

Case Report

Protamine-Induced Hypotension and Pulmonary Arterial Hypertension

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Abstract

Protamine is a routinely used safe antidote for heparin reversal in cardiovascular surgeries. Protamine was first introduced to prolong the action of insulin preparations. As protamine interacts with platelets and fibrinogen and has an anticoagulant effect of its own, minimal amount is given to neutralize heparin present in plasma. Although infrequent, protamine is associated with serious adverse drug reactions (ADRs), especially in patients with previous history of protamine hypersensitivity. Here, we report a case of protamine-induced pulmonary arterial hypertension and peripheral vascular collapse in a 60-year-old diabetic male patient who had undergone on-pump coronary artery bypass grafting in a tertiary care center. This was a definite, nonpreventable, severe ADR as per causality, preventability, and severity assessment scale. This patient had no previous history of protamine hypersensitivity and was not on any insulin preparations. Despite precise timely treatment and other resuscitative measures, the patient expired subsequent to these ADRs. This case report throws light on the grave requirement in urgent evolvement of pharmacogenetic and pharmacokinetic tools to detect patients who are at risk of precipitating these ADRs and thus to take precautions to prevent them.

Keywords: Adverse drug reactions, heparin reversal, on-pump coronary artery bypass grafting

INTRODUCTION

Protamine is a polypeptide isolated from salmon fish sperm. At present, it is prepared by recombinant DNA technology.^[1] Protamine, a strong base, binds and neutralizes unfractionated heparin which is a routinely used anticoagulant. Since heparin action ceases in a few hours due to metabolism, the use of protamine to reverse its action is seldom required. However, in cardiovascular surgeries where action of heparin is to be terminated rapidly, it is safely used as an antidote for years.^[2] But very rarely, protamine can cause fatal adverse drug reactions (ADRs) such as hypotension and pulmonary arterial hypertension (PAH).^[1]

CASE REPORT

A 60-year-old diabetic male with diagnosis of acute coronary syndrome and angiogram findings of triple-vessel disease underwent emergency on-pump coronary artery bypass grafting (CABG) on November 2, 2020, at the Department of Cardiovascular and Thoracic Surgery, Government Medical College, Kottayam. The patient was given injection heparin

400 U/kg during cardiopulmonary bypass (CPB). After separation from CPB, Injection protamine 250 mg was given for heparin reversal at 11.30 a.m., initial 10 mg of which was infused very slowly as a test dose. When 60% (150 mg) of protamine had been administered, the patient developed severe hypotension (systolic blood pressure: 50 mmHg). Pulmonary artery was severely tense, and pulmonary artery pressure as reflected on direct pulmonary arterial line was 70 mmHg which indicated PAH. Protamine was immediately stopped; CPB was re-established after re-heparinizing the patient. All the grafts were inspected and found patent. An hour after initial administration of protamine, a decision was made to wean off the patient from CPB and to re-administer protamine. On re-administering 25 mg (10% of initial 250 mg)

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of protamine, the patient again developed hypotension and PAH. Protamine infusion was completely stopped. CPB was re-established, and gradually, he was weaned off from CPB with inotropic (norepinephrine) support and the patient became hemodynamically stable and shifted to intensive care unit. Since heparin reversal was not complete, the patient continued to bleed. Re-exploration was done and intra-aortic balloon pump was inserted and the patient's hemodynamics improved. However, after 1 h, the patient developed severe hypotension again which failed to respond to all inotropes including vasopressin. All other resuscitative measures failed, and the patient expired on the same day at 10.30 p.m.

DISCUSSION

CABG was performed in this patient using CPB machine (on-pump CABG) which temporarily takes over the function of the heart and lung. The surgeon performs the graft procedure while the heart is stopped and the blood supply is maintained by CPB. When grafting is complete, CPB support is removed and the heart restarts. As per guidelines for "anticoagulation during CPB," heparin is to be used as the primary anticoagulant to prevent clotting in CPB circuit, and protamine as the reversal agent. The dose of heparin is 300 U–400 U/kg and an additional dose to maintain an activated clotting time of >480 s.^[3] For every 100 units of heparin remaining in the patient, 1 mg of protamine is used and is given intravenously at a slow rate.^[2] Heparin and protamine were administered as per guidelines in this case.

The ADRs of protamine reported are hypotension, anaphylaxis, PAH, bradycardia, hepatic-renal impairment, cardiovascular collapse, and death. The incidence is 0.06%–10.6%. Immunologic and nonimmunologic (pharmacogenetic variations) pathways are suggested for pathophysiology of ADRs.^[1]

As protamine when given through the central vein causes the release of histamine and hypotension, it was administered through the peripheral (cephalic) vein in this case. Protamine is administered as a small bolus (test dose) for early detection of any hemodynamic instability. If no ADR occurs with test dose, the remaining dose is infused.^[1] Initial 10 ml of the first dose was given very slowly in this case and no ADRs were noted then. There were two episodes of hypotension and PAH in this case. The first episode occurred after 60% of fresh infusion of protamine. The second episode was due to protamine rechallenge and occurred after infusion of 10% of protamine. As per Levy and Adkinson, the first episode of hypersensitivity leads to a refractory period due to depletion of inflammatory mediators and the second dose would not cause a similar episode.^[4] Hence, the decision of restating the protamine infusion is justified.

As per the Naranjo/WHO-UMC causality assessment scale, hypotension and PAH were the "definite/certain" ADRs.^[5,6] It was severe-level 7a (ADR was indirectly linked to death of the patient) as per Hartwig and Siegel and nonpreventable

as per Schumock and Thornton scale.^[7,8] These ADRs were reported to National Coordination Centre by the Institutional ADR Monitoring Centre.

ADR due to protamine is commonly observed in those with history of fish allergy, prior vasectomy, and patients on Neutral Protamine Hagedorn (NPH) insulin. Although these are not absolute contraindications, one should be cautious even with recombinant protamine and preoperative identification of these risk factors is necessary. Protamine shares antigens with fish proteins and causes cross-reactivity.^[9] Vasectomy interrupts blood testis barrier which sensitizes the host immunity to sperm antigens.^[10] NPH insulin is a crystalline suspension of protamine, zinc, and insulin. Chronic protamine exposure in this preparation induced the formation of specific immunoglobulin E antibodies in 50% of patients and had a 95-fold increased risk of severe protamine hypersensitivity reactions.^[11] This patient on recombinant protamine was not having any of the risk factors. Antidiabetic medication given to the patient was glimepiride. Skin prick testing done preoperatively to detect hypersensitivity gives false-negative response and not 100% specific.^[11] Hence, skin testing is not routinely done in our institution.

PAH is due to the release of thromboxane A2 (TXA2) during protamine infusion and can be treated by prostacyclin.^[1] PAH immediately resolved after stoppage of protamine without prostacyclin in this case. As aspirin acts by irreversibly inhibiting TXA2, not discontinuing aspirin before surgery can prevent PAH.^[1] Here, the patient was on clopidogrel which acts by inhibiting P2Y₁₂-ADP on platelets and not TXA2.^[2]

Hypotension is due to protamine-induced negative inotropic effect and release of nitric oxide. This is treated with vasopressors and prevented by antihistamines and anti-inflammatory agents.^[12] In this case, hypotension improved initially on stopping protamine and infusing norepinephrine, however, after rechallenge, the patient went into refractory hypotension and succumbed to death. Cause of death may be CPB-related coagulopathy which includes hemodilution, preoperative use of platelet inhibitors, or heparin/protamine itself. Protamine inhibits platelet adhesion and aggregation along with its heparin reversal action. Excess protamine administration can cause bleeding after surgery. Here, the dose of protamine used was as per guidelines, but actual protamine requirement may be lower. Heparin released from protein-binding sites after reversal (heparin-rebound effect) can increase bleeding.^[13] CPB had to be reinstituted twice here which required more heparin, and heparin reversal was not complete. Vasoplegic syndrome, a state of extensive vasodilation due to endothelial deregulation which causes hypotension refractory to vasopressors, is observed in 21% of patients on CPB and protamine. As adrenergic response is blunted, vasopressin which acts on V₁ receptors on vascular smooth muscles to cause vasoconstriction was administered in this case to increase arterial pressure.^[14] In spite of all resuscitative measures, hypotension did not improve and the patient could not be saved.

Development and implementation of advanced pharmacokinetic and pharmacogenetic testing may help to prevent protamine-induced ADRs. Newer agents like highly biocompatible, oligoethylene glycol functionalized guanidinocalixarene which specifically neutralizes heparin designed as an antidote can be a safer alternative.^[15]

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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