Case Reports

Plasma Exchange for Urgent Apixaban Reversal

in a Case of Hemorrhagic Tamponade after Pacemaker Implantation

Wilson W. Lam, MD
Meredith A. Reyes, MD
John J. Seger, MD

We report the case of an 82-year-old man in whom hemorrhagic pericardial effusion occurred one week after pacemaker implantation, while he was taking apixaban. Few therapies exist for reversing the anti-Xa effect of apixaban. To reverse anticoagulation, our patient underwent plasma exchange, which facilitated pericardiocentesis and prevented possible surgical intervention. To our knowledge, this is the first report of the use of plasmapheresis to reverse the anticoagulant effect of apixaban. ***(Tex Heart Inst J 2015;42(4):377-80)***

Key words: *Anticoagulants/administration & dosage/adverse effects/antagonists & inhibitors/therapeutic use; apixaban; atrial fibrillation/complications/drug therapy; factor Xa inhibitors; pacemaker, artificial/adverse effects; plasma exchange; risk factors; stroke/prevention & control; treatment outcome; warfarin/therapeutic use*

From: *Department of Cardiology (Drs. Lam and Seger), Texas Heart Institute; Section of Cardiology, Department of Internal Medicine, (Drs. Lam and Seger), Baylor College of Medicine; Department of Pathology, CHI St. Luke's Health–Baylor St. Luke's Medical Center (Dr. Reyes); and Department of Pathology (Dr. Reyes), Baylor College of Medicine; Houston, Texas 77030*

Dr. Seger serves on the speakers bureau (receives honoraria) for Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, and Johnson & Johnson.

Address for reprints: *Wilson W. Lam, MD, 6621 Fannin St., MC 19345-C, Houston, TX 77030*

E-mail: *wlam@bcm.edu*

Apixaban is a novel oral anticoagulant (NOAC) that is used to prevent stroke in patients who have nonvalvular atrial fibrillation (AF). This drug has predictable therapeutic levels that do not require laboratory monitoring; however, there is no specific antidote to reverse its toxicity.[1,2] We present a case of hemorrhagic pericarditis and cardiac tamponade after pacemaker implantation in a patient who was taking apixaban because of AF. Novel therapy and subsequent treatment are discussed.

Case Report

An 82-year-old man with sick sinus syndrome and paroxysmal AF presented at our catheterization laboratory from the clinic, with near-syncope and bradycardia ($CHADS_2$ score, 2 of 6). On 24-hour Holter monitoring, the predominant result was sinus rhythm. An echocardiogram revealed a normal left ventricular ejection fraction (>0.60), grade II (pseudonormal) diastolic dysfunction, no significant valvular regurgitation, and normal pulmonary artery pressures. A dual-chamber permanent pacemaker was implanted to treat the patient's brady-tachy syndrome and because ventricular pacing revealed pacemaker syndrome (hypotension that results from ventricular pacing due to the absence of the atrial kick that normally increases stroke volume during atrioventricular synchrony). During the procedure, the atrial lead was repositioned. One day postoperatively, the patient was discharged from the hospital after undergoing chest radiography (with normal findings), device interrogation, and incision evaluation. Because of his stroke risk, he was prescribed apixaban (5 mg twice/d) at discharge. He had normal renal function (Table I) and a body weight of 172 lb.

During the week after pacemaker implantation, the patient developed fatigue, a low-grade fever (99.2 °F), nausea, moderate pleuritic chest pain, and a productive cough with clear sputum. He was readmitted to the hospital. His blood pressure had decreased from 130/77 mmHg after pacemaker implantation to 100/68 mmHg upon readmission, when he was taking no antihypertensive medications. Physical examination revealed an irregular, tachycardic rhythm (100–130 beats/min), and distended neck veins; auscultation yielded diminished bibasilar breath sounds but no quiet heart sounds. Laboratory data revealed acute kidney injury (Table I) and a substantially elevated erythrocyte sedimentation rate and fibrinogen level. The patient's platelet count and coagulation times were normal; his hemoglobin level had decreased from 15 g/dL after pacemaker implantation to 12 g/dL on readmission. He was taken to the cardiac intensive care unit, where he remained hemodynamically stable.

Computed axial tomograms (CT) of the chest (Fig. 1) were not conclusive for right ventricular free-wall perforation, although a moderate-to-large circumferential pericardial effusion of 1.7 cm was detected; its Hounsfield density suggested the presence of

TABLE I. Postoperative Laboratory Values

Variable	Day of Discharge	Day of Readmission	Time after Apixaban Discontinuation[a]			
			12 hr	23 hr	31 hr	46 hr
Creatinine (mg/dL)	1.1	1.6	—	—	—	—
Hemoglobin (g/dL)	15	12	—	—	—	—
eGFR (mL/min/1.73 m^2)	65	43	—	—	—	—
Anti-Xa: UFH (IU/mL)[b]	—	—	0.89	0.76	0.22	0.07
Anti-Xa: LMWH (IU/mL)[c]	—	—	—	0.84	0.35	—

eGFR = estimated glomerular filtration rate; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin

[a]Plasma exchange was performed from hours 29 through 31 after apixaban discontinuation, to rapidly reduce the factor Xa effect.
[b]Normal range, 0.3–0.7 IU/mL
[c]Normal range, 0.6–2.0 IU/mL

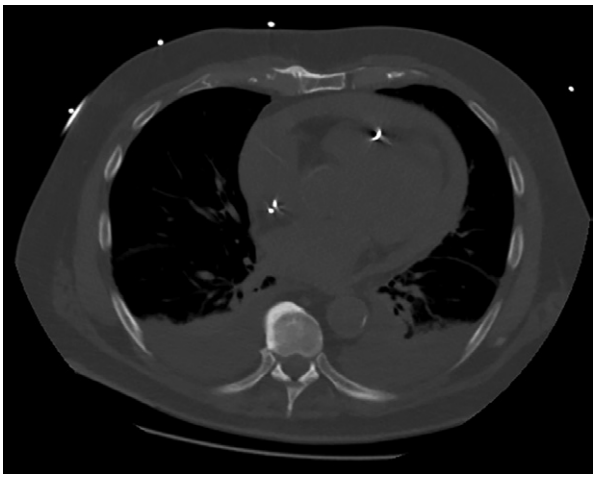

Fig. 1 *Computed axial tomogram shows pericardial effusion, a pacemaker lead, and bilateral pleural effusions.*

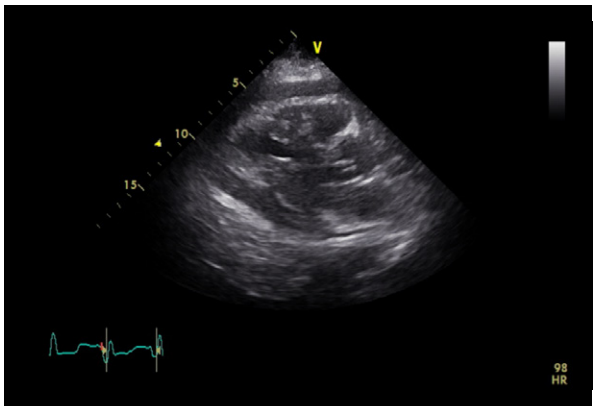

Fig. 2 *Echocardiogram shows cardiac tamponade and a moderate-to-large circumferential pericardial effusion with right ventricular diastolic collapse.*

blood. An echocardiogram confirmed the effusion (Fig. 2) and showed a dilated inferior vena cava, substantial mitral inflow variation (despite the presence of AF), and right ventricular diastolic collapse that suggested cardiac tamponade. Although the CT results could not rule out right ventricular lead perforation, device interrogation showed no alterations in device sensing, pacing threshold, or impedance of either the atrial or the ventricular lead. Therefore, we determined that we should use a conservative lead-management strategy without manipulation.[3]

Apixaban had been discontinued just before the readmission; however, the patient's anti-Xa level—measured by means of an assay calibrated for unfractionated heparin (UFH)—remained elevated 12 and 23 hours after his last apixaban ingestion (Table I). The anti-Xa level calibrated for low-molecular-weight heparin (LMWH) was also elevated 23 hours after ingestion. The patient's hemodynamic status remained stable, and this allowed time for evaluation. The chief treatment options were either pericardiocentesis with or without percutaneous lead repositioning, or surgical pericardial window with or without lead extraction. Surgery would necessitate the reversal of anticoagulation. The patient, a retired physician, preferred the least invasive approach and the fewest interventions. We acknowledged his urgent need for intervention and possible surgery but opted to reverse anticoagulation first, because of his wishes and the need to maintain hemodynamic stability. The patient declined prothrombin complex concentrate (PCC) because of his sedentary state and the thrombotic risk. After he gave his informed consent, he had a catheter placed by means of general surgery at the bedside, followed by a 2-hour course of plasma exchange with 3 L of fresh frozen plasma with calcium replacement—approximately a one-plasma-volume exchange. Immediately after apheresis, the anti-Xa levels were 0.22 and 0.35 IU/mL by means of UFH and LMWH assays, respectively (Table I and Fig. 3). The anti-Xa (LMWH) level of the plasma waste was 0.82 IU/mL, which was close to the patient's pre-apheresis value.

The patient underwent pericardiocentesis to remove 500 mL of bloody fluid. A pericardial drain was placed and was removed the next morning, after echocardiograms showed no pericardial effusion. The lead parameters were stable, and neither surgery nor lead repositioning was necessary. The patient's hemoglobin level remained stable, and the anti-Xa (UFH) level decreased to 0.07 IU/mL.

The patient was discharged from the hospital without further anticoagulation. Follow-up laboratory data showed normalization of his erythrocyte sedimentation rate and creatinine level. One month after the pericardial effusion had resolved, the patient was treated with warfarin, to reduce his stroke risk from AF. At his follow-up evaluation one year after conservative management of the pacing leads, his device settings remained stable. He had experienced no recurrence of symptoms or reaccumulation of pericardial effusion.

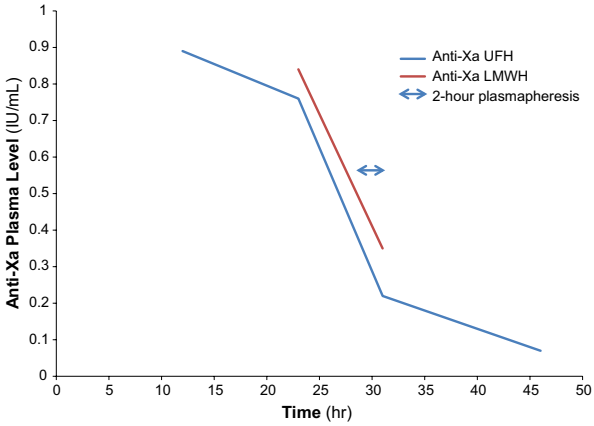

Fig. 3 *Graph shows anti-Xa plasma levels by time, before and after plasma exchange.*

LMWH = low-molecular-weight heparin; UFH = unfractionated heparin

Discussion

Novel oral anticoagulants include anti-Xa inhibitors such as apixaban that are used clinically in nonvalvular AF and deep vein thrombosis.[4] Apixaban has been shown to be superior to warfarin in reducing stroke, death, and major bleeding. In addition, cost-effectiveness analyses suggest that NOAC use might be advantageous, depending on factors such as the cost of the drug, the cost of warfarin monitoring, and time in the therapeutic range.[5]

A disadvantage of NOACs is the lack of a specific antidote; in contrast, warfarin is a vitamin K antagonist and can be reversed with use of fresh frozen plasma or PCC. Some organizations recognize this lack of a reliable agent for NOACs' reversal and have proposals, rather than recommendations, for counteracting their potential to cause life-threatening and non-life-threatening bleeding.[6] The cessation of anticoagulation is paramount, and pharmacokinetic data suggest that the elimination half-life in healthy persons is approximately 12 hours.[7] In our patient, acute impairment of renal function during tamponade diminished the drug clearance. Recommendations for decreasing apixaban dosage to 2.5 mg twice daily include 2 of these 3 factors: age, >80 yr; body weight, <60 kg; and creatinine level, >1.5 mg/dL. Age and worsening renal function eventually qualified our patient for reduced dosing, although this could not have been anticipated at the time of initial prescription.

Activated charcoal can be used for gastrointestinal binding of the anticoagulant but has a short effective time after ingestion, because after 6 hours the drug is already absorbed.[8] Factor eight inhibitor bypassing activity (FEIBA), PCC, and activated factor VII are all recommended by the Working Group on Perioperative Haemostasis and the European Heart Rhythm Association.[6,9] Recent reviews suggest that PCC is safe, with less than a 1% risk of thrombotic events.[10] Dabigatran is the only NOAC with a recommendation for removal by means of hemodialysis. Because the plasma protein binding of apixaban is 87%,[11] we considered plasma exchange to be a reasonable method for rapidly eliminating this drug, although no prior published reports supported this notion. Of note, rivaroxaban has 95% plasma protein binding, so it should have a comparable effect in elimination if apixaban can be eliminated in this way. A recombinant protein (r-Antidote, PRT064445) has been found to reverse anticoagulant effects in various animal models and might also be a useful agent in the future.[12]

Although few data exist regarding the therapeutic and toxic ranges of apixaban, its anti-Xa effect has been evaluated in small studies. Initial chromogenic anti-Xa levels had a direct correlation with the results of LMWH assays.[13] Subsequently, in a French study, 3 different anti-Xa assays had a direct correlation with apixaban concentration, whereas prothrombin time and activated partial thromboplastin time did not.[14] Last, results of a Chinese study showed that anti-Xa activity and plasma levels of apixaban were linearly correlated.[15] Hence, our monitoring of anti-Xa levels before and after plasma exchange appears to be valid, even though plasma and waste-plasma drug levels before and after exchange were unavailable.

Finally, in regard to healthcare costs and the risks of invasive procedures, plasmapheresis includes risks associated with placing a dialysis catheter in an anticoagulated patient. Other concerns are procedural hypotension, hypocalcemia from citrate use, and exposure to blood products. Adverse reactions are higher when plasma is used rather than albumin (risk rate, 20% vs 1.4%) as volume replacement, and hypocalcemic symptoms are

lower with calcium administration than without it (1% vs 9.1%). Major sequelae such as cardiovascular events (prevalence, 0.2%), respiratory events (0.2%), anaphylactic reactions (0.25%), and death (0.05%) are rare.[16]

Unlike previous investigators who have examined complications of therapeutic plasma exchange, we have shown that a single course of approximately one plasma volume was sufficient to reverse the anti-Xa effect. In contrast, most plasmapheresis therapies require multiple procedures. In addition, the cost of our therapy of plasmapheresis to hospitals and payors generally appears to be less than that of immunoglobulin therapy.[17] Therefore, even after a recombinant antidote for Xa inhibitors is approved for clinical use, plasmapheresis might still be a less expensive option. We think that this first reported case of successful plasmapheresis for apixaban toxicity warrants the initiation of multicenter registries to evaluate plasmapheresis as a reversal therapy for life-threatening NOAC-induced bleeding.

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