Case report

Heparin-induced thrombocytopenia and cardiopulmonary bypass: anticoagulation with unfractionated heparin and the GPIIb/IIIa inhibitor tirofiban and successful use of rFVIIa for post-protamine bleeding due to persistent platelet blockade

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Received 24 September 2007; received in revised form 25 March 2008; accepted 19 May 2008; Available online 24 June 2008

Abstract

Heparin-induced thrombocytopenia was diagnosed in a 50-year-old man on day 5 after cardiac surgery (aorto-coronary bypass and mitral valve replacement). He required redo (para-prosthesis leak) on day 13. The cardiopulmonary bypass (CPB) was performed with unfractionated heparin (UFH) and the platelet glycoprotein (GP) IIb/IIIa inhibitor tirofiban. Post-protamine bleeding likely due to documented persistent platelet blockade by tirofiban was successfully treated with one dose of recombinant activated factor VII (rFVIIa, 60 µg/kg). No thrombotic complications were detected. The management of CPB with UFH and tirofiban is a convenient option and rFVIIa seems appropriate to handle bleeding issues.

Keywords: Heparin-induced thrombocytopenia; Cardiopulmonary bypass; Unfractionated heparin; Tirofiban; rFVIIa

1. Introduction

Heparin-induced thrombocytopenia type II (HIT) is associated with poor outcome in the context of cardiac surgery [1]. Cardiopulmonary bypass (CPB) requires an efficient anticoagulation and unfractionated heparin (UFH) remains the gold standard. Successful use of a direct thrombin inhibitor such as lepirudin or argatroban during CPB has been reported several times [2] but the need for dedicated intraoperative laboratory monitoring and the lack of an antagonist make their management tricky and risky. Tirofiban, a platelet glycoprotein (GP) IIb/IIIa inhibitor, has been used during CPB for a little while, in association with UFH [3]. Tirofiban has a short half-life but its main elimination route is via the kidneys. By strongly inhibiting fibrinogen binding to GPIIb/IIIa onto the surface of activated platelets, tirofiban can block platelet aggregation (though not platelet activation) by HIT antibodies [2]. Recombinant activated factor VII (rFVIIa) is a powerful haemostatic agent increasingly used in cardiac surgery to stop refractory, life-threatening bleeding [4]. A case of HIT and CPB with porcine UFH and tirofiban is described hereafter, with the successful use of rFVIIa for post-protamine bleeding.

2. Case report

A 50-year-old man underwent four bypasses (LIMA and three saphenous grafts) plus a mechanical mitral valve replacement on the third day of a myocardial infarct. Since postoperative day 3 (POD 3), a continuous haemofiltration was required for anuric renal failure (creatinine-mia = 270 µmol/l). On POD 5, HIT was suspected in view of a persistent thrombocytopenia (45 G/l). UFH was stopped and danaparoid therapy was introduced through continuous intravenous infusion at the recommended dose. HIT was confirmed by positive ELISA and platelet aggregation tests. After a satisfactory evolution (increase in platelet count...
without thrombosis), acute haemodynamic failure occurred on POD 13. A para-prosthesis massive leak was diagnosed by trans-thoracic echocardiography. A surgical redo valve replacement had to be performed in emergency. Danaparoid infusion was stopped 1 h before surgery and CPB was performed with UFH and tirofiban. The platelet blockade was assessed by a photometric platelet aggregometry (Fig. 1). Thirty minutes before the end of CPB, tirofiban infusion was stopped. After adequate UFH neutralisation with protamine, a diffuse and important bleeding was noticed in the operating theatre. The blood from the CPB suction device was retransfused without being processed. Despite massive transfusion (11 units of blood product, including platelet concentrate), the bleeding was so important that the chest could not be closed. Persistent platelet blockade by tirofiban (2 h after the injection’s end) was documented by aggregometry (Fig. 2) and held as the main factor for haemorrhage, whereas platelet count and clotting times were within usual post-CPB values (aPTT = 39 s with 35 s mean normal time, PT = 22 s with 13.2 s mean normal time). At this time, danaparoid antiXa level was 0.2 IU/ml, which was rather low and could not be held responsible for the haemorrhage. We therefore decided to proceed to rFVIIa injection at the dose of 60 µg/kg, since it is our current policy to do a trial in case of intractable post-prothrombin bleeding and there is a strong rationale that this drug can improve haemostasis in case of defective GP IIb/IIIa function as discussed below. The bleeding dramatically decreased to 50 ml/h within 30 min and PT shortened to 13.2 s. The chest could be readily closed and the patient left the operating room 2 h after protamine injection. Back in the intensive care unit, neither recurrent bleeding nor thrombosis was noticed.

3. Comment

To the best of our knowledge this is the first report of the use of rFVIIa on a patient under tirofiban during cardiac surgery. Tirofiban effect on platelet aggregation is major but reversible, with a short half-life as long as the renal function is not compromised. In this particular case, the patient had severe renal failure. The long lasting antiplatelet effect of tirofiban could not be handled by blood product transfusion, presumably since transfused platelets are inhibited by the high amount of plasma drug [5]. We used rFVIIa at the moderate dose that we are used to [6] and as already reported in cardiac surgery [7]. The haemostatic effect was noticed in as short a time as 30 min. We believe that rFVIIa overcome the antiplatelet effect of tirofiban by boosting thrombin generation as previously demonstrated [8]. Patients with inherited GP IIb/IIIa deficiency have been successfully managed with rFVIIa [9], and two tirofiban-treated patients have received it for major haemorrhage [10].

Thus, rFVIIa seems appropriate to manage bleeding consequences of tirofiban persistent effect, especially on patients with renal failure. Alternately, ultrafiltration or modified zero-balanced ultrafiltration can be used [2]. By contrast, a failure of rFVIIa could be anticipated if a direct thrombin inhibitor such as lepirudin was chosen, with dramatic accumulation in case of renal impairment. In spite of high thrombotic risk associated with HIT and potential thrombotic risk of rFVIIa, none of these adverse effects were observed. However, we suggest considering a dose of rFVIIa lower than 90 µg/kg in order to reduce this risk [6].

References

[6] Blanloeil Y, Rigal JC, Bastien O, Carteaux JP, Toussaint-Hacquard M. Danaparoid effect on platelet aggregation is major but reversible, with a short half-life as long as the renal function is not compromised. In this particular case, the patient had severe renal failure. The long lasting antiplatelet effect of tirofiban could not be handled by blood product transfusion, presumably since transfused platelets are inhibited by the high amount of plasma drug [5]. We used rFVIIa at the moderate dose that we are used to [6] and as already reported in cardiac surgery [7]. The haemostatic effect was noticed in as short a time as 30 min. We believe that rFVIIa overcome the antiplatelet effect of tirofiban by boosting thrombin generation as previously demonstrated [8]. Patients with inherited GP IIb/IIIa deficiency have been successfully managed with rFVIIa [9], and two tirofiban-treated patients have received it for major haemorrhage [10].
