had an alert mental state. Five minutes later, as the patient was being moved to the operation bed, the patient became incontinent of urine and unconsciousness. She also developed cyanosis, wheezing, and airway obstruction during respiration. An oral airway was applied and ventilated with 100% oxygen. ECG and sphygmomanometer were used to check vital signs. At this point, her blood pressure was 105/65 mmHg, heart rate 62 beat/min, and arterial oxygen saturation 75%. Intubation was performed immediately without using muscle relaxants. On auscultation, wheezing was apparent in both lungs and airway pressure increased to 30 cmH_2O after the ventilator was applied. Sudden, profound hypotension (blood pressure 62/43 mmHg) and bradycardia (heart rate 45 beat/min) developed. The patient was promptly loaded with fluid along with two doses of ephedrine 20 mg. Her blood pressure rose to 85/54 mmHg and then dropped to 50/22 mmHg a minute later. Phenylephrine 100 mg was administered but there was no response. The patient showed severe diffuse erythematous skin rashes without urticaria over her full body. A central line was placed in the right internal jugular vein and an arterial cannula was inserted into the right femoral artery. Arterial blood gas values were FiO_2 1.0, pH 7.288, pO_2 355 mmHg, BE −6.1 mEq, and arterial oxygen saturation 98.3%. Since the patient received no special medications other than the intravenous antibiotic injection before arriving at the operation room, a clinical diagnosis of anaphylactic reaction was made and methyl prednisolone (solumedrol®) 500 mg was intravenously injected. Three doses of epinephrine 20 μg were administered but there was no response: blood pressure 60/36 mmHg, heart rate 113 beat/min, and blood pressure 49/37 mmHg, heart rate 130 beat/min. A slight ST depression started to show on ECG. Further 100 μg of epinephrine was given but without effect. After three additional doses of 200 μg of epinephrine were administered, the patient's blood pressure and heart rate were then maintained at 110-130/50-60 mmHg and 80-100 beat/min, respectively. As her blood pressure started to rise, the patient started to gain consciousness. Midazolam 3 mg was administered. Forty minutes after resuscitation, her blood pressure was maintained at around 120/60 mmHg with epinephrine infusion and the patient was transferred to the intensive care unit where a mechanical ventilator was applied. After an hour at the intensive care unit, the patient became hemodynamically stable with a blood pressure of 110-120/55-65 mmHg. Epinephrine infusion was tapered off and discontinued. There were no signs of regional wall motion abnormality according to bedside transthoracic echocardiography. Arterial blood gas values were FiO_2 1.0, pH 7.256, pO_2 346 mmHg, pCO_2 49.7 mmHg, BE −5.5 mEq, and arterial oxygen saturation 99.7%. After two hours in the intensive care unit, arterial blood gas value normalized: FiO_2 0.3, pH 7.345, pO_2 87.5 mmHg, pCO_2 42.3 mmHg, BE −5.8 mEq, and arterial oxygen saturation 97.1%. After three hours in intensive care unit, the patient's was alert, her mean arterial blood pressure was >80 mmHg, and she showed no signs of airway obstruction or wheezing on auscultation. After she was weaned off the ventilator, the patient was extubated. Five hours later, the patient was transferred to the general ward and surgery was postponed. Eight weeks later, a skin prick test confirmed a positive reaction (wheal 4 × 3.5, flare 7 × 6 mm) to cefbuperazone (Tomiporan®).

DISCUSSION

Anaphylactic reaction is an immediate life-threatening reaction mediated by IgE and propagated by mediators such as histamine, tryptase, leukotrienes, platelet activating factor, nitric oxide, inflammatory prostaglandins, and bradykinin. It can lead to intravascular volume depletion, myocardial suppression and increased airway resistance, that results in sudden severe hypotension, hypoxemia, tissue hypoxia, and acidosis [3].

The most common causes that trigger generalized reaction during anesthesia are neuromuscular blocking agents, latex, and antibiotics, with antibiotics reported as the cause in 10-15% of all cases [4,5]. β-lactam antibiotics, such as penicillin, cephalosporin, carbapenem, and monobactam antibiotics, are involved in generalized reactions in 80% of these cases [4].

Penicillin is the main causative drug in immediate drug reaction. However, recent wide spread use of cephalosporin antibiotics during perioperative period to prevent infections has led to an increase in the incidence of drug reactions due

to cephalosporin antibiotics. Cephalosporins are semi-synthetic antibiotics, derivatives of cephalosporin acremonium, and are composed of a β-lactam ring connected to a 6-member dihydrothiazine ring. Cephalosporin exerts its antibacterial effect by disrupting synthesis of the peptidoglycan layer in bacterial cell wall. This drug has broad spectrum activity and is administered as a first-line prophylactic drug to prevent infections in surgical procedures. Generally, the first generation cephalosporins work more effectively on gram positive bacteria and have less activity on gram negative bacteria. With few exceptions, third generation cephalosporins have greater gram negative activity. Only the fourth generation cephalosporins have both gram positive and gram negative effect.

The most common side effects of cephalosporins are skin reactions such as maculopapular exanthema and urticaria, which are reported to occur in 1-3% of patients [6]. Only 0.0001-0.1% of the side effects is anaphylactic reaction, which is thus very rare [7]. According to Fisher et al. [8], the most common clinical feature of anaphylactic reaction is cardiovascular collapse, occurring in their study in 389 out of 442 people, along with bronchospasm occurring in 161 people, of which 72 have having asthmatic bronchospasm. Among cutaneous signs, there were 201 people with erythema, 55 with rash, and 37 with urticaria [8]. In accordance with these statistics, our patient showed all the important clinical features such as cardiovascular collapse, asthmatic bronchospasm, and erythematous rash. It has been reported that most cardiovascular collapse is accompanied by vasodilation and supraventricular tachycardia. However, our patient had bradycardia. According to a report by Laxenaire, bradycardia was found to occur in 2.1% of their patients [9]. Furthermore, in patients with severe reactions, the first clinical features were a fall in blood pressure in 122 people, difficulty to inflate in 115, flush in 94, coughing in 28, rash in 20, desaturation in 15, and cyanosis is 12 out of 440 people. In our case, the patient had difficulty in inflating with wheezing immediately on arrival to the operation room, and considering the normal range of blood pressure with signs of bradycardia and oxygen desaturation (78%), difficulty in inflation was the first clinical feature. While it has been reported that anaphylactic reactions occur most commonly after the age of 40 in women and 50 in men, only 0.4% of all anaphylactic reactions occur in over 80 years of age. Therefore, the severe anaphylactic reaction noted in our 84-year-old patient is very unusual [9]. According to Laxenaire et al. [9], grade III life-threatening reactions including cardiovascular collapse, tachycardia or bradycardia, arrhythmia, and severe bronchospasm occurred in 62.6% of the patients in their study. Bronchospasm only occurred in 21.3% of grade II reactions, whereas 75.4% of the patients with grade III reactions had bronchospasm. The patient in our case also showed all signs of grade III reactions. Antibiotic-induced hypersensitivity reaction can be classified as immediate or delayed. Immediate reactions usually occur within minutes to an hour. In this case, it took 20 minutes for the symptoms to occur after antibiotic injection in the ward, which is still unlike most immediate reactions in which symptoms start to manifest promptly. Initiative resuscitation with ephedrine and phenylephrine failed to restore the patient's blood pressure but epinephrine was effective. The normalization of blood pressure can be explained by a decrease in allergic reaction due to β-2 agonists along with an increase in blood pressure to the effects of epinephrine.

Anaphylactic reactions that occur during induction or anesthesia can be treated immediately. However, if airway obstruction and severe hypotension occur during transfer, as in this case, they can be fatal. If anaphylaxis occurs during anesthesia, several causative agents can be considered: myocardial infarction, drug overdose, pulmonary embolus, irritant-induced bronchospasm, endotracheal tube malfunction, aspiration, hypoglycemia, and stroke [10]. However, our patient had no premedication before transferring to the operating room other than the antibiotics injection. Thus, we were able to make a fast diagnosis of anaphylactic reaction due to antibiotics.

Our patient was injected with antibiotics after a negative skin test with 2 mg/mL in normal saline concentration. According to Romano [11], 2 mg/mL in normal saline concentration is nonirritant in a control group but very sensitive in subjects that have immediate reactions to cephalosporin. Today, the highest concentration accepted for prick and intradermal testing in Europe is 2 mg/mL for cephalosporins [12]. On the other hand, other studies have used normal saline concentrations in the range of 0.5-250 mg/mL for hypersensitivity diagnosis. This is less than the amount used

in our case but the possibility of a false negative result cannot be eliminated because the test volume was too small [13-15].

One limitation of this study is that there was no IgE test result to corroborate the clinical findings that the patient had undergone an anaphylactic reaction. However, there were no other drugs were administered except for antibiotic before induction. Also, considering her clinical features, course of treatment, and the positive skin prick test, a diagnosis of anaphylactic reaction due to cephalosporin should still be made.

Anaphylactic reactions usually occur within minutes after prophylactic antibiotics injection. However, as demonstrated in the present case, if they occur 20-30 minutes after injection, they can take place during transfer from the ward to the operating room. Therefore, careful observation and monitoring is required when patients are being transferred after a prophylactic antibiotics injection.

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