Personal Practice

Haemophilia B: Should We Stop Using Prothrombin Complex Concentrates in Hong Kong?

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Abstract

The use of coagulation factor concentrates remains the mainstay treatment for haemophilias. Prothrombin complex concentrates, plasma-derived products that contain other vitamin K-dependent factors additional to factor IX, have been used for treatment of haemophilia B since 1959. However, they carry a small but significant risk of thromboembolic complications, and fatalities subsequent to myocardial infarction have been reported. We recommend that highly purified plasma-derived or recombinant products of factor IX concentrates should be the treatment of choice for patients with haemophilia B, especially those who are at higher risk for thromboembolism.

Key words

Coagulation factor concentrate; Haemophilia B; Prothrombin complex concentrate; Thromboembolism

Introduction

Haemophilia B, also known as Christmas disease, is an inherited form of bleeding diathesis due to deficiency or defective synthesis of circulating factor IX. It is usually transmitted as an X-linked recessive condition, but up to one-third of new cases may be due to sporadic mutations. Factor IX is one of the vitamin K-dependent serine proteases synthesised in the liver, and has a half-life of about 24 hours in the circulation. The gene for factor IX is located at the long arm of the X chromosome, and more than 2,000 mutations have been described. Clinically, haemophilia B is classified into three categories of severity depending on the residual clotting factor procoagulant activities (mild, >5-40%; moderate, 1-5%; and severe, <1%). Although remarkable progress in gene therapy has been made in the laboratory, and an occasional patient may reconstitute his plasma factor IX activity at puberty due to specific mutations or liver transplantation, haemophilia B remains an incurable condition. To date, the treatment of hereditary factor IX deficiency consists of replacement of the clotting factor, either on demand in the presence of bleeding complications or prophylactically.
Development of Replacement Therapy for Haemophilia B

In the middle of the twentieth century, transfusion of whole blood or fresh frozen plasma became the mainstay treatment for haemophiliacs. The large volume of plasma needed to stop bleeding sometimes resulted in circulatory overload and thus heart failure, as exemplified in a previously reported patient with severe factor VII deficiency before purified clotting factor concentrates were available locally. In 1959, a factor concentrate was manufactured from the cryoprecipitate supernatant of the plasma. Factor IX, together with other vitamin K-dependent clotting factors such as factors II, VII and X, was available for therapeutic use in a pharmaceutical product known as prothrombin complex concentrate (PCC) or factor IX complex concentrate. Treatment of haemophilias was revolutionised with the introduction of clotting factor concentrates, but the association of thrombotic complications with PCC was soon observed. In the 1990s, highly purified factor IX concentrates that were devoid of other vitamin K-dependent clotting factors became available. Because of the concerns of blood-borne infectious complications, recombinant factor IX concentrates that were free of human plasma were introduced towards the end of the twentieth century.

Blood-borne Infections Associated with Plasma-derived Products

Each lot of plasma-derived factor IX products is collected from as many as 10,000 persons, and the use of such initially minimally treated concentrates had been linked to the development of chronic hepatitis B, hepatitis C, and human immunodeficiency virus infection during the 1970s and 1980s. Since 1984, factor IX concentrates derived from human plasma have been subjected to various virus inactivation processes such as dry heat treatment, pasteurisation, moist heating in organic solvent, hot vapour treatment, solvent-detergent treatment, chemical disinfection, membrane ultrafiltration, and nanofiltration. The latter methodology has been developed to eliminate hepatitis A and parvovirus B19 which tend to elude from other treatment processes. Safety monitorings have documented that none of the haemophilic patients born after 1985, 1992, and 1993 has been infected with human immunodeficiency virus, hepatitis C virus, and hepatitis B virus, respectively, due to treatment with plasma-derived factor concentrates in the United States. However, none of these methodologies of viral inactivation has been proven to be completely safe, and the risk of transmission of blood-borne infections is greatly minimised, though not completely absent.

Thromboembolic Complications

The occurrence of disseminated intravascular coagulation after treatment with PCC has been noted as early as 1959, the year when PCC was available for clinical use. Other reported complications include myocardial infarction, deep vein thrombosis, and pulmonary embolism. The strong association of PCC with thromboembolic complications was first established in a 5-year observation study when Kasper reported postoperative thrombophlebitis, thrombosis, and pulmonary embolism in 6 of 13 (46%) haemophilia B patients, but in none of 72 haemophilia A patients treated with factor VIII concentrate or cryoprecipitate. The repeated occurrence of fatal myocardial infarction in young haemophilic subjects, including the findings of previously unrecognised subclinical infarcts at postmortem, was particularly worrying. Between 1987 and 1990, 72 incidents of thromboembolic complications were reported to the International Committee on Thrombosis and Haemostasis from an international registry. Seven of these were fatal. In Germany, a PCC product had been withdrawn from the market in 1994 when three fatalities associated with thromboembolic complications were observed. In addition, Kohler also quoted the occurrence of arterial thrombosis and disseminated intravascular coagulation in 8 premature neonates after treatment with PCC. The thrombogenic potential of PCC has not been clearly understood but the presence of activated clotting factors during the production process and overloading of factors II and X, the serine proteases with the longer circulating half lives, have been implicated as the causative mechanisms for the thromboembolic complications observed. Patients who have prothrombotic tendency such as pre-existing liver diseases, immobilisation, and patients who require large infusions of PCC such as those who undergo surgeries, especially orthopaedic surgeries, are at the highest risks. The Factor IX Task Force of the International Society on Thrombosis and Haemostasis (ISTH) once recommended...
the addition of 5-10 iu of heparin to each milliliter of reconstituted PCC, while others advocated using fresh frozen plasma or antithrombin III concentrates prior to elective surgical procedures.6,17 The effectiveness of each of these manoeuvres remains unproven, and there is a theoretical risk of heparin-induced thrombocytopenia,19 an immunological reaction to unfractionated heparin that leads to thrombosis paradoxically.

PCCs are also used for the treatment of bleeding associated other rarer congenital clotting factor (II, VII and X) deficiencies,20 excessive oral anticoagulation,21 and hepatic dysfunction associated with liver failure or liver transplantation.22,23 Nevertheless, thromboembolic complications have been specifically linked to their use under such circumstances.24

Because of its thrombogenicity, PCCs are not generally recommended for treatment of haemophilia B when purified factor IX concentrates are available.25 Indeed, highly purified or recombinant factor IX concentrates are now recommended for treatment of haemophilia B in Australia,26 Germany,27 Canada,28 Italy,29 New Zealand,30 the United Kingdom,31 and the United States of America.32 These newer generations of factor IX concentrates have been shown to be equally efficacious when compared with PCC for management of haemophilia B.33-36 They are of comparable or superior safety in terms of transmission of viral pathogens.18,36 Most importantly, laboratory markers of thrombogenicity were consistently reduced after the use of highly purified or recombinant products.18,34,35,37,38

Current Treatment of Haemophilia B in Hong Kong

Prothrombinex™-HT (CSL Bioplasma Division, CSL Limited, Broadmeadows, Australia), the most commonly used product for treatment of haemophilia B in Hong Kong, is a form of PCC containing factors II, IX and X (with low level factor VII).23 Heparin and in 1992, antithrombin III and a high temperature viral inactivation step (and the product was renamed from Prothrombinex™), have also been added according to the recommendations of the ISTH. The factor concentrate is manufactured from plasma collected from voluntary blood donors by means of a contract fractionation between the Hong Kong Red Cross and Blood Transfusion Service and the manufacturer.39 The viral inactivation procedures involves dry heat treatment at 80°C for 72 hours. There is limited published data on its safety with respect to viral inactivation and published results from similar products are only available prior to 1990. Thirty-two patients with haemophilia A or B treated with similar products in the United Kingdom had no laboratory features of hepatitis over a 4-month period.40 In a subsequent Scottish study, none of the 13 patients developed hepatitis after 6 months of treatment.52 However, because of the small number of patients enrolled in these two studies, the 95% confidence intervals for viral infectivity were wide and ranged from 0-9% and 0-30%, respectively. The risk of transmission of parvovirus B19 has not been eliminated,42 and a recent study suggests that haemophilia A patients who have serological evidence of parvovirus infection have worse outcomes in terms of arthropathy when compared with those who do not.43 There has been one report of thrombotic complication observed after the use of Prothrombinex™ prior to 1992.44 According to the data of CSL Bioplasma, there have been no reported incidences of thrombotic complications associated with Prothrombinex™-HT in Australasia where over 100,000,000 units have been distributed (personal communication with CSL Bioplasma).

Conclusions and Recommendations

Prothrombin complex concentrates are efficacious pharmaceutical products for the treatment of bleeding manifestations of haemophilia B. Thromboembolic complications, though uncommon, represent a potentially lethal threat to their recipients. With the availability of highly purified and recombinant factor IX concentrates, there has been a global trend of substituting prothrombin complex concentrates with the newer and safer products for the treatment of haemophilia B. Following the experience of most developed countries, patients with haemophilia B in Hong Kong should receive either highly purified or recombinant factor IX concentrates as the treatment of choice for bleeding complications. Alternatively, a selective approach may be adopted in the presence of cost limitations (see Table 1 for price comparison) where purified factor IX concentrates are given in certain high-risk individuals such as neonates, patients undergoing surgery, patients with crush injuries, those with liver dysfunction, patients with a history of thrombotic complications, or patients requiring prophylactic treatment.
Table 1  Factor IX concentrates currently available in Hong Kong

<table>
<thead>
<tr>
<th>Products (Manufacturer)</th>
<th>Clotting factor content</th>
<th>Source</th>
<th>Cost (HKD/USD per unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombinex™-HT (CSL)</td>
<td>Factors II, IX, X</td>
<td>Plasma-derived product</td>
<td>$0.80/$0.10</td>
</tr>
<tr>
<td>MonoFix-VF (CSL)</td>
<td>Pure Factor IX</td>
<td>Plasma-derived product</td>
<td>$1.28/$0.16</td>
</tr>
<tr>
<td>BeneFix (Wyeth)</td>
<td>Pure Factor IX</td>
<td>Recombinant product</td>
<td>$4.70/$0.60</td>
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</tbody>
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Information provided by the Hong Kong Red Cross & Blood Transfusion Service.

References


