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Review Article

The Role of Ranolazine in Stable Coronary Angina and in Some Cardiac Arrhythmias

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Abstract

Background: Chronic ischemic heart disease, atrial and ventricular arrhythmias are the leading causes of morbidity and mortality in Western Countries.

Methods: Ranolazine, a piperazine derivative drug with anti-ischemic effect via inhibition of the late inward sodium current, is useful, as second-line agent, in the management of chronic stable angina pectoris. But, this could be also used for its specific properties, as anti-arrhythmic agent to reduce enhanced focal activity of pacemaker-cells.

Results: Actually, the drug is employed as anti-ischemic agent in three different doses (375, 500, 750 mg), and was supplied alone or in association with conventional antianginal drugs (beta-blockers, calcium channel blockers, nitrates, antiplatelets, ACE-inhibitors, statins). In chronic angina pectoris, Ranolazine has demonstrated to reduce the frequency, duration and severity of angina, to improve exercise performance and reduce the frequency of angina attacks in those with refractory angina and in ischemic patients with type 2 diabetes mellitus. But, experimental and clinical studies also demonstrated that the drug, used alone or in association with other anti-arrhythmic drugs, is useful in some atrial and ventricular arrhythmias. Nevertheless, its use, as anti-arrhythmic agent, wasn't still approved.

Conclusions: Ranolazine is a relatively new therapeutic agent with anti-ischemic and anti-arrhythmic effects, that may be used in chronic angina and/or in patients with incomplete revascularization. For its mechanism of action, the drug could also act as anti-arrhythmic compound, alone or in association, in some atrial and ventricular arrhythmias.

Keywords: *Ranolazine; Conventional Anti-Ischemic Drugs; Stable Angina Pectoris; Cardiac Arrhythmias*

Introduction

Stable coronary artery disease (SCAD) is a debilitating illness affecting millions of patients throughout developed Countries. Its incidence increases with advancing age, avoiding about 4 - 6% in elderly individuals and representing one of the most common causes of death [1]. SCAD is caused by an imbalance between myocardial blood supply and oxygen demand, and is a consequence of significant obstruction of epicardial coronary arteries usually dependent on atherosclerosis. Less frequently, it is due to the impaired vasomotility (vasospasm) or microvascular disease. In addition, SCAD is often consequent to the insufficiency or impossibility to obtain an efficient surgical or interventional revascularization or to re-stenosis (refractory angina) [2,3]. Conventional antianginal drugs, such as nitrates, β-blockers and calcium channel blockers reduce myocardial ischemia by significantly decreasing the main determinants of myocardial oxygen demand, such as heart rate, blood pressure, or myocardial contractility both at rest and during exercise [4]. Other agents, such as antiplatelets, statins and Angiotensin converting enzyme inhibitors, were usually employed such as vascular protective drugs, acting by different mechanisms. Ranolazine was introduced in addition to conventional anti-anginal drugs previously described. It was given alone

or added to conventional therapy, as second-line of treatment of SCAD, acting with a mechanism unlike conventional agents [5,6]. On the other hand, it is known that atrial and ventricular arrhythmias are a most frequent causes of morbidity and mortality in the western world. Some experimental and clinical researches demonstrated that Ranolazine acts as antiarrhythmic drug by enhancing focal activity. The anti-arrhythmic effect of drug springs from its ability to modify multiple ion channels in cardiac cells for generation of action potential. Specifically, it inhibits the late inward of sodium current (late I_{NA}) (and rapidly activating delayed rectifier potassium current) in the atria [7] and blocks the late phase of the inward sodium current (late I_{NA}) in the ventricles [8]. In accordance with these mechanisms, Ranolazine could be employed, as antiarrhythmic drug in some atrial and ventricular arrhythmias [9].

Ranolazine

Ranolazine is a drug approved in the United States and Europe as antianginal agent, that has cardioprotective properties. It acts by preservation of myocardial blood flow during ischemia, through its effects on inhibition of late inward of sodium current (I_{NA}) [10].

During cardiac ischemia, enhanced sodium-calcium exchange due to augmented late phase of the inward sodium current activity reduces cytosolic calcium concentration. The increased Ca++ concentration in the cytosol activates contractile proteins, inducing diastolic dysfunction. On the other hand, the activation of contractile proteins and diastolic dysfunction are associated with extra energy consumption [11]. Inversely, the inhibition of late I_{NA} induced by Ranolazine prevents the sodium/calcium exchange and, consequently, the accumulation of calcium ion in the cells. That improves myocardial relaxation and reduces left ventricular stiffness improving myocardial perfusion [12,13]. Additionally, calcium overload has adverse effects on myocardial electrical activity, predisposing to arrhythmias (Figure 1) [14]. These anti-ischemic effects have been shown to be exerted without significant modifications in heart rate, blood pressure and inotropic state [15]. The drug must be particularly used in refractory SCAD, that was defined as the persistence of symptoms resistant to conventional treatment for CAD, including anti-anginal agents and revascularization [16].

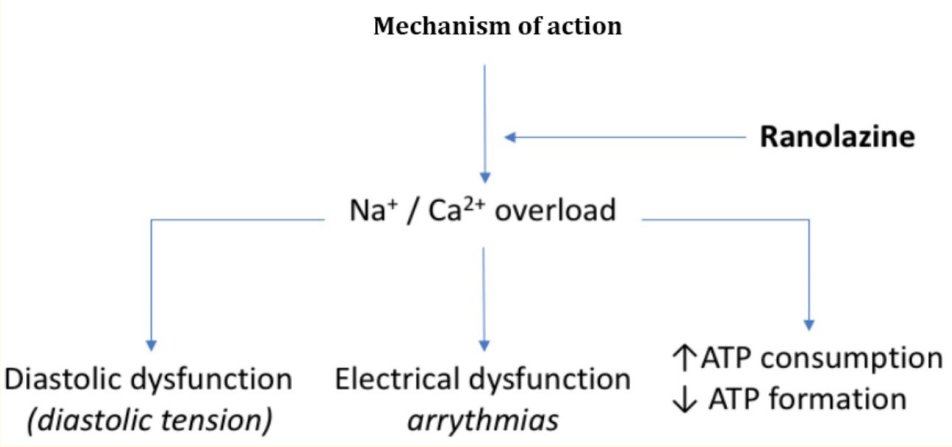

Figure 1: *Site of action of Ranolazine and effects of Na+/Ca2+ overload on myocardial cells.*

Ranolazine was approved by European Medicines Agency in 3 different extended doses: 375: 500; 750 mg. 375 mg BID for 7 - 10 days must be given as starting dose. Subsequently, 500 mg BID must be given for other 7 - 10 days, and a dose of 750 mg BID is employed, as a maximum dose [17]. Adverse events reported were dizziness, constipation and peripheral edema [18]. The drug must be administered with caution in the presence of hepatic or renal impairment [3]. Since Ranolazine prolongs the cardiac potential of action, a risk of torsade de pointes there is. QTc time can be also prolonged [19]. Consequently, an ECG is recommended after 1 or 2 weeks of drug administration.c

Coronary artery disease

The molecule has been shown to be safe and effective in treating SCAD both in monotherapy, as evidenced in MARISA (Monotherapy Assessment of Ranolazine In stable Angina) study [20] and in combination with common anti-ischemic drugs, as reported in the CARISA (Combination Assessment of Ranolazine In stable Angina) trial [21]. A recently published systematic review 0f 7 randomized controlled trials affirmed that Ranolazine improves exercise test-parameters, reduces nitroglycerin use and intensity/time-duration of angina pectoris [22]. In the Type 2 diabetes Evaluation of Ranolazine In Subjects with chronic stable Angina (TERISA) trial, 49 patients affected by diabetes mellitus and CAD were assigned to Ranolazine or placebo-treatment. The results indicate that Ranolazine significantly decreases the weekly doses of sublingual nitroglycerin and the angina frequency in comparison to placebo [23]. The use of Ranolazine in patients with incomplete revascularization was evaluated in the Ranolazine for Incomplete Vessel Revascularization post Percutaneous Coronary Intervention (RIVER-PCI) study. A randomized, double-blind trial involving more than 2000 patients underwent percutaneous coronary intervention induced incomplete revascularization, with consequent chronic angina. After a median follow-up of 643 days, no difference between patients receiving Ranolazine or receiving placebo for the end-point of ischemia-driven revascularization or hospitalization was found [24]. The cause of these negative results probably depends from the evaluation of a mixed group-patients with residual disease. In fact, almost half of patients' enrolled had three-vessels disease and one third had untreated chronic total occlusion.

The use of Ranolazine in acute non S-T elevation was evaluated in the Metabolic Efficiency with Ranolazine for Less Ischemia in Non S-T elevation (MERLIN)-Thrombolysis in Myocardial Infarction (TIMI) trial. In enrolled patients, Ranolazine was administered by intravenous bolus followed by an infusion for 12 to 96 hours. The primary end-point was cardiovascular death, myocardial infarction, or recurrent ischemia. The results shown no significant benefit of Ranolazine compared to placebo in the primary outcome. Based on these results, there is currently no role for Ranolazine in addition to standard ACS therapy in ischemic patients [25]. The trial also demonstrated that in a subgroup of patients with previous angina treated with PCI, a reduced risk of recurrent ischemia and reduced incidence of cardiovascular death there was, when these were treated with Ranolazine [26]. It is known that Micro-Vascular Angina (MVA) is characterized by chest pain evident during effort with ischemic signs at non-invasive tests, in the absence of epicardial coronary stenosis [27]. It is known that conventional anti-ischemic drugs remain the main MVA treatment. But often, the symptoms persist in spite of the treatment, with significant impairment of quality of life. In confirmation of that, Metha., *et al*. demonstrated a significant improvement in Seattle Angina Questionnaire (SAQ) in patients with evidence of ischemia but no obstructive CAD, treated with Ranolazine versus placebo [28]. In confirmation of the beneficial effects in MVA, recently Tagliamonte., *et al*. reported a significant improvement in trans-thoracic Doppler-derived coronary flow reserve in 58 patients suffering of MVA. After 8 weeks of Ranolazine therapy, coronary flow reserve increased in the Ranolazine group but not in the placebo group [29]. Finally, Villano and colleagues demonstrated that both Ranolazine and Ivabradine improved symptoms of MVA, although the magnitude of effects was mild to moderate. Of two medications, Ranolazine seemed to achieve better results [30].

Arrhythmias

The first clinical evidence of antiarrhythmic efficacy of Ranolazine has been provided by the MERLIN-TIMI 36 trial, which showed that Ranolazine may suppress both supraventricular and ventricular arrhythmias in patients with non ST-elevation [25]. The cause of its atrial anti-arrhythmic effects is consequent to action of inhibiting the late I_{NA} (and the late rectifying potassium channels) in atrial myocytes. Consequently, Ranolazine reduces atrial excitability and prolong atrial refractory time [31]. On the contrary, enhanced late I_{NA} in atrial myocytes has been shown to lower the threshold of action potential firing, increases excitability, and hence the risk of atrial arrhythmias, mainly Atrial Fibrillation. Analogously in ventricular arrhythmias, the inhibition of late I_{NA} with Ranolazine shortens action potential duration, with antiarrhythmic ventricular actions (Figure 1). The anti-arrhythmic effects of the agent were demonstrated in new onset

of Atrial Fibrillation, in which was given association with Amiodarone. Commonly, Amiodarone is used for pharmacological conversion of atrial fibrillation in sinus rhythm. But, the drug-effect is limited by moderate efficacy and delayed action. Instead, the study demonstrated that the addition of Ranolazine to Amiodarone is superior to Amiodarone alone for conversion of atrial fibrillation of recent-onset, for a synergistic action of two drugs [32]. The synergy is also evident when Ranolazine was given in association with Dronedarone. In fact, reduced doses of Ranolazine, given in association with Dronedarone, showed complementary electrophysiological properties in paroxysmal atrial fibrillation, as evidenced in HARMONY study [33]. The atrial anti-arrhythmic effect of Ranolazine was also recorded in a case series study [31]. Ranolazine demonstrated a beneficial effects on ventricular arrhythmias too. But, most experiences derive from experimental studies and fewer clinical studies were performed in humans with ventricular arrhythmias [34]. In an experience performed in the rats, the Ranolazine's effect on ventricular vulnerability was evaluated. In this study, the drug induced a significant increase in the threshold of ventricular fibrillation [35]. In addition, an experimental study confirmed that Ranolazine is effective, as adjuvant drug, in ventricular arrhythmias [36]. Specifically the agent, given in addition to sotalol and lidocaine, demonstrated to be able to prevent ventricular arrhythmias consequent to ischemia/reperfusion [37]. Finally, in Ranolazine Implantable Cardioversion Defibrillator (RAID) the drug, added to standard therapy, reduced the incidence of ventricular arrhythmias and death in patients with implantable-cardioverter defibrillator [38]. But, although both experimental and clinical results report clear antiarrhythmic effects of Ranolazine in atrial and ventricular arrhythmias [9], actually the drug is not indicated for the treatment of rhythm disturbances.

Summary

Ranolazine, a second-line anti-ischemic agent, acts with innovative mechanism represented by the inhibition of the late I_{NA} current in the myocytes, that also contributes to a reduction in intracellular calcium, reducing ischemic injury. The drug is been tolerated and effective in patients SCAD and refractory angina pectoris despite commonly used anti-anginals such as β-blockers, calcium channel blockers and nitrates. In the clinical practice Ranolazine, given alone or in combination with other drugs, revealed useful in patients with SCAD. It reduces their angina symptoms and improves quality of life also when conventional antianginal therapy by oneself revealed as ineffective. Some evidences also support its potential role in other ischemic areas, such as MVA, incomplete revascularization post PCI. It also exerts partial glycemic control in type 2 diabetes mellitus and chronic/or paroxysmal atrial fibrillation. In summary, Ranolazine represents an useful tool that, by an innovative mechanism, significantly improves the clinical symptoms of patients with chronic ischemic heart disease not responding to conventional anti-anginal drugs and/or dependent by incomplete post-interventional or surgical revascularization. But, Ranolazine also has antiarrhythmic effects happening both on atrial and ventricular rhythm disturbances, due to the inhibition of late I_{NA} current and sodium-potassium exchange, even if it, at moment, is not indicated as antiarrhythmic agent.

Conflict of Interests

There are no conflicts of interest.

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