

Heparin-induced Thrombocytopenia in a Patient Treated With Fondaparinux

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Case Report

A 45-year-old female presented with complaints of left leg cramps lasting 2 weeks and 1 day of leg swelling. Doppler ultrasound revealed left lower extremity deep vein thrombosis (DVT), which was thought to be secondary to trauma. The patient had a history of ampullary cancer that had metastasized to the liver, for which she underwent a Whipple procedure, radiotherapy, and chemotherapy. Additional history included hypothyroidism and a hysterectomy. The patient had a 20-year smoking history, but quit upon diagnosis of malignancy. She denied the use of alcohol or illicit drugs. Family history was negative for thrombophilia. Medications prior to admission included levothyroxine and pancrelipase.

Hematology was consulted, DVT treatment with enoxaparin and warfarin was started, and the patient was discharged without any other events. During her first outpatient evaluation, her international normalized ratio (INR) was found to be 8, and therefore warfarin and enoxaparin were discontinued. Two days later, her INR was greater than 5; 4 days later, her INR was 3.7, but she began developing pain and swelling in the right leg that day. Upon hospital admission 2 days later, she was diagnosed with a second DVT (idiopathic) in the right lower extremity. Because of the development of the new DVT with an INR greater than 3, the patient was anticoagulated with enoxaparin as an outpatient, but warfarin was not restarted. Cephalexin was prescribed for phlebitis, and the patient was discharged.

The patient was subsequently scheduled for an outpatient computed tomography (CT) scan, which showed evidence of pulmonary embolism, and she was re-admit-

ted to the hospital. Anticoagulation was continued with enoxaparin therapy, and then switched to an unfractionated heparin (UFH) weight-based treatment protocol. A Greenfield filter was placed, and treatment doses of enoxaparin were resumed. A liver biopsy was performed secondary to lesions being identified on CT scan; it revealed metastatic pancreatobiliary adenocarcinoma. Additionally, the patient was noted to have swelling and cyanosis in the first toe of the right foot. Vascular surgery was consulted, and mild phlegmasia was suspected, for which medical management was recommended. The patient was discharged on erlotinib (Tarceva, Genentech), gemcitabine, enoxaparin, oxycodone/acetaminophen, levothyroxine, lidocaine patch, and levofloxacin for pulmonary infiltrate and leukocytosis. Upon discharge, the platelet count was 148,000/ μ L.

Two days after discharge, the patient returned to the hospital via emergency medical services with complaints of increasing shortness of breath in the previous few days and chest pain that began the night before. Upon this admission, the platelet count was 22,000/ μ L, hemoglobin was 8.7 g/dL, and hematocrit was 26.0 g/dL. The previously cyanotic toe had progressed to become necrotic with involvement of multiple toes on the same foot. The patient was given 1 dose of enoxaparin prior to hematology consult, which was subsequently discontinued, and lepirudin (Refludan, Bayer Healthcare) intravenous infusion was started for suspected heparin-induced thrombocytopenia (HIT). Platelet factor 4 (PF4) antibodies were checked and were found to be positive. The next day, platelet count increased to 79,000/ μ L and to 138,000/ μ L the following day. At this time, fondaparinux (Arixtra, GlaxoSmithKline) 7.5 mg once daily was given in anticipation of discharge and continuation for outpatient anticoagulation. The next day, the patient was given the same dose, and platelets declined to 86,000/ μ L. Fondaparinux was discontinued and intravenous infusion of lepirudin was resumed. The next day, the platelet count

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increased to 158,000/ μ L. The following day, the count was 215,000/ μ L. Four days after lepirudin was resumed, the intravenous infusion was converted to subcutaneous administration at 50 mg, and the patient was discharged to hospice on lepirudin 60 mg subcutaneously every 12 hours with a platelet count of 168,000/ μ L.

Discussion

Thrombocytopenia associated with heparin use is a commonly encountered complication seen in clinical practice. In most cases, the reduction of platelet count is usually mild, not associated with thrombotic complications or hemorrhage, and is known as heparin-associated thrombocytopenia (formerly HIT I).¹ The more significant complication is the marked reduction of platelet count associated with immune heparin-related procoagulant activity (formerly HIT II) leading to life-threatening thrombo-occlusive complications rather than bleeding.²

The basic pathophysiology of HIT involves formation of immunoglobulin G antibodies directed against heparin-bound PF4 activating platelets, monocytes, and endothelial cells, leading to excessive thrombin generation and clot formation.³ HIT with platelet antibodies is seen more commonly in patients treated with UFH 20% compared to 8% in patients treated with low molecular weight heparin (LMWH).⁴

Treatment of HIT first involves discontinuing the use of heparin and direct thrombin inhibitors (DTIs). The U.S. Food and Drug Administration has approved 3 DTIs: lepirudin, argatroban (Pfizer), and bivalirudin (Angiomax, The Medicines Co.) for use in management of HIT. Fondaparinux, another DTI, has also been used successfully, off-label in many cases, with good results.⁵⁻⁹

Fondaparinux is a new anticoagulant that works by inhibiting factor Xa, thereby preventing thrombin formation.¹⁰ Fondaparinux is a synthetic pentasaccharide with molecular structure similar to UFH and LMWH. However, it does not contain the same portion of molecule that binds to PF4, thereby reducing the chances of HIT when compared to other heparins. There have been many reports of the successful use of fondaparinux to anticoagulate patients with established HIT.^{5-9,11,12}

In our case, fondaparinux was used after the platelet count recovered with lepirudin infusion, after HIT was triggered by UFH and LMWH. After starting fondaparinux, the patient again had thrombocytopenia, with a platelet count of less than 100,000/ μ L in the setting of arterial thrombosis with toe gangrene. Platelet count finally recovered after fondaparinux was discon-

tinued and lepirudin was restarted, indicating the role of fondaparinux in causing recurrent HIT in this patient.

A literature review shows many reports of successful outcome with fondaparinux usage in the setting of HIT.^{5-9,11,12} There have been only a few case reports suggesting the occurrence of HIT with fondaparinux.^{11,13,14} Most recently, a prospective study by Baroletti and colleagues¹⁵ reported a 94% incidence of HIT in patients treated with fondaparinux.

In summary, despite many reports of successful treatment of HIT with fondaparinux, there is a possibility of fondaparinux itself causing HIT, as suggested by our case and several recent reports. Hence, further research and large-scale prospective studies are necessary to guide the use of fondaparinux both in the treatment of DVT as well as in the management of HIT.

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Review

Heparin-induced Thrombocytopenia Associated with Fondaparinux

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Introduction

Fondaparinux (Arixtra, GlaxoSmithKline) is a new indirect anti-factor Xa anticoagulant of the heparin family. Unlike unfractionated heparin (UFH) and low molecular weight heparin (LMWH), which are proteoglycans isolated from animal tissues, fondaparinux is a synthetic compound. It comprises the 5 sugar moieties that mediate the anticoagulant activity of UFH and LMWH.

Recently, a few cases of thrombocytopenia associated with the use of fondaparinux have been reported.¹⁻⁴ In most of these cases²⁻⁴ the thrombocytopenia was induced initially by prior administration of UFH or LMWH. Therefore, it remains unclear in these patients whether fondaparinux actually caused the thrombocytopenia. For fondaparinux to be implicated as the cause of the thrombocytopenia, certain conditions must be met.

Fondaparinux-associated Thrombocytopenia

Pathophysiology

Since fondaparinux is a heparin-like drug, an interesting question is, "Can fondaparinux cause HIT?" HIT is a clinical syndrome that is quite different from other drug-induced thrombocytopenias (DITs) such as thrombocytopenia induced by quinine.⁵ The thrombocytopenia in HIT is not severe compared with other DITs,⁶ and thrombosis, but not bleeding, is a prominent feature.⁷ Pathophysiologically, HIT differs from other DITs in that the immunoglobulin (Ig) G antibody in HIT reacts with a drug/plasma protein complex (ie, heparin/platelet fac-

tor 4 [PF4] complex).^{6,7} The antibody/antigen complex is bound by the IgG Fc domain⁷ to Fc gamma RIIa receptors on platelets, cross-linking the Fc receptors and inducing platelet activation, platelet microparticle formation, and thrombin generation,⁶ leading to thromboembolic complications in patients with HIT. The thromboembolism is frequently severe, extensive, and potentially disabling or fatal. The antibody in other DITs rarely causes platelet activation and seldom leads to thromboembolism.⁵

The only other drug that can cause a clinical syndrome like HIT is LMWH, although it does so less frequently than UFH.⁶ This is not unexpected, as LMWH has a chemical structure similar to UFH except it consists of proteoglycans with shorter chain lengths. Like UFH, LMWH is capable of forming with HIT IgG and PF4 large molecular proteoglycan/PF4/antibody complexes,⁸ which can induce, and are necessary for, platelet activation and consequently thromboembolism in HIT. In contrast, fondaparinux is a small (or short-chain) molecule and is probably unable to form the large proteoglycan/PF4/antibody complexes⁸ necessary for inducing platelet activation and causing the clinical syndrome of HIT. Interestingly, both LMWH and fondaparinux are equally able to induce the formation of anti-PF4/heparin antibodies as demonstrated by Warkentin and colleagues⁹ in a cohort of orthopedic surgery patients receiving LMWH or fondaparinux for thromboprophylaxis. However, the anti-PF4/heparin antibodies in patients receiving fondaparinux did not cross-react with fondaparinux *in vitro* and the patients did not progress to develop HIT or HIT-like syndrome probably because the antibody and small size (or very short chain) of fondaparinux molecules do not form the large immune complexes necessary for causing platelet activation. Consistent with these findings, antibodies in patients with HIT cross-react strongly with LMWH¹⁰ but do not cross-react with fondaparinux.¹¹ Given the above immunopathologic data, it would be very rare for fondaparinux to cause HIT or a syndrome like HIT.

To date, clinical evidence also suggests that fondaparinux does not usually cause HIT except in very rare cases. In most of the reported cases of fondaparinux-associated thrombocytopenia, there was prior exposure to UFH or LMWH that induced the development of HIT.²⁻⁴ With subsequent administration of fondaparinux, thrombocytopenia occurred or recurred (if the thrombocytopenia had resolved following UFH or LMW withdrawal). In the case reported by Alsaleh and associates,⁴ the patient had delayed-onset HIT and the patient's thrombocytopenia was not initiated nor caused by fondaparinux; the onset of thrombocytopenia simply coincided temporally with the administration of fondaparinux. In delayed-onset HIT, thrombocytopenia occurs even in the absence

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of continuing UFH or LMWH, once heparin has initiated the immune reaction as the induced antibody reacts with platelets independently of heparin. It is possible that the previously reported cases of fondaparinux-associated thrombocytopenia with prior UFH or LMWH exposure²⁻⁴ were patients with delayed-onset HIT, and the onset of thrombocytopenia merely coincided with fondaparinux administration. It is only in the patient reported by Warkentin and colleagues¹ that there was compelling evidence that fondaparinux might have directly induced the thrombocytopenia, as there was no prior exposure to UFH or LMWH. Even in this case, the authors were unable to demonstrate the presence of a fondaparinux-dependent antibody in the serotonin-release assay, as the patient antibody reacted with platelets in the absence of heparin or fondaparinux.

Ratuapli and colleagues¹² describe a patient who was treated with enoxaparin and warfarin for bilateral lower limb vein thrombosis and pulmonary embolism. Two days after discharge from hospital, she developed digital gangrene of the right foot; the platelet count had dropped from $148 \times 10^9/L$ to $22 \times 10^9/L$. Upon cessation of enoxaparin, the platelet count rose to $138 \times 10^9/L$ but fell again to $86 \times 10^9/L$ when fondaparinux was given for one day. Thrombocytopenia resolved when fondaparinux was replaced by lepirudin (Refludan, Bayer Healthcare). In this patient, the evidence for fondaparinux causing the thrombocytopenia would have been stronger if (1) the fall in platelet level was verified by a repeat blood count, (2) a laboratory artifact such as in vitro platelet clumping was excluded by blood smear examination, and (3) cross-reaction of the antibody with fondaparinux was demonstrated by an in vitro assay.

Diagnosis

Similar to the diagnosis of HIT caused by UFH or LMWH, diagnosis of fondaparinux-induced or -associated thrombocytopenia should be based on the following criteria:

- Thrombocytopenia (platelet count $<150 \times 10^9/L$) or a fall in platelets to a level 50% or less from baseline⁶ occurring with administration of fondaparinux 5–14 days after its commencement, unless there is prior exposure to fondaparinux, UFH, or LMWH
- Other causes of thrombocytopenia are excluded⁷
- Demonstration of an anti-PF4/fondaparinux antibody or anti-PF4/heparin antibody⁶ that cross-reacts with fondaparinux
- Resolution of thrombocytopenia or a return of platelet count to baseline after cessation of fondaparinux, UFH, or LMWH⁶ (this criterion may not be applicable if the diagnosis is initially made when the patient is still

receiving fondaparinux, but it is helpful in confirming the diagnosis retrospectively)

If there is prior exposure to UFH or LMWH and the patient has a clinical picture consistent with delayed-onset HIT and a heparin-independent antibody, it is not possible to implicate fondaparinux confidently as the cause of the thrombocytopenia (as discussed above).⁴ The onset of thrombocytopenia may merely coincide with or at best be encouraged by fondaparinux administration. Technically speaking, the diagnosis of these patients is *fondaparinux-associated thrombocytopenia*. The term *fondaparinux-induced thrombocytopenia* should be reserved for patients in whom fondaparinux can be clearly implicated as the cause of their thrombocytopenia using the above diagnostic criteria.

Management

There are little or no clinical data to guide treatment of patients with fondaparinux-associated thrombocytopenia. The suggested treatment approach below is based on lessons we have learned from the treatment of HIT.

With or without prior exposure to UFH or LMWH, when the platelet count drops by more than 50% from baseline or to less than $150 \times 10^9/L$ during fondaparinux administration, the offending drug should be promptly ceased. The patient should not be treated with UFH or LMWH, as the antibody is likely to cross-react with UFH or LMWH.¹⁰ Even if a subsequent laboratory test shows no antibody cross-reaction with fondaparinux, it may not be safe to recommence fondaparinux until safety data from further research become available.

Patients who have fondaparinux-induced or fondaparinux-associated thrombocytopenia, with or without a clinical overt thrombosis, should be treated with an alternative anticoagulant used in the treatment of HIT⁶ (eg, lepirudin, argatroban [Pfizer], or danaparoid¹³). The alternative anticoagulant should be continued until the platelet count returns to normal, at which time it would be safe to commence warfarin.⁶ Warfarin should be continued for 3 or more months as is deemed appropriate for the thrombosis that the patient has. From clinical experience with HIT, it would seem likely that patients without clinically overt thrombosis will probably develop a thrombotic event in the next 30 days. These patients may benefit from a short course of lepirudin, argatroban, or danaparoid, which should be continued until resolution of thrombocytopenia without commencing warfarin thereafter.⁶

Conclusion

Immunopathologic data suggest that fondaparinux is unlikely to directly cause HIT. Clinical evidence to date

shows that fondaparinux usually does not cause thrombocytopenia, except perhaps in one previously reported patient. In several other patients who had prior UFH or LMWH exposure, the onset of thrombocytopenia probably coincided with fondaparinux administration. When fondaparinux-induced or fondaparinux-associated thrombocytopenia is suspected, every effort should be made clinically and by laboratory testing to establish that fondaparinux is the cause of the patient's thrombocytopenia. If the onset of thrombocytopenia is temporally related to fondaparinux administration, even if fondaparinux could not be established as its cause, the patient should be treated as if he or she has HIT, and should be given lepirudin, argatroban, or danaparoid.^{6,13}

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