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A Case of Periprocedural Discontinuation of Apixaban Resulting in Intra-aortic Thrombosis

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Abstract Apixaban, a novel oral anticoagulant is approved for anticoagulation in non-valvular atrial fibrillation. Apixaban is found to be superior to warfarin in prevention of stroke and thromboembolism and is associated with lesser risk of bleeding. Peri-procedural discontinuation of apixaban is safe, but the risk of thrombosis exists. We here present a case of arterial thrombosis that lead to lower limb ischemia upon periprocedural discontinuation of apixaban.

Keywords: *apixaban, anticoagulation, non-valvular atrial fibrillation, thrombosis*

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1. Introduction

Apixaban, a novel oral direct inhibitor of clotting factor Xa is increasingly being used for prevention of thromboembolism and stroke in patients with non-valvular atrial fibrillation [1]. Periprocedural discontinuation of apixaban may result in thrombosis [2]. The patient presented developed periprocedural thrombosis upon discontinuation of apixaban, despite low molecular weight heparin bridging.

A 73-year-old female with a past medical history of hypertension, diabetes mellitus, and breast cancer, status post right mastectomy and chemo-radiotherapy presented with exertional dyspnea for two weeks. Her brain natriuretic peptide was significantly elevated at 1335 picogram per milliliter, and the chest radiograph revealed bilateral hazy opacities, findings consistent with congestive heart failure. Electrocardiogram revealed atrial fibrillation with the rapid ventricular rate; apixaban therapy was initiated (5 milligrams twice daily, orally). Transthoracic echocardiography showed mild left ventricular dilation, mitral regurgitation and left ventricular ejection fraction (LVEF) of 25%. Synchronized biphasic defibrillator cardioversion converted the rhythm into normal sinus, however, atrial fibrillation recurred and amiodarone therapy (800 mg daily, orally) was initiated.

Cardiac catheterization was performed to evaluate the chest discomfort and possible ischemic etiology of low LVEF. Apixaban was discontinued 48 hours prior to cardiac catheterization and full dose anticoagulation with enoxaparin was initiated. Hemodynamically significant stenoticatheromatous lesion in the distal left circumflex artery was noted; a drug-eluting stent was placed and dual antiplatelet therapy with aspirin and clopidogrel was initiated. Apixaban was restarted 24 hours after cardiac catheterization. Two days following cardiac catheterization patient complained of acute onset of numbness and coldness of right lower extremity below knees; examination revealed absence of arterial pulses distal to and including popliteal pulse. An emergent arteriogram showed a filling defect consistent with nonocclusive saddle thrombus straddling at the iliac bifurcation (Figure 1). Distally extended segmental occlusion at the bifurcation of superficial and deep femoral arteries with complete occlusion of the proximal superficial femoral artery and the opening of collaterals were noted. Apixaban was discontinued and heparin drip was initiated. Surgical thrombectomy and bilateral iliac artery stent placement restored circulation to lower extremities. Post-thrombectomy anticoagulation was achieved with enoxaparin bridge and warfarin.

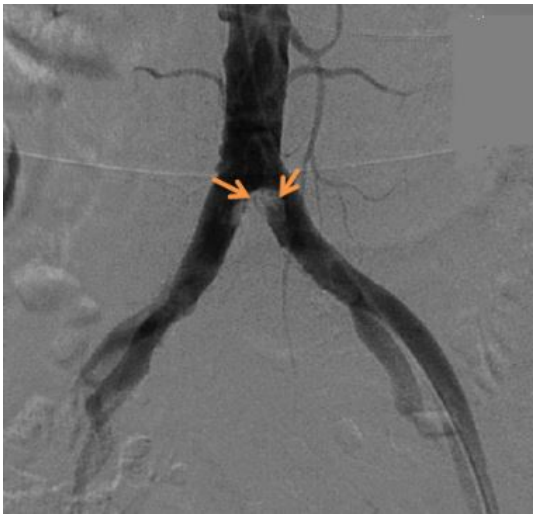

Figure 1. Arteriogram showing a filling defect (indicated by red arrows) consistent with nonocclusive saddle thrombus straddling at the iliac bifurcation

2. Discussion

Apixaban is a novel oral direct inhibitor of clotting factor Xa. Apixaban is superior to warfarin in prevention of stroke, thromboembolism, has lesser risk of bleeding and has lower mortality [3]. When ingested orally apixaban has greater than 50% bioavailability and reaches a maximum plasma concentration (t-max) in 1-3 hours with a half-life of about 8-15 hours; 87% of the drug is plasma protein bound and has a renal elimination of 25% [4]. The usual dose of apixaban for the prevention of thromboembolism in patients with atrial fibrillation is 5 mg two times daily. The dose is 2.5 mg twice daily if the patient has two of the following three characters: age >80 years, weight >60 kg, creatinine > 133 micromol/L. [3].

Apixaban anticoagulation does not require regular monitoring; patient who may need a measurement of apixaban anticoagulation are the ones who develop bleeding or whose clinical status changes, for example in patients who need surgery or develop thromboembolism [5]. Routinely used coagulation studies such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) do not accurately measure anticoagulant effect of apixaban. Drug specific anti-factor Xa chromogenic assay estimate apixaban anticoagulation effectively [6]. It is advised to individualize the risks and benefits of discontinuing the apixaban therapy in patients who need procedure; any elective procedure should be postponed if possible. The rapid onset and offset of action of new oral anticoagulants (NOACs) theoretically offers a safe drug-free period for procedure in a patient with normal renal and hepatic function (3). ARISTOTLE cleared established the relative safety of apixaban over warfarin in all-cause mortality, the incidence of stroke or systemic thromboembolism and bleeding [3]. Data extrapolated from ARISTOTLE revealed the safety of periprocedural discontinuation of apixaban and warfarin.

Analysis of ARISTOTLE revealed that the risk of significant bleeding in procedures was 1.62% in apixaban arm and 1.93% in warfarin arm. The same analysis revealed that the risk of stroke or systemic thromboembolism in a 30-day post procedure period was 0.35% in apixaban arm and 0.57% in warfarin arm. Percutaneous coronary interventions accounted for only 2.8% of the total procedures in this study. Thus, Garcia et al. extrapolated ARISTOTLE and concluded that periprocedural discontinuation of apixaban and warfarin without bridging is safe [7]. In low bleeding risk surgeries anticoagulation with apixaban is advised to be discontinued 24 hours prior to surgery in patients with creatinine clearance (CrCl) ≥ 50 ml/min and 48 hours prior to surgery if CrCl is 30-49 ml/min; in high bleeding risk surgery apixaban is advised to be discontinued 48-72 hours and 72 hours prior to surgery for a CrCl of ≥ 50 ml/min and 30-49 ml/min respectively [5].

The Spanish forum on anticoagulation and anesthesia recommends an alternative safer option that involves bridging anticoagulation prior to the procedure after discontinuation of NOACs. This approach requires discontinuation of NOACs five days prior to procedure and initiation of bridging anticoagulation with low molecular weight heparin(LMWH) till the day before the procedure; anticoagulation is resumed with NOVA's or LMWH the day after the procedure or after the hemostatic competency is reached [8]. The French agency for drugs and sanitary product safety, French working group on perioperative hemostasis and the French study group on thrombosis and hemostasis (GIHP and GEHP) agree on this safer option [9]. Though the exact time of starting bridging anticoagulation with enoxaparin is yet to be determined, the French group advocates to begin LMWH 12 hours after the last dose of NOACs in twice a day dosing and 24 hours after the last dose of NOACs in once a day dosing [9]. To avoid the risk of bleeding the Spanish group recommends LMWH bridging 24 hours after the last dose of NOACs [8]. This safer option of LMWH bridging peri-procedurally upon discontinuation of NOACs is ideal for the patients who are at moderate to high-risk thrombotic risk [8]. Most available guidelines agree to restart anticoagulation with NOACs 24 hours after the procedure [3].

3. Conclusion

To the best of our knowledge, the case we describe here is the first ever reported case of periprocedural thrombosis following discontinuation of apixaban anticoagulation. The periprocedural risk of thrombosis following discontinuation of apixaban/ NOACs is minimal, but there exists a risk of life-threatening thrombosis. Individualization and patient involvement in the informed decision making of periprocedural discontinuation of NOACs with or without heparin bridge will remain the key till detailed guidelines are formulated [10].

Acknowledgement

None.

Statement of Competing Interests

None.

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