

H. J. Ng · L. P. Koh · L. H. Lee

Successful control of postsurgical bleeding by recombinant factor VIIa in a renal failure patient given low molecular weight heparin and aspirin

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Abstract An end-stage renal failure patient with lupus nephritis was treated with low molecular weight heparin (LMWH) and aspirin for cardiac ischemia. She was then subjected to surgery to recreate a new arteriovenous fistula for dialysis 1 day after discontinuing LMWH and aspirin. Severe postsurgical bleeding required wound reexploration and multiple transfusions of blood products, which nevertheless, failed to arrest bleeding. Recombinant factor VIIa (rFVIIa) as a bolus dose of 120 µg/kg successfully secured hemostasis. Bleeding in this patient was attributed to the accumulation of low molecular weight heparin activity from poor renal clearance as well as the antiplatelet activity of aspirin. The potential of rFVIIa in securing hemostasis for excessive bleeding after use of these agents is promising.

Keywords Recombinant factor VIIa · Low molecular weight heparin · Renal failure · Aspirin

Introduction

Combinations of anticoagulants such as low molecular weight heparin and aspirin, when used in patients with underlying renal failure, can potentially give rise to serious bleeding complications. The successful use of recombinant factor VIIa (rFVIIa) in such a patient who developed severe bleeding is described, demonstrating the potential of rFVIIa as a hemostatic agent for bleeding related to low molecular weight heparin and aspirin therapy.

Case report

A 32-year-old lady with end-stage renal failure (ESRF) secondary to lupus nephritis was admitted for cardiac ischemia and cardiomyopathy. The low molecular weight heparin (LMWH) enoxaparin, at 1 mg/kg twice daily, was given together with aspirin at 100 mg daily for a total of 1 week.

Her vascular access for hemodialysis had been compromised by repeated arteriovenous fistula (AVF) thrombosis and the development of pseudoaneurysm. During this admission, heparin-free hemodialysis was carried out via a temporary internal jugular vein catheter. One week after admission, her cardiac symptoms abated and low molecular weight heparin was stopped together with aspirin. It was then decided that she proceed with plans for a brachiobasilic side-to-side AVF creation. She was inadvertently listed for the procedure 1 day after stopping LMWH and aspirin. Preoperative platelet level was 148,000/mm³ with a hematocrit of 34.2%. Partial thromboplastin time (PTT) was prolonged at 76 s with normal prothrombin time. No anti-Xa level was obtained before the procedure. She received however prior fresh frozen plasma transfusion.

Continuous slow oozing from the site of the AVF postoperatively marred the first 36 h. Transfusion of two units of packed red blood cells, six units of fresh frozen plasma, together with local measures of compression and superficial stitching reduced visible bleeding. One day later, wound inspection by removal of pressure bandaging resulted in torrential bleeding. This could no longer be controlled with local pressure and urgent reexploration of the anastomotic site was performed. The absence of clots was evident on opening the wound. Despite local surgical measures of suturing and the application of thrombin powder, bleeding persisted. Transfusion of further units of fresh frozen plasma, cryoprecipitate, platelets and tranexamic acid, an antifibrinolytic agent, did not stop her bleeding. Two further units of packed red cells were given. No attempt was made to reverse possible LMWH activity. Her PTT had by then become prolonged to 83 s with a decline in the hematocrit to 23.9% despite packed cell transfusion.

In view of the severity and degree of bleeding by the time we saw this patient, we decided to attempt using recombinant factor VIIa (rFVIIa) as a decisive measure to secure hemostasis. She was given 120 µg/kg as a slow bolus infusion. Bleeding stopped soon after the infusion. A second dose was given 6 h later to further ensure adequate hemostasis despite the absence of bleeding. The PTTs taken 0.5 and 12 h after first infusion were measured at 49.7 s and 40 s, respectively. No further bleeding was noted after infusion of the first dose of rFVIIa.

Tests on samples taken during bleeding showed normal clotting factor levels (factor VIII, IX, and fibrinogen) except for low levels of factor XI at 40% (range: 70–200). Repeat testing prior to discharge however showed normal levels of factor XI. No inhibitors

H. J. Ng (✉) · L. P. Koh · L. H. Lee
Department of Hematology,
Singapore General Hospital,
Outram Road, 169608 Singapore, Republic of Singapore
e-mail: ghenhj@sgh.com.sg
Tel.: +65-63214855
Fax: +65-62250210

to factor XI or the more common factor VIII and IX inhibitors were found. D-dimer and soluble fibrin monomers were not raised. Prolonged thrombin clotting time showed correction with the addition of protamine sulfate.

This patient was subsequently discharged 1 week later with a functioning AVF.

Discussion

The low molecular weight heparins (LMWH) are mainly eliminated renally, and patients with ESRF have markedly reduced clearance of this compound [1, 7]. When LMWH is used in ESRF patients, its pharmacological activity accumulates and the patients remain anticoagulated for a longer period than would otherwise be expected after discontinuing therapy. This was clearly the situation in this patient when she underwent the simple procedure of creating an arteriovenous fistula soon after discontinuing therapy with LMWH. The prolongation of the PTT with correction by protamine sulfate in the thrombin test despite the absence of unfractionated heparin use is likely contributed by LMWH. While the effect of LMWH on PTT is significantly less than unfractionated heparin, PTT may become prolonged at high doses with the intensity of this effect being variable [5].

Concomitant use of aspirin in this patient further increased the potential for bleeding. Platelet dysfunction occurs in uremic patients who may also demonstrate increased sensitivity to aspirin [3]. Her preceding problems with her vascular access made it likely that this patient would not have been optimally dialyzed. A lowered hematocrit due to the uncontrolled bleeding could have further contributed to a significant defect in platelet adhesion in this patient [2]. This may in part be explained by the role of red cells in displacing platelets to the periphery of a column of circulating blood [8] as well as the possibility of red cells enhancing the reactivity of platelets [6]. The sum of the above factors is the impairment of platelet adhesion, activation, and aggregation.

The success of using recombinant factor VIIa (rFVIIa) in this case underscores its potential use in controlling bleeding in patients with spontaneous or postsurgical bleeding following use of LMWH. LMWH's longer half-life as well as impaired clearance in patients such as ours will give rise to situations where excessive bleeding occurs following surgery. Reversal of the effect of LMWH by protamine sulfate is thought to be partial only, in contrast to that of unfractionated heparin. As

such, having rFVIIa at the surgeon's disposal may provide an important hemostatic tool in groups of patients who bleed despite presumed adequate periods of discontinuation of therapy or who require emergent surgery.

The likely mechanism of action of rFVIIa in this patient is via the enhancement of thrombin generation to the extent that full thrombin generation occurs at the site of bleeding. This gives rise to the formation of a fully stabilized hemostatic fibrin plug with a tight structure and reduced permeability [4].

Our dose of 120 µg/kg was highly effective in securing adequate hemostasis. This is higher than the standard recommended dose of 90 µg/kg and no significant side effects were seen during use. The second dose was given as a precautionary measure to secure hemostasis and may have been unnecessary. Rapid reduction in PTT times was seen soon after the administration of rFVIIa.

This case highlights the importance of careful preoperative assessment of patients and understanding the pharmacokinetics of drugs given to patients in order to reduce subsequent bleeding risk. It also provides evidence of the potential of rFVIIa as a hemostatic agent for patients given LMWH who bleed. In this respect, rFVIIa is gaining further credibility as a potential universal hemostatic agent.

References

1. Cadroy Y, Pourrat J, Baladre MF, Saivin S, Houin G, Montastruc JL, Vernier I, Boneu B (1991) Delayed elimination of enoxaparin in patients with chronic renal insufficiency. *Thromb Res* 63:385–390
2. Castillo R, Lozano T, Escobar G, Revert L, Lopez J, Ordinas A (1986) Defective platelet adhesion on vessel subendothelium in uremic patients. *Blood* 68:337–342
3. Eberst ME, Berkowitz LR (1994) Hemostasis in renal disease: pathophysiology and management. *Am J Med* 96:168–179
4. Hedner U (2001) Recombinant factor VIIa (NovoSeven) as a hemostatic agent. *Semin Hematol* 38 [Suppl 12]:43–47
5. Ip BK, Thompson AR, Moriarty HT (2001) A comparison of the APTT reagents to the effects of enoxaparin, a low molecular weight heparin. *Pathology* 33:347–352
6. Marcus AJ, Safier LB (1993) Thromboregulation: multicellular modulation of platelet reactivity in hemostasis and thrombosis. *FASEB J* 7:516–522
7. Sanderink GJ, Guimart CG, Ozoux ML, Jariwala NU, Shukla UA, Boutouyrie BX (2002) Pharmacokinetics and pharmacodynamics of the prophylactic dose of enoxaparin once daily over 4 days in patients with renal impairment. *Thromb Res* 105:225–231
8. Turrito VT, Weiss HJ (1980) Red blood cells: their dual role in thrombus formation. *Science* 207:541–543