Use of Prothrombin Complex Concentrates in the Treatment of a Hemophilic Patient With an Inhibitor of Factor VIII

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The course and treatment of a life-threatening hemorrhagic episode in a patient with hemophilia A whose plasma contained a high concentration of an inhibitor of factor VIII activity is presented. The inhibitor of factor VIII was localized to the most anodal fractions of immunoglobulin G on electrophoresis, and was thus presumed to be an antibody directed against factor VIII. No therapeutic benefit occurred with infusions of massive amounts of fresh blood and factor VIII concentrates, or with a brief course of immunosuppressive therapy. Administration of standard and activated prothrombin complex concentrates resulted in reduction of the partial thromboplastin time to almost normal values and control of hemorrhage. Eight months later, another hemorrhagic episode occurred. Although a higher titer of inhibitor of factor VIII activity was still present in the patient's plasma, a beneficial therapeutic response was again achieved with standard prothrombin complex infusions.

INTRODUCTION

Recent studies indicate that inhibitors of factor VIII activity occur in approximately 7% of patients with hemophilia A. Inhibitors also may occur spontaneously in nonhemophilic individuals, particularly in association with autoimmune diseases, the postpartum state, and drug reactions. Control of hemorrhage in the presence of an inhibitor of factor VIII presents a therapeutic dilemma. Therapy has only rarely altered the natural course of a hemorrhagic episode, despite massive infusions of fresh frozen plasma, human or nonhuman factor VIII concentrates, exchange transfusions, or immunosuppressive drugs. Recently, infusions of factor IX concentrates, i.e., concentrates of standard and “activated” factors that comprise the prothrombin complex, have been used to control bleeding in hemophilia A and nonhemophilic individuals whose plasmas contain inhibitors of factor VIII.

This report describes our experience with the use of prothrombin complex concentrates in the successful treatment of two separate hemorrhagic episodes in a patient with hemophilia A who had a high titer of an inhibitor of factor VIII.
MATERIALS AND METHODS

The partial thromboplastin time was measured by the method of Langdell et al., using cephaloplastin (Dade Reagents) as a platelet substitute. Factor VIII activity was measured using a technique based on the partial thromboplastin time. Factor VIII-deficient substrate was obtained from patients with factor VIII deficiency.

The titers of the inhibitor of factor VIII activity were measured by incubation of equal volumes of serial dilutions of the patient’s plasma with normal plasma for 1 hr at 37°C, and then assay of residual factor VIII activity, by the technique of Hardisty and MacPherson, using naturally deficient substrate. Normal plasma, incubated with barbital buffer (pH 7.35) or factor VIII-deficient substrate, served as controls to determine significant decreases in factor VIII activity during the incubation period. The titer of inhibitor was expressed as the greatest dilution of plasma from the patient that resulted in residual factor VIII activity less than the control incubations.

Cellulose acetate electrophoresis was performed with a Microzone apparatus (Beckman Instruments, Palo Alto, Calif.). Monospecific antisera to immunoglobulins G, A, M, and D and to κ and λ light chains were prepared in our laboratory and utilized in immunoelectrophoretic analyses. Zone (block) electrophoresis on polyvinyl chloride was performed as described.

CASE REPORT

A 33-yr-old white male with hemophilia A was referred on April 8, 1974 because of intra-abdominal, joint, and urinary tract hemorrhage. Since age 3 he had received transfusions of fresh blood or plasma several times yearly to control hemarthroses. The severity and frequency of spontaneous bleeding into joints and soft tissues increased markedly during the year prior to admission. The patient received 30-40 units of blood and monthly infusions of cryoprecipitate during this period. Ten days prior to admission, the patient developed acute pain and swelling in the left groin and lower abdomen; within 3 hr his abdomen became markedly distended. He was admitted to another hospital with a diagnosis of massive intra-abdominal hemorrhage. Because of sudden abdominal distension and diaphragmatic compression, an attempt was made to drain the blood from the peritoneal cavity through a stab wound. Dyspnea was temporarily relieved; however, the patient continued to bleed from the abdominal stab wound and required over 40 units of blood to maintain a hemoglobin concentration above 10 g/dl. Treatment with cryoprecipitate and approximately 2400 units of factor VIII concentrate (factor VIII, Hemophil, Hyland, Costa Mesa, Calif.) failed to control the bleeding, and he was referred for further evaluation and treatment.

Upon admission, the patient was jaundiced and had labored, rapid respirations. There was marked abdominal distension with tightness extending laterally into the flanks, inguinal region, scrotum, and thighs. Fresh blood was oozing from the abdominal stab wound. Initial laboratory results were as follows: hemoglobin, 9.4 g/dl; hematocrit, 0.28; white blood cells, 21.3 x 10⁹/liter; platelets, 232 x 10⁹/liter; prothrombin time (PT), 11.8 sec (control 10.8); partial thromboplastin time (PTT), 72.9 sec (control 30.3); factor VIII level, 1%; bleeding time (Ivy), 6 min; plasma fibrinogen, 4.5 g/liter; serum bilirubin > 10 mg/100 ml. The concentration of serum gamma globulins, determined by cellulose acetate electrophoresis and densitometry, was 1.2 g/dl (normal, 1.0 ± 0.2 g/dl). No monoclonal (M-protein) abnormality was apparent. Immunoelectrophoretic examination of a serum specimen with antisera specific for immunoglobulins G, A, M, and D, and for κ and λ light chains revealed a slight polyclonal increase in immunoglobulin G (IgG). An x-ray film of the abdomen showed a huge mass occupying almost the entire abdomen and displacing the entire large bowel gas pattern to the right.

The patient was treated with fresh whole blood transfusions, and approximately 2080 units of factor VIII concentrate (Hemophil) were infused during a 12-hr period. No therapeutic response was evident after 48 hr and factor VIII activity was less than 1% of normal, suggesting that the patient’s plasma contained an inhibitor of factor VIII. This postulate was confirmed by the observation that factor VIII activity in normal plasma was undetectable after incubation with the patient’s plasma; an effect was demonstrable with samples of the patient’s plasma that had been diluted 10,000-fold.

To determine the nature of the inhibitor of factor VIII, we fractionated a 5-ml specimen of the patient’s plasma by zone electrophoresis on a polyvinylchloride block. Eluates from 12 consecutive fractions were dialyzed extensively against distilled water and lyophilized. Each fraction was reconstituted in barbital buffer, tested at an equivalent protein concentration for factor VIII.
inhibitory activity, and analyzed for immunoglobulin content. The anticoagulant activity was localized primarily to the most anodal-migrating IgG-containing fractions. The IgG in these two fractions reacted with both anti-κ and anti-λ light chain antisera.

In an attempt to neutralize and overcome the effect of the inhibitor of factor VIII, the amount of factor VIII concentrate was increased on the third hospital day to 4160 units every 4 hr. Factor VIII activity remained less than 1%, the PTT increased to 150 sec, and the plasma fibrinogen concentration to 15.9 g/liter. Prednisone, 100 mg daily, was given orally for 3 days, and 500 mg of cyclophosphamide were given intravenously. However, the patient's condition deteriorated further. He began to have gross hematuria and febrile reactions to the blood transfusions. His blood type was A, RH(D) positive, and an increasing titer of anti-A isohemagglutinin was detected; this was attributed to the presence of anti-A in the factor VIII concentrates, and type O, RH(D) negative blood was used subsequently for transfusions.

On the ninth hospital day, infusions of factor VIII concentrate were discontinued, and with the informed consent of the patient, prothrombin complex therapy was begun: 2600 units of standard

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Fig. 1. Effects of transfusions of prothrombin complex and blood on the patient's plasma partial thromboplastin time and hemoglobin concentration, respectively. Open bar, Proplex (Hyland); closed bar, "Auto" factor IX (Hyland); striped bar, Konyne (Cutter). Proplex, "Auto" factor IX, and Konyne are concentrates of factors II, VII, IX, and X. The normal range of the partial thromboplastin time is indicated by the hatched bar.
prothrombin complex (Proplex, Hyland) were infused during a 10-min period. This therapy resulted in reduction of the PTT from 152 to 83 sec (Fig. 1). Two hours later, 4800 units of activated prothrombin complex concentrate (“Auto” Factor IX, Hyland) were given, and then infusions of the standard prothrombin complex concentrate (Proplex), 3120 units every 12 hr for 36 hr, were resumed. An additional 5400 units of activated prothrombin complex were administered on the 12th, 13th, and 14th hospital days. Infusions of standard prothrombin complex concentrate were resumed at the previous dosage (Fig. 1).

The decrease in the PTT that occurred after infusions of the standard and “activated” forms of prothrombin complex was associated with marked clinical improvement, as manifested by reduction in bleeding, decrease in transfusion requirements, and return of serum bilirubin concentration to normal. Persistent oozing of blood from the abdominal stab wound required suture ligation of a small arterial bleeder; cystoscopy was performed because of continued gross hematuria, and a small arterial bleeder on the bladder wall was fulgurated and the blood clots evacuated. After complete hemostasis was achieved on the 18th hospital day, 2600 units of prothrombin complex were infused every 12 hr for an additional 3 days; treatment was then discontinued (Fig. 1).

The PTT and PT were determined 1 hr prior to and after the prothrombin complex infusions. After the initial marked reduction in PTT, the PTT and PT were reduced approximately 10 sec and 2 sec postinfusion respectively, and returned to preinfusion values after 12 hr. The factor VIII activity in the patient’s plasma remained at less than 1%, and the titer of the inhibitor of factor VIII remained unchanged. The plasma fibrinogen concentrations had returned to normal levels within 3 days after discontinuing the infusions of factor VIII concentrates. No adverse reactions to the prothrombin complex infusions occurred.

After discharge from the hospital in May 1974, the patient was seen in the clinic at regular intervals for 15 mo, and the intra-abdominal hematoma had completely reabsorbed. The serum gamma globulin concentration, which had increased to 2.1 g/100 ml from April to May 1974, progressively decreased to normal levels. The titer of inhibitor of factor VIII, which had increased from 1:10,000 to 1:100,000 in June 1974, fell again to 1:10,000 from November 1974 to February 1975, and to 1:100 in August 1975. During this interval, there was only one hemorrhagic episode (a hemarthrosis in January 1975) which required treatment. Infusions of 1200 units of standard prothrombin complex (Proplex) every 12 hr for 3 days resulted in reduction of the PTT from 130 to 60 sec and promptly controlled the hemorrhage.

DISCUSSION

The presence of inhibitors of factor VIII should be suspected in patients with hemophilia A who continue to hemorrhage, or in whom an increase in plasma factor VIII activity does not occur after adequate infusions of factor VIII-containing materials. The diagnosis of an inhibitor of factor VIII is established by the demonstration that the factor VIII activity in normal plasma is neutralized by addition of the patient’s plasma.

Control of hemorrhage in a patient whose plasma contains an inhibitor of factor VIII presents a major therapeutic challenge. A large amount of factor VIII concentrate, sufficient to neutralize the inhibitor, may be effective, especially if the concentration of inhibitor is low. However, factor VIII-containing infusions may result in a further increase in inhibitor levels and an even poorer response to therapy. The extreme costliness of ineffective therapy should be noted (in our patient, approximately $65,000). Moreover, other substances in factor VIII preparations may introduce additional complications, e.g., serum hepatitis, hyperfibrinogenemia, isohemagglutinins, etc. Anti-A isohemagglutinins present in the factor VIII concentrates made it difficult to transfuse our patient whose blood group was A; in addition, the plasma fibrinogen rose to over 15 g/liter.

Inhibitors of factor VIII have been shown to be antibodies, most frequently of the IgG, and rarely of the IgM, class. The homogeneity of these anti-
bodies has been demonstrated electrophoretically and immunochemically. Most commonly, the inhibitor has been localized exclusively to the anodally-migrating portion of IgG, an electrophoretic mobility characteristic of the rare IgG4 subclass. Furthermore, neutralization and immunoglobulin depletion studies have indicated that most inhibitors of factor VIII are monoclonal immunoglobulins, usually possessing gamma 4 heavy chains and \(\kappa\) light chains (IgG4\(\kappa\)). Our patient had a slight polyclonal increase in IgG; and the major inhibitor of factor VIII activity was confined to the most anodal IgG-containing fractions. Although these fractions reacted with both anti-\(\kappa\) and anti-\(\lambda\) light chain antisera, in the absence of additional immunoochemical analyses, it is impossible to determine whether this antibody was monoclonal or polyclonal in nature. Both Shulman and Hirshman and Poon et al. have reported that inhibitors of factor VIII may be polyclonal.

Since inhibitors of factor VIII apparently are antibodies, various immunosuppressive drugs such as cyclophosphamide, methotrexate, 6-mercaptopurine, or prednisone have been administered. However, the effectiveness of these agents is questionable and, even when successful, they do not alter inhibitor levels rapidly enough to treat acute hemorrhagic emergencies. The brief course of immunosuppressive therapy given our patient did not apparently affect the course of his illness.

Breen and Tullis reported a beneficial clinical and laboratory response in a patient with hemophilia A whom they treated with infusions of a concentrate of the prothrombin complex (factors II, VII, IX, and X), and attributed control of hemorrhage to “activated surface factor” in the prothrombin complex. Abildgaard et al. achieved similar results with Konyne (Cutter). Analyses of some preparations of the prothrombin complex have revealed the presence of activated forms of factor IX and X (IX\(_a\) and X\(_a\)). and recently a prothrombin complex containing relatively more activated factors IX and X has been prepared (“Auto” Factor IX concentrate, Hyland). Fekete and co-workers, Kurczynski and Penner, and Sultan et al. have reported that “activated” prothrombin complex has controlled hemorrhage in patients whose plasma contained inhibitors of factor VIII.

We found that the administration of standard and “activated” prothrombin complex infusions to our patient who has an inhibitor of factor VIII shortened the PTT and resulted in adequate hemostasis on two occasions. The potential hazards of prothrombin complex therapy have been noted, especially thromboembolic complications and hepatitis. However, no adverse reactions occurred. Lane et al. recently reported that no evidence of intravascular coagulopathy or pulmonary embolism was observed in 72 patients who had received a concentrate of factors II, IX, and X. Nevertheless, because of limited data concerning the use of prothrombin complex concentrates in patients with high titers of inhibitors of factor VIII, this form of treatment should be considered experimental and reserved for patients with serious and refractory hemorrhagic episodes.

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