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MULTIPLE ROLES OF RANOLAZINE BEYOND ANGINA PECTORIS

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ABSTRACT
Ranolazine is a piperazine derivative accepted as an antianginal drug. Principally it is used as a second line antianginal in stable coronary artery disease. Ranolazine blocks the late Na + current and prevents the rise of cytosolic calcium. It decreases myocardial wall tension and improves coronary blood flow. Ranolazine is effective in atrial fibrillation (AF) as an appendage to electrical or pharmacological cardio version. It can be used in permutation with amiodarone, metoprolol or dronedarone. It has also been used in AF arising after coronary artery bypass grafting surgery. Role of ranolazine is also being evaluated in pulmonary arterial hypertension, diastolic dysfunction, and chemotherapy induced cardio toxicity. Ranolazine has some antiglycemic effect and has shown a reduction of hemoglobin A1C in several trials. The antianginal effect of ranolazine has also been seen to be more in patients with diabetes compared to those without diabetes. Ranolazine is being evaluated in patients with the peripheral arterial disease with discontinuous claudication and hypertrophic cardiomyopathy. Pilot studies have shown that Ranolazine may be beneficial in neurological conditions with myotonia. The evidence base on the use of ranolazine in various circumstances is rapidly increasing with results of further trials readily awaited. Accumulating verification may see Ranolazine in schedule clinical use for many conditions beyond its traditional role as an antianginal.

KEYWORDS: Ranolazine, angina, anti ischemic.

INTRODUCTION
Ranolazine hydrochloride is an anti ischemic agent. It was approved in January 2006 by the U.S. Food and Drug Administration (FDA), for the treatment of chronic stable angina. Based on current data, Ranolazine has been integrated as a second line antianginal treatment in North American and European guidelines for the management of chronic stable angina.[1,2] Since its authorization, the drug has shown benefits beyond angina relief. Extended benefits have been experiential in the managing of arrhythmias, particularly atrial fibrillation (AF), and in diastolic dysfunction, pulmonary hypertension (PH), and chemotherapy related cardiotoxicity.[3] Ranolazine has also shown, undertake in the management of diabetes mellitus.[3] In this article, we present a wide-ranging review of Ranolazine's pharmacology, mechanism of action, and recent preclinical and clinical evidence.

Pharmacology and mechanism of action
Ranolazine is a piperazine derivative existing as extended release tablets of 500 or 1000 mg.
Distinctive doses are 500–1000 mg twice daily. Plasma concentration peaks 2–5 h after oral administration with an elimination halflife of 2 h. The drug is metabolized primarily in the liver and excreted principally through the kidneys.[4,5] It acts by inhibiting sodium and potassium ion channel currents. This outcome is obtained as a result of the inhibition of peak and late sodium channels which in order increases myocardial function.[6] The outcome of Ranolazine in sodium channels is being reported to be tissue-specific as well as regularity and voltage-dependent for which Ranolazine has been proven to be more effective in the setting of tachycardia.[7] As well, Ranolazine inhibits delayed rectifier potassium currents with an inhibitory concentration of 11.5 microM which in order prolongs the ventricular action potential extent. As well, Ranolazine has been shown to have a small activity towards L-type calcium channels making it a weak direct vasodilator and presents a minimal direct

effect on atrioventricularnodal conduction.[7] In order, the effect of Ranolazine is obtained via a combination between the inhibition of the delayed rectifier potassium currents and the inward sodium current inhibition.[6] Some other mechanisms have been elucidated in which Ranolazine presents antagonistic activity towards the alpha1- and beta1-adrenergic in animal models as well as an inhibitory profile against fatty acid oxidation.[6]

Role in angina

Ranolazine is an antianginal with a non-haemodynamic mechanism of action. It is used as adjunctive therapy in patients with chronic stable angina whose angina is uncontrolled adequately with conventional treatment such as beta blockers and rate-limiting calcium antagonists. Randomised clinical trials show that the drug improves exercise performance, decreases angina and nitrate consumption, compared to placebo. Observational experience suggests that Ranolazine response rates are encouraging in additional therapeutically challenging patients after revascularisation and within the presence of multiple other antianginal medications. It is comparatively well tolerated with little effect on haemodynamics or cardiac conduction, apart from a modest increase in QT interval, which is not clinically compromising. Ranolazine has potential use during a number of other cardiovascular conditions but presently it offers a useful alternative and adjunct to standard antianginals in selected patients with chronic stable angina.[8]

Effects of Ranolazine on Astrocytes and Neurons in Primary Culture

Ranolazine also acts in the central nervous system and it has been proposed for the treatment of pain and epileptic disorders. Under the hypothesis that Ranolazine could act as a neuroprotective drug, we studied its effects on astrocytes and neurons in primary culture. We incubated rat astrocytes and neurons in primary cultures for 24 hours with Rn (10−7, 10−6 and 10−5 M). Cell viability and proliferation were calculated using trypan blue exclusion assay, MTT conversion assay and LDH release assay. Apoptosis was determined by Caspase 3 activity assay. The effects of Ranolazine on proinflammatory mediators IL-β and TNF-α decided by ELISA technique and protein expression levels of Smac/Diablo, PPAR-γ, Mn-SOD and Cu/Zn-SOD by western blot technique. In cultured astrocytes, it significantly increased cell viability and proliferation at any concentration tested, and decreased LDH leakage, Smac/Diablo expression and Caspase 3 activity indicating less cell death. It also increased anti-inflammatory PPAR-γ protein expression and reduced pro-inflammatory proteins IL-1 β and TNFα levels. Additionally, antioxidant proteins Cu/Zn-SOD and Mn-SOD notably increased after Ranolazine addition in cultured astrocytes. Conversely, Ranolazine didn't exert any effect on cultured neurons. In conclusion, it could act as a neuroprotective drug in the central nervous system by promoting astrocyte viability, preventing necrosis and apoptosis, inhibiting inflammatory phenomena and inducing anti-inflammatory and antioxidant agents.[9]

Role in diabetes mellitus

Type-2 diabetes is a global health problem with increasing prevalence, associated with significant cardiovascular morbidity and mortality. The incidence of type 2 diabetes is increased in patients with acute coronary syndrome (ACS), and such patients also have increased risk for coronary artery disease (CAD), CAD related death, and stroke. The presence of type 2 diabetes is related to a worse prognosis in patients with stable and unstable CAD. Thus, it's going to be desirable to possess drugs that focus on both type 2 diabetes and CAD. In clinical trials in chronic angina, Ranolazine treatment was related to significant reductions in glycosylated hemoglobin (HbA1c). Data from the CARISA study showed that Ranolazine, during a dose-dependent manner, lowered HbA1c in subjects with chronic angina and sort of type 2 diabetes. Data from the MERLIN-TIMI-36 study revealed that Ranolazine lowered HbA1c in subjects with diabetes and reduced the incidence of newly elevated HbA1c in initially normoglycemic subjects. In nonclinical studies, Ranolazine was found to lower fasting and nonfasting glucose levels and preserve pancreatic b-cells in streptozotocin-treated mice and Zucker diabetic fatty rats. More recent data show that Ranolazine inhibits glucagon secretion by blocking the $Na_v1.3$ isoform of sodium channels in pancreatic a-cells, leading to glucagon- and glucose lowering effects in animal models of diabetes. Given that increases in glucagon secretion by a-cells and the failure of glucagon suppression following oral glucose are well documented in type 2 diabetes, these data suggest a novel and plausible mechanism for Ranolazine's putative antidiabetic properties. Although the HbA1c-lowering effect double-blind, randomized, placebo controlled trial evaluating the safety and efficacy of Ranolazine monotherapy in subjects with type 2 diabetes and inadequate glycemic control with diet and exercise alone of Ranolazine has been observed in four previous clinical studies, those studies were not prospectively designed to determine the effect of Ranolazine on glycemic parameters. In addition, the effect of Ranolazine on HbA1c within these trials was studied in the presence of other antidiabetic medications (which weren't controlled). We present the primary double-blind, randomized, placebo controlled trial evaluating the security and efficacy of Ranolazine monotherapy in subjects with type 2 diabetes and inadequate glycemic control with diet and exercise alone.[10]

Ranolazine attenuates transtuzumab- induced heart dysfunction by modulating ROS production

Trastuzumab is the prototypical anti-ErbB2 drug, and the first developed and most widely used biologic

anticancer agent. Since its introduction in 1998, trastuzumab has dramatically improved the clinical history of breast cancer patients, but unfortunately it has been shown to cause cardiac dysfunction. It has been hypothesized that ErbB2 blockers can hamper cardiomyocytes, especially when exposed to other stressors, such as pressure or volume overload or anthracyclines, eventually leading to cardiac dysfunction. The late Na+ current inhibitor Ranolazine has emerged as a possible therapeutic to treat experimental coronary failure and has also been recently indicated as a promising cardio-oncological drug. The study here suggests that Ranolazine is also able to blunt trastuzumab cardiotoxicity, and this effect seems to involve a reduction in oxidative stress. Along this line, our leads to NRVM show that attenuation of trastuzumab toxicity with Ranolazine is indeed obtained by reducing ROS production, and our in vivo data show better LV function with Ranolazine+trastuzumab compared with Trastuzumab alone. The fact that Trastuzumab elicited only a modest rise in ROS in non-stressed NRVM is compatible with the cardiotoxic effect of ErbB2 blockers that might be negligible per se, but exacerbated when administered under conditions of cardiac stress or in previously diseased hearts (e.g., increased pressure or volume overload) or in presence of cardiovascular risk factors (age, obesity, smoking, hypertension, previous exposure to anthracyclines. This study support previous findings on the efficacy of Ranolazine in experimental heart dysfunction. Further experiments may be necessary to conclude that the mechanism of action involves the levels of ROS, also considering that Ranolazine has been recently shown to be able to antagonize b-adrenergic stimulation and decrease myofilaments Ca2+ sensitivity, with little therapeutic efficacy in a HCM murine model in vivo. Nevertheless, we show that in the cardio-oncologic setting, beside doxorubicin cardiotoxicity, RAN could also be a promising cardioprotective drug in the setting of Trastuzumab toxicity. More efforts involving both experimental and clinical studies will be needed in order to establish whether Ranolazine might be introduced clinically in the herapeutic strategies that aim at addressing cardiotoxicity induced by Trastuzumab or anthracyclines.[11]

Impact of Ranolazine on ventricular arrhythmias

Our systematic study showed that Ranolazine appears to have a beneficial effect in reducing the incidence of ventricular arrhythmias. This is consistent with its ventricular effects through inhibition of the late inward sodium current INa while possessing greater potency in modulating peak INa in atrial cardiomyocytes. Increased late INa leads to Ca2+ overload through Na/Ca exchange in the reverse mode, leading with that way in electrophysiologic instability with action potential duration prolongation, early after depolarizations, and delayed after depolarizations. Additionally, Ranolazine leads to a reduction in the transmural dispersion of repolarization response to agents and pathophysiological conditions that reduce the repolarization reserve with a preferential abbreviation of midmyocardial cell action potential duration (where late INa is most prominent). Furthermore, Ranolazine inhibits the IKr, which leads to action potential prolongation in the ventricles. Thus, the net effect of Ranolazine is determined by the relative magnitude of late INa (inward) and IKr (outward) currents during the repolarization period. Furthermore, Ikr inhibition is the reason of the QT interval prolongation caused by Ranolazine. Another possible mechanism for its beneficial role in arrhythmias is the anti-ischemic properties. Moreover, Ranolazine may be a weak inhibitor of L type calcium channel current (ICa, L), and for that reason, it does not affect significantly the myocardial contractility and heart rate at therapeutic doses. Ranolazine seems to have a beneficial role in ventricular arrhythmias in different clinical settings.[12]

Role in Prevention of Atrial Fibrillation after Cardiac Surgery

POAF is usually a transient, reversible phenomenon which will develop in patients in danger. Multiple mechanisms are involved within the development of POAF including pericardial inflammation, catecholamine surge, autonomic imbalance, and interstitial mobilization of fluid with resultant changes in volume. POAF is typically asymptomatic but is related to increased morbidity and mortality. Although perioperative beta-blockers, amiodarone, sotalol, calcium channel blockers, and magnesium are used for the prevention of POAF, they are limited by adverse events (including hypotension and bradycardia) and by their suboptimal efficacy and potential for pro-arrhythmia risk. Ranolazine, a piperazine derivative, exerts antiarrhythmic effects in both the ventricles and therefore the atria and has been evaluated to stop POAF. Although the precise mechanism for antiarrhythmic effect is unknown, within the atrial tissue, Ranolazine may suppress AF primarily by inhibiting peak sodium current (INa) and also causes inhibition of the delayed rectifier potassium (Ikr) current, resulting in a decrease in atrial myocardium sensitivity and vulnerability to AF. Ranolazine reduces acetylcholine (Ach) mediated AF through different mechanisms by inhibiting INa, Ikr and, peak INa resulting in a discount of nerve impulse upstroke and an increase within the diastolic threshold of excitation and post-repolarization refractoriness. Several studies have demonstrated the clinical efficacy of Ranolazine for the prevention of AF and was related to a big reduction of supraventricular tachyarrhythmia ($p < 0.001$) as well as a 30% reduction in new-onset AF ($p = 0.08$) within the Metabolic Efficiency with Ranolazine for fewer Ischemia in Non-ST-elevation acute coronary syndromes –Thrombolysis

in myocardial infarct (MERLIN-TIMI) 36 trial. Ranolazine is useful in maintaining sinus rhythm in patients with resistant AF. Another study by an equivalent authors suggested that one dose of Ranolazine 2000 mg is effective in converting 77% of AF patients to sinus rhythm with no significant adverse drug reactions. The Ranolazine in AF Following an Electrical Cardioversion (RAFFAELLO) study assessed the security and efficacy of Ranolazine within the prevention of AF recurrence after successful electrical cardioversion. AF recurred in 56.4%, 56.9%, 41.7%, and 39.7% of patients within the placebo, Ranolazine 375 mg, Ranolazine 500 mg, and Ranolazine750 mg groups, respectively. The reduction in overall AF recurrence within the combined 500-mg and 750-mg groups was of non-significance compared to the placebo group (P = 0.053) and significant compared to 375-mg group (P = 0.035). The results from this systematic review must be evaluated within the context of its potential limitations. Firstly, the included studies were single-sited, retrospective observational and prospective evaluations of the report of POAF after Ranolazine therapy. These studies included younger patients with a mean age of but 70 years and mean left ventricular ejection fraction >50% suggesting these patients were at low risk for developing POAF. Other important characteristics of left atrial size weren't included. Many of the studies had small sample sizes with varied duration times and surveillance methods. Therapy on top of things group is diverse among all the studies and two studies didn't disclose the sort of "standard therapy" being implemented. The dosing, initiation and termination of Ranolazine also varied among the studies. Although limited by lack of size and adequate control groups, the literature does suggest that Ranolazine could also be an efficacious and safe therapy for the prevention of POAF following cardiac surgery. However, multi-center, large, randomized controlled trials are necessary.[13]

Ranolazine in High-Risk Patients with Implanted Cardioverter-Defibrillators

In high-risk ICD (implantable cardioverter-defibrillators) patients, treatment with Ranolazine did not significantly reduce the incidence of the primary composite outcome of VT (ventricular tachycardia) or VF (ventricular fibrillation) or death. There was no significant variation in the risk of VT or VF requiring ICD shocks or death between treatment arms. However, Ranolazine administration was associated with a marginally significant 30% reduction in pre-specified secondary endpoint of recurrent VT or VF requiring an ICD therapy (Central Illustration). It is worth emphasizing that a significant reduction in the occurrence of recurrent VT or VF requiring ICD therapy on Ranolazine versus placebo was observed without significant difference in mortality between arms (HR for Ranolazine vs. placebo: 0.97), and without evidence for pro arrhythmia (the HR for VT or VF requiring ICD shocks was 0.97 and for polymorphic VT the HR (Hazard Ratio) was 0.81when comparing patients assigned to the Ranolazine arm vs. the placebo arm). There were no other significant reductions in any of the other pre-specified secondary endpoint. The absence of any difference in mortality between high-risk ICD patients treated with Ranolazine versus placebo is consistent with the results of the MERLIN and RIVER-PCI (Ranolazine in Patients with Incomplete Revascularization after Percutaneous Coronary Intervention) trials. We showed that there was no significant difference in the risk of first VT or VF requiring ICD shocks (HR: 1.01) or in the risk of recurrent VT or VF requiring ICD shocks (HR: 0.97).These observations indicate that the risk of fast ventricular tachyarrhythmias appears not to be influenced by Ranolazine, and is in contrast to some preclinical studies suggesting that late sodium current inhibition with Ranolazine reduces the susceptibility to VF. The significant reduction in the risk of pre-specified secondary endpoint of recurrent VT or VF requiring ICD therapy attributed to reduction of recurrent VT requiring ATP therapy and reduction in the first VT requiring ATP therapy in pre-specified sensitivity analyses in the ranolazine arm is consistent with preclinical observations showing that Ranolazine inhibits early and delayed after depolarizations; reduces transmural dispersion of repolarization; inhibits spatially discordant repolarization alternans; prevent spacing-induced re-entry; and reduces the incidence, frequency, and duration of VT. The late sodium current seems to be less prominent at high heart rates, and therefore VT or VF at high heart rates may not be driven by late sodium current. Treatment with Ranolazine in high-risk ICD patients did not significantly reduce the incidence of the primary composite outcome of VT, VF, or death. However, the study was underpowered to detect a difference in the primary endpoint. In pre-specified secondary endpoint analyses, Ranolazine administration was associated with a significant reduction in recurrent VT or VF requiring ICD therapy without evidence for increased mortality.[14]

CONCLUSION

By preventing calcium overloading and reducing diastolic tension in cardiomyocytes, Ranolazine is an important adjunct in the management of stable angina pectoris. However various studies shown that Ranolazine may be particularly attractive in diabetic patients with angina since it leads to a reduction in glucose levels. Experimental studies showed promising role of Ranolazine in the treatment of heart failure, neuroprotective, transtuzumab- induced heart dysfuntion, ventricular arrhythmias, Prevention of Atrial Fibrillation after Cardiac Surgery, in High-Risk Patients with Implanted Cardioverter-Defibrillators. There is a vast scope for study on other pharmacological actions of Ranolazine in future.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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