Probable Famotidine-Induced Thrombocytopenia

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Introduction

Thrombocytopenia is defined as a decrease in platelet count to less than 150 $x10^9$/L.[1] It can result in increased length of hospital stay and risk of death. Drug-induced thrombocytopenia (DITP) can result from a decrease in platelet production through a direct toxic effect on the thrombopoietic mechanisms in the bone marrow or an increase in platelet destruction through immune-mediated mechanisms.[2] In DITP, the platelet count typically falls from 50 to 80% of the normal value on exposure to the offending drug and returns to normal after drug withdrawal.[3]

Thrombocytopenia is a rare adverse effect of famotidine therapy.[4-7] Few cases of famotidine-induced thrombocytopenia have been reported. Case reports have suggested two potential mechanisms of H2 antagonist-induced thrombocytopenia. The first is bone marrow suppression secondary to inhibition of DNA synthesis. The second mechanism occurs rarely and is the development of platelet antibodies during H2-antagonist administration.[8] The diagnosis of this critical condition is based on clinical suspicion and is a diagnosis of exclusion.

We report a case of a male presenting with nausea, vomiting, and abdominal pain diagnosed with small bowel obstruction.

Case Report

A 56-year-old Caucasian male weighing 35 kg (77 pounds) with a history of human immunodeficiency virus (HIV), hypothyroidism, chronic obstructive pulmonary disease, chronic kidney disease and hypertension was hospitalized due to vomiting and abdominal pain. His vital signs on admission were within normal limits. He denied melena, hematochezia, or hematemesis. His home medications were sodium bicarbonate, furosemide, alendronate, L-thyroxine, emtricitabine-tenofovir, potassium chloride, lopinavir/ritonavir, and tiotropium bromide. All were taken orally and continued during hospitalization. Metronidazole and heparin were added. Routine admission labs revealed a white blood count of 4900 cells/mm^3 and platelet count of 275 x 10^9 platelets/L. Hemoglobin was 13.8 g/dL. An abdominal x-ray showed multiple air-fluid levels and he was diagnosed with small bowel obstruction.

On day three in the hospital, total parenteral nutrition (TPN) containing famotidine was initiated. The dose of famotidine was 40 mg daily. On day four, a complete blood count revealed a platelet count of 169 x 10^9 platelets/L. On day five, the platelet count dropped to 157 x 10^9 platelets/L. The patient was on heparin and heparin-induced thrombocytopenia (HIT) was suspected. After stopping all forms of heparin on day five, his platelet count continued to drop, a trend which continued on days six, seven, and eight: 119 × 10^9 platelets/L, 100 × 10^9 platelets/L, 80 × 10^9 platelets/L, respectively (Figure 1).

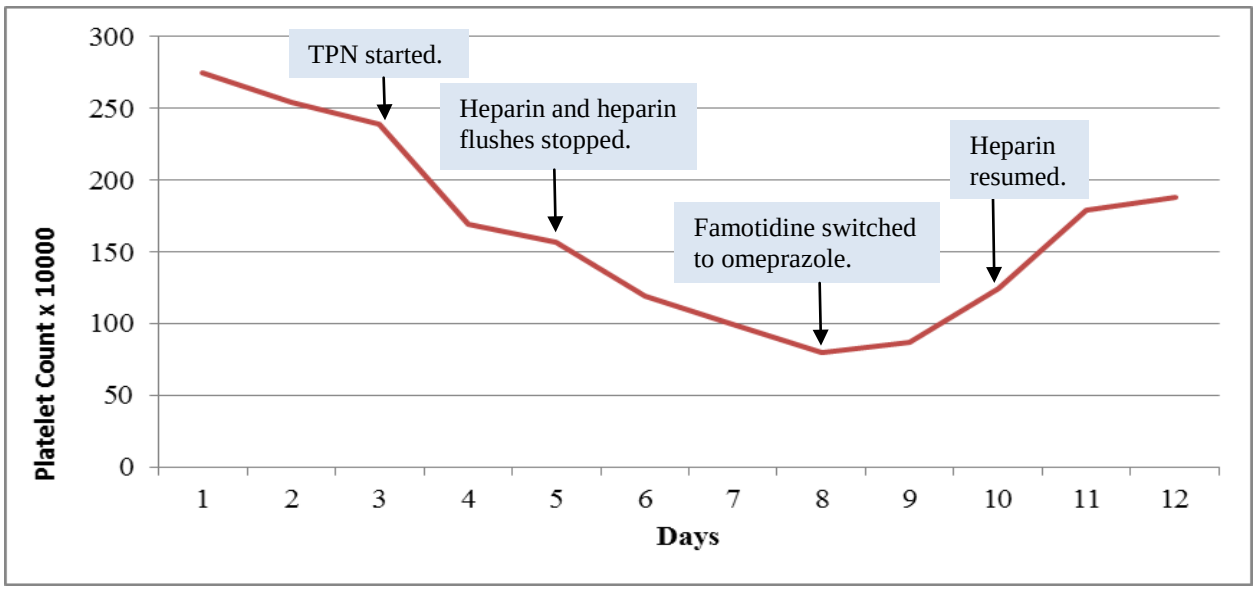

Figure 1. Platelet count changes over twelve hospital days.

Work-up for thrombocytopenia included a blood smear which showed platelets to be of normal size and no schistocytes. PT/INR, TSH, vitamin B12, serum and RBC folate levels, transaminases, haptoglobin, fibrinogen, and partial thromboplastin time (PTT) were within normal ranges. Further workup revealed a negative ANA and minimally elevated d-dimer (3.3; normal, 0.0-0.5). Hepatitis C was negative and HIV viral load was stable with no thrombocytopenia since 2009. The patient's heparin-induced antibody result by enzyme-linked immuno-sorbent assay (ELISA) was negative.

After reviewing his medications, famotidine was stopped on the eighth day. A significant improvement in the platelet count was noticed. Heparin was thought to be safe to reintroduce and the platelet count continued to improve. The patient had an uneventful recovery and was discharged four days later with normal platelet counts.

Discussion

Our patient was diagnosed with thrombocytopenia while hospitalized. The differential diagnosis included thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), liver disease, hepatitis C infection, heparin-induced thrombocytopenia (HIT), thyroid disease, autoimmune disease, and DITP. TTP was ruled out because there was no evidence of microangiopathic hemolytic anemia, evidenced by the absence of schistocytes in the peripheral blood smear and normal lactate dehydrogenase and bilirubin levels. There was no evidence of disseminated intravascular coagulation, as fibrinogen and activated PTT were within normal limits. Liver function test values were normal and hepatitis C antibody was negative. TSH was normal. HIT was ruled out after negative HIT antibody and platelet counts continued dropping after stopping heparin. Re-challenge with heparin was done after the platelet count returned to normal and continued to rise.

Since other causes of thrombocytopenia were ruled out, it was possible that the patient had DITP. DITP often is suspected in patients with acute thrombocytopenia unexplained by other causes, but documenting that the drug is the cause of thrombocytopenia can be challenging.

Several drugs have been implicated in the cause of acute thrombocytopenia, such as quinine, quinidine, trimethoprim/ sulfa-methoxazole and vancomycin.[9,10] The estimated incidence of DITP is around 1-2 per 100,000 per year.[11,12] There are three possible mechanisms by which a drug causes a decrease in platelet count: failure of production by bone marrow, immune destruction, and platelet aggregation in circulating blood. Antibodies that bind to normal platelets in the presence of a drug have been implicated for drugs like cinchona, quinine, and sulfa.[13,14] The median time for daily drug exposure before thrombocytopenia is six days (range 1 to 10),[15] but it may appear within 12 hours of drug intake in a sensitized individual.[16,17] Typically, the platelet count falls to 80% of the normal and thrombocytopenia may be associated with neutropenia and anemia.

Famotidine was the most likely cause of our patient's thrombocytopenia. After the patient was switched to omeprazole, his platelet count improved within 24 hours, reached the normal range on the third day off famotidine and remained in the normal range thereafter. There is an association between the elimination half-life of a drug and the time to platelet recovery; recovery takes longer with drugs that have longer elimination half-lives.[1] The average elimination half-life of famotidine is three hours. With four half-lives (i.e., 12 hours) approximately 94% of the drug is eliminated from the body. Therefore, it was reasonable to expect some improvement in platelet count within 12-24 hours after stopping famotidine.

In our case, there was a temporal relationship between the initiation of famotidine and the onset of thrombo-cytopenia, and reasonable exclusion of other potential causes, making famotidine the probable cause. According to the Naranjo adverse drug reaction probability scale,[18] the probability that famotidine caused thrombocytopenia in our patient is probable. The famotidine product label includes thrombocytopenia as a rare hematologic side effect. Re-exposure to famotidine was not done in our case for patient safety. Also, serum was not sent to demonstrate drug-dependent platelet reactive antibodies in vitro. This rare drug reaction due to famotidine is more common in critically ill neurosurgical and trauma patients.[19,20] Hence, precaution should be taken to put these patients on other medications for ulcer prophylaxis.

Conclusion

In cases of severe thrombocytopenia unexplained by other causes, a pharmacological cause must be suspected, particularly famotidine. Other alternate drug regimens for prophylaxis of stress ulcer should be considered, especially in critically ill patients.

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