

Hypersensitivity Reaction to Perioperative Drug Mistaken for Local Anesthetic Systemic Toxicity in a Patient under Brachial Plexus Block

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Perioperative anaphylaxis, although rare, is a severe, life-threatening unexpected systemic hypersensitivity reaction. Simultaneous administration of various drugs during anesthesia, the difficulty of communicate with patients in sedation and anesthesia, and coverage of the patient with surgical drapes are considered to be factors that impede early recognition of anaphylactic reactions. It is very important to perform an intradermal skin test because antibiotics are the most common cause of perioperative anaphylaxis. We report a case of negative-intradermal skin test antibiotic anaphylaxis mistaken for local aesthetic systemic toxicity without increase of serum tryptase for confirmative diagnostic biomarker during surgery under brachial plexus block. It is not possible to exclude the danger of anaphylaxis completely, even if it is negative-intradermal skin test and normal tryptase level. Therefore, anesthesiologists should be closely monitored and treated early for antibiotics related hypersensitive reaction, like other medicines during anesthesia.

Key Words: Anaphylaxis, Anesthesia, Antibiotics, Local anesthetic systemic toxicity Skin test, Tryptase,

Perioperative hypersensitivity is a clinical symptom associated with several mechanisms, including IgE and non-IgE mediated mechanisms, with various reports detailing minor symptoms such as skin rash to severe signs and symptoms of anaphylaxis including angioedema, bronchospasm, hypotension, tachycardia, and sudden failures of cardiopulmonary functions.¹ Reports of perioperative anaphylaxis vary in the literature and differ ac-

cording to country, ranging from approximately 1:2,000-1:20,000, and is associated with actual perioperative-related morbidity and mortality, with a high mortality rate of up to 9%.² The various drugs used in perioperative, the inability to communicate with sedated and anesthetized patients, and the body of the patient covered with a surgical drapes are considered to be factors that hinder early recognition of anaphylactic reactions.

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Neuromuscular blockers, latex-containing products, chlorhexidine, and antibiotics are known as the most common drugs to cause the disease, and preoperative preventive antibiotics such as Gurrieri C, in particular, beta-lactam antibiotics (penicillin and cephalosporins) account for 50% of IgE-mediated reactions as the most common cause of preoperative anaphylaxis.³ Therefore, in order to prevent and diagnose anaphylaxis, it is necessary to check the serum tryptase levels of patients suspected of developing anaphylactic symptoms along with an antibiotic skin reaction test before use.⁴

The authors intend to report a case where the anaphylactic reaction in a patient who underwent wrist fracture surgery under brachial plexus block was mistaken for local anesthetic systemic toxicity. In this case the anaphylactic reaction occurred while tryptase levels were in the normal range during the injection of antibiotics at which time the skin reaction test was negative (intradermal skin test negative antibiotics). This case is reported based on a review of the literature.

CASE

A 54-year-old female patient with a height of 160.6 cm and weight of 62 kg with a left radial head fracture was treated with open reduction and internal fixation under US-guided axillary brachial plexus block (Axillary BPB). There was no special medical history other than diabetes

controlled by medication and no previous history of allergies. Prior to surgery, the examination results were AST/ALT 37/69 (reference values: 0 - 40 IU/L), and except for elevated ALT findings, all of the blood tests, chest radiographs, electrocardiograms, and physical examinations were in the normal range without any abnormal findings.

After entering the operating room without pre-anesthetic medication, the blood pressure, heart rate, pulse oxygen saturation, and electrocardiogram were monitored, and the measured vital signs were: blood pressure (137/76 mmHg), heart rate (76/min), and pulse oxygen saturation (100%), and the electrocardiogram showed normal findings. The patient inhaled O₂ 3 L/min through a nasal cannula and received US-guided axillary BPB under shallow sedation with midazolam 3 mg and fentanyl 50 µg. The local anesthetic used was 1.5% lidocaine, and a total of 30 ml was injected around each nerve in 5 ml-10 ml increments after confirming no blood aspiration and no dysaesthesia. After 10 minutes of BPB, the vital signs were 126-135/70-80 mmHg, 60-70/min, 100%, so she was prepared for surgery as the surgical anesthesia level was confirmed. After 15 minutes of BPB, 2 g of Cefotetan (Yamatetan®, jeilpharm, Korea) a prophylactic antibiotic with negative skin reaction, was mixed with 100 ml physiological saline and slowly injected through IV. After 5 minutes, the pulse increased to more than 105 times per minute and the blood pressure dropped to 99/55 mmHg. However, the patient did not appear to have any abnormal symptoms, so the sur-

gical tourniquet was pressurized and it was decided to continue observations as the operation began. 10 minutes after IV injection and 5 minutes after surgery, the patient's heart rate increased to 130 and the blood pressure started to drop to 80/46 mmHg, so ephedrine 10 mg was administered twice with an injection of crystalloid fluid, but the blood pressure dropped to 60/38 mmHg without improvement and the heart rate suddenly dropped to 75/min, so 0.5 mg of atropine was injected. We tried to talk to the patient but she was drowsy and her response was not clear, and the patient's blood pressure continued to drop to 50-60/30-35 mmHg, so epinephrine 50 μ g was injected and we started to assist respiration with O₂ 6 L/min through a mask. At the same time as help was requested, we suspected local anesthetic systemic toxicity (LAST), and after injecting about 90 ml of 20% lipid emulsion (Intralipid®20%, Fresenius Kabi AG, Sweden), which was 1.5 ml/kg per body weight, we continued injections at 0.25 mL/kg/min. In terms of ECG, there was no arrhythmia except tachycardia. The operation was stopped after informing the surgeon about the patient's condition, and we observed a red rash all over the skin after removing the surgical drapes. As anaphylaxis was suspected, the injection of antibiotics was stopped immediately, and crystalloid fluid was quickly injected by securing another IV line, and we additionally injected methylprednisolone (Methysol, Alvogen, Korea) 250 mg, Chlorpheniramine (peniramin, Yuhan, Korea) 4 mg, epinephrine 100

mcg and stopped 20% lipid emulsion. The blood pressure was 50-70/30-35 mmHg and the pulse was 140-150/min, so epinephrine was continuously injected at 0.3 μ g/kg/min. In order to maintain the airway, etomidate 6mg and rocuronium 40 mg were injected and we started mechanical ventilation via endotracheal intubation. After examining with a stethoscope, there were no abnormal findings such as wheezing, and both lungs were clear as the peak inspiratory pressure was 14 cmH₂O. The blood pressure gradually increased to 80-90/42-50 mmHg, so tryptase blood tests were carried out for confirmation with an arterial blood gas analysis by holding the right radial artery tube. The arterial blood gas analysis showed normal values of pH 7.33 P_aCO₂ 44 mmHg, P_aO₂ 490 mmHg, HCO₃ - 23.2 mmol/L, base excess -2.8 mmol/L, SaO₂ 100%, and by monitoring the arterial blood pressure, the blood pressure was maintained at 90-100 mmHg, so the operation was resumed and the blood pressure remained stable at 110/50-60 mmHg until the end of the operation. The blood pressure was maintained at 90-100 mmHg right after the operation, and there were no abnormal findings such as pulmonary edema in the chest radiographs performed before the end of anesthesia. In addition, no abnormal findings were detected in the arterial blood gas test and by means of the stethoscope, so after injecting sugammadex (Bridion®, MSD, Korea) 200 mg, muscle relaxation was reversed and consciousness was regained, and the patient was moved to the recovery room after the intubation

tube was removed. The operation time was 65 minutes and the anesthesia time was 115 minutes. The amount of crystalloid fluid injected during the operation was 2,500 ml, the amount of blood loss was about 10 ml, and the amount of urine was 250 ml (Fig. 1).

In the recovery room, blood pressure was 90-120/50-80 mmHg, and the pulse was stable at 70-80 per minute, the patient was conscious and alert, and the systemic red rash had disappeared. The patient and guardian were informed about the suspicion of anaphylaxis caused by prophylactic antibiotics during the operation and were advised to visit the department of allergy and clinical immunology after 6 weeks for further examination and the patient was transferred to

the intensive care unit.

For postoperative antibiotic treatment, under consultation with the department of allergy and clinical immunology, we used levofloxacin (Cravit®, Jeilpharm, Korea) 500 mg, which is a quinolone antibiotic, but halted the injection after a rash was observed again on the face, and re-administered the antibiotic with 62.5 mg of methylprednisolone (Methysol, Alvogen, Korea) and 2 kinds of antihistamines, which were 10 mg of cetirizine (Zyrtec®, UBC, Korea) and 112.5 mg of pranlukast hydrate (Onon®, Donga-st, Korea). The patient's condition was stable two days after the operation, so she was transferred to the general ward and she was discharged five days after the operation, but no definite diagnostic exami-

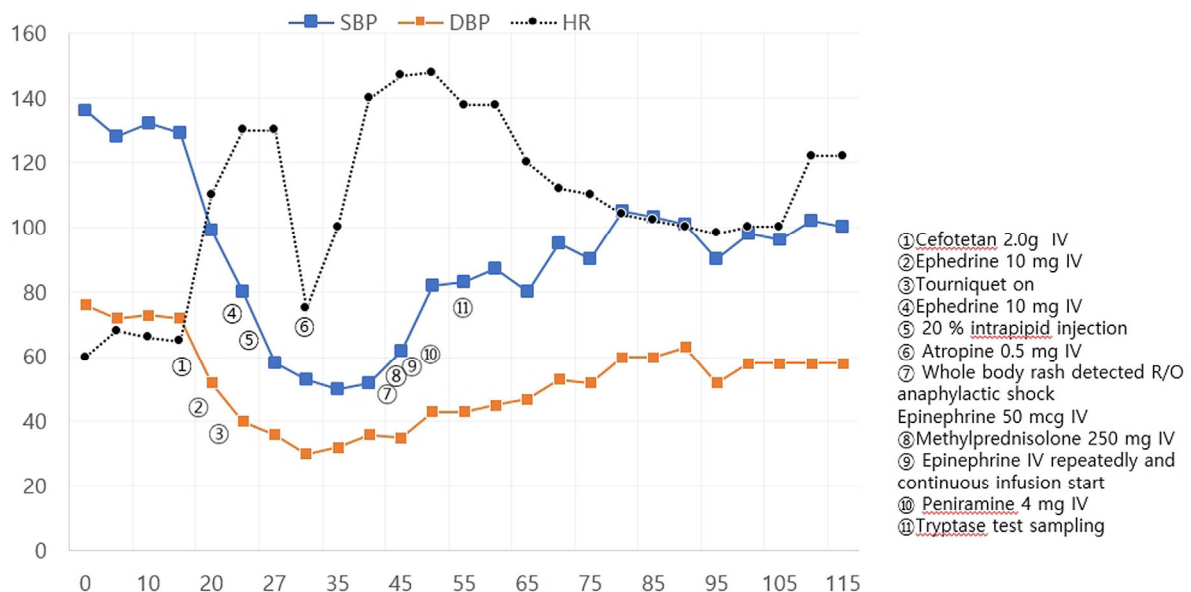


Fig. 1. Changes in vital signs during anesthesia (Axillary BPB). From about 5 minutes after antibiotic administration, instability of the vital signs was observed, which was followed by tachycardia, blood pressure was abrupt dropped to 50/32 mmHg and rapid fluid hydration was delivered with emergency medication including with ephedrine, atropine, epinephrine, steroid and antihistamine. As a result, the vital signs gradually stabilized, and the operation could be completed.

nations were performed due to the loss of follow-up, and the results of the tryptase test at the time of anaphylaxis were confirmed to be normal at 9.6 $\mu\text{g/L}$ (reference values; 0 - 11.0 $\mu\text{g/L}$).

DISCUSSION

Anaphylaxis is defined as 'a severe and life-threatening systemic hypersensitivity reaction' and 'a severe allergic reaction that starts rapidly which can also lead to death.' Because of exposure to various medications during surgery and anesthesia, the causative agents are generally unclear and the causal relationships are not well understood, so most cases are not recognized or reported, and this condition tends to be measured below the actual incidence rate with various reports in the range of 1:2,000-1:20,000.^{1,2,6,7}

The diagnosis is based on clinically manifested symptoms and signs, and is classified into five stages of Grade 1-5 depending on the degree of hypersensitivity.⁸ Grade 1, which consists of 66.7% of all hypersensitivity reactions, manifests minor conditions with only skin reactions. Grade 2 (18.5%) is observed in several organs and is indicated by tachycardia, coughing or bronchial hyper-reactivity, but is not life-threatening. Grade 3 is the stage where life-threatening symptoms such as cardiovascular collapse, cardiac arrhythmia, and bronchospasm occur. Grade 4 is defined as cardiac arrest or respiratory arrest, and Grade 5 is defined as death. Among them, Grade

3-5 is anaphylaxis, a serious hypersensitivity reaction, which is very rare with only about 2 cases per 10,000 operations, but accounts for about 15.8% of the total hypersensitivity reactions. Cardiovascular system and respiratory damage are the characteristics of perioperative hypersensitivity reaction, where cardiovascular collapse may be the first symptom to be found in 50% of cases, and may be recognized when it's too late because there are no skin symptoms; even if there were such symptoms, they would be covered by the surgical drapes.⁹

Many studies have reported that anesthetics, blood products, contrast medium, latex, chlorhexidine, antibiotics, and analgesics may be the cause. In terms of drugs used during the perioperative period, muscle relaxants and antibiotics are known to cause anaphylaxis with the highest frequency.^{6,10,11} Although rare, it can be caused by all of the drugs and supplies used during surgery and anesthesia. However, since there are various medications and many supplies that come in contact with one another from the induction of anesthesia to the operation, it is difficult to distinguish the cause from the anesthetized patient because you cannot know exactly when the symptoms began.¹²

The first symptom found in this case was a shock which started with tachycardia and hypotension, and the dermatological symptoms were not recognized because of the surgical drapes and abnormal respiratory symptoms were not observed. Therefore, we believe these non-specific symp-

toms were not diagnosed early as anaphylaxis, but they were misdiagnosed and treated as LAST. Although the potential risk of LAST during local anesthesia is always present and peripheral nerve blocks such as brachial plexus block is known to have the highest risk of occurrence, the incidence is reported to be very rare with 1~10 cases out of 10,000 cases.¹³ Nevertheless, the possibility of serious and fatal complications needs to be recognized and treated through education and training to reduce the likelihood of LAST. Furthermore, for preventive measures during anesthesia with local anesthetics, in addition to a standard monitor, drug injection, and caution against blood being aspirated through frequent aspiration during needle manipulation, it has been reported that the use of US-guided block may reduce the risk. The symptoms include a wide range of neurological signs and symptoms such as seizure, agitation, or obtundation, and cardiovascular signs and symptoms such as arrhythmia or conduction defect, hypertension, tachycardia or progressive hypotension, and bradycardia.¹⁴ Di Gregorui G showed that a rapid onset could occur within 5 minutes with CNS symptoms and cardiovascular symptoms in 60% of cases, and that 38% of cases were delayed more than 5 minutes, and some of the cases showed symptoms after 60 minutes. In 11% of cases cardiovascular symptoms without neurological symptoms were reported.^{15,16}

In particular, 52% of the cases with a delayed onset of more than 5 minutes were confirmed by US-guided nerve blocks. In addition, there was

no mention of skin reactions when referring to the symptoms. Management needs to stop the injection of local anesthetics first, ventilate with 100% oxygen after intubation, and inject 0.25 ml/kg/min after 20% lipid emulsion 1.5 ml/kg IV loading. Benzodiazepine may be used in the event of seizures.¹⁷ Although US-guided nerve block was performed in this case with frequent blood aspiration according to needle manipulation, the possibility of LAST had to be considered as a top priority, because 30 ml of local anesthetic was used to block 4 nerves including the musculocutaneous nerve when performing axillary BPB, and according to the immediate treatment under close monitoring of vital signs and ECG, 20% lipid emulsion and epinephrine were used with a relatively smaller amount of capacity than the anaphylaxis treatment capacity. However, in spite of the injection of 20% lipid emulsion and epinephrine, the operation was stopped for high-quality cardiovascular system therapy due to the progressive cardiovascular collapse, and after discovering the red rash all over the patient's body as we removed the surgical drapes we determined that there was a high possibility of anaphylaxis on the grounds that LAST could be excluded as skin rash rarely occurs in that circumstance. Therefore, we stopped the treatment of allergen-anticipated drugs, and performed treatment with high doses of epinephrine, steroids, and antihistamines. No respiratory-related symptoms were observed, but the possibility of airway mucosal edema developing and progressing could not be excluded, so imme-

diate airway intubation and mechanical ventilation were performed. In this case, the symptoms appeared 5 minutes after starting to inject antibiotics and 20 minutes after BPB using local anesthetics. The causes considered for this patient can be summarized as sedatives, local anesthetics, and prophylactic antibiotics used before BPB. In the case of identifying the cause considering the onset time and the dermatological and cardiovascular system symptoms and signs, cephalosporin, a prophylactic antibiotic, is the most likely cause because the symptom appeared within 5 minutes of antibiotic administration.

Currently, β -lactam antibiotics, such as penicillin and cephalosporins are the most commonly used prophylactic antibiotics, and account for about 70% of the anaphylaxis caused by antibiotics.^{18,19} Therefore, before using these antibiotics, a skin reaction test is performed to confirm type-1 IgE mediated response. However, because of the low sensitivity and low positive predictive value of cephalosporin antibiotics, even if the skin test is negative, the risk of anaphylaxis cannot be completely ruled out.^{1,12,20}

Along with the symptoms, laboratory tests help formulate the diagnosis, and when there is an anaphylactic event, immediate examinations of serum tryptase, plasma histamine, and 24-hour urinary histamine metabolites are known to be useful.¹ Among these, elevated levels of serum tryptase are the most useful biomarker to determine Ig-E-mediated hypersensitivity, reaching the maximum elevated level around 15–60 mi-

nutes after anaphylaxis and lasting for 4 hours. In the case of Ig-E-mediated hypersensitivity reactions that occur during general anesthesia with a sudden rise of serum tryptase of 15.7 $\mu\text{g/L}$ or more, even if the sensitivity, specificity, positive and negative predictive values show normal values of 75%, 68.4%, 82%, and 59%, respectively, the possibility of anaphylaxis cannot be ruled out. In this case, the serum tryptase test was performed within 60 minutes after symptom onset, but after five days, the test results were negative. In addition, after several weeks, a skin prick test may be performed on a number of medications used to identify the cause, but on this occasion, even though we explained to the patient the severity of the immune response and the necessity of visiting the department of allergy and clinical immunology for examination, there has been no follow-up until now.

In this case, we cannot confirm that the cause of anaphylaxis was antibiotics, but we are reminded through a review of the literature that anaphylaxis may appear in the administration of antibiotics even though the skin reaction test is negative. In other words, we should be aware that various drugs may cause anaphylaxis and should be aware of the symptoms and signs. Therefore, we need to be alert, intervene quickly and be ready to adopt various approaches when anaphylaxis occurs. The medical history of atopy, medication, and food hypersensitivity should be carefully considered in preoperative evaluations to predict and prevent anaphylaxis. In addition, after recovery

from anaphylaxis, identifying the causative agents and providing information on avoidance and first aid may prevent future fatal risks to patients in the future.

In conclusion, prophylactic antibiotics may be one of the causes of severe anaphylaxis among hypersensitivity reactions with regard to anesthetized patients. Although antibiotic skin reaction tests before use are recommended as a measure to prevent anaphylaxis, it may occur even when the skin reaction test is negative as shown in this case, so like other medications during anesthesia, anesthesiologists need to perform early diagnosis and treatment through close observation when administering antibiotics. In addition, elevated levels of serum tryptase may be a useful biomarker to confirm anaphylaxis, but may show a normal range as shown in this case. Therefore, in order to confirm anaphylaxis in case of doubt, the cause of the hypersensitivity reaction must be identified through a skin prick test of the drugs used after 4-6 weeks, to guarantee the health and safety of the patient and prevent risks that may arise in the future.

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