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Marked systemic hypotension accompanied by pulmonary hypertension following protamine reversal of heparin: Case report

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Introduction

We recently observed marked systemic hypotension accompanied by pulmonary hypertension following the intravenous administration of protamine sulfate. The abrupt onset and prompt disappearance of this adverse cardiovascular reaction of protamine suggest that a massive amount of chemical mediator was released transiently.

Case report

A 44-year-old, 70-kg man with a history of anterior chest pain was treated surgically for three-vessel coronary artery bypass grafting. The patient had no history of diabetes mellitus, allergy, or previous exposure to protamine.

Anesthesia was induced with 1.5 mg of fentanyl. After 12 mg of vecuronium, the trachea was intubated. Anesthesia was maintained with fentanyl, nitrous oxide, and oxygen (1:1); vecuronium was used for neuromuscular blockade. Before initiation of cardiopulmonary bypass, 2100 mg of hydrocortisone and 14 000 units of heparin sodium (Novo Industry, Copenhagen, Denmark) was given to the patient intravenously and 300 000 units of urinastatin was given to the patient during cardiopulmonary bypass. The patient underwent three-vessel coronary artery grafting without any technical difficulty. Following successful completion of the surgical repair, cardiopulmonary bypass was terminated with the aid of atrial pacing and continuous infusion of norepinephrine (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and dopamine (5 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Administration of 100 mg of protamine sulfate (Shimizu, Shizuoka, Japan) into the right atrial port of the pulmonary artery catheter over 2 min was associated with sudden severe systemic hypotension and pulmonary artery hypertension. His systemic blood pressure decreased from 121/64 (mean 86) to 49/38 (42) mmHg 3 min after completion of protamine infusion. Pulmonary arterial pressure increased from 20/7 (15) to 50/26 (33) mmHg 2 min after the completion of protamine infusion. Mean right atrial pressure increased from 8 to 15 mmHg after 3 min. His heart rate did not change remarkably. Skin rash was not present.

The patient was treated immediately with intravenous injection of 0.05 mg of norepinephrine and transfusion of blood withdrawn from the cardiopulmonary bypass circuit. Normal hemodynamics were promptly restored within 6 min (Fig. 1). The remainder of the surgery and postoperative course were uneventful.

Discussion

The hemodynamic change after infusion of protamine strongly suggests that protamine reversal of heparin could be the cause. Transfusion with blood withdrawn from the cardiopulmonary bypass circuit indicates that the cause of hemodynamic change was not the adverse effect of blood transusion. The hemodynamic changes occurred abruptly after protamine reversal of heparin and normal hemodynamics were promptly restored within 6 min. The characteristics of this response suggest that some chemical mediator was released transiently, causing a decrease in systemic arterial pressure and an increase in pulmonary arterial pressure.

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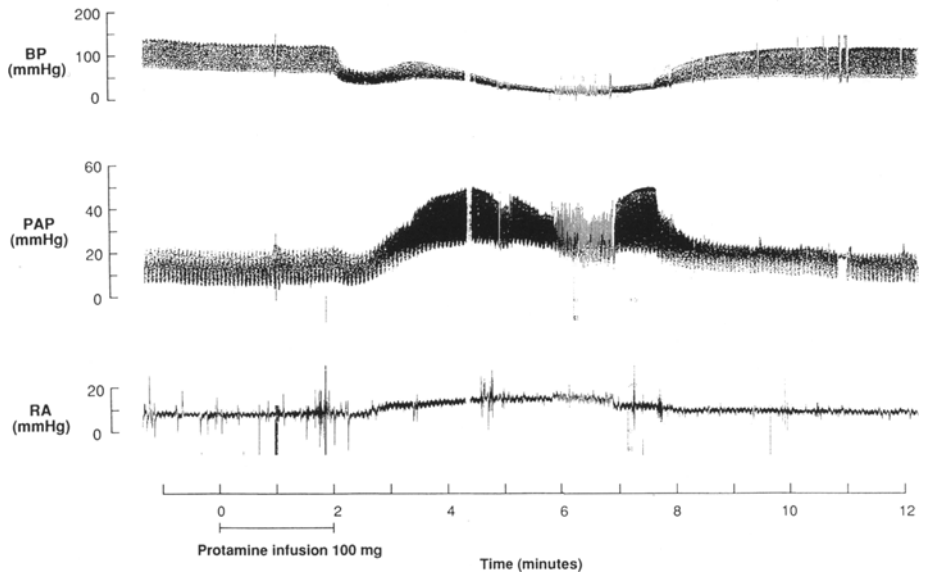

Fig. 1. Hemodynamic profile during the administration of protamine for reversal of heparin anticoagulation. An acute decrease in systemic arterial pressure and an increase in pulmonary arterial pressure occurred. Normal hemodynamics were promptly restored within 6 min. *BP* radial arterial pressure; *PAP* pulmonary arterial pressure; *RA* right atrial pressure

The characteristics of life-threatening adverse reaction after protamine reversal are characterized as follows. The first type is "catastrophic pulmonary vasoconstriction." Lowenstein et al. [1] reported five patients with increased pulmonary arterial pressure, low left atrial pressure, and acute right ventricular failure soon after receiving intravenous protamine. The primary event of this reaction consisted of severe pulmonary vascular constriction; they coined the term "catastrophic pulmonary vasoconstriction" to describe this reaction to protamine and demonstrated the concomitant release of large quantities of thromboxane A2 by the lung [2]. Though we did not measure left atrial pressure, pulmonary vasoconstriction probably occurred because systolic pulmonary arterial pressure increased to greater than the radial arterial pressure after protamine reversal of heparin.

The second type is an anaphylactic or anaphylactoid reaction. Moorthy et al. [3] reported profound and resistant hypotension plus tachycardia and generalized erythematous rush following administration of protamine. The mechanism would be associated with anaphylactic or anaphylactoid reaction. Several high-risk groups with an increased frequency of anaphylactic or anaphylactoid reaction to protamine were identified [4]. Diabetic patients receiving protamine-containing insulin preparations have a significant increased risk of life-threatening reactions when given protamine intravenously [5–7]. An association between protamine IgE and IgG antibodies and life-threatening reaction to intravenous protamine has been demonstrated [8,9]. However, our patient had no history of diabetes mellitus or previous exposure to protamine. His heart rate did not change markedly and there was no skin rash.

The third type is systemic hypotension, which is probably related to decreases in systemic vascular resistance. This mechanism may be related to release of endothelium-derived relaxing factor (EDRF) [10]. In our case, EDRF seemed not to be a major cause of the hemodynamic change, because systemic hypotension was accompanied by pulmonary hypertension. If EDRF had been a major cause, pulmonary vasoconstriction would not have occurred.

We previously reported two experiments on goats as follows. First, protamine reversal caused pulmonary hypertension and bronchoconstriction. Thromboxane A2 was the main mediator of this response [11]. In the second experiment, injection of histamine analogue caused pulmonary hypertension, bronchoconstriction, and systemic hypotension [12]. If thromboxane or histamine was released in our patient after protamine reversal, airway pressure would have increased. Unfortunately, we did not measure the time course of airway pressure, but these animal experiments suggested that some chemical mediators such as thromboxane or histamine were released transiently in our patients.

In summary, this report describes a case of protamine-induced marked systemic hypotension accompanied by pulmonary hypertension in a patient who had no history of previous exposure to protamine. Though we cannot identify the mechanism of this reaction, the abrupt onset and prompt restoration suggest massive amounts of chemical mediator substances were released transiently after protamine reversal of heparin.

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