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Case Report

Refractory atrial fibrillation effectively treated with ranolazine

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ABSTRACT

Atrial fibrillation is the most common sustained cardiac arrhythmia which is often troublesome to manage. Currently, rhythm and rate control medications are the mainstays of therapy. In 2 amiodarone-refractory highly symptomatic patients, an innovative approach using ranolazine, which selectively acts on Na+ channels and delays atrial depolarization, was tried successfully.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia characterized by abnormal automatic firing and the presence of multiple interacting re-entry circuits looping around the atria, with consequent deterioration of mechanical function. Episodes of atrial fibrillation are often initiated by rapid bursts of ectopic beats arising from muscle sleeves tissue in the pulmonary veins or from diseased atrial tissue.[1]

Currently, rhythm and rate control medications are the mainstays of therapy, with oral anticoagulation (OAC) therapy for the prevention of stroke. For rhythm control, amiodarone is the most potent drug available. In amiodarone-refractory highly symptomatic patients, innovative approaches are needed. In this context we tried ranolazine, actually by serendipity in the first patient. Ranolazine is an anti-anginal agent, which inhibits normal and abnormal late Na+ Channel current in the ventricle and peak Na+ channel current in the atrium thus delaying atrial depolarization and reducing the rate of myocardial contraction.[2,3]

2. Case report

2.1. *Case 1*

A 60-year-old mildly hypertensive physician had been diagnosed with hypertrophic non-obstructive apical cardiomyopathy in 2004. He developed the first episode of AF in April 2011, which lasted for 6 h. He continued to have paroxysmal AF at a frequency of 3 episodes a month, with each paroxysm lasting 6–7 h. Apart from rapid palpitations (ventricular rate @ 130/min), he used to experience uneasiness, exhaustion, occasional dizziness and exertional left arm pain. Drugs like

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amiodarone and beta-blockers failed to reduce the episodes of AF. He would take additional propranolol during the episodes. A coronary angiogram was performed and was found to be normal. With a suspicion of microvascular angina, ranolazine was advised. He started taking ranolazine 500 mg twice a day from July 2012. Amazingly, since then he has had no episodes of paroxysmal AF in the last 12 months.

2.2. *Case 2*

A 50-year-old hypertensive, obese and diabetic lady presented with a history of dyspnea on exertion and occasional chest pain in September 2012. Her routine biochemistry, hematology, ECG and Echocardiogram, in August 2012 had been normal. She had been on glimepiride and metformin for the last 2 years, with good sugar control. In addition, she was taking ramipril and atorvastatin. She started experiencing dyspnea on routine activities like speaking and walking so she underwent a re-evaluation in November 2012. The echocardiogram now revealed moderate pulmonary hypertension (systolic pulmonary artery pressure 52 mmHg). A CT pulmonary angiogram was done to rule out pulmonary embolism; it was normal. Torsemide was added. The chest X-ray showed no pleural effusion.

Two weeks later she complained of giddiness followed by altered sensorium for 3–5 min. She developed left-sided hemiparesis; the upper limb recovered within a few minutes but left lower limb paresis persisted. The ECG showed AF with ventricular rate of 120/min. The echocardiogram did not show a thrombus. The MRI of the brain was normal. She was treated with Low Molecular Weight Heparin and dabigatran was instituted. The left lower limb weakness resolved after 6 h. A sleep study revealed obstructive sleep apnea.

She was given a loading dose of amiodarone for 2 weeks followed by a maintenance dose of 400 mg/day. Verapamil was concurrently administered. After 6 weeks electrical cardioversion was attempted. Despite repeated synchronized shocks, even using 2 defibrillators simultaneously with 200 J biphasic shocks each, sinus rhythm could not be restored, even transiently. She was started on ranolazine 500 mg twice daily. Sinus rhythm spontaneously returned within a week of starting this treatment and she has had no recurrence of AF since then. At 6 months follow up, she was asymptomatic and the echocardiogram was normal.

3. Discussion

AF accounts for approximately one third of hospitalizations for cardiac rhythm disturbances.[4] Data from one of the largest epidemiological studies confirm that AF has a large population prevalence and incidence.[5] It is estimated that life-time risks for development of AF are 1 in 4 for men and women 40 years of age and older.[6] During the past 20 years, hospital admissions for AF have increased by 66%[7] due to the aging of the population and a rising prevalence of chronic heart disease. The incidence of AF in India is significantly high in younger age group (31–50 years) as compared to Western Europe and USA.[8]

The management of patients with AF involves three objectives: (1) Rate Control, (2) Prevention of Thromboembolism, and (3) Rhythm control. For a majority of patients with AF, there is no long-term cure. Beta-blockers or verapamil are the commonest drugs for rate control. Class Ic drugs such as propafenone or flecainide are reasonably effective for rhythm control in structurally normal hearts. Sotalol is an option for rhythm control. Amiodarone is the most potent for rhythm control, but its use is restricted to patients in whom other measures fail, due to its long-term side effects. Negative inotropy and ventricular proarrhythmia are limitations to the current drug therapies used in AF.[9] Thus, the development of agents that preferentially modulate the function of atrial ion channel currents is an attractive therapeutic strategy. One such approach is the use of agents that selectively act on atrial sodium channels.

In atria, unlike in ventricles, ranolazine produces a significant reduction in excitability, leading to the development of a prominent rate-dependent post repolarization refractoriness (PRR).[2] This effect could potentially block re-entrant pathways. However, it is its effect on triggered activity, which appear most powerful. Burashnikov et al[2] demonstrated significant differences in the inactivation characteristics of atrial versus ventricular sodium channels. This study identified ranolazine to be capable of exploiting the differences in sodium channel inactivation between atrial and ventricular cells. Ranolazine showed striking atrial selectively, leading to depression of excitability and suppression of AF. Ranolazine inhibits normal and abnormal late Na+ channel current in the ventricle and peak Na+ channel current in the atrium.[2,10,11] By this inhibition, it affects intracellular calcium handling, producing an energy sparing effect.[10] Ranolazine has also been shown to be a potent inhibitor of after-depolarization produced by a number of mechanisms.[11–13] It slightly prolongs the action potential duration by inhibiting the slow sodium current and the slow component of the delayed rectifying potassium current.[3,12]

Ranolazine suppresses proarrhythmogenic mechanisms in vitro[14] and has a low proarrhythmic potential in vivo.[3,15] The MERLIN–TIMI 36 trial[16] revealed that ranolazine significantly reduces the incidence of supraventricular arrhythmias and new episodes of AF in patients with non-ST segment elevation acute coronary syndrome. Miles et al[17] concluded that ranolazine could prove useful in the treatment of AF in general and AF after CABG in particular. A proof-of-concept study by Fragakis et al[18] reported the synergistic effect of amiodarone and ranolazine for conversion of AF. Richard L et al[19] observed that concurrent administration of ranolazine and dronedarone at doses in the low therapeutic range exerts dual protection against ischemia-induced vulnerability to AF and ventricular arrhythmias.

The complex nature of ranolazine's antiarrhythmic effects is largely a result of the drug's effect on multiple ion channels: it inhibits the late rectifying potassium channel, and the late L-type calcium channel. Whereas inhibition of the potassium channel increases the action potential duration, inhibition of the other 2 channels shortens the action potential.[20] This physiologic effect seems to explain the modest increase in QTc interval that was observed in some clinical trials. In the CARISA trial, the mean increase in QTC was 6.1 ms in the 750-mg ranolazine group and 9.2 ms in the 1000-mg group. Similar increases over the baseline QTc interval were seen in the