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The Use of Ranolazine in the Management of Recurrent Atrial Fibrillation After Percutaneous Radiofrequency Ablation

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Abstract

Long-term medical treatment options for atrial fibrillation (AF) include rate-control as well as rhythm-control therapy with various antiarrhythmics. However, because of the limited efficacy and potential side effects of these medications, percutaneous and surgical ablations in AF patients have evolved as alternative or additional approaches to achieve rhythm-control. Nonetheless, arrhythmia recurrences may also occur after these procedures. Thus, the search for complementary treatment options continues. Ranolazine possesses antiarrhythmic effects in atrial myocytes via blockade of sodium channels. These properties facilitate AF suppression in animal models and human subjects. We report a patient with persistent AF that was refractory to medical management and percutaneous catheter ablation. She has remained in sinus rhythm for at least 18 months after the initiation of ranolazine.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice. Multiple therapeutic approaches exist for the management of AF, including strategies for "rate-control" and "rhythm-control" .[1-5] Increasingly, catheter ablation is utilized, particularly for those patients with highly symptomatic AF refractory to or intolerant of antiarrhythmic therapy.[6] However, ablation therapy is also limited by recurrent arrhythmias in 10-40%, necessitating repeat ablation or continued antiarrhythmic medications.[6, 7] Ranolazine, an atrial-selective, sodium-channel blocker approved by the Food and Drug Administration for its antianginal properties, has clinical effects that are useful for the suppression of AF.[8-17] We report a case of a patient with persistent AF who failed traditional antiarrhythmic medications and radiofrequency ablation (RFA). However, after initiation of ranolazine, she has remained in sinus rhythm for at least 18 months without additional rhythm-control interventions.

Case Report

A 60 year-old woman with a history of hypertension, non-obstructive coronary artery disease, and symptomatic persistent atrial fibrillation of five

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year's duration was initially treated with a rate-control strategy. However, despite adequate heart rate control she continued to experience significant palpitations, fatigue, light headedness, and diminished exercise tolerance. She underwent direct-current cardioversion (DCCV) three times in January and February of 2009 for recurrent persistent AF. After each cardioversion she reported feeling much better with an improvement in exercise tolerance. After her second DCCV in February 2009, sotalol was initiated in an inpatient setting and titrated to 160 mg orally twice daily with a QT-corrected (QTc) interval of approximately 470 milliseconds (ms). Class 1C antiarrhythmics were avoided due to her hypertension and known non-obstructive coronary artery disease. The patient's left atrium was dilated (4.9 cm) and the left ventricle was normal in size (including thickness) and function. The patient remained in sinus rhythm for ten days and completed an uneventful one week outpatient cardiac rhythm monitoring. At a one month follow-up visit, she described pre-syncope and then, during an outpatient evaluation in her cardiologist's office, she experienced cardiac arrest secondary to torsades de pointes. She was successfully defibrillated and sotalol was discontinued.

She was ultimately referred for percutaneous RFA and underwent uncomplicated pulmonary vein isolation in May 2009. After ablation she was maintained on diltiazem 360 mg orally once daily and warfarin. Calcium channel blocker therapy with diltiazem was used for atrioventricular nodal rate-control because of a history of symptomatic asthma on beta-blocker therapy. However, after two weeks she reverted to symptomatic, persistent AF requiring DCCV. AF recurred again two weeks later. The heart rate was well controlled and a repeat ablation was planned if AF persisted at three months after the initial ablation.

While awaiting repeat RFA, she was cardioverted again and started on ranolazine 1000 mg orally twice daily in addition to diltiazem and warfarin. Symptoms improved and follow up ECG demonstrated sinus bradycardia with QTc interval of 450 ms. Twenty-one day rhythm monitoring revealed sinus rhythm throughout with no significant arrhythmia. Given the improvement in symptoms and the success of her oral pharmacologic regimen, she decided not to undergo repeat ablation. She has continued on diltiazem and ranolazine (now decreased to 500 mg orally twice daily due to intermittent dizziness on the higher dose). Her QTc interval at follow-up remains 440-480 ms. Serial outpatient cardiac rhythm monitoring showed no significant arrhythmia and she continues to be free of symptoms and AF.

Discussion

This report documents the long-term maintenance of sinus rhythm using ranolazine as adjunctive therapy in a patient with recurrent AF after catheter ablation. It is likely that pulmonary vein isolation contributed to the favorable outcome. However, she continued to manifest AF requiring repeat DCCV three months after the initial RFA.

Ranolazine was initially studied for its antianginal effects,[18-20] and as an adjunct to medical therapy for acute coronary syndromes.[21] Interestingly, subgroup analysis revealed significant reductions in episodes of non-sustained ventricular tachycardia, supraventricular tachycardia, and new-onset atrial fibrillation.[22] Increasingly, ranolazine is being investigated as a relatively atrial-specific antiarrhythmic.[8-17] Ranolazine blocks a number of cardiac ion channels including early INa, late INa, IKr, and late ICa.[9, 10] Experimental data demonstrated inhibition of sodium-channel activity in canine pulmonary vein sleeves by ranolazine, which suggests it may be useful in suppressing AF triggers that arise from the pulmonary veins.[12, 23] Importantly, ranolazine is atrial-selective and has little effect in the ventricle at clinical concentrations.[10] Despite IKr blockade and minimal QT prolongation, torsades de pointes has not been reported with ranolazine. This makes ranolazine an attractive choice for management of atrial tachyarrhythmias.

Several observational studies suggest that ranolazine may herald a safe and well-tolerated option in the medical management of AF.[12-17, 22] Ranolazine has been studied in a variety of clinical scenarios including paroxysmal, persistent and post-operative AF. A small case series focused on a variety of patients with AF, all refractory to medical therapy, some refractory to ablation. Of the seven subjects studied, four had long term maintenance

of sinus rhythm on ranolazine, ranging from a follow-up period of 12 to 42 weeks. However, the two subjects who had experienced recurrent AF after RFA did not derive any significant long-term antiarrhythmic benefit from ranolazine.[16]

Another study explored the use of ranolazine as a "pill-in-the-pocket" treatment for paroxysmal AF. Thirty-five subjects with episodes of new onset or paroxysmal AF lasting 3-48 hours were administered a large dose of ranolazine (2000 mg); approximately 70% patients converted to sinus rhythm within 6-8 hours.[17]

Not dissimilar from the case reported herein, another case of multidrug resistant AF responsive to ranolazine has been reported.[24] However, unlike the case reported here, ablation had not been utilized. Most recently, a retrospective analysis of 393 patients undergoing coronary artery bypass grafting examined the relative efficacy of amiodarone and ranolazine. The group treated with ranolazine had significantly less post-operative AF than the amiodarone group (17.5% versus 26.5%).[15]

Although the antiarrhythmic effects of ranolazine have never been studied in a large, prospective cohort of patients, data from the antianginal studies compiled in an open-label fashion demonstrate the safety of ranolazine in patients with cardiac comorbidities, and a relatively benign side effect profile, mainly consisting of dizziness and constipation.[22]

With regard to QT prolongation, ranolazine has been found to have relatively small effects on the QTc interval, prolonging it by anywhere from approximately 2-9 ms.[19, 20, 25] Data from population-based analyses including approximately 2700 patients treated with ranolazine show a linear relationship between the QTc interval and the plasma concentrations of ranolazine, translating into an average increase in QTc of approximately 2 to 5 ms for the dose range of 500 to 1000 mg orally twice daily.[20, 25] The absence of significant QT prolongation and minimal risk of torsades de pointes with ranolazine was important in our patient due to her history of long QT-induced torsades de pointes when treated with sotalol.

Building on the results of studies demonstrating the antiarrhythmic effects of ranolazine in the management of AF, our case illustrates an exciting opportunity for further investigation. Not only does ranolazine stand to become an important player in rhythm-control of patients with new onset or uncomplicated paroxysmal AF, but it has potential in the maintenance of sinus rhythm even in challenging and complex cases of AF patients who recur despite catheter ablation. Nonetheless, the scientific evidence for the use of this atrial-selective, multiple ion-channel inhibitor is derived from in-vitro studies and limited clinical series, generally with small numbers of subjects. Large trials for ranolazine have only been designed to study its antianginal properties and little is known about its long term safety. Further investigation with randomized clinical trials and extended follow up should be undertaken to establish the safety and efficacy of ranolazine as an antiarrhythmic.

Disclosures

- Dr. Reiffel: Consultant for Gilead Pharmaceuticals
- Steering Committee and national PI for the HARMONY trial (ranolazine plus dronedarone for AF).

Conclusions

This case report describes the successful use of ranolazine in a patient with recurrent AF despite percutaneous catheter ablation. Ranolazine possesses potential for use as a rhythm-control agent in the management of AF. Further study with randomized clinical trials is required to evaluate both the safety and efficacy of ranolazine for the treatment of AF.

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