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Case Report

Absence of elevated serum tryptase in rocuronium-induced anaphylaxis during discectomy under general anesthesia: A case report

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Abstract: A 43-year-old female patient, who had previously undergone surgery under general anesthesia without any problems, was scheduled for discectomy. Propofol and rocuronium were injected sequentially to induce general anesthesia. Twenty minutes after the rocuronium injection, severe hypotension, tachycardia and bronchospasm developed, and delayed skin rashes appeared. The operation was cancelled. No postoperative complications were evident, and the patient was discharged from the hospital. Serum tryptase value at the time of anaphylaxis was within normal ranges. But skin prick test and intradermal test was found to anaphylaxis caused by rocuronium after six weeks.
Keywords:anaphylaxis; general anesthesia; rocuronium; tryptases

INTRODUCTION

The incidence of hypersensitivity reactions during anesthesia is one per 1,250–10,000 rounds of anesthesia, considering the gap between actual incidences and the reporting system [1]. Almost all drugs and substances administered to patients or to which they are exposed perioperatively are known to potentially induce hypersensitivity reactions, and 50-70% of these are reported to be muscle relaxants [2, 3].

Diagnostic methods for hypersensitivity reactions involve taking blood samples during anaphylactic or anaphylactoid reactions to test for tryptase, histamine, complement, and immunoglobulin E (IgE), or performing skin prick and intradermal tests 6 weeks later [4].

It may also be helpful to measure tryptase immediately following the onset of symptoms and after recovery from symptoms to observe the changes in tryptase levels. However, anaphylaxis cannot be definitively excluded even if blood tryptase or histamine levels are within normal ranges [5].

The author of this study postponed the surgery of a 43-year-old female patient without a history of hypersensitivity to any drugs or food, due to an anaphylactic reaction that occurred following induction of general anesthesia. The blood tryptase tests showed normal levels, but the patient was definitively diagnosed with rocuronium-induced anaphylaxis from the results of skin prick and intradermal tests conducted 6 weeks later. The author reports this case with a review of relevant literature.

CASE REPORT

A healthy 43-year-old woman (56 kg, 158 cm) visited the hospital to undergo a discectomy after being diagnosed with lumbar disc herniation. The patient had a history of total abdominal hysterectomy (TAH) under general anesthesia due to uterine myoma 9 years earlier, but had not shown any abnormal reactions to anesthesia. Preoperative blood test, electrocardiogram, and chest X-ray findings were all normal. The patient was premedicated with glycopyrrolate 0.2 mg via intramuscular injection prior to arrival in the operating room (OR). Upon arrival in the OR, the patient was monitored via a non-invasive blood pressure monitor, EKG, and pulse oximeter. Before the induction of anesthesia, her vital signs were: blood pressure 126/87 mmHg, heart rate 85 beats/minute, and pulse oxygen saturation 99%, with EKG showing normal sinus rhythm. Anesthesia was induced with propofol 120 mg and rocuronium 50 mg. Manual ventilation was performed with 100% oxygen and 2 vol% sevoflurane, followed by endotracheal intubation. The patient showed a blood pressure of 143/97 mmHg, heart rate of 86 beats/minute, and pulse

oxygen saturation of 100% after intubation. The patient's vital signs were stable, and her position was changed from supine to prone to prepare for the operation.

After 20 minutes of intravenous (IV) rocuronium, the patient's blood pressure suddenly dropped to 84/53 mmHg. She was given phenylephrine 50 μg IV, but her systolic pressure remained at 51–68 mmHg, with a diastolic pressure of 33–41 mmHg, pulse of 110 beats/minute, and pulse oxygen saturation of 92%. To increase her blood pressure, we intermittently injected 10–40 μg of epinephrine and continuously infused dopamine. Her airway pressure was also high, at 28 cmH_2O.

We determined that the patient could not undergo surgery under such conditions and repositioned her in the supine position. The patient had an erythematous eruption on her face and entire body as well as edema of the lips and eyes, based on which we determined her condition to be drug-induced anaphylaxis.

After changing the patient's position, we manually ventilated her with 100% oxygen, during which time we performed left radial artery cannulation. The patient's arterial pressure was continuously monitored in real time, and a blood sample was collected and sent to the laboratory for blood tryptase level testing. We rapidly infused crystalloid while performing IV infusion of methylprednisolone 500 mg and ephedrine 10 mg, after which the blood pressure rose slightly to 80/61 mmHg. However, the pulse oxygen saturation level was still low at 90%, for which we performed IV injection of phenylephrine 50 μg, followed by dexamethasone 10 mg based on the suspicion that bronchospasm might have caused the reduction in oxygen saturation. After 10 minutes, the patient's vital signs had recovered to: systolic pressure 88–106 mmHg, diastolic pressure 62–78 mmHg, heart rate 94–106 beats/minute, and pulse oxygen saturation 97–98%. Airway pressure also decreased to 19 cm H_2O. Based on the fact that the patient displayed hypotension due to circulatory collapse, increased airway pressure, and facial and systemic erythematous eruption following exposure to agents for the induction of anesthesia, we suspected the patient's condition to be anaphylaxis and determined that the operation could not proceed without identification of the causative agent. We explained the details regarding the anaphylactic reaction during anesthesia to the patient's guardian, and the operating surgeon cancelled the surgery.

For continuous monitoring, the patient was moved to the intensive care unit (ICU) while receiving 5 L/min of oxygen with the endotracheal tube maintained. In the ICU, the patient's vital signs were stable with normal chest X-ray and arterial gas analysis findings and slight reduction of edema, so extubation was performed 6 hours later. The patient was transferred to a general ward the following day and was discharged without any notable problems. The blood test results (from an external laboratory) that came out a week later showed a serum tryptase level of 8.5 μg/L (normal: < 11 μg/L).

Six weeks after discharge, the patient visited the allergy clinic for examination of the cause of the previous hypersensitivity reaction. Skin prick and intradermal tests were performed for propofol and rocuronium, which were the agents used for induction. The patient tested positive for rocuronium in both the skin prick test and the intradermal test. On the following surgery, the patient was informed that the alternative agent would be selected based on the results of the allergy test.

DISCUSSION

The diagnosis of anaphylaxis during anesthesia is difficult for a few reasons. For one, several agents are concurrently administered in a short period of time. In addition, most anesthetics, including propofol, directly or indirectly act on the sympathetic nervous system and cardiovascular system, resulting in vasorelaxation, hypotension, and impairment of cardiopulmonary function. Furthermore, there are individual differences in the time until the initial onset of symptoms, ranging from 2–20 minutes [6]. In the present study, the anaphylactic reaction occurred 20 minutes after the induction of anesthesia.

An anaphylactic reaction is a type I hypersensitivity reaction, during which IgE stimulates mast cells or basophilic cells and isolates vasomotor substances, such as histamine. On the other hand, an anaphylactoid reaction is the result of direct stimulation of basophilic cells (without mediation by IgE) that release vasomotor substances [7].

Neuromuscular relaxants are the most common agents that induce anaphylactic reactions, followed by latex, antibiotics, hypnotics, colloids, and narcotics [8]. There have been increasing numbers of reports of rocuronium bromide-induced anaphylactic or anaphylactoid reactions [9]. Anaphylaxis may occur even in patients without a history of exposure to muscle relaxants. The main mechanism through which muscle relaxants induce anaphylaxis involves quaternary ammonium ions; as common daily products, such as detergents, shampoo, and cough medicines share a similar structure, prior exposure to such products may have caused the anaphylactic reaction [10].

Although the mechanisms of anaphylactic and anaphylactoid reactions are different, it is difficult to

distinguish them clinically. Anaphylaxis can be broadly categorized into four stages depending on the clinical severity (grade 1 = presence of cutaneous signs; grade 2 = presence of measurable but not life-threatening symptoms, including cutaneous effects, arterial hypotension [defined as a decrease of more than 30% in blood pressure associated with unexplained tachycardia], cough or difficulty in mechanical ventilation; grade 3 = presence of life-threatening reactions, including cardiovascular collapse, tachycardia or bradycardia, arrhythmias, severe bronchospasm; grade 4 = circulatory inefficacy, cardiac and/or respiratory arrest) [11]. The patient in the present study fell into the category of grade 3 anaphylaxis, which requires active treatment; however, the patient was in the prone position with her entire body covered by an OP drape, which delayed the detection of a systemic erythematous eruption and edema, consequently delaying the diagnosis. In addition, we overlooked the potential role of the anesthetics in inducing hypersensitivity reactions because they had been widely used previously without serious problems.

In the primary diagnosis of anaphylaxis, detection and assessment of clinical manifestations is important. Secondary diagnosis involves collection of a blood sample during the anaphylactic or anaphylactoid reaction to measure tryptase, histamine, complement, and IgE levels. Final diagnosis is determined based on the skin prick and intradermal tests 6 weeks after the onset [4, 10]. However, only some of these tests may be available in different institutions, so appropriate tests should be selected according to the circumstances.

Tryptase is a proteinase that is secreted when mast cells are stimulated. It has a longer elimination half-life than histamine, which renders it the most useful substance for testing as it can be detected from 30 minutes to 6 hours following the anaphylactic reaction and has a sensitivity of 60–70% [2]. Nevertheless, despite the usefulness of serum tryptase as an indicator of a hypersensitivity reaction, it must be noted that, as with clinical symptoms, it cannot distinguish between anaphylactic and anaphylactoid reactions [12]. In addition, even if serum tryptase is found to be in the normal range, anaphylactic reactions cannot be completely excluded [5] because a normal tryptase level may be significantly high if the baseline level was very low [13]. Hence, it is beneficial to measure tryptase by taking sequential measurements to identify a trend, rather than taking a single measurement. In the present study, we could not make an accurate diagnosis solely based on the serum tryptase level because although the blood testing indicated a level of tryptase within the normal range, we did not know the baseline serum tryptase level.

The skin prick test is a preferred method of testing due to its low cost and low false positive rate. However, findings must be interpreted with caution as the results may vary greatly even for one individual depending on the site from which the sample is taken. Furthermore, even if the same criteria are applied, the results may vary in accordance with the investigator's pricking technique. All agents used perioperatively as well as the muscle relaxants that were not used during anesthesia must also be tested because there is a possibility of cross-reactivity, although this is rare [9]. In the present case, we were able to definitively diagnose an IgE-mediated anaphylactic reaction based on the strong positivity for rocuronium bromide in the skin prick and intradermal tests conducted 6 weeks following the onset of symptoms. Although skin tests do not support an immediate diagnosis when a hypersensitivity reaction occurs, they can be helpful in selecting specific agents for the future surgery the patient may undergo[14, 15].

Treatment of anaphylaxis should be focused on eliminating the hypersensitivity-causing agent and blocking the mediators that are released in response to the antigen. The key aspects of treatment are to immediately terminate the infusion of anesthetics and other drugs and administer epinephrine as soon as possible [1,2]. The α_1 effect of epinephrine helps to maintain blood pressure and the β2 effect relaxes bronchial smooth muscle [1]. Oxygen consumption must be compensated for by increasing oxygen delivery with 100% oxygen. In addition, peripheral vasodilation, which sporadically accompanies anaphylaxis, should be compensated for with crystalloid infusion [1].

The best prophylactic measures for anaphylaxis are to avoid using agents that may cause hypersensitivity reactions. In general, anesthetic allergy testing prior to anesthesia is performed only in high-risk patients [16]. It is important to provide adequate explanation to and obtain written consents from high-risk patients regarding the avoidance of risk factors for anaphylactic reactions and the possibility of anaphylaxis. In addition, when anaphylaxis occurs during anesthesia, appropriate countermeasures should be undertaken promptly to reduce the incidence and mortality of anaphylaxis.

CONCLUSION

Although the serum tryptase level was normal during the anaphylactic reaction in this case, we were able to confirm the patient's hypersensitivity to rocuronium based on the clinical presentation during anesthesia and subsequent skin testing.

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