CASE REPORT

Hemopericardium in a Patient Treated with Dabigatran Etexilate

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Dabigatran etexilate is a new oral anticoagulant used for the prevention of systemic thromboembolism in patients with atrial fibrillation. Acute bleeding episodes are known to occur with dabigatran etexilate therapy; however, only a few case reports in the literature describe such events. We describe a 70-year-old man treated with dabigatran etexilate for newly diagnosed, nonvalvular atrial fibrillation who developed a large hemopericardium that appeared to be temporally related to dabigatran etexilate administration. One month after starting the drug, an incidental finding of a small pericardial effusion was found on echocardiography. One month later, the patient came to his pulmonologist's office complaining of shortness of breath; a large pericardial effusion was found on a noncontrast computed tomographic scan, and the patient was admitted to the hospital. Laboratory monitoring of his coagulation status was limited due to the lack of assays available to directly monitor the therapeutic effects of dabigatran. The internal laboratory was able to perform a dilute thrombin time (DTT) test as part of a quality improvement project aiming to validate an assay for monitoring patients receiving dabigatran therapy. A DTT was therefore performed in conjunction with routine coagulation assays to evaluate the patient's coagulation status. After pericardiocentesis, the patient recovered without incident and was discharged without anticoagulant therapy. Although the Naranjo adverse reaction probability scale only indicated a possible relationship (score of 1) between the patient's development of hemopericardium and dabigatran etexilate therapy, investigation into the patient's clinical course, comorbidities, and laboratory results led us to conclude that dabigatran etexilate was responsible for the hemopericardium. To our knowledge, this report is the first to describe a case of potentially life-threatening pericardial bleeding that was temporally related to starting dabigatran etexilate therapy. Although we found that the DTT was a viable method of monitoring coagulation status in a patient receiving dabigatran etexilate therapy, the assay lacks approval by the United States Food and Drug Administration, which limits its clinical utility and widespread use at this time. Clinicians should be aware of the potential for life-threatening bleeding with use of this agent and the difficulty associated with monitoring and reversing this therapy in the setting of acute bleeding.

Key Words: dabigatran, pericardial effusion, hemopericardium, dilute thrombin time.

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Atrial fibrillation is the most commonly encountered cardiac arrhythmia; it afflicts nearly 2.5 million people in the United States alone.[1] Therapeutic anticoagulants are frequently used to reduce the occurrence of untoward events from this disease, specifically embolic stroke. Dabigatran etexilate, approved by the United States Food and Drug Administration (FDA) in October 2010, is the first and only oral direct thrombin (factor IIa) inhibitor used to reduce the occurrence of systemic embolism in patients with nonvalvular atrial fibrillation.[2]

Dabigatran etexilate is a prodrug that is converted rapidly to the active moiety dabigatran through esterase-catalyzed hydrolysis.[3] Dabigatran is eliminated primarily through renal excretion and is also a substrate for P-glycoprotein–mediated efflux.[2] Recent studies have shown superiority of dabigatran over warfarin in the prevention of stroke or systemic embolism, without an increase in bleeding events.[4]

We describe the first case report, to our knowledge, of a slowly accumulating hemopericardium in a patient who started dabigatran etexilate therapy for anticoagulation management of nonvalvular atrial fibrillation.

Case Report

A 70-year-old, 75-kg, Caucasian man came to the pulmonary clinic complaining of increased shortness of breath. A noncontrast computed tomographic scan was obtained, and a large pericardial effusion (21-mm anterior effusion dimension, 29-mm posterior effusion dimension, 15-mm left lateral effusion dimension, and 55-mm right lateral effusion dimension) was discovered. He was sent urgently to the emergency department for further evaluation and treatment.

Approximately 2 months before admission, the patient had been prescribed dabigatran etexilate 150 mg orally twice/day and dronedarone hydrochloride 400 mg orally twice/day for the treatment of newly diagnosed, nonvalvular, paroxysmal atrial fibrillation. His medical history included interstitial lung disease, rheumatoid arthritis, coronary artery disease, hypertension, dyslipidemia, and gastroesophageal reflux disease. His other drug therapy consisted of cetirizine, metoprolol, rituximab (last dose taken 7 mo before admission), simvastatin, omeprazole, nabumentone as needed, calcium carbonate, and a multivitamin. The patient's serum creatinine concentration at this time was 1.2 mg/dl (normal range 0.7–1.5 mg/dl), with an estimated creatinine clearance of 53 ml/minute (using the Cockcroft-Gault equation).

Approximately 1 month before admission, the patient complained to his primary care physician of retrosternal chest pain and was found to have a small pericardial effusion (9-mm anterior effusion dimension, 11-mm posterior effusion dimension, and 12-mm right lateral effusion dimension; there was no report of a left lateral effusion dimension in the radiology report) on transthoracic echocardiography. No further action was taken, and no changes in his drug regimen were instituted at that time.

On arrival to the emergency department, the patient was given 2 L of oxygen by nasal cannula, and his oxygen saturation was 99%. Transthoracic echocardiography revealed pericardial effusion, without signs of tamponade. Pertinent laboratory findings on admission were troponin < 0.05 ng/ml (normal range < 0.81 ng/ml), creatine kinase 38 U/L (30–135 U/L), creatine kinase–myocardial band isoenzyme 0.7 ng/ml (0–5.0 ng/ml), white blood cell count 16.9 x 10^3/mm^3 (4.0–12.4 x 10^3/mm^3), hemoglobin 9.5 g/dl (11.6–15.2 g/dl), hematocrit 28.8% (34.9–44.4%), platelet count 422 x 10^3/mm^3 (141–320 x 10^3/mm^3), serum bicarbonate 23 mEq/L (24–32 mEq/L), blood urea nitrogen 19 mg/dl (10–26 mg/dl), serum creatinine 1.49 mg/dl, estimated creatinine clearance 43 ml/minute, prothrombin time 23.8 seconds (9.5–13.1 sec), international normalized ratio (INR) 2.0 (0.9–1.1), and activated partial thromboplastin time (aPTT) 55 seconds (24–35 sec).

A thrombin time test was ordered, but the blood sample did not form a clot and was considered a failed test. The thrombin time was repeated every 6 hours after that, but the samples failed to clot until 24 hours after the last dose of dabigatran etexilate had been taken. The internal laboratory was able to perform a dilute thrombin time (DTT) test as part of a quality

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improvement project aiming to validate an assay for monitoring patients receiving dabigatran therapy. The patient's blood samples were diluted in a 1:8 and a 1:20 ratio with Cryocheck (Precision Biologic, Dartmouth, Canada) pooled normal plasma. After dilution, the samples were evaluated by a coagulometer in a manner similar to the thrombin time. The DTTs were obtained every 6 hours during the first 24 hours of admission. Because this test is not FDA approved, the results of these DTTs were not available to the patient's providers during the course of his treatment. However, the DTT results became available for the writing of this case report (Figure 1). The admission DTT correlated with a dabigatran serum concentration of 0.28 μg/ml and decreased to 0.09 μg/ml in 24 hours. We calculated the half-life of dabigatran in this patient to be 11 hours, which is below the range stated in the package insert of 12–17 hours.[2]

The patient was admitted to the cardiology unit for telemetry monitoring on hospital day 1. Dabigatran etexilate was discontinued because of concern for hemopericardium and to allow for normalization of the drug-induced coagulopathy. He was hemodynamically stable; therefore, no attempt was made to reverse anticoagulation. The patient underwent echocardiographically guided pericardiocentesis on hospital day 2, which resulted in removal of 1.25 L of sanguineous fluid with minimal residual fluid noted. The fluid had a hemoglobin level of 7.8 g/dl, whereas the patient's serum hemoglobin level was 9.7 g/dl. Cytologic examination of the pericardial fluid revealed no malignant cells and was described as fresh blood. Chemical analysis showed a glucose level of 34 mg/dl, protein

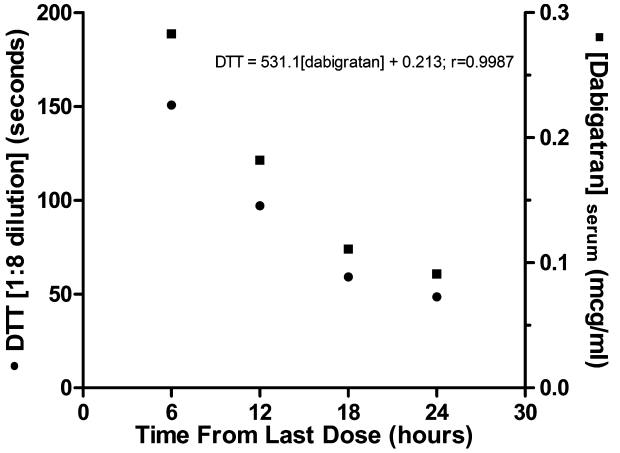

Figure 1. The patient's dilute thrombin time (DTT) results and dabigatran serum concentrations after taking his last dose of dabigatran etexilate before being hospitalized.

4.6 g/dl, lactate dehydrogenase 2537 U/L, red blood cell count greater than 0.1 x 10^6/mm^3, and white blood cell count 5.2 x 10^3/ mm^3 (neutrophils 66%, lymphocytes 19%, monocytes 9%, eosinophils 5%, and basophils 1% [Normal ranges are: white blood cells 4.0–10.4 K/cmm, neutrophils 45.5–79.7%, lymphocytes 15.0–46.8%, monocytes 1.8–12.0%, eosinophils 0.6–6.9%, and basophils 0.2–1.4%.]).

Over the patient's 4-day admission, the daily prothrombin time and INR decreased to 19.8 and 1.7, 17.2 and 1.5, and 14.1 and 1.2, respectively, and the daily aPTT decreased to 45, 31, and 27 seconds, respectively. His rheumatoid factor was 52 IU/ml (normal range: rheumatoid factor <20 IU/mL). Transthoracic echocardiography performed on hospital day 3 showed minimal residual pericardial effusion. Dabigatran etexilate was permanently discontinued while the dronedarone hydrochloride was continued, as it was providing adequate rhythm control. Other drugs continued on discharge included cetirizine, metoprolol, simvastatin, multivitamin, nabumetone, and omeprazole. The patient was discharged on hospital day 4, and he recovered without incident.

Discussion

Management of this patient with a life-threatening bleed while receiving dabigatran etexilate therapy presented a unique clinical challenge. Currently, there are no direct antidotes for dabigatran, nor are any blood products proven to reverse the effects of dabigatran.[5, 6]

In addition, laboratory monitoring of dabigatran etexilate therapy can also be challenging. There is no commercially available assay in the United States to directly measure active drug serum concentrations of dabigatran, and currently available coagulation tests are not precise in this application.[6] Thrombin time can be used to assess the activity of thrombin and directly measures the activity of direct thrombin inhibitors.[6] According to some authors, the currently available thrombin time assays are an ideal way to measure a patient's coagulation status while receiving dabigatran therapy.[6] Unfortunately, widely available coagulometers found in hospital laboratories are not adequately sensitive to fully describe thrombin activity while patients are receiving dabigatran etexilate, as seen in our patient's case.

An alternative test for monitoring dabigatran therapy is the DTT. The patient's blood samples

are diluted in a 1:8–1:20 ratio with normal pooled human plasma, and clotting is initiated by the addition of α-thrombin.[6] A linear relationship between a form of DTT (at a 1:8 dilution) and dabigatran serum concentrations has been described elsewhere,[6] and this relationship was also found by our hematology laboratory using samples of the active dabigatran compound at standardized concentrations.

We found that our patient's dabigatran serum concentrations were within the reported therapeutic ranges at his dosage of 150 mg twice/day, if not on the high end of the expected range. The previously reported therapeutic concentrations are a median peak of 0.184 μg/ml (5th and 95th percentiles 0.064 and 0.443 μg/ml, respectively) and a median trough of 0.090 μg/ml (5th and 95th percentiles 0.031 and 0.225 μg/ml, respectively).[4, 6]

There is one potential reason that the patient's extrapolated dabigatran concentrations were relatively elevated. Dronedarone hydrochloride is a known inhibitor of P-glycoprotein–mediated transport and is known to interact with dabigatran through inhibition of P-glycoprotein–mediated efflux. This interaction effectively increases exposure to dabigatran by 1.7–2-fold.[2] Although this interaction is known, we know of no published case reports of its clinical effect.

We believe that the initiation of dabigatran etexilate led to the development and enlargement of the pericardial effusion. It is common to see small pericardial effusions in patients with rheumatoid arthritis; however, they are usually associated with active inflammatory joint manifestations, which were absent in this patient. Hemopericardium has also been reported and attributed solely to rheumatoid arthritis, but this complication is considered exceedingly rare.[7] In addition, malignant pericardial effusion was eliminated from the differential diagnosis after cytologic evaluation revealed the absence of malignant cells. It is possible that a baseline pericardial inflammatory state, when combined with therapeutic or supratherapeutic anticoagulation, may have led to a small bleed that accumulated over the month before admission. It is also possible that anticoagulation alone caused the hemopericardium, given that acute hemopericardium has been reported with other systemic anticoagulants such as warfarin sodium, heparin sodium, and various thrombolytic agents.[8–13] The use of the Naranjo adverse reaction probability scale indicated a possible relationship (score of 1) between dabigatran etexilate use and hemopericardium development.[14]

Conclusion

Investigation into the patient's clinical course, comorbidities, and laboratory results led us to conclude that dabigatran etexilate was responsible for his hemopericardium. Dabigatran etexilate is being used with increasing frequency in outpatient care. Health care providers should be aware of the potential for life-threatening bleeding with use of this agent and the difficulty that is associated with monitoring and reversing this therapy in the setting of acute bleeding. We found that the DTT was a viable method of monitoring coagulation status in a patient receiving dabigatran etexilate therapy, but its lack of FDA approval limits its clinical utility and widespread use at this time. Providers should also be aware of common drug-drug interactions when prescribing newer anticoagulants for their patients, as adverse effects may go undetected more frequently because routine monitoring of coagulation status is considered unnecessary.

References

1. **Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG.** Prevalence, age distribution, and gender of patients with atrial fibrillation: analysis and implications. Arch Intern Med 1995;155:468–73.
2. **Boehringer Ingelheim Pharmaceuticals Inc.** Pradaxa (dabigatran etexilate) package insert. Ridgefield, CT: Author; 2011.
3. **Wann LS, Curtis AB, Ellenbogen KA, et al.** ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran). Heart Rhythm 2011;8: e1–8.
4. **Connolly SJ, Ezekowitz MD, Yusuf S, et al.** Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.
5. **Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M.** Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate. A randomized, placebo-controlled, crossover study in healthy subjects. Circulation 2011;124:1573–9.
6. **van Ryn J, Stangier J, Haertter S, et al.** Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost 2010;103:1116–27.
7. **Stables RH, Campbell S, Ormerod OJM.** Haemopericardium in rheumatoid arthritis. Int J Cardiol 1989;23:268–70.
8. **Braiteh F, Plana JC.** Spontaneous haemopericardium with subacute cardiac tamponade in a patient with lung cancer receiving Coumadin. QJM 2009;102:575.
9. **Griffiths Ap, Beddall A, Pegler S.** Fatal haemopericardium and gastrointestinal hemorrhage due to possible interaction of cranberry juice with warfarin. J R Soc Promot Health 2008;128:324–6.
10. **Hillyard RF.** Delayed clinical presentation of hemorrhagic pericardial effusion in a patient receiving warfarin sodium. Am J Orthop 2007;36:E144–7.

11. **Hong YC, Cheng YG, Hsiao CT, Kuan JT, Chiu TF, Chen JC.** Cardiac tamponade secondary to haemopericardium in a patient on warfarin. Emerg Med J 2007;24:679–80.
12. **Su HM, Voon WC, Chu CS, Lin TH, Lai WT, Sheu SH.** Heparin-induced cardiac tamponade and life-threatening hyperkalemia in a patient with chronic hemodialysis. Kaohsiung J Med Sci 2005;21:128–33.
13. **Mohammad S, Austin SM.** Hemopericardium with cardiac tamponade after intravenous thrombolysis for acute myocardial infarction. Clin Cardiol 1996;19:432–4.
14. **Naranjo CA, Busto U, Sellers EM, et al.** A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239–45.