The Effect of Non-Activated Prothrombin Complex Concentrate (Proplex[®] ST) on Intraperitoneal Hematoma in a Hemophilia A Patient with a Factor VIII Inhibitor

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A 28-year-old severe hemophiliac with a factor VIII inhibitor was admitted to our hospital with a massive and serious intraperitoneal hematoma. He was a high-responder patient showing maximal serum inhibitor levels as high as 255 Bethesda Units/ml (BU/ml). He was successfully treated with "bypass therapy" using a prothrombin complex concentrate (PCC). (Internal Medicine 35: 319–322, 1996)

Key words: bypass therapy, high-responder

Introduction

Non-activated or activated prothrombin complex concentrates (PCC) are often used in hemostatic management of hemophilia A patients with a factor VIII (FVIII) inhibitor. Intraperitoneal bleeding or hematomas in hemophilia A patients are treated surgically (1, 2) and there has been no success using only PCC. We report that non-activated PCC (NA-PCC) was effective in checking an intraperitoneal hematoma of a hemophilia A patient with a FVIII inhibitor (severe type).

Case Report

The patient was a 28-year-old male with severe hemophilia A complicated with a FVIII inhibitor (high responder). The initial episode of bleeding in 1965 was successfully treated with FVIII concentrate. A FVIII inhibitor appeared in 1976, and after that he was successfully treated with "bypass therapy" using a NA-PCC. He was admitted to our hospital with complaints of abdominal fullness and pain on January 5, 1994. On admission, his blood pressure was 120/60 mmHg, pulse rate 84/min and regular, and body temperature 37°C. He had epigastrium tenderness and abdominal fullness. The initial laboratory findings showed no abnormalities of the peripheral blood cell count, biochemistry or serology, except for elevation of C-reactive protein (CRP). He had severe hemophilia A (FVIII: C<1%) with a FVIII inhibitor (7.8 BU/ml) and was positive for hepatitis C virus (HCV) and human immunodeficiency virus (HIV) (Table 1). On the third hospital day, an abdominal

computerized tomography (CT) scan showed a massive and serious intraperitoneal hematoma (8×8 cm) below the stomach and hemorrhage in rectovesical excavation (Fig. 1A, B) with anemia (Hb 7.8 g/dl) and fever (37–38°C). Immediately, we started administration of piperacillin (4 g/day for 6 days) and intravenous infusion of NA-PCC (Proplex[®] ST, Baxter, Japan) (Fig. 2). We used NA-PCC 7–12 vials per day for 6 days (day 2 and day 3, we used it twice every 12 hours per day, nominal value of 500 units per vial). After treatment, the fever and abdominal fullness resolved, the CRP and hemoglobin were normalized, and the activated partial thromboplastin time (APTT) and the FVIII inhibitor were decreased (Fig. 2). After discharge, NA-PCC was effective for his joint bleeding, but laboratory improvement was not noted (APTT >60 s). Abdominal MRI showed absorption of the intraperitoneal hematoma 6 months after NA-PCC treatment (Fig. 3).

Discussion

FVIII concentrates are used for the management of bleeding in hemophilia A patients. FVIII inhibitors (antibodies to FVIII) have emerged as a major problem (3). Antibodies develop in about 3 to 20 percent of patients with hemophilia A (4). These antibodies are of the IgG class (5). Various methods are currently used to treat bleeding episodes in these patients. Treatment with high doses of FVIII to neutralize the inhibitor can be used in low titer patients (6). Treatment with immunosuppressive drugs has not proved beneficial (7, 8). The inhibitor titer can be decreased by double filtration plasmapheresis which

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Table 1. Laboratory Data on Admission (Jan. 5, 1994)

Hematology			
Red blood cell	491×10 ⁴ /μl	Blood urea nitrogen	3.0 mg/dl
Hemoglobin	15.0 g/dl	Cr	0.5 mg/dl
Hematocrit	41.7%	Uric acid	3.5 mg/dl
Platelet	26.1×10 ⁴ /μl	Na	140 mEq/l
White blood cell	8,000/μl	K	3.6 mEq/l
Neutrocyte	71.5%	Cl	98 mEq/l
Eosinophil	0.5%	Creatine phosphokinase	58 U/l
Basophil	0.2%	Amylase	33 U/l
Monocyte	7.7%	Total protein	7.8 g/dl
Lymphocyte	20.1%	Albumin	3.6 g/dl
		Fasting blood sugar	89 mg/dl
		Total cholesterol	140 mg/dl
		C-reactive protein	2.20 mg/dl
Coagulation		Serology	
Prothrombin time	196%	IgG	2,714 mg/dl
Activated partial thromboplastin time	88.4 s	IgA	577 mg/dl
Fibrinogen (Fbg)	348 ng/ml	IgM	319 mg/dl
VIII:C	1%↓	C3	52 mg/dl
VIII:Inh	7.80 BU/ml	C4	30 mg/dl
Fibrin/fibrinogen degradation product	72 ng/ml	HBsAg(-)	
Thrombin antithrombin III complex (TAT)	11.8 μg/l	HBsAb(+)	
Plasma α ₂ -plasmin inhibitor complex (PIC)	1.4 μg/l	HCV(+)	
		HIV(+)	
Blood chemistry			
Aspartate aminotransferase	38 IU/l		
Alanine aminotransferase	39 IU/l		
Cholinesterase	3,168 U/l		
Total bilirubin	2.2 mg/dl		
Direct bilirubin	0.7 mg/dl		
Alkaline phosphatase	169 U/l		
γ-Glutamyl transpeptidase	79 U/l		
Lactate dehydrogenase	885 U/l

A **B****Figure 1. Whole CT scan revealed a huge intraperitoneal hematoma (A) and hemorrhage in rectovesical excavation (B).**

Figure 2. Outline of the clinical course. Piperacillin (PIPC). Fbg: fibrinogen, FDP: fibrin/fibrinogen degradation products.

Figure 3. Abdominal MRI after 6 months of PCC treatment in July 1994.

may be useful in acute severe bleeding or before surgery (9).

A different approach to the treatment of bleeding episodes in patients with antibodies is the use of PCC. The original observation that these concentrates may stop bleeding in patients with hemophilia A who have an antibody has been followed by a number of case reports confirming these results (10–12). NA-PCC (Proplex® ST), used as a hemostatic for bleeding in hemophilia B patients, contains factors II, VII, IX and X. Following a report by Fekete et al, this concentrate has been used as a hemostatic in patients with FVIII inhibitors (13).

In this case, we used Proplex® ST because our patient, a high responder who presented with an inhibitor titer of 7.80 BU/ml on admission, did not need urgent hemostatic treatment although an intraperitoneal hematoma was observed. Treatment with FVIII concentrates can be used in this case when low titers are presented, but since replacement therapy had no effect on several of his earlier episodes in the presence of high titers, we used NA-PCC for this episode. A NA-PCC was also chosen since it is much less expensive than the activated form. Major signs in hemophilia A patients with a FVIII inhibitor include bleeding in joints, muscles, gums (3, 14) and occasionally include intracranial hemorrhage (15). Although intraperitoneal bleeding or hematomas in hemophilia A patients with a FVIII inhibitor have been treated surgically, there previously was no report of a NA-PCC being effective for these cases. Treatment with a NA-PCC allowed the present case to avoid surgical treatment, which suggests that this concentrate is an effective hemostatic agent in high responder cases. While an excessive dose of PCC can cause thromboembolic events, such as DIC (16, 17), we observed no side effects in our patient. Recently, there have been many reports of using recombinant factor VIIa for hemophilia A patients with a FVIII inhibitor (18, 19) and we would like to use this hemostatic for more severe hemorrhages in patients with a FVIII inhibitor in the future. We conclude that PCC should be used more frequently for severe bleeding in hemophilia A patients with a FVIII inhibitor.

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