Thrombosis

Treatment of heparin-induced thrombocytopenia with fondaparinux

Anticoagulation of patients with heparin-induced thrombocytopenia (HIT) may be limited by cross-reaction of HIT antibodies with danaparoid and generation of antibodies during therapy with lepirudin. We used fondaparinux to treat 6 patients with a history of HIT with thromboembolism and 2 patients with thrombocytopenia during low-molecular-weight heparin administration.

Table 1. Clinical features of type II HIT patients treated with fondaparinux.

<table>
<thead>
<tr>
<th>Initials</th>
<th>Age (y)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>episode, year, heparin, indication</th>
<th>HIPA</th>
<th>Indication for TEP with fondaparinux, duration</th>
<th>VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-G</td>
<td>82</td>
<td>152</td>
<td>91</td>
<td>HIT II, DVT, 1997, UFH post-operative TEP</td>
<td>pos</td>
<td>pneumonia, atrial fibrillation, 14 days</td>
<td>yes</td>
</tr>
<tr>
<td>D-K</td>
<td>31</td>
<td>207</td>
<td>135</td>
<td>HIT II, DVT 1995, UFH post-operative TEP</td>
<td>pos</td>
<td>cerebro-abdominal shunt operation, 15 days</td>
<td>yes</td>
</tr>
<tr>
<td>M-K</td>
<td>73</td>
<td>160</td>
<td>75</td>
<td>HIT I, thrombocytopenia, 2003, LMWH, non-operative TEP</td>
<td>n.a.</td>
<td>cerebral infarction, 14 days</td>
<td>no</td>
</tr>
<tr>
<td>A-S</td>
<td>74</td>
<td>147</td>
<td>57</td>
<td>HIT I, thrombocytopenia, 2003, LMWH, non-operative TEP</td>
<td>neg</td>
<td>cerebral infarction, 7 days</td>
<td>no</td>
</tr>
<tr>
<td>*K-L1</td>
<td>65</td>
<td>178</td>
<td>82</td>
<td>HIT II, PE, 1998, UFH post-operative TEP</td>
<td>pos</td>
<td>cholecystitis, yes</td>
<td>12 days</td>
</tr>
<tr>
<td>*K-L2</td>
<td>65</td>
<td>178</td>
<td>82</td>
<td>HIT II, PE, 1998, UFH post-operative TEP</td>
<td>pos</td>
<td>cholecystectomy, yes</td>
<td>15 days</td>
</tr>
<tr>
<td>E-E</td>
<td>75</td>
<td>170</td>
<td>64</td>
<td>HIT II, PE, 1999, LMWH post-operative TEP</td>
<td>pos</td>
<td>pancreatitis, yes</td>
<td>13 days</td>
</tr>
<tr>
<td>S-H</td>
<td>74</td>
<td>174</td>
<td>80</td>
<td>HIT II, MI, 1997, UFH post-operative TEP</td>
<td>pos</td>
<td>cerebral infarction, 14 days</td>
<td>no</td>
</tr>
</tbody>
</table>

HIPA: heparin-induced platelet aggregation assay; HIT: heparin-induced thrombocytopenia; DVT: deep vein thrombosis; PE: pulmonary embolism; MI: myocardial infarction; UFH: unfractionated heparin; LMWH: low-molecular-weight heparin; TEP: thromboembolic prophylaxis; VKA: current therapy with vitamin-K antagonist. *Patient K-L was treated twice on different occasions.
days was chosen due to the efficacy of this dosage for both prophylaxis and treatment of thromboembolism.

Table 1 presents the patients’ anthropometric data, history of HIT, results of the heparin-induced platelet aggregation assay (HIPA), indication for prophylaxis of venous thromboembolism, and the oral anticoagulation with phenprocoumon. Oral anticoagulation was stopped upon hospitalization and fondaparinux was started when the INR ≤ 2.0. Prophylaxis of thromboembolism was given for 7 to 14 days depending on the clinical indication and the need to restart phenprocoumon. All patients gave written informed consent following the approval of the study by the ethics committee. The anticoagulant effect was determined in order to obtain information on the changes of the coagulation parameters. The activated partial thromboplastin time (aPTT) was measured using a commercially available reagent, pathrombin (Dade Behring, Munich, Germany). Heptest assay was performed as described by Haemachem (St. Louis, USA). Factor Xa and Recalmix were from Laborservice (Augsburg, Germany). Normal values ranged from 13 to 20 sec. Factor Xa inhibition was measured by the S2222 chromogenic substrate assay and purified factor Xa (both reagents from Haemochrom Diagnostika, Essen, Germany). The lower limit of detection of fondaparinux was 0.1 µg/mL.

Platelet count remained unchanged in the 6 patients with a history of HIT, but increased in the 2 patients with thrombocytopenia during low-molecular-weight heparin therapy from 43-445×10^9/L and from 40-172×10^9/L (Figure 1). The aPTT values did not change during therapy (data not shown).

Trough levels of factor Xa inhibition ranged between 0.2 and 0.5 µg fondaparinux/mL and peak levels (Figure 1) between 0.3 and 1.1 µg/mL 2 hrs after s.c. injection. The Heptest coagulation values ranged between a minimum of 76 to 96 sec and a maximum of 80 to 112 sec (Figure 1). The correlation of the fondaparinux levels determined by the S2222 assay and the heptest was r = 0.73.

No hemorrhagic side effects or adverse events were observed. None of the patients developed thromboembolic complications. In 5 patients phenprocoumon was restarted and fondaparinux was stopped at an INR of ≤ 2.0.

We report on patients with a history of type II HIT or with thrombocytopenia during administration of low-molecular-weight heparin who were treated effectively and safely by 2.5 mg fondaparinux given subcutaneously once daily for 14 days. So far fondaparinux has been given safely to patients with local intolerance to heparin, low molecular weight heparin and danaparoid. The dose of 2.5 mg fondaparinux once daily was effective in reducing thromboembolism in patients undergoing orthopedic operations. We assumed those patients with a history of HIT or thrombocytopenia associated with heparin administration could be treated effectively with the same dose of fondaparinux. The anticoagulant parameters demonstrated that the S2222 chromogenic FXa assay and the heptest might be used to determine the anticoagulant effects of fondaparinux. An international collaborative study (personal communication) is currently being performed to assess the value of these assays during fondaparinux treatment.

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Key words: Heparin-induced thrombocytopenia, fondaparinux, platelets, thrombosis, factor Xa inhibition

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References