

Apixaban as a therapeutic option in chronic kidney disease patients with heparin-induced thrombocytopenia (HIT)

Guillermo Delgado-García^{1*}, Roberto Monreal-Robles¹, Daniel Gallegos-Arguijo¹ and Javier Marfil-Rivera²

¹Department of Internal Medicine; ²Division of Hematology, Hospital Universitario Dr. José Eleuterio González, Universidad Autónoma de Nuevo León, Monterrey, N.L., México

Abstract

Heparin-induced thrombocytopenia (HIT) is a prothrombotic condition caused by antibodies against the heparin-PF4 complex. This disorder is even more problematic in patients undergoing hemodialysis since they are repeatedly exposed to heparin. The diagnostic and therapeutic approach is particularly challenging in this population. We report the case of a woman with chronic kidney disease and a high pretest probability for heparin-induced thrombocytopenia who was acutely treated with apixaban, an oral selective factor Xa inhibitor. (Gac Med Mex. 2015;151:742-5)

Corresponding author: Guillermo Delgado García, grdelgadog@gmail.com

KEY WORDS: Apixaban. Chronic kidney disease. Thrombocytopenia/chemically induced. Thrombocytopenia/therapy. Heparin/ adverse effects. Anticoagulants/ therapeutic use. Deep venous thrombosis.

Introduction

Heparin-induced thrombocytopenia (HIT) is a clinicopathological syndrome with pro-thrombotic characteristics, mediated by antibodies that recognize FP4/heparin complexes^{1,2}. This condition is especially relevant in patients undergoing hemodialysis, since they are repeatedly exposed to unfractionated heparin (UFH). In this population, the diagnostic approach has some inconveniences, since antibodies against the FP4/heparin complex can be found in up to 17.4% of these patients without this entailing clinical manifestations. In addition to limited availability (they are only performed in a few reference laboratories), functional studies can also test positive in a small fraction

(3.7%) of these patients. Finally, in this population in particular, the therapeutic armamentarium is quite reduced^{3,4}.

Here we report the case of a female patient with chronic kidney disease and a high pre-test probability for HIT, who was acutely treated with apixaban, a new oral anticoagulant (NOAC) that inhibits factor Xa.

Case presentation

A 50-year-old woman presented to the emergency department with uremic syndrome. She was referred to our hospital to be started on renal replacement therapy (RRT). Her past medical history was notable for longstanding type 2 diabetes and arterial hypertension, both conditions with poor treatment adherence. The

Correspondence:

*Guillermo Delgado García
Departamento de Medicina Interna
Hospital Universitario Dr. José Eleuterio González
Madero y Gonzalitos, s/n
Col. Mitras Centro, C.P. 64460, Monterrey, N.L., México
E-mail: grdelgadog@gmail.com

Funding sources: None.

Conflict of interests: The drug used for the treatment of this patient was obtained as a free medical sample from Pfizer. This drug is not the only new oral antiagulant (NOAC) used in our hospital

Date of reception: 16-09-2014

Date of acceptance: 28-10-2014

patient's outpatient medications included NPH insulin (30 units daily) and enalapril (10 mg twice daily).

Laboratory findings confirmed the presence of renal dysfunction and its stage. The night of admission, due to the impossibility to place a central line into the internal jugular vein, an ultrasonography-guided right femoral Mahurkar catheter was placed in order to start acute hemodialysis. During this hemodialysis session, heparinization was performed with 3,000 units. After her admission in the general ward, pharmacological thromboprophylaxis was started with subcutaneous UFH. On day 4 of admission, she underwent a second dialysis session; the heparinization remained the same. No extracorporeal circuit clotting was reported. The patient improved clinically and paraclinically due to RRT and, therefore, on day 6 of hospitalization, a Tenckhoff catheter was placed for a definitive transfer to peritoneal dialysis, which was performed uneventfully. The Mahurkar catheter was removed on that very day, and 24 h later, the peritoneal catheter was first used.

Moderate thrombocytopenia (118 K/ μ l) was found on admission blood count. This finding was investigated in parallel. Initially, ethylenediaminetetraacetic acid (EDTA)-induced pseudothrombocytopenia was ruled out. On further questioning, the patient denied a history of bleeding, alcohol consumption, self-medication, recent travels and risky sexual behaviors. She had no systemic inflammatory response syndrome, no murmurs were heard on precordial auscultation and no organomegalies were found at abdominal palpation. No abnormally large platelets platelet aggregates, schistocytes or blasts were found on peripheral blood smear. Both liver function tests and coagulation time tests were within the limits of normal. Additionally, HIV and hepatitis C virus infections were ruled out.

On the morning of the tenth inpatient day, the patient referred pain and right lower limb edema; a painful, edematous limb, with positive pitting sign, and difficult mobilization was found on physical examination. Since she had a high pre-test probability for deep venous thrombosis (DVT), a Doppler ultrasonograph with venous compression was performed. We thus made the diagnosis of DVT from the femoral to the popliteal vein. Therefore, we decided to start her on UFH and warfarin.

On the next day, the patient had a platelet count decrease of 67%. In the setting of recent heparin exposure, thrombosis, and platelet count drop, early onset HIT was suspected. No cutaneous necrosis was found after specifically looking for it. According to the 4Ts score, the patient had a high pre-test probability

of HIT; both UFH and warfarin were therefore discontinued, and apixaban (2.5 mg twice daily) was started as alternative anticoagulant. Since this factor Xa inhibitor is not currently approved for the treatment of HIT, the therapeutic possibilities were discussed with the patient and she signed an informed consent form.

Four days after this switch, the platelet count reached the figure of day 10 of hospitalization and 7 days later it exceeded the figure found at admission (Fig. 1). After having exceeded the platelet count found at admission, on day 18 of hospitalization, low-dose warfarin was started (5 mg daily), and administered together with apixaban for 5 days. The international normalized ratio remained at therapeutic ranges during this time. No venous gangrene occurred during this period. On day 22 of admission, apixaban was discontinued and anticoagulation was continued with warfarin. During the time she was treated with apixaban, the patient did not experience petechiae or any other important sign of bleeding, and neither did she experience venous thromboembolic disease progression. In view of her satisfactory evolution, she was discharged from hospital with follow-up in the outpatient setting; on the day of discharge, her platelet count was 231 k/ μ l.

Discussion

The frequency of HIT in our country is unknown. In the setting of chronic kidney disease (CKD), our knowledge on the epidemiology of this syndrome stems from a British study that included more than 13,000 patients on hemodialysis and found a prevalence of 0.26 cases per 100 patients and an incidence of 0.32 cases per 100 patients⁵.

The diagnosis of HIT is particularly complicated in patients undergoing hemodialysis^{3,4}. There are two types of paraclinical tests used in the diagnosis of this syndrome: immunoassays and functional tests^{1,2}. False-positive results are among the drawbacks of immunoassays, since in up to 17.4% of these patients, antibodies against the FP4/heparin complex can be detected, even when the syndrome is not diagnosed due to the absence of clinical manifestations. On the other hand, false-positive results can also be found in a small proportion of patients (3.7%) in functional studies^{3,4}. Another setback of these tests is their limited availability, since they are performed exclusively in some reference laboratories^{1,4}.

Even when a high pre-test probability, estimated according to the 4Ts score, has a positive predictive value of only 64%¹, when HIT is suspected and an

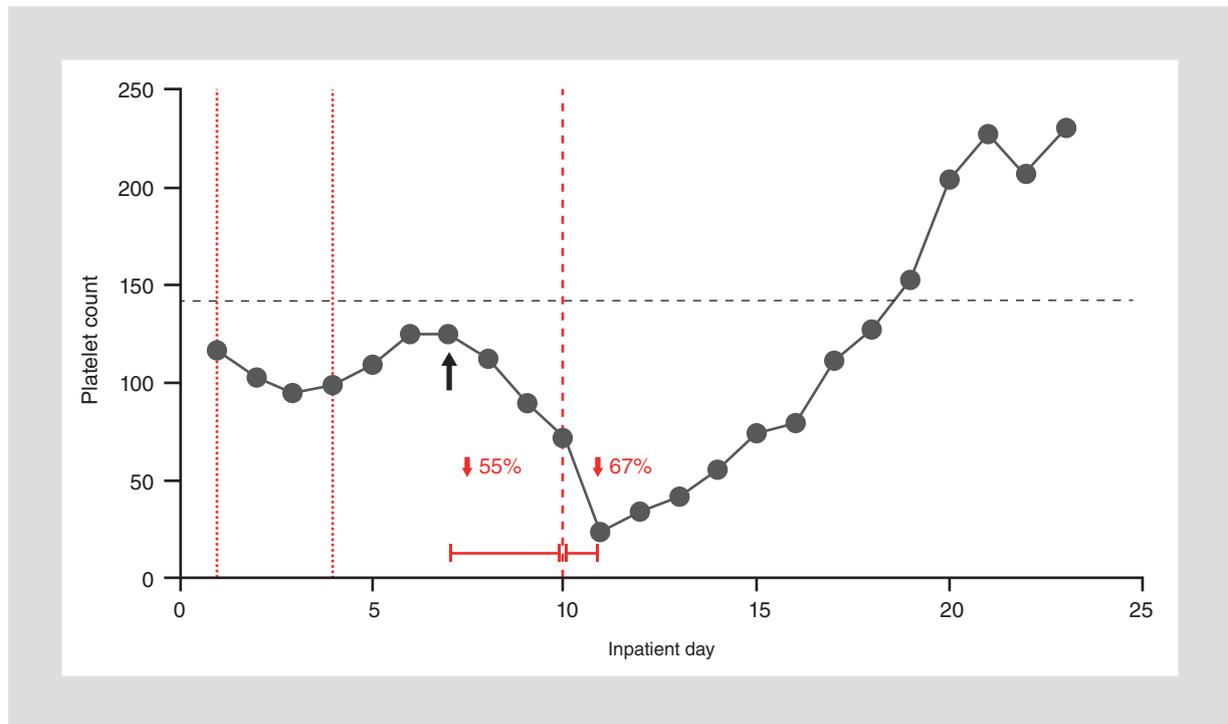


Figure 1. Platelet count evolution in time. All points found below the horizontal dotted line imply thrombocytopenia according to our laboratory ranges. The first two vertical dotted lines represent hemodialysis sessions where heparin was used, and the third indicates the day when heparin intravenous infusion was started. The first range indicates a 55% drop in the platelet count between days 7 and 10 of admission. The second range indicates a 67% drop in the platelet count between days 10 and 11 of admission.

intermediate or high pre-test probability is obtained, discontinuation of anticoagulation with heparin and starting a new alternative drug is recommended². This recommendation eases one of the main limitations of our diagnostic approach, the absence of confirmation with paraclinical tests. On the other hand, the therapeutic response of this patient after UFH discontinuation was as it is to be expected in a case of HIT⁶.

Among the treatment options for the management of HIT, argatroban is the drug of choice when it occurs in a patient with CKD, but its cost represents a major limitation: one day's treatment with argatroban has an approximate cost of \$1313⁶. Although previously recommended for this population, lepirudin was withdrawn from the market last year^{2,6}. Other alternatives described in these patients include bivalirudin and danaparoid sodium^{2,6}, which are not available in our country. On the other hand, fondaparinux is contraindicated in patients with CKD from stage IV (< 30 ml/min) on, due to its predominantly renal elimination⁶.

In this patient, we decided to acutely treat her with apixaban, a therapeutic option that so far has not been reported in medical literature. Early this year, the Food and Drug Administration (FDA) included a recommendation for the use of this drug in patients with end-

stage CKD; the suggested dose is based on pharmacokinetics and pharmacodynamics information obtained from patients on hemodialysis⁷. Given that apixaban is structurally different to heparin, the pathogenic antibodies of HIT do not recognize it, thus avoiding platelet activation and aggregation that are characteristic of this syndrome⁸.

Although originally in this patient early onset HIT secondary to UFH infusion started on day 10 of admission was suspected, a temporal evolution more resembling that observed in classic HIT, where manifestations occur 4-14 days after the use of heparin, was retrospectively perceived on her platelet count (Fig. 1)⁶. The patient had two thrombosis predictors: previous vascular lesion (secondary to femoral catheter placement) and low platelet nadir⁶.

At admission, the patient had already moderate thrombocytopenia. The presence of thrombocytopenia has already been reported in patients with end-stage CKD before RRT^{9,10}, and insufficient thrombopoiesis has been invoked as an explanation for this decreased platelet count⁹. However, a unifying pathophysiological mechanism that explains thrombocytopenia while also accounting for the remaining platelet defects occurring in patients with CKD has not yet

been described¹¹. The thrombocytopenia attributed to CKD has been independently associated with prolonged bleeding times¹² and can be improved (even in serious cases) after the administration of erythropoietin^{13,14}.

In the future, apixaban could represent a therapeutic option for the management of HIT, especially in patients with CKD. However, clinical trials are needed to assess its usefulness in the specific setting of HIT.

References

1. Cuker A. Clinical and laboratory diagnosis of heparin-induced thrombocytopenia: an integrated approach. *Semin Thromb Hemost.* 2014;40(1):106-14.
2. Cuker A, Cines DB. How I treat heparin-induced thrombocytopenia. *Blood.* 2012;119(10):2209-18.
3. Goździkiewicz J, Borawski J, Myśliwiec M. Treatment of heparin-induced thrombocytopenia type II in hemodialysis patients: the search for a Holy Grail continues. *Clin Appl Thromb Hemost.* 2007;13(1):110-1.
4. Syed S, Reilly RF. Heparin-induced thrombocytopenia: a renal perspective. *Nat Rev Nephrol.* 2009;5(9):501-11.
5. Hutchison CA, Dasgupta I. National survey of heparin-induced thrombocytopenia in the haemodialysis population of the UK population. *Nephrol Dial Transplant.* 2007;22(6):1680-4.
6. Lee GM, Arepally GM. Diagnosis and management of heparin-induced thrombocytopenia. *Hematol Oncol Clin North Am.* 2013;27(3):541-63.
7. Eliquis[package insert]. Princeton, New Jersey: Bristol-Meyers Squibb; 2012 [Revised: 01/2014].
8. Walenga JM, Prechel M, Hoppensteadt D, et al. Apixaban as an alternate oral anticoagulant for the management of patients with heparin-induced thrombocytopenia. *Clin Appl Thromb Hemost.* 2013;19(5):482-7.
9. Gafer U, Bessler H, Malachi T, et al. Platelet count and thrombopoietic activity in patients with chronic renal failure. *Nephron.* 1987;45(3):207-10.
10. Dorgalaleh A, Mahmudi M, Tabibian S, et al. Anemia and thrombocytopenia in acute and chronic renal failure. *Int J Hematol Oncol Stem Cell Res.* 2013;7(4):34-9.
11. Ho SJ, Gemmell R, Brighton TA. Platelet function testing in uraemic patients. *Hematology.* 2008;13(1):49-58.
12. Kim HY, Oak CY, Kim MJ, et al. Prevalence and associations for abnormal bleeding times in patients with renal insufficiency. *Platelets.* 2013;24(3):213-8.
13. Canaud B, Polito-Bouloux C, Garred LJ, et al. Recombinant human erythropoietin: 18 months' experience in hemodialysis patients. *Am J Kidney Dis.* 1990;15(2):169-75.
14. Thachil J, Szeki I. Erythropoietin corrects thrombocytopenia. *Am J Med.* 2013;126(10):e3-4.