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Catastrophic Bronchial Spasm Due to a Severe Anaphylactic Reaction to Protamine

Jae-Bum Kim, M.D., Jae Hyun Kim, M.D., Kyung Sub Song, M.D.

Department of Thoracic and Cardiovascular Surgery, Dongsan Medical Center, Keimyung University School of Medicine

Fatal anaphylactic reactions to protamine sulfate during cardiac surgery are very rare. We report a case of catastrophic bronchial spasm due to an anaphylactic reaction to protamine. The patient was managed successfully using a bronchodilator, steroid treatment, and extracorporeal membrane oxygenation.

Key words: 1. Protamines
2. Bronchial spasm
3. Extracorporeal menbrane oxygenation

Case report

During open-heart surgery, protamine is used after weaning the patient from cardiopulmonary bypass (CPB) in order to reverse the anticoagulation effects of heparin. However, protamine shows a wide spectrum of adverse effects, ranging from minimal cardiovascular deterioration to cardiovascular collapse, which can threaten the life of the patient.

A 54-year-old female with a history of gross hematuria due to acute tubular necrosis 1 month previously was admitted for symptomatic mitral regurgitation. Echocardiography showed prolapse of the anterior mitral leaflet due to rupture of the chordae. The patient was transferred to the operating room. Aorto-bicaval CPB was initiated, the patient was cooled to 32°C, and antegrade blood cardioplegia was administered. The patient underwent successful mitral valve annuloplasty with a 28-mm Carpentier-Edwards Physio annuloplasty ring (Edwards Lifesciences LLC, Irvine, CA, USA) and the creation of new chordae with Gore-Tex 6-0 sutures. The total aortic cross-clamping time was 54 minutes. The patient was successfully weaned from CPB with no inotropic support. The effects of heparin were reversed by the slow intravenous injection of 160.2 mg of protamine sulfate. Approximately 10 minutes after the completion of protamine administration, airway pressure was gradually increased under volume-controlled ventilation with a tidal volume of 350 mL. Approximately 30 minutes after the completion of protamine administration, tidal volume was 80 mL under pressure-controlled ventilation, and the peak inspiratory pressure was 40 cm H_2O. At that time, the patient's lung was not expanded in the operative field with manual ventilation. Her systolic pressure was down to 50 mm Hg and oxygen saturation was down to 60%. CPB was restarted and a bronchodilator with a steroid was administered. After 30 minutes of CPB assistance, the patient's hemodynamics had completely recovered, but her tidal volume was 170 mL with pressure-controlled ventilation, with a peak inspiratory pressure of 30 cm H_2O. With extracorporeal membrane oxygenator (ECMO) assistance, the patient

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Corresponding author: Jae-Bum Kim, Department of Thoracic and Cardiovascular Surgery, Dongsan Medical Center, Keimyung University School of Medicine, 56 Dalseong-ro, Jung-gu, Daegu 41931, Korea
(Tel) 82-53-250-7450 (Fax) 82-53-250-7307 (E-mail) juggang@dsmc.or.kr

was transferred to the intensive care unit. Following 4 hours of ECMO assistance, the patient's tidal volume was 380 mL under pressure-controlled ventilation, with a peak inspiratory pressure of 20 cm H_2O and a positive end-expiratory pressure of 5 cm H_2O. After weaning from ECMO with 50% FiO_2, arterial blood gas analysis showed a $PaCO_2$ of 38 mm Hg, a PaO_2 of 128 mm Hg, and 98.7% O_2 saturation. The patient was transferred to the operating room for removal of the ECMO cannulae and wound closure. Ventilator weaning was performed on the fourth postoperative day. The duration of her stay in the intensive care unit was 7 days. The patient had an uneventful postoperative recovery and was discharged on the 22nd postoperative day.

Discussion

Protamine is a polycationic peptide that is used to reverse the anticoagulant effects of heparin, a group of low-molecular-weight proteins contained in fish sperm. When injected intravenously, the basic protamine combines with the acidic heparin to form a neutral salt, thus eliminating the anticoagulation properties of heparin.

Adverse responses to protamine have been described over the course of many years. The incidence of such adverse reactions has been reported to vary from 0.06% to 10.6% [1]. Moreover, the incidence of catastrophic reactions to protamine during cardiovascular surgery has been reported to be 0.13% [2]. These include events, whether or not caused directly by protamine, that occurred within 30 minutes of the initiation of protamine, lasted longer than the 5-minute period of protamine infusion, and met one or more of the following criteria: (1) a decrease in systemic arterial blood pressure (either systolic or mean, compared to baseline blood pressure before protamine administration) after protamine administration of 25% of baseline or a decrease of 10% requiring inotropic medications, reinstitution of CPB, or use of an intra-aortic balloon pump; an (2) increase in pulmonary arterial pressure of at least 25% resulting in a decrease of systemic arterial blood pressure as defined in (1); (3) non-cardiogenic pulmonary edema, defined as any decrease in PaO_2 requiring an increase in ventilatory support (increase in the percent oxygen delivered, ventilator rate, or positive end-expiratory pressure) in the absence of evidence of cardiac failure (decreasing cardiac output or increase in pulmonary capillary wedge pressure); and (4) bronchospasm (the use of bronchodilator therapy for either an increase in peak inspiratory airway pressure of more than 5 mm Hg or wheezing). Thromboxane A2 is a potent pulmonary vasoconstrictor and bronchoconstrictor. Thromboxane is generated when complement activation produces a sufficient concentration of C5a anaphylatoxin fragments to elevate plasma levels. It has been demonstrated that heparin-protamine complexes cause complement activation. Clinically insignificant increases in pulmonary pressure without hemodynamic changes are not considered to be adverse events [3].

Some possible mechanisms of protamine anaphylaxis have been described. Protamine may act as an antigen and bind to immunoglobulin E antibodies. This process may lead to cross-linking with the antibody surfaces, which then initiates a process of cell degranulation. Adverse reactions may also be associated with the interaction between protamine and complement-fixing antiprotamine immunoglobulin G (IgG) antibodies. Protamine binds to cells. Circulating IgG antibodies recognize the drug as an antigen and bind to protamine. Cell-bound IgG activates the complement system. Moreover, adverse responses to protamine seem to be related to the formation of protamine-heparin complexes, which appear to activate the classical complement cascade with the subsequent generation of anaphylatoxins [4].

A significant risk of in-hospital mortality exists among patients who suffer an adverse intraoperative event after protamine administration. Protamine-related events may therefore account for a meaningful proportion of mortalities after CPB. Although a causal link between protamine and subsequent adverse events cannot be made definitively without a randomized trial, adverse events after protamine administration can be viewed as markers of subsequent mortality. Further studies to confirm these findings, as well as the development and testing of protamine alternatives or prophylactic therapies, are required to determine if mortality can be reduced [3].

Multiple studies have demonstrated increased cardiovascular effects with the rapid injection of protamine [5]. The American Hospital Formulary Service recommendation for dosing states that no more than

50 mg of the drug should be administered in any 10-minute period [6]. In the absence of a safe and efficient agent for the reversal of heparin, when the risk of adverse reactions to protamine overrides the risk of extensive bleeding, spontaneous reversal of heparin is acceptable.

The treatment of adverse responses to protamine is based on supporting the affected organs and reducing the effects of histamine. Aggressive resuscitative efforts must be initiated immediately, including the restoration of CPB when possible. Viaro et al. [7] suggested the use of methylene blue as a novel experimental approach to prevent and treat hemodynamic complications caused by the use of protamine after CPB. According to those authors, 6 patients presented anaphylactoid adverse reactions to protamine and were successfully treated with a methylene blue bolus infusion of 1.5 mg/kg (120 mg), followed by continuous infusion of another 120 mg diluted in 5% dextrose. The reversal of anaphylactic manifestations took 10–15 minutes to complete.

Patients who have had previous protamine injections during cardiovascular surgery, patients with diabetes who are taking protamine-containing insulin, patients with allergies to fish, and vasectomized patients potentially should be routinely tested for such sensitivity and be appropriately premedicated. Additionally, when a severe adverse reaction to protamine is suspected, we postulate that heparin should not be reversed, despite a greater risk of bleeding and subsequent re-exploration [8].

Our patient had an allergy to mackerel. We report a case of catastrophic bronchial spasm due to an anaphylactic reaction to protamine. The patient was managed successfully by a bronchodilator, steroid treatment, and extracorporeal membrane oxygenation.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References

1. Weiler JM, Gellhaus MA, Carter JG, et al. *A prospective study of the risk of an immediate adverse reaction to protamine sulfate during cardiopulmonary bypass surgery*. J Allergy Clin Immunol 1990;85:713-9.
2. Levy JH, Zaidan JR, Faraj B. *Prospective evaluation of risk of protamine reactions in patients with NPH insulin-dependent diabetes*. Anesth Analg 1986;65:739-42.
3. Kimmel SE, Sekeres M, Berlin JA, Ellison N. *Mortality and adverse events after protamine administration in patients undergoing cardiopulmonary bypass*. Anesth Analg 2002; 94:1402-8.
4. Porsche R, Brenner ZR. *Allergy to protamine sulfate*. Heart Lung 1999;28:418-28.
5. Horrow JC. *Protamine: a review of its toxicity*. Anesth Analg 1985;64:348-61.
6. McEvoy G. *American hospital formulary service*. Bethesda (MD): American Society of Hospital Pharmacists; 1998.
7. Viaro F, Dalio MB, Evora PR. *Catastrophic cardiovascular adverse reactions to protamine are nitric oxide/cyclic guanosine monophosphate dependent and endothelium mediated: should methylene blue be the treatment of choice?* Chest 2002;122:1061-6.
8. Panos A, Orrit X, Chevalley C, Kalangos A. *Dramatic postcardiotomy outcome, due to severe anaphylactic reaction to protamine*. Eur J Cardiothorac Surg 2003;24:325-7.