Anti-Inhibitor Coagulant Complex (Autoplex) for Treatment of Factor VIII Inhibitors in Hemophilia

By Charles F. Abildgaard, John A. Penner, and Edward J. Watson-Williams

Fourteen individuals with severe hemophilia complicated by factor VIII inhibitors (1 to 132 Bethesda Units) were treated for 33 bleeding episodes with a new activated prothrombin complex concentrate, Anti-Inhibitor Coagulant Complex (Autoplex, Hyland, Glendale, Calif.). Excellent or good results were observed in 21 of 25 minor bleeding episodes treated, which included joint, soft tissue, and mucous membrane hemorrhages. Eight major bleeding problems (an epidural bleed, a puncture wound, 2 serious soft tissue hemorrhages, 2 lacerations, and 2 major surgical procedures) were treated with excellent (6) or good (2) results. No serious complications were encountered, but two children developed transient hypofibrinogenemia following Autoplex infusion. Although some shortening of the prothrombin time and activated partial thromboplastin time was noted after infusion of Autoplex, there is no useful laboratory test for monitoring therapy. Despite the unknown mechanism of action for bypassing factor VIII, Autoplex appears to be a useful and needed interim product and is safe and effective. In view of the possible potentiation of thrombosis concurrent use of fibrinolytic inhibitors should be avoided.

Since the first report of the successful use of an “activated” prothrombin complex concentrate for treatment of bleeding in a patient with an inhibitor to factor VIII, 1 a number of investigators have described their experience using prothrombin complex concentrates (PCC) available in the United States for this purpose. 2-13 The initial experience was with a spontaneously activated PCC, which was found to promote hemostasis in a patient with classical hemophilia and an acquired inhibitor to factor VIII. 1

Using an investigational form of this concentrate (Auto-Factor IX), Kurczynski and Penner treated bleeding in a larger number of patients with inhibitors. 2 Subsequently, other investigators have described the successful use of both activated (Auto-Factor IX, Hyland) and nonactivated PCC (Konyne, Cutter, Berkeley, Calif.; Proplex, Hyland) for the treatment of patients with inhibitors. 3-13 These reports include experience with 408 episodes in 57 individuals treated for bleeding or prepared for surgery or dental extractions. More recently, a multicenter double blind trial of nonactivated PCC as single dose treatment for hemarthroses in patients with inhibitors has been completed, with the finding that approximately 50% of patients obtained pain relief with PCC compared to 25% of those receiving albumen placebo. 14

During the same period of time that PCC were being evaluated for efficacy in the treatment of patients with inhibitors to factor VIII, there were a number of reports of thrombotic complications associated with the use of nonactivated PCC in patients with liver disease or factor IX deficiency. 15 The factor(s) in PCC responsible for thrombogenicity and factor VIII bypassing activity are unknown. Recent studies have demonstrated the presence of both activated factor VII and activated factor IX in PCC, with greater amounts in activated products, 16-17 but the relationship of these findings either to thrombogenicity or to factor VIII bypassing activity remains to be determined.

Our experience during the past 2 to 3 yr has been that the nonactivated PCC have become less effective in the control of bleeding in patients with a factor VIII inhibitor; 18 others have had similar experience. 14 In the case of Proplex, the production process has been changed in an attempt to reduce thrombogenicity of the product when used for treating factor IX deficient patients. Although it is not known whether the factor that causes thrombogenicity is the same as that responsible for factor VIII bypassing activity, it is possible that this production change has affected the latter property of Proplex. There has been no change in the preparation of Konyne; nevertheless in our experience, there has been a marked decrease in the efficacy of this product to control bleeding in patients with factor VIII inhibitors.

For the past 2 yr, the investigational concentrate, Auto-Factor IX, has been prepared by a process of controlled activation and it is now produced as Anti-Inhibitor Coagulant Complex* (Autoplex, Hyland). The purpose of this report is to describe our experience using this concentrate for treatment of bleeding in factor VIII deficient patients with inhibitors. The material studied will be referred to as Autoplex in the remainder of this report.

*Generic designation.
MATERIALS AND METHODS

Patients Treated

Fourteen individuals with severe classical hemophilia (factor VIII < 1%) and inhibitor to factor VIII were studied. The inhibitor levels at the time of treatment ranged from 1 to 132 Bethesda Units, and all but one patient were proved high-responders (known to have had inhibitor levels of 5 Bethesda Units or greater following factor VIII therapy). Autoplex was administered for 33 separate episodes as listed in Tables 1, 2, and 4. These studies were approved by local human investigation committees in accord with an assurance filed with and approved by the Department of Health, Education, and Welfare. Informed consent was obtained from each patient or family before treatment. Seven patients were treated at the University of Michigan and seven were treated at the University of California, Davis.

Product Characteristics

Autoplex was supplied by Hyland Therapeutics Division, Traveler Laboratories, Inc., Glendale, Calif. It is prepared from pooled human plasma and contains, in concentrated form, variable amounts of activated and precursor clotting factors associated with the prothrombin complex (factors II, VII, IX, and X). Factors of the kinin generating system are also present. The product is standardized by its ability to correct the clotting time of factor VIII deficient plasma and the potency of each vial is labeled in factor VIII correctional units. One unit of factor VIII correctional activity is that quantity of activated prothrombin complex which, upon addition to an equal volume of factor VIII deficient plasma, will correct the clotting time to 35 sec (using an ellagic acid activated partial thromboplastin time). The reconstituted product contains heparin as a stabilizing agent (maximum of 2 U/ml), 0.02 M sodium citrate, a residual amount of polyethylene glycol (maximum of 2 mg/ml), sodium level of 177± 15 mg/liter, and total protein of less than 0.6 mg/dl. The product is reconstituted with sterile water for injection immediately before infusion and given at a rate of no more than 10 ml/min.

Laboratory Studies

Factor VIII inhibitor was measured using the Bethesda assay. A variety of hematologic and coagulation tests were performed serially in all patients by standard laboratory methods and included the following: platelet count, hematocrit, prothrombin time, fibrinogen level, fibrin split products, and fibrin monomer tests. Antithrombin III levels and specific assays for prothrombin, factors VII, IX, and X were performed in some patients.

RESULTS

Minor Bleeding Episodes

Nine patients were treated on 25 occasions for minor bleeding problems and the details are reported in Tables 1, 2, and 4. The bleeding included 16 episodes of hemarthrosis, 8 episodes of soft tissue bleeding, and 1 episode of hematuria. Response to treatment was judged as excellent, good, fair, or none, based on the following: improvement of symptoms within 8 hr following a single dose, excellent; improvement of symptoms within 24 hr following 1 or 2 doses, good; improvement of symptoms over 24-48 hr requiring 2 or more doses, fair; no change or increase in symptoms for 12-24 hr because of size and site of hemorrhage. No response to 100 U Konyne/kg given 24 and 12 hr before Autoplex.

Table 1. Hemarthroses Treated With Autoplex

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Inhibitor (Beth U)</th>
<th>Joint Involved</th>
<th>Dose Autoplex (U/kg)</th>
<th>Pain Relief in hr</th>
<th>Improved Range Of Motion in hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.J.</td>
<td>32</td>
<td>Shoulder</td>
<td>64</td>
<td>x</td>
<td>24</td>
<td>8-24</td>
</tr>
<tr>
<td>10 Ͽ</td>
<td>Shoulder</td>
<td>64, 64*</td>
<td>Ͽ</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>2</td>
<td>Shoulder</td>
<td>57</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.H.</td>
<td>16</td>
<td>Elbow</td>
<td>50, 50*</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>P.O.</td>
<td>35</td>
<td>Elbow</td>
<td>80</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>Elbow</td>
<td></td>
<td>63</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.R.</td>
<td>18</td>
<td>Elbow, arm</td>
<td>51</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.6</td>
<td>Elbow</td>
<td></td>
<td>50</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.6</td>
<td>Knee</td>
<td></td>
<td>53</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.C.</td>
<td>29</td>
<td>Elbow</td>
<td>62, 62*</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Hip, knee</td>
<td>60</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.A.</td>
<td>9</td>
<td>Knee, ankle ϼ</td>
<td>39</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J.S.</td>
<td>10</td>
<td>Ankle</td>
<td>30</td>
<td>30*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Ankle</td>
<td></td>
<td>23</td>
<td>38*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R.P.</td>
<td>18</td>
<td>Ankle, foot</td>
<td>41</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.8</td>
<td>Ankle</td>
<td></td>
<td>66</td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Second dose given at 12-24 hr because of size and site of hemorrhage.
†Second dose given at 12-24 hr because of size and site of hemorrhage.
§No response to 100 U Konyne/kg given 24 and 12 hr before Autoplex.

Table 2. Other Minor Hemorrhages Treated with Autoplex

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Inhibitor (Beth U)</th>
<th>Bleeding Site</th>
<th>Dose Autoplex (U/kg)</th>
<th>Swelling, Pain, or Bleeding Ceased in hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.A.</td>
<td>9</td>
<td>110</td>
<td>Hematuria ϼ</td>
<td>39</td>
<td>x</td>
</tr>
<tr>
<td>O.J.</td>
<td>8</td>
<td>2</td>
<td>Hand</td>
<td>48, 48*</td>
<td>x</td>
</tr>
<tr>
<td>P.O.</td>
<td>35</td>
<td>70</td>
<td>Forearm</td>
<td>66</td>
<td>x</td>
</tr>
<tr>
<td>R.P.</td>
<td>18</td>
<td>4.6</td>
<td>Deltoid</td>
<td>54</td>
<td>x</td>
</tr>
<tr>
<td>B.R.</td>
<td>18</td>
<td>3.7</td>
<td>Arm, abdomen</td>
<td>82</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.6 Subscapular</td>
<td>50</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.0 Cheek</td>
<td>60, 105*</td>
<td>x</td>
</tr>
</tbody>
</table>

*Second dose given at 12-24 hr because of size and site of hemorrhage.
†Second dose given at 12-24 hr because of size and site of hemorrhage.
§No response to 100 U Konyne/kg given 12 hr before Autoplex.

Within 48 hr, none. Improvement of symptoms included reduction of pain, decrease of swelling, and improved range of motion when measurable.

An excellent response was observed in 14 of 25 episodes that included all three types of bleeding (joint, soft tissue, hematuria). Good responses were
observed in 6 episodes of hemarthrosis and 2 soft tissue bleeds. Fair responses were observed in 3 episodes (2 hemarthroses, 1 soft tissue). There were no failures in this group (Table 3). In each of the three episodes judged to have a fair response to treatment, the dose of Autoplex was less than 50 U/kg (23/38, 39, 48/48), while in the 22 episodes with an excellent or good outcome 19 received greater than 50 U/kg.

**Major Bleeding Episodes**

Seven patients were treated for 8 major bleeding problems and the details are recorded in Table 4. The episodes include an epidural bleed, a puncture wound, 2 lacerations, 2 serious soft tissue hemorrhages, and 2 major surgical procedures. Six of these episodes were judged to have an excellent response to Autoplex and the outcome of the other 2 was good. Brief descriptions of 2 episodes follow.

**Epidural bleed** (J.B.). This 6 yr-old boy with severe factor VIII deficiency complicated by an inhibitor (40 Bethesda Units/ml) was admitted to the University of California, Davis Medical Center, Sacramento, after falling from a playground slide in Reno, Nevada, and sustaining a basilar skull fracture and fractured clavicle. By the time of arrival in Sacramento, he had significant lethargy and a computerized tomography scan revealed a large epidural bleed. He received daily treatment with Autoplex (100 U/kg every 8–12 hr) for 14 days with 3 further days of single dose infusion (50–100 U/kg). His lethargy cleared within 24 hr and serial scans revealed progressive resolution of the epidural bleed as shown in Fig. 1. For

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Inhibitor (Beth U)</th>
<th>Bleeding Site</th>
<th>Dose Autoplex (U/kg)</th>
<th>Response</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>J.B.</td>
<td>6</td>
<td>40</td>
<td>Epidural bleed</td>
<td>100 U/kg × 30 over 17 days</td>
<td>Excellent</td>
<td>See detailed report</td>
</tr>
<tr>
<td>R.Y.</td>
<td>2½</td>
<td>3.2</td>
<td>Puncture wound under tongue with recurrence of above bleed after reinjury 1 wk later</td>
<td>69 U/kg × 2</td>
<td>Good</td>
<td>Gradual resolution of bleed over 3-day period. Also received Amicar.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>84 U/kg × 1</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>92 U/kg × 1</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>69 U/kg × 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D.H.</td>
<td>27</td>
<td>132</td>
<td>Massive soft tissue bleed of lower abdominal wall, groin, thigh, and retroperitoneal space</td>
<td>89 U/kg × 1</td>
<td>Good</td>
<td>Life-threatening soft tissue bleed associated with hypotension resolved over 3-day period; required replacement of 4500 ml packed red cells in this 84 kg man</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>71 U/kg × 1</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>53 U/kg × 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B.R.</td>
<td>18</td>
<td>3.5</td>
<td>Laceration of forearm</td>
<td>9 infusions (50–100 U/kg over 14-days)</td>
<td>Excellent</td>
<td>Progressive healing of a deep irregular laceration involving a skin flap without significant blood loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>93 U/kg × 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R.P.</td>
<td>18</td>
<td>1.8</td>
<td>Multiple lacerations of scalp, back, and elbow</td>
<td>100 U/kg q. 12 hr × 4 doses (50 U/kg × 6 doses over next 9 days)</td>
<td>Excellent</td>
<td>Because of uncertain supply of Autoplex, multiple deep lacerations were not sutured. Good hemostasis was maintained and healing was complete but probably slowed because of failure to suture original wounds</td>
</tr>
<tr>
<td>P.A.</td>
<td>23</td>
<td>80</td>
<td>Total hip replacement</td>
<td>12 infusions (50–100 U/kg over 20 days)</td>
<td>Excellent</td>
<td>Preoperative plasmapheresis exchange reduced inhibitor to 0. Factor VIII replacement used until 6 days postop when inhibitor increased to 80 Beth U and large wound hematoma formed. Bleeding controlled with Autoplex from that time on</td>
</tr>
<tr>
<td>H.D.</td>
<td>28</td>
<td>63</td>
<td>Resection of abdominal wall</td>
<td>14 infusions (50–100 U/kg over 30 days)</td>
<td>Excellent</td>
<td>Preoperative plasmapheresis exchange reduced inhibitor to 0. Factor VIII replacement effective until 6 days postop when inhibitor rose to 68 Beth U and large wound hematoma formed. Bleeding then controlled with Autoplex. Wound became infected and was drained surgically and hemostasis controlled with Autoplex.</td>
</tr>
</tbody>
</table>
the first 6 days he had significant blood loss from the external auditory canal; presumably due to bleeding from a venous sinus overlying the large basilar skull fracture. Blood loss was replaced with packed red blood cells and whole blood and bleeding from the ear ended within 6 days of admission.

During treatment with Autoplex, two episodes of hypofibrinogenemia were observed (284 mg–84 mg on day 3, and 158 mg–73 mg on day 13). Platelet counts and factor V levels remained normal; protamine tests for fibrin monomer were negative; fibrin split products were not elevated, and the euglobulin clot lysis time remained normal. On both occasions infusion of cryoprecipitate resulted in sustained increases of fibrinogen. The patient recovered without neurologic sequelae.

**Sublingual bleed (B.R.).** This 18-yr-old boy with severe factor VIII deficiency and longstanding high-responding inhibitor developed marked swelling of the left side of his tongue 2 days after being in an auto accident. When first seen he was given 7500 U of Konyne (150 U/kg) because no Autoplex was available. Within 12 hr the bleed had progressed to involve the entire tongue and floor of his mouth and he had marked dysphagia and difficulty speaking. He was treated with Autoplex (93 U/kg) and there was no progression of the bleed. A second dose was given at 24 hr because of the serious nature of the bleed. By 48 hr his tongue had returned to normal size and swallowing was much improved. Complete resolution occurred within the next few days without further treatment.

**Side Effects**

Infusion of Autoplex was tolerated without problems in most patients. Side effects were limited to transient headache in 3 patients, transient chest discomfort in 1 child (when 100 U/kg dose was given in less than 15 min), and an erythematous pruritic eruption relieved by intravenous diphenhydramine in 1 patient. Thrombotic complications were not observed following the use of Autoplex.

**Laboratory Findings**

A significant shortening of the prothrombin time (usually 30%–40% of baseline) was observed by 15 min after Autoplex infusion and was demonstrable for several hours in most patients. A decrease in the activated partial thromboplastin time (APTT) was less striking and more variable than the change observed in the prothrombin time. The degree of shortening observed varied, depending on the APTT reagent used, and there was only a partial correlation with the clinical response to Autoplex (some patients had a favorable response to bleeding with little effect on the APTT result).

Platelet counts, fibrin split product, and fibrin monomer tests did not change from baseline. Hypofibrinogenemia was observed in two children (J.B., R.Y.) who received repeated doses of Autoplex. There was no evidence of disseminated intravascular coagulation in either child and in each case the hypofibrinogenemia was corrected by infusion of cryoprecipitate.
The cause of the observed hypofibrinogenemia in these children is not explained. Fibrinogen levels were monitored in all patients and remained stable in every other treatment episode including four adults who received repeated doses of Autoplex over prolonged periods of time.

Antithrombin III levels were measured in several patients and remained stable throughout the treatment period. Other coagulation factors contained in Autoplex were followed in a few patients and expected increases in levels of prothrombin, factor VII, factor IX, and factor X were observed with striking levels of factor VII in some patients (> 1000%). Factor VIII inhibitor levels were measured 14 days after each treatment episode and no significant increase was observed in any patient treated with Autoplex alone.

**DISCUSSION**

Antibodies capable of neutralizing factor VIII arise in approximately 10% of all patients with severe factor VIII deficiency (< 1%). Treatment of bleeding in such patients is a major problem. Individuals with low level inhibitors (< 5 U) who do not respond to factor VIII infusion with a marked anamnestic antibody increase can be managed with factor VIII replacement in greater than usual amounts. Although some investigators have suggested that patients with inhibitor levels up to 20 Bethesda Units can be treated with factor VIII therapy, this may require massive amounts of factor VIII (up to 70,000 U/day). Because of the cost and relative ineffectiveness of such an approach, we do not recommend factor VIII replacement therapy for patients with inhibitor levels of over 5 Bethesda Units. Other approaches to this problem have included plasmapheresis prior to factor VIII replacement and the use of animal factor VIII, but both have limited usefulness. Immunosuppressive therapy to eliminate the inhibitor has usually been ineffective. Efforts to induce immune tolerance by daily factor VIII therapy administered over a 12–18 mo period are being evaluated in one center in Europe, but the long-term outcome of this extremely expensive regimen remains to be evaluated.

The use of prothrombin complex concentrates as an alternative treatment for bleeding in patients with inhibitors has been controversial over the past 8 yr. The unknown mechanism of action of such concentrates and the variable efficacy of the nonactivated PCC (Proplex and Konyne) have contributed to the controversy surrounding the use of these products. Despite these problems, the results of the clinical trials of Autoplex as reported in this publication suggest that it is effective in controlling hemorrhage in factor VIII deficient patients with inhibitors. As of December 1979, 57 patients had been treated for 116 bleeding episodes in the United States, and no thrombotic complications or significant anamnestic inhibitor responses were observed according to D. A. McClure, Ph.D., Director of Scientific Affairs, Hyland Therapeutics. This total includes a few nonhemophilia patients with inhibitors to factor VIII who were treated successfully.

Although a controlled study of the efficacy of Autoplex, compared with a placebo, in the treatment of bleeding in patients with factor VIII inhibitors would be desirable, we are convinced that it is a useful, safe product for such patients. In the present study experienced observers noted pain relief within 8 hr in the majority of patients treated for hemarthroses. This response is a marked contrast to our prior experience and to that recorded in the literature regarding the natural course of hemarthroses treated without replacement therapy. In a 1949 study of 40 patients with hemophilia treated without replacement therapy, the authors found that full recovery of hemarthroses took 2–3 wk and stated the following: "Hemarthroses were usually exquisitely painful for four to six days when pain and swelling subsided a little."

That the outcome of the child treated for epidural hemorrhage was influenced favorably by the use of Autoplex seems highly likely. In a series of 14 patients with subdural and epidural hemorrhages reported in 1960, there were 11 deaths. Since our experience with this child, others have described favorable results using Autoplex in three episodes of intracranial bleeding in children.

Despite the modest benefit noted with Konyne or Proplex in the treatment of hemarthroses in the multicenter controlled study, 4 patients treated on 5 occasions in the present series failed to respond to large doses of Konyne and subsequently improved after receiving Autoplex.

Because the supply and cost of Autoplex may limit availability, the use of this product should be restricted to patients with hemophilia complicated by inhibitors to factor VIII. In our opinion, Autoplex should be used to treat bleeding in patients with inhibitor levels over 5 Bethesda Units (or those known to have a maximal inhibitor level of greater than 5 Bethesda Units at any prior time, i.e., high-responders). Patients known to be low-responders (those with less than 5 Bethesda Units) probably can be managed effectively with factor VIII replacement.

Experience to date suggests that a minimum dose of 50 factor VIII correctional U/kg be used for the treatment of minor bleeding episodes. As more experience is gained and minor bleeding problems are treated earlier, lower doses may prove effective.
Preliminary experience by one of us (J.A.P.) suggests that early hemarthroses can be controlled using significantly smaller doses of Autoplex. Serious bleeding problems should be treated with at least 100 U/kg with repeat doses at 6–24 hr intervals depending on the response and the nature of the problem.

Because the active ingredient(s) of Autoplex remain unknown, there is no information regarding longevity of the factor VIII bypassing activity. Although there is a regular shortening of the prothrombin time following administration of Autoplex, this may not relate to the factor VIII bypassing activity, and, at present, there does not appear to be a reliable laboratory test for monitoring therapy. However, some investigators have limited doses of Autoplex not to exceed an amount capable of reducing the prothrombin time below 8 sec (or two-thirds of baseline value).

Although thrombotic complications and instances of disseminated intravascular coagulation have not been observed following the use of Autoplex in patients with inhibitors, the experience remains limited and clinicians using this product should remain alert to the possibility of such complications—particularly in patients receiving repeated doses. This is particularly true in view of two recent anecdotal accounts of myocardial infarction occurring in patients less than 20 yr of age who received large repeated doses of Konyne. The occurrence of such thrombotic episodes in patients with inhibitors receiving large doses of PCC suggest that fibrinolytic inhibitors should not be used in association with Autoplex.

The cause for the hypofibrinogenemia in two children who received repeated doses of Autoplex is unknown. It is of interest that a similar occurrence has been reported in a child who received repeated doses of Konyne and that one of us (C.F.A.) has observed transient hypofibrinogenemia in two additional children associated with the use of Konyne. In view of these observations, it may be wise to monitor fibrinogen levels in young patients receiving repeated doses of Autoplex.

Despite the apparent clinical usefulness of Autoplex, the product does not represent a final answer and the mechanism of action remains an enigma. Resolution of this problem may lead to the development of a more specific material for the treatment of patients with inhibitors. In the meantime, we believe Autoplex is a useful and needed interim product and is safe and effective.

**ADDENDUM**

In January 1980 one of our patients (D.H.) suffered a major retroperitoneal bleed 1 yr after successful treatment of a similar episode with Autoplex. In spite of initial control with large amounts of Autoplex (approximately 80 U/kg every 6 hr), the bleeding resumed and eventually resulted in death.

**REFERENCES**


Anti-inhibitor Coagulant Complex (Autoplex) for treatment of factor VIII inhibitors in hemophilia

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