

First reported case series in the United States of hemopericardium in patients on apixaban



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Introduction

Apixaban, a direct factor Xa inhibitor, is one of the oral anticoagulant drugs (available since 2012) for stroke prevention in patients with nonvalvular atrial fibrillation.¹ Other indications for its use include deep venous thrombosis, postoperative venous thromboprophylaxis, and pulmonary embolism.² The ARISTOTLE trial showed that apixaban was superior to warfarin in preventing stroke or systemic embolic event and was associated with less bleeding and lower mortality rates. Major bleeding was the primary safety endpoint in the trial and was defined as “clinically overt bleeding accompanied by 1 or more of the following: bleeding that was fatal, bleeding that occurred in at least 1 of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, and retroperitoneal; a transfusion of 2 or more units of packed red blood cells; or a decrease in hemoglobin of 2 g/dL or more.”¹ Neither the supplementary appendices in the ARISTOTLE trial nor any of the study tables break down each of the sites of major bleeding, and they lump the safety outcome as any major bleeding. Bleeding in the pericardial space, hemopericardium, can be a life-threatening adverse reaction and should be monitored for. An extensive literature search showed 1 prior case report of spontaneous hemopericardium in a patient receiving apixaban, none reported in the United States. We present the first reported case series of hemopericardium in association with apixaban therapy in the United States.

Case report

Case 1

A 70-year-old man with a past medical history of hypertension, hyperlipidemia, chronic kidney disease (CKD) stage

3, and solitary functioning kidney (atrophic left kidney) initially presented to the hospital with a complaint of chest pain, which he described as pulsatile and squeezing, that was nonradiating and located in the middle of his chest, and that was not altered by position or breathing. His presenting electrocardiogram (ECG) showed normal sinus rhythm with a first-degree atrioventricular block, without any PR or ST-T segment changes. During the hospitalization for further evaluation of chest pain, he was noted to be in atrial fibrillation on telemetry with a controlled ventricular rate, which was confirmed with a 12-lead ECG. He underwent a Lexiscan nuclear stress test, which showed no evidence of infarct or ischemia with preserved ejection fraction. He subsequently had an echocardiogram (echo), which showed preserved ejection fraction, no pericardial effusion, and no structural heart disease. He was discharged home on apixaban 5 mg twice a day (CHA₂DS₂-VASc score 3 points), and his home atenolol was continued. His other home medications included allopurinol, atorvastatin, cholecalciferol, esomeprazole, fluoxetine, folic acid, niacin, amlodipine, and doxazosin.

He returned to our outpatient cardiology practice 10 days post discharge complaining of dyspnea on exertion, malaise, dizziness, and nausea. He was hypotensive with blood pressure 80/40, pulse irregular at 66 beats/min, and respiratory rate 14. His labs, done 1 day prior to his office visit, showed a serum creatinine (Cr) of 4.36, up from 1.93 on discharge (baseline Cr 1.7–1.9); his hemoglobin had decreased from 12.9 mg/dL on his recent discharge to 10.6 mg/dL. His International Normalized Ratio (INR) was 1.8 and PTT 20.2, up from INR 0.9 and PTT 12.2 on his last discharge 10 days prior. He was admitted to the hospital with discontinuation of both antihypertensive agents and apixaban. An echo was done immediately upon admission that demonstrated a large pericardial effusion (suspicious for blood) with evidence of hemodynamic compromise, and reduced right ventricular systolic function. A pericardial window was emergently performed and 1.4 liters of sanguineous fluid was removed. Fluid cytology was negative for malignancy; however, no fluid analysis was sent from the operating room. He slowly improved during the hospitalization, with improvement in his hemodynamics and marked improvement in his renal

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KEY TEACHING POINTS

- Novel oral anticoagulants are gaining more popularity for use because of their convenient dosing and no monitoring requirements.
- Although easy and convenient to use, they should be used cautiously in patients with renal dysfunction and those who are already predisposed to bleeding complications.
- Key drug interactions, especially with the use of apixaban and selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, should be monitored for. A true incidence of major and life-threatening drug interactions may be needed to determine the true safety profile of these agents.

function as well, and was discharged home without any anticoagulation medications.

Case 2

A 60-year-old man with a past medical history of hypertension, nonischemic cardiomyopathy (ejection fraction 40%), hyperlipidemia, diabetes, end-stage renal disease with kidney transplant 5 years ago (on immunosuppressive therapy), hypothyroidism, and recently diagnosed atrial fibrillation presented to our hospital with a complaint of dyspnea on exertion, bilateral leg swelling, and a 15-pound weight gain over the last 2 weeks. He was diagnosed with atrial fibrillation with a rapid ventricular rate of 110 beats/min, 15 days prior to this hospitalization by his primary care physician (PCP), and was started on metoprolol and apixaban 5 mg twice a day as an outpatient. He was referred to our cardiology practice for further evaluation and an echocardiogram was ordered by the PCP. His prior echocardiogram from 7 years ago showed an ejection fraction of 40% with global hypokinesis and no pericardial effusion; he also had a negative Lexiscan stress test 7 years ago at the time of diagnosis of his nonischemic cardiomyopathy. His other home medications included amlodipine, atorvastatin, ezetimibe, furosemide, insulin, levothyroxine, linagliptin, lisinopril, mycophenolate, pantoprazole, repaglinide, sertraline, tacrolimus, and tamsulosin. He was referred for an outpatient echocardiogram by his PCP, but was noted incidentally to have a pericardial effusion on magnetic resonance imaging of the abdomen and pelvis, which was performed to evaluate his transplanted kidney 1 day prior to his admission to the hospital; however, given his worsening dyspnea he presented to the emergency department and was admitted. He had stable vital signs on admission. Pertinent laboratory findings on admission were as follows: Cr 1.32 (baseline 1.2–1.3); INR 1.3, PTT 15.7, NT-proBNP 1043, and negative troponins. On admission, an echo was performed that

demonstrated normal left ventricular systolic function, biatrial enlargement, and a large pericardial effusion along with a mobile echo density measuring 1.3×0.3 cm on the visceral pericardial surface, which likely represented an organized fibrin strand. Apixaban was discontinued and, given his symptoms, pericardiocentesis was performed with removal of 1.3 L of sanguineous fluid. Fluid analysis was consistent with a hemorrhagic effusion, with 433 052 red blood cells and 315 white blood cells, with lactate dehydrogenase of 243 and total fluid protein of 5.4. He did well post pericardiocentesis but started to decompensate slowly overnight, with recurrence of dyspnea, tachycardia, and tachypnea. Emergent echo demonstrated recurrent large pericardial effusion with evidence of hemodynamic compromise. Pericardial window was performed emergently, and 600 mL of serosanguineous fluid was drained. During the next 4 days the pericardial drain continued to drain small amounts of serosanguineous fluid: 90 mL on the first day after the initial pericardial drain was placed, 60 mL on day 2, 25 mL on day 3, and 45 mL on day 4. The pericardial drain was discontinued on the fifth day; repeat echo demonstrated no recurrent pericardial effusion. Fluid cytology was negative for malignancy and cultures were negative for growth. The patient had no complications post removal of his pericardial drain and was medically treated for heart failure and atrial fibrillation, with anticoagulation being held. His immunosuppressive medications, tacrolimus and mycophenolate, were continued throughout the admission. He was discharged home in a stable condition without any anticoagulation.

Discussion

Sigaway and colleagues³ published the first case report on hemopericardium in a Turkish patient on apixaban therapy. Although it is difficult to establish a true causal relationship between the use of apixaban and hemopericardium in these patients, common predisposing factors must be acknowledged. The patient reported in Sigaway's case report had renal dysfunction and was initiated on 2.5 mg of apixaban. Both patients in our case series had CKD, with a baseline serum creatinine of 1.7–1.9 mg/dL in case 1 and 1.2–1.3 mg/dL in case 2. Several studies have reported that patients with CKD have an increased risk of bleeding complications.^{4–6} Renal excretion accounts for about 27% clearance of apixaban.² The rest is cleared in bile and feces through the gastrointestinal tract.² The apixaban dosing guidelines indicate that a dose of 2.5 mg twice a day should be used for patients meeting 2 of the following 3 criteria: weight \leq 60 kg, age \geq 80, and serum creatinine \geq 1.5 mg/dL.² None of the patients in our series met 2 of these criteria and hence they were placed on apixaban 5 mg twice daily by their physicians. In the ARISTOTLE trial 2.5 mg of apixaban was associated with an increased absolute event rate of 1.7% per year compared to 1.3% per year on apixaban 5 mg.¹ However, no safety data are available with head-to-head comparison of the 2 dosing regimens. It remains to be speculated whether a lower dose of apixaban may have prevented the

hemopericardium in these patients while giving them the same protection from stroke and systemic thromboembolism risk.

Interestingly, the temporal relationship of the adverse drug reaction should also be noted: hemopericardium occurred in both patients within 10 days of apixaban initiation. In contrast, the patient in Sigawy's case had a subacute presentation, with hemopericardium 6 weeks after initiation of apixaban. A drug interaction check on our patients' medications revealed an increased risk of bleeding with apixaban and concomitant use of selective serotonin reuptake inhibitors (SSRIs), which both of our patients were on.⁷ This is mediated by inhibition of platelet serotonin uptake and creates a synergistic anticoagulant effect.⁸ Sertraline and fluoxetine have the highest levels of serotonin reuptake inhibition and thus are more frequently associated with abnormal bleeding and changes in hemostasis markers. The most common hemostatic abnormalities include decreased platelet aggregation and activity and prolongation of bleeding time.⁹ In addition, the concomitant use of SSRIs and apixaban is risk category C, recommending that therapy be monitored but can be used.¹⁰ The patient in case 2 continued to have drainage of pericardial effusion for a few days, although the half-life of apixaban is approximately 12 hours.¹⁰ This was likely mediated by concomitant use of apixaban and tacrolimus, which is a strong P-glycoprotein inhibitor and thus inhibits efflux of apixaban.¹¹ Based on the medication, medical, and presenting history, none of the patients in our case series had a predisposition to developing a pericardial effusion, which could have turned hemorrhagic with the use of apixaban. Thus the temporal relationship of developing a spontaneous hemorrhagic pericardial effusion becomes important, especially in light of the finding that the only new change in both patients' medical condition was the introduction of a new medication. Perhaps as more cases of major bleeding with apixaban and SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) are reported, this recommendation for concomitant use may change to category D (consider modification) or X (avoid combination).

Another challenge with the use of apixaban is the lack of a reversible agent, although prothrombin complex

concentrate and activated factor VIIa can be used in the case of major bleeding. Using the Naranjo adverse drug reaction scale a score of 5 is obtained, indicating that an adverse drug reaction of apixaban is probable.¹² Another challenge with the use of oral anticoagulants is the inability to monitor serum drug concentration levels. Assays to monitor serum drug concentrations of apixaban would aid in the safety of their use as well.

Conclusion

Use of novel oral anticoagulants provides the convenience of easy dosing and less frequent monitoring and they are becoming more popular for patients with atrial fibrillation. However, as our use and understanding of these drugs continue to increase, we must be watchful for major and life-threatening adverse drug reactions. Most importantly, the use of apixaban in patients with renal dysfunction and concomitant SSRI or SNRI use should be done with extreme caution, as this case series demonstrates.

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