Massive Left Atrial Thrombi during Dabigatran Therapy for Nonvalvular Atrial Fibrillation

Velislava Bachvarova, PharmD, Claudia Bucci, BScPhm, PharmD, Natalie Ho, MD, Payam Yazdan-Ashoori, MD, and Christopher Morgan, MD, Newmarket and Toronto, Ontario, Canada

INTRODUCTION

Dabigatran is a direct thrombin inhibitor that binds to both free and clot-bound thrombin and is approved for use as an oral anticoagulant in patients with nonvalvular atrial fibrillation. Massive left atrial “ball thrombus” is a rare condition, described primarily in the setting of anatomic or functional obstruction to mitral inflow, and usually occurring in the absence of oral anticoagulation. We describe a case of massive left atrial ball thrombi occurring in a patient receiving dabigatran for atrial fibrillation who had neither left ventricular dysfunction nor mitral stenosis. Inadequate dosing of dabigatran, in combination with interruption of therapy, may have led to this complication.

CASE PRESENTATION

A 73-year-old woman presented with a several-month history of progressive shortness of breath and intermittent presyncope. Atrial fibrillation had first been diagnosed 9 years before admission, when she presented with a left hemispheric stroke. She was anticoagulated with warfarin (CHADS2 score 3), but 3 years before admission, dabigatran 150 mg twice daily was substituted. One year later, the dabigatran dose was reduced to 110 mg twice daily because of moderate renal impairment (creatinine clearance 45 mL/min) and patient concerns of bruising. In the 12 months before admission, anticoagulation had been temporarily discontinued on two separate occasions. The first was to permit minor hand surgery, and then, 3 months before presentation, the second interruption was for colonoscopy. The patient was off dabigatran for <1 week on each occasion, without the use of bridging anticoagulation. Routine transthoracic echocardiography performed 11 months before admission demonstrated a severely enlarged left atrium (left atrial volume index 53 mL/m²) but no evidence of left atrial thrombus (Figure 1A). Left ventricular function was normal, and there was no evidence of mitral stenosis. Concomitant medications included bisoprolol, diltiazem, atorvastatin, tolterodine, pantoprazole, and escitalopram. Full medication compliance was reported.

Figure 1 (A) Transthoracic apical four-chamber view (left) from echocardiography performed 11 months before admission showing left atrial enlargement but no filling defects in the left atrium (LA). (B) Transthoracic apical four-chamber view from admission echocardiography (right) showing two poorly defined filling defects in the LA (asterisk) (Supplemental Video 1). LV, Left ventricle; RA, right atrium; RV, right ventricle.

From the Southlake Regional Health Centre, Newmarket (V.B.); the Department of Pharmacy (C.B.) and the Department of Medicine (N.H., P.Y.-A., C.M.), Sunnybrook Health Sciences Centre; the Division of Cardiology, Schulich Heart Centre (N.H., P.Y.-A., C.M.); and the University of Toronto (C.B., N.H., P.Y.-A., C.M.), Toronto, Ontario, Canada.

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198
On initial examination the cardiac rhythm was atrial fibrillation. Auscultation revealed normal heart sounds with an intermittent soft low-pitched early diastolic sound at the apex. Immediate bedside transthoracic echocardiography was suspicious for a mobile left atrial mass (Figure 1B). Left ventricular function was visually normal, but there was inadequate endocardial definition for quantification of left ventricular ejection fraction. The mean mitral valve gradient was 2.5 mm Hg.

Transesophageal echocardiography confirmed the presence of two large ovoid masses within the enlarged left atrium. The masses appeared freely mobile within the left atrium and to have no apparent attachment to the atrial septum (Supplemental Video 2).

On admission, creatinine clearance was 47 mL/min. There was mild thrombocytopenia (platelet count 67 x 10^9/L) that was attributed to consumption. Because of the perceived urgency of proceeding to surgery, a formal evaluation for a hypercoagulable state was not performed. The patient underwent screening computed tomography of the thorax, abdomen, and pelvis showing no evidence of occult malignancy and no evidence of pulmonary emboli. Forty-eight hours after admission, the patient underwent cardiac surgery. The two left atrial masses were identified and removed, one of which had a string-like attachment to the atrial septum and the other of which was entirely free floating. Pathologic examination confirmed that these masses were organized thrombi (Figure 7). The posterior mitral leaflet appeared thin and macerated and was repaired by suture plication. The patient was discharged on warfarin. Postoperative transthoracic echocardiography confirmed that the previously imaged left atrial mass lesions were no longer present (Figure 8).

DISCUSSION

This case report is unique in that it describes the formation of two massive left atrial thrombi during dabigatran therapy in a patient with normal left ventricular systolic function and no evidence of mitral valve obstruction. There is a case report including two patients in whom "large" left atrial thrombi were associated with thromboembolism while on dabigatran therapy, but both had left ventricular dysfunction. There are two further reports of left atrial thrombus formation in patients without left ventricular dysfunction or mitral valve obstruction while on dabigatran treatment. In the first such case, a small left atrial thrombus developed during treatment with dabigatran 150 mg twice daily. The most recent report describes a patient in whom left atrial thrombus developed 5 months following initiation of treatment with dabigatran 110 mg twice daily. The left atrial thrombus resolved after treatment with a vitamin K antagonist and clopidogrel. In neither of these latter two cases was surgical removal of the left atrial thrombus required, and neither patient appeared to have symptoms related to mitral valve obstruction.

Dabigatran manifests predictable, linear pharmacodynamics with plasma levels influenced by age, sex, renal function, body weight, and few other drugs. Nonetheless there are fivefold differences in...
trough plasma levels of dabigatran in each of the 110 mg twice daily and 150 mg twice daily dosing regimens and an approximately 70% overlap in trough levels between the two doses. Dabigatran is eliminated mainly by the renal route, but dosage adjustment is not recommended for patients with creatinine clearance > 30 mL/min, for whom the recommended dose is 150 mg twice daily. The present case raises the question as to whether 110 mg twice daily dosing is adequate in patients with mild to moderate renal dysfunction. In this regard, the 110-mg twice daily dose has not been approved for use in the United States, although it has in Canada and Europe. Approval of the 110-mg twice daily dose in Canada and Europe was based on evidence from the Randomized Evaluation of Long Term Anticoagulant Therapy trial, as the 150-mg twice daily dose was associated with a trend toward increased risk for major bleeding and an increased risk for gastrointestinal, minor, and any bleeding. In contrast, the US Food and Drug Administration did not approve the 110-mg twice daily dose, because it was unable to find any subgroup of patients for whom the 110-mg dose improved the benefit-to-risk ratio. In our case, echocardiography, in particular transesophageal echocardiography, was essential to both diagnosis and management. The transesophageal echocardiographic images raised concerns for mitral valve obstruction and/or massive systemic embolism and led to a decision for early surgical intervention. It is possible that the brief interruptions of dabigatran therapy for medical procedures allowed the

Figure 5 Transesophageal biplane view of the left atrial appendage showing no definite evidence of left atrial appendage thrombus (Supplemental Video 5).

Figure 6 (A) Computed tomographic scan of the thorax showing a coronal view of the enlarged left atrium and two separate hypo-dense left atrial mass lesions. (B) Oblique three-dimensional reconstruction of computed tomographic transverse view of the thorax demonstrating the same pathology.
formation of left atrial thrombi that did not subsequently resolve despite the resumption of treatment, with potentially subtherapeutic dosing. There was no indirect evidence for the presence of an underlying hypercoagulable state in this case. The left atrium was substantially enlarged, likely the consequence of chronic atrial fibrillation and/or left ventricular diastolic dysfunction. In nonvalvular atrial fibrillation, 91% of left atrial thrombi are either confined to or have origins in the left atrial appendage. In our case, the left atrial appendage appeared to be free of thrombus. How such two massive left atrial thrombi formed without leading to systemic emboli before they were potentially too large to traverse the mitral orifice is unclear.

CONCLUSION

We postulate that the failure of anticoagulant therapy was due to inadequate dosing with the dabigatran 110-mg twice daily regimen despite moderate renal dysfunction, the earlier interruption of treatment for medical procedures, or both. This case underlines the potential consequences of inadequate dosing of dabigatran and the need for ongoing monitoring of patients on the low-dose regimen. The lack of readily available assays for in vivo anticoagulant activity of the direct-acting anticoagulant agents makes the detection of inadequate treatment problematic.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.case.2017.06.003.

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