A Case of Rivaroxaban Associated Intracranial Hemorrhage

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Rivaroxaban is a newer anticoagulant initially approved by the Food and Drug Administration to treat nonvalvular atrial fibrillation. Rivaroxaban has several characteristics that are more favorable than warfarin. One of the characteristics is decreased risk of hemorrhage. We report one of the first case reports of severe intracranial hemorrhage associated with rivaroxaban in an elderly patient with decreased renal function. We aim to alert emergency medicine providers regarding the likelihood of encountering these patient as newer anticoagulants rise in popularity. [West J Emerg Med. 2014;15(4):375–377.]

INTRODUCTION

Rivaroxaban (Xarelto) is an oral factor Xa inhibitor that has been approved by the Food and Drug Administration (FDA) in 2010 to treat nonvalvular atrial fibrillation. New anticoagulants emerge as warfarin requires frequent monitoring, and has multiple drug and food interaction. Rivaroxaban was developed with the goal of predictable pharmacokinetics that eliminates the need for monitoring the international normalized ratio.[1-5] Several characteristics have made rivaroxaban an attractive alternative to warfarin; once daily dosing, obviate the need for monitoring the international normalized ratio, noninferiority to warfarin in treating atrial fibrillation, and decreased risk of bleeding in comparison to warfarin.[6] Although the risk of bleeding is decreased in comparison, the risk remains. We believe this is the first case report of intracranial hemorrhage secondary to rivaroxaban use.

CASE REPORT

CJ is a 92-year-old man with a past medical history of atrial fibrillation and ischemic stroke five months prior to emergency department (ED) presentation. He presented to the ED with left upper extremity and left lower extremity weakness, left facial droop and slurred speech. His initial vital signs in the ED at 9:38AM were temperature 97.4°Fahrenheit, blood pressure 175/59 mmHg, heart rate 111 beats per minutes, respiratory rate 28 times per minutes, oxygen saturation 97% on room air. On physical exam the patient was alert and followed commands intermittently, extraocular movement was intact bilaterally, pupils were equal and reactive bilaterally. Cranial nerve exam revealed left facial droop. Strength exam were 5/5 in right upper extremity and right lower extremities and 1/5 in left upper extremity and left lower extremity. Patient was transported to computed tomography (CT) immediately. CT head revealed an acute 6.7 cm x 5.3 cm right parasylvian and right basal ganglia hemorrhage with surrounding edema, as well as 7 mm leftward midline shift at the level of the septum pellucidum. When the patient returned from CT, his eyes deviated to the right side. Fosphenytoin was initiated for likely seizure. His blood pressure was elevated to 230/100 mmHg. Labetalol 20 mg was administered intravenously with improvement of blood pressure. The patient became progressively lethargic while in the emergency department. He was intubated under rapid sequence intubation at 10:20AM. Since the patient was on rivaroxaban, the plan was to administer prothrombin complex concentrate (PCC). However, PCC was not available at the facility. Two units of fresh frozen plasma were administered intravenously at 10:58AM.

Laboratory result revealed white blood cell 12.93 bil/L, hemoglobin 11.3 g/dL, hematocrit 33.4%, platelet 135 bil/L, sodium 137 mMol/L, potassium 4.2 mMol/L, chloride 101 mMol/L, CO2 22 mMol/L, BUN 30 mg/dL, creatinine 1.3 mg/dL, protime 11.3 seconds, INR 1.1 IU, PTT 23.8 seconds, plasma rivaroxaban level 95 ng/mL. Neurosurgery service was consulted, and recommended no surgical intervention at this time. The patient was admitted to the intensive care unit (ICU). Two days after ICU admission, the family withdrew care.

According to the patient's family members, the patient was on warfarin for many years. However, due to warfarin's interaction with food and frequent need for clinic visits to assess patient's coagulation panel, the patient's physician switched him to dabagatrin nine months prior to this ED

Table 1. Recommended dose of rivaroxaban per package insert.

Recommended dose of rivaroxaban	Renal function for recommended dose
20 mg once daily	CrCl >50 mL/min
15 mg once daily	CrCl 15 to 50 mL/min

Table 2. Recommended reversal agents for hemorrhage associated with rivaroxaban.

Recommended reversal agents
Prothrombin complex concentrate (PCC)
Factor VIII
Factor eight inhibitor bypass activity (FEIBA)
Fresh frozen plasma (FFP)

presentation. The patient had difficulty swallowing the dabagatrin's capsule, so his physician switched him to rivaroxaban four months prior to the ED presentation.

DISCUSSION

Rivaroxaban (Xarelto) is a new anticoagulant that was approved by the FDA in 2011 for stroke and systemic embolism prophylaxis in patients with nonvalvular atrial fibrillation. Rivaroxaban is also indicated for treatment and prevention of pulmonary embolism and deep vein thrombosis.[7,8] The Factor Xa inhibitor is a major new anticoagulant drug class that emerged as warfarin requires frequent monitoring, and has multiple drug and food interaction. Rivaroxaban was developed with the goal of predictable pharmacokinetics that eliminates the need for monitoring the international normalized ratio.[1,2,3,4,5] Several characteristics have made rivaroxaban an attractive alternative to warfarin; once daily dosing, obviate the need for monitoring the international normalized ratio, noninferiority to warfarin for preventing stroke in patients with atrial fibrillation, lower risk of intracranial hemorrhage compared with warfarin.[6]

Rivaroxaban inhibits factor Xa activity and prolonging plasma clotting time.[2] Traditional coagulation studies do not determine the degree of anticoagulation of rivaroxaban.[9] Methods that measure the degree of anticoagulation of rivaroxaban include tissue factor-activated clotting time.[10] In overdose situations, rivaroxaban does increase INR. Study by Mueck et al reveals that rivaroxaban plasma concentrations and prothrombin time (PT) correlates with a linear model.[11] APTT prolongation also occurs in dose-dependent fashion.[12] The coagulation panel was within normal limit in our patient. Furthermore, the measured rivaroxaban level was 95 ng/mL, (the range of level of 0–666 ng/ml was found in patients on therapeutic dose of rivaroxaban by van Veen).[13] The level was measured from the first set of blood that was drawn when the patient presented to the ED. The rivaroxaban level was measured by time of flight (TOF) at the University of California, San Francisco laboratory several weeks subsequent to the event. The intracranial hemorrhage in this patient is most likely associated with therapeutic dosing.

Although the study lead by Patel[6] revealed statistically significant reduction in intracranial hemorrhage with rivaroxaban versus warfarin (0.5% vs. 0.7%, p=0.02), some characteristics of rivaroxaban may prevent its wide application. In the EINSTEIN DVT, PE, and Extension clinical studies, both thrombotic and bleeding event rates were higher in patients over the age of 65 than in those under the age of 65.[7] Furthermore, rivaroxaban is not recommended in patient with decreased creatinine clearance as drug exposure is increased, and the risk of bleeding is elevated.[14-16] Rivaroxaban is also contraindicated in patients with hepatic disease associated with coagulopathy.[17] In addition, rivaroxaban is associated with increased risk of gastrointestinal bleeding compare to warfarin.[18] Our patient was 92 years old with mild renal dysfunction. The recommended dose of rivaroxaban per package insert is 20 mg once daily for CrCl >50 mL/min, and 15 mg once daily for patient with CrCl 15 to 50 mL/min (Table 1). The patient's CrCl was 46.15 mL/min. Therefore, his recommended daily dose of rivaroxaban was 15 mg once daily. According to his family member, the patient was compliant with his medications. Therefore, rivaroxaban may not be the optimal choice of anticoagulant for him.

According to ISMP (Institute for Safe Medication Practices), rivaroxaban was associated with 356 adverse event in the first quarter of 2012. Of those, 158 cases were associated with serious thrombus, ie pulmonary embolism. One hundred and twenty one cases were associated with hemorrhage. Possible suboptimal anticoagulation due to the predominance of thromboembolic event, in additional to the risk of bleeding, should be balanced against the favorable characteristics of rivaroxaban in patients who plan to use this newer anticoagulant.

Emergency medicine (EM) clinicians are more likely to care for these patients as newer anticoagulants rise in popularity. Recommended reversal agents for rivaroxaban associated hemorrhage are included in Table 2 for EM providers.

CONCLUSION

Rivaroxaban is a newer anticoagulant that has several advantages to traditional anticoagulants. However, adverse effect does occur rarely. We report the first case report documenting intracranial hemorrhage associated with rivaroxaban. Caution should be used in selective patient populations, such as elder's and patients with hepatic or renal dysfunction.

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