

Successful use of bivalirudin for cardiopulmonary bypass in a patient with heparin allergy

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Heparin-induced IgE-mediated hypersensitivity and anaphylactoid reactions, although rare, can pose a serious clinical problem for patients requiring cardiopulmonary bypass (CPB). Bivalirudin is a bivalent reversible direct thrombin inhibitor, with a half-life of 25 min, eliminated mostly by proteolytic cleavage. There are some reports on

the use of bivalirudin for cardiac surgery, particularly for heparin-induced thrombocytopenia (HIT), but none on cases of heparin allergy. We report a case of heparin allergy successfully managed for CPB with bivalirudin anticoagulation. *Perfusion* (2007) 22, 67–69.

Introduction

Heparin-related, immediate-type hypersensitivity reactions, such as urticaria, angioedema or bronchospasm, are very rare and only a few cases of anaphylaxis-like responses caused by heparin have been described.^{1,2}

We report the uncomplicated use of the bivalent, reversible, direct thrombin inhibitor bivalirudin for anticoagulation in a patient with heparin-related, immediate-type hypersensitivity, who underwent cardiac surgery for aortic valve replacement.

Case report

A 70-year-old Caucasian female was admitted to our hospital with severe aortic valve regurgitation. Her medical history was significant for heparin allergy that had been observed 2 years earlier when she received subcutaneous injections for atrial fibrillation. Skin testing was performed with calcium and sodium heparin: patch, prick, intradermal and subcutaneous tests were all negative. An ELISA screening for heparin/PF4 antibodies was negative. Due to the strong suspicion of allergy, the patient was further investigated with increasing intravenous doses of heparin with pre-emptive administration

of corticosteroids (methylprednisolone 40 mg). The patient initially tolerated the iv administration of sodium heparin well, but, within 2 h, she developed thoracic erythema accompanied by intense itching and shortness of breath; the infusion was immediately stopped and intramuscular (im) epinephrine and H1 antagonists were administered, which immediately alleviated the symptoms.

In the absence of standardised tests for heparin hypersensitivity, the options available were to either desensitise the patient to heparin or to use an alternative anticoagulant. In view of the planned aortic valve replacement, it was decided to use the direct thrombin inhibitor bivalirudin (Angiox[®], Nycomed, Roskilde, Denmark) which had been successfully used in large studies of anticoagulation during cardiac surgery for both on-pump and off-pump surgery in non-HIT patients.^{3–6}

After standard monitoring, routine intravenous general anesthesia with propofol, fentanyl and pancuronium bromide was performed. Extracorporeal circulation was instituted by draining blood by gravity into an open venous reservoir, and by driving it by means of a roller peristaltic pump through a hollow-fiber membrane oxygenator (Avant D903 PhISIO, Dideco, Mirandola, Italy) coated with phosphorylcholine. The circuit was primed with 1500 mL Ringer lactate solution, 100 mL mannitol 18%, and 50 mg bivalirudin. Cold (4°C) blood cardioplegia was infused by means of a roller pump for induction, and a constant low flow was maintained between doses. The cardioplegia line

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was also flushed at the table before each dose. Normothermia was actively maintained.

Tranexamic acid was given as a bolus of 1000 mg over 20 min and then 400 mg/h throughout the procedure. As described in detail before,³ 50 mg of bivalirudin was added to the priming solution, while a bolus of 75 mg (1 mg/kg) was given to the patient before aortic cannulation. The bolus was followed by an infusion of 2.5 mg/kg per hour during bypass, which was stopped after release of the aortic crossclamp. In order to avoid aspiration of blood from the operative field by cardiotomy suction, we connected the suction tube directly to the cell saver, which had been previously prepared with sodium citrate 4%. After 60 min, we discontinued the patient from cardiopulmonary bypass. Modified ultrafiltration (MUF) was performed for 20 min, resulting in over 600 mL of ultrafiltrate; following MUF, the venous and arterial cannulae were removed. Hemostasis lasted approximately 60 min and 300cc of fresh frozen plasma was transfused as, at first, diffuse oozing from the surgical field was evident. The CPB volume was processed and returned to the patient after chest closure. Postoperative blood loss was 390 mL, and the chest tubes were removed on the first postoperative day. The activated partial thromboplastin time (aPTT), the partial thromboplastin time (PT) ratio values and ACT values (seconds) are shown in Figures 1 and 2. The patient was weaned from mechanical ventilation after 8 h, left the ICU after 24 h, and was discharged from the hospital after 5 days.

Discussion

Allergies to heparin have become more common because of its increasing use in daily medical practice for thromboprophylaxis. At least three

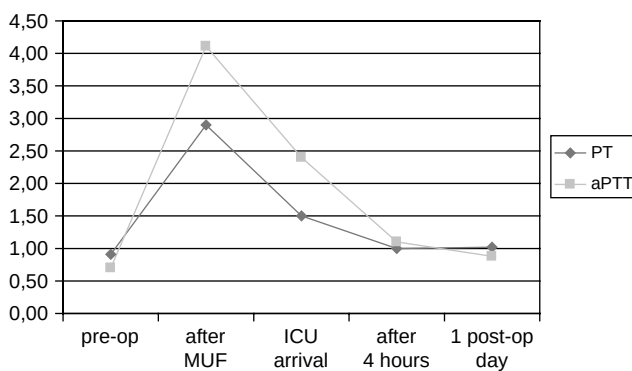


Figure 1 Coagulation profile (PT and aPTT) during the perioperative course.

types of immune-mediated reactions have been described to heparin:⁷

- an immediate type I hypersensitivity reaction with an urticarial rash, asthma and anaphylaxis.
- HIT resulting from IgG antibodies causing platelet activation. This is a progressive immune-mediated phenomenon, type III hypersensitivity reaction, occurring within 7–10 days of therapy, or within hours in a previously exposed patient.
- A delayed type IV hypersensitivity reaction causing erythematous plaques and eczematous patches within 10–20 days at the injection site.

Our patient presented a type I hypersensitivity reaction to heparin. A desensitisation protocol has been advocated for patients with heparin allergy, but its efficacy is still anecdotal and needs further investigation.¹ Heparin is the anticoagulant most commonly used in cardiac surgery to prevent clotting in the extracorporeal circuit; therefore, heparin-related, immediate-type hypersensitivity reaction mandates the use of alternative anticoagulation strategies.²

Alternative anticoagulation strategies for CPB have been predominantly described in patients with HIT. These strategies include

- 1) Due to the transient character of HIT antibodies, waiting until antibodies have declined and then perform CPB with heparin;⁸
- 2) Combining heparin with a potent short-acting anti-platelet agent to attenuate the HIT reaction;⁸ and
- 3) Using a non-heparin agent, namely the direct thrombin inhibitor lepirudin or, more recently, bivalirudin.⁸

In the present case of heparin anaphylaxis, any heparin exposure had to be avoided and, thus, the options were restricted to the use of a non-heparin agent.

Lepirudin has been used in large series of patients with HIT requiring CPB. However, the safety profile of lepirudin is limited because severe anaphylactic reactions have also been reported, the half-life is relatively long (60–80 min), elimination is exclusively renal, and the ecarin clotting time needed for monitoring lepirudin concentration is currently not commercially available as a point of care test.⁸

In contrast, to date, no anaphylactic reactions to bivalirudin have been reported, and the half-life of bivalirudin is relatively short (25–30 min) via proteolytic cleavage, and largely independent of the function of organ systems (20% is eliminated by the kidney). Moreover, standard ACT assays have

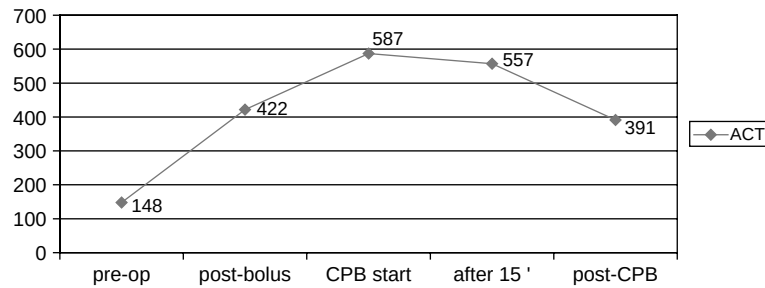


Figure 2 Intraoperative ACT changes during bivalirudin administration.

been shown to provide satisfactory monitoring of bivalirudin anticoagulation during CPB.⁹

Bivalirudin anticoagulation during cardiac surgery compared to unfractionated heparin has recently been validated in two prospective randomised trials,^{3,4} which showed safe and effective anticoagulation without increased postoperative bleeding. Management techniques for cardiopulmonary bypass and the surgical technique necessary

with bivalirudin have been reviewed.⁹ The use of bivalirudin during CPB is evolving and modifications of technique will undoubtedly occur as further data and experience accumulate. This case report shows a favourable outcome with bivalirudin for cardiac surgery requiring CPB in a patient with heparin allergy, possibly expanding the indications for use to this subset of patients.

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