

Hemopericardium and Cardiac Tamponade in a Patient Treated with Dabigatran Etxilate

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Dabigatran etexilate is one of the new oral anticoagulants approved to reduce the risk of stroke in patients with atrial fibrillation (AF). A variety of bleeding complications with dabigatran have been reported, but reports of hemopericardium are rare. We described a case of a 66 year-old female patient with non-valvular AF receiving dabigatran etexilate 150 mg twice daily for one year who suffered from hemopericardium. Her laboratory tests performed 1 year prior were normal and her admission tests revealed acute renal failure and elevated international normalized ratio (INR) level (4.79). Urgent pericardiocentesis was followed by improved renal functions and normalized INR. Dabigatran etexilate is a new oral anticoagulant that is increasingly used in daily practice. However, life-threatening complications warrant caution. Elevated INR may be related with overdose but the association of bleeding risk of dabigatran and INR requires further confirmation. (**Korean Circ J 2016;46(1):99-101**)

KEY WORDS: Pericardial effusion; Dabigatran etexilate; Atrial fibrillation.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in cardiology practice. AF is associated with 5-fold increased stroke and 2-fold increased mortality risk.¹⁾

Thromboprophylaxis is the cornerstone of treatment in these patients. Dabigatran etexilate is one of the new oral anticoagulants shown to reduce the risk for stroke in patients with AF. It is an oral direct thrombin (factor IIa) inhibitor approved by United States Food and Drug Administration (FDA) in 2010.²⁾

Dabigatran etexilate is a prodrug that is excreted mainly by the kidneys.²⁾ It is superior to warfarin for prevention of stroke or systemic emboli without increasing bleeding in patients with non-valvular AF.³⁾ Various bleeding complications associated with dabigatran were previously reported.⁴⁾⁵⁾ However, there are very few cases of hemopericardium associated with dabigatran use.⁶⁾⁷⁾ In this case, we described a patient with AF who suffered from hemopericardium under dabigatran treatment.

Case

A 66 year-old female patient was admitted to the emergency room for progressive shortness of breath and poor health condition for 1 week. Her blood pressure was 80/50 mmHg and arterial blood gas analysis was pH; 6.98, pCO₂; 99 mmHg, pO₂; 66 mmHg. She was immediately intubated and transferred to the coronary intensive care unit. Echocardiography revealed massive pericardial effusion with cardiac tamponade (posteriorly 3 cm, anteriorly 2.5 cm, laterally 2 cm and 2.7 cm in adjacency with the right ventricle). The patient had non valvular AF and been receiving dabigatran etexilate 150 mg twice daily for one year. In addition to dabigatran, the other medications included verapamil, budesonide, valsartan, and hydrochlorothiazide. She had a

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history of chronic obstructive pulmonary disease, hyperthyroidism, hypertension and gastroesophageal reflux disease. Her blood tests performed 1 year ago showed serum creatinine 0.5 mg/dL (normal range 0.5–0.9 mg/dL) and estimated creatinine clearance 136 mL/minute (using the Cockcroft-Gault equation).

On admission her blood tests showed blood urea nitrogen 163.9 mg/dL (normal range 16.6–48.5 mg/dL), creatinine 3.99 mg/dL (normal range 0.5–0.9 mg/dL), estimated creatinine clearance 16 mL/minute (using the Cockcroft-Gault equation), fasting glucose 83.9 mg/dL (normal range 74–109 mg/dL), sodium 130 mmol/L (normal range 136–145 mmol/L), potassium 5.3 mmol/L (normal range 3.5–5.1 mmol/L), prothrombin time (PT) 44.5 s (normal range 11.5–15 s), activated partial thromboplastin time (aPTT) 123.7 s (normal range 26–32 s), international normalized ratio (INR) 4.79, white blood cell count $10.59 \times 10^3/\mu\text{L}$ (normal range $4.4\text{--}11.3 \times 10^3/\mu\text{L}$), hemoglobin 7.7 g/dL (normal range 11.7–16.1 g/dL), hematocrit 25.7% (normal range 35–47%), and platelet count $183 \times 10^3/\mu\text{L}$ (normal range $152\text{--}396 \times 10^3/\mu\text{L}$).

Urgent pericardiocentesis was performed with echocardiographic guidance and 1500 mL of hemorrhagic fluid was removed. Pericardial fluid analysis showed hemoglobin 7 g/dL and plasma hemoglobin level of the patient was 7.7 g/dL. Cytologic exam was negative for malignancy. Biochemical tests showed total protein 5.4 mg/dL, lactate dehydrogenase 707 mg/dL and albumin 2.98 mg/dL.

Six hours after pericardiocentesis, the patients' blood pressure was over 100 mmHg systolic and she began to urinate. Red blood cell and fresh frozen plasma transfusions were made and post-transfusion hemoglobin level was 12 g/dL, PT 36.4 s (normal range 11.5–15 s), aPTT 100.5 s (normal range 26–32 s), and INR 4.1. On the second day after pericardiocentesis, hemorrhagic fluid flow via drainage catheter persisted and additional fresh frozen plasma transfusion was administered. Subsequently, PT was 25.3 s, aPTT 77.5 and INR was 2.3. Pericardial drainage was terminated after achievement of no flow through catheter and no pericardial effusion on control echocardiography.

Laboratory tests repeated on the fourth day of admission were as follows: blood urea nitrogen 109 mg/dL, creatinine 1.4 mg/dL, INR 1.4 and hemoglobin 12 g/dL. The patient was extubated after improved ventilation parameters. Dabigatran etexilate was omitted and other medications were continued. She was discharged 10 days after admission. Warfarin was initiated and the follow-up was uneventful.

Discussion

Dabigatran etexilate has many advantages over oral vitamin K antagonists (VKA). It has constant bioabsorption and limited

individual variability, hence, it does not require monitoring.^{8,9)} Since it is not metabolized by cytochrome p450 enzyme, drug interactions are scarce.⁹⁾ Bleeding rate associated with dabigatran was not higher than VKAs in relevant trials.⁸⁾ However, bleeding with dabigatran is a considerable problem because there is no direct antidote or blood product to reverse the anticoagulant effect entirely. Another issue with dabigatran is the unavailability of monitoring for the anticoagulant effect. The thrombin clotting time is not useful for coagulopathy with dabigatran since it is highly sensitive. Ecarin clotting time is a sensitive test providing dose-dependent response; however, it is not yet approved for routine coagulation test and not approved by the FDA for monitoring of dabigatran etexilate.¹⁰⁾

There are a small number of case reports about hemopericardium associated with dabigatran use.^{6,7)} Our patient had been using dabigatran etexilate for 1 year before she suffered hemopericardium and cardiac tamponade. She also had acute renal failure on admission without pathologic evidence of the etiology. Acute renal failure was attributed to hypotension due to dehydration and hemodynamic compromise secondary to AF with rapid ventricular rate. Impaired hemodynamics triggered by hemopericardium and impaired renal perfusion might have caused acute renal failure; however, dabigatran overdose due to acute renal failure might have induced hemopericardium as well.

Patients receiving dabigatran treatment are exposed to increased bleeding risks secondary to dabigatran overdose in cases of renal failure since more than 80% of dabigatran etexilate is excreted via the renal pathway.⁸⁾ Detection of aPTT > 90 s and INR > 2 was shown to be associated with dabigatran overdose in several trials.^{11,12)} Dabigatran inhibits thrombin that helps conversion of fibrinogen to fibrin therefore it effects all routine coagulation tests to a certain extent. Since INR measures prothrombin time of the extrinsic coagulation cascade, therapeutic concentrations of dabigatran cause only mild elevation of INR levels. However, increased plasma levels of dabigatran exhibit a linear relationship with INR.¹²⁾ Epistaxis and elevated INR levels (8.8) were reported in a patient with chronic renal failure, receiving both hemodialysis and dabigatran treatment.¹³⁾ Similarly, our patient had elevated INR levels (4.8) on admission. Meanwhile, many other studies demonstrated insensitivity of aPTT and INR at therapeutic doses of dabigatran and found no linear relationship between.¹⁴⁾ Further studies are needed to investigate the relationship between INR and bleeding risk of dabigatran etexilate.

Dabigatran etexilate is a new oral anticoagulant with increasing use in daily practice. However, life-threatening bleeding complications are a concern to healthcare providers. INR elevation under dabigatran treatment might be associated with drug overdose. Further evidence is required to evaluate the relationship between INR and bleeding risk of dabigatran etexilate.

References

1. Wang TJ, Larson MG, Levy D, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;107:2920-5.
2. Boehringer Ingelheim Pharmaceuticals Inc. Pradaxa (dabigatran etexilate) package insert. Ridgefield, CT: Author; 2011.
3. Connolly SJ, Ezekowitz MD, Yusuf S, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51.
4. Lal Y, Van Heukelom J. Dabigatran: a cause of hematologic emergency. *Am J Med Sci* 2013;346:190-3.
5. Nyby S, Hennes O. Fatal bleeding diarrhoea during dabigatran etexilate therapy. *Ugeskr Laeger* 2014;176. pii: V09140482.
6. Dy EA, Shiltz DL. Hemopericardium and cardiac tamponade associated with dabigatran use. *Ann Pharmacother* 2012;46:e18.
7. Barton CA, McMillian WD, Raza SS, Keller RE. Hemopericardium in a patient treated with dabigatran etexilate. *Pharmacotherapy* 2012;32:e103-7.
8. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 2011;123:2363-72.
9. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. *Clin Pharmacokinet* 2008;47:285-95.
10. Kernan L, Ito S, Shirazi F, Boesen K. Fatal gastrointestinal hemorrhage after a single dose of dabigatran. *Clin Toxicol (Phila)* 2012;50:571-3.
11. Lindahl TL, Baghaei F, Blixter IF, et al; Expert Group on Coagulation of the External Quality Assurance in Laboratory Medicine in Sweden. Effects of the oral, direct thrombin inhibitor dabigatran on five common coagulation assays. *Thromb Haemost* 2011;105:371-8.
12. Douxfils J, Mullier F, Robert S, Chatelain C, Chatelain B, Dogné JM. Impact of dabigatran on a large panel of routine or specific coagulation assays. Laboratory recommendations for monitoring of dabigatran etexilate. *Thromb Haemost* 2012;107:985-97.
13. Kim J, Yadava M, An IC, et al. Coagulopathy and extremely elevated PT/INR after dabigatran etexilate use in a patient with end-stage renal disease. *Case Rep Med* 2013;2013:131395.
14. 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.