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Does an allergy to fish pre-empt an adverse protamine reaction? A case report and a literature review

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The operating theatre exposes patients to myriad potential agents which could result in a life-threatening anaphylactic reaction. Anaesthetic drugs, blood products, and latex are only some of the possible allergens. Reactions are deemed to be anaphylactic when immediate sensitivity is combined with cardiovascular collapse. A patient who had a known allergy to shellfish presented for first time cardiopulmonary bypass. The perfusion team were con-

cerned that there was a realistic possibility that an adverse reaction to protamine could occur. Anaphylactic reactions to protamine in patients allergic to fish have been reported. The anaesthetic team were informed and the necessary precautions taken. We report on the outcome for our patient and also discuss other risk factors and the types of reactions that can result when an adverse reaction to protamine occurs. *Perfusion* (2008) 23, 369–372.

Introduction

Protamine sulphate is a polycationic peptide mainly used to reverse the anticoagulant effects of heparin during cardiac and vascular surgeries. It is commercially produced from the sperm of salmon or related species and it is considered that persons who have an allergy to fish could be at risk of protamine reactions. Although a number of cases of adverse reaction to protamine have been reported, the exact mechanisms by which it causes anaphylaxis are not fully understood. We report on the precautions adhered to for a patient presenting for elective cardiac surgery who had a known allergy to shellfish.

Case report

A 63-year-old lady presented for first time, elective coronary artery bypass grafts. She had been investigated for shortness of breath and retrosternal discomfort. Her medical history included hypertension, a strong family history for ischaemic heart disease; she was non-diabetic and an ex-smoker. Review of her angiogram indicated 2-vessel coronary artery disease with a well-preserved left ventricle function.

According to the patient's notes, she had a known allergy to shellfish, although the exact nature of her reaction was not described. The information prompted the perfusion team to alert the anaesthetist to the

potential of an allergic reaction to protamine when the heparin was reversed.

A standard bypass circuit was set up, consisting of a venous hard-shell reservoir (MaquetVHK 2000/2001, Maquet Cardiopulmonary AG, Hirrlingen, Germany), a microporous hollow-fibre membrane oxygenator (Quadrox, Maquet) and HLM tubing set (Maquet). The oxygenator was SOFTLINE coated (Maquet), which is a non-heparin biopassive material. The extracorporeal circuit was primed with 1 litre of Hartmann's solution, 25 g mannitol, 5000 IU heparin, and 50 mEq of sodium bicarbonate. Activated clotting time (ACT) was monitored using celite-activated tubes and the Hemochron ACT (Hemochron ACT; International Technidyne, Edison, NJ, USA). A target ACT of 480 seconds is standard for our unit. An initial dose of 2.5 mg/Kg of heparin was administered centrally (approximately 18000 IU), but the ACT failed to reach the target (458 s), therefore, an additional dose of 5000 IU of heparin was given and a final ACT of 557 s was achieved.

The surgery proceeded without any untoward events. When the heparin was to be reversed, the effect of a test dose of 30 mg of protamine was observed. Notably, no adverse reaction was experienced by the patient. The anaesthetist continued to deliver the remaining 270 mg of the protamine through a central venous line over a time span of 20 minutes. The post-protamine ACT returned to normal at 152 s with no adverse effects experienced by the patient; she made a full recovery and was discharged ten days later. The genetic difference between shellfish and vertebrate fish is a significant factor in

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determining a patient's potential to develop an adverse reaction to protamine.

Discussion

Protamine sulphate is a positively charged protein molecule, which is found in the heads of salmon sperm or that of the clupeidea family; it is also found in man. The commercial source of protamine is salmon milt and it is used clinically to neutralize heparin or to delay insulin absorption in slow-release preparations of insulin. The complex formed between protamine and heparin is a very stable one, devoid of anticoagulant activity. A 1989 study investigated the incidence of adverse reactions to protamine and reported an occurrence of 0.06%.¹ More recently, an in depth literature review of the occurrence of serious reactions to protamine sulphate revealed the incidence of anaphylactic reactions in prospective studies was 0.69% compared to 0.19%² in retrospective studies. The reactions to protamine are of three main types:

- a) Transient systemic hypotension
- b) Anaphylaxis
- c) Severe pulmonary vasoconstriction.

Transient systemic hypotension can occur due to rapid administration of protamine, resulting in histamine release. The production of histamine decreases the peripheral vascular resistance, but does not compromise myocardial function. This temporary decrease in arterial blood pressure can be treated successfully by fluid replacement, but may, in some instances, require inotropic support.

A reaction is termed anaphylactic when immediate sensitivity is combined with cardiovascular collapse. Protamine, being a non-human protein, can be antigenic, resulting in the production of specific anti-protamine IgE and IgG antibodies and, thereby, mediate an anaphylactic reaction. Patients who have had previous exposure to protamine and who may have produced anti-protamine antibodies would be most at risk of this type of life-threatening reaction to the drug. A case report from Switzerland relates an incident in which a patient undergoing replacement of the ascending aorta had a fatal anaphylactic reaction to protamine.³ Ten minutes after administration of the protamine, rapid right ventricular dilatation occurred combined with a mean systemic pressure of 38 mmHg and pulmonary artery pressure of 60 mmHg. CPB was recommenced and, after 20 minutes, the patient was haemodynamically stable. On the second attempt to administer protamine approximately 40 minutes

after weaning from the second CPB, half the dose of protamine was administered. Within 5 minutes the patient again reacted and, despite CPB, inotropes, steroids, anti-histamines and implantation of an assist device, the patient died. Autopsy showed a general vascular eosinophilia which is indicative of a severe anaphylactic shock.

Severe pulmonary vasoconstriction, right ventricular dysfunction, elevated right atrial pressure and systemic hypotension have been reported following heparin reversal with protamine.⁴ This reaction differed to classic anaphylaxis in that there was no significant change in histamine levels, but a large increase in plasma levels of C5a and thromboxane A₂. The increased levels of C5a and thromboxane A₂ imply the activation of the complement system. Cardiopulmonary bypass causes complement activation as well as in vitro complexes formed by protamine and heparin. A pig model⁵ was used to investigate the manifestation of pulmonary hypertension following protamine neutralization of heparin. It was demonstrated that the presence of a thromboxane A₂ antagonist might prevent the occurrence of the reaction. Also, it was found that no reaction resulted if protamine was administered in the absence of heparin.

The patients who are considered to be most at risk for a reaction to protamine are those with

- a) An allergy to fish
- b) Prior protamine exposure, including protamine-insulin-dependent diabetics
- c) Vasectomy

Commercial protamine is extracted from the sperm of salmon or related species and an allergy to fish has been implicated as a cause of protamine reaction. The patient investigated by Knappe, *et al.* was found to be allergic to codfish and have high levels of IgG, IgM, and IgE antibodies against protamine sulphate.⁶ Alternatively, a different study which followed 6 cardiac patients¹ who had a history of vertebrate fish allergy found that none of these patients exhibited any detrimental reaction to protamine. There is a distinct genetic difference between shellfish and vertebrate fish, thus, as a result, an allergy to shellfish does not predispose one to an adverse protamine reaction. If a patient is considered to be at risk, it may be beneficial to perform a skin test pre-operatively to assess the potential risk of adverse events. The patient from the Knappe case report had a positive skin test four days after his event, but a prospective risk study indicated that a positive skin test did not predict a patient's reaction to protamine.⁷ Later we will refer to some other case reports where

positive skin tests to protamine sulphate prompted an alternative cardiopulmonary bypass strategy to be employed.

Some slow-release insulin preparations contain protamine. Diabetic patients receiving insulin in this form have been found to produce antibodies to the drug. The incidence of antiprotamine IgG increased with the duration of use of protamine containing insulin.⁸ An alternative form of the slow-release insulin produced IgE antibodies in 53% of patients, but this antibody was not present in non-diabetics or in diabetic patients not on the protamine insulin.⁹ A study which specifically investigated the relationship between the presence of antiprotamine IgG and IgE antibodies and adverse protamine reactions (in diabetic and non-diabetic patients) concluded that, in protamine-insulin-dependent diabetics, there is a greater risk of adverse reaction in the presence of these antibodies.¹⁰ Previous exposure to protamine in vascular or cardiac surgeries would, in theory, increase a patient's risk of adverse reaction to protamine. A case study from South Africa¹¹ details an immediate allergic reaction to protamine in a female patient undergoing redo cardiac surgery. Following protamine administration, there was a sudden drop in blood pressure, an increase in heart rate and severe oedema of the face and trunk. The patient was successfully treated with epinephrine, methylprednisolone and sodium succinate. Six weeks after the event, a skin test proved positive for protamine sulphate.

Another patient group who may be considered to be at risk of protamine reaction would be men who had undergone vasectomy. As a result of the procedure, the normal ejaculatory path for sperm is blocked; therefore, it is reabsorbed systemically, leading to the possibility of antibody production. According to a report by Adourian, *et al.*, 50–60% of men produce antibodies to spermatozoa and 22–30% produce antibodies to human protamine up to a year after their vasectomy.¹² They also report the case of a vasectomised patient who had two life-threatening reactions upon intravenous administration of protamine. The same report investigated 55 vasectomised men and showed that 29% had significant serum levels of antiprotamine IgG compared to 0% in the control group. A previous study by the same group indicated that the presence of protamine-specific IgG presented a significant risk for protamine reaction even in the absence of IgE.¹⁰ Alternatively, the Levy, *et al.* report found no difference in the occurrence of protamine reactions between vasectomized men and those who would not have had any predisposing condition.¹

Conclusion

In recent years, alternatives to replace heparin as an anticoagulant have been investigated. Direct thrombin inhibitors such as lepirudin, argatroban, and bivalirudin (Angiomax) are the more common available alternatives. The advantage of these products is their lack of reactivity with heparin antibodies while disadvantages include no known antidote, cost and the limited experience in their use. Argatroban and bivalirudin both have short half lives, 25 and 30 minutes, respectively, and can be effectively monitored using ACT measurement during CPB. Lepirudin has a longer half life at 80 minutes and is not compatible with ACT monitoring.¹³ Heparinase 1 has been used to reverse heparin in both off-pump and on-pump cardiac surgery, but a recent study concluded that it would not be the preferred choice due to its inferior safety profile.¹⁴ In the past, other drugs which have been considered as alternatives to protamine include vancomycin, methylene blue and hexadimethrine.¹⁵ Neutralization of heparin with each of these elements is based on their acid-base interaction. The results of the study found that neither vancomycin nor methylene blue were effective reversal drugs, but hexadimethrine was effective; however, it was limited in its use due to lack of availability.

In our particular case study, the patient's allergy was to shellfish not to vertebrate fish and, therefore, did not predispose her to an adverse protamine reaction. Although this was so, at the time she was treated as being at risk, therefore, protamine was administered with extreme caution and all resuscitation drugs were ready in case of emergency. In 1989, when Levy undertook his study to determine patients at risk for protamine reactions, he concluded that allergy to fish, previous vasectomy and use of protamine-insulin did not preclude patients from receiving protamine following cardiac surgery. A year later, Weiler prospectively analyzed 243 cardiac surgery patients, the incidence rate was 10.7% and his conclusion was that alternatives to protamine were urgently required.⁷ In 1998, Kimmel produced a comprehensive analysis of risk factors which led to clinically significant adverse events following protamine administration in cardiac surgery.¹⁶ The conclusion was that a large number of patients – 39% in this instance – are at increased risk and, thus, the most likely strategy would be the development of prophylactic measures together with protamine alternatives. Kimmel also investigated the occurrence of in-hospital mortality following an adverse protamine reaction. The findings showed that those who suffered adverse reactions

had a higher mortality – 13.2% – than those who did not experience any adverse reaction.¹⁷

Technological advancements in the extracorporeal equipment used during cardiopulmonary bypass may provide a means of dealing with a patient at risk of an adverse protamine reaction. Some circuits can be heparin-coated and, when used, the heparin requirement for systemic anticoagulation is reduced. A study from 1992 cites a 25% reduction in the dose of heparin, ACTs of 300 s were acceptable, with a potential 50% reduction in the dose of protamine.¹⁸ Two case reports from 2001 detail the experience of a centre when presented with patients having both a history of fish allergy and exhibiting a positive skin test to protamine sulphate.¹⁹ In order for the patients to undergo their cardiac surgeries, a modified strategy was employed, using heparin-bonded circuits and low systemic heparinisation. Activated clotting

times (ACT) were maintained between 250 and 350 seconds and heparin assays were also performed simultaneously to monitor anticoagulation. Protamine was not used, but each patient received 4 units of fresh frozen plasma as a prophylactic measure. When the circuits were checked with scanning electron microscopy they were found to be clear of any clot formation. The potential of a life-threatening reaction was avoided for these patients, using available technology. While alternatives to heparin and protamine are being investigated, heparin continues to be the preferred anticoagulant during cardiopulmonary bypass and protamine will remain the drug of choice for heparin reversal. As we have shown, adverse reactions do occur, therefore, being aware of potential risks and ready to address the possible outcome remains the strategy of choice for clinical professionals.

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