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Case report

Dramatic post-cardiotomy outcome, due to severe anaphylactic reaction to protamine

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Abstract

Immunologic reactions to protamine sulfate during cardiac surgery are very rare. The frequency and outcome of such adverse reactions is unclear. We report a case of lethal anaphylactic reaction to protamine that occurred in a non-diabetic patient following the uneventful replacement of the ascending aorta. We also briefly review the mechanisms of this adverse reaction and emit some considerations on the management of this situation.

Keywords: Cardiac surgery; Protamine; Allergy

1. Introduction

Protamine is a polycationic peptide that is mainly used to reverse the anticoagulant effects of heparin. Although protamine is a relatively safe drug, it is occasionally associated with a severe systemic reaction and significant morbidity and mortality [1].

A 64-year-old male, with a history of smoking and arterial hypertension, but no diabetes mellitus, was admitted for a symptomatic aneurysm of the ascending aorta diagnosed by computed tomography (CT)-scanner. Echocardiography showed severe aortic valve insufficiency, but no signs of aortic wall rupture. Coronary angiography revealed normal coronary arteries. The patient was transferred to the operating room. Femoro-femoral cardiopulmonary bypass (CPB) was initiated, the patient was cooled to 30°C and antegrade blood cardioplegia was administered in the coronary ostia. The aortic aneurysm was resected and replaced by a 26 mm Dacron tube (Sulzer Medica) according to Tirone David's technique. Total aortic cross-clamping time was 61 min. The patient was successfully weaned from CPB with no inotropic support. Heparin was reversed by a slow intravenous injection of 40,000 IU protamine sulfate. Ten minutes after the complete administration of protamine, rapid right ventricular dilatation was observed. Mean systemic and pulmonary arterial pressure were 38 and 60 mmHg, respectively, without any electrocardiographic alterations. CPB was restarted. Following 20 min of CPB assistance and a complete hemodynamic recovery, the CPB was weaned. A transesophageal echocardiography did not show any cardiac anomalies. At that time, an isolated pulmonary vascular reaction to protamine was suspected and only half-dose of the necessary protamine was infused very slowly via the arterial cannula, 40 min after having stopped the second CPB. However, once again, the patient responded with a marked blood pressure drop, with the mean index of systemic vascular resistance of 860 dyne s cm^{-5} and pulmonary hypertension simultaneously with global cardiac failure, 5 min after completion of the protamine administration. We strongly suspected an anaphylactic reaction to protamine. No cutaneous manifestations were present at any moment. CPB was re-started, but this time without any myocardial recovery despite the administration of inotrope drugs, steroids, and anti-histamines. A Berlin Heart assist device (Fehling Medical, D-13355 Berlin, Germany) was implanted and the CPB could be stopped without administration of any protamine. Suddenly, ventricular fibrillation occurred and after prolonged unsuccessful reanimation associated to ventilation difficulties with increased airway resistance and resultant fall in PaO_2, the patient succumbed in the operating room. The autopsy failed to demonstrate any

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cardiac or pulmonary anomalies but showed a generalised vascular eosinophilia, suggesting a severe anaphylactic shock in response to the administration of protamine.

2. Discussion

Protamine is a polycationic polypeptide belonging to a group of low molecular proteins contained in fish sperm. It is used extensively to neutralize heparin following cardiac and vascular surgical procedures, but it is also used in dialysis and leucopheresis. Another major use of protamine occurs in the complexing of insulin to delay absorption and prolong duration of action. When injected intravenously, the basic reacting protamine combines with the acidic heparin to form a neutral salt, thus eliminating the anticoagulating properties of heparin.

Adverse responses to protamine have been identified for many years. The incidence of such adverse reactions has been reported as varying from 0.06 to 10.6% [2]. They have been reported in patients with fish allergy, in those previously exposed to protamine, principally diabetics who have received protamine zinc insulin. In addition, both vasectomised and infertile men have a theoretical risk of sensitivity via antibodies raised to protamine, contained in sperm released into the blood stream. The incidence of catastrophic reactions to protamine during cardiovascular surgery is reported to be 0.13% [3]. Although the exact mechanisms by which protamine produces anaphylaxis are not completely understood, some possible mechanisms are described. Protamine may act as an antigen and bind to the IgE 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 IgG antibodies. Protamine binds to a cell. Circulating IgG antibodies recognize the drug as an antigen and bind with the protamine. The 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 subsequent generation of anaphylatoxins [4]. Protamine adverse reactions fall into three different categories: transient systemic hypotension related to rapid drug administration, anaphylactoid reactions, and catastrophic pulmonary vasoconstriction [5]. Anaphylactoid responses to protamine are characterized by edema of the skin, mucosa, and viscera, decreased systemic vascular resistance, bronchospasm, and occasionally flushing. Catastrophic pulmonary vasoconstriction is accompanied by right ventricular dilation, pulmonary arterial hypertension, decreased left ventricular filling pressure, and systemic hypotension. This type of reaction appear to occur in patients with abnormal pulmonary hemodynamics [5]. A well-controlled study [6] with constant monitoring of cardiac output, systemic blood pressure, and ventricular pressures of patients during protamine infusion after CPB established that protamine causes significant reduction in peripheral vascular resistance. Hypotension occurred when the increase in cardiac output was insufficient to offset the decreased peripheral resistance. A small reduction in left ventricle contractile activity is present only in patients with a decrease >10 mmHg in systemic blood pressure. However the precise mechanism that explains protamine-mediated systemic hypotension is unknown. Evora et al. [7] reported that pulmonary circulation is extensively involved in protamine-mediated effects on endothelial function. In vitro organ chambers and canine pulmonary artery studies indicate that protamine induces endothelium-dependent vasodilation, instead of a vasoconstriction, as previously documented [5]. Heparin, in contrast to the systemic circulation, inhibits the endothelium-dependent vasodilation to protamine [7]. However, this inhibitory effect can be overcome by higher doses of protamine, concluding that protamine complexed with heparin does not induce vasodilation. As in the systemic circulation, the precise mechanism is still unknown. Since the direct effect of protamine is vasodilation due to EDRF/NO release, it appears that this vasoconstriction may be secondary. It is possible that the protamine use for anticoagulation reversion causes release of thromboxane, which induces catastrophic pulmonary vasoconstriction [8]. Horrow [5], who reported multiple animal studies, demonstrated a depressed ventricular contractility and thrombocytopenia. In our case, we observed similar reaction with a pulmonary hypertension, a dramatic decrease of the systemic blood pressure accompanied by major depression of ventricular contractility. Multiple studies demonstrated increased cardiovascular effects with rapid injection of protamine [5]. The American Hospital Formulary Service recommendation for dosing is "no more than 50 mg of the drug is administered in any 10-min-period" [9]. We think that a major step in the surgical outcome of our patient was the decision to again administer protamine after the weaning of the second CPB period. This decision was initially taken because we did not think that we were dealing with a protamine-related anaphylactic reaction, as there was no drop in peripheral resistances and the patient completely recovered under CPB assistance. After the second administration of protamine, cardiac failure was global and unfortunately irreversible despite the prolonged CPB assistance and implantation of an external ventricular assist device (Berlin Heart). The mechanism of this irreversible cardiac failure remains unexplained and supports the hypothesis of a direct effect of the heparin–protamine complexes on cardiac contractility [5]. At the present time, no alternatives to the use of protamine are available. Hexadimethrine bromide (polybrene) and some heparinases are agents that have been used occasionally as reversal agents for heparin. Both have significant side effects.

In the absence of a safe and efficient agent for the reversal of heparin, when the risks of adverse reaction to

protamine outweigh the risks of extensive bleeding, spontaneous reversal of heparin is allowed. We estimate that this strategy should have been used in our patient after the first major hemodynamic alteration. 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 restoration of CPB, when still available. Viaro et al. [10] suggest methylene blue as a novel experimental approach to prevent and treat hemodynamic complications caused by the use of protamine after CPB. According to them, six patients presented an anaphylactoid type adverse reaction to protamine and were treated successfully with methylene blue 'bolus' infusion of 1.5 mg/kg (120 mg), followed by continuous infusion of another 120 mg diluted in 5% of glucose in water. The anaphylactic manifestation reversion was complete in 10–15 min. Immunologic reactions to protamine have received little attention among clinicians. In view of our experience, we should like to suggest that anaphylactic reactions to protamine are uncommon but potentially devastating. Patients, who have had previous protamine injections during cardiovascular surgery, diabetics on protamine containing insulin, as well as patients with allergy to fish and vasectomised patients should perhaps be routinely tested for such sensitivity and be appropriately premedicated. Finally, when suspecting a severe adverse reaction to protamine, we estimate that heparin should not be reversed even with a greater risk of bleeding and subsequent re-exploration. It is hoped that the future will also provide increased knowledge to prevent and improve patient outcomes related to adverse response to protamine.

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