Case Report

Fondaparinux used for severe heparin induced thrombocytopenia with subacute instent thrombosis

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ABSTRACT

Heparin induced thrombocytopenia (HIT) is an immune mediated event that may result in life and limb threatening complications. We report a 52 year old diabetic woman with subacute instent thrombosis and severe heparin induced thrombocytopenia treated successfully with fondaparinux. Not only platelet count returned to normal but also thromboembolic or hemorrhagic events were prevented under treatment. The low rate of de novo antibody formation and the scarce cross-reactivity with HIT antibodies offer fondaparinux as a relatively safe alternative anticoagulant agent for use in patients with HIT. Fondaparinux should be kept in mind in severe HIT if direct thrombin inhibitors are unavailable.

Key Words: Heparin induced thrombocytopenia, fondaparinux, instent thrombosis,

INTRODUCTION

Thrombocytopenia is a potentially serious side effect following administration of heparin. Heparin induced thrombocytopenia (HIT) is an immune mediated event that can result in severe life and limbthreatening complications. It is caused by the formation of antibodies against complex of heparin and platelet factor4 (PF4), that activate platelets[1].
Diagnosis of HIT is based primarily on clinical presentation and supported by confirmatory laboratory testing. The criteria for diagnosis of HIT include thrombocytopenia defined as a drop in platelet count by 30% to <100000/µL or a drop of 50% from the patient's baseline platelet count, typical onset of thrombocytopenia 5–10 days after initiation of heparin treatment, which can occur earlier with previous heparin exposure (within 100 days), acute thrombotic event, the exclusion of other causes of thrombocytopenia, the resolution of thrombocytopenia after cessation of heparin and HIT antibody seroconversion[1].
With discontinuation of unfractionated heparin (UFH), low molecular weight heparin (LMWH) or alone risk of subsequent thrombosis rises up to 50%[2]. LMWH cannot be used in patients with HIT because of the strong crossreactivity of the HIT antibody with the LMWH–PF4 complex[3,4]. Currently, direct thrombin inhibitors (argatroban, lepirudin, bivalirudin) are the only treatments for managing HIT[5-7]. These agents have chemical structures different from UFH and LMWH and do not cross-react with HIT antibodies[8]. 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[5-7]. Moreover these agents are not available in some countries commercially. Therefore, other treatment options for HIT are needed.

CASE

We report a 52 year-old diabetic woman admitted to the emergency department with ongoing chest pain and dyspnea for 12 hours. Her blood pressure was 160/90mmHg and pulse was 102 beat/min. Diabetic ketoacidosis and acute anterior myocardial infarction were the diagnoses. Intravenous (iv) bolus of unfractionated heparin (UFH) 5000 IU was followed by an infusion of 1000 IU/hr infusion. Coronary angiography revealed total occlusion of Left Anterior Descending Artery

(LAD) after first diagonal branch and two consecutive 90% stenoses in midsegment of Right Coronary Artery (RCA) and 80% stenosis in distal RCA. LAD was recanalized by primary angioplasty and stenting after 600 mg clopidogrel loading dose was given PO. Meanwhile insulin and tirofiban infusion was started. 48 hours later tirofiban infusion was stopped and UFH was replaced with enoxaparin 1 mg/kg sc twice daily. On fifth day of her admission enoxaparin was stopped. But due to recurrent angina pectoris UFH and tirofiban infusion was restarted. On 6th day control angiography was done, LAD stent was patent. RCA lesions were presumed as culprit lesions for recurrent angina and two stents were deployed to RCA lesions. After this intervention iv tirofiban and UFH infusion continued 1 more day. Then sc enoxaparin was started. On 9th day she experienced acute inferior myocardial infarction. Her pain and inferior ST segment elevation were resolved with tPA infusion. In the complete blood count taken same day the fall in platelet count to 28000/µL was not percieved (Figure 1).

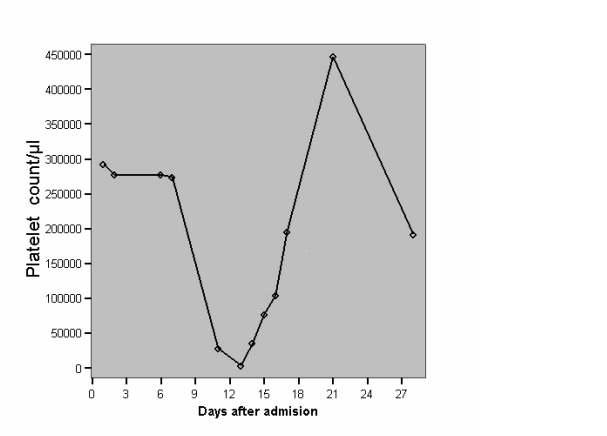

Figure 1. Platelet counts

Enoxaparin treatment was continued. 36 hours later due to inferior reinfarction immediately performed coronary angiography revealed subacute instent thrombosis in distal RCA (Figure 2). PTCA was done and platelet count of 2000/µL was realized. Enoxaparin was immediately discontinued because of the clinically diagnosed HIT syndrome. After pseudothrombocytopenia was ruled out by periferic smear and using tubes with citrate or heparin for blood count ASA and clopidogrel tratments were also terminated. Fondaparinux 2,5mg sc once daily was started. Next day platelet count rose to 20000/µL. The following day since it rose beyond 50000/µL, ASA and clopidogrel was again started. Under fondaparinux treatment the platelet count rose to normal values and stayed stable during the following days. Neither venous nor arterial thrombi occured. The patient did not experience any other ischemic episode under fondaparinux treatment. In predischarge electrocardiography and echocardiography there wasn't any evidence of inferior infarction.

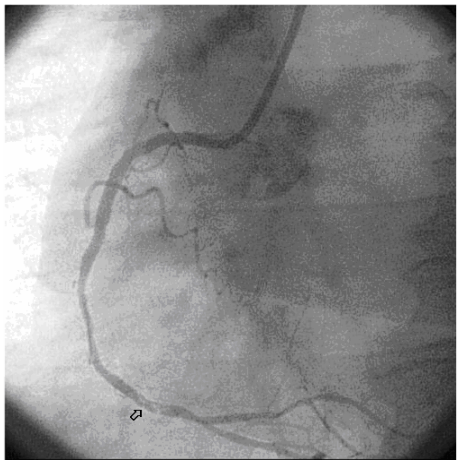

Figure 2. Thrombosis of RCA stent (arrow)

DISCUSSION

Thrombocytopenia secondary to tirofiban might have been an alternative explanation for this patient. However, thrombocytopenia associated with tirofiban generally occurs early after infusion and usually resolves even under UFH or LMWH treatment[9]. Decline in platelet count continued despite of the cessation of tirofiban infusion. Unfortunately we didn't have the capability of testing antibodies against heparin/PF4 complex which would be more decisive in distinguishing HIT from thrombocytopenia secondary to tirofiban. Presence of thrombosis instead of bleeding favours HIT as diagnosis. Additionally, high "4T" score revealed high probability of HIT in our patient[10]. Venous thrombosis was not detected in our patient. Arterial thrombosis occurs more frequently than venous thrombosis in HIT patients receiving heparin for cardiovascular diseases[11].

It is 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[12]. To date only one case of HIT has been reported among fondaparinux-treated patients which was probably a drug induced, HIT-like autoimmune reaction[13]. Fondaparinux is better than direct thrombin inhibitors as a bridge to warfarin, but its efficacy as a primary non-heparin anticoagulant for severe HIT-associated hypercoagulability is not established with randomized studies[14].

Fondaparinux can induce the epitope on PF4 leading to anti-PF4/ heparin antibody formation[15].

However, the number of PF4/fondaparinux complexes is much lower and their size is much smaller than with UFH or LMWH[16]. In the presence of HIT sera, although 79.8% of evaluable assays were reactive with unfractionated heparin; only 3.3% of samples were positive with fondaparinux[17]. This supports the idea that F4/fondaparinux complexes do not lead formation of sufficient immune complexes to permit platelet activation in the presence of anti-PF4/heparin antibodies.

CONCLUSION

In our case fondaparinux treatment after PTCA of instent thrombosis in severe HIT has been successful. Not only platelet count returned to normal but also thromboembolic or hemorrhagic events were prevented. The low rate of de novo antibody formation and the scarce cross-reactivity with HIT antibodies offer fondaparinux as a relatively safe alternative anticoagulant agent for use in patients with HIT. It should be kept in mind in severe HIT if direct thrombin inhibitors are unavailable. Further studies comparing fondaparinux with direct thrombin inhibitors in HIT treatment are needed.

REFERENCES

1. Ahmed I, Majeed A and Powell R. Heparin induced thrombocytopenia: diagnosis and management update Postgrad. Med J 2007;83: 575–82.
2. Efird LE, Kockler DE. Fondaparinux for Thromboembolic Treatment and Prophylaxis of Heparin-Induced Thrombocytopenia. Ann Pharmacother 2006;40: 1383-7.
3. Klein HG, Bell WR. Disseminated intravascular coagulation during heparin therapy. Ann Intern Med 974;80:477–81.
4. Keeling DM, Richards EM, Baglin TP. Platelet aggregation in response to four low molecular weight heparins and the heparinoid ORG 10172 in patients with heparin-induced thrombocytopenia. Br J Haematol 1994; 86: 425–6.
5. Package insert. Argatroban (argatroban). Research Triangle Park, NC: GlaxoSmithKline, April 2005.
6. Package insert. Refludan (lepirudin). Montville, NJ: Berlex, October 2004.
7. Package insert. Angiomax (bivalirudin). Parsippany, NJ: The Medicines Company, December 2005.
8. Hassell K. The management of patients with heparin-induced thrombocytopenia who require anticoagulant therapy. Chest 2005;127: 1S-8S.
9. Mulot A, Moulin F, Fohlen-Walter A, Angioi M, Sghaier M, Carteaux JP, et al. Practical approach to the diagnosis and management of thrombocytopenia associated with tirofiban treatment. Am J Hematol 2004;77: 67-71.
10. Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost 2006;4: 759–65.
11. Boshkov LK, Warkentin TE, Hayward CP, Andrew M, Kelton JG. Heparin-induced thrombocytopenia and thrombosis: clinical and laboratory studies. Br J Haematol 1993;84: 322–8.
12. Bussey H, Francis JL. Heparin Consensus Group. Heparin overview and issues. Pharmacotherapy 2004;24:103S-107S.
13. Warkentin TE, Maurer BT, Aster RH. Heparin-induced thrombocytopenia associated with fondaparinux. N Engl J Med 2007;356: 2653–5.
14. Warkentin T.E. Fondaparinux versus direct thrombin inhibitor therapy for the management of heparin-induced thrombocytopenia (HIT)-Bridging the River Coumarin editorial Thromb Haemost 2008;99: 2–3.
15. Pouplard C, Couvret C, Regina S, Gruel Y. Development of antibodies specific to polyanion-modified platelet factor 4 during treatment with fondaparinux. J Thromb Haemost 2005;3: 2813–5.
16. Greinacher A, Gopinadhan M, Gunther JU, Omer-Adam MA, Strobel U, Warkentin TE, et al. Close approximation of two platelet factor 4 tetramers by charge neutralization forms the antigens recognized by HIT antibodies. Arterioscler Thromb Vasc Biol 2006;26: 2386–93.
17. Savi P, Chong BH, Greinacher A, Gruel Y, Kelton JG, Warkentin TE, et al. Effect of fondaparinux on platelet activation in the presence of heparin-dependent antibodies: a blinded comparative multicenter study with unfractionated heparin Blood 2005;105: 139-144.

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