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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.

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Thrombocytopenia is a potentially serious side effect following administration of heparins. In type I heparin-induced thrombocytopenia (HIT) there is a temporary decrease of platelets following heparin administration. Type II HIT is an immune-mediated reaction which usually develops 5 to 10 days after heparin administration but can manifest earlier in cases of re-exposure to heparin. It is mediated by antibodies against a neoantigen of platelet factor 4 formed by complexing with heparin. In the presence of HIT antibodies, thromboembolic complications develop in up to 50% of patients, producing a thrombotic risk ratio of more than 30.[1] Discontinuation of heparin and alternative anticoagulation is required. Lepirudin,[2] danaparoid[3] and argatroban[4] are effective anticoagulants for continuing anticoagulation in these patients, although anticoagulation of patients may be limited by cross-reaction of HIT antibodies with danaparoid and generation of antibodies during therapy with lepirudin.[5]

The linear, polysulfated glycosaminoglycan heparin contains a unique pentasaccharide sequence that binds to antithrombin. This pentasaccharide does not bind to platelet factor 4[6] and does not react with heparin-induced antibodies in the presence of platelet factor 4 and platelets. The synthetic compound, fondaparinux has been proven to be more effective than enoxaparin for post-operative prophylaxis of thromboembolism at a once daily dose of 2.5 mg subcutaneously.[7] Given that fondaparinux does not bind to platelet factor 4 or HIT antibodies,[8] we used it to treat 8 patients with an acute episode or a history of type II HIT. The once daily subcutaneous administration of 2.5 mg for 7-14

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

Initials	*Age (y)*	*Height (cm)*	*Weight (kg)*	*episode, year, heparin, indication*	*HIPA*	*Indication for TEP with fondaparinux, duration*	*VKA*
M-G	82	152	91	HIT II, DVT, 1997, UFH post-operative TEP	pos	pneumonia, atrial fibrillation 14 days	yes
D-K	31	207	135	HIT II, DVT 1995, UFH post-operative TEP	pos	cerebro-abdominal shunt operation, 15 days	yes
M-K	73	160	75	HIT I, thrombocytopenia, 2003, LMWH, non-operative TEP	n.a.	cerebral infarction, 14 days	no
A-S	74	147	57	HIT I, thrombocytopenia, 2003, LMWH, non-operative TEP	neg	cerebral infarction 7 days	no
*K-L 1	65	178	82	HIT II, PE, 1998, UFH post-operative TEP	pos	cholecystitis 12 days	yes
*K-L 2	65	178	82	HIT II, PE, 1998, UFH post-operative TEP	pos	cholecystectomy 15 days	yes
E-E	75	170	64	HIT II, PE, 1999, LMWH post-operative TEP	pos	pancreatitis 13 days	yes
S-H	74	174	80	HIT II, MI , 1997, UFH post-operative TEP	pos	cerebral infarction 14 days	no

*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.*

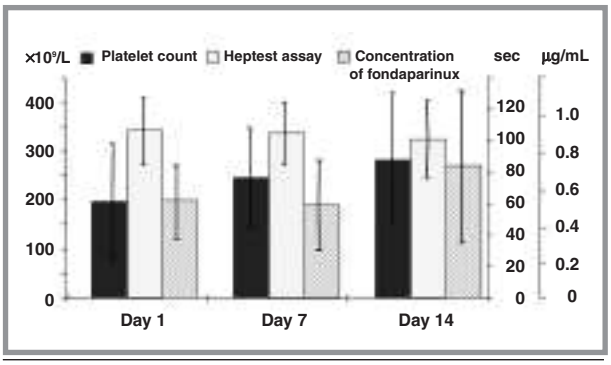

Figure 1. Platelet count and peak levels of fondaparinux determined by the S2222 chromogenic substrate assay (concentration of fondaparinux, µg/mL) and Heptest (coagulation time, sec) at days 1, 7 and 14 during treatment with 2.5 mg fondaparinux once daily subcutaneously.

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 agggregation 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, pathromtin (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.[9] The dose of 2.5 mg fondaparinux once daily was effective in reducing thromboembolism in patients undergoing orthopedic operations.[10] 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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