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Case report

# The plight of protamine for heparin reversal in sensitized individuals

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ABSTRACT

*Introduction:* Anaphylaxis to protamine is a rare and potentially fatal complication. Risk factors for protamine reaction may include history of prior cardiac surgery (with intraoperative protamine exposure), true fish allergy (as protamine is commonly derived from salmon sperm), history of vasectomy (due to formation of anti-sperm antibodies), insulin-dependent diabetes (due to exposure to neutral protamine Hagedorn (NPH) and other protamine containing forms of insulin), as well as excessively rapid administration of protamine.

*Aim:* To report a case of anaphylaxis to protamine, increase awareness of protamine anaphylaxis and its treatments.

*Case study:* Our patient had several risk factors not identified preoperatively and experienced a type 1 allergic reaction with anaphylaxis upon protamine administration. The patient was appropriately treated and made a full recovery from this potentially catastrophic event.

*Results and discussion:* We present this case of a known drug reaction to remind our colleagues of the importance of screening for risk factors for protamine reaction, which include: shellfish allergy, insulin-dependent diabetes, prior protamine exposure, and vasectomy. The patient presented in this case had risk factors for allergic reaction to protamine including prior protamine exposure and vasectomy. The risks and benefits of protamine administration in a patient with multiple risk factors for protamine reaction are discussed, as is the controversy surrounding the clinical utility (or lack thereof) for protamine administration in elective peripheral vascular procedures.

*Conclusions:* Identification of patient risk factors prior to protamine administration could result in (1) avoidance of protamine administration or (2) improved preparation for potential anaphylaxis.



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## 1. Introduction

Protamine is used to neutralize heparin given during a procedure and to retard insulin absorption in intermediate and long-acting insulin preparations. Sperm heads from salmonidae/clupeidae and human males are rich in protamine, and salmon milt is the commercial source of most protamine preparations. However, protamine has been known to cause reactions from mild hypotension to full anaphylaxis that can result in catastrophic outcomes, including death. The reported incidence of anaphylactic reactions to protamine varies from 0.06% to 10.60% and range from minor hemodynamic instability to fatal cardiovascular collapse.[1] The incidence of catastrophic reactions to protamine during cardiovascular surgery is reported to be 0.13%.[2] Risk factors for protamine reaction may include history of prior cardiac surgery (with intraoperative protamine exposure), true fish allergy (as protamine is commonly derived from salmon sperm), history of vasectomy (due to formation of antisperm antibodies), insulin-dependent diabetes (due to exposure to neutral protamine Hagedorn (NPH) and other protamine-containing forms of insulin), as well as excessively rapid administration of protamine (Fig. 1).[3,4] Vasectomized males have been reported to be at risk, though there are conflicting studies that refute this claim.[5,6] Non-vasectomized men have a 'blood-testes' barrier that sequesters sperm from the remainder of the body. A vasectomy occludes the normal ejaculatory path and allows sperm to be absorbed systemically and possibly stimulate antibody production.

We present a case of anaphylactic reaction to protamine administered in the operating room to a patient with multiple risk factors. We tried to reach out to the patient to obtain an informed consent on several occasions via phone number provided in the patient chart but were unable to do so. We thus sought approval from our local Institutional Review Board (IRB) who determined that approval is not required.

## 2. Aim

To report a case of anaphylaxis to protamine, increase awareness of protamine anaphylaxis and its treatments and provide a brief literature review of protamine and its use for peripheral vascular surgery.

## 3. Case study

A 66 year-old male, 93 kg in weight and 6 feet 2 inches tall, with past medical history of hypertension, multi-vessel coronary artery disease, chronic heart failure, history of cerebrovascular accident, insulin dependent diabetes and end-stage renal disease, presented for an arteriovenous fistula creation after his prior fistula developed thrombosis. He was not receiving NPH insulin. The procedure was performed with a supraclavicular block under monitored anesthesia care due to his extensive comorbidities. Intravenous (IV) heparin 5000 units were administered prior to anastomosis creation. Upon completion of the anastomosis, the surgeon noticed oozing from the edges of the wound and requested administration of protamine IV 30 mg. This was given slowly over 7 min. Within 5 min after administration of protamine, the patient complained of nausea and difficulty breathing. He was noted to be mildly distressed, diaphoretic and wheezing. His heart rate increased from approx. 60 bpm to 90 bpm and blood pressure dropped to 80 s/50 s from his baseline 150 s/80 s during the case. His oxygen saturation ($SaO_2$) dropped to approx. 70%. An anaphylactic reaction to the protamine was suspected. His blood pressure was

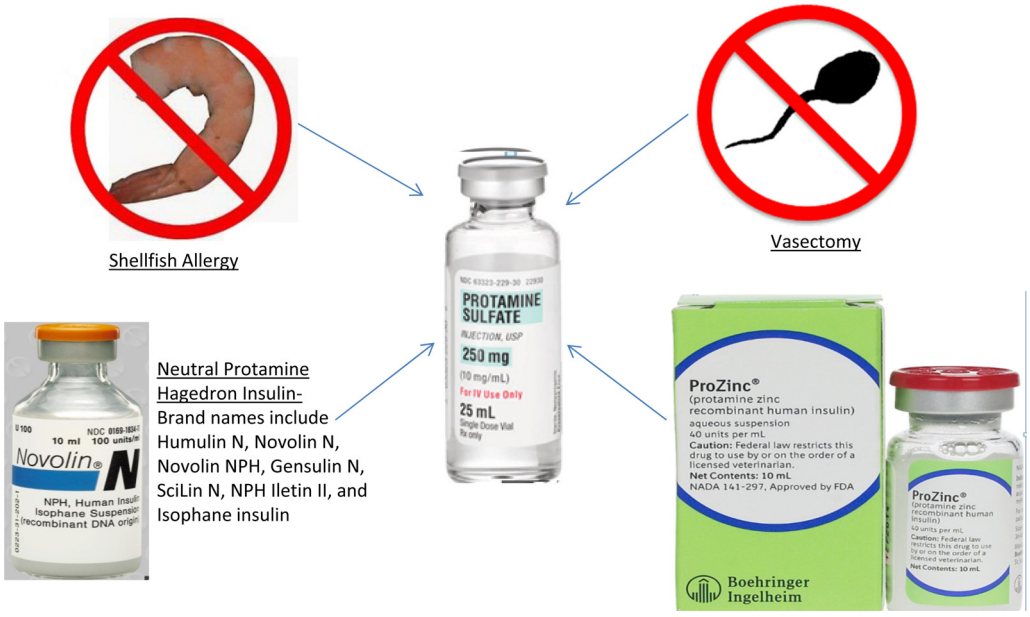


**Fig. 1 – Risk factors for protamine anaphylaxis.**

stabilized with vasopressors and ionotropes (phenylephrine 100 mcg and ephedrine 5 vmg) and fluids (IV). An oxygen (100%) was provided via face mask. Steroids (dexamethasone IV 10 mg), a histamine $H_1$ receptor antagonist (diphenhydramine IV 12.5 mg), and 4 puffs of inhaled (INH) aerosolized albuterol were given, as well. The lower dosage of diphenhydramine was given to decrease sedative effects. His $SaO_2$ increased to approx. 95%, but he continued to wheeze and had expiratory stridor on breathing. Epinephrine (IV) was avoided given his cardiac comorbidities and stable vital signs. He was taken to the recovery room on a non-rebreather mask with high-flow oxygen. Racemic epinephrine 0.5 mL of a 2.25% solution in 2.0 mL of normal saline was given INH to treat anaphylaxis while minimizing systemic absorption. Albuterol INH 2.5 mg was also administered. His wheezing resolved after this. A histamine $H_2$ receptor antagonist (famotidine IV 20 mg) was given for additional anti-histaminergic effect. Upon further investigation in the recovery room, it was discovered that the patient had received protamine two months prior for a different procedure and was several years post-vasectomy. The decision was made to admit him for observation, and he was discharged on post-operative day one with no further events.

## 4. Results and discussion

Anaphylaxis is a severe, life-threatening, generalized type I allergy in a previously sensitized patient. It affects multiple organ systems and occurs after the sudden release of chemical mediators from tissue mast cells or circulating basophils mediated by the cross-linking of immunoglobulin E (IgE) antibodies. Cross-linking of IgE antibodies initiates a signal-transduction cascade, which culminates in the increase of intracellular calcium and the release of pre-formed mediators such as histamine, proteases (tryptases), proteoglycans, and platelet-activating factor within minutes. Phospholipid metabolism then leads to the generation of potent inflammatory leukotrienes and prostaglandins. Cytokines, such as TNF-α and interleukins, are released hours after mast cell activation and are thought to have a role in biphasic anaphylaxis.[7]

Prompt initial treatment is essential in the management of anaphylaxis. This includes supportive treatment, with drawing the offending drug or agent, interrupting the effects of the pre-formed mediators that were released, and preventing more mediator release. Epinephrine is the drug of choice in the treatment of anaphylaxis. Epinephrine exerts its pharmacologic effects through alpha- and beta-adrenergic receptors. Through alpha-1 adrenergic receptor stimulation, epinephrine increases vasoconstriction, peripheral vascular resistance, and blood pressure, thereby preventing and relieving life-threatening hypotension, shock, laryngeal edema, and upper airway obstruction.[8] Through beta-1 adrenergic receptor stimulation, it has inotropic and chronotropic effects. Epinephrine also leads to bronchodilation through beta-2 adrenergic receptors,[8] and when used promptly, it suppresses the release of mediators from mast cells and basophils.[9] Transient pharmacologic effects of epinephrine such as pallor, tremor, anxiety, and palpitations potentially occur after administration by any route and cannot be dissociated from beneficial pharmacologic effects.[8,10] Serious adverse effects including hypertension, ventricular arrhythmias, myocardial infarction, and pulmonary edema are most commonly reported when epinephrine (IV) is administered.[11–14] In patients with cardiovascular disease, concerns about potential adverse effects from epinephrine administration need to be weighed against concerns about possible death from untreated anaphylaxis. In our case, since the patient had severe coronary artery disease and blood pressure responded immediately to other vasopressors and ionotropes, racemic epinephrine INH was given for its bronchodilator effect while minimizing systemic absorption. Airway support with 100% oxygen increases oxygen delivery and compensates for increased oxygen consumption. Crystalloid (2–4 L IV) replacement offsets the peripheral vasodilation that often accompanies anaphylaxis. $H_1$ receptor antagonists (e.g., diphenhydramine IV 0.5–1 mg/kg), $H_2$ receptor antagonists (e.g., ranitidine 150 mg or cimetidine 400 mg IV bolus), bronchodilators (e.g., albuterol and ipratropium bromide nebulizers), and corticosteroids (e.g., hydrocortisone IV 1–5 mg/kg) should be given.[15,16] $H_1$ receptor antagonists are used in the early phases of anaphylaxis, but once cardiovascular collapse occurs, their role is controversial. Corticosteroids can decrease airway swelling and prevent recurrence of symptoms, as seen in biphasic or protracted anaphylaxis. Hydrocortisone is the preferred steroid because it has a fast onset. We used an equipotent dose of dexamethasone (0.1 mg/kg IV), as it was more readily available. Airway swelling and inflammation may continue for 24 h post-anaphylaxis.[15] An epinephrine infusion may be necessary to maintain blood pressure, and bronchodilators should be continued during bronchospasm. $H_1$ receptor antagonists should be continued in the presence of urticaria and angioedema, and a $H_2$ receptor antagonist should be added to a $H_1$ receptor antagonist in the setting of hypotension.[16]

Our patient had multiple risk factors for allergic reaction to protamine including prior exposure and vasectomy, but should this have precluded him from receiving protamine for heparin reversal or even receiving heparin in the first place? Although intraoperative systemic anticoagulation during vascular access surgery for hemodialysis tends to decrease early thrombosis at anastomotic site, it can result in longer operative times to achieve hemostasis and also early post-operative bleeding complications. Moreover it is not clear that patients undergoing a peripheral vascular operation require protamine neutralization of heparin, because the initial dose of heparin is relatively low, and heparin is cleared from the plasma with a half-life at normothermia that ranges from 90 to 120 min.[17] 1n 1955 Dorman et al. conducted a double blind randomized control trial with 120 patients undergoing peripheral vascular surgery to investigate the routine heparin reversal with protamine. They concluded that although protamine effectively reverses heparin anticoagulation, its routine use after elective peripheral vascular surgical reconstruction does not appear to provide any clinical benefit.[18] We present this case of a known drug reaction to remind our colleagues of the importance of screening for risk factors for protamine reaction, which include a shellfish allergy, insulin dependent diabetes, prior protamine administration, and vasectomy. If risk factors are found, discussion with the

surgeon should include the possibility of avoiding heparin and/or protamine for the case. If, however, protamine is deemed necessary despite risk factors, a test dose of protamine should be considered, in addition to preoperative prophylaxis with steroids and anti-histaminergic agents, perhaps even skin testing if time allows.[19] In conclusion, extreme caution and vigilance should be practiced when administering protamine, to avoid or be prepared for adverse reactions that could potentially result in catastrophic events.

## 5. Conclusions

1. Risk factors for protamine allergy include shellfish allergy, NPH-insulin use, prior protamine administration, and vasectomy and should be identified prior to protamine administration.
2. In patients with risk factors, avoiding protamine for heparin reversal should be considered.
3. Epinephrine is a mainstay of treatment of anaphylaxis, however, in patients with cardiovascular disease, a risk: benefit analysis should be performed prior to administration.

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