

Trimetazidine, Ranolazine, Ivabradine Antagonize Stable Coronary Artery Disease Otherwise From Conventional Anti-Ischemic Drugs

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ABSTRACT

Stable coronary artery disease (SCAD), is caused by an imbalance between myocardial blood supply and oxygen demand. It occurs when the heart muscle doesn't get as much blood as it needs. Specifically, it isn't acute coronary angina, but suggests that a heart attack is more likely to happen in the future. Sometimes, conventional anti-ischemic drugs can be insufficient to improve the symptoms in the presence of SCAD. But, their association with some agents having different mechanisms from traditional anti-ischemic compounds, such as Trimetazidine, Ranolazine or Ivabradine (second line of treatment) may be effective. These (especially when given in association with nitrates, beta-blockers or calcium-antagonists) obtained significant results in numerous SCAD-studies when conventional drugs alone were ineffective. In addition, Ranolazine

shown interesting anti-arrhythmic effects both in supra-and-ventricular arrhythmias and, given alone or in association with other anti-arrhythmics (as Cordarone or Dronedarone) obtained promising results in these rhythm disturbances.

Key words: Stable coronary artery disease (SCAD); Conventional anti-ischemic drugs; Trimetazidine; Ranolazine; Ivabradine

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INTRODUCTION

Despite the increasing success of conventional medical therapies and percutaneous coronary intervention (PCI) or coronary artery by-pass graft surgery (CABG), a significant number of patients with CAD persists to suffer of subjective and/or objective signs of myocardial ischemia^[1]. Several causes may be responsible for these unsatisfactory results, such as: diffuse CAD due to complex anatomical structure of coronary circulation and/or metabolic conditions that further complicate the course of disease; insufficiency of previous PCI or CABG, lack of vascular conduits to perform or repeat CABG, inadequate general conditions and advanced age. In these eveniences, CAD shows such as stable coronary artery disease (SCAD). At the present time, SCAD persists in about 45-50% of ischemic patients.

STABLE CAD

This condition is a consequence by reversible myocardial demand/supply mismatch related to ischemia or hypoxia. The symptoms (absent at rest) are usually brought on by exertion, emotional stress, exercise, cold, or heavy meal and manifest as substernal discomfort, heaviness or a pressure-like feeling, which may radiate to the jaw, shoulder back or arm^[2].

Electrocardiographic evidence of ST-T changes at rest or after exercise or conduction disturbances can be present as consequence of SCAD. Stress nuclear and cardiac resonance imaging are more sensitive than echocardiography for its non-invasive diagnosis. But, coronary angiography represents the reference-investigation for its diagnosis of conventional medical treatment for SCAD is classified as antianginal or vascular protective drugs. Antianginal compounds improve exercise duration until onset of angina, decrease severity and frequency of anginal episodes and time to onset of exercise inducing S-T depression. In other words, these drugs reduce myocardial ischemia by decreasing the main determinants of myocardial work. On the contrary, vascular protective agents may reduce the progression of atherosclerosis and of intracoronary thrombi growth/rupture and stabilize coronary plaques, consequently reducing the number of future cardiovascular events^[3,4].

In table 1 are reported the main conventional anti-ischemic drugs and their action-mechanisms^[5].

But, in addition to these compounds, other substances there are (non-traditional anti-ischemic drugs), that improve the anginal symptoms. These may be given alone or in association with conventional drugs.

NON-TRADITIONAL ANTIANGINAL DRUGS

These drugs act by a mechanisms different respect that of the conventional agents^[6,7], and are reported with their mechanisms in table 2.

Trimetazidine

It is oldest pharmacologic agent of three non-conventional anti-ischemic compounds and is classified as belonging to the class IIb. Its administration induces a partial inhibition of fatty-acid β -oxidation and causes an increase in glucose oxidation (more useful energetically in ischemic heart)^[8]. These metabolic changes could also induce a reduction in ROS-production (responsible for cell damaged) and an inhibition of apoptosis. In addition, the drug increases plasma concentration in adenosine^[9]. The final effect of these actions is an improvement in cardiac function. Besides, it is known that myocardial ischemia causes cellular acidosis responsible for an overload of Ca^{2+} , favouring arrhythmias, contractile failure and cells death. These detrimental effects also are antagonized by Trimetazidine^[10]. Finally, Trimetazidine reduces inflammation, improves endothelial function and acts as potent antioxidant, during ischemia-reperfusion, both in pre-procedural phase and in stable chronic angina^[11,12].

With reference to its beneficial effects on SCAD, previously we have demonstrated that in diabetics suffered from previous AMI, Myocardial Performance Index (MPI) increased in baseline conditions, reduced after one year of Trimetazidine. This reduction was in accordance with Isovolumetric Relaxation Time (IRT) and Ejection Time (ET), as expression of improved left ventricular function^[13]. Previously, TRIMPOL I, II (TRIMetazidine in POLand) studies showed a decrease in the number of angina attacks, an improvement in exercise tolerance, and a reduction in nitrate consumption during treatment with Trimetazidine in combination with conventional drugs in diabetics with SCAD^[14,15]. These are the main evidences of the beneficial effects obtaining with Trimetazidine in chronic ischemic heart.

Ranolazine

Belonging to the class IIa, Ranolazine is a piperazine derivative well

tolerated drug, that selectively inhibits the late sodium current.

During myocardial ischemia, it is known that a build-up of intracellular sodium, which leads to increase in intracellular calcium via the sodium-calcium exchange, there is^[16,17]. The consequent intracellular Ca^{++} overload favors the link between actin and myosin, increasing myocardial contractility and thus, oxygen consumption. On the contrary, the inhibition of late sodium (and calcium) inwards current, obtained with Ranolazine, improves myocardial relaxation, reducing left ventricular diastolic stiffness^[18]. The anti-ischemic effect of Ranolazine happens without significant modifications in heart rate, blood pressure and inotropic state^[19]. The molecule has been shown to be safe and effective in treating chronic angina both in monotherapy, as evidenced in MARISA (Monotherapy Assessment of Ranolazine in Stable Angina) trial^[20], and in combination with the conventional anti-ischemic drugs, as reported in CARISA (Combination Assessment of Ranolazine In Stable Angina) study^[21]. It must also added that no benefits were obtained in the RIVER-PCI (Ranolazine for Incomplete Vessel Revascularization) trial. The study involved more than 2000 patients affected by chronic stable angina. After a follow-up of 644 days, no difference between patients receiving Ranolazine or placebo was found^[22]. But, these negative results probably depend on the heterogeneity of patients evaluated. In fact, patients with three vessels involved and patients with untreated chronic coronary occlusion were contemporarily evaluated. In addition, the results obtained seem indicate that Ranolazine, even though cannot prevent recurrent myocardial ischemia in these patients, appears useful in to reduce its severity.

Referring to the inhibition of peak and late Na^+ current, Ranolazine seems to be effective in the prevention and treatment of both atrial and ventricular arrhythmias. The nature of ranolazine's antiarrhythmic effects is due to its action of inhibiting the late sodium current and the late rectifying potassium channels. The effect is frequency and voltage-dependent being more potent in the setting of tachycardia rather than the normal heart rate^[23]. The anti-arrhythmic role of Ranolazine in new-onset and paroxymal atrial fibrillation was evaluated in the HARMONY trial. A combined therapy with Ranolazine and Dronedronone was used in these patients, because it was hypothesized that two drugs have complementary

Table 1 The main conventional, anti-ischemic drugs used in coronary artery disease and their mechanisms.

Classes	Mechanisms
Nitrates	Increase of cardiac blood flow by dilating coronary arteries
Beta-blockers	Reduce cardiac work-load by dilating coronary arteries
Calcium channel blockers	Reduce cardiac work-load by reducing cardiac contractility
Antiplatelets	Clots' prevention
Angiotensin converting enzyme inhibitors	Limiting key-enzyme in maintaining cardiac pressure
Statins	Contribute to the plaque stability; anti-inflammatory effect; lipid lowering therapy

Table 2 Non-conventional, anti-ischemic drugs used in chronic stable angina, and their mechanisms.

Non-conventional anti-ischemic drugs	
Drugs	Mechanisms
Trimetazidine	Inhibition of reduction of ATP, Stimulation of glucose by the myocardium
Ranolazine	Inhibition of the late inward sodium channel
Ivabradine	Reduction of pace-maker activity in the sinus node

electrophysiological properties on the mechanism of atrial fibrillation^[24]. Ranolazine (750 mg) plus Dronedarone (225 mg) BID significantly reduced atrial fibrillation burden. On the contrary, no reduction was observed with Dronedarone alone, whereas only a modest, non significant reduction was observed with Ranolazine alone. Moreover, the sum of the anti-arrhythmic effect of Ranolazine plus Dronedarone exceeded that of either drugs alone. In a prospective randomized study, a combined therapy with amiodarone and Ranolazine significantly induced cardioversion in respect to amiodarone alone in patient with new-onset atrial fibrillation^[25]. The effect of Ranolazine as an adjunctive anti-arrhythmic agent was also positively recorded in two small studies^[26,27]. In addition, in an experimental study, Ranolazine was found to be as effective, as adjuvant drug in ventricular arrhythmias, in addition to sotalol and lidocaine in the prevention of ischemic/reperfusion inducing arrhythmias^[28]. In cardiac surgery, Tagarakis *et al* demonstrated that a moderate dose of Ranolazine given pre- and post-operatively in patients underwent CABG significantly reduced the incidence of post-intervention atrial fibrillation^[29]. Finally, in Ranolazine Implantable Cardioversion Defibrillator (RAID) trial the drug, added to standard therapy, was able to reduce the incidence of ventricular arrhythmias and death in patients with implantable-cardioverter-defibrillator^[30]. But, although these studies report certain atrial and ventricular anti-arrhythmic effects of Ranolazine, actually it is not indicated too for the treatment of these rhythm disturbances.

Ivabradine

Ivabradine (class IIa) has a chemical structure like to verapamil. It acts on sinoatrial node, selectively inhibiting the pacemaker I_f current in a dose-dependent manner. This effect reduces heart rate, both at rest and during exercise and thus, decreases oxygen consumption is obtained with a mechanism different from that carried out by conventional anti-ischemic drugs, as beta-blockers^[31,32].

It is known that, acute ischemic events are enhanced by increased heart rate. This causes an imbalance between myocardial oxygen supply and consumption with prevalence of this last. On the other hand, the increased oxygen consumption extends the frequency, severity and duration of acute ischemia^[33]. On the contrary, low heart rate reduces the time in which the heart stays in systole, decreasing the number and the duration of anginal episodes^[34], without effects on blood pressure and intracardiac conduction^[35,36].

Several trials have demonstrated the efficacy of Ivabradine in SCAD, with or without left ventricular dysfunction^[37,38]. The drug can be used alone or in association with the conventional anti-ischemic drugs. Concerning this issue, the INITIATIVE (INternational TRIal on the treatment of Angina with Ivabradine vs, atenolol) study compared the effects of Ivabradine (5 mg, twice daily for 12 weeks) to atenolol on performance of treadmill exercise testing. Overall, Ivabradine produced antianginal and anti-ischemic effect like to those of atenolol^[39]. Subsequently, the ASSOCIATE (evaluation of the Antianginal efficacy and Safety of the aSsociation Of the I_f Current Inhibition Ivabradine with be Ta-block Er) trial evaluated the effect on exercise duration of Ivabradine (5 mg/twice daily) added to atenolol (50 mg/die) in ischemic patients. The results demonstrated that total exercise duration significantly increased when two drugs were contemporary administered, in comparison with that obtained giving one agent^[40]. Ivabradine was also combined low dose of bisoprolol. Results confirmed the additional, beneficial effects on ischemic symptoms obtained with two drugs given at the same time^[41]. A study has also compared Ivabradine and Amlodipine. The results demonstrated that Ivabradine improved exercise tolerance as

well as Amlodipine, but was superior to that with regard the reduction of heart rate and frequency of ischemic episodes^[42].

Beside myocardial ischemia and heart failure in sinus rhythm, Ivabradine can be usefully used in the rate control of atrial fibrillation. Two recent clinical studies found that the drug reduces heart rate in this atrial rhythm disturbance^[43,44]. The rate control in this condition probably depends on recent identified hyperpolarization-activated cyclic nucleotide-gated cation channel 4 (HCN4), the primary gene responsible for I_f current expression throughout the myocardium (in the SA node)^[45]. In addition, Mackiewicz *et al* previously have experimentally demonstrated that Ivabradine also protects against ventricular arrhythmias in acute myocardial infarction in rats. The mechanism hypothesized includes: prevention of diastolic Ca^{++} -leak from sarcoplasmic reticulum; upregulation of I_f current in left ventricle and dispersion of cardiac repolarization. But, these anti-arrhythmic hypotheses about the effects of Ivabradine must be clearly demonstrated in a wide range. Thus, other evaluations performed in humans are requested to confirm these properties of Ivabradine^[46].

CONCLUSIVE REMARKS

Trimetazidine, Ranolazine, Ivabradine represent an adjunctive therapeutic means to SCAD, to be employed alone or (more frequently) added to conventional, anti-ischemic drugs in patient with untreatable SCAD. Particularly, Trimetazidine (in association with long acting nitrates), given with beta-blockers, showed benefits for most but not all outcomes. The beneficial anti-ischemic action of Trimetazidine seems to be particularly effective in diabetic patients with myocardial ischemia. Ranolazine, added to beta-blockers or calcium channel blockers, shown positive results across all outcomes contrarily to Trimetazidine. Finally, Ivabradine evidenced positive results when used in ischemic patients with increase LVEDP, but showed no consistent effects when associated with beta-blockers^[47]. Because their different and synergistic mechanisms, in addition two drugs (Ranolazine and Ivabradine) could be used together.

In addition, besides its anti-ischemic action, Ranolazine showed interesting anti-arrhythmic effects too, that remarkably amplify its use in other cardiologic fields. Likewise, Ivabradine may act, as a rate control drug, both in atrial fibrillation and in sinus rhythm.

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