

Protamine-Induced Allergic Reaction Following Cardiopulmonary Bypass

Robert K. Stoelting, John W. Brown, Brad A. Winn, and Munier S. Jallad

Indiana University School of Medicine
Indianapolis, IN

Abstract

A 59 year-old male with a 37-year history of diabetes mellitus treated with protamine zinc insulin (26 units daily) experienced cardiovascular collapse shortly after infusion of protamine (250 mg) at the conclusion of cardiopulmonary bypass for elective coronary artery bypass graft surgery. Generalized erythema of the face and arms and massive facial edema accompanied the hypotension suggesting an allergic reaction to protamine. Presumably, the patient's prior chronic exposure to low doses of protamine in the insulin preparation (25 units contains 0.7 mg of protamine) caused the formation of antibodies to protamine. The massive dose of intravenous protamine used to reverse heparin anticoagulation relative to that present in the insulin preparation resulted in an antigen-antibody interaction manifesting as cardiovascular collapse.

Introduction

Prior exposure to protamine may stimulate the production of drug-specific antibodies such that a subsequent administration of protamine results in an allergic reaction.¹⁻³ For example, patients who have received protamine uneventfully to reverse heparin-induced anticoagulation as during certain operative procedures or donation of blood com-

ponents using a cell separator may be at an increased risk for developing an allergic reaction during a subsequent exposure to protamine.^{1,2} Another group of patients who may form antibodies to protamine are those individuals receiving protamine zinc insulin to treat diabetes mellitus.³

This report describes profound cardiovascular collapse following the intravenous administration of protamine at the conclusion of cardiopulmonary bypass in a patient with diabetes mellitus who had been taking protamine zinc insulin for 37 years. This patient had not previously undergone surgery requiring reversal of heparin anticoagulation with protamine. The presumed mechanism for the cardiovascular collapse in this patient was an allergic reaction to protamine secondary to the presence of drug-specific antibodies, the production of which was due to the chronic low dose exposure to protamine contained in the insulin preparation.

Case Report

A 59 year-old 79 kg male was scheduled for an elective coronary artery bypass graft operation. Pertinent past medical history included diabetes mellitus for 37 years and a documented myocardial infarction 12 years earlier. Medications at the time of admission to the hospital included protamine zinc insulin 26 units subcutaneously every morning, triamterene 50 mg daily, digoxin 0.25 mg daily and isosorbide 20 mg every 4 hours. There was no pre-operative history of infertility, drug or food sensitivities.

Direct communications to: Robert K. Stoelting, M.D., Department of Anesthesia, Fesler Hall Room 204, 1120 South Drive, Indianapolis, IN 46223

Submitted 1/84.

Accepted 2/84.

Four proximal and five distal aortocoronary bypass grafts were placed during cardiopulmonary bypass requiring 150 minutes. The patient was subsequently weaned from cardiopulmonary bypass and was able to maintain an adequate blood pressure (124/70 mm/Hg), pulmonary artery end-diastolic pressure (10 mmHg) and cardiac output (5.6 L/min) without pharmacologic support. In view of the apparent stable cardiovascular function as well as documentation of adequate vein graft flow, it was elected to begin reversal of heparin anticoagulation with protamine, 250 mg. At the conclusion of infusion of 125 mg of protamine administered continuously over 3 minutes, the venous and aortic cannulae were removed and the remaining 125 mg of protamine was administered over a similar time frame. At the conclusion of protamine infusion, the blood pressure remained at 116/64 mmHg and the pulmonary artery end-diastolic pressure was 10 mmHg. Approximately 1 minute later, there was a rapid decline of the blood pressure to 36/16 mmHg in association with a reduction in pulmonary artery end-diastolic pressure to 5 mmHg. At this time, the heart was contracting vigorously and the cardiac output was 6.2 L/min. No anesthetic drugs had been administered since the cessation of cardiopulmonary bypass and the lungs were being ventilated with pure oxygen. Generalized erythema of the face and arms and massive facial and periorbital edema were present. Bronchospasm was not detectable. Despite administration of phenylephrine, 4.5 mg in divided doses, ephedrine 25 mg, epinephrine 100 ug, calcium gluconate 1000 mg, diphenhydramine 100 mg, cortisol 200 mg and the infusion of fluids (approximately 1000 ml whole blood in 5 to 7 minutes) the systolic blood pressure remained less than 40 mmHg in the presence of sinus tachycardia. Evidence of myocardial ischemia was not apparent during continuous recording of a precordial lead (V₅) of the electrocardiogram. One of the previously removed venous cannulae was replaced in the right atrium and 5 liters of fluid infused via the cardiopulmonary bypass machine. Despite this fluid infusion, the systolic blood pressure remained below 60 mmHg. It was elected, therefore, to again administer heparin (24,000 units) and institute cardiopulmonary bypass. In view of the unknown adverse effects of the prior hypotension, it was elected to place an intra-aortic balloon through the

left femoral artery. One hour later, the patient was again weaned from cardiopulmonary bypass with the aid of intra-aortic balloon counterpulsation. The heparin effect was allowed to wane spontaneously requiring about 4 hours for the activated clotting time to return to less than 250 seconds (control 105 seconds), despite the administration of 2 units of fresh frozen plasma. The post-operative course was complicated by a mediastinal hematoma requiring surgical evacuation 7 hours following arrival in the Intensive Care Unit. The activated clotting time was 140 seconds at this time.

Blood for analysis for immunoglobulin E (IgE) and G (IgG) antibody concentrations was obtained 30 minutes, 18 hours and 72 hours following the administration of protamine (Table 1). Subsequent questioning of the patient elicited a history of skin erythema at the insulin injection site early in the use of protamine zinc insulin. This reaction had been attributed to "allergy." Nevertheless, the patient continued to use protamine zinc insulin daily for the subsequent 37 years.

The patient was discharged on the eleventh day post-operatively and instructed that he was allergic to protamine and should not receive this drug in the future. His insulin preparation had been changed in the immediate post-operative period to lente insulin.

Discussion

The clinical manifestations following infusion of protamine plus the likelihood of prior stimulation of antibody production due to chronic treatment with low dose protamine support the occurrence of an allergic reaction in this patient. The intravenous administration of 250 mg of protamine over 6 minutes represented a dose about 300 times that contained in the daily protamine zinc insulin injection of 26 units (25 units of protamine zinc insulin contains 0.7 mg protamine) administered subcutaneously. Presumably, the massive dose of intravenous protamine relative to that present in the insulin injection resulted in an antigen-antibody interaction manifesting as cardiovascular collapse. The speculated presence of drug-specific antibodies to protamine is attributed to the chronic antigenic stimulation provided by the insulin therapy.

TABLE 1
Immunoglobulin Antibody Concentrations

Time following administration of protamine	Plasma concentration	
	IgE (units/ml)	IgG (mg/ml)
30 minutes	66	2.1
18 hours	230	5
24 hours	230	10.5
normal values for laboratory	less than 250	9.8 ± 3

Measurements of plasma IgE antibody concentrations suggested the occurrence of an antigen-antibody interaction as depicted by the early consumption of antibody (30 minute sample) followed by an increase 18 and 72 hours later (Table 1).⁴ Conceivably, the initial decrease in the plasma concentration of IgE antibody reflected complexing with the recently injected protamine. Following this initial decrease, there is typically an increased production of antibodies manifesting as an increased plasma concentration several hours following the allergic reaction.⁴ Plasma IgE antibody concentrations did increase in our patient but never exceeded the upper limit of normal. In addition to the acute reduction in plasma IgE antibody concentration, the simultaneous reduction of IgG antibody concentration also suggested consumption of this protein. Although IgE antibody is usually responsible for an allergic reaction there is a report of an anaphylactic reaction to protamine mediated by complement-dependent IgG antibody.² However, the occurrence of an allergic reaction characterized by simultaneous consumption of IgE and IgG antibody is unlikely and lends support to our speculation that the plasma concentrations of antibody measured at 30 minutes following the administration of protamine were influenced (hemodiluted) by the massive fluid infusion and reinstatement of cardiopulmonary bypass that was occurring at this time.

An alternative explanation to an allergic reaction for the cardiovascular collapse observed in our patient would be direct toxic effects of protamine on the heart and peripheral vasculature. For example, previous reports using the dog as the experimental model have suggested the occurrence of cardiovascular depression in association with the intravenous administration of protamine.⁵⁻⁶ However, the cardiovascular system of the dog is uniquely vulnerable to the myocardial and periph-

eral vascular depressant actions.⁷ Therefore, data obtained in dogs is not likely to reflect the cardiovascular effects of protamine administered to patients. Indeed, infusion of 3 mg/kg of protamine over 5 minutes to 15 patients at the conclusion of cardiopulmonary bypass did not produce any cause and effect reductions in blood pressure, central venous pressure or cardiac output.⁷ It should be noted that the infusion rate of protamine in this study (5 minutes) was similar to that in our patient (6 minutes). Clearly, the infusion of 50 mg/10 min recommended in the package insert for protamine is both unrealistic and unsupported by controlled measurements in patients.

The exact mechanism responsible for the allergic reaction elicited by protamine in our patient cannot be stated with certainty. The initial decrease in the plasma concentrations of IgE and IgG antibody could be interpreted as evidence for an antigen-antibody interaction but the more likely explanation is hemodilution due to the massive fluid replacement required for treatment of the reaction. Measurements of the plasma concentrations of complement proteins C3 and C4, which would help identify an allergic reaction due to activation of the complement pathway were not obtained. Documentation of specific antibodies for protamine in our patient could be provided by the radioallergosorbent test (RAST).⁸ Unfortunately, protamine is not available as an antigen for the performance of this test. All factors considered, it seems most likely that our patient experienced an allergic reaction due to the pre-existing presence of drug-specific IgE antibodies secondary to stimulation provided by chronic low dose exposure to protamine in the insulin preparation.

A patient known to be allergic to protamine or considered to be an increased risk (Table 2) for allergy and undergoing an operative procedure requiring heparin anticoagulation represents a therapeutic dilemma. When allergy is suspected but undocumented the recommendation is to administer an initial 5 to 10 mg test dose of protamine over 5 to 10 minutes with epinephrine and intravenous fluid solutions readily available.¹ This small dose of protamine should be associated with attenuated manifestations should an allergic reaction occur. When protamine cannot be administered, the only alternative drug for reversal of heparin is hexadimethrine (Polybrene).^{1,9} This

TABLE 2

Patients at increased risk for allergy to protamine

1. Previous exposure during surgical procedures requiring antagonism of heparin anticoagulation
 2. Chronic treatment with protamine zinc insulin
 3. History of allergy to fish
 - *4. Males with autoantibodies to sperm — history of infertility or following a vasectomy
- *theoretically possible but not yet supported by scientific data or clinical experience.

drug is effective but its sales market is limited and, more importantly, an agglutinating effect on erythrocytes has been observed.¹⁰ As a result, hexadimethrine is not currently available for use in the United States. Therefore, the only approach to patients who cannot receive protamine is administration of fresh frozen plasma and reliance on in vivo biodegradation of heparin. This may take several hours and be associated with post-operative hematoma formation as illustrated by our patient. Perhaps, the occasional need for an alternative to protamine should prompt a reconsideration of the

need to make hexadimethrine available on a limited basis.

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