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CASE REPORT

Treatment of postoperative bleeding after fondaparinux with rFVIIa and tranexamic acid

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ABSTRACT

Treatment of a haemorrhagic shock after just a single dose of fondaparinux in an orthopaedic patient with reduced renal clearance is presented. Since all routine haemostatic parameters were nearly normal, single doses of rFVIIa (90 μg/kg) and of tranexamic acid (15 mg/kg) were administered to improve thrombin generation and reduce fibrinolysis.

This case is the first showing the effectiveness of combining single doses of rFVIIa and tranexamic acid in controlling severe postoperative bleeding after fondaparinux.

KEYWORDS

Activated, clearance, factor VII, female, fibrinolysis, fondaparinux, haemorrhagic, orthopaedic, pentasaccharide, postoperative bleeding, recombinant, renal, shock, surgery, tranexamic acid

INTRODUCTION

Venous thromboembolism (VTE) develops in about 15% of orthopaedic patients after total hip replacement, despite the use of the current thromboprophylactic treatment, particularly low-molecular-weight heparins (LMWHs).[1] Recent studies suggest a superior efficacy of the new pentasaccharide fondaparinux over LMWHs in major orthopaedic surgery, resulting in no increase in the risk of fatal bleeding and need for reintervention, despite a higher nonfatal bleeding rate.[2] The present case is the first report of a patient developing severe postoperative bleeding after 2.5 mg of fondaparinux, which was successfully terminated after the administration of 6 mg recombinant activated factor VII (rFVIIa), combined with tranexamic acid.

CASE REPORT

A hip prosthesis was revised in a 79-year-old female patient. The patient had documented hypertension, and had previously undergone a subtotal thyroidectomy, and total hip replacement on both sides. There was no patient or family history of bleeding tendency. Perioperative medical treatment (aminocetophen as necessary, omeprazol 20 mg, calcium citrate 500 mg, raloxifene 60 mg, indapamine 2.5 mg, all once daily) was interrupted eight hours prior to surgery. During the surgical procedure the femur was exposed subtotally. Peroperative blood loss (1500 ml) was replaced by crystalloids. Postoperative blood management was according to the hospital's transfusion algorithm developed to reduce allogeneic red blood cell transfusions for major orthopaedic surgery, restricting red cell transfusion to patients over 60 years of age and with Hb levels <5.0 mmol/l, and to patients with cardiac disease and with Hb levels <5.5 mmol/l.[3] In order to prevent deep venous thrombosis the first dose of fondaparinux (2.5 mg) was administered subcutaneously six hours postoperatively (t=6 h). At that time the haemoglobin level was 6.5 mmol/l, blood pressure 135/60 mmHg, heart rate 60 beats/min, and blood loss per drain 75 ml/h. At t=17 hours the patient had received just one single dose of fondaparinux and haemorrhagic shock developed due to a severe bleed from the operative site as monitored by wound drains: haemo-

globin (Hb) 3.7 mmol/l, blood pressure 90/40 mm Hg, heart rate 110 beats/min. Three units of red blood cell concentrates were transfused resulting in a clear rise in haemoglobin level (5.8 mmol/l) and blood pressure (130/50 mmHg). However, in the following hours blood loss persisted at an average drain rate of 75 ml/h, with deterioration of the anaemia (Hb 3.5 mmol/l), and development of atrial fibrillation. At t= 39 hours three additional units of red blood cell concentrates were transfused resulting in an increased Hb level (5.4 mmol/l). Coagulation parameters were checked as bleeding persisted 35 hours after a single dose of 2.5 mg fondaparinux. Since the platelet count was 69 x 10^9/l, and all routine coagulation parameters (INR 1.5, prothrombin time (PT) 15 seconds, activated partial thromboplastin time (APTT) 38 seconds, and Ca^{2+} 1.39 mmol/l) were nearly normal, plasma concentrates and platelets were not administered.

However, rFVIIa, being the only known antidote for severe bleeding after fondaparinux, was administered intravenously.[4-6] Simultaneously, intravenous tranexamic acid therapy (1 g three times a day) was started to stop fibrinolysis. Within one hour, blood loss diminished from 75 to an average of 2 ml/h by drain, which did not increase during the following 24 hours. Arterial blood pressure and Hb level rose after one final unit of red blood cell concentrate: RR 160/60 mmHg, heart rate 80 beats/min, Hb 5.9 mmol/l. The coagulation parameters (INR 0.9, PT 9 sec, APTT 38 sec) and platelet count (59*10^9/l) remained stable.

DISCUSSION

This case shows the risk of severe postoperative bleeding even after a single dose of fondaparinux in orthopaedic patients with reduced renal clearance. Furthermore, it is the first case showing the effectiveness of a single dose of rFVIIa in combination with tranexamic acid in controlling severe bleeding after postoperative thromboprophylactic treatment with fondaparinux in elective orthopaedic surgery. Fondaparinux, the first of a new class of synthetic pentasaccharides, binds to antithrombin (AT-III), thereby increasing its activity towards inactivation of factor Xa by about 300 times, and delaying tissue factor-induced clot formation. Furthermore, fondaparinux accelerates fibrinolysis due to downregulation of the activation of thrombin-activatable fibrinolysis inhibitor (TAFI).[6] However, it has no direct effect on thrombin, nor on platelets.[7]
Fondaparinux has improved antithrombotic effectiveness after both total knee and hip replacement in comparison with low-molecular-weight heparins.[2] In a meta-analysis of four trials, patients receiving fondaparinux had a >50% reduction in the relative risk of VTE at day 11 compared with LMWHs, but more postoperative bleeding.[2]
Fondaparinux is completely resorbed two hours after subcutaneous injection and has a variable half-life depending on kidney function and age: $T^1/_2$ is 17 hours in young healthy adults, 21 hours in the elderly, 29 hours at creatinine clearance 30 to 50 ml/min, and 72 hours when creatinine clearance <30 ml/min[7] and is registered for once-daily usage. Consequently, the drug must still be active after two half-lives. In this case report the patient's creatinine clearance was 45 ml/min according to the Cockroft formula, which resulted in an estimated fondaparinux $T^1/_2$ of 29 hours at minimum, suggesting the drug was effective for up to 58 hours.
Since the classical coagulation parameters (INR, APTT and PT) were (nearly) normal and the platelet count was adequate at the time of the haemorrhagic shock, administration of coagulation factors and suppletion of platelets was not necessary.[8] According to some studies severe bleeding after fondaparinux in the presence of sufficient coagulation factors is best stopped by recombinant FVIIa.[4-6] Factor VIIa activates factor X, which initiates the conversion of prothrombin into thrombin, also partially improves thrombin-activatable fibrinolysis inhibitor (TAFI)-mediated inhibition of fibrinolysis.[6] The potential clinical use of rFVIIa as haemostatic treatment of major bleedings related to fondaparinux has not been evaluated, but its *ex-vivo* effectiveness has been proven.[5,6] Furthermore, rFVIIa is capable of normalising coagulation times and thrombin generation during fondaparinux treatment in healthy subjects.[4] Accordingly, both 90 μg/kg rFVIIa and 15 mg/kg tranexamic acid, an antifibrinolytic agent with active serum plasma levels for seven to eight hours, were administered intravenously. Within one hour bleeding stopped and blood pressure normalised. Despite rFVIIa's short $T^1/_2$ no additional doses were needed, possibly because of the additional antifibrinolytic activity of the tranexamic acid. Since the direct cost of rFVIIa was € 3900 and of tranexamic acid was just € 21, it is suggested from the present case to use combined treatment of just a single dose of rFVIIa and an antifibrinolytic agent to resolve bleeding problems after the use of fondaparinux in orthopaedic surgery and in the presence of near-normal coagulation parameters. Otherwise, in case of a prolonged prothrombin time and APTT, the coagulation should be first normalised using human plasma.

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