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Case Report

Case Report: Apixaban in End Stage Renal Disease Causing Massive Gastrointestinal Bleeding

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Abstract

The treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) and their recurrence in patients with end-stage renal disease (ESRD) has long been limited to a single agent: warfarin. However, with the advent of the novel oral anticoagulants, it is tempting to use these medications in this patient population, especially given the challenges of warfarin use. Although apixaban currently has Food and Drug Administration approval for use in patients with DVT/PE and atrial fibrillation in ESRD on hemodialysis, its safety in these populations has not been well studied. Apixaban has not been studied in clinical safety and efficacy studies with serum creatinine > 2.5 mg/dL or CrCl < 25 mL/min, but it is currently being used in ESRD based on pharmacokinetic data. We present a case in which apixaban was used for PE treatment in a patient with ESRD on hemodialysis who developed a gastrointestinal hemorrhage requiring multiple transfusions. This case highlights the need for further investigation into the safety of apixaban in patients with ESRD.

Keywords: Apixaban; End-stage renal disease; Anticoagulation; Deep vein thrombosis; Pulmonary embolism

Introduction

Apixaban is an oral direct factor Xa inhibitor approved for the prevention of stroke in atrial fibrillation, as well as the treatment and prevention of pulmonary embolism (PE) and deep venous thrombosis (DVT) [1]. According to its package insert, apixaban is acceptable for use in patients with decreased creatinine clearances (CrCl) [1]. However, we performed a literature review and found little research to support safety and efficacy in patients with moderate to severe renal failure. The original trials evaluating apixaban for atrial fibrillation and DVT and PE excluded patients with a serum creatinine > 2.5 mg/dL or CrCl < 25 mL/min [2,3]. In January 2014, the labeling for apixaban was changed to include dosing recommendations for patients treated for atrial fibrillation and DVT and PE with end-stage renal disease (ESRD) on hemodialysis. However, the package insert states that patients on hemodialysis were not studied in clinical efficacy and safety studies, and that their dosing is based on the recommendation of a single site pharmacokinetic and pharmacodynamic study [4].

The routine use of apixaban in patients with ESRD is extremely tempting because approximately one-third of patients with atrial fibrillation have some form of chronic kidney disease (CKD), and one-sixth of all elderly hemodialysis patients have atrial fibrillation [5]. With an estimated 300,000 ESRD patients with atrial fibrillation worldwide, there is clearly a need for anticoagulants that are safe and effective in this patient population.

Here, we report the case of an elderly Caucasian female on hemodialysis who was treated with apixaban for a PE. During her treatment, she developed a severe gastrointestinal bleed requiring hospitalization, transfusion, cessation of apixaban, and placement of an inferior vena cava (IVC) filter. This case highlights the need for further investigation into apixaban use in ESRD patients based on clinical safety and efficacy studies.

Case Presentation

A 65-year-old, 72.6-kg Caucasian female presented to the Emergency Department with four days of dark stools and bright red blood per rectum. Her history included a PE two months prior, coronary artery disease (CAD) status post coronary artery bypass graft, ESRD of unclear etiology on Monday-Wednesday-Friday hemodialysis, chronic obstructive pulmonary disease, anxiety, gastroesophageal reflux disease, and hypothyroidism. It was unclear from her history if her prior PE was provoked or not. Her medications at presentation included apixaban 2.5 mg twice daily, atorvastatin 20 mg daily, levothyroxine 112 mcg daily, trazodone 200 mg at bedtime, clonazepam 0.25 mg twice daily, metoprolol tartrate 25 mg daily, lisinopril 2.5 mg at bedtime, aspirin 81 mg daily, esomeprazole 40 mg daily, calcium acetate 2,001 mg three times daily, cinacalcet 30 mg daily, fluticasone/salmeterol 250/50 mcg/act twice daily, ipratropium/albuterol 0.5-3 mg/3 mL four times a day, and a multivitamin daily. The physician prescribing the apixaban had consulted nephrology, per the records, and made a joint decision to empirically lower the dose given her concomitant use of aspirin for CAD.

Her complaints at presentation included fatigue and progressive weakness, and her initial physical exam was significant for tachycardia. Laboratory assessment revealed a hemoglobin of 7.2 g/dL, compared with a baseline of 10.5-12 g/dL measured in the last two years. She was admitted to the hospital for management of gastrointestinal bleeding and symptomatic anemia. Her international normalized ratio (INR) on admission was 1.74 and this value decreased to 1.09 on day five of admission. An antifactor Xa level was drawn on day five of admission, and it was < 0.1 antifactor Xa units/mL. She was hemodynamically stable on admission with a systolic blood pressure of 110 mmHg.

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Apixaban and aspirin were held on admission. She received dialysis according to her usual schedule during this hospitalization. She received 2 units of fresh frozen plasma and 6 units of packed red blood cells to maintain hemoglobin levels of 9-10 g/dL. The gastroenterology service was consulted, and they performed a tagged red blood cell scan, which located a rectosigmoid bleed. Colonoscopy confirmed diffuse mucosal bleeding in that same area. An IVC filter was placed after discussion with the patient, hematology service, and surgery service. She recovered well and was discharged to home in stable condition on hospital day five. Hematology recommended starting warfarin two weeks after her bleeding had ceased, but she refused anticoagulation. At that point, she had received two months of anticoagulation for her PE, had an IVC filter in place, and considered the risk of bleeding to be greater than the benefits of preventing another venous thromboembolism.

Discussion

Using the Naranjo method for estimating the probability of adverse drug reactions [6], the chances that our patient's gastrointestinal bleed was related to her apixaban use was estimated as 'probable' with a score of 6; a score > 9 is 'definite' and the range for 'probable' is 5–8. While it is not uncommon to have major bleeding on anticoagulation, we believe that her ESRD contributed to an increased likelihood of bleeding and that current prescribing recommendations make apixaban appear to be a safer option for anticoagulation than evidence actually suggests.

Another potential contributor to her gastrointestinal bleed washer concomitant use of aspirin. Aspirin use with a novel anticoagulant (NOAC) significantly increases the risk factor for major bleeding. One trial by Davidson, et al. showed a 50% increase in the risk of major bleeding associated with aspirin use in patients who were taking rivaroxaban [7]. Although apixaban is thought to have a lower bleeding potential than rivaroxaban or other NOACs [8,9], the addition of aspirin to apixaban would significantly increase the risk of a major bleeding event.

In our review of the literature, only one paper appeared to deal specifically with the safety of apixaban in ESRD patients [4]. It is hard to make generalized conclusions based on this study because it was performed in only one site, it focused solely on changes in the pharmacokinetic profile of apixaban rather than safety or efficacy, and it only looked at a single 5 mg dose given before and after a session of hemodialysis rather than multiple doses. Results from this study compared drug levels in eight patients in the ESRD group to levels in a group of eight healthy volunteers. Their findings showed a 10% lower maximum serum concentration (C_{max}) and a 36% higher area under the curve (AUC) in ESRD patients before getting hemodialysis compared to healthy participants. After receiving hemodialysis, these patients had a 13% lower C_{max} and a 14% lower AUC compared to healthy volunteers.

This study prompted changes to the Food and Drug Administration (FDA) package insert for apixaban in patients with ESRD on hemodialysis [1]. Based on the package insert, patients with ESRD on hemodialysis treated for atrial fibrillation should use apixaban 5 mg twice daily unless they weigh ≤ 60 kg or are ≥ 80 years old; in those cases, the dose should be reduced to 2.5 mg twice daily. Interestingly, according to the insert, patients with ESRD on hemodialysis treated for DVT or PE should use apixaban 5 mg twice daily regardless of their weight and age. Therefore, if apixaban is being used in ESRD, the indication should be clearly delineated because it could potentially impact the dose recommended. Despite these changes to the package insert, CHEST guideline recommendations for DVT and PE still prefer warfarin in the setting of severe kidney disease or ESRD because warfarin can be more easily monitored and there is more clinical safety data with warfarin [10].

A recent case report of gastrointestinal hemorrhage while using apixaban for atrial fibrillation in ESRD highlights the risks of using apixaban in this patient population [11]. The safety of apixaban in an ESRD patient has several concerning points – the foremost being that up to 27% of the drug is eliminated unchanged in the urine in patients without significant renal impairment. However, in a patient with ESRD on hemodialysis, dialysis removes only 14% of the drug because of the high protein binding of apixaban [1,4]. Thus, it is possible that a higher blood concentration of apixaban may occur when used in ESRD, and this may lead to increased bleeding events over time. A recent article by Wendte, et al. reported the effects of apixaban on antifactor Xa levels in a patient experiencing acute kidney injury. These authors showed elevated antifactor Xa levels believed to be caused by apixaban four days after stopping apixaban [12].

Apixaban is likely a better option than other NOACs in patients with renal dysfunction because of the 27% renal elimination of unchanged drug compared to 35% with rivaroxaban, 40% with edoxaban, and 80% with dabigatran [7]. Warfarin also requires close titration in patients with severe renal impairment, as warfarin dose requirements are often approximately 20% lower than those in patients with normal renal function [13]; however, with warfarin it is much easier to determine the true level of anticoagulation based on INR testing. Interestingly, the 2015 Beers Criteria update included a list of medications to be avoided or have their doses reduced in patients with decreased kidney function [14]. Although this list is specifically aimed at older adults, it addressed the potential safety issues with the NOACs. These guidelines recommended that apixaban be avoided in patients with a CrCl < 25 mL/min due to potential increased risk of bleeding.

Conclusion

To our knowledge, this is the second case report showing major gastrointestinal bleeding when apixaban is used in patients with ESRD on hemodialysis. Our patient's risk of bleeding was further increased by using apixaban with aspirin. This case highlights the need for further investigation of apixaban in the setting of ESRD, with and without aspirin. While apixaban is a tempting option for patients with DVT/PE, the potential for major bleeding in a patient with ESRD is possibly increased. As a result, warfarin should remain the preferred treatment option until more safety and efficacy data is obtained in patients with ESRD on apixaban. Moreover, care should be taken when prescribing apixaban because the indication may impact the dosing recommendations in patients with poor renal function, according to the FDA-approved package insert.

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