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Case Report

Three Cases of Anaphylaxis to Protamine: Management of Anticoagulation Reversal

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CARDIAC SURGERY with cardiopulmonary bypass (CPB) has become routine for a variety of cardiac disorders, including coronary artery disease, valvular pathology, and related intrathoracic structural defects. In the United Kingdom alone, 36,134 cardiac surgical procedures were performed in 2013.[1] CPB requires reliable anticoagulation, which is achieved with heparin in the majority of cases.[2] Heparin has a fast onset, and its anticoagulant actions can be reversed rapidly by the administration of protamine after the patient is separated from CPB.[3] Heparin has been placed on the World Health Organization's list of essential drugs[4] for its ease of use, reliability, availability, and cheap price, but its antidote, protamine, has a more difficult side-effects profile.

Protamine is a large molecule and can produce allergic reactions such as erythema, angioedema, and, in rare cases, life-threatening anaphylaxis.[5] The management of anaphylaxis during anesthesia has been described extensively, and there are several national guidelines.[6–9] However, the relevance of protamine anaphylaxis to cardiac surgery or other areas for which extracorporeal support commonly is used is discussed minimally, if at all.

In the wake of the 6th National Audit Project,[10] anaphylaxis during anesthesia has been documented rigorously at the authors' institution since November 2015. In the 24 months since then, 3 cases (incidence of 1 in 1,500) of protamine-induced anaphylaxis with typical clinical characteristics and subsequent laboratory and clinical confirmation have occurred at the authors' institution.

Those cases of anaphylactic reaction immediately after protamine administration are described in this case report. Two different approaches to its management were used. In the first approach, the authors demonstrated that re-administration of protamine to reverse anticoagulation can be performed safely and resulted in better outcome compared with protamine avoidance despite the scarcity of evidence and the authors' limited experience with protamine anaphylaxis. In the second approach, the authors used a combination of blood products to reverse anticoagulation after the patient experienced protamine anaphylaxis. These management approaches and the current

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state of the literature on protamine allergy during cardiac surgery are discussed in this case report.

Case Report

Case 1

A 78-year-old male diabetic patient underwent elective coronary artery bypass grafting (CABG). His insulin therapy had been changed recently to human insulin (Humulin M3; Eli Lilly Italia, Sesto Fiorentino), which contains protamine sulfate. He reported multiple allergies and had experienced episodes of angioedema after switching to Humulin.

After CABG, the patient was weaned from CPB; had stable hemodynamics, with a mean arterial pressure of 60 mmHg; and ventilation resumed with similar parameters to the pre-CPB period. Protamine (Wockhardt, Wrexham, UK) was administered 4 minutes after cessation of CPB. After 3 minutes and 200 mg (of an intended total of 350 mg) of administered protamine, the patient developed hypotension, bronchospasm with peak airway pressures in excess of 40 cmH_2O, and a drop in oxygen saturation to 80%. Immediate treatment with metaraminol, 5 mg, calcium chloride, 1 g, epinephrine, 200 μg, and hydrocortisone, 100 mg, improved the patient's condition only marginally. Heparin was re-administered and CPB was reinstated emergently. Infusions of dopamine, 5 μg/kg/min, and norepinephrine, 0.006 mg/kg/min, were commenced. The patient's hemodynamic and ventilatory parameters stabilized, and he was weaned off CPB uneventfully after 23 minutes. After an additional 10-minute period of stability, infusion of protamine with the aim of administering 300 mg over 5 minutes was started. After anticoagulation was fully reversed, the surgery was concluded without additional problems.

The postoperative course was complicated by the need for 5 days of renal replacement therapy and noninvasive ventilatory support due to a chest infection. He was discharged from the intensive care unit on postoperative day 10 and from the hospital on day 16.

The patient's tryptase levels taken 45 minutes, 1 hour and 45 minutes, and 12 hours and 45 minutes after the anaphylaxis were all greater than 200 ng/mL. The tryptase level 24 hours later was 48 ng/mL, and 48 hours later it still was elevated at 25 ng/mL. The patient presented for follow-up in an allergy clinic several months later. Skin prick tests to protamine were performed and were found to be negative. However, intradermal testing to 1/10 and 1/100 were positive, making the intraoperative episode indicative of anaphylaxis to protamine.

Case 2

An 84-year-old male diabetic patient underwent elective aortic valve replacement, and his current medication included metformin; Humulin; and insulin aspart (NovoRapid; Novo Nordisk, Bagsvaerd, Denmark). No allergies were recorded. Six minutes after separation from CPB and a period of stability with hemodynamic and ventilatory parameters similar to those pre-CPB, 350 mg protamine was infused over 5 minutes. At the end of the infusion, profound bronchospasm, vasodilation, and cardiovascular collapse occurred. An anaphylactic reaction, possibly to protamine, was diagnosed and treated with intravenous epinephrine, 200 μg, and the reinstitution of CPB within 6 minutes after re-anticoagulation with heparin. In addition, 500 mg of methylprednisolone was added to the extracorporeal circuit, and profound vasoplegia was treated with 20 mg of metaraminol and 3 mg of phenylephrine. Despite treatment with inhaled isoflurane, intravenous magnesium, and additional muscle relaxation, mechanical ventilation of the lungs was impossible for the following 30 minutes. Fiberoptic bronchoscopy revealed bronchorrhea, and mechanical problems with the endotracheal tube were ruled out. After an additional 120 minutes of CPB, the vascular tone was restored and the bronchospasm relaxed, allowing for the renewed weaning of the patient from CPB. Additional administration of protamine was avoided, and the decision was made to support coagulation with blood products during the decay of heparin. A total of 12 U of fresh frozen plasma, 2 U of platelets, and 4 g of fibrinogen were administered in addition to 8 U of packed red blood cells to achieve sufficient hemostasis. Unfortunately, tissue swelling did not allow the chest to be closed at the end of surgery.

Postoperative progress was hampered by a return to the operating room for chest closure, the need for renal replacement therapy, and slow neurologic recovery. After extubation on day 4, the patient was transferred to the ward on day 8 and to a recovery facility on day 18, where he developed a chest infection and died.

The tryptase level taken within 10 minutes of the initial anaphylaxis was elevated to 62 ng/mL and returned to 12 ng/mL by 24 hours. Although the patient was transferred to another institution for further mobilization after 3 weeks, he did not survive to undergo detailed allergy testing in the postoperative period.

Case 3

A 75-year-old diabetic male patient underwent elective CABG. His medication included gliclazide; metformin; and isophane insulin containing protamine (Insulatard InnoLet; Novo Nordisk). He was allergic to furosemide (photosensitive reaction). Separation from CPB was uneventful. Protamine administration commenced 2 minutes after separation from CPB. Two minutes later (after 150 mg of an intended total of 350 mg had been administered) the blood pressure had decreased to 60/38 mmHg and did not respond to boluses of metaraminol, calcium chloride (10 mmol), or fluid. Protamine administration was stopped, and the blood pressure continued to decrease to 38/28 mmHg without response to intravenous epinephrine boluses (400 μg total) or metaraminol (4 mg total). At the same time, there was an increase in peak airway pressure from 21 to 31 cmH_2O, indicating bronchospasm. Heparin was re-administered as an emergency with reinstitution of CPB. Phenylephrine boluses of 1 to 2 mg were required to correct profound vasoplegia, which resolved over 20

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minutes. Anaphylaxis was suspected, blood was taken for mast cell tryptase measurement, and chlorpheniramine, 10 mg, and hydrocortisone, 200 mg, were administered. Hemodynamic stability resumed 20 minutes after institution of CPB. After an additional10 minutes of stability, a decision was made based on the team's knowledge of the previous 2 recent cases to attempt separation from CPB and re-administer protamine 350 mg slowly over 10 minutes. This was completed without any hemodynamic or airway consequence. Subsequent boluses of 2 × 50 mg of protamine also were given over the next 20 minutes without consequence. Mast cell tryptase measurements taken 10 minutes, 1 hour, and 24 hours after the start of the reaction were 48 ng/mL, 35 ng/mL, and 8 ng/mL, respectively. The patient's condition remained stable with an uneventful postoperative course, and he was discharged to home 6 days later. He was seen in allergy clinic 2 months later. Skin prick testing revealed dermographism, but was negative to protamine (10 mg/mL and 1/10 dilution). Intradermal tests were positive to protamine (1/1,000).

Discussion

Protamine is not a perfect tool for reversing the coagulant activity of heparin. It is not a specific antagonist. Associated hypotension can be attributed to histamine release by basophils rather than mast cell degranulation.[11,12] Fortunately, anaphylactic reactions to protamine are rare (0.6%-1%).[13,14]

Protamine used as an excipient in long-acting insulins for diabetes may predispose patients to an increased reaction rate, and it is noteworthy that 2 patients in these report had used Humulin and 1 had used Insulatard. Chu et al suggested that sensitization to protaminized insulins can present as an allergic problem later,[15] and Levy et al[14] suggested that the anaphylaxis incidence of 0.6% increased to 2% in patients exposed to protamine in insulin.

The present case series highlights 3 issues regarding protamine anaphylaxis. First, the authors' experience with protamine anaphylaxis incidence is lower than that reported in the literature. The 3 cases reported here are equivalent to a 1-year incidence of 1:1,500. Although determining a direct reason for this lower incidence is difficult, the authors believe that the cause may be related, in part, to the relatively low usage of insulin products with protamine.

Second, the use of CPB is not widely discussed in such cases. The authors believe that most cardiac units resort to returning the patient to CPB if the patient does not respond to conventional treatment of anaphylactic reactions quickly.

Lastly, the authors describe the safe use of an intentional second dose of protamine in patients after protamine anaphylaxis. There is little published on this subject, and the authors' speculative reasons why they believe this practice is safe is discussed below.

In all the patients in this report, the anaphylactic reaction was grade 4 in severity,[16] temporally related to protamine, and confirmed as anaphylaxis by tryptase testing. Subsequent outpatient testing in an allergy clinic confirmed the initial diagnosis in 2 of the cases (the 2 patients who received protamine re-dosing). In order to secure oxygenation and circulation, CPB had to be reinstituted, requiring the patients to be re-heparinized. Separation from CPB was successful after a period of stabilization with symptomatic and anti-inflammatory treatment. However, this presented the problem of potential renewed protamine exposure.

During CPB, ACTs were maintained over 400 seconds. The management of heparin reversal was different for each patient. In one case, standard management was used with avoidance of the triggering agent protamine. Reversal of anticoagulation in that case was achieved with a combination of blood products and the passage of time. The obvious risk of excessive bleeding and massive transfusion with associated sequelae[17] was believed to be lower than the risk of administering a second dose of protamine.

In the other 2 patients, protamine was re-administered within a relatively short time, and the authors accepted the risk of a second anaphylactic reaction. Levy et al reviewed the mechanisms of anaphylaxis with protamine.[14] The original concept that prompted the use of a second protamine dose was that the initial anaphylaxis would lead to a post-anaphylaxis refractory period, possibly caused by depletion of inflammatory mediators, such that a second dose would not release a similar cascade.

Panos et al[18] described unintentional repeat dosing of protamine for which anaphylaxis was not considered after significant right ventricular failure. On subsequent catastrophic ventricular failure and death, they diagnosed anaphylaxis, but the authors of the present case report cannot agree that they had evidence of anaphylaxis; hence their report did not influence management of patients in this case report.

In the cases described here, the anaphylactic reactions were confirmed using serum tryptase (Table 1) and were so severe that CPB had to be reinstituted, requiring the patients to undergo re-heparinization. In all cases, separation from CPB was successful after a period of stabilization and symptomatic treatment.

The authors believe that most cardiac units will reinstate CPB if cardiorespiratory function does not improve. This helps secure oxygenation and circulation, albeit at the expense of the problem of renewed heparin reversal once the patient's

Table 1
Immunologic Test Results

	Case 1	Case 2	Case 3
Body weight (kg)	104	114	123
BMI (kg/m^2)	37	35	43
Tryptase at 1 h	> 200 ng/mL	62 ng/mL	48 ng/mL
Tryptase at 24 h	48 ng/mL	12 ng/mL	8 ng/mL
Tryptase at 48 h	25 ng/mL	N/A	N/A
Skin prick tests to protamine	Negative	Did not survive to investigate	Negative
Intradermal test 1/100	Positive		Positive
Intradermal test 1/1,000	Positive		Positive

Abbreviation: BMI, body mass index.

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condition has stabilized. Most anesthesiologists, having diagnosed an anaphylactic reaction to a drug administered by them, rightly will be reluctant to re-administer the same agent. However, in some cases this should be considered as a safe and possibly better option. Based on the outcomes of the 3 cases presented here, the authors believe that the sequence described in cases 1 and 3 (ie, reinstating CPB, supportive treatment, steroids before eventual protamine re-administration) presents a reasonable method of managing protamine anaphylaxis after CPB. Even if renewed anaphylaxis had ensued, extracorporeal circulation could have been reinstituted immediately while additional options for heparin reversal or hemostasis were considered.

Literature Search

Much has been written about protamine and cardiac surgery over the years.[19] Currently, protamine is the only drug licensed for reversing the anticoagulant activity of heparin and is used worldwide despite its well-documented side-effect profile, which includes systemic hypotension, pulmonary vasoconstriction, and allergic reactions.[20] Large doses of protamine may impair coagulation.[21] Fortunately, anaphylactic reactions to protamine are rare ($< 1\%$).[5] The authors searched the literature for cases in which protamine anaphylaxis was documented.

Anaphylactic reactions to protamine have been subject to investigation by at least one group that used and suggested methylene blue in animal experiments to treat the anaphylactic shock.[22] Although methylene blue blocks nitric oxide synthase, it addresses the vasoplegia, but it does not treat the residual heparin.[23]

In the literature search, 3 case reports and series[24–26] that described a total of 17 cases of protamine anaphylaxis in which CPB was used were found. Although in some of the cases the post-anaphylaxis management is unclear,[24] CPB was re-instituted in at least 6 cases,[25,26] and protamine was re-administered successfully after the second time the patient was separated from CPB in at least 2 cases.[26] Unfortunately, in those case reports and series, the authors did not comment on their management strategy during the second bypass run. Another case report described control of the anaphylactic reaction without the need of reinstituting CPB.[27] The data from Cao et al[26] are in Japanese and hence not frequently reported. Now, with the authors' experience of the management of protamine anaphylaxis in 2 additional patients, there are at least 4 cases in the literature in which protamine was re-administered after anaphylaxis and patients made a full recovery.

Skin prick testing does not result in 100% specificity, and in some cases of cardiovascular collapse and bronchospasm believed to be due to an anaphylactic reaction, it does not show a positive skin reaction.[28] However, in the 2 patients in this case report who were tested, the intradermal injection demonstrated a positive reaction to protamine.

Anaphylactic reactions in modern perioperative medicine have become an important issue, and in 2016 and 2017 the Association of Anaesthetists of Great Britain and Ireland conducted a National Audit Project,[10] the results of which will be published in 2018. There has been some discussion that protamine used as an excipient in long-acting insulins predisposes patients to an increased reaction rate,[15] and it is noteworthy that all 3 patients in the present report were using such insulins preoperatively. The incidence of allergic or anaphylactic reactions to protamine in patients on this type of glycemic control has been reported to be 0.6% to 2%.[29,30] There is no recent guidance on whether patients receiving these insulins should undergo protamine allergy testing routinely before cardiac surgery.

Conclusion

There is no evidence or literature guidance as to how best to manage such anaphylactic reactions when CPB is readily available. Herein the authors described 3 cases of anaphylactic reactions to intravenous protamine when used for heparin reversal after separation from CPB. In all cases, CPB and re-heparinization were used as salvage treatment due to cardiorespiratory collapse. In 2 cases, protamine was re-administered within 30 minutes after stabilization and treatment with steroids, and anticoagulation was reversed successfully. Both patients survived and were discharged from the hospital with good surgical outcomes. The authors believe that re-administration of protamine within a short time of an anaphylactic reaction, provided that adequate treatment has been given and extracorporeal support is immediately available, is a reasonable method of managing critical cardiorespiratory collapse.

In addition, the authors advocate for the creation of a prospective database of such cases to serve as reference for clinicians if they encounter such rare, but life-threatening, events.

References

1 Society for Cardiothoracic Surgery in Great Britain and Ireland. Blue Book online. Available at: http://www.bluebook.scts.org/#ActivityRates. Accessed August 6, 2017.
2 Sniecinski RM, Levy JH. Anticoagulation management associated with extracorporeal circulation. Best Pract Res Clin Anaesthesiol 2015;29:189–202.
3 Meltzer J, Guenzer JR. Anticoagulant reversal and anesthetic considerations. Anesthesiol Clin 2017;35:191–205.
4 World Health Organization. 19th WHO model list of essential medicines (April 2015) Available at: www.who.int/medicines/publications/essentialmedicines/EML2015_8-May-15.pdf. Accessed April 5, 2018.
5 Nybo M, Madsen JS. Serious anaphylactic reactions due to protamine sulfate: A systematic literature review. Basic Clin Pharmacol Toxicol 2008;103:192–6.
6 Association of Anaesthetists of Great Britain and Ireland. Guidelines: Suspected anaphylactic reactions associated with anaesthesia. Available at: http://www.aagbi.org/sites/default/files/anaphylaxis_2009.pdf. Accessed April 5, 2018.
7 Australian and New Zealand College of Anaesthetists. Perioperative anaphylaxis management guidelines. Available at: http://www.anzca.edu.au/getattachment/resources/endorsed-guidelines/bp_anaphylaxis_2016.pdf. Accessed March 13, 2018.
8 Muraro A, Roberts G, Worm M, et al. Anaphylaxis: Guidelines from the European Academy of Allergy and Clinical Immunology. Allergy 2014;69:1026–45.

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9 Dhami S, Panesar SS, Roberts G, et al. Management of anaphylaxis: A systematic review. Allergy 2014;69:168–75.

10 National Institute of Academic Anaesthesia. NAP6: Perioperative anaphylaxis. Available at: www.nationalauditprojects.org.uk/NAP6home. Accessed April 5, 2018.

11 Madani H, Sadiki EO, Bouziane M, et al. Anaphylaxis to protamine during cardiovascular surgery. Ann Pharm Fr 2014;72:143–5.

12 Stone SF, Brown SG. Mediators released during human anaphylaxis. Curr Allergy Asthma Rep 2012;12:33–41.

13 Fayaz KM, Pugh S, Balachandran S, et al. Histamine release during adult cardiopulmonary bypass. Anaesthesia 2005;60:1179–84.

14 Levy JH, Adkinson NF. Anaphylaxis during cardiac surgery: Implications for clinicians. Anesth Analg 2008;106:392–403.

15 Chu YQ, Cai LJ, Jiang DC, et al. Allergic shock and death associated with protamine administration in a diabetic patient. Clin Ther 2010;32:1729–32.

16 Mertes PM, Lambert M, Guéant-Rodriguez RM, et al. Perioperative anaphylaxis. Immunol Allergy Clin North Am 2009;29:429–51.

17 Turan A, Yang D, Bonilla A, et al. Morbidity and mortality after massive transfusion in patients undergoing non-cardiac surgery. Can J Anaesth 2013;60:761–70.

18 Panos A, Orrit X, Chevalley C, et al. Dramatic post-cardiotomy outcome, due to severe anaphylactic reaction to protamine. Eur J Cardiothorac Surg 2003;24:325–7.

19 Dunning J, Versteegh M, Fabbri A, et al. Guideline on antiplatelet and anticoagulation management in cardiac surgery. Eur J Cardiothorac Surg 2008;34:73–92.

20 Sokolowska E, Kalaska B, Miklosz J, et al. The toxicology of heparin reversal with protamine: Past, present and future. Expert Opin Drug Metab Toxicol 2016;12:897–909.

21 Mochizuki T, Olson PJ, Szlam F, Ramsay J, et al. Protamine reversal of heparin affects platelet aggregation and activated clotting time after cardiopulmonary bypass. Anesth Analg 1998;87:781–5.

22 Albuquerque AA, Margarido EA, Menardi AC, et al. Methylene blue to treat protamine-induced anaphylaxis reactions: An experimental study in pigs. Braz J Cardiovasc Surg 2016;31:226–31.

23 Kikura M, Lee MK, Levy JH. Heparin neutralization with methylene blue, hexadimethrine, or vancomycin after cardiopulmonary bypass. Anesth Analg 1996;83:223–7.

24 Freundlich RE, Duggal NM, Housey M, et al. Intraoperative medications associated with hemodynamically significant anaphylaxis. J Clin Anesth 2016;35:415–23.

25 Ford SA, Kam PC, Baldo BA, et al. Anaphylactic or anaphylactoid reactions in patients undergoing cardiac surgery. J Cardiothorac Vasc Anesth 2001;15:684–8.

26 Cao Y, Shioi K, Narumiya C, et al. Catastrophic pulmonary vasoconstriction associated with protamine reversal of heparin. Kyobu Geka 2000;53:390–5.

27 Hrubý M, Skrovina B, Vaněk I. Anaphylactic reaction to protamine in cardiovascular surgery. Rozhl Chir 1995;74:282–3.

28 Mertes PM, Laxenaire MC, Alla F. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999-2000. Anesthesiology 2003;99:536–45.

29 Levy JH, Schwieger IM, Zaidan JR, et al. Evaluation of patients at risk for protamine reactions. J Thorac Cardiovasc Surg 1989;98:200–4.

30 Levy JH, Zaidan JR, Faraj B. Prospective evaluation of risk of protamine reactions in patients with NPH insulin-dependent diabetes. Anesth Analg 1986;65:739–42.

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