Can fondaparinux be used for thromboembolic treatment or prophylaxis in patients with heparin-induced thrombocytopenia (HIT)?

**REQUEST**

**RESPONSE**

**BACKGROUND**

Immune-mediated HIT is an uncommon but serious clinical event that has been reported in patients receiving unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) (ie, dalteparin, enoxaparin, tinzaparin) therapy. The prevalence of HIT varies between agents (range 1–5% for UFH, 0–0.8% for LMWH) and occurs more commonly with bovine-derived heparin compared with porcine-derived heparin. The diagnosis of HIT typically includes a positive response to a heparin-platelet factor 4 (PF4) enzyme-linked immunosorbent assay along with a 50% or more reduction in platelet count, skin lesions at the site of heparin injection, or an acute systemic reaction after intravenous heparin bolus administration. Platelet count reduction is generally noted on days 5–10, although thrombocytopenia is usually not detected until days 7–14 after initiating UFH or LMWH. Although less

Author information provided at the end of the text.
common, platelet count reduction may occur within 24 hours of prior UFH or LMWH exposure with circulating antibodies (rapid onset) or after 1 or more weeks of heparin cessation (delayed onset).\textsuperscript{6}

The heparin molecule is made up of linear chains of repeating disaccharide units. Approximately 75–90\% of these sequences are trisulphated, creating a negatively charged molecule. PF4 molecules consist of lysine and arginine residues producing a positively charged molecule. The interaction between the charges of these molecules causes the formation of a PF4/heparin complex that binds to the platelet surface at the Fc receptor site, thereby triggering immunoglobulin G production.\textsuperscript{6-8} These antibodies cause platelet activation and aggregation, which results in increased thrombin generation and possible venous or arterial thrombosis (ie, HIT with thrombosis syndrome).\textsuperscript{5,6,9}

Complications resulting from thrombosis include deep venous thrombosis, pulmonary embolism, cerebral dural sinus thrombosis, adrenal hemorrhagic infarction, limb arterial occlusions, myocardial infarction, aortic occlusion, cardiac intraventricular thrombosis, and acute thrombotic stroke.\textsuperscript{10-12} With discontinuation of UFH or LMWH alone, up to a 50\% risk of subsequent thrombosis has been reported.\textsuperscript{13,14} Moreover, morbidity and mortality rates for treated HIT range from 6\% to 18\% and 9\% to 22\%, respectively.\textsuperscript{15} Because cross-reactivity exists between UFH and LMWH, these agents should be immediately discontinued when HIT is suspected and treatment started.\textsuperscript{6}

Currently, direct thrombin inhibitors (argatroban, lepirudin, bivalirudin) are the only treatments approved by the Food and Drug Administration for managing HIT.\textsuperscript{16-18} These agents have chemical structures different from UFH and LMWH and do not cross-react with HIT antibodies.\textsuperscript{19} While direct thrombin inhibitors have shown some reduction in morbidity and mortality, their use is sometimes complicated by an indication for continuous intravenous infusion administration, dose modification based on coagulation, and acquisition cost.\textsuperscript{16-18} Therefore, other HIT treatment options are essential.

Evidence suggests that an increased risk for HIT-related antigen production is dependent on molecular weight and length of polysaccharides (>2.4 kDa and >10 saccharide units, respectively). Structural components for UFH and LMWH are above the minimum requirements for increasing the risk of these antigens (Table 1).\textsuperscript{20-24} Investigators have hypothesized that fondaparinux, a selective factor Xa inhibitor with a structure consisting of a pentasaccharide chain, is too short to induce an antibody response and could be useful for treating HIT.\textsuperscript{25} Fondaparinux, administered subcutaneously, is currently indicated for deep venous thrombosis (DVT) prophylaxis in patients undergoing hip fracture surgery (including extended prophylaxis), hip or knee replacement surgery, and abdominal surgery and who are at risk for thromboembolic complications, as well as for treatment of DVT and pulmonary embolism (PE). It binds to and potentiates the effect of antithrombin and has negligible or no cross-reactivity in vitro with HIT antibodies.\textsuperscript{26} A study comparing the effects of UFH and fondaparinux on platelet aggregation in the presence of HIT sera reported a positive result in 79.8\% of UFH samples compared with 3.3\% of fondaparinux samples (p < 0.001).\textsuperscript{27}

### Literature Review

Four case reports,\textsuperscript{28-31} 2 case series,\textsuperscript{32,33} and a retrospective medical record review\textsuperscript{34} describing fondaparinux treatment in patients with HIT have been published. The American College of Chest Physicians’ (ACCP) diagnostic criteria for HIT were consistently used throughout the reports and review.\textsuperscript{5} Results of these reports and review are described here.

### Case Reports

One of the first cases of fondaparinux use in a patient with HIT involved a 32-year-old female with systemic lupus erythematosus who presented with abdominal pain, vomiting, diarrhea, and acute renal failure.\textsuperscript{29} Her blood work was notable for a platelet count of 80 \times 10^9/L and HIT antibodies were confirmed. UFH was started and, secondary to renal failure, a reduced dose of fondaparinux 0.5 mg once daily was administered. Platelet levels returned to normal (no value reported) 2 days after fondaparinux was started. Five days after fondaparinux was initiated, the therapy was transitioned to warfarin; the duration of fondaparinux therapy was not specified. No adverse effects were noted at day 34 of follow-up. Because of fondaparinux’s selective inhibition of activated factor Xa and lack of binding to PF4, the authors suggested that it may be an alternative to UFH and LMWH in patients with HIT.\textsuperscript{28}

### Table 1. Comparison of Factors Associated with Increased HIT Antigenicity\textsuperscript{20-24}

<table>
<thead>
<tr>
<th>Agent</th>
<th>Average Molecular Weight (kDa)</th>
<th>Saccharide Residues</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>15</td>
<td>-45</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>5.5–7.5</td>
<td>-15</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>5.0</td>
<td>-15</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>4.5</td>
<td>-13</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>1.7</td>
<td>5</td>
</tr>
</tbody>
</table>

HIT = heparin-induced thrombocytopenia; UFH = unfractionated heparin.
In another case, physicians used fondaparinux in a 36-year-old male with a history of systemic lupus erythematosus, recurrent thromboembolic episodes, and HIT (antibody titer confirmed). The patient was admitted to the hospital for a recurrent PE (diagnosed by spiral computed tomography scan), despite excessive anticoagulation with warfarin (international normalized ratio [INR] 10.6, goal 3–4). Other medications on admission included clopidogrel and aspirin. Warfarin, clopidogrel, and aspirin were discontinued, and lepirudin 0.4 mg/kg (bolus) followed by 0.15 mg/kg/h was administered for 5 days. On day 6, the lepirudin dose was reduced to 0.075 mg/kg/h and fondaparinux 2.5 mg once daily was added. On day 14 of combination therapy, the platelet count normalized (no value reported) and lepirudin was discontinued. Upon the patient’s discharge, fondaparinux, with alternating doses of 2.5 mg and 5 mg once daily, clopidogrel, and aspirin were continued. Fondaparinux was administered for at least 8 months without complications. The authors concluded that fondaparinux is safe for long-term use in patients with a history of HIT who are refractory to anticoagulation with warfarin.

Rubin reported a case of a 29-year-old female who developed HIT during pregnancy and was successfully treated with fondaparinux. The patient had previously experienced 2 miscarriages and, as a result, underwent a hypercoaguable workup. Anticardiolipin and factor V Leiden mutation were negative, but a low protein S level was noted. During her third pregnancy, the woman developed a PE (ventilation-perfusion scan confirmed) and was started on UFH. Five days after starting UFH, a 50% reduction from baseline for platelet count was noted and HIT was confirmed by antibody assay. UFH was discontinued and lepirudin was started. However, due to risks of its use in pregnancy, lepirudin was discontinued and fondaparinux 2.5 mg twice daily was initiated (duration unspecified). No further complications of HIT or bleeding were noted throughout the pregnancy. The authors concluded that fondaparinux may be a therapeutic alternative in pregnancy due to its absence of placental transfer and decreased incidence of HIT.

Another case report supplemented the available data supporting fondaparinux use in patients with HIT. A 32-year-old male with a history of paroxysmal nocturnal hemoglobinuria presented with increased abdominal volume and tenderness. An abdominal ultrasound revealed thrombosis of the suprarenal veins and inferior cava vein consistent with Budd–Chiari syndrome. Recombinant tissue type plasminogen activator (rt-PA) and UFH were initially started, and treatment was later switched to enoxaparin. On day 11 of enoxaparin therapy, a 50% reduction in platelet count from baseline was noted (baseline 93 × 10^9/L). Enoxaparin was discontinued and fondaparinux 2.5 mg once daily along with 2 infusions of rt-PA were initiated. The patient’s platelet count increased to 101 × 10^9/L and remained within normal limits during use of fondaparinux (duration unspecified). No adverse events were reported. The author postulated that additional data were needed before fondaparinux could be considered safe in patients with HIT.

**Case Series**

Harenberg et al. conducted a case series to evaluate the efficacy of fondaparinux for thromboembolic prophylaxis in patients with a history of HIT (n = 6) or an acute episode of thrombocytopenia (n = 2) while receiving UFH (n = 5) or LMWH (n = 3). Six patients had a positive heparin-induced platelet aggregation assay response, one had a negative response, and one had no results available. All patients received thromboembolic prophylaxis with fondaparinux 2.5 mg once daily for 1–2 weeks. Platelet counts remained unchanged in patients with a history of HIT, while the platelet counts increased in patients with an acute episode of thrombocytopenia (43–445 × 10^9/L and 40–172 × 10^9/L). Thromboembolic events or hemorrhagic adverse effects were not reported. The authors concluded that fondaparinux is a safe alternative for thromboembolic prophylaxis in patients with a history of HIT or thrombocytopenia associated with UFH or LMWH at a dose of 2.5 mg daily.

Fondaparinux was administered to 5 surgical patients who developed HIT (antibody assay confirmed) and thrombosis while receiving UFH. Thrombocytopenia was noted between days 6 and 10 of UFH therapy. PE (n = 2), DVT (n = 2), and left atrial and mechanical mitral valve thrombosis (n = 1) were noted. UFH was discontinued in all patients and fondaparinux 7.5 mg once daily was initiated. After fondaparinux was started, platelet counts increased to normal in all patients between days 2 and 9. Warfarin was added when platelet counts exceeded 100 × 10^9/L. After the INR was 2.0 or more for 2 consecutive days, fondaparinux was stopped. At follow-up, recurrent thrombosis was not reported; however, major bleeding did occur in 2 patients. The authors remarked that further studies are needed to evaluate fondaparinux in the treatment of HIT.

**Retrospective Medical Record Review**

Bradner et al. conducted a retrospective analysis of 20 patients with confirmed HIT who were treated with fondaparinux. All of the patients lacked evidence for alternative etiologies of thrombocytopenia and were treated with fondaparinux for at least 5 days (average 17). The primary endpoint was time to platelet recovery. Patients who were thrombocytopenic while receiving fondaparinux had an average platelet recovery of 3.7 days. Ninety percent (18/20) of the patients were treated initially with fondaparinux 2.5 mg once daily. Ten patients received fondaparinux after direct thrombin inhibitor therapy, while the other 10 patients received fondaparinux directly after HIT diagnosis. Neither thrombotic complications nor a recur-
rence of thrombocytopenia were reported during fondaparinux therapy (duration unspecified). The authors postulated that fondaparinux may be a well tolerated, effective treatment for HIT.

LIMITATIONS OF DATA

Evaluation of the evidence on the use of fondaparinux for thromboembolic treatment and prophylaxis in patients with HIT is complicated by several limitations. The data are from case reports (often published in abstract form) or retrospective reviews, included small patient numbers, and were conducted over relatively short time periods. Patient types, time of overlap with concomitant HIT therapy, and doses of fondaparinux were not consistent across reports, which limits extrapolation to all patients with HIT.

SUMMARY

The production of HIT-related antigens seems to be dependent on molecular weight and a polysaccharide length greater than 10. Accordingly, fondaparinux has been shown to have negligible cross-reactivity in vitro with HIT antibodies. Fondaparinux is not currently recommended for HIT treatment in guidelines established by the ACCP Consensus Conference on Antithrombotic Therapy; however, its use in this population has been described in several case reports and a retrospective review. Based on data from these reports, doses of fondaparinux for thromboembolic treatment or prophylaxis in patients with HIT are similar to the approved doses, which are based on weight and renal function. Length of fondaparinux therapy was often unspecified; however, it was reportedly administered for more than 8 months in one case. The time of overlap (if any) of fondaparinux with concomitant HIT treatment or anticoagulation was inadequately described in most cases. Although minimal, current evidence suggests that fondaparinux may be a viable option for thromboembolic treatment or prophylaxis in patients with antibody assay confirmed HIT who do not have a contraindication for fondaparinux use. Nonetheless, conducting placebo-controlled trials in patients with HIT can be challenging, and well controlled trials have not been published. Therefore, questions remain regarding patient types, efficacy, safety, optimal dosing, treatment duration, and incidence of thromboembolic events when fondaparinux is used in this setting. Prospective trials evaluating the efficacy and safety of fondaparinux for this patient population need to be conducted to answer these questions.

Leigh E Efird PharmD, Pharmacy Practice Resident, Virginia Commonwealth University Medical Center/Medical College of Virginia Hospitals, Richmond, VA
Denise R Kockler PharmD BCPS, Director, Drug Information Services, Virginia Commonwealth University Medical Center/Medical College of Virginia Hospitals

Reprints: Dr. Efird, Virginia Commonwealth University Medical Center/Medical College of Virginia Hospitals, 401 N. 12th St., PO Box 980042, Richmond, VA 23298-0042, fax 804/828-5589, lefird@mcvh.vcu.edu

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CONCLUSIONES. Los datos limitados apoyan el uso de fondaparinux para el tratamiento tromboembólico o la profilaxis en pacientes con TIH confirmada con ensayos de anticuerpos que no tienen una contraindicación para el uso de fondaparinux. No se han publicado ensayos aleatorios y controlados; por tanto, quedan pendientes cuestiones relativas a la eficacia, la seguridad, la dosis óptima, la duración del tratamiento y la incidencia de eventos tromboembólicos cuando se utiliza fondaparinux en este marco. Deberían llevarse a cabo ensayos prospectivos que evalúen la eficacia y la seguridad de fondaparinux en esta población de pacientes para contestar a estas preguntas.

Enrique Muñoz Soler

RÉSUMÉ

OBJECTIF: Revoir la littérature évaluant l'utilisation du fondaparinux pour la prévention et le traitement des événements thromboemboliques chez les patients ayant présenté une thrombocytopenie induite par l'héparine (TIH).


RÉSUMÉ: Le fondaparinux, un pentasaccharide inhibant façon sélective le facteur Xa, est reconnu pour avoir peu ou pas de réactivité croisée in vitro avec les anticorps anti-héparine. La prévention et le traitement des événements thromboemboliques avec le fondaparinux chez les patients ayant présenté une TIH ont été décrits dans la littérature. Un rapport de cas traitant de l’utilisation du fondaparinux en prévention chez un patient ayant présenté une TIH après avoir reçu l’héparine non fractionnée (HNF) s’est avéré positif. Trois rapports de cas font état du traitement avec succès d’événements thromboemboliques avec le fondaparinux suite à une TIH à l’HNF ou à une HBPM. De plus, 2 séries de cas, l’une utilisant le fondaparinux en prévention chez des patients ayant un antécédent de TIH et l’autre utilisant le fondaparinux en traitement chez des patients ayant présenté une TIH à l’HNF ou à l’HBPM, ont montré le maintien d’un décompte plaquettaire normal pendant le traitement au fondaparinux. Finalement, les résultats d’une revue rétrospective ont démontré que le fondaparinux prévenait les événements thromboemboliques ou la récidive de thrombocytopenie chez les patients ayant un antécédent de TIH.

CONCLUSIONES: Des données limitées supportent l’utilisation du fondaparinux pour la prévention et le traitement des événements thromboemboliques chez des patients avec antécédent de TIH confirmée (anticorps positifs) et qui n’ont pas de contre-indications à son utilisation. Aucune étude randomisée et contrôlée n’ayant encore été publiée; plusieurs questions demeurent: efficacité, innocuité, doses optimales, durée de traitement et incidence des événements thromboemboliques lorsque le fondaparinux est utilisé dans ce contexte. Des études prospectives évaluant l’efficacité et l’innocuité du fondaparinux chez ces patients devront être réalisées afin de répondre à ces questions.

Alain Marcotte