Fondaparinux (Arixtra®), a Safe Alternative for the Treatment of Patients With Heparin-Induced Thrombocytopenia?

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Fondaparinux (Arixtra\textsuperscript{R}), a Safe Alternative for the Treatment of Patients With Heparin-Induced Thrombocytopenia?

NaaDede O. Badger, PharmD, BCPS

Abstract
Fondaparinux, a pentasaccharide which selectively binds to antithrombin III, has negligible to no cross-reactivity with heparin-induced thrombocytopenia (HIT) antibodies in in vitro studies. The lack of cross-reactivity suggests a potential role in the management of HIT, and indeed, there are several such case reports and small studies. These published data have used both the prophylactic and weight-based treatment doses. However, due to the small possibility of developing HIT with thromboembolic complications while receiving fondaparinux, it is suggested that the appropriate weight-based treatment dose be used. In all these reports, fondaparinux provided adequate anticoagulation, prevented further thromboembolic events, and platelet counts returned to normal. However, there have been a couple of case reports on possible HIT or HIT-like syndrome secondary to fondaparinux use. Conclusion: Fondaparinux is an attractive anticoagulant therapy in patients with HIT. There is still the need for larger randomized trials evaluating the true efficacy, appropriate dose, safe duration of treatment, and the true incidence of HIT associated with fondaparinux.

Keywords
fondaparinux, heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is an immune-mediated reaction in which thrombocytopenia occurs within 1 week of the initiation of unfractionated heparin (UFH) or low molecular weight heparin (LMWH) therapy.\textsuperscript{1-3} This adverse effect is due to the formation of platelet-activating antibodies against platelet factor 4 (PF4)-heparin complexes.\textsuperscript{4,5} Due to the risk of arterial and venous thrombosis that could develop in 30\% to 75\% of patients with HIT, guidelines recommend that prompt action be taken as soon as HIT is suspected or confirmed: the offending agent must be discontinued and an alternate anticoagulant initiated.\textsuperscript{6-8} The agents approved for use in HIT in the United States are the direct thrombin inhibitors (DTIs); lepirudin (Refludan\textsuperscript{1}), argatroban, and bivalirudin (Angiomax\textsuperscript{2}), with bivalirudin approved for use in patients with HIT undergoing percutaneous coronary intervention (PCI).\textsuperscript{9-13} These agents have limitations including the need to be given by continuous intravenous infusion, and frequent monitoring of activated partial thromboplastin time (aPTT). DTIs, especially argatroban, have also been shown to falsely elevate the international normalized ratio (INR) when given concurrently with warfarin, complicating transition to oral therapy.\textsuperscript{14}

Fondaparinux, a pentasaccharide that inactivates factor Xa is approved in the United States for the prevention of deep vein thrombosis (DVT) after orthopedic and abdominal surgeries, and in high-risk medicine patients, and for the treatment of DVT and pulmonary embolism (PE).\textsuperscript{15} It is an agent that is being increasingly used in the management of HIT due to differences in properties from DTIs. Some of the clinically appealing properties of fondaparinux include administration via subcutaneous route, once-daily dosing due to a long half-life of about 25 hours, little to no need for monitoring, and no effect on INR.\textsuperscript{15} One of the drawbacks to the use of fondaparinux is a lack of dosing guidelines for patients with severe chronic kidney disease (CKD)—estimated creatinine clearance (CrCl) of less than 30 mL/min. Although fondaparinux has been shown to have a similar incidence of formation of anti-PF4/heparin antibodies as LMWH, there is a low cross-reactivity between fondaparinux and HIT antibodies in vitro.\textsuperscript{16-18} The 2008 American College of Chest Physicians Guidelines for the treatment of HIT recommends the use of fondaparinux (Grade 2C).\textsuperscript{19} Most of the in vivo data on the use of fondaparinux in the management of HIT is limited to small

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studies, case reports, case series, and abstracts. There have been mixed data on the use of fondaparinux in HIT, as well as the appropriate dose of fondaparinux to use in the setting of HIT. Some cases and studies evaluating the use of fondaparinux for HIT are discussed below.

Case Reports/Series

One of the first reports on the use of fondaparinux for HIT was a case of a 29-year-old pregnant woman with hypercoagulable state, who developed a PE and was started on UFH. Five days after starting heparin, the patient’s platelet count decreased by 50%, and HIT was confirmed by a positive HIT antibodies test. This patient was initially treated with lepirudin then transitioned to fondaparinux 2.5 mg twice daily for the duration of her pregnancy (exact duration was not reported). She developed no complications and she delivered a healthy baby.20

Another case involved a 36-year-old male with a history of lupus antibodies, multiple PEs, and acute myocardial infarctions associated with HIT. The patient was admitted with a recurrent PE despite a supratherapeutic INR. The patient was initially started on lepirudin then switched to fondaparinux 2.5 mg alternating with 5 mg daily for a total of 8 months. He tolerated this therapy well without any further complications.21

In another case, a 32-year-old male with a diagnosis of paroxysmal nocturnal hemoglobinuria, who later developed Budd Chiari syndrome and HIT (from LMWH) was successfully treated with fondaparinux 2.5 mg daily. The patient’s platelet count remained within normal limits during the duration of the fondaparinux therapy, and he developed no adverse events. The authors concluded that fondaparinux could be considered safe in patients with HIT.22

A 60-year-old man post double coronary artery bypass grafting (CABG) developed HIT on postoperative day (POD) 6; the diagnosis was confirmed by an enzyme-linked immunosorbent assay (ELISA) test. UFH was stopped, and the patient was started on danaparoid. However, his platelet count continued to decrease, and on POD 8, he was switched to fondaparinux 7.5 mg daily. The patient was maintained on fondaparinux for a total of 26 days. Platelet counts improved, and there was no evidence of thrombosis during the therapy.23

Kovacs et al reported a study of 5 patients with confirmed HIT, who were started on fondaparinux 7.5 mg subcutaneously daily after discontinuing the offending agents. All patients had thrombosis associated with the HIT and were started on warfarin once their platelet counts were >100 000/mm³. Three-month follow-up data showed no major bleeding or recurrent thrombosis.24

In 2004, Harenberg and colleagues reported using fondaparinux 2.5 mg subcutaneously daily in 8 patients with an acute episode or a history of HIT. These patients were treated for 7 to 14 days, with no incidence of thrombocytopenia, thromboembolic events, or adverse drug events. These authors also concluded that fondaparinux is a safe alternative in patients with a history of HIT or thromboembolic complications associated with UFH or LMWH at a dose of 2.5 mg daily.25

Studies

In a study involving 20 patients with HIT, 10 received fondaparinux after receiving DTI, and 10 received fondaparinux as the initial therapy. Of the 20 patients, 18 received a 2.5 mg daily dose of fondaparinux. Fondaparinux was tolerated and platelet count recovered in all 20 patients, and there were no cases of new thromboembolic complications.26

Lobo et al published the first prospective study evaluating the use of fondaparinux in HIT patients in 2008. This study compared 7 patients treated with fondaparinux to 10 patients treated with a DTI.27 Of the 7 patients in the fondaparinux arm, 3 received less than 24 hours of DTI prior to initiating fondaparinux. Of the 7 patients, 6 had thrombosis associated with HIT and received a weight-based dose of fondaparinux, whereas the seventh patient, who did not have thrombosis—received the prophylactic dose of 2.5 mg daily. The results showed no difference in platelet recovery between the treatment groups. There was also no development of new thromboembolic complications in either group; however, 1 patient in the fondaparinux group had progression of an existing thrombosis leading to amputation. Although these results are intriguing, the small number of patients studied cannot allow for any large-scale extrapolation.

A retrospective study conducted at The Ohio State University Medical Center reviewed the use of fondaparinux in 46 patients with a history of HIT or a suspicion of HIT over a 1-year period. Thirty of these patients received the thromboprophylaxis dose of fondaparinux, while 16 received the weight-based treatment dose for confirmed thromboembolism. The efficacy data from this study showed no new thrombosis during the study period. Bleeding was recorded in 18 of the patients, 4 of which were documented as major as defined in the study. The authors concluded that fondaparinux may be an effective anticoagulant in patients with HIT.28

Despite these cases and studies—and despite the very low incidence of cross-reactivity between fondaparinux and the HIT antibodies—there is still some concern among clinicians regarding using fondaparinux for HIT. This is partly due to a few reports of cross-reactivity. One case reported a patient with a previous episode of LMWH-associated HIT 3 years prior to the second presentation, who developed fondaparinux-related thrombocytopenia. The patient was placed on fondaparinux for DVT prophylaxis following an orthopedic surgery, and his platelet count decreased by more than 50% by POD 11. HIT was confirmed using an ELISA test, but the patient did not develop any venous or arterial thrombosis. The investigators concluded that although very rare, caution should be taken when initiating fondaparinux in patients with a remote history of HIT.29

An earlier study by Warkentin comparing fondaparinux to enoxaparin in the development of antiplatelet factor 4/heparin antibodies showed that a phenomenon similar to HIT could occur, although less frequently with fondaparinux.16 However, in 2007, another case was reported by Warkentin and colleagues of a 48-year-old woman who had undergone
bilateral total knee replacement. The patient was placed on fondaparinux for DVT prophylaxis postoperatively. On POD 7, her platelet count dropped to 39,000/mm³, and she developed a bilateral adrenal infarction and an asymptomatic DVT, diagnosed by ultrasonography. The platelet serotonin-releasing assay was strongly positive for HIT antibodies. Fondaparinux was discontinued and the patient was successfully treated with argatroban and warfarin. The authors concluded that fondaparinux can cause a disorder resembling HIT in rare cases.

Renal Dosing of Fondaparinux

Although there are no dosing guidelines for fondaparinux use in patients with CrCl less than 30 mL/min, there have been cases of using fondaparinux in HIT on patients with renal dysfunction. One such report was one of the first cases of fondaparinux use for HIT. This case involved a 32-year-old female with systemic lupus erythematosus, who underwent voluntary abortion. A few days later, she developed abdominal pain, vomiting, diarrhea, and acute renal failure. A renal biopsy revealed type IV glomerulonephritis. The patient was started on UFH for DVT prophylaxis. On day 11 of heparin therapy, her platelet count decreased from 150,000/mm³ to 50,000/mm³, and HIT antibodies were confirmed. Heparin therapy was discontinued and fondaparinux was started at 0.5 mg daily. No increase in fondaparinux dose was needed based on anti-factor-Xa activity measured. The patient’s platelet count returned to normal and renal function progressively improved. The patient tolerated this therapy well and was subsequently transitioned to oral anticoagulation therapy.

Another case report describes the use of fondaparinux in a dialysis patient. This patient with a diagnosis of HIT with associated thrombosis was started on fondaparinux 2.5 mg instilled directly into the dialysis circuit on days of dialysis only. The patient tolerated this well and there were no further thromboembolic complications or bleeding complications during the 10-week treatment course.

Discussion/Conclusion

Fondaparinux is increasingly becoming an intriguing alternative to DTIs for the management of patients with HIT. With recent changes to the American College of Chest Physician’s guidelines, there might be an increasing trend in the use of the pentasaccharide in this high-risk patient population. The combination of once-daily dosing, predictable response and minimal monitoring requirement makes fondaparinux more appealing than DTIs, especially in patients with low risk of having HIT. Although the use of fondaparinux in clinical setting for the management of HIT is limited and based on small studies as well as case reports and series, it appears that fondaparinux could be a safe alternative anticoagulation therapy in patients with HIT. One suggestion made in a recent editorial on a possible niche for fondaparinux use in HIT patients was to use DTIs during the thrombocytopenic phase, then transition the patient to fondaparinux—warfarin bridging therapy. It could also be a safe alternative to patients with HIT who cannot be transitioned to warfarin but need an extended duration of anticoagulation therapy, for example in pregnant patients.

An unresolved concern is the question of the optimal dose of fondaparinux in HIT with or without thrombosis. The cases and studies summarized in this article used both the prophylactic and treatment doses, although it seems the more current reports used the treatment doses of fondaparinux. Based on a case of a patient who developed HIT with multiple thrombotic complications while receiving the prophylactic dose of fondaparinux, it would seem prudent that in the setting of HIT, the weight-based treatment dose should be used. The exact duration of use of fondaparinux in HIT patients is still unknown but based on one report, patients could potentially be maintained on it for up to 8 months. With regard to fondaparinux dosing in renal insufficiency, there is still very little data so specific recommendations cannot be made.

Fondaparinux seems to be a safe alternate to the DTIs in the treatment of patients with confirmed or suspected HIT. However, more studies with larger sample sizes need to be conducted to give more definite answers to some of the concerns with its use. With the recent recommendation from the CHEST guidelines, hopefully more studies will be published on this subject in the near future.

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