

Case Report / Olgu Sunumu

Is Fondaparinux an Effective Alternative Anticoagulant in Patients With Heparin-Induced Thrombocytopenia Type II? A Case Report and Review of the Literature

*Fondaparinux Heparinin İndüklediği Trombositopeni Hastalarında Etkili Bir Alternatif Antikoagülan Mıdır?
Olgu Sunumu ve Literatür Derlemesi*

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Although rare, heparin-induced thrombocytopenia (HIT) is one of the most feared complications of heparin therapy. It is an antibody-mediated, acquired and transient thrombotic disorder following exposure to heparin. Unfractionated heparin is the standard anticoagulation used in hemodialysis sessions and hemodialysis patients who are continually exposed to heparin are at increased risk for HIT. We report a 75-year-old male patient with acute-on-chronic renal failure who subsequently developed HIT while on hemodialysis. The patient was presented with deep vein thrombosis and successfully treated with fondaparinux. In this report we also review the off-label use of fondaparinux for the treatment and prophylaxis of thrombosis in patients with HIT. As fondaparinux is too small to be recognized by the majority of heparin-reactive antibodies it could be a reasonable alternative anticoagulant for symptomatic HIT patients where licensed drugs like lepirudin and danaparoid are not available.

Key words: Heparin-induced thrombocytopenia, thrombosis, hemodialysis, fondaparinux.

Heparine bağlı trombositopeni (HIT) nadir olmasına karşın heparin tedavisinin en çok korkulan komplikasyonlarından biridir. Heparine bağlı trombositopeni heparin ile temas sonrası oluşan, antikor aracılı edinsel ve geçici bir trombotik bozuluktur. Fraksiyone olmayan heparin hemodiyaliz sırasında kullanılan standart antikoagülandır ve heparin ile sürekli temas eden hemodiyaliz hastalarında HIT riski artmıştır. Burada kronik zeminde akut böbrek yetersizliği olan ve hemodiyaliz sonrasında HIT gelişen 75 yaşında bir erkek hastayı bildiriyoruz. Hastada derin ven trombozu saptandı ve fondaparinux ile başarıyla tedavi edildi. Bu yazımızda ayrıca HIT hastalarında gelişen trombozun profilaksi ve tedavisinde fondaparinuxun endikasyon dışı kullanımını derledik. Fondaparinux heparin ile reaksiyon veren antikorların çoğunluğunca tanınmayacak kadar küçük olduğundan lepirudin ve danaparoid gibi lisanslı ilaçların bulunmadığı durumlarda, semptomatik HIT hastaları için mantıklı bir alternatif antikoagülan olabilir.

Anahtar sözcükler: Heparine bağlı trombositopeni, tromboz, hemodiyaliz, fondaparinux.

Heparin-induced thrombocytopenia (HIT) type II is an acquired, transient, prothrombotic disorder and a life-threatening complication of unfractionated (UFH) and low-molecular-weight heparin (LMWH) therapy presenting

with thrombocytopenia and/or complicating venous or arterial thromboembolism that is associated with increased in vivo thrombin generation.^[1,2] It is generally recognized that HIT can be divided into two types: HIT type I

(non-immune mediated HIT) and HIT type II (immune-mediated HIT).^[3] For the remainder of this paper the term HIT indicates HIT type II. Heparin-induced thrombocytopenia is a clinicopathologic condition and adverse drug reaction caused by platelet-activating antibodies of IgG class which are directed against a molecular complex formed by heparin and platelet α -granule protein, platelet factor 4 (PF4).^[4,5] Heparin-induced thrombocytopenia occurs in 3% to 5% and 0.5% of patients receiving UFH and LMWH, respectively.^[6] In the absence of alternative anticoagulation, the risk of thrombosis is ~5% to 10% per day in the first few days after cessation of heparin^[7] and mortality from HIT range from 18% to 50%.^[3] Currently, direct thrombin inhibitors (argatroban, lepirudin) and danaparoid are approved agents as nonheparin anticoagulants for the prevention and treatment of HIT. Although they are effective, all of these drugs have their limitations and adverse effects. The synthetic pentasaccharide fondaparinux, a subcutaneously administered indirect acting factor-Xa inhibitor, offers a new alternative for both prevention and treatment of HIT, especially where licensed drugs are not available. Here we report the successful use of fondaparinux in the treatment of a patient presenting with acute-on-chronic renal failure requiring hemodialysis and HIT associated with thrombosis (HITT). We also review the current role of fondaparinux in the treatment and prophylaxis of thrombosis in patients with HIT.

CASE REPORT

A 75-year-old male patient admitted to our emergency department with dyspnea, tachypnea and bilateral low extremity edema. At admission, his blood pressure was 180/90 mmHg and heart rate 96 per minute. Laboratory findings included a complete blood cell count with Hb 8.8 g/dL, Hct 26.8%, MCV 84.3 fL, WBC $16800 \times 10^9/L$, and PLTS $504 \times 10^9/L$. Serum creatinine and creatinine clearance values were measured as 6.3 mg/dL and 17.2 ml/min, respectively. His physical examination and laboratory assessment revealed acute lung edema, uremic acidosis and acute-on-chronic renal failure requiring urgent

renal replacement therapy. His history revealed hypertension for 15 years and diabetes known for one year. A double-lumen hemodialysis catheter was inserted into the left femoral vein and regular (three times a week) hemodialysis therapy with low dose subcutaneous (sc) (5000 U/d) unfractionated heparin as anticoagulant on the days of hemodialysis sessions, for prevention of clotting of the extracorporeal circuit, was started. Ten days later after starting hemodialysis the platelet count dropped to $47 \times 10^9/L$ and there were pain and swelling on his left leg. Doppler ultrasound examination showed left femoral vein thrombus formation. Thereafter, enoxaparin 0.6 ml sc. bid therapy was started for the treatment of deep vein thrombosis. Four days later when platelet count was found to be $22 \times 10^9/L$ the patient was consulted with one of our hematology team members. The course of the platelet count before and after fondaparinux treatment is presented in Figure 1. As the patient had no other possible explanation for thrombocytopenia, HIT was strongly suspected. Anti-PF4/heparin enzyme-immunoassay (EIA) (Diagnostica Stago, France) complexes were positive (OD 2.375). Both functional assays, heparin-induced platelet aggregation test (HIPA) and C^{14} -serotonin release assay (SRA) (83%) were found to be positive. Low-molecular-weight heparin therapy and UFH during hemodialysis sessions were stopped and hemodialysis catheter was removed. Fondaparinux (ARIXTRA®) 2.5 mg

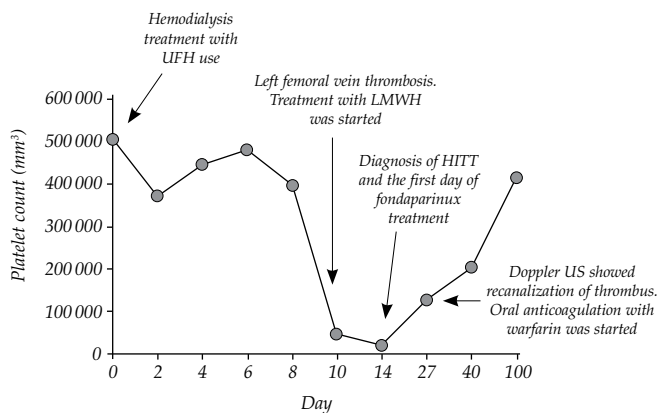


Fig. 1. The course of the platelet count of a patient with heparin-induced thrombocytopenia.

daily sc. was started. We could not monitor the anti-Xa activity because of technical problems. During fondaparinux treatment platelet count increased to $203 \times 10^9/L$ and repeated Doppler ultrasound showed recanalization of left femoral vein thrombus. When the platelet count reached $100\,000/mm^3$ oral anticoagulation with warfarin was initiated. The dose of warfarin was adjusted to maintain a target international normalized ratio (INR) of 2.5. When INR was therapeutic for two consecutive days fondaparinux was stopped. During six months of follow-up no new thromboembolic attack was observed.

DISCUSSION

Here we present a patient with HIT and femoral vein thrombosis while on dialysis who was successfully treated with fondaparinux. In this case HIT and catheter-induced vessel wall damage were two independent risk factors for venous thrombosis as we know that thrombotic complications of HIT frequently occur at sites of vascular injury, especially in the presence of central venous catheters.^[8] As the femoral vein thrombosis occurred at the site where hemodialysis catheter was inserted, at first glance it was misinterpreted as a complication of vessel wall damage and the remarkable drop of the platelet count was overlooked. Because HIT was unrecognized enoxaparin was commenced for the treatment of deep vein thrombosis, which could exacerbate the thrombotic process and even cause death of the patient. The platelet count decreased further on LMWH therapy as a result of probable cross-reaction of HIT antibodies with enoxaparin. At first time when we were aware of the patient we applied the proposed 'four Ts' model of HIT^[9] for estimating the pretest probability and calculated a score of 8, which was highly suggestive of HIT. As the SRA is considered to be the "gold standard" in the diagnosis of HIT;^[10] the combination of sensitive platelet activation and PF4-dependent antigen assay has a high sensitivity and specificity, reaching 100% and 80% to 97%, depending on time of the platelet fall, respectively,^[11] the diagnosis of HIT type II is confirmed with both serologic (EIA) and functional (HIPA, SRA) assays. The platelet

count began to fall on the 10th day following UFH exposure, when thrombotic complication was observed. After the diagnosis of HIT was made on clinical grounds and before the results of confirmatory tests were available, we stopped LMWH and searched for an alternative anticoagulant. As approved agents for the treatment of HIT like argatroban, lepirudin and danaparoid were not available in Turkey, we decided to go on with fondaparinux.

Currently two direct thrombin inhibitors (DTI), lepirudin and argatroban, are FDA-approved agents for the treatment of HIT and the third agent, danaparoid, is licensed for the treatment and prevention of HIT in Canada, European Union, Australia and Japan.^[11] We are unaware of a large, randomized, prospective study making head-to-head comparison between these drugs. So it is still unknown which one of these anticoagulants is superior in terms of efficacy and bleeding complications in patients with HIT. Although effective, all these agents have some shortcomings which could make the management of patients with HIT problematic. Lepirudin is a foreign protein which has been associated with the formation of antihirudin antibodies in up to 50% of patients who are treated for prolonged intervals and this may increase the anticoagulant effect of the drug due to delayed renal elimination of hirudin-antihirudin complexes.^[12] As the correlation between aPTT and plasma levels of lepirudin is not always linear at higher lepirudin concentrations, monitoring the efficacy of anticoagulant therapy with ecarin clotting time may be needed, which is not widely available.^[13] Although rare (~0.015% at first exposure and 0.16% in reexposed patients), lepirudin treatment has also been associated with anaphylaxis which can be reduced by avoiding initial bolus of the drug.^[11,14] Careful attention should be paid to monitoring patients receiving lepirudin and argatroban as both agents require coagulation monitoring and have a high frequency of bleeding. The major bleeding risks requiring transfusion of patients receiving lepirudin and argatroban were found to be 5.4%-20.4% and 6.1%-11.1%, respectively.^[11] As argatroban increases INR this can complicate optimal dosing

of vitamin K antagonists (VKAs) during overlapping argatroban/warfarin therapy and may lead to early cessation of argatroban with the potential for venous limb gangrene in patients with active HIT.^[11] A prospectively recruited cohort of patients who were enrolled in HAT (heparin-associated thrombocytopenia)-I and HAT-II trials and were treated with lepirudin were compared with patients with HIT from the same centers who were treated for some reasons with danaparoid instead of lepirudin at the same time period.^[15] Although the study was not randomized and prospective in a true sense, it concluded that danaparoid in a high-dose regimen was equivalent to lepirudin in the treatment of HIT and danaparoid treatment was associated with a significantly less major bleeding compared with lepirudin (2.5% vs. 10.4%, respectively; $p=0.009$). But this conclusion about low bleeding rate in danaparoid arm may be misleading as it could reflect the low level of anticoagulation in significant number (34.9%) of patients who were treated with prophylactic doses of danaparoid.^[9,15] Expert opinion suggests that danaparoid may be used without monitoring of anti-Xa levels except in patients with severe renal failure and extremes of body weight.^[9]

Fondaparinux is a novel anticoagulant that catalyses inhibition of factor Xa by antithrombin resulting in inhibition of thrombin, which is the ultimate factor of thrombosis in patients with HIT.^[16] It is approved by the FDA for prophylaxis of venous thromboembolism (VTE) following orthopedic surgery as well as for the treatment of VTE.^[17] The rationale behind the use of fondaparinux in the prevention and treatment of HIT relies on the following reasons:

1. Although the drug is identical in structure to the pentasaccharide domain found on UFH, its length is shorter than the 10 to 12 saccharides required for binding to PF4 to be recognized by the majority of HIT antibodies.^[16]

2. Except one recent case report of delayed onset HIT,^[18] no episodes of HIT was reported in the phase II and phase III trials of fondaparinux, in which it was used by approximately 5000 patients.^[19]

3. Although fondaparinux may be associated with the formation of anti-PF4/heparin antibodies in-vitro data suggests that it does not interact with HIT related antibodies to induce platelet activation and aggregation. Indeed, Savi et al.^[19] showed the inability of fondaparinux to activate platelets in the presence of HIT sera by using three highly sensitive markers of platelet activation such as flow cytometric analysis of GpIIb/IIIa activation, dense granule release and expression of phospholipid molecules on platelet membrane.

4. Even with prompt treatment with a DTI, 5.6%-10%, 9.8%-18.3% and 8.5%-21.3% of patients with HIT/HITT will require an amputation, experience a new thromboembolic event and still die, respectively.^[20]

5. Subcutaneous administration without the need for aPTT and INR monitoring, low cost and long half-life are potential advantages of fondaparinux over DTI and danaparoid.

As far as we know there are 67 reported HIT/HITT cases in the literature who were treated with fondaparinux (Table 1). None of the patients experienced a new thromboembolic complication while on fondaparinux treatment indicating 100% treatment efficacy. But this could be related to referral biases because there is a well-known trend for publication of cases with positive/successful outcomes. One out of 44 (2%) patients had bleeding complications. In 23 patients information about bleeding was not available. On the other hand, fondaparinux is a subcutaneously administered drug with a long (18 h) half life making it suitable for once-daily administration and in general it doesn't need monitoring except in patients with renal failure.^[3] But all the licensed anticoagulants mentioned above require intravenous administration and therefore prolonged hospitalization. These results indicate that fondaparinux seems to be a very effective alternative drug for HIT with a quite acceptable bleeding risk compared to licensed drugs. We should keep in mind that except one recently reported pilot study by Lobo et al.^[21] with small patient size and historical controls who were treated with DTI, there are

Table 1. Fondaparinux experience in the treatment/prophylaxis of HIT/HITT

Reference	Indication (patient number)	Dose (mg/day)	Treatment duration	Diagnosis	Follow-up	Monitorization	Major bleeding	New TEC
21	HITT (6)							
HIT (1)	2.5-10	7-19 d	Anti-PF4	4 w	-	0/7	0/7	
22	HITT (1)	7.5	18 m	Anti-PF4 (-) ^{&}	18 m	-	NR	0/1
23	HITT (5) [¶]							
HIT (2)	2.5	12-15 d	HIPA					
5/7 (+)	NR	aPTT						
anti-FXa	0/7	0/7						
24	SP (1)	2.5	3 m	NR	NR	Anti-FXa [#]	0/1	0/1
25	HIT (1)	2.5	NR	HIPA (+)	NR	-	NR	0/1
26	SP (1)	2.5	8 m	NR	8 m.	NR	0/1	0/1
27	HIT (20)	2.5 [*]	NR	Anti-PF4	NR	NR	NR	0/20
28	HITT (5)	7.5	3 m	5/5				
Anti-PF4 (+)	3 m.	NR	0/5	0/5				
29	HITT (1)	5	NR	PF-4	NR	NR	0/1	0/1
30	HIT (1)	0.5 [§]	NR	PF-4	NR	anti-FXa	0/1	0/1
31	HITT (1)	2.5 ^ψ	10 w	Anti-PF4 (-) ^{&}	10 w	anti-FXa	0/1	0/1
32	HITT (17)							
HIT (3)	2.5-7.5 ^φ	NR	NR	NR	NR	1/20	0/20 ^ζ	
33	HITT(1)	7.5	28 d	Anti-PF4	10 m	-	NR	NR

& The diagnosis was made on clinical grounds alone without serologic confirmation; ¶ One patient with HITT was treated twice on different occasions; # The anticoagulant effects of fondaparinux was also determined with Heptest (coagulation time, sec); * Initial dose of fondaparinux was 2.5 mg/d sc. for 18 patients. Exact doses for the entire cohort during follow-up unknown. 10 patients received fondaparinux following treatment with a DTI and 10 patients were treated with fondaparinux upfront; § The dose of fondaparinux was adjusted because of renal failure; ψ The patient required regular hemodialysis and received 2.5 mg fondaparinux on dialysis days only (every second day); φ 17 patients with HITT received ≤ 7.5 mg/d and 3 patients with HIT received 2.5 mg/d fondaparinux; ζ In one patient the thrombocytopenia was not resolved. The platelet count returned to near normal levels after the treatment was switched from fondaparinux to lepirudin; m: month; w: week; d: day; NR: not reported; SP: secondary prophylaxis; TEC: thromboembolic complication.

no prospective, comparative studies with fondaparinux and reports on fondaparinux use in HIT are not uniform in terms of clinical presentation, dose and treatment duration, laboratory methods used for HIT/HITT diagnosis, follow-up period and monitorization. On the other hand, the majority of the patients (43 patients - 64%) were reported only in abstract form.^[26,27,29,30,32] So it is still impossible to draw firm conclusions about fondaparinux use in HIT.

Because of renal elimination half-lives of lepirudin, danaparoid and fondaparinux significantly increase in patients with azotemia. In case of renal failure, argatroban, with hepatobiliary elimination, should be the drug of choice, but the drug was unavailable in Turkey. As we know there are only two patients with HIT and renal failure who were successfully treated with

fondaparinux.^[30,31] The dosages of fondaparinux used were 0.5 mg/d and 2.5 mg on dialysis days only, respectively. In both cases efficacy of treatment was assessed with anti-FXa monitoring. We treated our patient with 2.5 mg/d fondaparinux without monitorization.

On the other hand, DTI-warfarin overlap is a high-risk period for warfarin-induced venous limb gangrene. Prolongation of INR by DTI and aPTT by warfarin could cause early cessation and underdosing of DTI, respectively. The study of Lobo et al.^[21] showed that bridging to warfarin was more successful in patients on fondaparinux arm compared with historical controls who were treated with DTI and this finding brought new ideas for use of fondaparinux in HIT. As Warkentin^[34] suggested, fondaparinux could be a promising agent for safe bridging to warfarin

and DTI-fondaparinux bridging instead of DTI-warfarin transition could be more rational for reducing venous limb gangrene.^[34]

As HIT is a life-threatening complication of heparin therapy all physicians using heparin anticoagulation should be aware of it and all patients receiving heparin of any sort should have platelet counts monitoring from days 4 to 14.^[9] Fondaparinux could be an effective and safe option for treatment and prevention of HIT, even in patients with renal failure, where licensed drugs are unavailable. In case of renal failure fondaparinux should be used with caution and the therapy should be tailored with anti-FXa monitoring. Prospective, randomized studies will define the role and optimal dose of fondaparinux in the treatment and prophylaxis of HIT.

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