

Immediate hypersensitivity reaction to Ketamine in children with history of atopic disease

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Abstract

Many investigators have demonstrated that a large number of patients who experience anaphylaxis during anesthesia have a history of atopic disease or allergy to a specific substance. Here, we review a hypersensitivity reaction to ketamine in a nine-year-old child with a history of atopic disease.

Keywords: allergy, drug, anaphylaxis, anesthesia, ketamine

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Introduction

Anaphylaxis during anesthesia is unpredictable and potentially life-threatening. Despite its frequent use, allergic reactions to ketamine are extremely rare. We review our experience of an allergic reaction following intravenous administration of ketamine in a nine-year-old child and present the investigation and treatment of anaphylaxis during anesthesia.

Case report

A nine-year-old female admitted for operation for a chalazion under monitored anesthesia care (MAC) granted consent for this report. The patient was 31 kg in weight and 133 cm in height. She has a history of atopic dermatitis and allergic rhinitis. Moreover, one month ago, she experienced an allergic reaction accompanied by angioedema on both eyelids and facial swelling after a cat licked her face. The patient denied other systemic disease and she had a surgical history without complication for tonsillectomy and an operation for trigger thumb two years previous at other hospital. Blood tests, chest x-ray, and physical examination were normal.

The patient, with 8 hours of NPO (“nothing by mouth”) status, received 30 mg of intravenous ketamine in the waiting room reduce anxiety. Immediately after the injection, the patient was transferred to the operating room 25 m away under the surveillance of the anesthesiologist and surgeon. Upon arriving at the operating room, we discovered that the patient showed labored breathing, edema of the face, and an erythema on the neck. We immediately supplied 100% oxygen via mask ventilation and checked the patient’s vital signs.

Monitors demonstrated a pulse rate of 112 beats per minute, normal sinus rhythm, blood pressure 133/81 mmHg, a respiratory rate of 25, pulse oximetry of 100%, and bilaterally clear breath sounds without difficulty inflating the lungs by mask ventilation. We administered 2 mg of chlorpheniramine maleate intravenously. After 15 minutes, the erythema began to fade and all vital signs remained stable. After discussion with the surgeon, we decided to continue the operation under anesthesia with sevoflurane 2-3 vol% by face mask. The operation took 15 minutes. Following 30 minutes of observation in the post-anesthesia care unit, the patient was transferred to the general ward and discharged 3 hours after the operation without complications.

The patient was referred to the allergy clinic and underwent a skin test 12 weeks later. We conducted a skin prick test at a concentration of 1 mg/mL and an intradermal test at concentrations of 1 mg/mL and 0.25 mg/mL. Despite a negative result in the skin prick test, the intradermal tests showed a positive reaction to ketamine at both concentrations (**Table 1, Figure 1**). As a result of the investigation, it was

Table 1. Intradermal skin test

Agent	Concentration	Response
Histamine (positive control)	0.01 mg/mL	8 x 7 mm
Ketamine	0.25 mg/mL	8 x 5 mm
Ketamine	1 mg/mL	13 x 9 mm
Normal saline (negative control)		No response

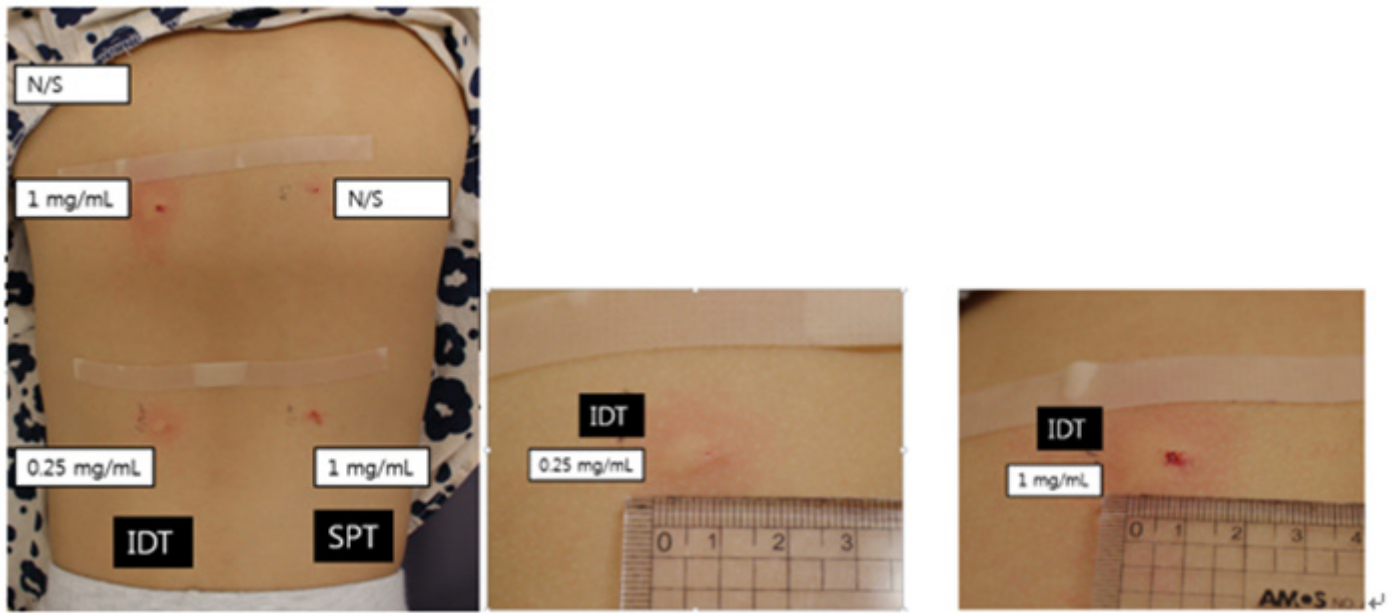


Figure 1. The results of skin tests. IDT: intradermal test, SPT: skin prick test, 0.25 mg/mL: ketamine at a concentration of 0.25 mg/mL, 1 mg/mL: ketamine at a concentration of 1 mg/mL.

confirmed that the patient had IgE-mediated anaphylaxis to ketamine with a mild hypersensitivity reaction according to the clinical grading system for anaphylaxis.

Discussion

Anaphylaxis during anesthesia is an unpredictable and potentially life-threatening allergic reaction. Anaphylaxis is type 1 hypersensitivity reaction mediated by immunoglobulin E (IgE). By contrast, an anaphylactoid reaction is not mediated by IgE or an antigen-antibody process.¹ Although the clinical response of both are often indistinguishable, an accurate diagnosis through comprehensive investigation is important for future anesthesia. Several European countries have been investigating the nature and causes of perioperative anaphylactic reactions. Though there is considerable variability in the reported rate of immediate hypersensitivity reactions during anesthesia, the overall incidence ranges from 1 in every 1250 to 10000 anesthetic uses, and mortality has been estimated to vary between 3% and 6%. Neuromuscular blocking agents (NMBAs) are the most frequently incriminated substance, followed by latex and antibiotics.¹⁻⁵ In children, the most common cause is latex, followed by NMBAs and antibiotics.⁶

Despite its frequent use, allergic reactions to ketamine appear to be extremely rare. A study by Stellato et al.⁷ demonstrated that ketamine can induce the release of histamine from lung and skin mast cells which might explain the wide spectrum of the anaphylactoid reactions observed after the administration of ketamine. Occasional case reports have demonstrated hypersensitivity reactions to ketamine.⁸⁻¹¹

This patient developed erythema, face edema and difficulty breathing following the administration of ketamine intravenously. The onset of the reaction was immediate and the intradermal test showed a positive reaction to ketamine, though it was not certain that the patient had previous exposure to ketamine. The most likely, the present

case is consistent with a type 1 hypersensitivity reaction to ketamine. While this case did not present life-threatening respiratory or cardiovascular compromise, the presumed IgE-mediated mechanism identifies that the patient is at risk of anaphylaxis with future exposure to ketamine. It is important that a comprehensive evaluation including skin tests or oral challenge as well as a detailed medical history be performed to identify the cause of anaphylaxis and which other anesthetic agents are likely to be safe for future use.

We performed skin tests 12 weeks after the reaction. Although skin tests are usually performed 4-6 weeks after an acute reaction, it took a great deal of time to explain the necessity of the test to patient's parents. In reference to the literature, a study by Ozcan et al.¹¹ conducted intradermal tests 12 weeks after the reaction. The ketamine concentrations for skin tests vary in different studies. The UK recommendation is that skin prick tests to anesthetic agents should be performed at two concentrations: "neat" (i.e. ketamine 10 mg/mL) and at a 1/10 dilution simultaneously. The UK recommendation is that the intradermal test for ketamine should be performed at a 1/10 dilution.² Guyer et al.¹² suggested that the ketamine concentration for a skin prick test should be 10 mg/mL and 0.25 mg/mL for the intradermal test. Ozcan et al.¹¹ performed intradermal tests for ketamine at concentrations of 1 mg/mL and 0.1 mg/mL.

We conducted the skin prick test at a concentration of 1 mg/mL and the intradermal test at the concentrations of 1 mg/mL and 0.25 mg/mL, because intrinsic histamine release activity is more marked in the intradermal test. If higher concentrations of the drug are used for the intradermal test, there is a greater likelihood of false positive results. Hagau et al.¹³ found that the maximum non-reactive intradermal test concentration for ketamine is 0.25 mg/mL in healthy volunteers. In the present case, although a negative result was found in the skin prick test, intradermal tests showed a positive reaction to ketamine

at both concentrations of 1 mg/mL and 0.25 mg/mL, indicating IgE-mediated anaphylaxis to ketamine.

This patient has a history of atopic dermatitis, allergic rhinitis and allergic reactions accompanied by angioedema. However, it is unclear as to whether a history of atopic disease or allergy to a specific substance is a risk factor for anaphylaxis to anesthetics. Guyer et al.¹² showed that 55% of patients reported a history of drug allergy, 48% reported a previous diagnosis of allergic rhinitis, 32% reported a diagnosis of asthma, 15% reported a history of a severe allergic reaction, 8% reported a history of food allergy and 4% reported a previous diagnosis of eczema. No patient had a history of allergy to any anesthetic agent, and there was no case of accidental exposure to a previously identified drug allergen during anesthesia. A retrospective study conducted by Gurrieri et al.¹⁴ showed that 26 of 38 patients experiencing an anaphylactic reaction during anesthesia had a history of atopic disease. Furthermore, some recent publications have demonstrated that a positive history of non-anesthetic drug allergy is the only predictive factor for a positive skin test when screening for allergy to anesthetic drugs was performed.^{15,16} In a study by Hagau et al.,¹⁷ the prevalence of a positive skin prick test and intradermal test was 1.6% and 5.8%, respectively, and the prevalence of patients with a positive skin prick test to NMBAs was higher (10%) than that reported in the general population (2.8-4.65%). Considering the results of recent studies, this patient might need allergy tests for other anesthetics, including NMBAs.

In a study by Guyer et al.,¹² recommendations were made regarding subsequent anesthesia after an allergy evaluation. If a patient had a positive skin test result to an agent, suggesting an IgE-mediated hypersensitivity reaction, they advised avoidance of that specific agent. If the skin test result was negative, no specific avoidance of medication was recommended, although cautious intraoperative monitoring was suggested given the potential risk for a non-IgE-mediated reaction. On follow-up, 47 of the 73 patients with a hypersensitivity reaction during anesthesia underwent subsequent anesthesia, and 45 of these 47 patients successfully tolerated subsequent anesthesia.

Here, we present a case of likely IgE-mediated hypersensitivity to ketamine, supported by a positive intradermal test in a nine-year-old child with a history of atopic disease and allergic reaction. Anesthesiologists must always consider anaphylaxis during anesthesia and be able to perform a comprehensive investigation and management of suspected anaphylaxis to minimize the risk for subsequent anesthesia. Especially, as in this patient, patients with a history of atopic disease or allergic reaction to a specific substance require more caution during anesthesia and might need to undergo allergy tests for anesthetic drugs to minimize the risk of anaphylaxis.

Acknowledgments

1. Any necessary ethical approval(s); none
2. The source of funding for the study with grant numbers; none
3. Any conflict of interest; none

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