

Spontaneous hemopericardium and cardiac tamponade induced by dabigatran in combination with p-glycoprotein inhibitor

Hemopericárdio espontâneo e tamponamento cardíaco induzidos por dabigatrana em combinação com inibidor da glicoproteína-p

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ABSTRACT – Direct oral anticoagulants have been presented as a novel option for prevention and treatment of nonvalvular atrial fibrillation. However, significant hemorrhagic side effects have been observed with the use of these medications in recent years. The use of dabigatran in combination with p-glycoprotein inhibitors have been discussed due to its interactive effects. We present the case of a 74-year old female who developed spontaneous hemopericardium and cardiac tamponade induced by dabigatran combined with a p-glycoprotein inhibitor.

Keywords: Cardiac tamponade/chemically induced; Pericardial effusion/chemically induced; Anticoagulants/adverse effects; Dabigatran; ATP-binding cassette, sub-family B, member 1

RESUMO – Os anticoagulantes orais diretos foram apresentados como nova opção para prevenção e tratamento de fibrilação atrial não valvar. Recentemente, foram observados efeitos colaterais hemorrágicos significativos com o uso desses medicamentos. O uso da dabigatrana em combinação com inibidores da glicoproteína-p foi discutido devido a seus efeitos interativos. Apresentamos o caso de uma paciente de 74 anos que desenvolveu hemopericárdio espontâneo e tamponamento cardíaco induzidos pela dabigatrana em combinação com inibidor da glicoproteína-p.

Descritores: Tamponamento cardíaco/induzido quimicamente; Derrame pericárdico/induzido quimicamente; Anticoagulantes/efeitos adversos; Dabigatrana; Membro 1 da subfamília B de cassetes de ligação de ATP

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INTRODUCTION

In the last 50 years, vitamin K antagonists (VKAs) such as warfarin have been the only option for anticoagulation; but nowadays direct oral anticoagulants (DOACs) have become an alternative in patients with nonvalvular atrial fibrillation (AF). According to the Framingham Heart Study, the nonvalvular AF accounts for 14% cases of stroke in men and 16% in women.¹ Anticoagulation is recommended for the prevention of stroke in patients with moderate to high risk (CHA₂DS₂-VASc score 2 or more).

The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy Trial) demonstrated that nonvalvular AF patients over 65 years, treated with dabigatran 150mg twice a day, showed a lower incidence of ischemic and hemorrhagic stroke as compared to those on warfarin. It was also more efficacious than rivaroxaban 20mg once a day, and apixaban 5mg twice a day.² Nonetheless, the clinician must consider the limitations of an indirect comparison (i.e., differences in study cohorts and trial design) when comparing efficacy and cost-effectiveness of these agents.

Dabigatran is a competitive and reversible direct inhibitor of thrombin, which prevents conversion of fibrinogen into fibrin.² The use of dabigatran has been associated with gastrointestinal adverse effects, such as dyspepsia and, in more severe cases,



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gastrointestinal bleeding.^{3,4} In the last years, a greater association of hemopericardium has been observed as an adverse effect of DOACs.⁵⁻⁷

As a rare complication, we described a patient who developed hemopericardium with dabigatran in combination with verapamil, a p-glycoprotein inhibitor, as well as the rapid reversal of its anticoagulant effect with the antidote idarucizumab.

CASE REPORT

We present a case of a 74-year-old female patient from Mexico, with a history of type 2 diabetes mellitus, hypertension stage 2 (Eighth Joint National Committee – JNC 8) and a 3-year evolution nonvalvular AF. Clinical background of several episodes of thrombosis under anticoagulation therapy, with rivaroxaban 15mg once a day, to which she presented left upper extremity arterial thrombosis (Figure 1) and, with a dose of 20mg daily, she developed ischemic stroke without neurologic sequelae. Anticoagulation therapy was adjusted to dabigatran 150mg twice daily and aspirin 100mg a day. Management for heart rate control with bisoprolol 5mg, verapamil 90mg daily and flecainide 100mg a day.

Four weeks later, she presented 24-hour evolution progressive dyspnea, fatigue, generalized weakness and diaphoresis. In the emergency department, the vital signs were blood pressure 70/40mmHg, heart rate 98bpm, electrocardiogram (EKG) in atrial fibrillation rhythm, oxygen saturation 95%, with clinical evidence of cardiac tamponade, jugular venous distention and peripheral edema. Trans-thoracic echocardiogram revealed global pericardial effusion >300mL, quantified by ultrasound (Figure 2), tricuspid annular plane systolic excursion (TAPSE) 19mm, vena cava 21mm, inspiratory collapse <50%, CHAD₂DS₂-VASC

score of 8 and HAS-BLED of 5. Upon admission, laboratory tests showed prolonged clotting time, and impaired renal function as compared to previous results 2 months before (Table 1).

Due to hemodynamic compromise, two doses of idarucizumab 2.5g were administered, the first in rapid infusion, and the second, 5 minutes later, to reverse the anticoagulant effects of dabigatran. Subsequently, urgent subxiphoid pericardiocentesis guided by echocardiography and fluoroscopy was performed, draining 600mL of hematic content, with an immediate improvement of hemodynamic status. Two hours after procedure the blood pressure rise 90×50mmHg, and heart rate dropped to 70bpm. Pigtail catheter was placed in the pericardial sac for continuous drainage. The accumulated pericardial fluid in 24 hours was of 800mL. Culture of pericardial fluid showed no growth of microorganisms, and Gram stain revealed no leukocytes

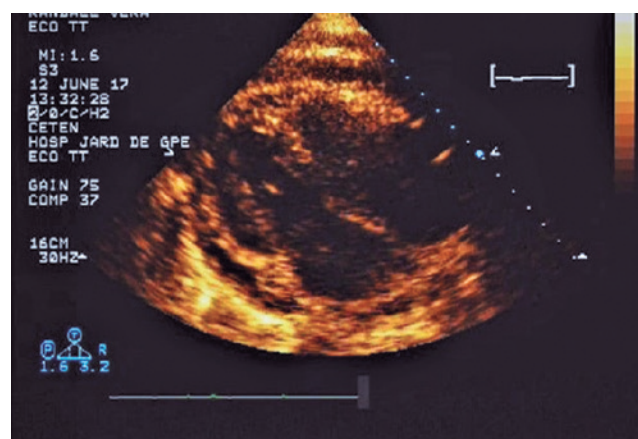


Figure 2. Global pericardial effusion observed by echocardiogram.

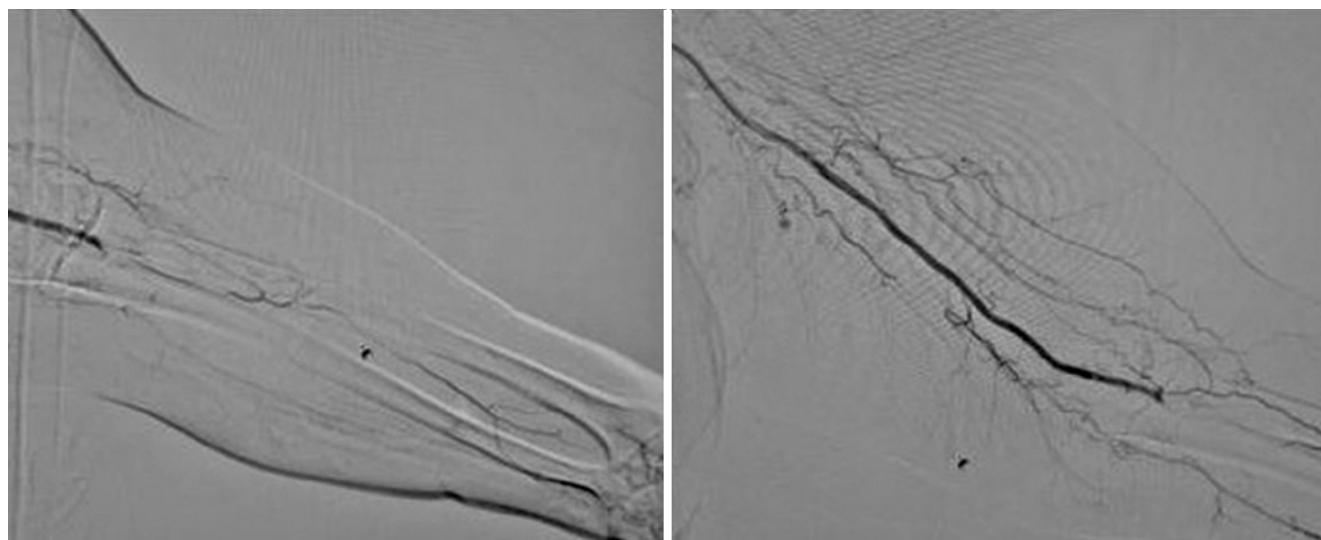


Figure 1. Radial-ulnar arterial occlusion.

Table 1. Laboratory results

	2 month before admission	Upon admission	72 hours later
White blood count, thousands/uL	7.7	4.2	5.6
Hemoglobin, g/dL	14.8	9.0	9.8
Hematocrit, %	45.1	32.3	33.4
Platelets, thousands/uL	291	183	189
Urea, mg/dL	29.0	52.2	22.5
Creatinine, mg/dL	0.7	1.2	0.6
Creatinine clearance, mL/minutes	89	52	104
Sodium, mmol/L	143	138	140
Potassium, mmol/L	4.5	5.3	4.1
Calcium, mg/dL	8.9	9.3	9.1
Magnesium, mg/dL	1.5	1.5	1.6
PTTa, seconds	28.5	120.9	63.6
PTT, seconds	30.30	18.60	13.90
INR	2.20	1.48	1.11

PTTa: activated partial thromboplastin time; PTT: partial thromboplastin time; INR: International Normalized Ratio.

or bacteria. In direct smear microscopy, acid-fast bacilli (BAAR) were not observed, and cultures performed 72 hours after were negative. In cytological examination, no squamous epithelial cells were found, with observation of more than 100 erythrocytes per field. The pericardial drainage was removed when no flow was observed, and there was no evidence of pericardial effusion by echocardiography. Seventy-two hours later, coagulation time and renal function improved.

She was discharged 8 days after hospitalization with no complications. We decided the next therapeutic option would be acenocumarol 2mg daily. After 10 days, with an INR 1.7, the treatment was adjusted to maintain INR levels between 2.5 and 3.0. Three months later, it was still difficult to maintain the INR levels between 2.5 and 3. It was not possible to stabilize the patient, since she also showed lability with VKA.

DISCUSSION

Dabigatran is a DOAC approved by the Food and Drug Administration (FDA) in 2010, indicated to reduce risk of stroke and systemic embolism in patients with nonvalvular AF. The recommended dose of 150mg orally, twice daily in patients with creatinine clearance (CrCl) >30mL/min.⁸ DOACs have greater advantages compared to warfarin, being as effective as warfarin in the management of anticoagulation. Dabigatran 150mg twice daily has a lower incidence of ischemic and hemorrhagic stroke compared to warfarin, according to RE-LY study. The major limitations in using warfarin are slow onset of action, a narrow therapeutic index, numerous drug-food interactions, variable pharmacokinetics, and the need for monitoring for therapeutic INR. In addition, the lack of an antidote was a di-

sadvantage of DOACs against warfarin; however, this has changed with the FDA approval of idarucizumab for dabigatran, in 2015, and of andexanet alfa, for apixaban and rivaroxaban in 2018.⁹

Dabigatran undergoes little hepatic metabolism and does not affect CYP450 activity; hence, there are few drug interactions.¹⁰ In recent years, hemopericardium has been associated with adverse effects of the DOACs. The first case of hemopericardium by dabigatran was reported in 2012,⁵ and since then, seven more cases were reported regarding use of dabigatran¹⁰⁻¹⁵ as well by apixaban⁶ and rivaroxaban.⁷

The absorption of the pro-drug dabigatran is mediated by p-glycoprotein. Therefore, it has been observed that p-glycoprotein inhibitors can ultimately increase the area under the curve (AUC) and the maximum concentration (Cmax) of the active drug. Currently, the FDA recommends reducing the dose of dabigatran to 75mg twice a day, when co-administered with p-glycoprotein inhibitors in patients with moderate renal dysfunction (CrCl 30-50mL/minute) or avoid the medication.⁸

Several cases of hemopericardium by dabigatran have been reported, but not in combined use of dabigatran and p-glycoprotein inhibitors.^{5,11-14} The first case report of hemopericardium by dabigatran in combination with p-glycoprotein inhibitors with a previously documented normal renal function was described by Kizilirmak et al.¹⁰ The case reported a 66-year old patient who developed hemopericardium under management with dabigatran 150mg twice daily and verapamil, and 1 year before the creatinine clearance was 136mL/minute. Song et al. reported a case of an 84 year-old patient who developed hemopericardium by dabigatran in combination with p-glycoprotein modulators, with a prior 10-day creatinine 0.7mg/dL.¹⁵

Our case, with verapamil 90mg plus dabigatran 150mg twice daily, and a normal renal function with previously documented CrCl 89mL/minute, the patient developed spontaneous hemopericardium with cardiac tamponade, 4 weeks after initiating dabigatran. It has been observed that by co-administering verapamil, the AUC and Cmax of dabigatran increases, and that administering dabigatran 2 hours before verapamil eliminates this interaction impact. However, there is not enough evidence to make this definitive conclusion.⁸ In addition, in the RE-LY study no significant changes were found in the levels of dabigatran of patients who were also administered verapamil.²

Since this is the second case report of hemopericardium by dabigatran in combination with p-glycoprotein inhibitors, in patients with a previously documented normal renal function, we believe further studies emphasizing the adverse effects of the combination of these groups are necessary. The reason is even in patients with normal renal function, important hemorrhagic side effects are observed, such as hemopericardium, which calls into question the safety of the drug and its high interactions with p-glycoprotein inhibitors. Furthermore, the doses of dabigatran in combination with p-glycoprotein inhibitors should be standardized.

SOURCE OF FINANCING

None

CONFLICT OF INTEREST

The authors declare there are no conflicts of interest.

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