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■ Case Report ■

# Management of Cardiac Arrest following Anaphylactic Reaction to Cisatracurium Using Extracorporeal Membrane Oxygenation

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Anaphylactic reaction during the perioperative period typically exhibits rapid onset, varying clinical manifestations, and an expected mortality rate of 1.5-9%. Neuromuscular blocking agents are the leading cause of perioperative anaphylaxis. Here, we report a severe case of anaphylaxis that developed in a 66-year-old man due to cisatracurium administration. And he was successfully managed by extracorporeal membrane oxygenation. Cardiopulmonary resuscitation was performed by extracorporeal membrane oxygenation, and the patient was successfully weaned off 24 hours later.

**Key Words:** anaphylaxis; cisatracurium; extracorporeal membrane oxygenation.

An anaphylactic reaction during the perioperative period demonstrates rapid onset, various clinical manifestations, and occasionally fatal consequences.[1-3] The expected mortality rate of perioperative anaphylaxis is reportedly 1.5-9%.[4-6] Various materials can cause perioperative anaphylaxis. Neuromuscular blocking agents (NMBAs) are the known leading cause of perioperative anaphylaxis. Among these, cisatracurium, a stereoisomer of atracurium, is an intermediate-acting bisbenzylisoquinoline agent that rarely affects the cardiovascular system.

Early recognition and diagnosis is crucial for managing anaphylaxis. Proper intensive care, including airway maintenance, proper fluid therapy, and administering epinephrine and vasoactive agents to restore cardiovascular homeostasis, is important. However, due to the risk of a cardiac arrest, additional expeditious management could be required to maintain hemodynamic stability. Here, we report a case of a severe anaphylactic reaction that developed after the administration of cisatracurium in a 66-year-old man who required intensive care, including Cardiopulmonary resuscitation (CPR) and extracorporeal membrane oxygenation.

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## Case Report

A 66-year-old male patient (weight,70 kg; height,160 cm) was admitted to our hospital for laparoscopic distal gastrectomy due to early gastric cancer. He had been taking 60 mg t.i.d. of diltiazem 10 mg t.i.d. of nicorandil, and 29 mg q.i.d. of atorvastatin due to myocardial infarction that had occurred 17 years prior. The patient had no history of allergic reac-

tions to drugs. Preoperative thallium single-photon emission computed tomography (SPECT) revealed a fixed medium-sized region of moderately decreased perfusion in the basal anterolateral and inferolateral walls. Transthoracic echocardiography (TTE) revealed 60% left ventricle ejection fraction (EF), preserved right ventricle contractility, and inferoposterior wall akinesia in the left ventricle. However, no new lesions were noted in comparison with prior imaging analyses.

In the operating room, normal sinus rhythm (75 beats/min) and baseline arterial blood pressure (160/90 mmHg) were recorded prior to the induction of general anesthesia. Midazolam 2 mg and 2% lidocaine were administered. General anesthesia (target effect site concentration: 1 μg/mL propofol and 5 ng/mL remifentanil) was induced. After 18 mg of cisatracurium was administered, mask ventilation became very difficult. At this point, ST segment depression at electrocardiogram, hypotension (70/40 mmHg), and bradycardia (40 beats/min) developed. Tracheal intubation was quickly performed after event. Epinephrine 0.2 mg was given intravenously. And norepinephrine 0.1 μg/kg/min was started after 1 L of crystalloid was given. However, pulseless polymorphic ventricular tachycardia developed 15 minutes after cisatracurium administration. CPR was initiated, and 200-J defibrillation using a biphasic defibrillator was performed 5 times. Five intravenous boluses of epinephrine (1 mg each) were administered during CPR. Emergent venoarterial extracorporeal membrane oxygenation (ECMO; Capiox EBS, Terumo, Tokyo, Japan) which was previously primed of circuit was established by Seldinger method during cardiac massage. Cardiac contractility and wall motion were dysfunctional on anesthesiologist-monitored TTE. After ECMO was initiated, systolic blood pressure was maintained between 80 and 100 mmHg. Thirty minutes after ECMO was initiated, the patient was transferred to the surgical intensive care unit (SICU). ECMO and intubation remained in place.

In the SICU, initial neurological examination confirmed that both pupils were dilated to 6 mm and demonstrated sluggish light reflex. The patient was unresponsive to verbal and pain stimuli. Blood pressure was 75/50 mmHg and heart rate was 84 beats/min. We maintained a 4.0 L/min ECMO (95% of estimated cardiac index [CI] ) and 0.08 μg/kg/min epinephrine. Heparinization was initiated, and the activated clotting time was maintained between 150-200 seconds. Blood tests revealed 11.3 mg/dL lactic acid, 107.3 ng/mL creatine kinase-mioglobin and 42.656 ng/mL troponin-I. The patient demonstrated spontaneous eye opening and responded to verbal stimuli after 1 hour in the SICU. The patient was then sedated with 2 μg/kg/h fentanyl and 2 mg/kg/h propofol. TTE revealed no significant interval changes in comparison with prior results. Systolic blood pressure was maintained between 80-100 mmHg, and serial laboratory blood tests confirmed that lactic acid and cardiac markers had gradually decreased with 2.5 L/min ECMO (50% of estimated CI) and 0.08 μg/kg/min epinephrine. ECMO was maintained at 2.5 L/min (50% of estimated CI) for 16 hours, then reduced to 1.4 L/min (20% of estimated CI) and maintained for 6 hours. ECMO was successfully tapered using 0.08 μg/kg/min epinephrine at 1428 minutes after ECMO initiation. After ECMO was weaned off, blood pressure was maintained over 90/50 mmHg with 0.05 μg/kg/min epinephrine. Epinephrine was gradually decreased and stopped at 2 days after the initial incident. Extubation was performed on day 3. One day later, the patient was transferred to the general ward. Neurological and cardiopulmonary sequelae were absent. Blood analysis performed 80 minutes after cisatracurium administration revealed abnormally high IgE (618.4 IU/mL) and serum tryptase levels (28.10 μg/L). Prick and intradermal testing was performed 3 weeks later. Cisatracurium demonstrated positive results in intradermal test (1:100). Other drugs, including propofol, remifentanil, and rocuronium were negative down to a 1:10 dilution.

The patient was finally diagnosed with anaphylactic shock due to cisatracurium (a tetrahydroisoquinoline derivative). He was fully informed of the results and returned 4 weeks later for a laparoscopy distal gastrectomy under general anesthesia with vecuronium, fentanyl, and etomidate. This surgery was uneventful.

## Discussion

The estimated incidence of intraoperative anaphylaxis ranges between 1of 3,500-20,000 patients , and an estimated mortality rate of 1.5-9% has been reported. The severity of intraoperative anaphylaxis is classified into four levels according to symptoms and signs: grade I, generalized cutane-

ous signs only; grade II, moderate multiorgan involvement with cutaneous signs; grade III, life-threatening multiorgan involvement; and grade IV, cardiac and/or respiratory arrest.[7] Sadleir et al[3] recently reported that 14% and 68% of intraoperative anaphylaxis events were grade 4 and 3, respectively.

Anaphylaxis is initiated by the degranulation of mast cells or basophiles, regardless of the immunological or non-immunological triggering mechanism, and releases various mediators such as histamine and tryptase. IgE-mediated (i.e., immunological) anaphylaxis typically presents with more severe manifestations than non-immune-mediated anaphylactic reactions, even if they are clinically indistinguishable.[7] Laboratory testing for serum tryptase, which has a 90-minute half-life and can be detected at ≥ 6 hours after anaphylaxis, is often used to confirm the diagnosis of immune-mediated anaphylaxis.[8] NMBAs are the leading cause, and are responsible for 60-70% of perioperative anaphylactic reactions. Previous exposure is not necessary for an anaphylactic response to NMBAs, and approximately 15% of affected patients develop reactions at the first known contact.[9] Cross-reactivity to the tertiary and quaternary ammonium ions, which are the main components of the antigenic determinants of NMBAs, has been suggested as the triggering reaction.[10] Here, severe grade IV anaphylaxis developed during anesthesia in a 66-year old man with no previous exposure to NMBAs. IgE-mediated anaphylaxis to cisatracurium was confirmed by laboratory and skin tests in this case.

Managing general anaphylaxis involves airway patency maintenance, proper fluid therapy, the administration of epinephrine and vasoactive drugs such as noradrenaline, metaraminol, glucagon, and vasopressin in order to restore cardiovascular homeostasis.[7] With recent technological advances, various attempts have been made to increase the survival rate following cardiac arrest in intensive care units. Using ECMO to treat cardiac arrest in adults, also known as E-CPR, is one such approach. According to recent studies, E-CPR should increase the chance of survival and hospital discharge following cardiac arrest. To shortening of ECMO deployment time was recommedated to improve the survival.[11]

In our current case, anaphylaxis led to the abrupt development of cardiac arrest while performing general management for anaphylaxis including fluid infusion, epinephrine and vasoactive drug. The patient was required more expeditious cardiopulmonary resuscitation. We expected repeated ventricular fibrillation and pulseless electrical activity to lead to death. ECMO was urgently initiated, and CPR was terminated after 35 minutes. Cardiovascular hemostasis recovered after ECMO was applied. Lafforque E. et al[12] reported that successful extracorporeal resuscitation of a anaphylactic shock. They described the anaphylactic shock with cardiac arrest was unresponsed to CPR during 60 mintues and recoveried after E-CPR.

As we used prepared ECMO which was previously primed of circuit, we shortened the time of ECMO established and CPR. We think that ECMO is a valuable method for managing severe anaphylaxis in patients who are unresponsive to general resuscitation. And in order to minimize the deployment time of ECMO support in critically conditions, it is need preparation like previously primed circuit of ECMO.

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