Role of ranolazine in the management of refractory angina

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Despite increasing success of percutaneous coronary interventions, there exists a subset of patients whose angina continues to be refractory to conventional medical and interventional therapies. Apart from standard guideline directed medical therapy, Ranolazine is the only drug approved for treatment for refractory angina. This article discusses the clinical pharmacology of Ranolazine and its role in the management of refractory angina.

Key Words: *Refractory angina; Ranolazine; Coronary artery disease; Chronic pain*

INTRODUCTION

Angina pectoris is the syndrome complex arising from the imbalance between myocardial oxygen supply and demand. The most common cause of this imbalance is progressive atherosclerotic disease of the coronary arteries, resulting in decreased blood flow to the myocardium. There are several definitions for Refractory Angina (RA), but before a patient is labeled with the diagnosis of RA, two of the following criteria must be met [1].

- Objective evidence of ischemia should be demonstrated by exercise treadmill testing, stress imaging or invasive coronary testing such as Fractional Flow Reserve measurement.
- Patient has angina despite conventional medical therapy.

The European Society of Cardiology (ESC) Joint Study Group defined RA as 'a chronic (>3 months), persistent, painful condition characterized by the presence of angina caused by coronary insufficiency in the presence of coronary artery disease which cannot be controlled by a combination of medical therapy, angioplasty/percutaneous interventions, and coronary bypass surgery. While the presence of reversible myocardial ischemia must be clinically established to be the root cause, the pain experienced may arise or persist with or without this ischemia' [2,3].

Scope of the problem

The exact estimates of the prevalence and incidence of RA are unknown due to the heterogeneity of patients labeled with a diagnosis of RA. The Joint Study group estimates that the incidence of RA is from 5% to 10% with patients undergoing cardiac catheterization [4]. It is estimated that there are 600,000 to 1.8 million patients with RA in the United States with at least 75,000 new cases diagnosed per year [5]. The Canadian Community Health Survey suggests that approximately 500,000 Canadians are living with RA. In the late 1990s, one-year mortality from 1% to 22% has been reported by several studies [6-8]. A more recent, contemporary data from the Minneapolis Heart Institute, MN, USA has described a mortality rate of 3.9% at 1 year and 28.4% at 9 years [4-9].

These patients experience a significantly impaired quality of life with extremely high utilization of health care resources in the forms of recurrent emergency room visits, hospitalizations, repeated stress tests and sometimes repeated invasive procedures such as cardiac catheterization [3]. These patients also leave the work force secondary to their poor quality of life and subsequently go on disability. There is also increased psychological stress and increased levels of depression in this population. In the United Kingdom, evaluation and management of RA accounts for 1.3% of the total National Health Service expenditure which is around £ 669,000,000 annually. In 2008, an Ontario based study quoted an annualized cost of CAD\$ 19,209 per patient [10]. The incidence and prevalence of RA will continue to rise as the CAD related survival rates and the age of the population increases.

Causes

Most of the time, patients are not candidates for revascularization therapy for the following reasons [3]:

- Unsuitable coronary anatomy, such as diffuse coronary artery disease or severe distal vessel disease which are not amenable to PCI or CABG.
- Prior history of Coronary Artery Bypass Surgery (CABG) which precludes further surgical intervention (redo-CABG, unavailable conduits for bypass grafting).
- Severely depressed systolic function (especially presence of left ventricular thrombus).
- Severe concurrent co-morbid conditions that increase peri-procedure mortality and morbidity (e.g., Chronic Kidney disease, severe cerebrovascular disease, severe peripheral arterial disease).
- Advanced age.

In this era of complex coronary interventions with many centers performing PCI for coronary chronic total occlusions, a consensus regarding the inappropriateness of revascularization should be established by second or third opinions before labeling a patient with RA, as the most common cause of RA is incomplete revascularization [1].

Pathophysiology

The increase in myocardial oxygen demand can be triggered by increase in physical, emotional or metabolic activities. While most patients respond to conventional therapy, those with RA are resistant to the usual modes of treatment. These patients are thought to have an important link between recurrent myocardial ischemia and the neuropathophysiology of persistent pain [2]. In the presence of noxious stimuli such as ischemia secondary to severe stenosis of epicardial coronaries or microvascular disruption, bradykinin, adenosine, lactate and potassium are released into the effluent of the coronary sinus [11,12]. These stimulate the polymodal afferent cardiac sensory neurons. Calcitonin gene – related peptide and Substance P are also synthesized and augment adenosine-provoked pain. These noxious inputs enter the upper thoracic spinal cord and synapse with the second order sensory neurons in the dorsal horn. This information is amplified and ascends via multiple pathways including Lissauer's tract, the spinothalamic tract, spinoamygdaloid and spinohypothalamic

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pathways to cortical and subcortical areas of the brain with somatic receptive fields in the chest and arm. The parietal cortex and anterior cingulate cortex cognitively apprise these stimuli as threatening. This in turn causes activation of the bilateral prefrontal cortex and limbic system producing an impending sense of doom and further pain [13-17].

Non-invasive conventional drug therapies for Refractory Angina (RA)

Conventional medical therapy for chronic stable angina includes the following:

Beta blockers – They cause negative ionotropy and chronotropy of the heart, thereby increasing diastolic filling time available for coronary perfusion. They increase exercise tolerance and reduce the frequency of angina attacks

Calcium channel blockers – they act as vasodilators with variable effect on cardiac conduction and contractility. Phenylalkylamines such as verapamil and benzothiazepenes such as diltiazem cause negative ionotropy and chronotropy causing angina relief. Dihydropyridines, such as Nifedipine, do not change myocardial oxygen demand, instead, they increase coronary blood flow through changes in vascular tone.

Nitrates – These are endothelial-independent vasodilators. They exert their vasodilatory effects on the systemic veins and conductance arteries which in turn results in an increase in myocardial oxygen supply and a decrease in myocardial oxygen demand. Nitrates also cause some dilation of the stenosis and relieve any associated vasoconstriction related to endothelial dysfunction. They increase the flow through collateral channels thereby increasing exercise tolerance

Aspirin – recommended for all patients with the diagnosis of Coronary artery disease. Aspirin is an irreversible inhibitor of platelet cyclooxygenase, thereby limiting the production of proaggregatory thromboxane A2. Disruption of atherosclerotic plaque causes platelet aggregation which then leads to formation of thrombus causing an acute coronary syndrome. Aspirin works on inhibition of the initial platelet plug and thereby preventing acute myocardial infarction. Patients allergic to aspirin can be given clopidogrel or ticlopidine as an alternate antiplatelet therapy.

Angiotensin Converting Enzyme Inhibitors (ACE-I) – the role of ACE-I in patients with angina is unknown. However, patients on ACE-I have demonstrated a significant decrease in mortality and recurrent ischemic events especially in the presence of vascular disease or diabetes [18].

Statin therapy – Several studies have shown than patients with known CAD have decrease in recurrent cardiovascular event with statin therapies. Apart from reducing the levels of low density lipoproteins, statins also have plaque stabilizing properties which help in reducing future cardiac events [19,20].

Other therapies for RA

The ESC now considers Ivrabadine, Nicrodanil and Ranolazine as second line therapy for the treatment of RA [4]. Neuromodulation with spinal stimulators, Stellate ganglion blockade, anti-depressants, external enhanced counterpulsation, Transmyocardial Laser revascularization and finally Cognitive Behavior Therapies (CBT) have also been tried with some success. Other non-conventional drug therapies are listed in Table 1. Ranolazine received FDA approval in 2006 for the treatment of RA. We will now focus on the role of Ranolazine in the treatment of RA.

Table 1: Action of Drugs.

Drugs	Action
Ivrabadine	Negative Ionotropy, If current inhibition
Nicrodanil	KATP channel opener, vasodilator, decreases preload and afterload, no tolerance issues (Not for use in USA)
Trimetazidine	Reversible 3-ketoacyl-thiolase inhibition, reduced mitochondrial fatty acid oxidation (Not for use in USA)
Perhexiline	Reduced free fatty acid oxidation and transport into mitochondria (Not for use in USA)
Allopurinol	Xanthine oxalate inhibitor, reduces oxygen wasting, endothelial dysfunction and substrate depletion – questionable effectiveness in angina relief
Molisidomine	NO donor, vasodilation (Not for use in USA)
Fasudil/hydroxyfausidil	Rhi-kinase inhibition, maintains coronary vasodilation (Not for use in USA)
L-Arginine	NO donor, vasodilation (Not for use in USA)

ROLE OF RANOLAZINE

Pharmacology

Ranolazine is a racemic mixture and is described chemically as N-(2,6-dimethylphenyl)-4(2-hydroxy-3-[2-methoxyphenoxy]-propyl)-1-piperazine acetamide dihydrochloride.

The exact mechanism of action of Ranolazine as an anti-anginal is not fully understood. The initial anti-anginal effect was believed to be due to intracellular metabolic changes [21]. Ranolazine was thought to inhibit fatty acid oxidation which shifted cardiac energy metabolism from fatty acid oxidation to glucose oxidation [21]. Given that glucose oxidation requires less energy than fatty acid oxidation, it was believed that Ranolazine would increase the amount of myocardial ATP production per mole of oxygen consumed, thereby reducing lactic acid and acidosis, which then helps to maintain myocardial function during times of ischemia [21,22]. However, more recent data suggests that this is not the case and it has subsequently been determined that at therapeutic levels, Ranolazine inhibits the cardiac late sodium current (INa) [23]. Proper cardiac function requires equilibrium between intracellular concentrations of Calcium (Ca) and Sodium (Na) that is maintained by ion channels,

pumps, and exchanges [23]. In the setting of myocardial ischemia as well as other cardiac conditions, there is an increase in Na that leads to an increase in exchange of intracellular sodium for extracellular calcium [23,24]. This resultant increase in calcium causes calcium overload that can lead to electrical and mechanical dysfunction such as decreased left ventricular relaxation caused by ischemia or reperfusion [23,25]. By inhibiting the late sodium current (INa), Ranolazine is believed to attenuate these effects. Unlike conventional anti-anginal medications, Ranolazine has minimal to no effect on heart rate or blood pressure. In clinical trials evaluating Ranolazine in chronic stable angina patients, the mean heart rate reduction was less than 2 beats per minute and the mean reduction systolic blood pressure was less than 3 mmHg. However, there is some recent data to suggest that Ranolazine did have an effect on peak heart rate in patients undergoing pharmacologic stress [26].

Ranolazine also inhibits the delayed rectifier potassium current IKr, which results in prolongation of the ventricular action potential. The overall effect on QTc is dose and concentration dependent. At treatment doses of 1000 mg twice daily, the mean increase in QTc was 6 msec. However, the maximum observed increased was 15 msec.

Pharmacokinetics

Ranolazine reaches peak plasma concentrations following oral administration in 2 to 5 hours. The bioavailability is approximately 73% and is not affected by food [27]. In terms of metabolism, Ranolazine is metabolized mainly by cytochrome P-450 CYP4A4 and to a lesser degree by CYP2D6. CYP2D6 accounts for less than 20% of the metabolism of ranolazine. Ranolazine is also a substrate for p-glycoprotein, an efflux transporter that pumps foreign substances out of cells.

Ranolazine is contraindicated in patients with any degree of hepatic impairment secondary to an approximate 3-fold increased risk of QT prolongation. In patients with mild hepatic impairment (Child-Pugh Class A), the Cmax of Ranolazine was increased by 30%. In patients with moderate hepatic impairment (Child-Pugh Class B), the concentration of Ranolazine was increased by 80%. There are no specific dose adjustment recommendations for Ranolazine in patients with renal impairment. However, acute renal failure has been observed in patients with underlying renal insufficiency (Creatinine clearance <30 mL/min). Therefore, periodic renal function monitoring is recommended in patients with moderate to severe renal impairment, and Ranolazine should be discontinued should acute renal failure occur.

Trial data

The efficacy of Ranolazine as an effective treatment strategy for RA has been demonstrated in several randomized trials. In the MARISA trial, monotherapy with Ranolazine resulted in a dose-dependent increase in the angina free exercise duration and time to angina in 191 patients. The 1000 mg twice a day dose was more effective than the 500 mg twice a day dose [28]. In another trial, Chaitman randomly assigned 823 patients receiving anti-anginal therapies to placebo or one or two doses of Ranolazine (750 or 1000 mg twice a day). After 12 weeks of therapy, both Ranolazine arms noted a significant increase in their symptom-limited exercise duration, time to angina onset and time to ST segment depression (at peak Ranolazine blood level) and reduced angina frequency by 0.8 and 1.2 episodes per weeks, compared to the placebo arm [29]. In the ERICA trial, 565 patients with more than three angina attacks per week (on amlodipine ± nitrates but no beta blockers) were randomized to placebo or Ranolazine 1000 mg twice a day. These patients had 5.63 episodes of angina at baseline. The Ranolazine arm had a significant improvement of angina episodes per week compared to the placebo arm (2.88 vs 3.31)[30]. In another study, over 949 diabetic patients with angina on one or two anti-anginal drugs were randomly assigned to Ranolazine or placebo for 8 weeks. The Ranolazine arm had lower weekly angina episodes (3.8 vs 4.3 episodes; p=0.008) compared to the placebo arm. The Ranolazine arm also had lower sublingual nitroglycerin use (1.7 vs 2.1 doses; p=0.003) [31]. Bennett designed the Ranolazine Refractory Angina Registry to evaluate the safety, tolerability and effectively of Ranolazine treatment in RA patients. Extensive data on over 100 patients were collected. Overall 43% of patients had a ≥ 2 class improvement in angina. At 1 year, 57% patients remained on Ranolazine (91.2%; 500 mg BID), including 58% with a ≥ 2 class improvement in angina. Reasons for discontinuation included: side effects (n=16), major adverse cardiac events (n=10), cost (n=5), ineffective (n=6), cost and ineffective (n=3), and unknown (n=3). The authors concluded, Ranolazine is an effective anti-anginal therapy in patients with RA; still at 1 year only 57% of patients remained on Ranolazine because of side effects, suboptimal effectiveness, cost, or progression of disease [32]. Ling evaluated the impact of Ranolazine on clinical outcomes and healthcare resource utilization in patients with RA. A total of 150 patients with RA were studied. They noted a non-significant reduction in the frequency of clinic and emergency room visits during Ranolazine treatment. The number of patients hospitalized were significantly lower during Ranolazine therapy than in the pre-Ranolazine period (p=0.002) [33].

CONCLUSION

Patients with RA have advanced coronary artery disease and represent a complex population which is growing. Along with standard therapy for angina, Ranolazine therapy is a useful adjunct for the treatment of RA.

Careful attention to side effect profile, cost and drug interactions should be balanced against quality of life and healthcare resource utilization during Ranolazine therapy. A multidisciplinary approach is often essential for the overall management of patients with refractory angina.

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