Treatment of the heparin-induced thrombosis-thrombocytopenia syndrome by very low dose streptokinase

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Heparin-induced thrombocytopenia (HIT) is a serious complication of heparin treatment. The onset of thrombosis in this context raises a very difficult therapeutic problem because 29% mortality and a 21% limb amputation rate are reported when this complication occurs. Oral anticoagulant treatment does not always prevent complications, which may occur before the oral anticoagulant becomes effective. In addition to stopping heparin treatment and starting treatment with oral anticoagulant, interruption of the vena cava, thrombectomy, and antiplatelet agents have all been tried, with a low success rate. We describe a patient with HIT in whom extensive venous thrombosis was treated very effectively with low-dose thrombolyis.

A 71 year old woman was admitted to hospital for investigation of arrhythmia. Endocavitary exploration required a lengthy procedure (more than 3 hours) and involved many venous routes of access, the right femoral in particular. She was treated with subcutaneous heparin for the five days after this investigation. Three weeks later, she was readmitted because of deep venous thrombosis of the right leg. Phlebography revealed right venous thrombosis extending up to the femoral vein. Treatment with heparin (25 000 units/day) was started. Forty eight hours later the platelet count had fallen from an initial count of 290 000/mm³ to 80 000/mm³ and then to 36 000/mm³. The detection of anti-platelet antibodies directed against PF₄ confirmed HIT (Asserachrom elisa test). Heparin was stopped (D0).

Oral anticoagulants were started on D0 and a temporary vena cava filter was inserted via the brachial vein to bridge the interval before the oral anticoagulants became effective. Opacification of the vena cava during this procedure revealed the extension of venous thrombosis. The tip of the non-occlusive thrombus was now highly mobile in the inferior vena cava, 6 cm above the junction with the renal veins. There was a fresh thrombosis in the left femoral and iliac system, contralateral to the initial thrombophlebitis. Clotting studies on D0 gave the following results: platelets 34 000/ml; PT 49%; factor V, VII, and X 80–100%; APTT 44 s (control 32 s); fibrinogen 4 6 g/l; D dimers 16 µg/ml; FDP 320 µg/ml; soluble complexes, positive. Extension of thrombosis within the vena cava together with the presence of thrombus above the renal veins in this non-anticoagulated patient with HIT suggested a high risk of renal vein thrombosis and/or serious pulmonary embolism. After the risks of surgery were explained the patient and her family refused to consent to an operation to remove thrombus from the vena cava.

Medical thrombolysis was started, with the patient's consent. She was given 25 000 units/hour of streptokinase (without bolus dose) for 96 hours. This unusually low dose was believed to be appropriate in the circumstances.

Prothrombin time (PT) fell to values < 10% immediately after the start of thrombolysis (PT uninterpretable because of thrombolysis and hypofibrinogenemia). Satisfactory anticoagulation with oral anticoagulant was achieved on the fourth day (factor VII and II < 40%) (table). During the course of thrombolysis, soluble complexes disappeared and the platelet count increased to 60 000/ml, 90 000/ml, and 160 000/ml on D1, D2, and D6 respectively. The increase in D-dimers during thrombolytic treatment confirmed fibrinolysis.

On D4, when oral anticoagulants had become effective (factors II, VII, X < 40%), iliocaval angiography through the temporary filter showed a spectacular improvement. The inferior vena cava and renal, iliac, and femoral veins were free of thrombus and patent. Thrombolysis was stopped. It had caused no bleeding. Phlebography on D7 showed only a persistent bilateral calf thrombosis. On D12, the patient was discharged from hospital on oral anticoagulants and with the absolute con-

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**Treatment regimen**

<table>
<thead>
<tr>
<th>Streptokinase</th>
<th>D0</th>
<th>D1</th>
<th>D2</th>
<th>D4</th>
<th>D6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platelets (x10⁹)</strong></td>
<td>34 000</td>
<td>60 000</td>
<td>90 000</td>
<td>100 000</td>
<td>160 000</td>
</tr>
<tr>
<td><strong>PT (%)</strong></td>
<td>43</td>
<td>&lt; 10</td>
<td>&lt; 10</td>
<td>&lt; 10</td>
<td>38</td>
</tr>
<tr>
<td><strong>Factor II (%)</strong></td>
<td>100</td>
<td>85</td>
<td>80</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td><strong>Factor V (%)</strong></td>
<td>100</td>
<td>80</td>
<td>105</td>
<td>115</td>
<td>90</td>
</tr>
<tr>
<td><strong>Fibrinogen (g/l)</strong></td>
<td>3 2</td>
<td>0 6</td>
<td>0 6</td>
<td>0 6</td>
<td>4</td>
</tr>
<tr>
<td><strong>D-dimer (µg/ml)</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

D0, before start of thrombolysis; D4, end of thrombolysis; PT, Prothrombin time; D, D dimer; SC, Soluble complexes.
traindication for heparin therapy. HIT is a serious complication of heparin treatment. In our patient, HIT was complicated by extensive venous thrombosis of both legs and a threatening clot above the renal veins. The treatment strategy was intended to limit the thrombogenic effects of HIT while the oral anticoagulants became fully effective. The increase in D-dimers, disappearance of soluble complexes, and the increase in platelet count indicated that the thrombolytic treatment was effective.

Thrombolytic treatment while dissolving clots may have prevented platelet consumption and have impeded the process of heparin-induced thrombocytopenia.

Thrombotic complications secondary to immuno-allergic heparin-induced thrombocytopenia are relatively common because of the widespread use of heparin. An effective treatment is vital because the mortality and morbidity are high in patients with this syndrome. Few cases of thrombolytic treatment of HIT have been described. In all of them a full-dose thrombolytic treatment was used. The risk of bleeding associated with these full doses must be weighed against the potential benefit of lysis of thromboses, and this is bound to limit the use of such a treatment. In our case small doses of streptokinase were totally effective. Perhaps, as our case seems to show, the platelet-fibrin composition of thrombi in this syndrome is amenable to a lower thrombolytic dose regimen. Bearing in mind the very poor prognosis of HIT with extensive thrombosis, its iatrogenic cause, and the lack of an effective treatment, thrombolysis is certainly worth evaluating.