

Anaphylaxis occurred immediately after prophylactic antibiotics injection with negative intradermal skin test during laparoscopic cholecystectomy

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Prophylactic antibiotics that are used to prevent post-operative infection can commonly cause anaphylactic reactions during anesthesia. It is therefore necessary to perform a skin test before antibiotics are administered in order to diagnose and prevent anaphylactic reactions. However, the results of the antibiotic skin test can differ according to the drug, dose, and reagent concentration.

We report a case of anaphylactic shock with bronchospasm and cardiovascular collapse immediately following administration of the prophylactic cefazidone after induction of general anesthesia for laparoscopic cholecystectomy.

Key Words: Anaphylaxis, Antibiotics, Intradermal tests, Shock

Anaphylactic reactions caused by medications during general anesthesia rarely occur, but they can range from mild vasodilation to life-threatening cardiovascular events.¹ Prophylactic antibiotics used to prevent postoperative infections are also one of the common agents that cause anaphylactic reactions during anesthesia.² Therefore, in order to diagnose and prevent an anaphylactic reaction, it is necessary to first perform an antibiotic skin test (AST) before administering antibiotics to a patient. The specificity of the AST is known to be very high, greater than 90%.³ However, the results of the AST can differ

according to the target drug, volume, and reagent concentration.⁴

We report a case of anaphylactic shock accompanied by cardiovascular collapse and bronchospasm immediately after administration of cefazidone, to which a negative preliminary AST was obtained, after induction of general anesthesia for laparoscopic cholecystectomy.

CASE

A 20-year-old female (height 161 cm, weight

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55 kg) with acute cholecystitis was scheduled for laparoscopic cholecystectomy. She had a prior history of hemorrhoidectomy under spinal anesthesia without incident two years prior. There were no specific abnormalities on the preoperative physical examination, including allergy history, electrocardiogram, chest radiograph, and blood test.

After entering the operating room, the patient underwent electrocardiography, pulse oximetry, noninvasive blood pressure cuff, and bispectral index (BIS). Vital signs of the patient before induction of anesthesia were measured as follows: blood pressure (BP) 125/76 mmHg, heart rate (HR) 83 beats/min, and oxygen saturation measured by pulse oximetry 99%. After preoxygenation with 100% oxygen, propofol 80 mg, midazolam 3 mg, and continuous remifentanyl infusion (0.2 $\mu\text{g}/\text{kg}/\text{h}$) were used to induce anesthesia. Rocuronium 40 mg was given for muscle relaxation, and intubation was performed 90 seconds later. After intubation, vital signs were measured as BP 125/60 mmHg, HR 85 beats/min, oxygen saturation 100%, end tidal CO_2 (ET CO_2) 31 mmHg, 13/11 mmHg (peak/plateau) airway pressure, and BIS 55. The fraction of inspired oxygen (FiO_2) was set at 0.5, and volume-controlled ventilation was initiated with a tidal volume (TV) of 7 ml/kg and a respiratory rate of 12 breaths/min. Anesthesia was maintained using sevoflurane 1.2 vol% and continuous remifentanyl infusion.

After allowing the surgeon to prepare for surgery, the anesthesiologist moved the patient's head slightly to the right for management of the endo-

tracheal tube. After confirming that the intradermal test performed on the ward 1 hour before entering the operating room was negative, an anesthesia nurse intravenously administered a mixture of 2 g of refosporon (cefazedone sodium) in 10 ml of normal saline over 20 seconds. After administration, the anesthesiologist confirmed that the HR increased sharply from 85 to 140 beats/min. It was assumed that the HR increased due to the patient's head stimulation. Esmolol 10 mg was administered with no response. Then, BP was measured at 60/30 mmHg, and ET CO_2 was confirmed to be 15 mmHg. Phenylephrine (100 μg) was administered twice, but the HR further increased to 155 beats/min, and the BP was measured at 55/28 mmHg (Fig. 1). As the peak airway pressure increased to 53 cmH_2O , mechanical ventilation failed to transmit. Therefore, manual ventilation was attempted using manual ventilation mode; however, signs of adequate ventilation were still absent. The patient's oxygen saturation began to decrease rapidly to below 80%.

Five minutes after the decrease in BP, an anaphylactic reaction was considered, and epinephrine 200 μg , peniramin 4 mg, and dexamethasone 5 mg were administered intravenously. After administration of epinephrine, BP increased to 80/50 mmHg, and HR decreased to 125 beats/min. Simultaneously, norepinephrine was continuously administered at 0.05 $\mu\text{g}/\text{kg}/\text{h}$, after which epinephrine 200 μg was administered once more. In order to monitor BP continuously, a 22G catheter was inserted into the left radial artery. The oxygen

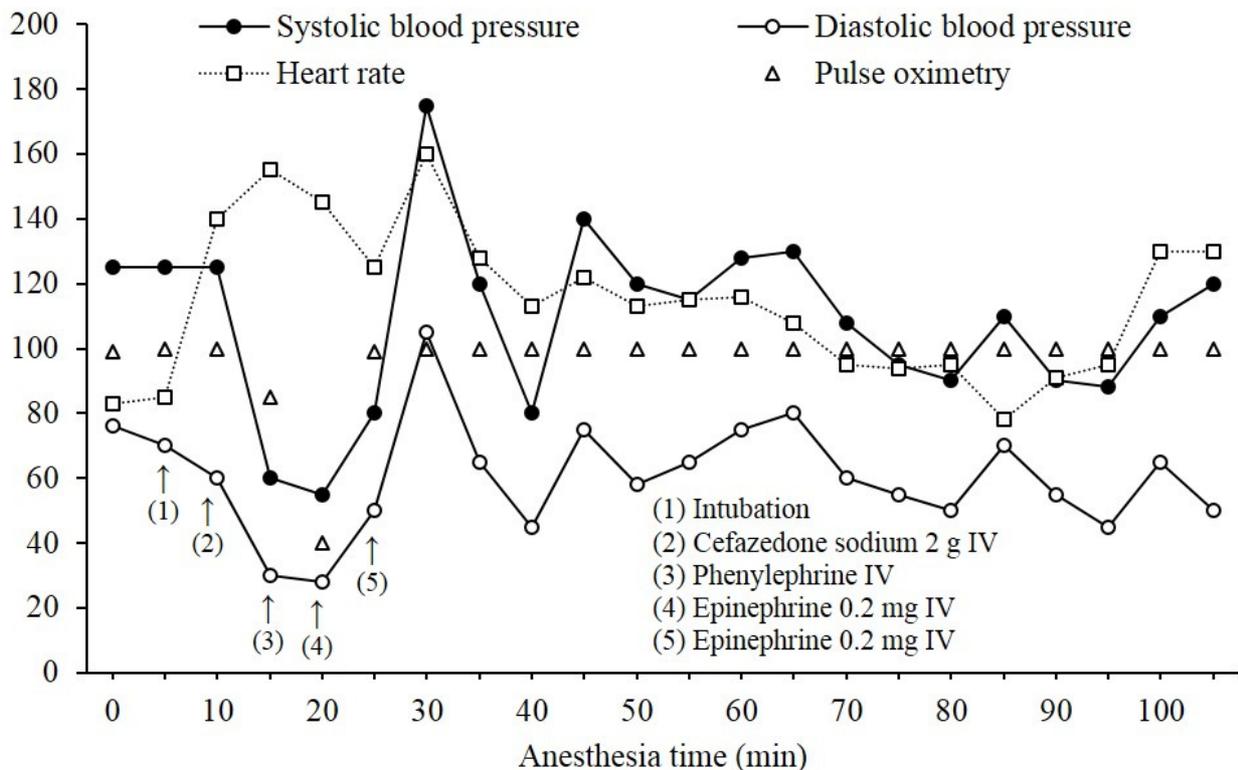


Fig. 1. Graph of vital signs after induction of anesthesia. After refofopren (cefazodone sodium) administration, a sudden increase in heart rate, decrease in blood pressure, and desaturation were observed. After aggressive treatment with 2 administrations of epinephrine 0.2 mg, the patient's hemodynamics stabilized to some extent, and the operation could be completed.

saturation, which was 100% immediately after induction of anesthesia, decreased to 40% after anaphylaxis. Fifteen minutes after the decrease in BP, the patient's BP increased to 175/105 mmHg, and HR increased to 160 beats/min. As peak airway pressure decreased to 20 cm H₂O, manual ventilation became possible, and ETCO₂ was measured at 42 mmHg with a gradual rise in oxygen saturation from 40%. The patient was converted to volume-controlled ventilation with a TV of 6 ml/kg. Salbutamol was sprayed twice through the endotracheal tube. Thirty minutes after the initial de-

crease in BP, it was measured at 80/45 mmHg, and the HR was 113 beats/min. We started a continuous epinephrine infusion at 0.03 μ g/kg/h. The arterial blood gas values included a pH of 7.27, an arterial carbon dioxide partial pressure of 48 mmHg, and an arterial oxygen partial pressure of 373 mmHg with a FiO₂ of 1.0. BP was maintained at 120-140/58-75 mmHg, and HR was maintained at 100-120 beats/min for 10 minutes. We decided to proceed with the laparoscopic cholecystectomy as planned. Norepinephrine infusion was terminated after restarting the operation, and epi-

nephrine was continued until the end of the surgery. The laparoscopic cholecystectomy was completed in 45 minutes. Sugammadex 200 mg was intravenously injected to restore muscle relaxation, and extubation was performed in the operating room. After 30 minutes in the post anesthesia care unit, she was transferred to the intensive care unit. She was discharged without complication after 3 days. After 4 weeks, a skin test was performed in the outpatient allergy clinic, and a positive reaction to refosporen (cefazedone sodium) was confirmed. The response to other anesthetic agents including muscle relaxants was negative. Additional skin prick tests also showed positive skin reactions to house dust mites. The patient received preventive education and avoidance training for refosporen (cefazedone sodium) and house dust mites.

DISCUSSION

This was a case of anaphylaxis with unexpected cardiovascular collapse and bronchospasm after administration of an antibiotic with an initially negative intradermal test, after induction of general anesthesia.

Administration of prophylactic antibiotics is recommended immediately before or 1 hour before surgical incision to reduce the risk of postoperative infection and can be administered by the anesthesiologist in the operating room.⁵ B-lactam antibiotics, including cephalosporins, can produce a

specific immune response due to their structure.⁶ Therefore, AST is performed before administration to prevent a hypersensitivity reaction. AST is a skin prick test or an intradermal test depending on its method.⁴ The skin prick test was performed using a non-irritant antibiotic diluted to 1/100, a positive control (histamine, 1 mg / ml), and a negative control (normal saline). The skin was slightly raised with a needle to allow the test solution to penetrate into the epidermis on the medial side of the forearm, and then the reaction to the solution was examined. The intradermal skin test involves subcutaneously injecting the antibiotic solutions or standard controls using a 1 ml syringe to form a 3 mm wheal. After 15-20 minutes, the inspector performs an evaluation by comparing the reaction to the positive and negative controls. Both tests are regarded as positive if swelling greater than 3 mm or larger than the positive control is accompanied by erythema. While it is very important to accurately perform ASTs, a domestic questionnaire study showed that, in many cases, only the intradermal test is performed due to time limitation, and that positive and negative control tests were not performed. In addition, there were reports that the criteria for positive and negative results differed according to hospital and practitioner.⁷ In the previous case of a patient who had an anaphylactic reaction 30 minutes after antibiotic administration with a negative response to the intradermal test, it is possible that the exact concentration of reagent was not used in the AST.⁸ In this case report, only the intradermal test was

performed on the patient, and the positive and negative controls were not performed. This case shows that performing a preliminary AST for antibiotic prophylaxis and accurately interpreting positive and negative results can help the anesthesiologist predict adverse drug reactions.

Another important point in the use of antibiotics is that they can cause hypersensitivity reactions, even if judged negative on skin prick tests.⁹ There have not been active studies on the use of appropriate skin test reagents for cephalosporin antibiotics and their usefulness in comparison with penicillin.¹⁰ In one study, the specificity of skin tests for β -lactam antibiotics ranged from 97 to 99%, while the sensitivity was about 50%.¹¹ In addition, in a domestic study using cephalosporin, 1413 patients showed negative response to the AST, but only 32 (2.26%) patients showed slight skin sensitization due to IgE-mediated hypersensitivity. This suggests that hypersensitivity reactions can occur even after negative results are reported in the AST, especially when considering that the prevalence of skin hypersensitivity to cephalosporins is 1-3%.⁷ Even if the antibiotic is negative on the AST, hypersensitivity reactions can occur. Therefore, the anesthesiologist should pay close attention to the patient's hemodynamics after administration of these drugs.

The initial diagnosis of anaphylaxis during anesthesia should be assessed by noting the severity and pattern of symptoms in relation to the timing of administration of the suspected drug.¹² Early biologic investigations, including serum tryptase

and histamine levels, are useful for diagnosis and are recommended for early differential diagnosis of anesthetic hypersensitivity reactions from other causes of perioperative adverse reaction.¹³ However, as in the present case, rapid and active resuscitation is essential if cardiovascular collapse and bronchospasm occur immediately after induction of anesthesia.¹ In particular, the more rapidly an anaphylactic reaction occurs after exposure to the antigen, the more severe the clinical manifestations will be. Additionally, the early onset of skin reactions might not appear in rapidly progressing anaphylaxis. In the present case, anaphylactic reactions involving cardiovascular collapse within 5 minutes of antibiotic administration and skin reactions, like urticaria, were not obvious. Epinephrine is crucial in the treatment of anaphylaxis and should be administered promptly when symptoms such as cardiopulmonary collapse are present. Epinephrine 100-200 μ g should be used at intervals of 1-2 minutes according to the severity of symptoms, and continuous infusion should be considered. If epinephrine is used late, the prognosis can be negatively affected. In this case, BP could be maintained after twice administrations of 200 μ g of epinephrine. If bronchospasm is visible, an inhaled β -2 agonist should be used, and intravenous injection should be considered when symptoms continue. However, epinephrine should be used first if bronchospasm and cardiovascular abnormalities coexist, as in this case, because the β -2 effect of epinephrine can alleviate bronchoconstriction. In this case, ventilation was

reestablished with a decrease in peak airway pressure after epinephrine administration, which occurred prior to administration of salbutamol.

The early diagnosis of anaphylaxis is not easy because a decrease in BP and an increase in HR occur frequently during induction of anesthesia due to stimulation from intubation and drug used. In addition, when there is severe bronchospasm before and after intubation and no ventilation can be delivered, a careful differential diagnosis is necessary, including esophageal intubation or clogging of the tube due to foreign bodies.¹⁴ In this case, an anesthesiologist who entered the operation room 5 minutes after the occurrence of the event posited esophageal intubation and considered extubation because of the high airway pressure and no active ventilation. In fact, it was reported that a patient with bronchospasm was re-intubated after suspected esophageal intubation.¹⁵ In severe anaphylactic reactions, bronchospasm should be considered, as it is a common symptom occurring in 40% of cases.⁶ In such cases, extubation can be accompanied by a risk of hypoxia, which should be carefully differentiated from other problems through accurate physical exam, initial carbon dioxide partial pressure, and tube placement.

In conclusion, even if a medical team has an anesthetic plan based on a negative AST result, they should always pay attention to the patient's vital signs and allergic reactions when administering antibiotics.

REFERENCES

1. Dewachter P, Mouton-Faivre C, Emala CW. Anaphylaxis and anesthesia: controversies and new insights. *Anesthesiology* 2009;111:1141-50.
2. Kroigaard M, Garvey LH, Gillberg L, Johansson SG, Mosbech H, Florvaag E, et al. Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. *Acta Anaesthesiol Scand* 2007;51:655-70.
3. Torres MJ, Romano A, Mayorga C, Moya MC, Guzman AE, Reche M, et al. Diagnostic evaluation of a large group of patients with immediate allergy to penicillins: the role of skin testing. *Allergy* 2001;56:850-6.
4. Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P. General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002;57:45-51.
5. Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. *N Engl J Med* 1992;326:281-6.
6. Harper NJ, Dixon T, Dugué P, Edgar DM, Fay A, Gooi HC, et al. Suspected anaphylactic reactions associated with anaesthesia. *Anaesthesia* 2009;64:199-211.
7. Park JE, Hwang SY, Lee YS, Lee HK, Lee YM. Analysis on Results of Cephalosporin Skin Testing and Developments of Hypersensitivity Reactions. *J Kor Soc Health-Syst Pharm* 2013;30:343-61.
8. Kim KN, Kim DW, Sin YH, Oh SY. Anaphylactic

- shock caused by an intradermal skin test-negative antibiotic during general anesthesia : A case report. *Anesth Pain Med* 2016;11:260-3.
9. Trautmann A, Seidl C, Stoevesandt J, Seitz CS. General anaesthesia-induced anaphylaxis: impact of allergy testing on subsequent anaesthesia. *Clin Exp Allergy* 2016;46:125-32.
 10. Moreno E, Macías E, Dávila I, Laffond E, Ruiz A, Lorente F. Hypersensitivity reactions to cephalosporins. *Expert Opin Drug Saf* 2008;7:295-304.
 11. Torres MJ, Blanca M, Fernandez J, Romano A, Weck A, Aberer W, et al. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy* 2003;58:961-72.
 12. Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ. Anaphylaxis during anaesthesia: diagnostic approach. *Allergy* 2007;62:471-87.
 13. Mertes PM, Malinovsky JM, Jouffroy L, Aberer W, Terreehorst I, Brockow K, et al. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol* 2011;21:442-53.
 14. Woods BD, Sladen RN. Perioperative considerations for the patient with asthma and bronchospasm. *Br J Anaesth* 2009;103:i57-65.
 15. Dewachter P, Mouton-Faivre C, Emala CW, Beloucif S. Case scenario: bronchospasm during anesthetic induction. *Anesthesiology* 2011;114:1200-10.