Treatment of a High Titer Anti-Factor-VIII Antibody by Continuous Factor VIII Administration: Report of a Case

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Daily administration of large doses of factor VIII concentrate in a hemophiliac with a high titer factor VIII inhibitor resulted in marked reduction in the titer and response of the inhibitor to factor VIII administration and made possible eradication of the inhibitor to factor VIII administration and made possible persistent factor VIII recovery. Studies performed during the course of treatment indicated that the reduction in the inhibitor was the result of specific tolerance to factor VIII.

Inhibitors to factor VIII develop in approximately 15% of patients with hemophilia with an incidence of approximately 8 per 1,000 patient-years of observation. Clinically, these can be divided into high response inhibitors, which exhibit an anamnestic response after exposure to factor VIII, and low response inhibitors, which do not exhibit significant anamnestic response. Because of their neutralizing activity, high response inhibitors severely compromise the effectiveness of factor VIII replacement for bleeding episodes.

The recent development of control-activated factor IX concentrates and safer animal factor VIII concentrates has provided new approaches to the treatment of bleeding in hemophiliac patients with high responding inhibitors to factor VIII. While these and other modalities have been of unquestioned benefit to some patients, they may not be uniformly efficacious, and they do not solve the basic problem—the inhibitor itself. Treatment methods aimed at eradicating the inhibitor, like immunosuppressive therapy, have been described in the past, but are effective in only a small number of patients. Recently, Brackmann and co-workers from the Bonn Hemophilia Center have reported the use of long-term high-dose factor VIII replacement together with concurrent administration of activated factor IX concentrate in a large number of patients with both high and low responding factor VIII inhibitors. Of 17 patients with high responding inhibitors, 15 have completed therapy and all but one of these patients has had complete disappearance of their inhibitor as judged by postinfusion fall-off and recovery of factor VIII. Eradication of the inhibitor occurred within an average of 25 mo from the initiation of treatment. Subsequently, other investigators have reported similar treatment methods with variable success.

Although many patients treated by the Bonn protocol remain on prophylaxis with factor VIII, at least three patients have been off maintenance factor VIII for periods of time up to 5 yr without reappearance of the inhibitor. We report an additional patient treated with a continuous high-dose factor VIII replacement regimen, modified after that of Brackmann and Egli.

CASE REPORT

The patient (E. J., #43-91-38) is a 41-yr-old white male with severe classical hemophilia. As a child, he had numerous joint and soft tissue bleeds, resulting in severe hemophilic arthropathy. In 1954, at the age of 16, after an estimated 50-75 treatment-days of factor VIII replacement, he was found to have a factor VIII inhibitor and was unresponsive to factor VIII therapy. He was first seen at the University of North Carolina Comprehensive Hemophilia Diagnostic and Treatment Center in 1979. Examination then revealed severe flexion contractures of the elbows, knees, and ankles, with range of motion measurements as follows: right elbow, 30°-105°; left elbow, 50°-120°; right knee, 25°-95°; left knee, 15°-107°; right ankle, 15° dorsiflexion; 35° plantar flexion; left ankle, 0° dorsiflexion, 35° plantar flexion. There was valgus deformity of both knees and a Volkmann's contracture of the right hand. Radiologically, there were grade V changes of the knees and left elbow. His factor VIII inhibitor titer was 32 Bethesda units. Liver function tests were aspartate aminotransferase (AST) 17 U, alanine aminotransferase (ALT) 15 U, alkaline phosphatase 52 U, and bilirubin 0.3 mg/dl. Serologic studies revealed a positive anti-HBs and negative HBsAg. The blood group type was 0°.

From June 1979 until December 1979, he was treated on several occasions with nonactivated factor IX concentrates for joint bleeds, but these were without obvious effect. In April 1980, after careful financial planning and discussion with the patient, he was admitted for treatment of his inhibitor using the modified protocol described below.

MATERIALS AND METHODS

Factor VIII concentrates (Hemofil, Hyland Laboratories, Glendale, CA) were low isoagglutinin preparations. Eight lots of activated factor IX concentrates (Hemofil, Hyland Laboratories, Glendale, CA) were used for treatment of his inhibitor using the modified protocol described below.
Clinical course showing inhibitor titer (●) and factor VIII recovery (●). Blood for inhibitor titer determination was obtained prior to the morning infusion of factor VIII. Blood for factor VIII recovery was obtained 30 min after the morning infusion of factor VIII. Changes in factor VIII lots are indicated (✓). Bleeds that occurred during the treatment course are indicated by arrows. The first bleed was treated with factor IX concentrate (●). The T½ of infused factor VIII is indicated in parentheses above the 30-min postinfusion factor VIII level. Double arrows indicate changes in the dose of factor VIII concentrate during the tapering process.

Laboratory Studies

Factor VIII coagulant activity (VIII:C) was assayed by a one-stage assay16 using factor-VIII-deficient plasma as substrate. Factor VIII inhibitor was measured by the Bethesda assay.17 Complement component (C3 and C4) and immunoglobulin (IgG, IgA, and IgM) levels were measured by kinetic rate nephelometry using specific antisera to C3, C4, and the immunoglobulin classes.

Inhibitor Treatment

The protocol followed for treatment of the inhibitor was similar to that described from the Bonn Hemophilia Center by Brackmann et al.18 Their patients were initially treated with 75–100 U of factor VIII/kg and 40–60 U of activated factor IX concentrate/kg twice daily until the inhibitor titer reached 0.5 Oxford units.† The patients were then changed to a regimen in which treatment in the same doses was alternated between twice a day and once a day. This was continued until the inhibitor titer reached zero. Administration of factor VIII was then reduced to once a day and was continued until the recovery and half-life of the infused factor VIII was normal.

In the present case, two changes were made in the Bonn protocol. First, activated factor IX concentrates were not administered during the treatment. Second, phase II of the Bonn protocol was eliminated. Thus, the patient was started on 100 U of factor VIII/kg twice daily at 900 and 1600 hr. Treatment twice daily was continued until the inhibitor titer was 0, then changed to 100 U of factor VIII/kg once daily. At the conclusion of his treatment, the dose of factor VIII was tapered according to the following schedule: 80 U/kg once a day for 1 mo, 60 U/kg once a day for 1 mo, 40 U/kg once a day for 1 mo, 20 U/kg once a day for 1 mo, 20 U/kg every other day for 2 wk, 20 U/kg every third day for 2 wk, then to demand treatment.

RESULTS

Clinical Course

On 6,000 U (100 U/kg) of factor VIII twice a day, there was a rapid rise in the inhibitor titer from a pretreatment value of 30 Bethesda units to a peak value of 750 Bethesda units 3 wk after initiation of therapy (Fig. 1). After approximately 11 wk of treatment, and following a decline in his titer to 150 Bethesda units, the patient experienced a spontaneous bleed into the right elbow and received 4,500 U (75 U/kg) of Konyne. The following week, perhaps as a result of increased administration of immunoreactive
factor VIII from the VIII:CAg in the Konyne, the inhibitor titer had increased to 998 Bethesda units (Fig. 1). Thereafter, there was a progressive reduction in the inhibitor titer. Recovery of factor VIII:C activity 30 min after infusion was first demonstrated 27 wk after therapy and was highly variable with no apparent relationship to the corresponding inhibitor titer obtained preceding the infusion. By 42 wk, the inhibitor was undetectable, although recovery of factor VIII at 30 min was only 32% of predicted and the half-life of infused factor VIII was 3 hr.

After 44 wk of treatment, a total knee replacement was undertaken under coverage with continuous infusion of factor VIII to maintain a factor VIII level of at least 75%. An infusion rate of 688 U/hr was initially required to maintain this level. Except for a transient increase in factor VIII requirement on days 9–15 to as high as 2,000 U/hr, the postoperative course was uncomplicated and without any postoperative bleeding.

On the 24th postoperative day, continuous infusion factor VIII was stopped and intermittent therapy with 6,000 U once a day was started. The inhibitor at the resumption of intermittent therapy had increased to 3.8 Bethesda units. With treatment once a day, the inhibitor fell and was again undetectable at 68 wk after initiation of therapy. The recovery of factor VIII at 30 min was 37% of the predicted value and the half-life of infused factor VIII was 12.8 hr.

At 72 wk, replacement of the right knee and left elbow was undertaken under coverage with factor VIII as for the previous operation, except that factor VIII was given at 540 U/hr. No increase in factor VIII requirement was observed during this operation.

Postoperatively, the inhibitor titer was again increased at 1.5 Bethesda units, although the half-life of factor VIII was 11.9 hr. He was maintained on 6,000 U of factor VIII once daily until 90 wk after initiation of treatment, when the dose of factor VIII began to be tapered by 1,000 U/mo. Six months later, on a daily dose of 1,000 U of factor VIII, the inhibitor was undetectable. His dose of factor VIII was then changed to every other day for 2 wk, every third day for 2 wk, and then stopped. One month after regular treatment was stopped and 2 wk after a demand treatment, the inhibitor titer was 1.3 Bethesda units and a fall-off study showed a factor VIII recovery of 37% and a half-life of 4.2 hr.

At no time during the treatment was there clinical evidence of immune complex disease, renal impairment, or microscopic hematuria. Complement C3 levels fell during the first 2 wk of therapy from 146 to 98 mg/dl, while C4 levels fell from 39 to 26 mg/dl, but they returned to normal (Fig. 2). Complement levels were again reduced at the end of his treatment course. Serum levels of immunoglobulins G, A, and M were obtained biweekly and remained within normal limits throughout the study. Total white counts and absolute lymphocyte counts were within normal limits during the study. Routine ABO blood typing performed 2 mo after the cessation of factor VIII infusion revealed anti-A and anti-B antibodies in the patient's serum that were quantitatively similar to normal type O controls. A skin test with mumps antigen was positive at the end of treatment.

**DISCUSSION**

The long-term administration of factor VIII resulted in marked reduction in the titer of the inhibitor in a hemophiliac who was previously shown to have a high titer inhibitor and to exhibit anamnestic responses to factor VIII administration. Although the inhibitor did not disappear, the patient was able to achieve therapeutic levels of factor VIII and safely undergo major surgical procedures.

Several changes were made in the Bonn protocol, which might have contributed to the failure of the inhibitor to disappear in the present case. First, activated factor IX concentrates were not used. Factor IX concentrates are known to contain significant amounts of factor VIII:CAg, although their factor VIII:C content is small. Nevertheless, while the administration of this functional material might somehow participate in the immunologic changes that occur during...
treatment and may play an important role in providing hemostasis during treatment, it is unlikely that omission of this concentrate was responsible, as several patients have been successfully treated without them. Second, phase two of the Bonn protocol was deleted and phase three was interrupted on two occasions for surgery. On both occasions, the inhibitor titer was undetectable at the start of surgery, but the factor VIII recovery and/or half-life were abnormal. Also, on both occasions, the inhibitor titer postsurgery was increased. The third phase of the protocol appears to be a critical one. Alterations in the dose of factor VIII during this phase may result in increases in the inhibitor titer. Premature cessation of therapy may cause a reappearance of the inhibitor or failure of the inhibitor to disappear as determined by fall-off studies. The decision in this case to proceed with surgery prior to completion of the final phase was based entirely on financial considerations and may have been responsible for the failure of the inhibitor to disappear.

The reduction in the level of the inhibitor during treatment was documented functionally and appears to represent a decreased concentration of factor-VIII-specific antibody. The levels of total immunoglobulins and immunoglobulin G remained unchanged during the treatment, and there was no evidence that the reduction in the inhibitor was the result of the creation of a state of general immunologic tolerance since posttreatment antibody levels against blood group antigens were detectable. Thus, the patient appeared to develop specific tolerance to factor VIII. The patients reported by Brackmann and Gormsen, who remain responsive to factor VIII long after treatment is stopped, suggest that this is indeed tolerance and not desensitization.

Because of the extreme cost of the prolonged treatment with factor VIII, the Bonn method of therapy has been controversial. The present modification, in which the use of activated factor IX concentrates was eliminated, is less costly than the original Bonn method, but the cost was still considerable. A total of 5,695,230 U of factor VIII were used over the 26-mo course. At an average nationwide cost of $0.11/U, the total cost for factor VIII was $626,500. Nevertheless, if one considers the two operative procedures and their cost using activated factor IX concentrates, with 20 days of coverage for each operation and 100 U/kg twice a day, it would take 480,000 U which, at an average worldwide cost of $1.10/U would be $528,000, which is close to the cost of factor VIII. The advantage of the Bonn protocol over the use of activated factor IX concentrates is that the inhibitor can be eradicated or markedly decreased, as was the case in our patient. The disadvantage is the extremely large commitment of time it requires from both the patient and physician, the prolonged hospitalization required in this case, and the delay required for surgery. It should also be emphasized that because of the cost and the limitations on the availability of factor VIII concentrate worldwide, this form of treatment can only be considered for a very limited number of patients in this country. Perhaps with a better understanding of the immunologic mechanisms involved in eradicating the inhibitor, schedules that utilize less factor VIII can be devised and make this type of treatment more readily available to patients with inhibitors.

Finally, this method of treatment may have implications for the treatment of other immunologic disorders. If specific tolerance to factor VIII is indeed achieved, this treatment method may lead to a better understanding of the mechanisms by which tolerance to other antigens might be achieved in humans.

NOTE ADDED IN PROOF

Subsequent to submission of this manuscript, the patient died unexpectedly at home with no antecedent illness. At autopsy, there was no evidence of intracranial or other hemorrhage, and there was no evidence of classical acquired immunodeficiency syndrome as defined by identifiable opportunistic infection. Toxicology studies revealed nontoxic plasma levels of diazepam, nordiazepam, and ethanol. Oxycodone, pentazocine, dextromethorphan, and acetaminophen, all prescribed medications, were present in urine.

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