Histamine$_2$ receptor blocker in the treatment of protamine related anaphylactoid reactions: two case reports

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Two case reports are described of acute anaphylactoid reactions following the administration of protamine to reverse the anticoagulation effect of heparin in patients undergoing coronary artery bypass graft surgery. The administration of cimetidine seemed to reverse the anaphylactoid reaction after conventional treatment with epinephrine, H_1 receptor blocker, and steroids had failed. We recommend that H_2 receptor blockade be included with other drugs in the treatment of anaphylactoid reactions following protamine, and possibly after anaphylactoid reactions associated with other substances.

Key words
ALLERGY: anaphylactoid reactions, protamine, H_2 antagonists, cimetidine; ANESTHESIA BLOOD: coagulation, protamine, cardiovascular; COMPLICATIONS: anaphylaxis; SURGERY: cardiovascular, cardiopulmonary bypass.

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Protamine, a highly alkaline polycationic compound, is routinely used to reverse the anticoagulation effect induced by heparin in patients undergoing cardiovascular surgery. Protamine administration is associated with a variety of adverse haemodynamic responses including mild hypotension, severe pulmonary vasoconstriction, hypoxaemia, and acute anaphylactoid reactions.[1–4] Investigators have ascribed some of these adverse haemodynamic effects to histamine release from mast cells following the administration of protamine.[5] Histamine is the chief mediator of allergic reactions, and two distinct histamine receptors, histamine$_1$ (H_1) and histamine$_2$ (H_2), mediate these effects.

The role of H_1 receptor blockers has been established in the treatment of some of the histamine-related adverse haemodynamic effects, whereas the importance of the administration of H_2 receptor blockers in the treatment of anaphylactoid reactions has not been widely investigated. We present two case reports where an anaphylactoid syndrome occurred following the administration of protamine, was not alleviated by conventional therapy with fluids, epinephrine, diphenhydramine, calcium chloride and steroids, but appeared to be relieved promptly by the administration of an H_2 receptor blocker, cimetidine.

Case reports

Case #1

A 48-year-old obese white male with severe unstable angina and recent subendocardial myocardial infarction; was in good health until approximately ten days before admission. One day before this admission, he attended a local emergency room with complaints of dyspnoea, nausea, indigestion, and jaw pain. An electrocardiogram (ECG) taken at that time showed a 4 mm ST segment elevation in V_2 through V_6, lead 1, and lead aVL and ventricular tachycardia. He was stabilized with nitroglycerin, nifedipine, and acetylsalicylic acid, and transferred to our hospital. His past medical history was noncontributory except for smoking (two to three packs per day for 30 years). Preoperative physical examination showed a

blood pressure of 130/100 mmHg, heart rate of 103 bpm, and weight of 104 kg. He displayed good pulses distally and normal jugular venous distension. Significant laboratory values included elevation of CPK enzyme (305 IU with slight elevation in MB fraction), and chest *x*-ray changes including mild cardiomegaly and a small right pleural effusion.

The following day cardiac catheterization showed a 90 per cent occlusion of the left anterior descending artery (LAD), 50 per cent occlusion of left circumflex, and 20 per cent occlusion of right coronary artery (RCA). During cardiac catheterization, the patient developed severe chest pain and hypotension which was controlled somewhat with nitroglycerin. The patient was sent to the operating room (OR) immediately for an emergency coronary artery bypass graft surgery.

The patient arrived with IV nitroglycerin, 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and lidocaine 2 $mg \cdot min^{-1}$. General anaesthesia was induced with 1000 μg fentanyl and 7.5 mg diazepam IV, and maintained with fentanyl (a total of 50 $\mu g \cdot kg^{-1}$), N_2O (50 per cent) and O_2 (50 per cent). The patient received 4 $mg \cdot kg^{-1}$ heparin IV before the aortic and vena cava cannulas were inserted. Saphenous vein grafts to the LAD and left obtuse marginal arteries were performed after cooling to 28° C. He tolerated general anaesthesia and surgery well until he was weaned from extracorporeal circulation (ECC). The total ECC time was one hour and ten minutes and aortic cross-clamp time was 29 minutes. He was rewarmed to 37° C and weaned from ECC without any difficulty. After the aortic and vena caval cannulae were removed, 8 $mg \cdot kg^{-1}$ of protamine were administered IV (peripheral route) over approximately ten minutes to reverse the anticoagulation effect of heparin. At this time his systolic blood pressure decreased suddenly from 110 mmHg to 50 mmHg, central venous pressure (CVP) decreased from 6 mmHg to 0 mmHg, and heart rate increased from 100 to 130 bpm. A diagnosis of anaphylactoid reaction was made and the following measures were taken during the next 15 minutes: ephedrine 5 mg IV (× 3), epinephrine 1:10,000, 0.5 ml IV (× 2), diphenhydramine 50 mg IV, methylprednisolone 500 mg IV, calcium chloride 1000 mg IV, and a fluid bolus of 1000 ml lactated Ringer's solution. The systolic blood pressure remained between 50 and 60 mmHg with a heart rate of about 130 bpm. However, when the patient was given 300 mg IV cimetidine, the blood pressure increased very rapidly to 120/60 mmHg and the heart rate gradually decreased to about 100 bpm. The rest of the intraoperative course was stable and he was transferred to the cardiac recovery room. A generalized erythematous rash was seen over the entire body immediately postoperatively when the surgical drapes were removed. The rash disappeared during the next two hours and his further postoperative course was unremarkable.

Case #2

A 38-year-old black female who had been healthy during her life presented with severe crushing chest pain. Her pain was relieved with sublingual administration of nitroglycerin and nifedipine. She was admitted to ICU and was given nifedipine 20 mg PO, diltiazem 30 mg PO, and propranolol 10 mg PO, all four times a day and lidocaine IV 2 $mg \cdot min^{-1}$. She had smoked one pack of cigarettes per day for several years. She had no history of known drug allergies. Her preoperative blood pressure was 130/70 mmHg, body weight was 68 kg, and heart rate was 76 bpm and regular. Significant laboratory findings included inferior T-wave changes on her ECG, nonspecific ECG changes in her exercise treadmill testing, and severe two vessel proximal coronary artery disease with inferior myocardial hypokinesia at cardiac catheterization.

On the night of admission the patient experienced refractory chest pain, an IV infusion of nitroglycerin was commenced and she was scheduled for coronary artery bypass grafting the next morning. The patient received diazepam 10 mg PO as preoperative medication. General anaesthesia was induced with d-tubocurarine 3 mg IV, midazolam 5 mg IV, and fentanyl 500 μg IV. Succinylcholine 100 mg IV was given to facilitate tracheal intubation. Anaesthesia was maintained with fentanyl (total dose 50 $\mu g \cdot kg^{-1}$ IV), pancuronium (total dose 20 mg IV), and nitrous oxide and oxygen via a semiclosed system with a carbon dioxide absorber. She received a left internal mammary artery graft to the RCA and a saphenous vein graft to the LAD with ECC and moderate hypothermia. She received 4 $mg \cdot kg^{-1}$ of heparin IV before the commencement of ECC.

The patient required atrial pacing with a rate of 90 per min before coming off cardiopulmonary bypass and maintained a systemic blood pressure between 120/60 and 130/70 mmHg for ten minutes before protamine was started. Five minutes after protamine was commenced (peripheral route), when approximately two-thirds of the dose had been given (5 $mg \cdot kg^{-1}$), the patient developed an acute decrease in systolic blood pressure to 40 mmHg from 130/70 mmHg, and CVP to 1 mmHg from 7 mmHg. A diagnosis of anaphylactoid reaction was made and the patient was treated with intracardiac and IV epinephrine (total 1mg), calcium chloride 1 g IV, hydrocortisone 100 mg IV, diphenhydramine 50 mg IV, with 250 ml 5 per cent albumin and 1000 ml balanced salt solution IV. Her systolic blood pressure remained between 40 and 60 mmHg for the next eight minutes at which time cimetidine 300 mg IV was given slowly. The patient's blood pressure promptly improved and stayed around 130/60 mmHg for the remainder of the operating room course. She experienced a stable course in the cardiac recovery room for three hours following the surgery, at which time she developed sudden ventricular fibrillation. In spite of

multiple resuscitative efforts, she could not be resuscitated.

Discussion

Protamine is a protein derived from fish sperm and is immunogenic. Adverse haemodynamic effects varying from mild hypotension to severe anaphylactoid reaction have been reported in the literature following its administration. Many investigators suggest that mild hypotension is the result of minimal histamine release and is usually associated with either rapid administration and/or administration via a central route. Mild hypotension usually responds well to calcium chloride administration together with a fluid bolus. True anaphylactoid reactions are rare and are usually not related to the rapidity of administration of protamine. Patients with a history of (a) diabetes mellitus receiving either PZI or NPH insulin, (b) previous exposure to protamine, and (c) allergy to cod fish are particularly prone to these anaphylactoid reactions.[6–8] Other adverse haemodynamic effects associated with protamine administration include a rare syndrome of severe pulmonary vasoconstriction and pulmonary oedema (probably related to thromboxane release), hypoxaemia (related to inhibition of hypoxic pulmonary vasoconstriction), and platelet dysfunction.[9–11]

Hypotension resulting from a direct action of histamine on blood vessels is mediated by both H_1 and H_2 receptors and this hypotensive effect is blocked only by a combination of H_1 and H_2 receptor blockers. For example the hypotension resulting from massive release of histamine as seen in systemic mastocytosis requires the concurrent administration of both types of histamine receptor antagonists.

Our patients developed acute anaphylactoid reactions although they had received protamine slowly and had an absence of risk factors such as previous exposure to protamine, allergy to fish, or a history of protamine containing insulin therapy. Both patients were given the usual recommended drugs to treat an anaphylactoid reaction without much improvement in the haemodynamic status. Only after a single dose of IV cimetidine were the adverse haemodynamic variables reversed. The reason for the delay in the administration of H_2 receptor blocker was that cimetidine was not kept routinely in our drug cart and thus was not available for immediate use. We strongly suggest from this experience that one should include H_2 receptor blocker in the armamentarium of drugs necessary to treat an anaphylactoid reaction.

References

1 *Moorthy SS, Pond W, Rowland RG.* Severe circulatory shock following protamine. Anesth Analg 1980; 59: 77–8.

2 *Conahan TJ III, Andrews RW, MacVaugh H.* Cardiovascular effects of protamine sulfate in man. Anesth Analg 1981; 60: 33–6.

3 *Shapira N, Schaff H, Piehler JM et al.* Cardiovascular effects of protamine sulfate in man. J Thorac Cardiovasc Surg 1982; 85: 505–14.

4 *Michaels I, Barash P.* Hemodynamic changes during protamine administration. Anesth Analg 1983; 62: 831–5.

5 *Casthely PA, Goodman K, Fyman PN, Abrams LM, Aaron D.* Hemodynamic changes after the administration of protamine. Anesth Analg 1986; 65: 78–80.

6 *Levy J, Saiden J, Faraj B.* Prospective evaluation of risk of protamine reactions in patients with NPH insulin-dependent diabetes. Anesth Analg 1986; 65: 739–42.

7 *Knape J et al.* An anaphylactic reaction to protamine in a patient allergic to fish. Anesthesiology 1981; 55: 32–4.

8 *Hellema HWT, Rumke P.* Serum auto antibodies as a consequence of vasectomy. Clin Exp Immunol 1978; 31: 18–29.

9 *Lowenstein E et al.* Catastrophic pulmonary vasoconstriction associated with protamine reversal of heparin. Anesthesiology 1983; 59: 470–3.

10 *Kim YD, Michalik R, Lees DE, Jones M, Hanowell S, Macnamara TE.* Protamine induced arterial hypoxaemia: the relationship to hypoxic pulmonary vasoconstriction. Can Anaesth Soc J 1985; 32: 5–11.

11 *Wakefield TW, Whitehouse WMJr, Stanley JC.* Depressed cardiovascular function and altered platelet kinetics following protamine sulfate reversal of heparin activity. J Vasc Surg 1984; 1: 346–55.

Résumé

En chirurgie cardiovasculaire on utilise souvent de la protamine, un composé polycationique alcalin, en tant qu'antidote à l'anticoagulation de l'héparine. L'usage de la protamine peut causer diverses réactions telles que: hypotension légère, vasoconstriction pulmonaire marquée, hypoxémie et choc anaphylactoïde.[1–4] D'aucuns croient que ces complications peuvent être expliquées par la libération d'histamine par des mastocytes mis en contact avec la protamine. Transmetteur par excellence des réactions allergiques, l'histamine agit sur deux types de récepteurs, H_1 et H_2. Certains des effets hémodynamiques de l'histamine peuvent être contrés par des antagonistes des récepteurs H_1, mais le rôle des anti-H_2 dans le traitement des réactions anaphylactoïdes n'a pas encore été établi. Avec la protamine, deux de nos patients ont eu une réaction anaphylactoïde résistante à la thérapie suivante: hydratation intraveineuse, adrénaline, diphenhydramine, chlorure de calcium et stéroïdes. Nous avons alors injecté de la cimétidine, un anti-H_2, qui a rapidement corrigé le problème.