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Ranolazine in Hypertrophic Cardiomyopathy

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Ranolazine was initially introduced as an anti-anginal agent. Later the antiarrhythmic properties were recognized [1]. MERLIN-TIMI 36 study (Metabolic Efficiency with Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36) showed that incidence of arrhythmia was lower in the active treatment arm with ranolazine [2]. A modernized classification of anti-arrhythmic agents designated late sodium current inhibitor ranolazine as a novel Class Id anti-arrhythmic agent [3].

Studies on cardiomyocytes retrieved from hypertrophic cardiomyopathy patients undergoing myectomy have shown prolonged action potential duration with increased late sodium and calcium currents and decreased repolarizing potassium currents [4]. Ranolazine was shown to reverse these cellular abnormalities by inhibition of late sodium current. Shortening of action potential duration with ranolazine in hypertrophic cardiomyopathy lead to reduced occurrence of early and delayed after depolarizations. Faster calcium kinetics and lower diastolic calcium lead to amelioration of diastolic function in the trabeculae of hypertrophic cardiomyopathy.

A case report in which a patient who was symptomatic despite extensive myectomy and implantation of cardiac resynchronization therapy had excellent final result with ranolazine was published in 2012 [5]. This was based on the effect of ranolazine on the severe diastolic dysfuncion in patients with hypertrophic cardiomyopathy. In another report, two cases of hypertrophic cardiomyopathy with angina refractory to beta blockers had improvement with ranolazine [6].

RHYME study (Ranolazine for Treatment of Angina or Dyspnea in Hypertrophic Cardiomyopathy Patients) was a single center open label pilot study of ranolazine in hypertrophic cardiomyopathy patients symptomatic despite maximally tolerated medical therapy [7]. Of the 14 patients enrolled in this study, 3 did not complete the study due to various reasons. No serious adverse events were noted in the study. Three patients had lightheadedness during dose titration, of which one had palpitations. Patients had less angina and heart failure symptoms and improvement in health-related quality of life. This study provided a proof-of-concept of the role of ranolazine in symptomatic hypertrophic cardiomyopathy patients.

RESTYLE-HCM was a multicenter, double-blind, phase 2 study which enrolled 80 adult patients

with nonobstructive hypertrophic cardiomyopathy [8]. The study showed an excellent safety profile for the drug and was associated with reduced premature ventricular complex burden. But there was no overall effect on exercise performance, plasma prohormone brain natriuretic peptide (pro BNP), diastolic function or quality of life.

Though pre-clinical studies, case reports and open label pilot studies have documented the beneficial effect of ranolazine in hypertrophic cardiomyopathy, double blind phase 2 trial did not show significant benefit in the symptomatic profile of hypertrophic cardiomyopathy.

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