Serious bleeding in a haemodialysis patient treated with recombinant hirudin

Alexander Müller1, Günter Huhle2, Rainer Nowack1, Rainer Birck1, Dieter L. Heene2 and Fokko J. van der Woude1

1Fifth Medical Clinic and 2First Medical Clinic, University Hospital Mannheim, Medical Faculty of the University of Heidelberg, Germany

Key words: anticoagulation; ecarin clotting time; haemodialysis; heparin-induced thrombocytopenia (HIT); hiradin; thrombosis

Introduction

Heparin is at present the most widely used anticoagulant for haemodialysis to prevent clotting in the extracorporeal circuit. Heparin-induced thrombocytopenia (HIT) type II is a serious complication rendering the further administration of unfractioned heparin as well as low-molecular-weight heparin impossible. Even available heparinoids such as danaparoid exhibit a significant cross-reactivity with HIT antibodies in 5–10% of patients and is sometimes not suitable for anticoagulation in cases of heparin intolerance. Hirudin is a direct thrombin inhibitor which forms non-covalent complexes with thrombin. In contrast to heparin it does not require endogenous cofactors. Chronic administration of r-hirudin in haemodialysis carries the risk of accumulation since unchanged hirudin is exclusively cleared by the kidney [1]. It is not removed by haemodialysis. To avoid accumulation and bleeding complications in anuric patients dose reduction has been suggested (bolus of 0.02–0.17 mg/kg prior to each haemodialysis) followed by careful monitoring with the activated partial thromboplastin time (aPTT) [2–5].

Case

A 49-year-old male patient developed renal failure presumably because of glomerulonephritis secondary to acute endocarditis in June 1994. He was treated with antibiotics and replacement of the aortic-valve by a bioprosthesis. In March 1998 he became dialysis dependent and was dialysed using a polysulphone low-flux dialyser (F7 HPS, Fresenius Medical Care, Bad Homburg, Germany). For anticoagulation a bolus of 4000 units of unfractionated heparin was administered at each haemodialysis session.

After three dialysis sessions the patient developed retinal-vein thrombosis and thrombocytopenia of 128 000/mcl. The suspected diagnosis of heparin-induced thrombocytopenia (HIT II) was confirmed by the heparin-induced platelet activation test (HIPA). The HIPA test was performed as described with a few modifications [6]. Further dialysis treatments were performed without anticoagulation at a blood flow rate of 250–300 ml/min for 3-h haemodialysis sessions without clotting events. The patient was on 100 mg acetyl salicylic acid daily and did well. In August 1998 overall KT/V decreased below 1.0 because of declining residual renal function and haemodialysis duration was increased to 4.5 h per session. This led to repeated clotting of the dialyser or the extracorporeal circuit during the last treatment hour. Anticoagulation with r-hirudin (Refludan®. Fa. Hoechst-Marion Roussel, Frankfurt, Germany) was started at a dose of 0.06 mg/kg (5 mg) as a bolus at the beginning of each dialysis-session. The anticoagulatory effect of r-hirudin was monitored by aPTT with a recommended range of 36–44 s.

After 16 dialysis sessions using r-hirudin the patient developed spontaneous haemorrhage into the left quadriceps muscle following an episode of post-dialytic cramps. Haemoglobin level decreased from 9.4 g/dl to 8.1 g/dl. Two days later he suffered rectal bleeding, and haemoglobin level decreased further to 6.6 g/dl; PT (114%), fibrinogen (319 mg/dl), and platelets (214 000/µl) were within normal limits, aPTT was 44 s. r-Hirudin and acetyl salicylic acid were discontinued and 3 units of blood were transfused. Bleeding stopped spontaneously. The ecarin clotting time (ECT) was 289 s (normal range <50 s [8]). aPTT was measured with Pathrombin-Kit (Behring, Marburg, Germany). Until the ECT had normalized no further anticoagulation was administered during haemodialysis; then
r-hirudin was further reduced to a dose of 0.018 mg/kg (1.5 mg) per session as bolus at the beginning of the treatment. With this reduced dosage of r-hirudin ECT remained normal or slightly elevated and no clotting or bleeding tendency occurred for 3 months.

Discussion

Recombinant hirudin can be used as an anticoagulant for haemodialysis when heparin is contraindicated. Especially in haemodialysis patients with HIT type II, hirudin is the anticoagulant of choice. Low-molecular-weight heparin cannot be used as an alternative because of marked cross-reactivity. Even with heparinoids (danaparoid sodium, Orgaran®, Thiemann Arzneimittel Waltrop, Germany), cross-reactivity was found in 5% of patients with HIT type II. There is a paucity of long-term experience with r-hirudin in chronic haemodialysis, and dosage recommendations have been based on few anecdotal observations. Only for a single dialysis session the minimum dose to prevent clotting and avoid bleeding complications is a single bolus of 0.08 mg/kg [3]. The first long-term experience with hirudin covering more than 50 haemodialysis sessions in one single patient has been reported, and a bolus of 0.145–0.170 mg/kg r-hirudin was administered for each haemodialysis session [7]. Elimination of r-hirudin depends almost exclusively on residual renal function, and the drug will not be cleared by many dialysers. To avoid accumulation and bleeding complications, drug monitoring by a sensitive test is needed. Currently the aPTT is recommended for this purpose by the manufacturers. In our patient without residual renal function serious bleeding occurred, although we used the recommended low dose of hirudin and the aPTT was still in the therapeutic range. The bleeding risk would have been detected by the ECT, which was elevated more than five times above the upper normal value. A reduced dose of r-hirudin was administered as a bolus, and ECT as well as aPPT were monitored. With this approach no further bleeding occurred.

References


Received for publication: 14.4.99
Accepted in revised form: 7.6.99