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Case Report

Acute Ischemic Stroke in a Patient with Documented Compliance to Rivaroxaban

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Abstract

Objective: To report a case of Acute Ischemic Stroke (AIS) in an elderly patient with known compliance to rivaroxaban and to present a brief literature review regarding when to restart and which anticoagulant to choose after new oral anticoagulant (NOAC) failure.

Case Summary: An 88-year-old female with atrial fibrillation and history of transient ischemic attack experienced AIS twelve days into her hospital stay for dehydration and hypernatremia. She had received rivaroxaban throughout her hospital stay during which she had poor oral intake. She was treated with intravenous heparin for four days. Hemorrhagic transformation of AIS was ruled out with computed tomography of the head and she was converted to dabigatran for continued AIS prophylaxis.

Discussion: Risk of hemorrhagic transformation after AIS should be considered when restarting oral anticoagulation. Literature recommends assessing prior compliance when deciding which agent to restart. If a patient was on a NOAC prior to AIS, it is reasonable to consider switching to warfarin given the ability to monitor levels, practitioner familiarity, and warfarin's effect on both intrinsic and extrinsic coagulation pathways. Rivaroxaban's labeling instructs that it should be taken with the evening meal as food increases its bioavailability. An alternate agent may be considered in patients who are unable to maintain this administration.

Conclusions: In a patient who has experienced AIS on a NOAC, there is little evidence in the literature to guide when andwhich anticoagulant to restart. Practitioners should consider patient-specific factors in these decisions.

Keywords: Anticoagulation; Rivaroxaban; Apixaban; Dabigatran; Stroke; Cerebrovascular accident; Atrial fibrillation

Introduction

Atrial Fibrillation (AF), one of the most common cardiac arrhythmias, increases a patient's risk of ischemic stroke by approximately 5% per year [1]. Initiation of a vitamin K antagonist (VKA) can decrease this risk by about 60%, and, for decades, was the mainstay of therapy for this indication [2]. Currently, there are three new oral anticoagulant (NOAC) agents, dabigatran (a direct thrombin inhibitor), rivaroxaban, and apixaban (direct factor Xa inhibitors), approved for the prevention of stroke in patients with AF [3]. These agents offer benefits over VKAs including no required laboratory monitoring, fewer drug interactions, and quick onset of action, with similar efficacy [3-6]. Despite appropriate use of these new agents in patients with AF, clinical trials suggest that approximately 1-2% will experience an acute ischemic stroke (AIS) [4-7]. We describe a case of NOAC failure in an elderly female with known compliance of rivaroxaban.

Case Presentation

An 88-year-old Caucasian female presented to the hospital in January of 2014 with a two-week history of decompensation including a seventeen pound weight loss. Per her husband, she had been declining since a previous admission to the hospital three weeks prior in December 2013 during which time she experienced two 30 minute episodes of inability to speak and facial droop and was diagnosed with a transient ischemic attack (TIA). At this time, she was already taking rivaroxaban for prevention of stroke due to AF. Computed tomography (CT) of the head at that time was negative; the patient was unable to have magnetic resonance imaging (MRI) due to pacemaker placement. After observation of the patient for 24 hours, she was discharged home with a new prescription for aspirin 81mg oral daily to take in addition to rivaroxaban 15mg oral daily with dinner (an appropriate dose for her renal function).

Upon presentation to the hospital in January 2014, the patient was alert and oriented to person only. Her past medical history included AF, dementia, hyperlipidemia, hypertension, hypothyroidism, lumbar compression fractures, osteoporosis, pacemaker placement and TIA. Prior to admission, the patient was maintained on aspirin 81mg oral daily, atenolol 100mg oral daily, brimonidine-timolol ophthalmic drops one drop into each eye every 12 hours, donepezil 5mg oral twice daily, ferrous sulfate 325mg oral twice daily, folic acid 0.8mg oral daily, latanoprost ophthalmic drops one drop into each eye at bedtime, levothyroxine 50mcg oral daily, potassium chloride 40mEq oral twice daily, pravastatin 20mg oral daily at bedtime, rivaroxaban 15mg oral at 6:00pm, thiamine 100mg oral daily, and tramadol 50mg oral four times daily as needed for pain. The patient lived at home with her husband prior to admission and consumed

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alcohol daily to a total of one to two quarts of liquor per week. Her husband denied her use of tobacco or illicit drugs.

All medications were continued upon admission with the addition of sodium chloride 0.9% continuous infusion for hydration. The patient's serum creatinine was elevated at 1.43mg/dL (serum creatinine was 0.85mg/dL during her previous month's admission); creatinine clearance as estimated by Cockroft-Gault was 25mL/min. Other than an elevated white count of $13.5x10^9$/L, complete blood count (CBC) was within normal limits. Neither routine nor special coagulation markers were obtained upon admission. Basic metabolic panel (BMP) was within normal limits with the exception of sodium which was 151mmol/L and BUN which was 61 mg/dL. Additionally, her AST was 164U/L, ALT was 103U/L, and albumin was 2.9g/dL. Vitals included a blood pressure of 99/69 mmHg, pulse of 70 beats/minute, respiratory rate of 20 breaths/minute and temperature of 36.6C.

The patient was treated for dehydration and hypernatremia with intravenous fluids, but continued to have poor oral intake with documented refusal of meals. On the day of her planned discharge, twelve days after admission, she developed left arm weakness, left leg weakness and slurred speech. A CT perfusion study of the head revealed a peripheral wedge-shaped area of decreased perfusion in the right frontal lobe in the anterior middle cerebral artery (MCA) watershed. Additional adjacent perfusion defect was seen in the right anterior cerebral artery (ACA) territory in the right frontal lobe. A small area of decreased perfusion matching an old MCA infarct on the left was also seen.

The patient was diagnosed with an AIS and transferred to a specialized vascular institute within the same health care system for treatment. At the time of the stroke, with the exception of potassium and tramadol, the patient was receiving all medications from prior to admission with the addition of intravenous hydration and mirtazapine 7.5mg oral daily at bedtime. The patient's prothrombin time was 15.5 seconds and international normalized ratio was 1.28. During the time from admission to the time of stroke, the patient was administered rivaroxaban and aspirin without interruption, per the electronic medical record medication administration record. The patient was unable to have an MRI due to her pacemaker placement. She was unable to receive tissue plasminogen activator (tPA) due to administration of rivaroxaban the night prior to the stroke. Her National Institutes of Health Stroke Scale (NIHSS) was 20. Rivaroxaban was held and the patient was started on intravenous heparin dosed via the facility's stroke protocol adjusted based on activated partial thromboplastin times. She received serial CT's of her head to rule out hemorrhagic transformation of the stroke at two and five days post-AIS.

After receiving intravenous heparin for four days, she was transferred back to our facility for continued management and rivaroxaban was reordered. Due to the patient's failure of therapy with rivaroxaban, alternative therapy was considered, and the patient was changed to an alternate NOAC (dabigatran 150mg oral twice daily). She was discharged home with home-health care with improving left-sided weakness and facial droop.

Discussion & Conclusion

Clinical trials of NOACs suggest that each year approximately 1-2% of individuals with AF receiving these agents (apixaban, dabigatran, rivaroxaban) are expected to experience an AIS [4-7]. AF is the most important cause of cardioembolic AIS which is the subtype of AIS associated with the highest in-hospital mortality (approximately 25%) and a higher rate of functional limitation at discharge from the hospital [8]. Several questions arise after a patient experiences AIS while receiving a NOAC including when and what AIS prophylaxis and/or anticoagulant to restart.

There are many factors to consider in the decision of when to restart anticoagulation therapy after AIS. In AIS patients with known AF or other conditions that require anticoagulation, there is little data available providing consistent guidelines on when to reinitiate anticoagulation [9]. Individual patient characteristics including the indication for anticoagulation, volume of ischemic injury, age, reperfusion strategies used (including administration of tPA) and type of anticoagulant may contribute to the decision. Anticoagulant administration is contraindicated within the first 24 hours after treatment with intravenous tPA [9]. Practitioners should consider the risk of AIS hemorrhagic transformation. Hemorrhagic transformation more frequently occurs in patients who have received reperfusion therapy, but may still occur in those who have not. Patients require vigilant monitoring for signs of hemorrhagic transformation especially those with larger strokes, older age and those with a cardioemobolic pathogenesis as they may be at increased risk [9-10]. Oral anticoagulation may generally be initiated one to two weeks after AIS [11-12]. Earlier initiation of oral anticoagulation may be considered for patients at low risk of bleeding complications such as those with a small infarct size and no evidence of hemorrhage on brain imaging [9]. The European Heart Rhythm Association [12] advocates for a rule of thumb of "1-3-6-12 day" for re-initiation based on infarct size. The rule suggests that anticoagulation may be initiated one day after TIA, three days after small, non-disabling infarct, six days after moderate stroke and not before two to three weeks in large infarcts involving large parts of arterial territory. The patient had two post-AIS CT's negative for hemorrhagic transformation and a moderate stroke. Anticoagulation was restarted four days after AIS occurrence in the aforementioned case.

Once the decision to restart anticoagulation is made, a review of adherence and patient-specific risk factors for AIS should be conducted. If problems with adherence are suspected, it may be reasonable to switch from a NOAC to warfarin given the ability to monitor levels. Long term studies assessing this switch have not been performed. Compliance was not an issue in the patient described as administration of rivaroxaban was documented by the electronic medical record medication administration record. Rivaroxaban's bioavailability decreases by approximately 30% when taken without food and should be administered with the evening meal to provide optimal bioavailability [6,13-14]. Although scheduled appropriately at the time of the evening meal, the patient described had been consistently refusing meals and this potentially may have contributed to decreased bioavailability, and thus decreased efficacy, of rivaroxaban.

If adherence has been confirmed, the question of which anticoagulant to restart remains. It may be appropriate to switch to warfarin as levels may be monitored, practitioners are familiar with it and it effects on both intrinsic and extrinsic coagulation pathways

[15]. In the case of our patient, as her refusal to eat may have affected rivaroxaban's bioavailability, and she experienced an AIS while taking rivaroxaban, an alternate NOAC or warfarin may be considered. The patient was placed on dabigatran 150mg oral twice daily based on the alternate mechanism of action, physician preference, and lack of necessity of taking with food.

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