Evidence for the Use of Activated Prothrombin Complex Concentrates (aPCCs) in the Treatment of Patients with Haemophilia and Inhibitors

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Key Words
Autoplex®T · FEIBATM · Inhibitor · aPCC · Bypassing agent

Abstract
FEIBATM and Autoplex®T have been used to control bleeding in patients with factor VIII or IX inhibitors for over 25 years. The major components of FEIBATM are thought to be activated factor X and prothrombin, whereas the main active components in Autoplex®T are thought to be activated factors IX and VII. Both products have been found to effectively control approximately 80% of bleeds involving joints and soft tissues. Published experience of their use in surgery is limited. Thrombotic complications have been reported with high dose FEIBATM therapy and have led to maximum dosage guidelines for this product.

Constituents of FEIBATM and Autoplex®T

Turecek et al [1] have determined the constituents of FEIBATM. The concentrate contains prothrombin, factors (F) VII, IX and X, activated FVII and FX, thrombin and protein C. Using a rabbit inhibitor model, FEIBATM triggered coagulation similar to that induced by an enzyme substrate complex of FXa and prothrombin. It has therefore been postulated that when FEIBATM is introduced, activated FX binds to the phospholipid surface of acti-
vated platelets at the site of bleeding. Prothrombin is incorporated and the activated FX converts transfused and endogenous prothrombin directly into thrombin, bypassing the need for FVIII and FIX.

Following a detailed analysis of 10 separate batches of Autoplex®T using chromogenic active site-specific immunoassay (CASSIA) technology [2] it has been proposed that this product may work in quite a different way. The CASSIA technique enables the direct specific quantitation of the activated forms of individual clotting factors. High but quite variable concentrations of activated FVII and activated FIX were present within Autoplex®T. Smaller concentrations of activated FX, and negligible concentrations of activated FXI and thrombin were also found. The concentrations of activated FVII were considered not sufficient to directly activate significant amounts of FX. The authors proposed that the activated FIX was in sufficient concentrations to be incorporated on to phospholipid membranes causing activation of endogenous FVII. This coupled with the activated FVII in the concentrate were considered sufficient to enable direct FX activation in large enough quantities to bypass the need for endogenous FVIII and FIX.

**Clinical Efficacy**

FEIBATM and Autoplex®T have been reported to have similar clinical efficacy, controlling approximately 80% of spontaneous joint and soft tissue bleeds in inhibitor patients.

Table 1 summarises the major trials assessing the clinical efficacy of FEIBATM in spontaneous bleeds. Sjamsoedin et al. [3] studied the effect of FEIBATM on joint and muscle bleeding in haemophilia A inhibitor patients. This randomised double-blind trial compared FEIBATM with a non-activated PCC. Outcome comparison showed that

<table>
<thead>
<tr>
<th>Study</th>
<th>FEIBA dose</th>
<th>Patients</th>
<th>Bleeding episodes</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sjamsoedin [1981]</td>
<td>88 U/kg</td>
<td>15</td>
<td>150</td>
<td>64% (24 h)</td>
</tr>
<tr>
<td>Hilgartner [1983]</td>
<td>50–70 U/kg</td>
<td>49</td>
<td>165</td>
<td>91% (72 h)</td>
</tr>
<tr>
<td></td>
<td>12 hourly</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hilgartner [1990]</td>
<td>50–75 U/kg</td>
<td>41</td>
<td>106</td>
<td>79% (36 h)</td>
</tr>
<tr>
<td></td>
<td>12 hourly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negrier [1997]</td>
<td>65–100 U/kg</td>
<td>60</td>
<td>433</td>
<td>81% (up to 3 doses)</td>
</tr>
<tr>
<td></td>
<td>6–12 hourly</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FEIBATM produced significant improvements in bleeding control and joint mobility. In 1983, Hilgartner and Knatterud described the outcomes of FEIBATM use in 165 bleeding episodes in 49 inhibitor patients [4]. The majority of bleeds involved joints, but there were also 3 central nervous system bleeds and 4 surgical procedures. Ninety-three percent of bleeds were controlled, 36% with one infusion in 12 h and another 42% within 36 h. Hilgartner et al. later reported on the efficacy and safety of the second generation vapour-heated product, FEIBA-VH [5]. Seventy-nine percent of 106 bleeding episodes in inhibitor patients were controlled within 36 h, without significant toxicity. These results compared favourably with earlier studies and confirmed that the heat treating process did not alter efficacy. The largest observational trial on the use of FEIBATM was a retrospective multi-centre French study [6]. Data was presented on 433 bleeding episodes, including surgical procedures, involving 60 patients. Efficacy was good or excellent in 81.3% and poor in 16.9% of treatment episodes. Tolerance was assessed as good in 98.8%, however an anamnestic response was noted in 31.5% of cases.

The first significant study reporting the use of Autoplex®T was by Kurczynski and Penner in 1974 [7]. Single doses of Autoplex®T were used to treat 60 bleeds in 8 severe haemophilia A inhibitor patients. Treatment was considered effective in most cases. A later study by Abildgaard [8] used up to two doses of Autoplex®T within a 24-hour period to treat 25 bleeds in 9 severe haemophilia A inhibitor patients. Efficacy was reported at 88%. Multiple doses were effective in the treatment of 8 major bleeds occurring in 7 patients. Lusher et al. [9] conducted a controlled double-blind study to compare the effectiveness of Autoplex®T with Proplex, a prothrombin complex concentrate for the treatment of acute haemarthrosis. Efficacy at 6 h was just over 50% in all treatment groups and indicated that no additional benefit was derived from
using the activated PCC. The largest study assessing the efficacy of Autoplex®T was reported by Kantrowitz et al. [10]. 454 infusions of Autoplex®T were used to treat 120 bleeding episodes in 60 severe haemophilia A patients with inhibitors. Autoplex®T was effective in the treatment of 87% of the bleeds.

Experience with aPCCs in Surgery

FEIBA™ and Autoplex®T have also been reported to be effective in providing cover for minor and major surgery and dental extractions in patients with inhibitors [6, 11]. The evidence base for use of FEIBA™ in surgery is restricted to only a few reports. Negrier et al [6] reported FEIBA™ was haemostatically effective in the treatment of 19 minor surgical procedures and effective in 4 major procedures in 3 patients. One patient had bilateral knee replacements and, subsequently, musculo-skeletal grafting. A second patient had a prostatectomy and a third patient had a full dental clearance. FEIBA™ was also reported to be effective as second-line treatment in 7 individuals who had undergone major surgical procedures complicated by development of anamnesis to either human or porcine factor VIII.

Published experience with the use of Autoplex®T in surgery on haemophilia A inhibitor patients is restricted to just one report [12]. Multiple doses of Autoplex®T effectively controlled haemostasis during a full dental clearance in 2 patients and a right forearm haematoma bleed in 1 patient.

Safety of aPCCs

Both FEIBA™ and Autoplex®T undergo viral inactivation procedures during manufacture [13]. The starting material for Autoplex®T undergoes an augmented Cohn alcohol fractionation and then the final product is dry heat treated for 6 days at 57°C. FEIBA™ undergoes a two-stage vapour-heating treatment, initially for 10 h at 60°C and then 1 h at 80°C. Although FEIBA™ was associated with transmission of hepatitis B and C, there have been no reports of viral transmission since the introduction of viral inactivation procedures. Autoplex®T has not been associated with viral transmission.

Minor reactions have been reported in association with both FEIBA™ and Autoplex®T. These include headache, nausea, pruritus, skin rashes and diarrhoea. Such reactions were reported to have occurred in association with 8% of Autoplex®T infusions [10] and in 3.7% of FEIBA™ infusions [4].

Thrombotic complications including myocardial infarction and subclinical disseminated intravascular coagulation, although very rare, have been reported in association with FEIBA™, especially in patients undergoing surgery or in those who have received repeated high doses of the concentrate. A maximum daily dose of FEIBA™ of 200 U/kg has been recommended to minimise the risk of thrombogenicity. Moreover, the product should be avoided in patients with a history of vascular occlusive disease [14]. Although there has been no report of myocardial infarction or disseminated intravascular coagulation associated with the use of Autoplex®T as a single agent, the potential thrombogenic risk of this product is recognised and concomitant treatment with antifibrinolytic agents should be avoided.

Anamnestic increases of inhibitor levels have been reported in up to 30% of patients with haemophilia A receiving FEIBA™, due to the presence of small amounts of FVIII in the product [15]. However, in over 50% of these patients who remain on regular FEIBA™ therapy the antibody level gradually falls. Autoplex®T has also been associated with the development of anamnestic responses in some patients. However, anamnestic responses to aPCCs are not associated with a reduction in the efficacy of these products.

Conclusion

Both FEIBA™ and Autoplex®T appear to be effective and safe in the management of bleeding episodes and surgery in haemophilia inhibitor patients. There is currently no laboratory test for monitoring the efficacy of aPCCs and dosage must be determined solely by clinical assessment. However, it is believed that the clinical effect of FEIBA™ may correlate with circulating thrombin generating potential and a fluorogenic substrate assay is being developed to enable monitoring of FEIBA™ dosage in vitro.
References


