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Hemopericardium and Cardiac Tamponade Associated with Dabigatran Use

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Abstract

OBJECTIVE: To describe 2 cases of hemopericardium following treatment with dabigatran.

CASE SUMMARIES: A 70-year-old male with a history of dabigatran use presented with cough, fatigue, and bloody stools. The patient had a large hyperdense pericardial effusion caused by accumulation of bloody fluid, leading to hypotension and shock. Approximately 1000 mL of hemorrhagic fluid was drained from the pericardial space. A 77-year-old female was admitted for treatment of pneumonia and atrial fibrillation. Dabigatran was initiated and, after 6 doses, the patient developed abdominal pain, respiratory distress, and shock. She was diagnosed with pericardial effusion leading to cardiac tamponade. Pericardiocentesis and thoracentesis procedures removed a cumulative total of 2000 mL of bloody fluid.

DISCUSSION: Dabigatran is an oral direct thrombin inhibitor approved for the reduction of stroke and systemic embolism risk in patients with nonvalvular atrial fibrillation. In December 2011, the Food and Drug Administration released a statement describing serious bleeding events associated with dabigatran use. According to the Naranjo scale, the cases presented here had probable associations between hemopericardium and dabigatran. While there is no known literature supporting this relationship, there are documented cases of warfarin-induced hemopericardium.

CONCLUSIONS: These case reports highlight the potential for dabigatran to cause hemopericardium and cardiac tamponade. Additional reports may better elucidate (or characterize) the risk of dabigatran-induced hemopericardium and cardiac tamponade.

Dabigatran is an oral direct thrombin inhibitor approved by the Food and Drug Administration (FDA) in 2010 for the reduction of stroke and systemic embolism risk in patients with nonvalvular atrial fibrillation.[1] Dabigatran competitively inhibits thrombin, thereby preventing the conversion of fibrinogen to fibrin, a necessary step in the formation of a thrombus. Dabigatran, similar to the intravenous direct thrombin inhibitor argatroban, can increase the international normalized ratio (INR); however, due to the unpredictable nature of INR results with dabigatran use, it is generally recommended to avoid routine INR monitoring.[1,2]

In December 2011, the FDA released a statement describing a postmarketing evaluation of serious bleeding events associated with dabigatran use.[3] One of these potential bleeding events is hemopericardium. Hemopericardium is defined as a collection of hemorrhagic fluid in the pericardial space.[4] Large amounts of fluid in this space can lead to cardiac tamponade, an acute increase in pressure and cardiac compression.[4] We describe 2 patients who experienced these serious adverse events following treatment with dabigatran.

Case Reports

CASE 1

A 70-year-old white male presented to the emergency department (ED) on June 25, 2011, reporting 7 days of mild cough and fatigue and 1 day of bloody stools. The patient had a history of atrial fibrillation and was receiving anticoagulation therapy for primary stroke prevention ($CHADS_2$ score = 3). In addition to atrial fibrillation, the patient's history was significant for chronic left ventricular systolic dysfunction with an ejection fraction (EF) of 45% in July 2010, stage 3 diastolic dysfunction, chronic kidney disease stage 3 (baseline serum creatinine 1.1 mg/dL, baseline estimated creatinine clearance 66 mL/min), type 2 diabetes mellitus, hypertension, hyperlipidemia, osteoarthritis, benign prostatic hypertrophy, peripheral vascular disease, and gout. The patient had been admitted twice in the 3 months leading to this event, once for generalized weakness and once for hypoglycemia, at which times he had stable serum creatinine concentrations of 1.04 mg/dL (creatinine clearance [CrCl] 70 mL/min) and 1.17 mg/dL (CrCl 64 mL/min).

Since August 2010, the patient had received warfarin. For a reason not clearly indicated in the patient's medical history, therapy was switched from warfarin to oral dabigatran 150 mg twice daily in March 2011. At that time, the patient was also receiving chronic antiplatelet therapy with aspirin 81 mg daily. Additionally, the medication reconciliation history revealed that the patient began taking pantoprazole 40 mg daily sometime after initiation of dabigatran therapy.

Laboratory results upon admission revealed an elevated serum creatinine concentration of 6.26 mg/dL (estimated CrCl of 11 mL/min) and serum potassium concentration of 8.2 mEq/L. The INR was greater than 6. He reported adherence to dabigatran and confirmed that he had not been taking warfarin. The patient's weight upon presentation was 109 kg. A Hemoccult stool test in the ED was positive, and hemoglobin and hematocrit were 10.9 g/dL and 33.7%, respectively; these values did not significantly differ from baseline values (10-11 g/dL and 33-34%) found in previous admission records. While the patient was in the ED on June 25, a left pleural effusion was observed on chest X-ray and was confirmed by bedside ultrasound performed shortly after admission. The patient was admitted for treatment of suspected septic shock, acute-on-chronic renal failure, and coagulopathy. Dabigatran was discontinued upon admission.

On the evening of June 25, the patient was intubated for respiratory failure. Intravenous broad-spectrum antibiotic therapy with vancomycin, piperacillin/tazobactam, and azithromycin was continued to treat possible infectious etiologies of shock, including pneumonia. Blood cultures obtained on June 25 did not reveal bacterial growth. The patient continued treatment with vasopressin and norepinephrine for hypotension, with limited improvement in blood pressure.

A computed tomography (CT) image of the chest, performed on June 26, did not reveal findings of pneumonia but rather a large hyperdense pericardial effusion. An emergent pericardiocentesis was performed by a consulting cardiologist to treat the cardiac tamponade. Approximately 1000 mL of hemorrhagic fluid was drained from the pericardial space, resulting in improved hemodynamics and gradual weaning of vasopressors. Hemoglobin decreased to 6.7 g/dL following removal of the hemorrhagic fluid, and the patient required transfusion of 2 units of packed red blood cells (PRBCs).

On June 27, the critical care team acknowledged that this hemorrhagic pericardial effusion was likely the cause of the patient's hypotension and shock and was likely due to “dabigatran in the setting of chronic kidney disease… contributing to an increased risk of bleeding.”

The patient was discharged after 17 days and was transferred to a subacute rehabilitation facility, at which time stroke prevention with warfarin was restarted.

CASE 2

A 77-year-old African American female presented to the ED on May 12, 2011, with dizziness, shortness of breath, incontinence, and cough. The patient had been discharged for a diagnosis of pneumonia on April 27 and again on May 1. The patient was admitted on both of these dates. She was prematurely discharged the first time, which led to readmission on May 1 for unresolved pneumonia. Her history at the time of the current admission was significant for chronic obstructive pulmonary disease, pulmonary hypertension, hypertension, left ventricular systolic dysfunction with an EF of 40% in June 2010 (via 2-dimensional echocardiogram), gastroesophageal reflux disease, coronary artery disease, anemia, chronic kidney disease stage 3 (baseline serum creatinine 1.2 mg/dL, baseline estimated CrCl 28 mL/min), dyslipidemia, hypothyroidism, hemorrhoids, and diverticulosis. The patient's pertinent home medications included aspirin 81 mg once daily.

Initial evaluation in the ED revealed an elevated white blood cell count (14.7/μL), and a chest X-ray revealed left lower lobe opacities and resolution of the right lower lobe opacities for which she had previously been treated. Serum creatinine upon admission in the ED was consistent with a baseline value of 1.22 mg/dL and an estimated CrCl of 28 mL/min. INR on admission was 1.21, hemoglobin was 11.6 g/dL, and weight was 55 kg. The patient was found to have atrial fibrillation, with heart rates of 86-136 beats/min. An electrocardiogram performed in the ED demonstrated a ventricular rate of 134 beats/min and an atrial rate of 134 beats/min; this was interpreted as “atrial fibrillation with rapid ventricular response. … When compared with electrocardiogram of May 2, 2011, [it shows that] atrial fibrillation has replaced sinus rhythm.” The patient was consequently admitted for treatment of health care–associated pneumonia (HCAP) and atrial fibrillation.

In addition to beginning treatment for HCAP with piperacillin/tazobactam and vancomycin, new-onset atrial fibrillation workup continued following admission. A cardiology consult to evaluate the patient was conducted on May 17, and need for anticoagulation was discussed ($CHADS_2$ score = 3). At that time, dabigatran 150 mg twice daily was initiated, with the first dose administered later that evening.

On May 20, the patient developed respiratory distress and severe abdominal pain. She was subsequently transferred to the intensive care unit. Soon thereafter she developed shock, requiring intubation and treatment with intravenous 0.9% NaCl, dopamine, and norepinephrine. Infectious diseases consultants recommended empiric treatment with linezolid and meropenem to rule out infectious causes; these were later discontinued when there was no bacterial growth in blood cultures. A 2-dimensional echocardiogram performed later that day showed a moderately sized pericardial effusion with right ventricular diastolic compression, leading to cardiac

tamponade. At this time, aspirin and dabigatran were discontinued. At the time of discontinuation, the patient had received a total of 6 doses of dabigatran 150 mg.

A cardiologist immediately performed pericardiocentesis, which led to the removal of approximately 400 mL of bloody pericardial fluid. Cultures taken from fluid samples did not indicate infectious involvement. An echocardiogram following the procedure confirmed minimal fluid residuals. Following this procedure, the patient was weaned from vasopressors. After pericardiocentesis, the hemoglobin and hematocrit decreased (7.6 g/dL and 23.9%, respectively), necessitating transfusion with 2 units of PRBCs. Cardiogenic rather than septic shock was thought to be the likely cause of the patient's decline.

A chest X-ray taken on May 21 revealed a new right pleural effusion. A thoracentesis performed on May 22 removed approximately 400 mL of bloody fluid. Again, the patient's hemoglobin decreased to 7.5 g/dL and hematocrit decreased to 22.8% following removal of the fluid, and an additional 2 units of PRBCs were administered. The patient received 4 more units of PRBCs within the following 7 days.

Meanwhile, the patient's renal function continued to decline (Table 1). Concerns regarding overanticoagulation from dabigatran secondary to acute renal failure were discussed by consulting nephrologists and hematologists. Acute renal failure necessitated the initiation of hemodialysis beginning on May 24. A consulting nephrologist expressed hope that dialysis would help remove dabigatran and therefore resolve the coagulopathy.

A chest X-ray performed following another acute respiratory decompensation on May 29, however, revealed development of a new left pleural effusion. Thoracentesis on May 29 removed approximately 1200 mL of bloody fluid. The critical care physicians who performed the procedure noted that the fluid from May 29 was significantly bloodier than that from May 22. A repeat 2-dimensional echocardiogram on May 29 revealed resolution of the pericardial effusion.

Dabigatran was identified as the most likely cause of coagulopathy in this patient. The course of events by which dabigatran led to cardiac tamponade and acute renal failure versus acute renal failure leading to dabigatran toxicity and cardiac tamponade remains unclear.

The patient was discharged without anticoagulation for stroke prevention to a long-term acute care facility after a 1-month stay in the intensive care unit. She died a few months later because of respiratory failure.

Table 1. Case Report 2: Serum Creatinine Values Relative to Dabigatran Doses**.**

Date	Serum Creatinine (mg/dL)	Estimated Creatinine Clearance (mL/min)	Dabigatran Dose (mg)
5/12	1.22	28	
5/13	1.21	28	
5/14	1.37	24	
5/15	1.26	27	
5/16	0.99	34	
5/17	0.99	34	150
5/18	0.99	34	150
			150
5/19	1.07	32	150
	1.46	23	150
5/20	1.84	18	150
	2.34	14	
5/21	2.64	13	
5/22	3.20	11	
5/23	2.93	12	
	4.02	8	
5/24	4.24	8	

Discussion

The 2 cases presented here may demonstrate dabigatran's potential to cause serious bleeding events, particularly in the setting of acute renal failure. According to the FDA-approved dosing, dabigatran should be decreased to 75 mg by mouth twice daily for patients with a CrCl of 15-30 mL/min. For patients with severe renal dysfunction, dabigatran should not be used, as there are no dosing recommendations for this population. Both patients in this report were started on dabigatran 150 mg twice daily. At the time that hemopericardium occurred, both patients were experiencing acute renal failure, with CrCl values less than 15 mL/min. The use of dabigatran 150 mg in the setting of acute renal failure likely contributed to increased drug accumulation and increased risk of serious bleeding events. Additionally, it does not appear that periodic renal monitoring, as is currently recommended by the manufacturer, was performed in the first patient; these events occurred in both patients prior to publication of this renal monitoring recommendation.[1]

Spontaneous, nontraumatic hemopericardium, as described in these 2 cases, has an incidence of 2.5-11% in patients receiving any form of anticoagulation.[5,6] Patients who progress to the development of cardiac tamponade require immediate intervention to remove the fluid via pericardiocentesis.[4]

According to the Naranjo probability scale, each of the cases outlined in this report had a probable association between hemopericardium and dabigatran use.[7] While there is no known literature, and only one published case report[8] outlining the relationship between hemopericardium and dabigatran use, there are a handful of documented cases of warfarin-induced hemopericardium.[8–11] At the time of writing, we identified 10 published case reports of warfarin-induced hemopericardium and cardiac tamponade.[9–11]

Katis reported a 67-year-old female who presented to the ED in 2005 with sudden new-onset chest pain.[9] The patient had experienceed a pulmonary embolus 3 weeks prior to presentation, and she had subsequently received anticoagulation therapy with warfarin. Her INR upon admission was 3.51. A CT image revealed pericardial effusion, and pericardiocentesis removed 400 mL of blood. A pericardial drain led to the removal of an additional 600 mL of blood.

Hong et al. described a case of a 70-year-old male who presented to the ED in 2007 with progressive dyspnea and orthopnea.[10] The patient's history was significant for a mitral valve replacement 12 years prior to admission, and he was receiving warfarin. His INR upon admission was 7.52. An echocardiogram revealed cardiac tamponade, which led to 400 mL of blood being drained via pericardiocentesis. An emergency pericardiotomy removed an additional 1300 mL of dark blood.

Levis et al. reported a case of a 54-year-old male who presented to the ED in 2009 following a syncopal episode.[11] His history was significant for atrial fibrillation for which he received chronic warfarin therapy. The patient's INR upon admission was 6.0. A bedside cardiac ultrasound revealed a cardiac effusion. A portable echocardiogram revealed a cardiac tamponade, leading to a pericardiocentesis that removed 1100 mL of blood.

In 2012, Barton et al. did report a case of hemopericardium in a patient taking dabigatran.[8] A 70-year-old male presented to an outpatient pulmonologist office with complaints of increasing shortness of breath. His history was significant for atrial fibrillation and anticoagulation with dabigatran for 2 months. A CT scan revealed a large pericardial effusion, and the patient was emergently sent to the ED. Upon admission, his serum creatinine concentration was 1.49 mg/dL with an estimated CrCl of 43 mL/min. Pericardiocentesis later removed 1250 mL of bloody fluid, and the patient was discharged without anticoagulation after 4 days.

These cases raise concern regarding the impact that oral anticoagulants can have on development of hemopericardium and cardiac tamponade. Clinical studies are needed to establish the risk factors between individual anticoagulants and potential for hemopericardium.

This report highlights the potential for dabigatran to cause hemopericardium and cardiac tamponade. Additional reports of hemopericardium associated with dabigatran may help to clarify the true risk of this life-threatening condition.

References

1. Product information. Pradaxa (dabigatran). Ridgefield, CT*:* Boehringer Ingelheim Pharmaceuticals, Inc., *January* 2011.
2. Thomson Micromedex. *Drugdex evaluations. Dabigatran. Greenwood Village, CO.* www.thomsonhc.com/hcs/Librarian *(accessed 2011 Oct 20).*
3. US Food and Drug Administration. FDA Drug Safety Communication: safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate). www.fda.gov/Drugs/DrugSafety/ucm282724.htm (accessed 2011 Dec 20).

4. Jacob R, Grimm RA. Pericardial disease. In: Carey WD, ed. Cleveland Clinic: current clinical medicine. 2nd ed. Philadelphia, PA: Saunders Elsevier, 2010: 145–53.
5. Krikorian J, Hancock E. Pericardiocentesis. Am J Med 1978; 65: 808.
6. Thomas T. Emergency evacuation of acute pericardial tamponade. Ann Thorac Surg 1970; 10: 566.
7. Naranjo CA, Busto U, Sellers EM, et al. A method of estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239–45.
8. Barton CA, McMillian WD, Raza SS, Keller RE. Hemopericardium in a patient treated with dabigatran etexilate. Pharmacotherapy 2012; 32: e103–7.
9. Katis PG. A traumatic hemopericardium in a patient receiving warfarin therapy for a pulmonary embolus. Can J Emerg Med 2005; 7: 168–70.
10. Hong YC, Chen YG, Hsiao CT, Kuan J, Chui TF, Chen JC. Cardiac tamponade secondary to haemopericardium in a patient on warfarin. Emerg Med J 2007; 24: 679–80.
11. Levis JT, Delgado MC. Hemopericardium and cardiac tamponade in a patient with an elevated international normalized ratio. West J Emerg Med 2009; 10: 115–9.