The Continuous Infusion of Recombinant Activated Factor VIIa (rFVIIa) in Patients with Factor VIII Inhibitors Activates the Coagulation and Fibrinolytic Systems without Clinical Complications

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Abstract

The standard modality of administration of rFVIIa to patients with FVIII and FIX inhibitors is the intermittent infusion every 2 to 6 hours. No untoward local or systemic effects have been reported; laboratory data of activation of coagulation were reported in the presence of coexistent problems (sepsis, septic shock) or with high doses. We treated four patients with FVIII inhibitor with rFVIIa administered by continuous infusion by a central vein catheter, monitoring the signs of systemic activation of the hemostatic system. The F\textsubscript{1+2}, prothrombin fragments and the D-dimer increased after the bolus, and remained above the baseline values throughout the treatment period. These variations observed during the infusion period were not accompanied by clinical events.

Key Words: rFVIIa; Continuous infusion; Systemic hemostasis activation

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Abbreviations: rFVIIa, recombinant activated factor VII; CVC, central vein catheter; F\textsubscript{1+2}, prothrombin fragment 1+2.

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We have treated four patients with FVIII inhibitor with rFVIIa administered by continuous infusion through a central vein catheter (CVC). The patients were monitored throughout the duration of therapy for signs of systemic activation of the clotting system.

1. Materials and Methods

1.1. Patients History

- **Patient number 1.** A 52-year-old man with severe hemophilia A was admitted on June 16th 1997 because of severe anemia (Hb 6 g/dl) secondary to a spontaneous extensive hematoma of the right shoulder and of the right lateral region of the chest. Bleeding was controlled with human FVIII concentrates (aPTT ratio 1.4 after infusion of FVIII 50 U/kg). On June 25th, the patient experienced a complete atrial ventricular block, and a pacemaker was implanted under coverage with human FVIII concentrate. On June 26th, severe bleeding occurred at the point of insertion of the electrocatheter in spite of the intensive replacement therapy (FVIII 5000 U every 12 hours). The aPTT ratio was not modified by the treatment (R 2.8). FVIII inhibitor assay: anti-human 17 BU, anti-porcine 6 BU. On June 27th, surgical revision was carried out under coverage with rFVIIa: 90 μg/kg (4.8 mg) by bolus followed by 11.5 μg/kg/hr (3.6 mg every 6 hours) for 18 days by continuous infusion through a CVC, and evidenced the displacement of the electrocatheter and a lesion of the cephalic vein. Bleeding ceased after the surgical procedure. Local bleeding recurred on July 3rd and persisted in spite of rFVIIa treatment until July 11th, when the surgeon agreed to intervene. The surgical revision evidenced a new lesion of the cephalic vein; the pacemaker was removed and the bleeding ceased.

- **Patient number 2.** A 26-year-old severe hemophilia A patient was admitted because of massive hemoperitoneum with severe anemia (Hb 8.5 g/dl). The patient was known to be a high responder and was on an immuno-tolerance program. FVIII inhibitor assay: anti-human 12 BU, anti-porcine undetectable. Bleeding was not controlled by continuous infusion of rFVIIa (bolus 90 μg/kg followed by 20 μg/kg/hr for 4 days), but by the subsequent infusion of porcine FVIII (8000 U/day for 3 days and 3600 U/day for 5 days).

- **Patient number 3.** A 76-year-old woman with hypertension, atrial fibrillation, diabetes mellitus, presented with extensive buttock hematoma secondary to i.m. injection and severe anemia (7 g/dl). The anti-FVIII inhibitor titer was anti-human 620 BU, anti-porcine 160 BU. The patient was treated with rFVIIa (bolus 90 μg/kg followed by 15 μg/kg/hr for 8 days), and the bleeding was completely controlled. The patient was discharged on immunosuppressive therapy (prednisone + cyclophosphamide).

- **Patient number 4.** A 57-year-old severe hemophilia A patient underwent total knee arthroprotesis in May 1998. Prior to surgery, the FVIII inhibitor activity, routinely assayed, was absent. Perioperatively, he was treated with human FVIII concentrate for 18 days. On August 27th he developed extensive hematoma of the thorax while on prophylactic treatment during rehabilitation. The anti-FVIII inhibitor titer was antihuman 18 BU, anti-porcine 2 BU. The bleeding was controlled by rFVIIa treatment (bolus 90 μg/kg followed by 18 and 10 μg/kg/hr for 3 days, respectively). The patient is on home treatment with rFVIIa on demand.

In all patients a CVC was positioned through the external jugular vein. The rFVIIa was administered by continuous infusion by a pump-driven syringe; heparin was not added to the regimen. The dose was adjusted during the whole treatment period with the aim of achieving a plasma level of FVII:C at or above 10 U/mL.

2. Methods

Platelet count, fibrinogen, FVII:C, D-dimer, and F1+2 prothrombin fragments were determined throughout the treatment period. The FVII:C was assayed by one stage-method using human placenta as thromboplastin (Thromborel, Behring, Marburg, Germany). The FVIII inhibitor was assayed by the Nijmegen modification of the Bethesda method [10]. D-dimer and F1+2 were determined by Nycoard Nycomed (Oslo, Norway) and Enzygnost Behring (Marburg, Germany) methods, respectively.

3. Results

The details of the treatment and the relevant laboratory data are reported in Table 1. A FVII:C level above 10 U/mL was obtained in all four patients after the bolus and maintained in three out of four throughout the maintenance treatment. No signifi-
Table 1. rFVIIa administered by continuous infusion in patients with FVIII inhibitor: details of the treatment and the relevant laboratory data

<table>
<thead>
<tr>
<th>Pt</th>
<th>Treatment</th>
<th>rFVIIa (µg/kg/hr)</th>
<th>Total dose (mg)</th>
<th>FVII:C (U/mL)</th>
<th>Platelet (10^9/L)</th>
<th>Fbg (g/L)</th>
<th>D-d (µg/mL)</th>
<th>F1+2 (nM/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pre</td>
<td></td>
<td>0.6</td>
<td>200</td>
<td>4.5</td>
<td>0.5</td>
<td>1.11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bolus</td>
<td>90</td>
<td>23</td>
<td>205</td>
<td>4.9</td>
<td>2.0</td>
<td>3.17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C.I.×18 days</td>
<td>11.5</td>
<td>239</td>
<td>5.2-6.9</td>
<td>165-205</td>
<td>3.4-5.3</td>
<td>0.5-2.0</td>
<td>1.2-2.5</td>
</tr>
<tr>
<td>2</td>
<td>Pre</td>
<td></td>
<td>1.03</td>
<td>185</td>
<td>3.4</td>
<td>0.5</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bolus</td>
<td>90</td>
<td>16</td>
<td>187</td>
<td>3.3</td>
<td>2.0</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C.I.×4 days</td>
<td>20</td>
<td>92</td>
<td>11-14</td>
<td>154-187</td>
<td>3.1-3.8</td>
<td>0.7-2.0</td>
<td>3.9-6.4</td>
</tr>
<tr>
<td>3</td>
<td>Pre</td>
<td></td>
<td>0.7</td>
<td>198</td>
<td>3.8</td>
<td>0.5</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bolus</td>
<td>100</td>
<td>24</td>
<td>186</td>
<td>4.2</td>
<td>1.5</td>
<td>2.8</td>
<td></td>
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<tr>
<td></td>
<td>C.I.×8 days</td>
<td>15.4</td>
<td>283</td>
<td>15-24</td>
<td>58-183^b</td>
<td>3.0-3.4</td>
<td>0.5-1.5</td>
<td>2.5-3.1</td>
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<tr>
<td>4</td>
<td>Pre</td>
<td></td>
<td>0.8</td>
<td>185</td>
<td>6.24</td>
<td>0.7</td>
<td>1.0</td>
<td></td>
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<tr>
<td></td>
<td>Bolus</td>
<td>90</td>
<td>14</td>
<td>178</td>
<td>7.21</td>
<td>1.0</td>
<td>1.25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C.I.×6 days</td>
<td>18-10</td>
<td>125</td>
<td>10-14</td>
<td>152-215</td>
<td>6.3-6.7</td>
<td>0.7-2.0</td>
<td>1.1-1.9</td>
</tr>
<tr>
<td>R.I.</td>
<td>—</td>
<td></td>
<td>0.7-1.3</td>
<td>140-320</td>
<td>1.76-4.1</td>
<td>&lt;0.5</td>
<td>0.4-1.2</td>
<td></td>
</tr>
</tbody>
</table>

^a Pt = patient; C.I. = continuous infusion; R.I. = reference interval; Fbg = fibrinogen; D-d = D-dimer; F1+2 = prothrombin fragments 1+2.

^b thrombocytopenia and neutropenia because of the concomitant cyclophosphamide therapy.

4. Discussion

The main object of this study is the evaluation of the systemic activation of the coagulation-fibrinolytic system with the continuous infusion of the rFVIIa. Experience with rFVIIa in the treatment of bleeding in the patients with hemophilia and FVIII/IX inhibitors, and in patients with acquired hemophilia, is quite extensive [2]. Thrombotic clinical events were very rare, and in some patients the relation to rFVIIa was uncertain. Data related to the systemic activation of the hemostatic and fibrinolytic systems with the intermittent schedule are very scarce and do not provide a definite answer. rFVIIa was administered by continuous infusion to 26 patients with different hemostatic defects (hemophilia A and B, acquired haemophilia A, Glanzmann’s thrombasthenia) either for prophylaxis in surgical procedures or for treatment for bleeding episodes [11]. Local thrombophlebitis occurred in four patients; the only episode of DIC was secondary to septic shock. Laboratory data indicative of systemic activation of the hemostatic-fibrinolytic system as a consequence of the treatment were not observed in the few patients investigated [7,11]. In our four patients, the continuous infusion was carried out for 4–18 days. A level of FVII:C greater than 10 U/mL was obtained after the bolus infusion in four patients and maintained throughout the infusion period. No untoward effects were observed.

References

2. Hedner U. Treatment of patients with factor VIII and factor IX inhibitors with special focus


