Clinical Cross-Reactivity Between Danaparoid and Heparin Antibodies Successfully Managed with Bivalirudin

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Heparin is a drug widely used in the intensive care unit for thromboprophylaxis or for treatment of many clinical situations including acute coronary events, atrial fibrillation, venous thromboembolism and peripheral vascular disease, and during extracorporeal circulation. However, heparin has been associated with serious adverse effects including immune mediated heparin-induced thrombocytopenia (type 2 HIT) and heparin-induced thrombocytopenia and thrombosis syndrome. Immune mediated HIT develops within 5 to 14 days of heparin exposure, though it may occur within hours if the patient has had recent heparin exposure, or rarely days to weeks after heparin is discontinued. It develops in 2%–5% of patients treated with unfractionated heparin and in less than 1% in patients who receive low molecular weight heparin. Immune mediated HIT occurs due to a hypersensitivity reaction to the platelet factor 4/heparin complex. Immunoglobulin G antibodies are produced and form immune complexes comprising IgG/PF4/heparin on the platelet surface, which leads to platelet activation, aggregation, release of prothrombotic platelet-derived microparticles and eventually the development of thrombocytopenia and thrombosis. These complexes may also cause endothelial damage, platelet-leukocyte aggregation and thrombosis. The diagnosis of type 2 HIT is made when thrombocytopenia or thrombosis is present in the face of antibodies to unfractionated heparin or low molecular weight heparin. Without treatment, mortality in HIT patients with new thromboembolic complications is 20–30%. When immune mediated HIT is suspected clinically, immediate cessation of all formulations of heparin is mandatory while laboratory confirmation or refutation is sought. Discontinuation of heparin alone does not halt continuing thrombin generation nor does it avoid subsequent thrombotic events, which occur in as many as 20–53% of patients despite cessation of heparin [1]. Patients will therefore require antithrombotic therapy with an alternative anticoagulant, especially if there is recent or new thrombosis.

Today there are several good options available for treating HIT. Direct thrombin inhibitors (lepirudin, argatroban, bivalirudin) and factor Xa inhibitors (danaparoid, fondaparinux) have been used effectively in HIT. Danaparoid is commonly used in Israel, Canada, Australia and Europe in the setting of HIT and HITT. Cross-reactivity between heparin antibodies and danaparoid resulting in thrombocytopenia or thrombosis is extremely rare. We present a patient with proven type 2 HIT, who demonstrated clinical cross-reactivity between danaparoid and heparin antibodies resulting in persistent thrombocytopenia.

HIT = heparin-induced thrombocytopenia
IgG = immunoglobulin G
PF4 = platelet factor 4

HITT = HIT and thrombosis syndrome

PATIENT DESCRIPTION

A 52 year old previously healthy man with a history of heavy smoking was admitted to hospital complaining of retrosternal chest pain. A non-ST elevation myocardial infarct was diagnosed. Treatment with enoxaparin, aspirin and beta-blockers was started. Cardiac catheterization was promptly performed which revealed single-vessel disease requiring the insertion of a stent into the diagonal artery. The procedure was complicated by hemorrhagic shock due to extensive retroperitoneal bleeding from a tear of the right external iliac artery, which resulted in cardiac arrest. The patient underwent successful cardiopulmonary resuscitation. He received blood, fresh frozen plasma and platelets and surgical repair of his iliac artery was performed. Administration of enoxaparin was halted. His hemodynamic state as well as hematological parameters stabilized. Four days after surgery there was no evidence of ongoing bleeding. International normalization ratio, partial thromboplastin time, fibrinogen and platelets returned to normal. The patient was still ventilated and started showing signs of neurological recovery. Thromboprophylaxis was initiated with subcutaneous enoxaparin 40 mg daily.

Eleven days after receiving the first dose of enoxaparin he developed severe thrombocytopenia [Figure] and a thrombosis of his right subclavian vein was detected. Enoxaparin was immediately discontinued. The PF4/heparin enzyme immunoassay confirmed the presence of HIT. Danaparoid was instituted to

attain complete anticoagulation based on anti-Xa levels. Cessation of enoxaparin and the administration of danaparoid resulted in a slight improvement of platelet levels from 30 x 10^9/L to 55 x 10^9/L. However, 2 weeks after starting danaparoid, the platelet level had not increased above 55 x 10^9/L [Figure]. In the absence of any other obvious reason for thrombocytopenia, *in vivo* cross-reactivity of danaparoid with the heparin immune complex was suspected. A functional test to determine *in vitro* cross-reactivity was not performed. Danaparoid was discontinued and bivalirudin started. Within 2 days of stopping danaparoid platelet levels increased to 73 x 10^9/L and after a further 2 days to 135 x 10^9/L. Since the platelet levels reached more than 100 x 10^9/L, coumadin was added. When the target INR was achieved, bivalirudin was discontinued. The patient was discharged to a rehabilitation facility; his platelet level was normal and he was taking coumadin. He had no further hematological sequelae.

COMMENT

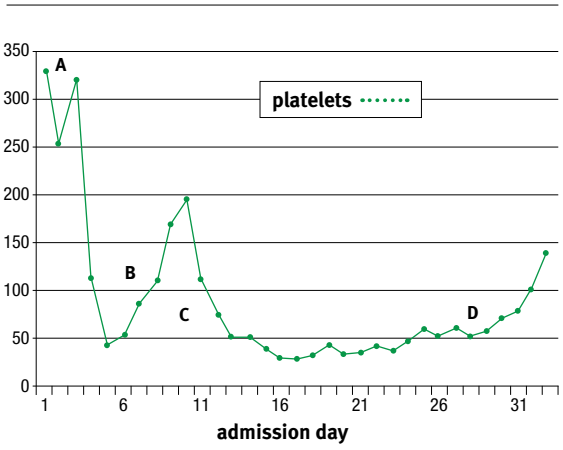
HIT can have catastrophic consequences resulting in multiple thrombosis, emboli, limb ischemia and gangrene, and even death. The increased thrombin generation present in HIT may continue even after discontinuing heparin administration [1]. Alternative anticoagulant therapy is urgently required [2]. Vitamin K antagonists may precipitate severe thrombosis in patients with HIT and are contraindicated until the platelet count has risen above 100,000/µl. Currently, treatment is directed at reduction of thrombin generation either directly (lepirudin, bivalirudin, argatroban) or by means of factor Xa inhibition. (danaparoid, fondaparinux).

Danaparoid is a low molecular weight heparinoid derived from porcine gut mucosa. Its active components consist of heparan sulfate, dermatan sulfate and chondroitin sulfate. The major difference between danaparoid and other LMWHs is that danaparoid is devoid of heparin or heparin fragments. It inhibits thrombin generation by accelerating antithrombin inactivation of factor Xa and inhibits thrombin activity via both antithrombin and heparin cofactor II [3]. Problems with danaparoid include its long half-life, difficulties in monitoring its effect, and the absence of well-grounded dosing schedules. A particular worrisome problem is the cross-reactivity of danaparoid with pathogenetic heparin-induced PF4 antibodies.

Although *in vitro* cross-reactivity occurs in about 10% of patients, thromboembolic events as well as thrombocytopenia have rarely been described in patients with HIT or HITT who are subsequently treated with danaparoid [4]. The great majority of patients with such *in vitro* cross-reactivity is clinically irrelevant, with patients improving on therapy despite laboratory cross-reactivity confirmation. Nevertheless, there are reports in the literature where antibody cross-reactivity has led to new complications and unsatisfactory outcomes [4,5].

In these rare cases of *in vivo* cross-reactivity, it is not clear whether the thrombocytopenia and thromboembolic events were due to immune mediated cross-reactivity or other factors such as delay in danaparoid treatment initiation, insufficient dosing intensity or premature cessation of danaparoid administration.

Our patient developed HITT with thrombocytopenia and thrombosis of the right subclavian vein. After discontinuing enoxaparin, danaparoid was started. The platelet count increased slightly but then stabilized at 55,000/µl without further increase. Unfortunately, a confirmatory functional assay of danaparoid cross-reactivity was not performed.



Graph showing changes in platelet numbers during the patient's admission. **[A]** First dose of enoxaparin. **[B]** Enoxaparin re started. **[C]** Evidence of heparin-induced thrombocytopenia, enoxaparin stopped, danaparoid started. **[D]** Danaparoid stopped, bivalirudin started

Danaparoid was discontinued and bivalirudin was started. Within 4 days of stopping danaparoid, the platelet count had returned to normal. The patient did not develop any further thromboembolic phenomena. It appears that *in vivo* danaparoid cross-reactivity was the reason the thrombocytopenia did not resolve.

Magnani and Gallus [5] examined the clinical outcomes of 1478 patients with HIT who were treated with danaparoid. Danaparoid use in patients with known pretreatment danaparoid cross-reactivity was found to have an increased risk of non-fatal thrombotic events, whereas patients who develop seroconversion during treatment show a dramatic increase in both thromboembolic and other causes of death. Mangnani and Gallus recommended that danaparoid be withheld if pretreatment cross-reactivity is present. If cross-reactivity develops during treatment, then danaparoid should be stopped immediately and an alternative form of anticoagulation initiated [5].

Although rare, patients who are treated with danaparoid should be closely monitored for *in vivo* cross-reactivity. Magnani and Gallus recommend daily platelet counts during the first week of danaparoid administration, on alternative days during the subsequent 2 weeks

INR = international normalized ratio

LMWH = low molecular weight heparin

and then on a weekly basis while continuing danaparoid administration [5].

Our case clearly demonstrates the possibility of clinical cross-reactivity of danaparoid with heparin antibodies. If *in vivo* cross-reactivity is suspected, serological confirmation should be sought. If cross-reactivity is confirmed serologically, or in the event of strong clinical suspicion of cross-reactivity, danaparoid administration should be stopped immediately and an alternative anticoagulant started.

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