Rocuronium anaphylaxis in a 3-year-old girl with no previous exposure to neuromuscular blocking agents

Sun-Hee Choi,[1] Jae-Woo Yi[2] and Yeong-Ho Rha[1]

Summary

During the perioperative period, anaphylactic reactions rarely occur. Neuromuscular blocking agents (NMBAs) are responsible for 60-70% of perioperative anaphylactic reactions. This case, we report a case of rocuronium-induced anaphylaxis in a 3-year-old girl with no previous exposure to NMBAs. This case cautions and informs practitioners that an IgE-mediated anaphylactic reaction with rocuronium is possible even in young children with no previous exposure to NMBAs *(Asian Pac J Allergy Immunol 2013;31:163-6)*

Key words: *Anaphylaxis, perioperative, rocuronium, NMBAs*

Introduction

During the perioperative period, anaphylactic reactions rarely occur, but can be a devastating complication of general anesthesia. Agents used in the perioperative period, such as drugs, intravenous fluids, and latex material, have the potential to produce allergic reactions, including life-threatening immune-mediated anaphylaxis. Neuromuscular blocking agents (NMBAs) are responsible for 60-70% of perioperative anaphylactic reactions. Among patients who have an anaphylactic reaction to NMBAs, 15% have had no previous administration of any type of muscle relaxant.[1,2]

The tertiary or quaternary ammonium ion is the epitope that is the antigenic determinant of NMBAs.[3,4] One of the NMBAs, rocuronium is a non-depolarizing muscle relaxant and its main benefits are the rapid onset of neuromuscular blockade with minimal cardiovascular side effects and negligible histamine release.[5,6] A few cases of rocuronium-related anaphylaxis in patients with no previous exposure to NMBAs have been reported in adults[7-9] since rocuronium was introduced in 1996.[1-3] In this article, we report a case of rocuronium-induced anaphylaxis in a 3-year-old girl with no previous exposure to NMBAs.

From 1. Department of Pediatrics, School of Medicine, Kyung Hee University, Seoul, Republic of Korea
2. Department of Anesthesiology, School of Medicine, Kyung Hee University, Seoul, Republic of Korea
Corresponding author: Sun-Hee Choi
E-mail: chsh0414@khu.ac.kr
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Report of Case

A 3-year-old healthy girl weighing 15 kg was admitted to undergo a pin fixation of her fractured right distal humerus under general anesthesia. She was born at 38 weeks of gestation by vaginal delivery and had no relevant perinatal history. She had no previous history of anesthesia and had no known documented allergies. Her immunizations were up to date, and she had a normal developmental history. Pre-operative routine laboratory tests were normal. The patient was given intravenous antibiotic cefminox (Meicelin®, Yeongjin Pharm, Seoul, Korea) 3 hour before the operation. Routine intradermal skin test before its injection was negative. Any blood products were not administered.

When she arrived at the operating room, her vital signs were as follows: heart rate (HR) of 156 beats/min, respiratory rate (RR) of 30 breaths/min, blood pressure (BP) of 105/63 mmHg, and oxygen saturation of 99% in room air. Anesthesia was induced with atropine (Atropine sulfate®, Daewon Pharm. Co. Ltd., Seoul, Korea) at 0.01 mg/kg. Several minutes later thiopentone (Pentotal sodium®, Choongwae Pharm Co. Ltd., Seoul, Korea) at 5 mg/kg was administered, followed by rocuronium (Esmeron®, Hanwha Pharm. Co. Ltd., Seoul, Korea) at 0.6 mg/kg. All drugs were administered through the same injection port in the intravenous line.

Approximately 50 to 60 seconds after rocuronium administration, the patient had a fit of coughing, and her lungs became moderately difficult to ventilate with bag and mask. Tracheal intubation was promptly performed, and bronchospasm was diagnosed with auscultation, revealing wheezing.

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The patient's lungs were ventilated with sevoflurane (Sevorane®, Abott Korea Ltd, Seoul, Korea) in oxygen. At the same time, her HR increased to 182 beats/minute, and her BP dropped to 72/40 mmHg. Her trunk and face became erythematous, and the patient also developed significant periorbital edema. Since epinephrine was not available in the operating room, the patient was treated with an increased infusion rate of intravenous fluid (normal saline), 30 mg of hydrocortisone, and 100% oxygen. Immediately following these interventions, her oxygen saturation was 100%, and her BP remained above 70/40 mmHg. Approximately 25 minutes after treatment, her BP stabilized at approximately 90/60 mmHg, and signs of bronchospasm slowly resolved. Surgery was postponed for about one hour, and when reinitiated, proceeded uneventfully. Blood draws for arterial blood gas analysis and serum tryptase were not feasible in this situation.

To determine which drug is involved and to exclude the false negative for the provisional culprit, intradermal allergy test for rocuronium and thiopentone were performed 12 days later, because the operation for removal of the fixed pin was scheduled to be performed four weeks after the first operation and the patient was too young to be taken several needle-prick. The intradermal injection, using a 26-gauge needle, was 0.01-0.03 mL and produced a 3-4 mm wheal. Physiologic saline and histamine at 0.01 mg/mL (Allergopharma Joachim Ganzer KG, Reinbek, Germany) were used as negative and positive controls, respectively. Rocuronium and thiopentone were diluted by 1:1,000-fold and 1:100-fold, respectively. At 15 minutes following the injection, the mean wheal diameter of histamine and rocuronium were 10 mm and 10 mm, respectively. The wheal diameter of normal saline and thiopentone were 0 mm, both. The next step of thiopentone was the commercial concentration and the result was nothing but mild redness. Three months after the anaphylactic event, skin prick tests for cross-reactivity to drugs related to rocuronium, including vecuronium (Vecron®, Myungmoon Pharm. Co. Ltd., Seoul, Korea), atracurium (Acrium®, Myungmoon Pharm. Co. Ltd., Seoul, Korea), and suxamethonium (Succicholine®, Ilsung Pharm. Co. Ltd., Seoul, Korea), were administered and all were negative, except rocuronium(4 mm) and histamine (3 mm). For the second operation in which the pin was removed, only thiopentone was used for induction of anesthesia. The operation proceeded uneventfully and lasted for 40 minutes.

Discussion

To our knowledge, this article describes the first case of rocuronium anaphylaxis in young children with no previous exposure to NMBAs who is confirmed by skin tests. Neuromuscular blocking agents are responsible for 50-70% of perioperative anaphylactic reactions, which are especially common in patients who have had many previous operations, a noted drug allergy to an anesthetic agent, are aged in their forties to fifties, and/or are female.[1,2] Given that the patient described in this report was 3 years of age, had no known documented allergies, and an unremarkable perinatal and surgical history, an anaphylactic reaction could not have been expected. How then, did rocuronium stimulate IgE antibody production and subsequently provoke an allergen-mediated anaphylactic reaction in our patient?

With regard to allergic reactions to NMBAs, about 15% of affected patients have never before been exposed to a NMBA.[1,2] This patient population suggests the existence of a cross-reaction with IgE antibodies generated by previous contact with substances unrelated to NMBAs. A wide range of findings and observations points to the importance of substituted ammonium groups as allergenic determinants in many drugs or chemicals.[1,3,10] Cross-reactivity not only exists among NMBAs, but also exists between NMBAs and narcotics including morphine, codeine, and pholcodine that have a single tertiary ammonium ion. Compounds containing tertiary and/or quaternary ammonium groups can be found in the environment, such as drugs, disinfectants, food and industrial materials.[3,10,11] Those environmental chemicals were found to be cross-reactive with morphine or NMBAs, such as succinylcholine.[12] The tertiary or quaternary ammonium ion is an epitope and antigenic determinant of NMBAs.[3,4] Aminosteroid NMBAs including rocuronium and pancuronium also have one or more tertiary or quaternary ammonium ions that are epitopes that stimulate IgE production.[3,6] Rocuronium has different ammonium groups.[3]

Anaphylaxis is a rapid, potentially fatal systemic allergic reaction. Regardless of the immunologic or non-immunologic triggering mechanism, mast cells and basophils play an important role in initiating and amplifying the acute response.[1-3,13,14] Mediators

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releasing from these cells, such as histamine and tryptase, may be very helpful to monitor in order to support the clinical diagnosis of anaphylaxis[13]. However, it is critically important to understand the effector mechanism involved in the pathogenesis of anaphylaxis in order to develop optimal risk reduction strategies and prevent recurrence. Confirmation of sensitization to the allergen that is suspected of triggering anaphylaxis on the basis of clinical history is traditionally performed by using a skin prick test or an intradermal allergy test, or a serum specific IgE to the drug. Optimally, the tests are performed at least four to six weeks after the episode of anaphylaxis and repeatedly should be underwent.[1,15]

In our patient, the diagnosis of anaphylaxis was based on the rapid onset of facial angioedema, skin rash, bronchospasm diagnosed with auscultation, and the significant drop in blood pressure to 72/40 mmHg. The severity of anaphylaxis in our patient was less severe, grade II.[1] The epinephrine and any antihistamine were not feasible as the first-line drug in our operating room. The atropine was used as a routine premedication in our hospital and considered to attenuate the anaphylactic reaction, chiefly respiratory symptoms, in this patient.[16] The IgE-mediated reaction for rocuronium was confirmed with both intradermal skin testing and skin prick test. The serum or plasma histamine or tryptase were not measured at the time of the reaction to confirm the diagnosis of anaphylaxis. Those laboratory tests have minimal role in pediatric population because special handling of the blood sampling for histamine is required and tryptase is rarely elevated in anaphylaxis episodes characterized chiefly by respiratory symptoms which, rather than hypotension or shock, are typical of anaphylaxis in the pediatric population.[13] Based on the diagnostic criteria for anaphylaxis proposed by Sampson et al., which is thought to identify more than 95% of cases of anaphylaxis, the patient's clinical manifestation was compatible with the diagnosis of anaphylaxis.[1,13,14]

In the assessment of medication-induced anaphylaxis, skin testing is only predictive of IgE reactions and the sensitivity of skin testing for muscle relaxants is approximately 94% to 97%.[17,18] One of the limitations of intradermal tests for the diagnosis of sensitization to NMBAs stems from their ability to induce histamine release from mast cells within the skin through non-IgE-mediated mechanisms such as calcium channel. Thus, false-positive results may occur, depending on the maximum concentration used. However, this maximum concentration will vary from one compound to another, according to their respective nonspecific histamine-releasing properties.[19] In our case, all drugs administered during the perioperative period should be considered as a potential cause of the patient's anaphylactic reaction. The intradermal test properly performed 12 days after the event resulted in a wheal for rocuronium that was compatible to that of histamine. Previous studies suggest that skin testing for hypersensitivity to rocuronium should be performed at concentrations less than 10^{-4} M. As rocuronium is prepared as a 10 mg/mL solution and is approximately 10^{-2} M, rocuronium therefore needs to be diluted at least 100-fold before skin testing to confirm hypersensitivity and to rule out a false-positive response.[17,18,20] In this patient, the intradermal test was performed with 1000-fold dilutions of commercial compounds and resulted in positive response for rocuronium. Furthermore, rocuronium causes a lower histamine release than other NMBAs such as vecuronium and atrcurium[5,6] and positive response for rocuronium was confirmed repeatedly by skin prick test 3 month after the event.

This case cautions and informs practitioners that an IgE-mediated anaphylactic reaction with rocuronium is possible even in young children with no previous exposure to NMBAs. This case highlights the serious need for a greater awareness of anaphylactic reactions secondary to NMBAs and the importance of developing strategies for the prevention and acute management of drug-related anaphylaxis in any situation.

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