Case Report

DOI: 10.4274/haseki.galenos.2024.9471
Med Bull Haseki 2024;62:51-53

Potential Failure of Novel-generation Oral Anticoagulants in Preventing Pulmonary Embolism: A Case Report and Current Literature Review

Asli Bicen, Seda Tural Onur, Fatma Tokgoz Akyil, Kaan Kara, Hulya Abali, Neslihan Boyraci, Betul Kinik

University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Clinic of Chest Diseases, Istanbul, Turkey

Abstract

In this case report, we evaluated the risk of pulmonary embolism in patients using new-generation anticoagulant drugs. Laboratory tests for follow-up and effective dose measurement of new-generation oral anticoagulants, which are very popular in the medical community today, are not available. Therefore, patients can be at risk for effective doses and drug selection. Although our cases received novel oral anticoagulant treatment, it was determined that they had thromboembolism. We emphasized that we do not have enough information about the complications and effective use of these drugs, which are advantageous in terms of use and side effects. This situation may lead us to negative situations that we cannot manage in the future.

Keywords: Pulmonary embolism, NOAC, warfarine

Introduction

The treatment landscape for pulmonary embolism faces challenges, particularly regarding patient adherence, complicated warfarin titration, high follow-up costs, and the predominant risk group of elderly patients (1). This has led to a shift toward considering novel oral anticoagulants (NOACs) as alternatives to warfarin (2). Novel oral anticoagulants, such as dabigatran (a direct factor IIa inhibitor) and rivaroxaban, apixaban, and endoxaban (direct factor Xa inhibitors), offer comparable efficacy to warfarin but don't need to be dose-monitored and don't interact as much with food. Despite these advantages, there have been reported cases from various countries highlighting potential failures in embolism protection with NOAC treatment. The two cases presented highlight the ongoing controversy surrounding the effectiveness of NOACs as a replacement for warfarin.

Case 1

A 72-year-old female patient presented to our emergency department with complaints of dyspnea. When the patient's medication history was queried, it was found that she was regularly taking furosemide, ramipril, metoprolol, and rivaroxaban 20 mg. It was emphasized that the patient has been consistently using rivaroxaban for 5 years, along with other medications, for the diagnoses of congestive heart failure and atrial fibrillation for approximately 10 years. It was learned that she did not have a history of tobacco or cigarette use or surgery. In the physical examination, respiratory sounds were not detected in bilateral basal breath sounds in pretibial edema ++/++; other system examinations were normal. The patient's vital signs were as follows: blood pressure was 130/80 mmHg, and fingertip oxygen saturation was 97%. In the examinations performed, D-dimer=2.65 mg/L (normal range: 0-0.5

Address for Correspondence: Asli Bicen, Y*University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Clinic of Chest Diseases, Istanbul, Turkey*
Phone: +90 538 056 54 32 **E-mail:** asli-kocaoglu@hotmail.com
Received: 28.08.2023 **Accepted:** 06.02.2024

mg/L), creatinine=0.85 mg/dL, eGFR=68.3 mL/min/m^2, and troponin T=0.037 ng/mL were detected. Bilateral pleural effusion was observed on the chest X-ray, and pulmonary angiography was performed on the suspicion of pulmonary thromboembolism. A computed tomography scan showed a filling defect that was consistent with a pulmonary embolism in the segmental branches that extended to the lower lobe of the right lung. There was also pleural effusion that was about 4 cm thick on the right side and 2 cm thick on the left (Figure 1). The patient, who was admitted to our service for further examination and treatment, was referred to the cardiology department; electrocardiogram: atrial fibrillation, ejection fraction (EF) 50%, PABS: 22 mmHg, tricuspid annular plane systolic excursion (TAPSE): 18 mm on echocardiography (ECHO), widening of the right heart chambers, advanced tricuspid regurgitation, and moderate mitral valve regurgitation were detected. Diltiazem tablets 90 mg 2x1 and furosemide ampoules 20 mg 2x2 were recommended. Deep vein thrombosis was not observed on lower venous Doppler ultrasonography. We started the patient on a dose regimen of 100 IU/kg (1 mg/kg) of enoxaparin sodium twice daily, and based on the international normalized ratio (INR) result, we added warfarin 5 mg loading dose therapy after 24 hours.

Case 2

A 75-year-old female patient had been hospitalized for 15 days because of coronavirus disease (COVID) 1 month before her admission, and after discharge, dyspnea continued and intensified for 1 week. When her anamnesis was questioned, it was learned that she had a diagnosis of hypertension and atrial fibrillation, and she has been regularly using edoxaban 30 mg and furosemide 40 mg for 2 years, metoprolol 50 mg after COVID, and methylprednisolone 16 mg. It was learned that she did not have a history of tobacco or cigarette use or surgery. In the physical examination, respiratory sounds decreased bilaterally, and other system examinations were unremarkable. In the examinations performed, D-dimer: 12.82 mg/L (normal range: 0-0.5 mg/L), creatinine=1.12 mg/dL, eGFR=50.4 mL/min/m^2, troponin T=0.022 ng/mL, and other laboratory tests were found. The patient, who was evaluated in the emergency department and had a Wells score of 3, stable vital signs, and no suspicion of high-risk pulmonary embolism, did not undergo pulmonary angiography because of acute kidney failure. The patient was admitted to our service and started on hydration, and low-molecular-weight heparin at the treatment dose was initiated because of our suspicion of pulmonary embolism. In terms of etiological investigation, lower extremity venous Doppler ultrasonography was performed. A homogeneous acute thrombus was detected in the right superficial femoral vein. She was consulted on cardiology, and ECHO was performed with cardiology consultation; EF 60%, moderate mitral valve regurgitation, moderate-severe tricuspid valve regurgitation, TAPSE: 19 mm, and PABs: 25 mmHg were detected. Diltiazem 90 mg 2x1 was recommended. After hydration, the patient's creatinine levels returned to normal levels. There were "filling defects consistent with thromboembolism, showing lobar and segmental branches extending from the distal of both pulmonary arteries" on the pulmonary angiography (Figure 2). The outpatient follow-up of our patient, who was started on warfarin with INR follow-ups after enoxaparin treatment, continues.

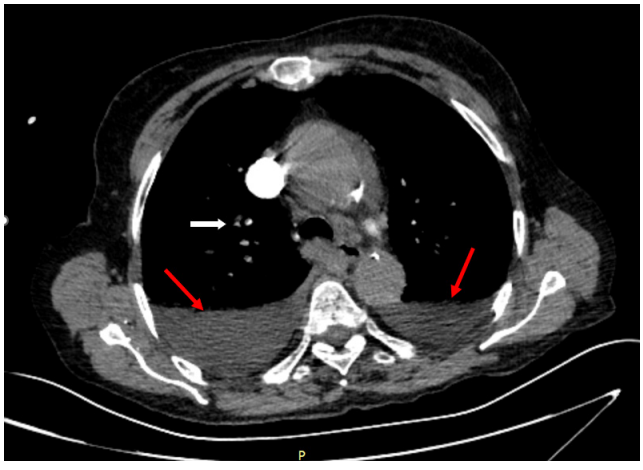

Figure 1. Computed tomography; it was reported as "Filling defect compatible with pulmonary embolism in the segmental branches going to the lower lobe of the right lung and pleural effusion with a thickness of approximately 4 cm on the right and approximately 2 cm on the left bilaterally"

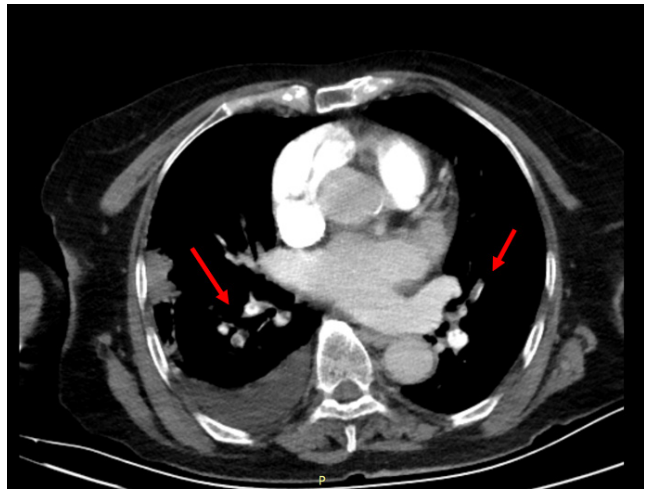

Figure 2. At computer CT filling defects consistent with thromboembolism were observed, showing lobar and segmental branches extending from the distal of both pulmonary arteries
CT: Computed tomography

Discussion

Novel oral anticoagulants have shown that they are equally effective at treating heart disease as warfarin in the EINSTEIN-PE, AMPLIFY-EXT, and HOUKASI-VTE studies. However, there aren't enough studies on them yet because there have only been non-inferior studies on follow-up and antagonist mechanisms and no superior studies (3-6). Randomized double-blind multicenter studies of these drugs, which benefit many patients with their advantages, are not enough in terms of the number of cases.

In these cases, because the patients used their drugs regularly, it was observed that the novel-generation oral anticoagulants they used were insufficient in terms of protection. In terms of embolism risk, we do not have any data or studies in terms of adequate dose intake, except that the use of edoxaban and rivaroxaban once a day facilitates regular use. Especially in our second case, we observed that despite the use of effective anticoagulants, the tendency for advanced inflammation and thrombosis in COVID could not be prevented by the NOACs. In NOACs that do not have follow-up laboratory analysis, it cannot be clearly determined whether the effective dose is reached in patients, as in warfarin (2). In the research conducted by Murtaza et al. (7), no significant difference was found in terms of resolution of the left atrial appendage thrombus between warfarin and rivaroxaban. Simultaneously, in the case series by Rankin et al. (6), potential failures of NOACs for treating pulmonary embolism have been reported.

The biggest question mark in our cases is that patients are more likely to skip at least 4 doses of NOAC drugs, which have a shorter half-life compared with warfarin, due to their multiple drug use and age. Changes in cytochrome p450 metabolism are known to reduce the effectiveness of NOACs, so we should be more careful when using NOACs in people who have used multidrugs (6,8). For this reason, it is imperative that multicenter studies with strict follow-up be increased, rather than a few cases where physician control of the most important discussion topic on NOACs-Emboli Protection and Effective Dose-is weak.

Rather than giving us an approach on this subject, these cases will guide us to start further studies on this subject.

Ethics

Informed Consent: Written informed consent was obtained from the patient's parent for publication of the case report and the accompanying images.

Authorship Contributions

Surgical and Medical Practices: A.B., S.T.O., F.T.A., B.K., Concept: A.B., S.T.O., K.K., H.A., Design: A.B., S.T.O., F.T.A., H.A., Data Collection or Processing: A.B., S.T.O., K.K., B.K., Analysis or Interpretation: A.B., S.T.O., F.T.A., Literature Search: A.B., S.T.O., K.K., N.B., B.K., Writing: A.B.

Conflict of Interest: The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

Financial Disclosure: The authors received no financial support for the research and/or authorship of this article.

References

1. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol 2015;12:464-74.
2. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Heart J 2020;41:543-603.
3. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369:799-808.
4. Bavalia R, Bistervels IM, Boersma WG, et al. Quality of life in patients with pulmonary embolism treated with edoxaban versus warfarin. Res Pract Thromb Haemost 2021;5:e12566.
5. EINSTEIN-PE Investigators, Büller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287-97.
6. Rankin J, Nagar M, Crosby J, Toomari N, Pietras R, Ben-Zur UM. Possible failure of novel direct-acting oral anticoagulants in management of pulmonary embolism: a case report. J Med Case Reports 2016;10:346.
7. Murtaza G, Turagam MK, Garg J, Velagapudi P, Atti V, Lakkireddy D. Response to the Editor: Warfarin versus non-vitamin K oral anticoagulants for left atrial appendage thrombus: A meta-analysis. JCE 2020;31:2263.
8. Grymonprez M, Vanspranghe K, Steurbaut S, De Backer TL, Lahousse L. Non-vitamin K Antagonist Oral Anticoagulants (NOACs) Versus Warfarin in Patients with Atrial Fibrillation Using P-gp and/or CYP450-Interacting Drugs: a Systematic Review and Meta-analysis. Cardiovasc Drugs Ther 2023;37:781-91.