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CASE REPORT

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Medication non-adherence as a cause of apixaban failure in venous thromboembolism: The importance of pharmacist medication reconciliation

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Abstract

Venous thromboembolism is often treated with direct oral anticoagulants. In order for direct oral anticoagulants to be effective, patients must adhere to a specific dosing strategy. We report a case of apixaban failure, the clinical workup that ensued, and the eventual discovery of unsuccessful medication adherence as the cause.

KEYWORDS

apixaban, failure, medication reconciliation, patient education, pharmacology

1 | INTRODUCTION

Venous thromboembolism (VTE) is a highly prevalent medical condition with high morbidity and mortality.[1] However, the development of the novel direct oral anticoagulants (DOACs) have revolutionized this treatment realm as this drug class introduced a safe alternative to the traditionally used vitamin K antagonists (VKA). DOACs are indicated for the treatment of DVT, pulmonary embolism, and atrial fibrillation and have been shown to be non-inferior or superior to VKAs in terms of safety (less major bleeding including intracranial bleeding) and efficacy.[2] Apixaban is a popular DOAC due to its efficacy in treatment of VTE while having the advantage of decreased risk of both major and minor bleeding events when compared to other DOACs.[3] Treatment failure with apixaban is rare, and when it does occur, can be due to several causes, including drug–drug interactions, poor absorption, and medication non-adherence.[4] In this article, we report a case of apixaban failure in the treatment of a VTE, both describing the workup that ensued with the eventual discovery of unsuccessful medication adherence leading to the treatment failure. We also review the complexities of DOAC dosing and the importance of proper medication reconciliation.

2 | INITIAL PRESENTATION

A 58-year-old gentleman presented to the emergency department (ED) with a chief complaint of left-sided chest pain associated with shortness of breath. His past medical history included hypertension, hyperlipidemia, and hypertriglyceridemia. In the ED, he was hemodynamically stable, afebrile, had a heart rate of 105 beats per minute, a respiratory rate of 18 breaths per minute,

saturating 98% on room air, with an elevated blood pressure of 174/95 mmHg. D-dimer was elevated and a computed tomography of the chest with intravenous contrast showed multifocal segmental and subsegmental pulmonary emboli in the left lingula, left lower lobe, and right lower lobe. There was minimal evidence of right heart strain. Additionally, there were bibasilar pleural parenchymal opacities likely representing evolving infarcts. Laboratories including complete blood count, renal profile, and troponin T were all within normal limits. The patient was given one dose of subcutaneous enoxaparin 1 mg/kg in the ED and admitted to the medical ward. No etiology of his emboli was evident. He denied a history of known risk factors including immobilization, recent surgery, trauma, or a hypercoagulopathic disease. His Pulmonary Embolism Severity Index score was 0. On hospital day 1, he was transitioned to apixaban 10 mg twice daily for 7 days, followed by 5 mg twice daily thereafter. He remained stable throughout his hospitalization and did not require any supplemental oxygen. He was discharged after 23 h of observation and was advised to continue anticoagulation therapy for the next 3–6 months.

3 | THREE WEEKS LATER

Three weeks later, the patient presented again to the ED, this time with new right lower extremity swelling and erythema of 1 day duration. He reported difficulty obtaining his apixaban for 2 days following discharge but had been compliant since, taking it twice daily and not missing any doses. He again denied any known risk factors including recent long drives, flights, trauma, or surgery. In the ED, laboratories were significant for a platelet count of 97, normal renal function, international normalized ratio (INR) 1.2, and normal liver function tests. Venous ultrasound of the right lower extremity revealed an acute appearing occlusive thrombus involving the mid right femoral vein to popliteal vein and extending down into the lesser saphenous vein. He was re-admitted for further evaluation and management of possible apixaban failure. Other diagnoses such as heparin-induced thrombocytopenia were ruled out as an anti-human platelet factor antibody test was negative. Antiphospholipid antibody syndrome and other hypercoagulable states due to genetic conditions or malignancy were less likely as the patient had no family or personal history of these disorders or symptoms. Genetic testing revealed no genetic coagulopathies. Hematology was consulted, and the patient was treated with fondaparinux injections per their recommendations. He was set to discharge with 7 days of fondaparinux and 3 months of anticoagulation with warfarin and outpatient follow-up with our anticoagulation clinic.

4 | ONE LAST THING

As no clear cause for repeat VTE was found, the medical team made a repeat inquiry on medication adherence. The patient finally reported that he was not entirely sure of his medication adherence and agreed to have a pharmacy consult and medication reconciliation/adherence confirmation. The outpatient pharmacy reported he only filled one bottle of a 30-count of 5 mg tablets. Given he was originally prescribed 10 mg twice daily × 7 days (2–5 mg tabs × 2 (twice daily) × 7 days = 28 tabs), followed by 5 mg twice daily thereafter for 3 months with refills, he would have run out of this medication on day 8 if fully compliant. The pharmacist discovered that the patient was prescribed refills but none of these were ever filled at any pharmacy. After this extra investigative step, the clinical team concluded that rather than apixaban failure, this was a case of non-adherence. The patient admitted that he did not realize the importance of strict adherence to the medication regiment in order to prevent further blood clots. The patient was educated on the importance of apixaban adherence, and his questions were answered on why it was critical to take the medication as prescribed in order to prevent further blood clots. The teach-back method was used in order to confirm understanding. The prescription was re-written to cover the entire 3-month treatment course. The team also insured that no financial constraints would limit him from getting a full course of the medication. He had no other VTE episodes after discharge and follow-up with Hematology clinic was set to conduct a future hypercoagulable workup once treatment therapy was completed.

5 | DISCUSSION

There are two prevailing elements in this case: DOAC dosing is complex and requires careful execution especially during transitions of care and medication reconciliations are time consuming but vital parts of admission and discharge. Furthermore, complex methods of confirming adherence such as pill counting are useful resources when deciphering whether treatment failure or rather non-adherence is the culprit of a late-onset DVT.

5.1 | Complexity of DOAC dosing

The treatment of VTE with DOAC therapy has been a revolution in care. This drug class has provided a safe and convenient alternative to the traditionally used warfarin or heparin therapy for the treatment and prevention of thrombi. Their lack of need for regular monitoring for

therapeutic range can be viewed as both beneficial (less INR checks) and harmful (less certainty that patient is actually taking the medication).

Transitions of care from hospital to outpatient care represent an unfortunate opportunity for medical errors and DOAC prescribing in transition of care is no exception. Approximately 50% of patients experience a medical error after hospital discharge and nearly one quarter experience an adverse event.[5] Further confounding this opportunity for error is the fact that DOACs have complex initial therapeutic dosing involving dose de-escalation and varying from drug to drug with the most commonly used being apixaban, dabigatran, rivaroxaban, and edoxaban.[6] All of these DOACs have individualized dosing and some require dose de-escalation following initial loading doses (rivaroxaban and apixaban) while others require bridging with a heparin product (dabigatran and edoxaban).[6] This complex dosing can lead to physician errors in prescribing, pharmacy errors in dispensing, and patient errors in taking an oral anticoagulant. In our case, initial therapeutic dosing for apixaban is 10 mg orally twice daily for 7 days followed by 5 mg orally twice daily thereafter for patients with eGFR >15. Given this complexity, it is imperative for clinicians to be familiar with DOAC dosing strategies and to carefully complete medication reconciliations especially on discharge. Strong hospital enterprise infrastructures to prevent medication errors and thorough handoffs can also be helpful; however, the onus of responsibility for accurate dosing of DOACs on discharge ultimately falls upon the physician.[7]

The second factor of DOAC discharge dosing is assuring patient understanding to ensure adherence. Clinicians should strive to provide discharge instructions to patients face to face and assure the patient understands DOAC dosing regimen at time of discharge.[5] Teach-back method can be used to politely assess patient and/or next of kin for understanding.[8-10]

5.2 | Medication reconciliation: time consuming but imperative

Careful medication reconciliation is one checkpoint to assess if patients are correctly taking their medications. This becomes especially important in cases of medical treatment failures or hospital readmissions. In the most ideal situation, the patient has all home pill bottles with them to help complete this task. If this is not possible, pharmacists or pharmacy technicians can be used to cross-reference with the patient's home pharmacy to help correctly detail home dosing of medication on admission to ultimately detect discrepancies before they may be incorrectly labeled as treatment failures. Full, precise medication reconciliation can take up to 20 min if done correctly through cross-comparison of chart and patient history and subsequent data entry.[11] However, most physician-performed reconciliations occur in much less time and can they often be incomplete due to inadequate documentation of the patient's medication history and a lack of time to search for the necessary information. Pharmacy-based reconciliations can be useful alternatives for hospital systems where physicians do not have enough time to accurately complete admission medication reconciliation. This was shown to be a more effective method in some emergency room studies as pharmacists had a significantly lower number of discrepancies per patient and reductions in adverse drug events leading to improved patient safety when compared to those completed by physicians.[12]

Although quickly verifying home medications against electronic medical records can be efficient, physicians must understand the limitations with this method as patient knowledge of their home medications is often inaccurate and electronic data are often incomplete. With physician time constraints, it is often easy to mislabel a diagnosis as treatment failure rather than doing a thorough investigation such as an in-depth chart review or timely communication with pharmacies to check if prescriptions have been appropriately filled. Assistance from a pharmacist in medication therapy management both supports the medical team with this task as well as provides directed expertise to insure proper medication reconciliation. Although traditionally done face to face, one emerging option is a virtual medication reconciliation process with patients, connecting to them by video.[13] As seen in this case, knowing when and how often a pharmacy is dispensing the medication can prove useful for determining the adherence and preventing the inappropriate mislabeling of a treatment failure.

A small subset of patient's prescribed DOACs for VTE will experience recurrence of VTE while on oral anticoagulation, which would be a treatment failure.[4] These patients present a clinical obstacle, and deciphering between treatment failure vs non-adherence is critical in order to correctly treat your patient. Patients determined to have treatment failure may require exchange of therapeutic agent, addition of a vena cava filter, or an extended duration of anticoagulation versus those with non-adherence who can be treated with increased education and continuation of their original DOAC.

6 | CONCLUSION

Careful dosing of DOACs for the treatment of venous thromboembolism by clinicians is imperative, especially in transitions of care. Furthermore, face-to-face discussion

and teach-back assessment for understanding prior to discharge improve patient adherence. Involving caregivers such as spouses or next of kin in discharge discussion and assessment for understanding of discharge medication regimen is beneficial in the long run and can prevent future adverse events. Careful medication reconciliation conducted by a pharmacist can help clarify the clinical picture and ascertains when non-adherence or treatment failure is the cause of a late-onset DVT.

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CONFLICT OF INTEREST

None of the authors have any conflict of interest to report.

AUTHOR CONTRIBUTIONS

Jethwa, Trisha E involved in patient history and data collection, case presentation, and literature search. Moran, Kaitlin M involved in literature review, paper writing, formatting, and re-editing. Maniaci, Michael J involved in literature review, paper writing, formatting, re-editing, and submission.

ETHICAL APPROVAL

This study conforms to all standards of the Mayo Clinic Ethics Committee.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT

Access to data is restricted to keep the patient's privacy. However, if deemed necessary, data will be provided by the corresponding author upon reasonable request after approval from the needed institutional committee.

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