Haemophilia (2001), **7**, 220–223

CASE REPORT

Prophylactic treatment of severe factor X deficiency with prothrombin complex concentrate

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Summary. Factor X (FX) deficiency is an autosomal recessive trait that occurs in fewer than 1 in 500 000 people. Not surprisingly, reports of prophylactic treatment for FX deficiency are exceedingly rare. We now report our experience of the use of prophylactic therapy in a FX-deficient patient. This 18-year-old African-American male presented at the age of 4½ years with an FX level < 1%. Treatment was on demand with prothrombin complex concentrates (PCCs) given at two times the dose per kilogram of body weight for factor IX. He experienced frequent epistaxis, soft tissue bleeding and joint bleeding. The development of a target joint (right ankle) prompted the initiation of prophylactic treatment in the beginning of 1998 to the present with 30 units kg^{-1} Profilnine twice per week via a home infusion programme. If breakthrough bleeding occurred, he was instructed to infuse another dose. He was instructed that Profilnine should not be infused in more than two doses in 24 h or on more than three consecutive days. A trough level drawn 48 h post-infusion showed an FX level of 30%. In the initial 12 months with prophylactic treatment, there was no breakthrough bleeding. Subsequently, with an additional 11 months of follow-up, he has reported one bleed. He rates his quality of life improved since starting prophylactic treatment. There have been no thrombotic events. Prophylaxis with PCC for FX deficiency with adequate education and follow-up can be performed capably in the home setting with a resultant decrease in the frequency of bleeding and attendant complications.

Keywords: factor X deficiency, prophylactic treatment, prothrombin complex concentrate.

Introduction

Factor X (FX) deficiency is a rare disorder, with only 1 in 500 000 people affected [1,2]. An autosomal recessive trait on chromosome 13 can cause varying degrees of severity [3]. Homozygotes for FX deficiency can exhibit severe haemorrhagic complications. Patients with severe FX deficiency (levels less than 1%) exhibit deep tissue and joint bleeding similar to severe haemophiliacs. However, in contrast to haemophilia A and B, mucosal bleeding is also common [4]. In one series of 32 Iranian patients with FX deficiency, the most common bleeding symptom was epistaxis, occurring in 72% of patients. Menorrhagia was noted in half of the female patients of reproductive age [4].

Bleeding can be managed by fresh frozen plasma infusions or prothrombin complex concentrates (PCCs). The half-life of FX is ~40 h [2]. The minimum haemostatic level is 10–20% [2,5]. Fresh frozen plasma (FFP) infusions have been recommended for haemarthrosis and minor bleeding, while PCCs have been used for major bleeding and preparation for surgery [2]. The use of PCCs for prophylaxis in FX deficiency has not been extensively studied [6,7]. Thrombosis is a concern [8,9] and may lessen the enthusiasm of haemophilia caregivers to administer PCCs for prophylaxis. We now report the use of PCC prophylactically in a male with severe FX deficiency and recurrent epistaxis and haemarthroses.

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Accepted 17 October 2000

Case history and methods

This 18-year-old African-American male presented at the age of 4½ years with a FX level of < 1%. He had frequent epistaxis that did not respond to pressure, ice, topical thrombin or Amicar. He required packing and cautery multiple times by an ear, nose and throat specialist. He had chronic anaemia due to his frequent bleeding episodes and required red blood cell transfusion on one occasion. Iron supplements were given during his childhood. He was treated on demand for his bleeding episodes and was frequently seen 1–2 times per month for treatment. During his period of severe and frequent epistaxis, school attendance was poor.

Historically, his bleeding episodes were always treated with PCCs dosed at two times the usual dose per kilogram of body weight for factor IX (FIX), as the PCC typically used in this patient, Profilnine (Alpha Therapeutics, Los Angeles, CA, USA), contains ~50–80% of FX per unit of FIX (J. Gross, Alpha Therapeutics, personal communication, 2000). He continued with epistaxis, soft-tissue bleeding and joint bleeding. He became very active in sports and played basketball at school and for recreation. The development of a target joint in his right ankle prompted the consideration of a prophylactic treatment regimen. X-rays of the ankle joint revealed early signs of haemophiliac arthropathy. The patient was doing very well in high school and wanted to attend college. On-demand treatment would make this difficult. Prophylactic treatment was proposed. The patient was very motivated to do this and willing to be compliant with home infusion instructions. The patient was instructed to infuse with Profilnine-S/D (solvent/detergent), the PCC readily available to the haemophilia treatment centre at that time. The dose was 30 units kg^{-1} twice a week at least 3 days apart. For minor bleeding, correction to 30% was the goal. Due to the long half-life of FX it was decided that this schedule would minimize the risk of thrombosis. If the patient experienced breakthrough bleeding he was to infuse another dose when that occurred. He was instructed not to infuse Profilnine in more than two doses in 24 h or on more than 3 consecutive days. The patient was required to report any bleeding episodes that occurred and his response to the additional treatment.

Results

Pre-prophylaxis

The patient had been treated on demand from 3 to 14 times per year. As outlined in Table 1, over the years, epistaxis was the most common site of bleeding, followed by joint bleeds, and haematomas usually occurred as the result of a trauma.

On prophylaxis

The patient has been compliant about administering his prophylactic factor and attending regular follow-up to assess any potential for thrombosis. During the initial 12 months, with the prophylactic regimen described, there was no breakthrough bleeding. To date, with an additional 11 months of follow-up, he has reported one bleed that was the result of trauma. He rates his quality of life as improved since starting prophylactic treatment. He has been able to remain in school and there were no absences during the last 2 years due to bleeding. He continued to work

Table 1. Tabulation of bleeding events.

Year	Total no of bleeds	Types of bleed [% (no.)]			
		Nose	Joint	Haematomas	Prophylaxis
1987	11	100 (11)	–	–	
1988	14	86 (12)	14 (2)	–	
1989	6	89 (5)	11 (1)	–	
1990	9	27 (3)	9 (1)	64 (5)	
1991	3	33 (1)	33 (1)	33 (1)	
1992	4	75 (3)	–	25 (1)	
1993	13	47 (6)	15 (2)	38 (5)	
1994	6	47 (3)	19 (1)	34 (2)	
1995	9	56 (5)	22 (2)	22 (2)	
1996	12	66 (8)	9 (1)	25 (3)	
1997	10	50 (5)	–	50 (5)	
1998	0	–	–	–	100
1999	1	–	–	4 (1)	96
2000-YTD	0	–	–	–	–

part-time and was able to continue recreational basketball and high school track without bleeding problems. To date, there have been no thrombotic events. A trough level drawn 48 h post-infusion showed an FX level of 30% (a peak level was not obtained).

Discussion

There is one case report to our knowledge of prophylactic treatment with PCCs for FX deficiency [7]. Sandler and Gross described a child with severe FX deficiency with three episodes of intracranial haemorrhage (ICH). Consequently, the child was successfully managed with PCCs (40 U kg^{-1} Konyne, Bayer County, Clayton, USA) for prophylactic treatment. During a follow-up of 8 months, there were no thrombotic events. The child continued to grow and develop normally. There is also a case report of prophylaxis with FFP in a severe FX-deficient infant with recurrent ICH [6]. The use of a prophylactic regimen (technically, 'secondary' prophylaxis as our patient had radiographic evidence of arthropathy) in older patients with FX deficiency has not previously been reported. For severe hamophilia A and B, there is expanding support in the literature for prophylactic therapy in order to reduce the frequency and morbidity of chronic joint disease. This is based on retrospective and prospective cohort studies of primary [10–12] and secondary prophylaxis with the intent to achieve a trough > 1% [13]. Randomized studies comparing on-demand therapy to prophylactic therapy are in progress [13]. In this patient, the 30% FX level after 48 h would suggest a trough at 4 days of ~15%, well above the minimal haemostatic level. Additional FX levels were not obtained, but if indeed they were in this range, treatment in this patient could best be defined as 'continuous' rather than 'prophylaxis'. This may explain the excellent control of bleeding episodes.

Presently, the decision for prophylaxis must take into account cost considerations [14] and the risk of inhibitor development. In the case of congenital FX deficiency, inhibitor development appears to be minimal. This may be explained by the finding that, similar to FIX deficiency, the majority of FX deficiency cases arise from point mutations rather than large gene deletions [1].

Additional considerations in deciding on prophylaxis for FX deficiency must include viral safety[15] and thrombogenicity [8,9]. Regarding the latter, the risks for thrombosis associated with PCC include crush injury or large intramuscular bleed and dosing > 75 μg kg^{-1} in a 24-h period. This is probably interrelated, as such patients with extensive bleeding are usually immobilized and can be conceivably prothrombotic on that basis while the extensive bleeding may necessitate repeat PCC administration. Detection of coagulation activation (e.g. prothrombin fragment F1 + 2) after PCC administration has been suggested, particularly in these high-risk situations [16]. Additional risk factors for thrombosis are concurrent liver disease and/or the use of antifibrinolytic therapy [17]. This patient had no evidence of liver disease. The excellent control of epistaxis while on prophylaxis precluded the need for antifibrinolytic therapy.

In the International Society of Thrombosis and Hemostasis FVIII-FIX Subcommittee registry of thrombotic complications, there were no reports of thrombosis following a PCC in an FX-deficient patient [8]. This may be merely a reflection of the small number of affected individuals and the possibility that many of them have been treated with FFP rather than a PCC. Alternatively, it could be hypothesized that patients with relatively less substrate for the activity of FIXa will be at lower risk for thrombosis. Conversely, an FIX-deficient patient treated repeatedly with PCCs may have a treatment-induced supranormal elevation of FX, given its long half-life Consequently, this high level of FX could be activated by contaminating FIXa in the PCC. As such, an FX-deficient patient may be relatively less at risk from PCCs than an FIX-deficient patient.

We conclude that prophylaxis with PCCs for FX deficiency with adequate education and follow-up can be performed in the home setting with resultant decrease in the frequency of bleeding and attendant complications. A worldwide registry of FX deficiency patients undergoing prophylactic PCC therapy could prove informative in determining the optimal minimum dose and frequency, the risk for inhibitor development and the risk for thrombosis.

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