Isolated hemopericardium after initiation of rivaroxaban: Implications and potential mechanisms

Adwait Mehta,1 David Burkland,1,2 Nilesh Mathuria1
1Texas Heart Institute; 2Baylor College of Medicine, Texas, USA

Abstract

Direct oral anticoagulants have become increasingly used for atrial fibrillation and venothromboembolic disease. Thus far, there have been a few published cases of pericardial effusion associated with rivaroxaban. However, there has been little published regarding the effects of concurrent medications and their effect on the cytochrome enzymes involved in rivaroxaban metabolism. We present a case of a 76-year-old female who develops a spontaneous haemopericardium after initiating rivaroxaban. After thorough medical reconciliation, we offer pharmacokinetic mechanisms that may have contributed to the haemopericardium. This case demonstrates the importance of reviewing patients medication lists and utilizing basic pharmacokinetics to prevent adverse events.

Introduction

Atrial Fibrillation (Afib) is associated with an increased risk of ischemic stroke.1 Anticoagulation with Warfarin reduces the risk of ischemic stroke (and other embolic events) by about two-thirds, irrespective of baseline risk.2 In the rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF), rivaroxaban was shown to be non-inferior to warfarin for the prevention of stroke and systemic embolism, with less intracranial and fatal bleeding.1,3,4

During this trial, there were no documented cases of hemopericardium.5 Furthermore, based on best available evidence, no safety alerts have been raised for an increased risk of pericardial bleeding with Direct Oral Anticoagulants (DOACs).3 Here we report a case of Spontaneous Haemopericardium associated with rivaroxaban use for prevention of thromboembolic events in Afib.

Case Report

76-year-old female with a past medical history significant for Paroxysmal Afib with Tachy- Brady Syndrome, hyperlipidemia and muscle spasms who presented to the emergency room (ER) with dizziness, chest discomfort and presyncope. The patient underwent uneventful placement of a dual chamber permanent pace maker (PPM) placed 3 weeks before the ER visit being described. Rivaroxaban 20 mg PO daily was started as a new medication 3 days after placement of the PPM. Blood work confirmed no renal or hepatic impairment. Her CHADS2Vasc score at time of initiating rivaroxaban was 3.

Her home medicine consisted of Flecainide, Pravastatin, Cilobenzaprine and a Multivitamin complex. These were also continued post procedure. Patient’s past surgical and family history were unremarkable.

In the ED, her systolic blood pressure was 70, Heart rate of 74. Physical exam revealed an alert and oriented patient. Normal jugular venous pressure and normal intensity heart sounds with no friction rub. Her lungs were clear on auscultation and abdomen was soft without tenderness.

An echocardiogram revealed a moderate-large Pericardial Effusion with early tamponade physiology. Her lab investigations were significant for an INR (International Normalized Ratio) of 1.7 with a PTT (PLEASE EXPLAIN THE ABBREVIATION) of 39 seconds, platelet count was 216, creatinine of 0.89 mg/dL and creatinine Clearance of 64.7 mL/min based on Cockcroft-Gault equation. ECG revealed sinus rhythm at a rate of 74 bpm with normal QRS amplitude. There was no evidence of ST segment abnormalities or electrical alternans.

The patient was stabilized with intravenous fluid and vasopressors and taken to the cath lab for pericardiocentesis. A total of 350 cc of gross bloody fluid was removed. Post-procedure, drains were placed and removed 48 hours thereafter with no evidence of reaccumulation. Evaluation of the fluid confirmed a haemopericardium (RBC (red blood cell) count of 472,000 cells/microliter) with gram stain and culture confirmed no recurrence of the pericardial effusion. Patient was noted to have recurrent atrial fibrillation 1 year later and Apixaban was initiated without complication.

Discussion

Spontaneous hemopericardium unrelated to trauma is known to occur in 2.5-11% of patients receiving an anticoagulation.6 Although a rare clinical event, there are published cases of hemopericardium associated with DOACs.5,7

Unlike other DOACs, rivaroxaban is not administered as a prodrug. More specifically, the pharmacologically active compounds are active prior to oxidative metabolism by the Cytochrome P450 enzymes associated with the drug: CYP3A4, CYP 3A5 and CYP2J2.8,9

Given the above described pharmacokinetics of rivaroxaban, it is possible that the co-administration of Cilobenzaprine and Pravastatin, both minor substrates of CYP 3A4,10,11 and thus competitive compounds, lead to a higher serum concentration of metabolically active rivaroxaban and thus an increased bleeding risk.

Competitive compound binding describes individual compounds (i.e. medications) that compete for the active site of
an enzyme to form an enzyme-compound complex. This becomes clinically relevant when drugs are given concurrently, who themselves are either enzyme substrates, inducers, or inhibitors of an oxidative enzyme system (e.g. CYP 450) resulting in variable pharmacokinetics of each co-administered drug.

Conclusions

The use of DOACs has provided increasing options in the management of atrial fibrillation and venothromboembolic disease.

Through a process of exclusion, we suspect our patient suffered a spontaneous hemopericardium after exposure to rivaroxaban. Furthermore, the inherent bleeding risk associated with rivaroxaban was increased by simultaneous use of other CYP 3A4 substrates.

We hope our case contributes to the post marketing surveillance of rivaroxaban and facilitates comprehensive decision making for prescribing professionals. Therefore, we recommend a careful medication reconciliation when prescribing rivaroxaban. Special consideration should be paid to medications whose pharmacokinetics is closely linked to the CYP 3A4, CYP 3A5 and CYP 2J2 oxidative cycles.

References