Original Article

Case Report: Dabigatran-Associated Gynecologic Bleeding

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Abstract

Purpose: The case of a patient who experienced major gynecological bleeding after initiation of dabigatran therapy for atrial fibrillation is reported.

Summary: A 33-year-old Hispanic female with multiple medical problems presented to the emergency department (ED) with a 5-day history of menorrhagia and a 3-day history of dizziness, fatigue, and weakness. Prior to ED presentation, she had been initiated on dabigatran 150 mg twice daily for atrial fibrillation. Four days later, she began having profuse vaginal bleeding. She discontinued all of her home medications including dabigatran, and her bleeding subsided the next day. Upon presentation to the ED, her hemoglobin was 7.1 g/dL, for which she was transfused 2 units of packed red blood cells, increasing her hemoglobin to 9.6 g/dL. Because the patient was in atrial fibrillation, warfarin was initiated once she was clinically stable and she was never restarted on dabigatran. Her hemoglobin was stable throughout admission with no further bleeding. She was discharged on warfarin and closely followed without incident.

Conclusion: A 33-year-old Hispanic female with no pre-existing gynecologic abnormalities had a major gynecological bleed shortly after starting dabigatran that resolved after discontinuation.

Key Words—dabigatran, gynecologic bleed, major hemorrhage

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Atrial fibrillation is the most common significant cardiac rhythm disorder. It is estimated that about 12 million people will have atrial fibrillation by the year 2050.¹ The incidence of stroke in people with atrial fibrillation increases with the elderly; patients with diabetes, hypertension, and congestive heart failure; and patients with a history of stroke or transient ischemic attacks (TIAs).² Warfarin had been the only oral anticoagulant for more than 50 years proven effective in preventing ischemic stroke in patients with atrial fibrillation. It has been the standard of care for many years for this purpose. However, warfarin has many disadvantages, including the need for frequent monitoring, the variability of dose response, and drug-drug and drug-food interactions. Thus, the development of newer agents without many of these disadvantages has been the priority of researchers.

Dabigatran etexilate is a direct thrombin inhibitor approved by the US Food and Drug Administration (FDA) in 2010 for the prevention of embolic stroke in

patients with non-valvular atrial fibrillation.³ Dabigatran inhibits both free and fibrin-bound forms of thrombin, thereby inhibiting thrombin-mediated effects, such as activation of factors V, VII, IX, and X, cleavage of fibrinogen to fibrin, and thrombin-induced platelet aggregation.^{4,5} As seen in other anticoagulants, dabigatran possesses inherent bleeding risks as shown in large, randomized clinical trials such as the RE-LY and RE-COVER trials.^{6,7} However to our knowledge, no published studies or case reports citing specifically major gynecological bleeding exist.

Here, we present a case of dabigatran-induced gynecological bleeding and the management of the patient's anticoagulation after the bleeding event.

PATIENT CASE

A 33-year-old Hispanic female with past medical history of atrial fibrillation, hypertension, congestive heart failure, pulmonary hypertension, and mitral valve regurgitation presented to the emergency department (ED) with a 5-day history of menorrhagia

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associated with dizziness, fatigue, and weakness. Prior to her menorrhagia, the patient's cardiologist had recently initiated dabigatran 150 mg twice daily for her newly diagnosed atrial fibrillation (CHADS2 score = 2). Four days after starting dabigatran (after 7 doses), she began having heavy vaginal bleeding requiring 1 pad per hour for 5 days. She described her menstrual periods as irregular (last menstrual period was 6 months ago), however she stated that this bleeding episode was atypical for her normal menstrual cycle. She self-discontinued all her medications and, according to her, the bleeding ceased after 2 days. She continued having dizziness, weakness, and fatigue, requiring an ED visit.

Her home medications included furosemide 40 mg orally (PO) daily, carvedilol 12.5 mg PO twice daily, dabigatran 150 mg PO twice daily, potassium chloride extended release 20 mEq PO daily, and lisinopril 5 mg PO daily. She denied any inappropriate use of her medications, use of over-the-counter medications, or any herbal products. Her height was 5 feet, 2 inches, and her weight was 171 lbs. She had no known drug allergies.

Emergency Department Management

Upon admission to the ED, the patient was anemic with a hemoglobin level of 7.1 g/dL, hematocrit 23.5%, platelet level of 281 K/ μ L, and an international normalized ratio (INR) of 1.1. Her baseline hemoglobin and hematocrit levels were in the range of 12 to 13 g/dL and 38% to 39%, respectively. Her serum creatinine was 0.8 mg/dL with an estimated creatinine clearance of 94 mL/min via Cockcroft-Gault equation. She received 2 units of packed red blood cells, and her hemoglobin rose to 9.6 g/dL. To rule out any obstetrics and gynecologic (OB/GYN) cause of bleeding, the OB/GYN team was consulted. Pelvic examination, transvaginal ultrasound, and pelvic ultrasound determined that no structural abnormalities caused her menorrhagia. The patient was diagnosed with dabigatran-associated bleeding, and dabigatran was never restarted. While in the ED, she was also in atrial fibrillation with rapid ventricular rate and was admitted to the hospital.

Inpatient Management

The consulting cardiologist recommended restarting all home medications except for dabigatran. Initiation of alternative anticoagulation as soon as possible was recommended for her atrial fibrillation considering her CHADS2 score of 2. The patient was still in atrial fibrillation with heart rate in the 160s, and she was started on metoprolol for rate control. Her hemoglobin

remained stable after receiving the 2 units of packed red blood cells and no signs or symptoms of bleeding. On day 3, considering the patient had stable hemoglobin and was free of symptoms, she was initiated on warfarin 5 mg daily with close monitoring. The decision was also made not to bridge the patient with any type of rapid anticoagulation (ie, unfractionated heparin or enoxaparin) because of the recent bleeding episode.

By day 4 of admission, the patient's heart rate was still elevated in the 130s, however her systolic blood pressures were in the low 90s. The cardiologist recommended beginning digoxin for atrial fibrillation, as increases in metoprolol dose would precipitate hypotension. After intravenous digoxin loading, she was transitioned to oral therapy and her rate was controlled. Warfarin 5 mg daily was continued, and her hemoglobin remained stable with no further bleeding. On day 5 of admission, the patient was discharged home on warfarin 5 mg daily along with her other home medications. Her INR on discharge was 1.1 with a hemoglobin level of 10.9 g/dL.

Outpatient Follow-up

Upon follow-up at the anticoagulation clinic 1 week after discharge, the patient's INR was 1.9 (INR goal 2-3) with no report of vaginal bleeding. Subsequent review of her outpatient follow-ups revealed therapeutic INR levels and no major vaginal bleeding. Minor vaginal "spotting" was reported at the third visit, however, the patient stated that it was normal and denies any further abnormal gynecological bleeding. See Table 1 for INR values on subsequent follow-up visits.

DISCUSSION

Dabigatran in major clinical trials has shown an overall similar incidence of major bleeding when compared to warfarin. Major bleeding was defined as clinically overt if it was associated with a fall in the hemoglobin level of at least 2 g/L, resulted in the need for transfusion of 2 or more units of red cells, involved a critical site, or was fatal based on well-accepted criteria.⁸ In the RE-LY trial, the rate of major bleeding was 3.36% per year in the warfarin group and 3.11% per year in the group that received dabigatran 150 mg twice daily (relative risk [RR], 0.93; 95% CI, 0.81 to 1.07; $P = .31$). However, the rate of gastrointestinal bleeding was significantly higher in the dabigatran 150 mg arm (1.51% per year) compared to warfarin (1.02% per year) (RR, 1.50; 95% CI, 1.19 to 1.89; $P < .001$), and rates of intracranial hemorrhage were

Table 1. Warfarin clinic follow-up international normalized ratio levels

	INR	Dose	Comments
Warfarin dose # 1 (hospital day 3)	1.1	5 mg	Closely monitored for bleeding
Warfarin dose #2 (hospital day 4)	1.1	5 mg	Closely monitored for bleeding
Warfarin dose #3 (hospital day 5)	1.1	5 mg	Patient to follow-up 1 week after
1 week after	1.9	5 mg/day	Denied bleeding and bruising
2 weeks after	2.2	5 mg/day	Minor spotting for 5 days, but resolved
1 month after	2.5	5 mg/day	No bleeding

significantly lower in the dabigatran 150 mg arm (0.30% per year) compared to the warfarin arm (0.74% per year) (RR, 0.40; 95% CI, 0.27 to 0.60; $P < .001$). No gynecologic bleeding was reported in this trial.⁷ In the RE-COVER trial, a total of 20 patients in the dabigatran group (1.6%) and 24 patients in the warfarin group (1.9%) had major bleeding episodes (hazard ratio [HR], 0.82; 95% CI, 0.45 to 1.48). Urogenital bleeding was reported in both arms of this trial, 53 patients for dabigatran (0.26%) and 95 patients for warfarin (0.34%); but P values and confidence intervals were not reported for these data. Also, it was not specified whether these urogenital bleeds were major, clinically relevant nonmajor, or minor. Furthermore, no breakdown of types of urogenital bleeding was reported.⁹ Of note, our patient is also different from those in both the RE-LY and RE-COVER trials. Most patients in both of these trials were male, significantly older, and Caucasian.^{7,9} Thus, this case report describes not only a specific type of bleed that was previously unreported, but it also describes bleeding in a demographic that was not well represented in major dabigatran clinical trials.

Based on the aforementioned information from clinical trials, it is reasonable to consider that dabigatran could induce some type of nonspecified urogenital bleeding. However, to our knowledge, this is the first reported case of major gynecologic bleeding specifically associated with dabigatran use. The timing of dabigatran initiation and occurrence of bleeding in our patient along with the resolution of bleeding with dabigatran discontinuation strongly suggest dabigatran-induced gynecologic bleeding. This was a “probable” dabigatran-induced adverse drug reaction according to the Naranjo algorithm estimation of adverse event causality (her score was 5).¹⁰

Currently, no robust clinical trials exist addressing the management of dabigatran-induced bleeding. The 2011 American College of Cardiology Foundation/American Heart Association guidelines recommend

fresh frozen plasma, packed red blood cells, or surgical correction in patients with severe dabigatran-induced hemorrhage.¹¹ Our patient was transfused with packed red blood cells in the ED in accordance with this recommendation.

CONCLUSION

Dabigatran may be favored over warfarin in some patient populations for its predictable anticoagulation effect and no need for monitoring. However, in this particular case, this reason seems to be its disadvantage. In our patient, warfarin was chosen over dabigatran because it can be monitored and can be easily reversed if necessary. Dabigatran is an acceptable alternative to warfarin, however a need exists for more clinical trials investigating enhanced coagulation monitoring methods and reversal agents for dabigatran-associated bleeding.

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