Since the diagnosis of IPN has seldom been made before death, therapy has not been adequately evaluated. Steroids alone or steroids in combination with azathioprine and cyclophosphamide have been tried with some success.\(^{11,12}\) Regression of coronary artery aneurysms in an infant with polyarteritis nodosa after treatment has been reported.\(^{13}\)

I should like to thank Professor A. Olinsky, Department of Paediatrics, University of the Orange Free State, for help and advice, as well as Professor G. F. Rohm and his staff, Department of Anatomical Pathology, University of the Orange Free State, for performing the autopsy and reporting on the histological findings.

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**Inactivated Proplex for the Haemophiliac with Inhibitors**

**A Case Report**

**P. B. HESSELING**

**SUMMARY**

Inactivated prothrombin complex (Proplex) with a Kingdon time between 100 and 138 seconds effected functional recovery and adequate haemostasis in a haemophiliac with inhibitors of the high-responder type at comparatively low cost, and with no adverse effects. Home treatment was successful.

Liver function remained normal during treatment. Statistically significant changes occurred in the prothrombin time (PT), fibrinogen levels and the thrombin time after each infusion. No evidence of diffuse intra-vascular coagulation (DIC) was ever detected. The inhibitor level decreased from 10 to 2 Bethesda units, and the radio-immunoassay (RIA) for Australia antigen remained negative.


The development of inhibitors or antibodies to human factor VIII in 5 - 21% of patients with severe haemophilia A who receive repeated transfusions of blood or plasma derivatives containing factor VIII constitutes a major hazard.

personal experience (unpublished data) with bovine factor VIII, which stopped bleeding in a haemophiliac of the high-responder type who bled profusely after synovectomy despite massive infusions of human factor VIII, proved that it might be life-saving. Another similar patient was treated successfully with inactivated prothrombin complex (Proplex). The clinical details of this patient are presented, and the implications of the treatment are discussed.

**CASE REPORT**

A 5-year-old haemophiliac with inhibitors of the high-responder type (a patient whose antibody titre increases after each antigenic stimulation, or whose antibody titre persists for a long time in the absence of transfusion, is called a high-responder haemophiliac) had developed repeated spontaneous haemarthroses of the left knee associated with severe pain and progressive severe impairment of function since May 1978.\(^{14}\)

Conservative therapy consisting of immobilization and high doses of human factor VIII plus e-aminoacproic acid proved ineffective. By August 1978 the patient had developed chronic pain, and the knee was fixed at 120\(^{0}\) flexion deformity.

Investigations at this stage showed a moderate inhibitor level of 10 Bethesda units. (A titre of more than 20 Bethesda units is considered to be a high antibody titre.\(^{15}\)) Antithrombin III activity was 95% and results of radio-immunoassay (RIA) for Australia antigen were negative.

An infusion of 80 U/kg ‘inactivated’ prothrombin complex (Proplex: Hyland), with a Kingdon time varying between 100 and 138 seconds, depending on the batch used, was given intravenously on 55 different occasions, at 1 - 3-day intervals between 25 August and 13 December.

Since 11 October the child’s mother has administered the Proplex at home. Weekly administrations by the mother proved to be life-saving.

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**REFERENCES**

at the haematology clinic ensured proper supervision and allowed continuous monitoring of changes in the patient’s clotting profile. The haemarthroses resolved. Physiotherapy given after each Proplex administration has aided recovery, and the knee joint is functional and has full extension. During this period of treatment 8 minor haemorrhages developed in the right ankle, right forearm, right knee, left thigh, and from the nose. A single dose of Proplex 80 U/kg resulted in resolution of the haematomas within 36 hours in all but the right ankle haemorrhage, which resolved after 3 daily administrations of Proplex.

The mother remarked on the quick relief of pain after the infusion. A hoarse voice or slight abdominal cramps developed within minutes of the infusion of Proplex on 4 occasions, but these minor side-effects disappeared when the infusion was given over 20 instead of 10 minutes.

TABLE I. LIVER FUNCTION TESTS

<table>
<thead>
<tr>
<th>Date</th>
<th>Protein (g/l)</th>
<th>Albumin (g/l)</th>
<th>Aspartate transaminase (U/l)</th>
<th>Alanine transaminase (U/l)</th>
<th>Lactic dehydrogenase (U/l)</th>
<th>Alkaline phosphatase (U/l)</th>
<th>Globulin (g/l)</th>
<th>Total bilirubin (µmol/l)</th>
<th>Direct bilirubin (µmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
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<td>58</td>
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<td>57</td>
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<td>238</td>
<td>223</td>
<td>7</td>
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</tbody>
</table>

Liver function tests (SMAC Technicon) have remained negative (Table I).

The inhibitor level declined to 2 Bethesda units on 10 October. The RIA for Australia antigen was still negative. The partial thromboplastin time (PTT) was measured before and just after infusion of Proplex, using the General Diagnostics Platelin plus activator kit. The PTT remained shortened 4 hours after infusion, as measured on 3 occasions. Fibrinogen levels were measured before and after infusion with the Hyland Quik-Pak TM fibrinogen test. A small decrease occurred on each occasion. The thrombin time increased after each infusion. Paired t statistical analysis proved these changes to be significant (Table II).

Fibrinogen degradation products measured with the ThromboWellcote kit and monomers measured with the ethanol gelation test were always absent before and after Proplex infusion. The Kingdon time for each batch of Proplex was supplied by the manufacturer.

**DISCUSSION**

Very high doses of glycine-precipitated factor VIII given as a bolus every 12 hours or in the form of a continuous infusion may be effective in stopping bleeding in patients with inhibitors of the low-responder type or a low-inhibitor titre. This therapy may be ineffective in patients with high-responder type inhibitors or in patients with a high-inhibitor titre. It is reserved for serious bleeding and is ineffective in the treatment of the patient with inhibitors who is being crippled by repeated joint bleeding. The exorbitant cost, the possibility of an anamnestic rise in factor VIII inhibitors, the possible induction of haemolytic anaemia, and a high risk of hepatitis are other unfavourable aspects of this therapy.

TABLE II. CHANGES IN THE CLOTTING PROFILE WITH PAIRED t STATISTICAL ANALYSIS

<table>
<thead>
<tr>
<th>Date</th>
<th>PTT (s)</th>
<th>Fibrinogen (mg/dl)</th>
<th>Thrombin time (s)</th>
<th>Kingdom time of Proplex (s)</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
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<td>13.12.1978</td>
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<tr>
<td>Mean</td>
<td>70,27</td>
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<td>± SD</td>
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<tr>
<td>t</td>
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<td>&lt;0,001</td>
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</table>
Immunosuppressive agents, e.g. azathioprine, corticosteroids and cyclophosphamide used alone or in combination with large doses of factor VIII, have been used with limited success in patients with low titres of inhibitors. Animal factor VIII (bovine or porcine) may be life-saving in emergencies. However, allergic reactions 7-10 days later, thrombocytopenia and a higher risk of inducing inhibitor formation than that attached to human factor VIII, limit the use of this material.

In 1972, Fekete et al. reported the use of Autofactor IX in the management of patients with inhibitors. Other reports of the use of activated prothrombin complex concentrates (PCC), such as Autofactor IX and Proplex, followed. Non-activated PCC was also found to be effective and safe for the haemophiliac with inhibitors using Proplex and Prothrombinex.

Achievement of haemostasis and restoration of function have been reported after the use of very high doses of human factor VIII and PCC over a prolonged period. Inhibitors disappeared. The mechanism whereby PCC bypasses factor VIII inhibitors is uncertain, and is ascribed by some authors to the presence of factors Xa or IXa. The platelets in the starting plasma from which PCC is manufactured are related to the difference in clot-promoting activity of various PCCs. There is evidence that activated PCCs enhance platelet coagulant activity by increasing the activity of platelet factor X activator.

Thrombotic episodes and disseminated intravascular coagulation have been well documented following infusion of PCC in patients with Christmas disease or liver disease, and after operation in these patients, but these complications have not been documented in the patient with inhibitors to factor VIII.

A Kingdon time assay is performed in order to detect the presence of thrombogenic materials in PCCs. The Kingdon time process is insensitive to the presence of catalytically inactive, pro-enzyme forms of the clotting factors which occur in plasma, but does react with shortened clotting times to the presence of traces of the enzymatically active forms of the clotting factors such as thrombin, and factors Xa, IXa and XIa. Non-activated human plasma has a Kingdon clotting time in excess of 200 seconds. F. Th. Lenich (personal communication) recommends a Kingdon time of less than 150 seconds if human plasma has a Kingdon clotting time in excess of 200 seconds.

REFERENCES