

Successful Treatment of Anaphylactic Shock after Protamine Administration-Report of a Case

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Abstract

Protamine sulfate is administered intravenously to reverse heparin induced anticoagulation during open heart surgery. Allergic reactions to protamine occur sporadically, but arguably with increased incidence in diabetic patients, especially those who receive protamine zinc insulin preparations, patients with true fish allergy or a history of previous protamine exposure, and those who have undergone vasectomy.

Adverse effects of protamine administration vary from urticaria and rash to systemic hypotension, bronchospasm, pulmonary hypertension, cardiovascular collapse, and death. The most common reaction in adults is a transient decrease in systemic arterial blood pressure, which is usually associated with the rate of administration. Despite adverse effects, it remains widely used for this purpose.

Life-threatening reactions to protamine, although extremely rare, entail substantial risk. We are herein report a case of coronary artery disease received the coronary artery bypass grafting and then life-threatening reactions to cardiovascular collapse after protamine administration without risk factor.

Keywords: Anaphylactic shock; CABG; Protamine

Introduction

The administration of protamine sulfate is currently widely used method of reversing heparin anticoagulation after the cardiac surgery. Protamine, a basic polypeptide derived from salmon sperm, reverses heparin, an acidic glycosaminoglycan derived from bovine or porcine tissues by nonspecific acid-base interactions to form heparin-protamine complexes [1].

Anaphylactic reactions to protamine that they have been reported in patients with fish allergy such as salmon sperm and in those previously exposed to protamine, principally diabetics who have received protamine zinc insulin or vasectomised men via antibodies raised to protamine contained in sperm released into the blood stream [2].

The life-threatening reactions to protamine appear to represent anaphylaxis due to prior sensitization. However, protamine administration has occasionally been associated with clinically significant side effects, including systemic decreased arterial pressure, bradycardia, cardiovascular collapse, and pulmonary hypertension [3-5]. Incidence of protamine allergy was 0.28%-2.6% [5,6].

We herein report a rare case of coronary artery disease received the coronary artery bypass grafting and then life-threatening reactions to cardiovascular collapse after protamine administration without risk factor. Successful treatment with open cardiac massage 40 minutes, 9 mg of epinephrine and intra-arterial balloon pump support.

Case Report

A 43-year-old man, with a past history of hypertension without regular medical control, presented to our hospital with intermittent chest tightness and shortness of breathing about one day. At emergent department, the blood pressure was 180/110 mmHg, and pulse rate was 78 beats per minute. Troponin I was 3.19 ng/ml. EKG showed V1-V4 ST elevation. Coronary angiography showed near total occlusion of left anterior descending coronary artery and circumflex coronary artery. The right coronary artery was total occlusion. We did an emergent coronary artery bypass grafting the next day. After the cardiopulmonary bypass was discontinued, protamine was given via the right atrium ten

minutes later. The systolic blood pressure dropped from 110 mmHg to 40 mmHg and the heart stopped to beat. We immediately performed cardiopulmonary resuscitation and 9mg of epinephrine were given. After 40 minutes of open cardiac massage, the heart function was recovery and intra-arterial balloon pump was inserted via right femoral artery. After the operation, the patient was sent to intensive care unit. The patient had no significant neurologic deficit after the operation. Five days later, we removed the intra-arterial balloon pump and the patient was discharged on the post-operative day 13.

Discussion

The administration of protamine sulfate is currently widely used method of reversing heparin anticoagulation after the cardiac surgery. Adverse effects of protamine sulfate administration vary from local skin rash to systemic hypotension, bronchospasm, transient pulmonary hypertension, cardiovascular collapse, and death.

Although catastrophic events are rare, major adverse responses related to protamine sulfate administration occur during 0.28%-2.6% of cardiac surgical procedures [5-7]; Overall mortality was 2-2.6% [6].

The protamine sulfate is a group of low molecular weight proteins found in the sperm of salmon family as well as in human sperm. Protamine sulfate is used clinically in insulin preparations as an absorption-delaying agent and as an intravenous preparation to neutralize heparin, the latter being associated with instances of profound cardiovascular collapse.

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Several studies have demonstrated that the number of patients presenting for cardiac surgery who are risk factors developing adverse reaction to protamine in adults include previous protamine reaction or protamine zinc insulin or fish allergy [2,4-7]. Vasectomized men also may be at risk. Some infertile men also may have antisperm antibodies that cross-react with protamine. Twenty-two percent of this population will contain antiprotamine antibodies to the protamine in human sperm [5].

A direct link between catastrophic hemodynamic collapse after protamine and mortality is easy to comprehend. Anaphylactic reactions, although rare, are a major problem because of significant morbidity and mortality.

The etiology of this phenomenon may be responsible for protamine-induced vasodilation or hypotension: endothelium-dependent relaxation and an immune-mediated anaphylaxis or nonimmunologic anaphylactoid reactions. Recent investigations reported that protamine causes endothelium-dependent relaxation through the supply of L-arginine, a physiologic precursor of nitric oxide [4]. Immune anaphylactoid events to protamine which have been reported include potentially fatal IgG or IgE mediated anaphylaxis after too rapid administration with cardiovascular collapse; severe bronchospasm, hypotension, urticaria and local cutaneous reactions [2,8,9]. Binding of protamine to specific IgE or possibly to subclass noted. However, an antibody-mediated mechanism is the likely cause for the increased risk of life-threatening reactions to protamine in patients with diabetes who receive neutral protamine zinc insulin.

More common are nonimmunologic anaphylactoid reactions to protamine sulfate. Mast cell and basophil activation and subsequent mediator release is triggered through pathways not involving IgE or IgG antibody. Protamine may cause adverse reactions by several non-immunological routes including release of vasoactive platelet substances, degranulation of mast cells, activation of complement [2].

The interpretation of minor changes in hemodynamic parameters immediately after the completion of cardiopulmonary bypass is difficult and it requires the consideration of many factors. However, probably because of the large number of factors conditioning the function of circulatory system, it is difficult to show the possible effect of the H1 histamine receptor blockers on haemodynamics [3]. Probably, the increase in histamine concentration is not a result of a direct stimulation of its release by mast cells, but it is an element of reaction that is mediated by complement system [3]. It is possible that the administration of H1 receptor blocker leads to limited increase of endothelial permeability in the heart associated with increased histamine concentration, and therefore to reduced access of protamine to cardiac cells, and to the following limitation in its negative influence on inotropism [3].

There were many attempts to delimit the protamine negative effect on hemodynamics, including H1 and H2 histamine receptor blockers administration, slowed protamine administration, and its infusion into the left atrium, or into aorta. Previous studies on the delimitation of hemodynamic disorders associated with protamine sulfate administration through the blockade of histamine receptors do not allow for explicit conclusions [3].

A diagnosis of adverse reaction to protamine required, 10 minutes after protamine administration there is increased activity of complementary system, decrease in mean arterial blood pressure; audible wheezing via esophageal stethoscope, increase in plateau airway pressure; increase in mean pulmonary arterial pressure, or a new skin

rash [3,8]. A rash that was not seen until drape removal would satisfy the last criterion.

The absence of a history of fish allergy or previous protamine exposure, including insulins, suggested that the mechanism of response in both patients was nonimmunologic anaphylactoid reactions [9].

Although major adverse events related to protamine administration are associated with in-hospital mortality, the extent to which so-called minor hemodynamic responses to protamine are associated with outcome is not known [6].

Others investigated the role of tumor necrosis factor α (TNF- α) in protamine-induced cardiotoxicity and the possibility of preventing or decreasing this effect by anti TNF- α antibodies and heparin [4].

Protamine sulfate was followed immediately by severe hypotension, urticaria, and facial numbness. Resuscitation consisted of oxygen, intravenous fluids, methoxamine, diphenhydramine, and methylprednisolone and epinephrine. The extreme hypotension necessitated a brief period of external cardiac massage as well as appropriate fluid and pharmacologic therapy.

In addition to these alternatives, management of the potential anaphylactoid reactor may include steroid-antihistamine pretreatment and cautious protamine administration [5]. Pretreatment with steroids and histamine (H1 and H2) receptor blockers has been shown to attenuate anaphylactoid responses. The incidence of second anaphylactoid is strong clinical history of hypersensitivity reaction, the unavailability of hexadimethrine, and uncertainty regarding the efficacy of steroid-antihistamine pretreatment prior to protamine reexposure [5].

Platelet concentrates instead of protamine were used to neutralise their systemic heparinisation [2]. Because platelet factor 4 is a basic polypeptide stored in platelets in humans that reverses heparin, it would also have the advantage of being less antigenic [1]. Platelets, however, are known to contain platelet factor 4, which has potent antiheparin activity and others investigated the use of platelet concentrates instead of protamine for reversing the systemic heparinisation during cardiopulmonary bypass in two patients with a history of serious anaphylactoid reactions to Protamine [2]. Hexadimethrine bromide (polybrene) is a synthetic heparin antagonist. The antiheparin effect of platelet factor 4 in platelets to reverse systemic heparinisation since alternative heparin neutralizing agents such as hexadimethrine are no longer generally available [2].

Nevertheless, for those potentially allergic patients a small intravenous dose of protamine of 5-10 mg should be given to test for sensitivity [2]. Avoidance of protamine may be preferable for the suspected immunologic reactor; however, the choice of management is less clear for the nonimmunologic reactor [5]. Because of the risk of a severe anaphylactic reaction with intravenous protamine administration at the end of cardiopulmonary bypass, we consider that any patient with a history of anaphylactoid reactions to protamine should be carefully assessed before surgery. Skin tests are the basic tool for testing immunoglobulin class E (IgE)-mediated hypersensitivity [8]. Induration ~8 mm diameter indicated a positive skin test, since the usual 10 mm criterion was insensitive to the standard dilution of curare that should elicit that response [8]. But skin testing appears to be of little value in predicting the likelihood of anaphylactoid response [5].

Although we do not have access to the specific rates of protamine administration for our patient, protamine infused to aorta or to the left atrium more than 90 seconds suggestion. After protamine sulfate was

administration, the 10-minute period observation is long enough not to cause any substantial arterial pressure falls.

References

1. Levy JH, Cormack JG, Morales A (1995) Heparin neutralization by recombinant platelet factor 4 and protamine. *Anesth Analg* 81: 35-37.
2. Walker WS, Reid KG, Hider CF, Davidson IA, Boulton FE, et al. (1984) Successful cardiopulmonary bypass in diabetics with anaphylactoid reactions to protamine. *Br Heart J* 52: 112-114.
3. Lango R, Mrozinski P, Wujtewicz M, Suchorzewska J, Rogowski J et al. (2000) Administration of clemastine H1 histamine receptor blocker in the prevention of haemodynamic disorders after protamine sulfate administration in patients subjected to coronary artery bypass grafting in extracorporeal circulation. *Med Sci Monit* 6: 769-775.
4. Pevni D, Frolkis I, Iaina A, Wollman Y, Chernichovski T, et al. (2001) Protamine-induced cardiotoxicity is prevented by anti-TNF-alpha antibodies and heparin. *Anesthesiology* 95: 1389-1395.
5. Campbell FW, Goldstein MF, Atkins PC (1984) Management of the patient with protamine hypersensitivity for cardiac surgery. *Anesthesiology* 61: 761-764.
6. Welsby IJ, Newman MF, Phillips-Bute B, Messier RH, Kakkis ED (2005) Hemodynamic changes after protamine administration: association with mortality after coronary artery bypass surgery. *Anesthesiology* 102: 308-314.
7. Seifert HA, Jobes DR, Ten Have T, Kimmel SE, Montenegro LM, et al. (2003) Adverse events after protamine administration following cardiopulmonary bypass in infants and children. *Anesth Analg* 97: 383-389.
8. Horrow JC, Pharo GH, Levit LS, Freeland C (1996) Neither skin tests nor serum enzyme-linked immunosorbent assay tests provide specificity for protamine allergy. *Anesth Analg* 82: 386-389.
9. Takenoshita M, Sugiyama M, Okuno Y, Inagaki Y, Yoshiya I, et al. (1996) Anaphylactoid reaction to protamine confirmed by plasma tryptase in a diabetic patient during open heart surgery. *Anesthesiology* 84: 233-235.