

CASE REPORT

Recombinant factor VIIa prophylaxis in a patient with severe congenital factor VII deficiency

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Summary. Use of recombinant factor VIIa (rFVIIa, NovoSeven®) in patients with congenital FVII deficiency has been reported for the prophylactic management of surgical bleeding and for the treatment of acute bleeding episodes. Because of its short half-life, the use of rFVIIa on a regular prophylactic regimen has not been routinely adopted. In this report, we

describe our successful experience with rFVIIa prophylaxis in preventing recurrent target joint bleeding in a severely FVII-deficient adolescent.

Keywords: factor VII deficiency, NovoSeven®, recombinant FVIIa

Introduction

Congenital factor VII deficiency is a rare autosomal recessive bleeding disorder with an estimated prevalence of 1 per 500 000 in the general population [1,2]. The severity of the deficiency is defined by an individual's FVII levels, but in contrast to patients with haemophilia A or B, the correlation between factor level and bleeding tendency is variable. In general, bleeding symptoms are seen in severely affected homozygous or compound heterozygous individuals with FVII levels <1%. Bleeding manifestations include mucosal bleeding (menorrhagia, epistaxis, postextraction bleeding, haematuria, melena), easy bruising, soft tissue haematoma, haemarthrosis and intracranial haemorrhage (particularly in the neonatal period) [3–5].

Traditionally, fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs), or plasma-derived FVII concentrates have been used for replacement therapy in severe FVII deficiency. Their inconsistent efficacy as a result of the variable content of FVII and their inherent infectious and thrombotic risks render these treatment options less

than ideal. FFP has the added disadvantage of requiring large infusion volumes to achieve adequate FVII levels. The recombinant FVIIa (rFVIIa; NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark) provides an alternative treatment option for specific FVII replacement without the potential risk for infectious complications. Use of rFVIIa in patients with congenital FVII deficiency has been reported for the prophylactic management of surgical bleeding and for the treatment of acute bleeding episodes such as gum bleeding, haemarthrosis, retroperitoneal bleeding and intracranial haemorrhage [6–9].

The efficacy of replacement factor prophylaxis in haemophilia A and B, as measured in clinical outcomes and academic achievement has been well-documented [10,11]. However, the use of rFVIIa replacement on a regular, prophylactic schedule has not been routinely adopted primarily because of its short half-life ($t_{1/2}$) and hence, questionable efficacy. We describe our successful experience with rFVIIa prophylaxis in preventing recurrent target joint bleeding in a severely FVII-deficient adolescent with improvement of joint function and quality of life.

Case report

A 15-year-old Egyptian male with severe congenital FVII deficiency (FVII:C <1%) experienced severe episodes of epistaxis during early childhood, requiring treatment with FFP and red blood cell transfusions. He acquired the hepatitis C virus as a result of

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his repeated exposure to blood products. As he became older, he experienced frequent haemarthroses and developed a target joint in his right elbow with two to three bleeds per month. Because of the patient's hepatitis C status, the family was very reluctant to administer plasma-derived products, therefore, the patient was often under-treated. He was treated with a sporadic 'on-demand' regimen of Proplex-T™ (PCCs; Baxter BioScience, Thousand Oaks, CA, USA). When he presented to our institution at 14 years of age, the patient had become increasingly more physically active, and the frequency of his target joint bleeds had increased to over five bleeds per month. His current on-demand treatment regimen was completely ineffective.

In an attempt to accommodate the patient's desired level of physical activity and the family's wishes to avoid plasma-derived products, a prophylactic rFVIIa treatment regimen was started in conjunction with a physical therapy programme. Because standardized prophylactic dosing was lacking, an empiric twice-weekly regimen of rFVIIa at $80 \mu\text{g kg}^{-1} \text{dose}^{-1}$ (4.8 mg dose^{-1} , i.e. a single 4.8 mg vial) was initiated. rFVIIa infusions were administered at home by the mother via a Port-a-cath. The patient tolerated the infusions well without complications. His platelet counts and DIC (disseminated intravascular coagulation) parameters remained within normal limits.

After initiation of rFVIIa prophylaxis, the number of target joint bleeds into his right elbow decreased from over five bleeds per month (5 month^{-1}) to just three bleeds over 5 months (0.6 month^{-1}). In addition, the patient's right elbow mobility improved, with his right arm flexion increasing from 128° pre-rFVIIa prophylaxis, to 142° (Table 1). Subjectively, the patient reported less pain in his right elbow and improved function despite his higher level of physical activity.

Pharmacokinetic studies were performed and FVII activity was measured at 2, 4, 12, 17, 24 and 72 h following rFVIIa infusion (Fig. 1). Following the $80 \mu\text{g kg}^{-1} \text{dose}^{-1}$ of rFVIIa, the postinfusion FVII level was extremely high (535% at 2 h) and

Table 1. Joint mobility after 5 months of recombinant factor VIIa (rFVIIa) prophylaxis.

Right elbow examination	Pre-rFVIIa prophylaxis (°)	Post-rFVIIa prophylaxis (°)
Flexion	128	142
Extension	-40	-10
Supination	45	90
Pronation	40	80

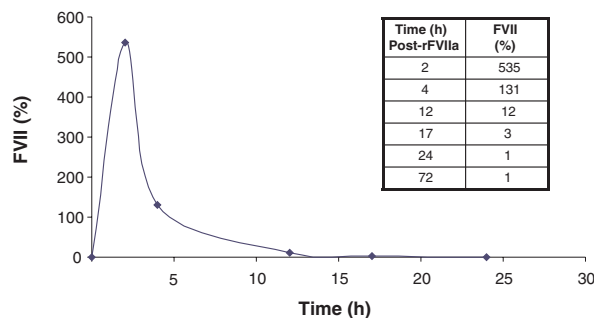


Fig. 1. Plasma factor VII activity (%) after i.v. administration of an $80 \mu\text{g kg}^{-1} \text{dose}^{-1}$ of NovoSeven®.

remained above 10% through 12 h postinfusion. The level dropped to approximately 1% by 24 h postinfusion and remained at this low level over the next 48–72 h before the next dose of rFVIIa was due. The estimated half-life of rFVIIa in this patient was 2.4 h, similar to previous reports [12,13].

Discussion

The FVII is a vitamin K-dependent serine protease that is synthesized in the liver. It has the shortest half-life of the coagulation factors (2.5–4 h) and is present in normal plasma at a concentration of $0.5 \mu\text{g mL}^{-1}$ [14,15]. Approximately 1% of FVII in the blood circulates in the active form (FVIIa). Exposure of FVIIa to tissue factor (TF) results in the formation of the TF:FVIIa complex, the most potent known activator of the clotting cascade. The TF:FVIIa complex activates surrounding TF:FVII complexes, FIX and FX ultimately leading to thrombin generation. Thrombin, FIXa, FXa and FXIIa can also activate FVII [14]. The minimum level of FVII required for haemostasis is not known, but levels of 10–25% of normal are generally adequate for normal haemostasis.

Recombinant FVIIa was originally introduced as a bypassing agent for the treatment of bleeding in haemophilia A and B patients with inhibitor antibodies to FVIII or FIX [16]. Its efficacy and safety has also been demonstrated in congenital FVII-deficient patients, primarily in short-term surgical prophylaxis and in the management of acute bleeding episodes such as gum bleeding, haemarthrosis and intracranial haemorrhage [7–9,17]. rFVIIa has a short half-life similar to FVII, therefore, adopted treatment regimens typically involve frequent dosing intervals every 3–6 h. In contrast to the high doses used in haemophilia inhibitor patients for its bypassing activity ($90 \mu\text{g kg}^{-1} \text{dose}^{-1}$ every 3 h), factor replacement doses in FVII-deficient patients are

significantly lower. Common doses reported for surgical prophylaxis and treatment of acute bleeding in patients with FVII deficiency range from 15 to 30 $\mu\text{g kg}^{-1}$ dose $^{-1}$ every 4–6 h [7–9].

Haemarthroses occur with a prevalence of 21–66% in patients with congenital FVII deficiency [4,5]. Recurrent joint bleeding can lead to a chronic and debilitating arthropathy that is clinically indistinguishable from patients with classic haemophilia. Numerous studies have supported the benefit of prophylactic treatment in preventing or delaying the progression of arthropathy in children with severe haemophilia [18–20]. In severe haemophilia patients with inhibitors, long-term studies of factor concentrates administered prophylactically on a regular schedule have demonstrated marked reductions in joint disease as measured both clinically and radiologically [21].

With a twice-weekly prophylactic regimen of rFVIIa infusion and regular physical therapy, our patient had an eightfold decrease in the number of bleeds. In addition, he experienced significant improvement in the mobility of his right elbow. Despite the FVII level falling to 1% by 24 h postinfusion and remaining low for 48–72 h prior to the next dose, our patient had significant clinical improvement. It may be postulated that the initial high postinfusion level of FVII was enough to generate the necessary thrombin burst required to maintain haemostasis for our patient—especially if his activities occurred within a few hours of the prophylactic dose. However, our patient did not consistently administer his dose just prior to planned physical activities and still had clinical benefit. Alternately, given that FVIIa normally circulates as just 1% of FVII, and that FVII may act as a competitive inhibitor of FVIIa for TF complex formation [22], a lower level of FVIIa in a FVII-deficient patient, may be clinically effective.

The prophylactic regimen that we used for this patient was arrived at empirically, partly based on similar clinical experiences with FVIII prophylaxis. Our goal was not to achieve a certain peak FVII value, but rather to demonstrate some degree of clinical benefit. This limited experience demonstrates that, despite rFVIIa's short half-life, a prophylactic regimen with infrequent rFVIIa dosing is both practical and beneficial, and can result in dramatic clinical improvement in FVII-deficient patients with frequent haemarthroses. Alternative treatment regimens with lower doses or less frequent dosing may have clinical effect and should be investigated. Each patient should be assessed on an individual basis

with the clinical history and needs of the patient taken into consideration. Further studies are necessary to assess optimal prophylactic dosing regimens, consequences of long-term rFVIIa therapy, and the long-term clinical outcomes of severely FVII-deficient patients on prophylaxis.

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