HEMATURIA ASSOCIATED WITH CONTINUOUS INFUSION OF RECOMBINANT FACTOR VIIa

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Patients with hemophilia and high-titer inhibitors are a therapeutic challenge, since hemorrhagic episodes may result in life-threatening hemorrhages that cannot be adequately treated by conventional therapies. Successful prevention or treatment of clinically significant bleeding in such patients can generally be achieved through the use of bypassing therapies, such as recombinant factor VIIa (rFVIIa, Novoseven®, Novo Nordisk), and activated prothrombin complex concentrates, such as factor eight inhibitor bypassing activity (FEIBA). Recombinant FVIIa can be administered by intermittent bolus injection (generally using doses of 60-90 µg/kg administered every 2 to 3 hours) or by continuous infusion.

This paper describes two unique cases of mild hemophilia A with high-titer factor VIII (FVIII) inhibitors, who were treated with rFVIIa administered by continuous infusion. Of interest and not anticipated was the fact that gross hematuria developed as a secondary hemorrhagic complication following initial hospital admission and after the start of rFVIIa therapy in both cases.

Case Reports

Case 1

The first case was a 16-year-old male with mild hemophilia A (FVIII level 29%). He developed inhibitors against both human and porcine FVIII (peak levels: 51 Bethesda Units to human and 35 BU to porcine). He was admitted with a right forearm hematoma, for which he was treated with rFVIIa, 90 µg/kg intravenous bolus, followed by 25-30 µg/kg/h as a continuous infusion. Despite therapeutic FVII levels of 3000%-4700% (30-47 U/mL) throughout the treatment period, he developed painless gross hematuria on the eighth day of his hospital stay (Figure 1). No cause for his hematuria, other than his coagulation disorder, could be identified. Renal function tests were normal and he had a normal renal ultrasound. He was treated with oral prednisone (2 mg/kg/day) and hydration to maintain a good urine output.

Case 2

The second case was a 17-year-old boy with mild hemophilia A (FVIII level 16%). He had circulating inhibitors against both human and porcine FVIII (peak levels: 12 BU to human and 9 BU to porcine). He was admitted with a right elbow hemarthrosis, for which he received rFVIIa, 90 µg/kg intravenous bolus, followed by 30-40 µg/kg/h as a continuous infusion. FVII levels were maintained in the range of 2300%-3800% (23-38 U/mL). As in the first case, this patient developed painless gross hematuria on the fifth day of his hospital stay (Figure 2), as well as a large left forearm compartment hematoma.

There was no clinical or laboratory evidence of disseminated intravascular coagulation (i.e., he had no fall in platelet counts or fibrinogen levels). Due to the limb-threatening nature of the forearm hemorrhage, his treatment with rFVIIa was discontinued, and a decision was made to start a program of intensive plasmapheresis (to remove circulating FVIII antibody) combined with high-dose corticosteroid therapy and FVIII substitution therapy. The therapeutic program (Figure 2) consisted of daily plasmapheresis (one blood volume=6 litres), using fresh-frozen plasma as replacement fluid on three consecutive days, intravenous methylprednisolone 1 g daily for three days, and recombinant factor VIII (rFVIII, Kogenate®, Bayer) 200 U/kg intravenous bolus, followed by 20 U/kg/h as a continuous infusion. As in the first case, the cause for the patient’s hematuria, other than his coagulation disorder, could not be identified. He was maintained on a liberal fluid intake to ensure good urine output. Following plasmapheresis and the institution of a continuous infusion of rFVIII, the patient’s circulating FVIII level was maintained in a hemostatic range (approximately 100%). With this regimen, the hematuria resolved by the 10th day of his hospital stay and gradually the hemarthrosis and left forearm compartment hematoma also resolved.

Discussion

The development of inhibitors to FVIII occurs in approximately 25%-50% of hemophilia A and 3%-5% of hemophilia B patients. Recombinant FVIIa has been used to successfully treat hemorrhagic episodes in hemophiliacs...
AL-TRABOLSI

FIGURE 1. Summary of hospital course, case 1. rFVIIa= recombinant factor VIIa (Novoseven®, Novo Nordisk); PT= prothrombin time; VII:C= coagulant factor VII.

FIGURE 2. Summary of hospital course, case 2.

with high-titer inhibitors (≥10 BU). Its mechanism of action involves the generation of thrombin at the site of vessel injury, where tissue factor or phospholipid are exposed.4 Recombinant FVIIa also activates factor IX and X on the surface of the activated platelets.5,6 It has been established that an effective therapy for bleeding in patients with hemophilia A and B and high-titer inhibitors requires a dose of rFVIIa greater than 60 µg/kg given every 2-4 hours.7 Subsequent studies determined that a dose of 90 µg/kg is highly effective for patients undergoing both major and minor surgical procedures.8 This product has a predictable, well-characterized pharmacokinetic profile, including a half-life of 2.9 hours.9,10

Due to the short half-life of rFVIIa, which necessitates injections every two hours, continuous infusion is becoming an increasingly adopted mode of administration. Attractive features of continuous infusion include convenience of administration and a potential cost saving associated with the use of less rFVIIa to maintain a target hemostatic level. The technique has not been perfected, however, and some questions remain. For example, the minimum dosage to achieve hemostasis is not well defined.11,12

The two cases reported are of interest, since gross hematuria developed a few days following the administration of rFVIIa by continuous infusion, and at a time when target hemostatic levels of FVII had been achieved. In both cases, there was no apparent cause of the hematuria, such as infection or renal calculi. This pattern of bleeding has not, to the author’s knowledge, been reported as a “downstream” complication in patients started on intermittent-dose rFVIIa.

One possible explanation for the development of hematuria during treatment with continuous infusion rFVIIa in both cases is that mucosal bleeds, such as hematuria, are characterized by high fibrinolytic activity locally, and may require higher peak levels of FVII to generate sufficient thrombin to achieve and sustain hemostasis. The need for a full thrombin burst could relate to the role of thrombin in the activation of thrombin-activatable fibrinolysis inhibitor (TAFI).13 Further prospective clinical and laboratory studies are required to determine the true frequency of secondary mucosal bleeding in patients with hemophilia and high-titer inhibitors treated with this novel bypassing therapy.

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