



Anaphylactic shock caused by intramuscular injection of midazolam during the perioperative period -a case report-

Kyu Nam Kim, Dong Won Kim, Yeong Hun Sin, and Soo Kyung Lee

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

Although anaphylactic shock during the perioperative period is rare, it can be lethal due to severe cardiovascular and respiratory collapse. Midazolam is generally used as premedication for relieving anxiety about the operation, and the danger of anaphylactic shock after intramuscular injection is not widely recognized. We report the first case of anaphylactic shock occurring during the perioperative period after intramuscular injection of midazolam. Since anaphylactic shock after intramuscular injection can be of slow onset, the operation should be delayed if an anaphylactic reaction is suspected, even if the symptoms are limited. In addition, anesthesiologists should be prepared for the occurrence of anaphylaxis at any time in the perioperative period.

Key Words: Anaphylaxis, Intramuscular injections, Midazolam.

Anaphylaxis is a systemic hypersensitivity reaction that develops when patients are exposed to a specific antigen to which they have been previously sensitized [1]. In spite of the rarity of anaphylaxis during the perioperative period, with rates of 1 : 2,800 to 1 : 20,000, it can be fatal and contributes up to 3% of anesthesia-related deaths caused by severe cardiovascular and respiratory collapse [2-5].

Although midazolam is widely used as premedication for re-

lieving anxiety during operations, rare hypersensitivity reactions have only been reported when it was injected intravenously [6-8]. We present the first case of anaphylactic shock caused by midazolam administered intramuscularly as premedication.

Case Report

A 59-year-old male, height 170 cm and weight 68 kg, was admitted for open reduction and internal fixation of ankle fracture. The patient underwent an open reduction and internal fixation of ankle fracture under spinal anesthesia with bupivacaine 2 years ago. During the surgery, he was sedated by intravenously administered midazolam without premedication and the anesthesia-or surgery-related complications were not reported. He has not experienced sedation management with the exception of the surgery. There was no known history of atopy, asthma, or allergies. Preoperative evaluations such as laboratory tests, electrocardiography, and chest radiography were normal.

For the preoperative treatment, atropine 0.5 mg and midazolam 3.0 mg were intramuscularly administered 30 minutes

Corresponding author: Dong Won Kim, M.D., Ph.D.
Department of Anesthesiology and Pain Medicine, Hanyang University Hospital, 222, Wangsimni-ro, Seongdong-gu, Seoul 04763, Korea
Tel: 82-2-2290-8680, Fax: 82-2-2299-8692
E-mail: dongwkim@hanyang.ac.kr
ORCID: <http://orcid.org/0000-0003-2492-3144>

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before the operation. His blood pressure was 122/75 mmHg with a heart rate of 85 beats/min, and a respiratory rate of 16 breaths/min before he transferred to the operation room. After his arrival in the operating room, the patient's vital signs were monitored by noninvasive blood pressure measurement, electrocardiography, and pulse oxymetry. Before induction of general anesthesia, he complained generalized pruritus. Urticarial skin rashes of upper and lower extremity and an angioedema of face and tongue were observed.

Because an anaphylactic reaction was suspected judging from these generalized skin symptoms, the operation was delayed and he was moved to the recovery room. Although 250 mg of methylprednisolone and 40 mg peniramin were injected intravenously to treat the anaphylactic reaction, his blood pressure decreased to 70/40 mmHg with heart rate of 98 beats/min and pulse oxygen saturation on pulse oximetry (SpO₂) of 90% 25 minutes after skin symptoms (Fig. 1). Although he began to experience mild dyspnea, the sound of wheezing was not auscultated. The patient was given 100% oxygen via face mask. Simultaneously, epinephrine 50 µg and hydrocortisone 100 mg

were injected intravenously with plasmalyte solution (Plasma Solution-A, CJ Pharma, Seoul, Korea) hydration. And then, the serum tryptase level and the total serum immunoglobulin E (IgE) level were measured for confirming anaphylaxis. After transient tachycardia of heart rate of 130 beats/min, heart rate decreased to 100 beats/min within 10 minutes and the blood pressure increased to 90/60 mmHg, SpO₂ to 95%. Except the tachycardia, other specific changes of electrocardiography were not observed. During the rest of the period, vital status was stably maintained without medication other than intramuscular epinephrine 0.3 mg. The elevated tryptase level to 29.9 µg/L (normal range: 0–11 µg/L) was detected from laboratory test. Except that systemic erythematous rash and swelling of the skin around the eyes could still be seen, there were no other abnormal findings. The skin symptoms resolved after 2 hours in the recovery room. Arterial blood gas analysis (ABGA) gave pH 7.32, pCO₂ 44 mmHg, pO₂ 155 mmHg, and BE 0.5 mM at fraction of inspired oxygen 0.3. Since the results of ABGA and chest radiography were normal and there were no further specific clinical presentations, the patient was transferred to a general ward.

After 2 months, skin prick and intradermal tests were performed to establish the allergen. As a result, midazolam was identified as a cause of anaphylactic shock (Table 1) and the patient was informed to avoid this agent. The patient underwent an open reduction and internal fixation of ankle fracture under spinal anesthesia without sedation. After one week following surgery, the patient was discharged without any other problems.

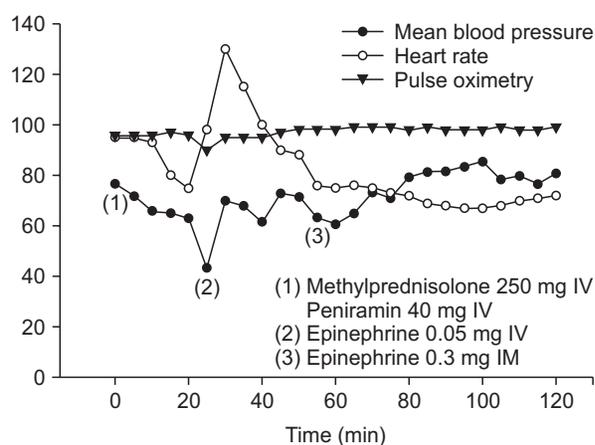


Fig. 1. Graphs of vital signs in the recovery room. At 25 minutes after appearance of the skin lesions, blood pressure dropped to 70/40 mmHg with pulse rate 98 beats/min, and pulse oxygen saturation dropped to 90%. Epinephrine 50 µg and hydrocortisone 100 mg were injected intravenously with hydration to treat the anaphylactic shock. Thereafter, after transient tachycardia, blood pressure increased to 100–110/50–60 mmHg, and pulse rate decreased to 70 beats/min.

Discussion

Because shocks that develop during the perioperative period affect patients' safety, rapid identification of their cause and management are vital. Judging by the absence of abnormalities during the preoperative evaluations and the fact that no procedure except premedication was performed, the possibility of cardiogenic, hypovolemic or neurogenic shock was minimal in the present case. However the appearance of specific skin lesions in the form of urticarial skin rashes and angioedema made us suspect anaphylaxis.

The diagnosis of anaphylaxis during perioperative period can be quite difficult. The symptoms cardiovascular collapse of

Table 1. Results of Skin Tests to Agents

Drugs	Skin prick test		Intradermal test	
	Concentrations (mg/ml)	Response	Concentrations (mg/ml)	Response
Histamine (1 mg/ml)	1	5 × 5	0.1	12 × 13
Saline (control)	-	Negative		Negative
Atropine (0.5 mg/ml)	1	Negative	0.1	3 × 3
Midazolam (1 mg/ml)	5	4 × 5	0.5	13 × 13

anaphylaxis can be mistaken as effects of the anesthetic agents and mechanical ventilation after application of a muscle relaxant may mask respiratory symptoms, which can also make it difficult to diagnose. Furthermore, even if anaphylaxis is identified, it is difficult to establish the cause because the variety of agents is exposed to the patients during the brief period of surgery.

The most important clues for diagnosing anaphylaxis are clinical presentations such as skin and mucosal involvement, respiratory symptoms, and cardiovascular dysfunction [5,9]. Information about antigen exposure can provide an indication of the cause of the anaphylaxis. Laboratory tests that detect an increase of serum tryptase are the most commonly used diagnostic methods for confirming anaphylaxis. Serum tryptase, a neutral serine protease released by mast cells, increases within 1–2 hours after presentation of clinical symptoms of anaphylaxis, and its level returns to normal after about 24 hours [5,10]. Therefore, anesthesiologists should be aware that detecting elevated serum tryptase is an important indicator confirming the diagnosis when skin reactions are not obvious [11]. Lastly, the gold standard for identifying the cause of immunoglobulin-E mediated anaphylaxis are skin tests such as the skin prick test and intradermal test [9,12,13]. In order to avoid false negative results caused by depletion of specific immunoglobulin-E antibodies and mast cells, the skin test should be performed 4–6 weeks after anaphylaxis [5,9].

Of the anaphylaxis occurring during the perioperative period, 55–59% are caused by muscle relaxants, while latex (20–22%) and antibiotics (13–15%) are other major causes [2,10,12]. Reports of midazolam-associated hypersensitivity reactions have been rare and all such cases occurred after intravenous injection [6–8]. In this case, atropine and midazolam were administered intramuscularly for premedication. Fortunately, rapid detection of skin lesions deterred us from using other drugs, to induce anesthesia. Therefore, detecting the cause of the anaphylaxis was not difficult; the candidates were the two drugs injected,

and the skin test pointed to midazolam. Midazolam is widely used intramuscularly for relieving anxiety before surgery, and anaphylactic shock presenting as severe cardiovascular collapse can occur when it is injected intramuscularly. As this present case has shown, anaphylactic shock can occur about 1 hour after intramuscular injection despite treatment. Therefore, if the skin lesions of anaphylaxis are observed, surgery must be postponed until the patient's safety is secured.

Cross-reactivity between benzodiazepines is a part that should not be overlooked. Cross-reactivity between neuromuscular blocking agents and antibiotics is known to be common due to structural similarity in these drugs [4,5,14]. In case of neuromuscular blocking agents, cross-reactivity occurs in up to 60% of the patients [4,5]. However, allergic reactions to benzodiazepines have been reported for individual agents and such reactions are rare. Except one study of anaphylaxis caused by tetrazepam which showed there was no cross-reactivity among benzodiazepine [15], cross-reactivity between drugs in this class is not as well known. Therefore, further studies regarding the cross-reactivity between benzodiazepines are needed.

In conclusion, although midazolam is generally used as premedication for relieving anxiety of surgery, the danger of anaphylactic shock after intramuscular injection of midazolam is not widely recognized. When it was injected intramuscularly, slow onset of severe anaphylactic shock can occur. Therefore, the surgery should be postponed when the anaphylactic reaction was suspected even though the symptoms were limited. Additionally, anesthesiologists should be prepared for the occurrence of anaphylaxis at any time in the perioperative period.

ORCID

Kyu Nam Kim, <http://orcid.org/0000-0003-2526-8348>

Dong Won Kim, <http://orcid.org/0000-0003-2492-3144>

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