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CASE REPORT

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A case report on the use of recombinant hirudin as an anticoagulant for cardiopulmonary bypass in open heart surgery

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Abstract We present a patient with coronary heart disease and a heparin-induced thrombocytopenia, who was successfully treated by coronary artery bypass grafting (CABG) using recombinant hirudin as an anticoagulant for cardiopulmonary bypass (CPB) instead of heparin. [Eur J Cardio-thorac Surg (1996) 10: 386–388]

Key words Recombinant hirudin · Anticoagulation · Heparin-induced thrombocytopenia · Cardiopulmonary bypass · Open heart surgery

Introduction

Recombinant hirudin (r-hirudin) is a potent thrombin-specific inhibitor originally derived from the natural hirudin of the leech [5]. The efficacy and safety of r-hirudin as an anticoagulant has been proven in several experimental and clinical trials (for a review see [7]). Based on the positive results gained from previous animal studies [11, 13] and one clinical case [10] r-hirudin is proposed to be a possible anticoagulant in patients requiring cardiac surgery and showing a history of immune-mediated heparin-associated thrombocytopenia (HAT). In those patients re-exposure to heparin is associated with a high risk of developing arterial and venous thrombosis. We report on one patient in whom r-hirudin was used as an anticoagulant for cardiopulmonary bypass (CPB). The patient was involved in a clinical study conducted by the Behringwerke, Marburg, Germany, in which r-hirudin is used instead of heparin.

Case report

A 71-year-old female patient, weighing 54 kg, came to admission with the diagnosis of coronary heart disease and a history of HAT (occurrence of platelet activating antibodies which are directed against heparin/PF4-complexes) which had been confirmed by means of the HIPA-test (Heparin-induced platelet aggregation). The only anticoagulant suitable for use during extracorporeal circulation proved to be r-hirudin HBW 023[1] since all heparins and heparinoids caused platelet aggregation.

Because of severe calcification of the ascending aorta, coronary artery bypass grafting (CABG) was performed on the patient in deep hypothermia (20 °C) on the fibrillating heart without cross-clamping to avoid thromboembolic complications. The left anterior descending artery was revasculated with the left internal mammary artery (IMA). The right coronary artery and the circumflex artery were grafted using a right IMA – saphenous vein composite graft. The anesthesia was maintained with intravenous infusion of propofol and a single bolus injection of pancuronium bromide (0.15 mg/kg body weight) along with intermittent doses of fentanyl (up to 25 μg/kg

[1] Behringwerke, Marburg, Germany

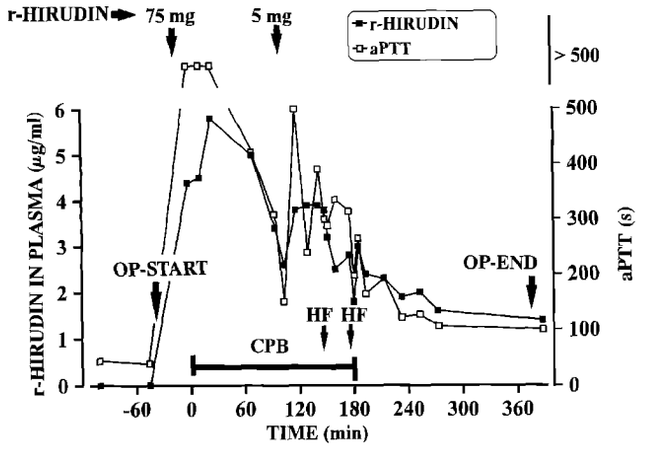

Fig. 1 Anticoagulantion monitoring: Change of the activated partial thromboplastin time (aPTT) in correlation to the r-hirudin plasma concentration before, during and after cardiopulmonary bypass (CPB). The start of each hemofiltration period (HF) is indicated by an *arrow*

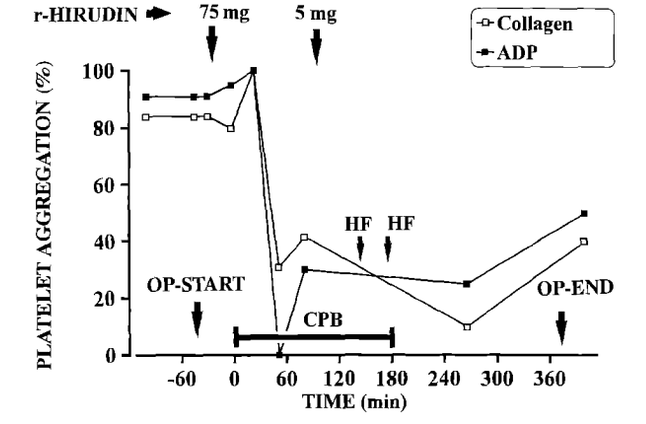

Fig. 2 Platelet function: ADP- and collagen-induced platelet aggregation before, during and after cardiopulmonary bypass (CPB). Platelet counts were adjusted by dilution or centrifugation to 100 000 platelets/µl and aggregation in induced by addition of ADP (10 mM/l) or collagen (4 µg/ml). The start of each hemofiltration period (HF) is indicated by an *arrow*

body weight). The patient received a bolus of 50 mg r-hirudin HBW 023 20 min before going on CPB. A further i.v. bolus injection of 5 mg r-hirudin (100 min after the start of CPB) was necessary to keep the plasma level of r-hirudin above 2.5 µg/ml during the entire CPB. Aprotinin was administered as infusion therapy (500 000 kiu/h) during the entire period of CPB. A capillary-membrane oxygenator (BARD 5701) was used and 25 mg r-hirudin HBW 023 and 2 Mio kiu aprotinin were added to the priming solution. The CPB was started with a flow of 2.4 l/m^2 per min in normothermia, which was reduced to 2.0 l/m^2 per min when hypothermia with 20 °C was achieved. The perfusion time was 180 min including a circulatory arrest period of 12 min. To monitor the anticoagulation during CPB we measured the ecarin clotting time (ECT) [9] along with the activated partial thromboplastin time (aPTT) (Fig. 1). In order to determine the r-hirudin plasma concentration, the thrombin activity was measured using the synthetic substrate chromozyme TH[2] [4]. Two periods of hemofiltration (Hemoflow F 60, High Flux)[3] lasting 10 and 5 min, were performed during the last 30 min of CPB to speed up the removal of r-hirudin. The hemofiltrate volume amounted to 5700 ml. The platelet function was measured by means of the ADP- and collagen-induced platelet aggregation. Postoperatively the aPTT was kept within a range of 50–70 s by subcutaneous administration of r-hirudin (10–30 mg/day) during the first 10 days. On the 24th postoperative day the patient was discharged home in good condition.

Results and discussion

Heparin, the commonly used anticoagulant for CPB, can not be used in patients with HAT, because these patients are at high risk of developing thromboembolic complications after exposure to heparin. In the present case report we describe one patient with confirmed HAT in whom r-hirudin was successfully used as an alternative anticoagulant to heparin in CPB. A bolus regimen of r-hirudin administration was chosen in order to avoid accumulation [6]. During CPB, aPTT- and ECT-values ranged from 150 to over 500 s and from 400 to 1000 s, respectively, indicating efficient anticoagulation. Since we had feared an intensified bleeding tendency due to the great wound areas following bilateral IMA preparation, the platelet damage due to extracorporeal circulation, and the deep hypothermia, we administered aprotinin to the r-hirudin anticoagulation. Plasma levels of r-hirudin started with 6.0 µg/ml and decreased during CPB (Fig. 1). Because of severe ascending aortic calcifications the revascularization technique had to be modified to avoid calcareous embolizations from manipulation of the ascending aorta [8]. Both IMAs we used in combination with saphenous vein grafts. The CABG was performed on the fibrillating heart in deep hypothermia without cross-clamping. Although this regimen required a perfusion time of 180 min, including a period of 12 min of circulating arrest, no problems concerning the anticoagulation occurred.

During the last 30 min of CPB the plasma concentration of r-hirudin was decreased from 3.2 µg/ml to 1.8 µg/ml by two periods of hemofiltration. These data give further evidence that hemofiltration allows effective and rapid elimination of r-hirudin from plasma even in man [10] and support previous animal studies [1, 12]. The increase in r-hirudin plasma concentration seen after the end of CPB could be explained by volume substitution with r-hirudin-containing blood from the heart-lung machine (HLM). The pressure measured proximal to the oxygenator was constant during the CPB and all components of the HLM, in-

[2] Boehringer Mannheim, Mannheim, Germany

[3] Fresenius, Bad Homburg, Germany

cluding oxygenator, cardiotomy reservoir, filters and tubing, remained free of any clots throughout the CPB time. No fibrin deposits were found even in electronmicroscopic scans of the filter membranes as a indication of successful anticoagulation and effective thrombin inhibition.

During and after surgery neither bleeding and thromboembolic complications nor allergic reactions were observed, demonstrating an effective and safe r-hirudin anticoagulation. First clots were observed in the pericardium 60 min after the end of CPB, when aPTT was 120 s, ECT 148 s and r-hirudin plasma level 1.9 μg/ml. Despite the prolonged aPTT and ECT, the blood loss into the thorax drainages amounted to only 240 ml within the first 12 h after operation.

Due to the dilution and mechanical trauma of CPB the platelet count decreased from 271 000 to $80\,000 \times 10^9$/l at the end of CPB. The platelet function remained normal after administration of r-hirudin and prior to CPB, supporting the in vitro findings, that r-hirudin does not influence platelet function [2, 3]. During CPB, however, the platelet function decreased rapidly due to the deep hypothermia and CPB-mediated trauma (Fig. 2). Four hours after the end of surgery the platelet function was almost fully restored (ADP-induced: 78%, collagen-induced: 81%). Since anticoagulation with r-hirudin had been continued during this time, these data indicate that the platelet function is not altered by r-hirudin.

In summary, the present case shows that even a difficult procedure under CPB with a long perfusion time, deep hypothermia, and circulatory arrest could be safely performed using r-hirudin instead of heparin for anticoagulation. Furthermore, ECT and aPTT are suitable parameters to monitor the plasma concentration of r-hirudin. As a result of the intact kidney function and the short half-life time of r-hirudin, the plasma concentration decreased rapidly during CPB, requiring the administration of an additional r-hirudin bolus to provide stable plasma levels of r-hirudin. By means of hemofiltration, it was possible to quickly and effectively lower the r-hirudin plasma level at the end of CPB.

We think that r-hirudin is a suitable alternative to heparin in cases of patients suffering from HAT. A randomized clinical study, however, comparing anticoagulation with r-hirudin to the conventional heparin regimen during CPB should clarify whether r-hirudin represents an anticoagulant which is superior to heparin.

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