CASE REPORT
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Suspected Anaphylactic Reaction Associated with Microemulsion Propofol during Anesthesia Induction

Se Jin Lee, Soon Im Kim, Bo Il Jung, Su Myung Lee, Mun Gyu Kim, Sun Young Park, Sang Ho Kim, and Si Young Ok

Department of Anesthesiology and Pain Medicine, Soonchunhyang University Seoul Hospital, Seoul, Korea

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Address for Correspondence:
Soon Im Kim, MD
Department of Anesthesiology and Pain Medicine, Soonchunhyang University Seoul Hospital, 59 Daesagwan-gil, Yongsan-gu, Seoul 140-743, Korea
Tel: +82.2-709-9302, Fax: +82.2-790-0394
E-mail: soonnim@schmc.ac.kr

Although rare, intraoperative anaphylaxis can lead to significant morbidity and mortality. Aquafol® (Daewon Pharmaceutical Co. Ltd., Seoul, Korea), a microemulsion propofol, was developed to eliminate lipid solvent-related adverse events, and was used in clinical anesthesia since 2009 with little data about severe side effects such as anaphylaxis. A healthy 16-yr-old male patient who had past medical history with two previous operations of no complications developed cardiovascular shock with generalized erythema following administration of microemulsion propofol during anesthesia induction. Intravenous injection of epinephrine and steroid rescued him. He remained in a stable state without any problems postoperatively and was discharged. Clinicians should consider this rare but serious complication during induction of anesthesia with propofol.

Key Words: Anaphylactic Reaction; Anesthetics; Aquafol; Complications; Microemulsion Propofol

INTRODUCTION

Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction. Although it rarely occurs during anesthesia, it can lead to significant morbidity and mortality (1). The most common causes of anaphylaxis during anesthesia include neuromuscular blocking agents (approximately 60%), followed by latex, and antibiotics. Hypnotics, opioids, local anesthetics, colloids, aprotinin, and protamine were found to be less frequently involved (2). Several cases of anaphylaxis associated with propofol have been reported, attributing to approximately 2.3% of anaphylaxis cases occurring during anesthesia (2-6). Remifentanil, the synthetic phenylpiperidine derivatives opioid, rarely have been reported associated with anaphylactic reaction (2, 7).

Aquafol® (Daewon Pharmaceutical Co. Ltd., Seoul, Korea), a microemulsion propofol, was developed to eliminate lipid solvent-related adverse events such as infection, fat embolism, hypertriglyceridemia, and pancreatitis associated with lipid emulsion propofol (8). Although the new drug is safer than lipid emulsion propofol, the clinical history of microemulsion propofol is relatively short, with little data about severe side effects such as anaphylaxis.

We report a case of a patient who developed cardiovascular shock with generalized erythema associated with microemulsion propofol administration during anesthesia induction.

CASE DESCRIPTION

A healthy 16-yr-old male patient was scheduled for incision and drainage under general anesthesia for a postoperative femur fracture infection on August 25, 2009. His past medical history included two previous operations not associated with any complications. The year prior, he underwent an operation for a closed reduction and internal fixation of a femur fracture with Sirus IM-nail under general anesthesia using propofol, rocuronium, desflurane and remifentanil. One month prior, he underwent an operation to remove the IM-nail under general anesthesia using propofol, rocuronium, and sevoflurane. He has no history of atopy, or known drug or food allergy. Physical and preoperative examinations were unremarkable and included laboratory results, chest x-ray, and EKG.

The patient received intramuscular injection of glycopyrrolate 0.2 mg and midazolam 3 mg respectively for premedication before the operation. Upon arrival to the operating room, standardized monitoring was initiated to include non-invasive automatic blood pressure measurement, EKG, and continuous peripheral oxygen saturation. Initial blood pressure (BP) was 140/75 mmHg, heart rate (HR) 71 beats per min, with a peripheral oxygen saturation (SpO2) of 99%.

General anesthesia was induced with a microemulsion propofol using a plasma target-controlled infusion (8 μg/mL) 1 min after continuous infusion of remifentanil (20 μg/min). When

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the patient became asleep, BP decreased to 84/35 mmHg, HR increased to 135 beats per min, and a generalized erythema over the entire body developed. It was thought strange, but not so seriously, and decided to continue the anesthesia induction. Then rocuronium 40 mg administered intravenously. And after 1 min, the laryngeal mask airway (LMA) ProSeal was inserted. After insertion of the LMA ProSeal, the BP decreased to 58/37 mmHg with a HR to 119 beats per min and a SpO2 of 100%. The infusion of microemulsion propofol and remifentanil were immediately stopped and IV ephedrine 8 mg was injected two times in addition to dexamethasone 10 mg intravenously. Despite these interventions, hypotension did not improve increasing our suspicion for anaphylaxis. Epinephrine infusion was then started after an epinephrine 50 μg intravenous bolus and solucortef 100 mg intravenous injection. Within 10 min the BP gradually increased to 107/46 mmHg with a HR of 101 beats per min and SpO2 of 99% while the patient received a low concentration of sevoflurane with oxygen. After an additional 5 min, epinephrine infusion was discontinued as his BP and HR stabilized to 136/85 mmHg and 84 beats per min, respectively. The BP and HR continued to remainstable while the patient's generalized erythema disappeared. After discussing about this event with surgeon, surgery was then resumed using sevoflurane with 50% oxygen for general anesthesia. During the surgery, BP maintained stable at 100-120/60-80 mmHg with a HR of 70-80 beats per min. After skin incision closure, neuromuscular blockade was reversed with pyridostigmine and glycopyrrolate. LMA ProSeal was removed when the patient was fully awake with normal spontaneous respiration. The BP was 144/106 mmHg with HR of 106 beats per min. In the recovery room, there were no identified problems.

Based on the course of events, anaphylactic shock due to microemulsion propofol had been presumed. The patient remained in a stable state without any problems postoperatively and discharged satisfactorily 8 days after surgery. The patient underwent skin test 6 weeks after the event in the allergy clinic center of our hospital by trained physician and nurse. Skin tests including prick and intradermal test for microemulsion propofol, propofol, and remifentanil were performed and was verified by negative (saline solution) control test and positive control test (a 10 mg/mL solution of histamine). But skin tests showed negative results for all of the tested medications.

DISCUSSION

The incidence of anaphylaxis during anesthesia is very difficult to estimate but has been reported to be 1 in 10,000-20,000 cases. Although rare, these reactions may lead to death, even when appropriately treated, with a mortality rate ranging from 3.5% to 4.7% (9).

Anaphylactic reactions usually occur within second to minutes of exposure to the allergen. The most common clinical features occurring during anesthesia include cardiovascular symptoms (hypotension, tachycardia or bradycardia), cardiovascular collapse, bronchospasm, and cutaneous-mucous signs (erythema, edema, urticaria, and angioedema). Any delay in the recognition of initial signs and symptoms of an anaphylactic reaction can result in a fatal outcome either because of airway obstruction or vascular collapse. Recognition of anaphylaxis during anesthesia is usually delayed because anaphylaxis is a rare event with hypotension and bronchospasm more commonly due to different causes (1). In the present case, although the patient showed hypotension and tachycardia with generalized erythema involving the entire body approximately 2 min after intravenous infusion of microemulsion propofol, we initially did not recognize the anaphylactic reaction because mild to moderate hypotension can frequently appear with simultaneous use of microemulsion propofol and remifentanil during induction of anesthesia. We suspected anaphylactic shock when the hypotension did not improve despite intravenous ephedrine administration.

When anaphylactic reaction is suspected, prompt management is required. Immediate discontinuation of anesthetics and offending drugs with the administration of epinephrine is the treatment cornerstone. Epinephrine is the drug of choice in the treatment of anaphylaxis, because its α_1 effects help to support the blood pressure while its β_2 effects provide bronchial smooth muscle relaxation. It is imperative to ensure that the patient's airway is maintained and that 100% oxygen is provided during resuscitation. Intravenous solution is required to account for the peripheral vasodilation that often accompanies anaphylaxis (10).

The initial diagnosis of anaphylaxis is presumptive because anaphylaxis may progress within minutes to become life-threatening. The clinical history is the most important tool to establish the diagnosis of anaphylaxis and takes precedence over diagnostic tests. In the present case, the patient also showed hypotension and tachycardia with generalized erythema involving the entire body approximately 2 min after infusion of microemulsion propofol and remifentanil, and progressed rapidly into cardiovascular shock which was improved by intravenous epinephrine administration.

Serum tryptase is a helpful indicator of an anaphylaxis. Tryptase concentration should be determined approximately 1 hr after the start the reaction. Tryptase's half-life is 2 hr, and the levels gradually decrease over time, and can still be detected for 1-6 hr or more. Unfortunately, we did not know how to assess the biochemical test to the diagnosis at the time of event, so we did not assess the serum tryptase. Skin test or in vitro specific IgE antibody tests that determine the presence of specific IgE antibodies can identify specific causes for anaphylaxis. Skin test and in vitro IgE tests are only valid when the reaction is due to

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an IgE-mediated anaphylactic reaction and not as a result of non-IgE-mediated anaphylactic reactions. In general, skin tests are more sensitive than in vitro test and are the diagnostic procedure of choice for the evaluation of potential causes for anaphylaxis (11). In addition, radioimmunoassay for IgE antibodies for microemulsion propofol, propofol, and remifentanil is not available in this country.

In this case, we performed skin tests for microemulsion propofol, propofol, and remifentanil to identify the causative agent postoperatively at the allergy clinic in our hospital. The skin test showed negative results for the all the tested medications. Therefore, we suspected that the patient's anaphylactic reaction was due to a non-IgE-mediated anaphylactic reaction rather than IgE-mediated anaphylactic reaction.

The patient previously received propofol, remifentanil, rocuronium, desflurane and sevoflurane anesthetics during his two previous operations without any complications or reactions. Although his anaphylactic reaction occurred 2 min after intravenous infusion of microemulsion propofol and remifentanil, remifentanil was excluded as a causative agent given his prior usage history.

A microemulsion propofol is formulated with 1% propofol, 10% purified poloxamer 188 (PP188) and 0.7% polyethylene glycol 660 hydroxystearate. Poloxamer 188, one component of microemulsion propofol, has been reported to cause a non-IgE-mediated anaphylactic reaction, known as complement activation-related pseudoallery (12, 13). Therefore, it is assumed that the anaphylactic reaction occurred most likely due to microemulsion propofol, although unknowing about exact causative agent.

In conclusion, we present a case of a patient who developed an anaphylactic reaction with cardiovascular shock and generalized erythema associated with a microemulsion propofol during the anesthesia induction.

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