The Use of Factor Eight Inhibitor By-Passing Activity (FEIBA Immuno) Product for Treatment of Bleeding Episodes in Hemophiliacs With Inhibitors

By Margaret W. Hilgartner, Genell L. Knatterud, and the FEIBA Study Group

FEIBA (factor eight inhibitor by-passing activity) Immuno was used to achieve hemostasis in 46 patients with factor VIII inhibitors with titers greater than 4 Bethesda units, and 3 patients with factor IX inhibitors. One-hundred and sixty-five bleeding episodes were treated with 50-70 U/kg; 102 of these episodes occurred in joints, 20 in mucous membranes, 33 muscle and soft tissue, and 10 were emergency episodes including 3 central nervous system and 4 surgical procedures. Ninety-three percent of the bleeding episodes were controlled, while 7% were not controlled: 36% were controlled by one infusion in 12 hr, another 42% with 1 or more infusions in 36 hrs, and an additional 14% were controlled in more than 36 hr. There were no serious side effects, and while the inhibitor titer rose in 10 of the patients, the product continued to be efficacious.

The term inhibitor has long been used to describe an antibody that inactivates transfused clotting factor in a patient with a congenital clotting factor deficiency. The development of an inhibitor in a patient with hemophilia represents a major problem in management of bleeding episodes. In the past, patients with inhibitors have been treated with bed rest and ice alone or with large doses of clotting factor. They have been subjected to plasmapheresis or exchange transfusion to decrease the inhibitor titer to allow for a more effective binding of the inhibitor with clotting factor to achieve hemostatic control. Animal factor VIII has been used with short-term success. However, the anamnestic response that follows any clotting factor treatment often produces an increase in inhibitor level that makes the control of subsequent bleeding episodes more difficult. Immunosuppressive therapy, although useful for the patient with an acquired inhibitor, has not been successful in controlling inhibitors in congenitally deficient patients.

Prothrombin complex concentrates (PCC) were found effective for control of bleeding in patients with factor VIII inhibitors, but produced thromboembolic complications in hemostatically normal patients and patients with congenital factor deficiencies of the prothrombin complex. As the products were improved and the risk of these complications was reduced, the PCC became less effective in inhibitor patients, although a small portion of their beneficial effect remained. Efforts were subsequently made to produce activated prothrombin complex concentrates that would be safe and effective in the control of bleeding episodes in inhibitor patients. One such product, FEIBA Immuno, was prepared from normal human plasma by Oesterreichisches Institut Fuer Haemoderivate and contains a property that appears to by-pass factor VIII in hemostasis.

FEIBA has been used extensively in Europe since 1974 to treat bleeding episodes in patients with inhibitors who have few available therapy alternatives. Since approximately 14% of patients with factor VIII deficiency in the United States have developed inhibitors to factor VIII, it has become necessary to investigate effective and safe methods for the treatment of bleeding episodes in these patients. Therefore, the goal of this Familiarization Study was twofold: (1) to demonstrate in the U.S. the efficacy and safety of FEIBA Immuno for the treatment of bleeding episodes in hemophilia patients with inhibitors, and (2) to enable investigators in the U.S. to gain experience and become familiar with the use of FEIBA for the management of serious bleeding episodes in these patients.
Nine hemophilia treatment centers, scattered throughout the United States, participated in this study. Each center was responsible for recruiting, examining, and entering patients into the study for treatment. The data generated by these clinical centers were collected, processed, stored, and analyzed by the Coordinating Center at the Maryland Medical Research Institute in Baltimore, Md. No attempt was made to compare efficacy with a control product or with another activated prothrombin complex concentrate for this initial familiarization study.

**STUDY DESIGN**

Patients known to have inhibitors to factor VIII were recruited into the study at the time of routine examination, during which baseline joint function and general medical status were assessed. Patients with inhibitors to factor IX and nonhemophilic patients with acquired factor VIII inhibitors were not originally part of the study but were added at a later date. Laboratory data collected included complete blood count, serum glutamic pyruvate transaminase (SGPT), hepatitis B surface antigen and antibody status (HB,Ag, HB,Ab), and current inhibitor titer. Hemophilic patients over 4 yr of age who had a history of an inhibitor titer of 4 Bethesda units or more, without acute or severe chronic liver disease (as assessed by an SGPT of greater than twice normal), were eligible. Patients were considered ineligible for the study if they had evidence of severe liver disease because of the possibility of not clearing activated clotting products and the potential for thromboembolism. They were also ineligible if they had a history of thromboembolic disease, any previous allergic reaction to FEIBA, or had had an antifibrinolytic agent within 12 hr prior to FEIBA treatment.

The following types of bleeding episodes were included in the study: (1) joint: shoulder, elbow, wrist, hand, hip, knee, and ankle; (2) mucous membrane: bleeding in oral cavity (surgical and nonsurgical in origin), epistaxis, and hematuria; (3) Muscle and soft tissue bleeding: including retroperitoneal and abdominal; and (4) emergency: including central nervous system (CNS).

When bleeding occurred, patients were seen and treated with FEIBA at 50 U/kg, calculated to the nearest bottle (500 U), and administered at a rate of 2 U/kg/min at 12-hr intervals except for mucous membrane bleeding, which was treated every 6 hr. Although the FEIBA dosage was calculated at 50 U/kg to the nearest bottle, resuspended material was not discarded to comply with dosage exactness. Therefore, patient size resulted in a slight variation in infusion dosage. There were too few patients who received greater than 70 U/kg to evaluate whether a larger dose increased efficacy. Treatment was continued for 72 hr and, if bleeding was not controlled, alternate therapy was given.

Clinical control of joint bleeding was evaluated first by the physician within 1 hr and subsequently by the patient at home at 12-hr intervals as necessary. Three criteria were used to assess the efficacy of an infusion: (1) qualitative evaluation of pain—severe, moderate, or mild; (2) joint circumference, where possible; and (3) joint function as assessed by goniometer measurements of flexion and extension of the involved joint, as compared to baseline values taken at entrance to the study. Of these criteria, pain had to be assessed by the patient. However, the physician could evaluate the circumference and function. Patients and center physicians had been instructed in the use of the goniometer for entrance into a previous study and were instructed again for the current study. A positive effect was judged present when the patient and the physician felt the bleeding had stopped, when pain improved, when circumference decreased by 1 cm, and when flexion or extension improved as compared to the baseline values. Mucous membrane bleeding was observed for cessation of bleeding. Control of other bleedings, muscle, intra-abdominal, and CNS, was assessed on the basis of clinical judgment plus hemoglobin and hematocrit levels.

The patients were monitored for 120 min post-infusion for acute side effects: allergic reactions, such as shock, hives, wheezing, chills, or changes in temperature and blood pressure. Blood was drawn prior to the infusion and 1 hr after the infusion for clotting studies to monitor for disseminated intravascular clotting (DIC) with prothrombin time, partial thromboplastin time, platelets, fibrinogen, and fibrinogen split products. The patients were monitored for chronic side effects at 2–3 wk postinfusion, with blood studies for inhibitor titer, hepatitis B surface antigen (HB,Ag) and hepatitis B surface antibody (HB,Ab), and SGPT.

**RESULTS**

One-hundred and sixty-five episodes were treated with FEIBA in 49 patients. Of these, 102 were joint bleeding episodes, 20 were mucous membrane, 33 muscle and soft tissue, and 10 were emergency bleeding episodes including 3 central nervous system, 4 surgical procedures, and 3 listed as “other” that were miscellaneous sites: bridge of the nose, chest wall, and auditory canal.

A total of 91% of these 165 episodes were controlled within 72 hr. Three cases (2%) were extremely severe episodes that included 1 CNS, 1 ilipsoas, and 1 thigh hemorrhage and required 20 or more infusions and more than 72 hr for complete resolution. Of the 155 episodes in the first 3 categories (Table 1), 38%

### Table 1. Summary of Outcome of Treatment With FEIBA

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of Episodes</th>
<th>1 Infusion 12 hr</th>
<th>≥1 Infusion</th>
<th>Not Controlled &gt;72 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≤36 hr</td>
<td>&gt;36 hr</td>
<td>Total</td>
</tr>
<tr>
<td>Joint</td>
<td>102</td>
<td>41 (40%)*</td>
<td>13 (13%)</td>
<td>98 (96%)</td>
</tr>
<tr>
<td>Mucous membrane</td>
<td>20</td>
<td>9 (45%)</td>
<td>5 (25%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Muscle/soft tissue</td>
<td>33</td>
<td>9 (27%)</td>
<td>17 (52%)</td>
<td>7 (21%)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>3</td>
<td>1 (33%)</td>
<td>1 (33%)</td>
<td>2 (67%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>4</td>
<td>1 (25%)</td>
<td>3 (75%)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>1 (33%)</td>
<td>—</td>
<td>1 (33%)</td>
</tr>
<tr>
<td>Total</td>
<td>165</td>
<td>60 (36%)</td>
<td>70 (42%)</td>
<td>23 (14%)</td>
</tr>
</tbody>
</table>

*No. of episodes (% of episodes).*
responded within 12 hr with one infusion and 43% with one or more infusions in 36 hr; a total of 93% responded within 72 hr. Response was judged primarily by the patient’s evaluation of pain and physician’s subjective judgment that the bleeding was controlled. Circumference measurements were carried out in 65 of the joint bleeding episodes with no change in 35, a 1–4 cm decrease in 24, and an increase of 1–2 cm in 6.

The efficacy of FEIBA for control of central nervous system and surgical bleeding is difficult to evaluate because of small numbers. Of 3 CNS episodes treated, 1 responded in 36 hr and 1 within 72 hr. Of the 4 patients treated for surgical procedures, 3 were controlled in 36 hr and 1 required more than 72 hr for hemostasis and was therefore considered a failure of response. In the category “other” or miscellaneous sites, 1 of the 3 responded in 12 hr and 2 were not controlled within 72 hr. The patients whose joint bleeding episodes were not controlled at 72 hr were treated with a variety of conventional measures, including factor VIII and factor IX concentrates and prednisone. Packing and Amicar were used for mucous membrane bleeding. All nonresponsive bleeding episodes finally stopped, but were markedly prolonged, up to 20 days.

Minor adverse systemic reactions were seen in only 18 of 489 (3.7%) infusions and included chills, fever, nausea, dizziness, and an unusual taste in the mouth. No major reactions were noticed.

Laboratory studies carried out to monitor the appearance of DIC revealed a decrease in the APTT of greater than 10 sec from the pretransfusion level in 54% of the cases, and a rise in 3%: there was a decrease in the PT in 4% of the cases. However, the change in the APTT and PT could not be used as a measure of clinical efficacy. The maximum fall in fibrinogen was 300 mg/dl in one patient from a high of 450 mg/dl. The maximum platelet fall was to 260,000 in one patient from a high of 410,000/cu mm.

The long-term changes monitored at 2 wk or more after the infusion revealed no HBsAg in any of the patients, no serologic changes in the hepatitis B marker, and no clinical evidence of hepatitis B infection. However, since all patients had HBsAb on entrance to the study, the increase in the SGPT of greater than 40 U in 9 patients was considered due to another viral agent.

There appeared to be no difference in patient response between those patients with titers of 2 Bethesda units as opposed to those with 3840 Bethesda units. Inhibitor titers were measured by the investigators and the control laboratory in Vienna and showed a surprising consistency. A significant rise, defined as greater than 10 Bethesda units, was seen within 2–3 wk in 10 patients, without a change in efficacy of the product with subsequent infusions (Table 2). The majority of the patients had a fall in titer following therapy.

**DISCUSSION**

FEIBA appears to be a safe product for the treatment of bleeding episodes in patients with factor VIII or IX inhibitors with either congenital or acquired deficiency. In this study, 3/49 patients had a factor IX inhibitor and 2 patients had an acquired factor VIII inhibitor. The response of these latter patients was identical to the congenitally deficient patients. The response was judged primarily on the subjective evaluations. In those patients where the other criteria were evaluated, no more information was gained. This is a similar finding to that of the NHLBI study, and therefore, the subjective evaluation alone was deemed valid.

No attempt was made to evaluate the time between onset of bleeding and therapy, although this might be a valuable observation. One such detailed report done by Aronstam in a hospital–school setting with noninhibitor patients bleeding into the elbow shows the need for therapy within 2 hr of onset for efficacy using 10 U factor VIII/kg. Since the patients in the current study had to travel to the hospital and wait for the infusion material, it seems most unlikely that they were treated within 2 hr of onset of bleeding. Such an observation would be very useful in a subsequent dosage study.

The response of bleeding episodes in inhibitor patients treated with FEIBA is similar to the response seen in noninhibitor patients treated with factor VIII. FEIBA appears to work as well for joint bleeding in the patient with an inhibitor as factor VIII does for the factor VIII deficient patients when all joints, both orthopedically normal and those with synovitis, are included.
As in the treatment of bleeding episodes in factor VIII deficient patients, the need for repeated doses of FEIBA for the inhibitor patient is not unusual. In the NHBLI factor VIII inhibitor study, the noninhibitor patients had an average of 34 bleeds per year and treated themselves 74 times, or more than once per bleeding episode. There are no objective criteria to judge whether the patient was retreated because of continued bleeding or for prophylaxis. Since all patients were on a home-care program, direct medical observation was impossible. When using FEIBA, 79% of the patients were controlled with one or more infusions within 36 hr.

The question as to minimal dosage for efficacy is as yet unanswered. The present dose of 50 U/kg was chosen based on previous studies. Insufficient data were collected to prove that a smaller dose would be useful. Certainly, the 100 U/kg for surgical episodes and 50–70 U/kg for the joints and muscle or soft tissue appear adequate.

The laboratory data show a minimal shortening of the APTT 50% of the time, which was unrelated to the dosage. The same was seen in the PT in a smaller number of patients. Neither could be used as a measure of efficacy. In one patient, the fibrinogen fell 300 mg, but there was neither a rise in split products nor a fall in platelet count. Since the minor changes in fibrinogen and platelet count were minimal, and there were no split products, FEIBA is indeed safe and does not cause disseminated intravascular clotting when used at 50–100 U/kg. However, since there is no predictive laboratory measure for efficacy in the patient, care and caution should be maintained when considering its use for elective surgical procedures. The hepatitis B monitoring revealed no changes in these markers. The transient rise in SGPT is postulated as due to non-A, non-B virus disease.

The systemic side effects appear to be the same as those seen in a small number of hemophiliacs when treated with factor VIII concentrate, i.e., headache, nausea, dizziness, chills, and an unusual taste in the mouth. The first three have never been well explained and may be related to protein load and speed of infusion. The taste in the mouth measures circulation time and is probably related to a residue from the processing. There have been no other systemic reactions.

The monitoring of long-term side effects did show a rise of inhibitor titer in 10 of 49 patients as a response to the factor VIIIC:Ag known to be present in FEIBA. However, three of these patients had been pretreated with factor-VIIIC:Ag-containing materials within 2 wk prior to using FEIBA. This same rise has been seen when other nonactivated prothrombin complex concentrations were used for treatment of bleeding episodes in patients with factor VIII inhibitors; an even greater number of patients showed an anamnestic response to these products. This finding is therefore not unexpected, since FEIBA is known to contain small amounts of factor VIIIC:Ag.

The in vivo mechanism of action of prothrombin complex concentrate remains unknown. In vitro experiments with FEIBA suggest two possible explanations. One is that the active principle is a factor-Xa-like substance that has a molecular weight of 120,000–130,000 and is only slightly inhibited by plasmatic inhibitors. Another theory suggests that the active principle may be complex factor VIIIC:Ag, factor IXa, and phospholipid, which is less inhibited by the factor VIII inhibitor.

Clinical safety seems to be proven and clinical efficacy is present. The investigators recognize, however, that this is a clinical study with observations based primarily on patient interpretations or results. The patients were educated to judge response, but they are psychologically set for a positive rather than a negative response. The efficacy as related to the only activated prothrombin complex (Autoplex) already licensed for use in inhibitor patients has not been evaluated. This study, as well as a controlled clinical study, must be done.

REFERENCES


The use of factor eight inhibitor by-passing activity (FEIBA immuno) product for treatment of bleeding episodes in hemophiliacs with inhibitors

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