www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating 2017: 5.03
TPI 2017; 6(3): 232-234

www.thepharmajournal.com
Received: 06-01-2017
Accepted: 07-02-2017

Sergiy Fedorov
Department of Therapy and Family Medicine of Postdiploma Faculty, Ivano-Frankivsk National Medical University Ivano-Frankivsk, Ukraine

Correspondence
Sergiy Fedorov
Department of Therapy and Family Medicine of Postdiploma Faculty, Ivano-Frankivsk National Medical University Ivano-Frankivsk, Ukraine

Ranolazine: Antianginal medicine or more?

Sergiy Fedorov

Abstract
Ranolazine, a piperazine derivative sold, is a well-tolerated medication that selectively inhibits the late sodium current. It has beneficial metabolic properties and does not affect heart rate or blood pressure. Ranolazine is currently approved in the United States and Europe as a second-line agent in the management of stable angina pectoris. In this review we showed that ranolazine is perspective medication for arrhythmia treatment.

Keywords: Ranolazine, atrial fibrillation, ventricular arrhythmia

1. Introduction
Coronary artery disease (CAD) is a major cause of death and disability in developed countries [1]. Although the mortality for this condition has gradually declined over the last decades in western countries, it still causes about one-third of all deaths in people older than 35 years [2]. The Framingham Heart Study perfectly summarizes the risk factors that contribute to the development of CAD, providing critical information regarding objectives for the primary and its secondary prevention.
The 2016 Heart Disease and Stroke Statistics update of the American Heart Association (AHA) has recently reported that 15.5 million persons ≥20 years of age in the USA have CAD, whilst the reported prevalence increases with age for both women and men and it has been estimated that approximately every 42 seconds, an American will suffer for an myocardial infarction (MI) [3].
Ranolazine, a piperazine derivative sold, is a well-tolerated medication that selectively inhibits the late sodium current. It has beneficial metabolic properties and does not affect heart rate or blood pressure. Ranolazine is currently approved in the United States and Europe as a second-line agent in the management of stable angina pectoris (SAP) [4].
The American College of Cardiology Foundation and the American Heart Association published the Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease in 2012, where ranolazine was recommended for patients with stable ischemic heart disease if unable to use acceptable doses of β-blockers (Class of recommendation IIa, Level of Evidence B) [5]. Lastly, The European Society of Cardiology 2013 guidelines recommend ranolazine among agents for second-line symptomatic treatment for angina, without evidence of benefit on prognosis (Class of recommendation IIa and Level of Evidence B) [6].
The aim of this study is review of results of current trials of anti-arrhythmic properties of ranolazine.

2. Material and Methods: We reviewed of PubMed database for last years. In this base 819 items were founded published in the last 5 years.

3. Results and Discussion
Ranolazine is *N*-(2,6-dimethylphenyl)-4(2-hydroxy-3- [2-meth-oxyphenoxy]-propyl)-1-piperazine acetamide dihydrochloride. At clinically therapeutic levels, ranolazine inhibits sodium and potassium ion channel currents. Inhibition of the late phase of the inward sodium current during cardiac repolarization has been well studied [7]. In disease states, enhanced sodium–calcium exchange due to augmented late phase of the inward sodium current activity leads to increased cytosolic calcium concentration. Intracellular calcium overload is believed to be critical to the mechanism of decreased left ventricular relaxation caused by ischemia and reperfusion. Elevated left ventricular diastolic wall tension compromises myocardial blood flow even further.

Additionally, calcium overload has adverse effects on myocardial electrical activity predisposing to ventricular tachycardia [8]. While this mechanism has been well studied primarily in rats, the anti-ischemic effect of ranolazine as a result of late Na channel inhibition improving myocardial perfection lacks data to support this mechanism in patients with ischemic heart disease.

Ranolazine also inhibits the delayed rectifier potassium current (IKr) at clinically therapeutic concentrations, which prolongs the ventricular action potential duration. The net effect of ranolazine on action potential duration is a balance between the effects of rectifier potassium current and late phase of the inward sodium current inhibition, which is generally a prolongation of QTc by 2 to 6 ms. [9]

Additional mechanisms of ranolazine activity have been studied such as adrenergic receptor binding and fatty acid oxidation inhibition. Ranolazine has α_1- and β_1-adrenergic antagonist activity in animal models, classically without negative chronotropic, dromotropic, or inotropic activity at rest or exercise [10]. However, a recently reported effect on both heart rate and rate pressure product has been observed in human subjects during stress. Inhibition of fatty acid oxidation by ranolazine was initially proposed as the main anti-ischemic mechanism. However, further evaluation using the therapeutic doses of ranolazine disproved this theory. Currently, the mechanism of action as an anti-anginal medication is not yet understood [4].

In summary, ranolazine inhibits the late phase of the inward sodium current in ventricular myocardial cells, which reduces intracellular calcium overload and associated diastolic contractile dysfunction. The recently reported effect of ranolazine on heart rate and rate pressure product in humans is novel and will need further evaluation.

The role of ranolazine as an adjunctive anti-arrhythmic agent for atrial fibrillation (AF) has been evaluated in several studies. The mechanism of its action has been proposed to reduce atrial excitability and prolong the atrial refractory period [11].

The role of ranolazine as an adjunctive anti-arrhythmic agent for atrial fibrillation (AF) has been evaluated in several studies. A randomized study of 121 patients with recent onset AF (<48 hours) evaluated the effect of amiodarone infusion (loading dose 5 mg/kg followed by maintenance of 50 mg/h) plus ranolazine (1500 mg single dose) versus amiodarone infusion alone for conversion to sinus rhythm. A significantly higher conversion rate at 24 hours (87% versus 70%, respectively; P=0.024) and at 12 hours (52% versus 32%; P=0.021) in the ranolazine plus amiodarone infusion group was observed [12].

In the recent Combined Ranolazine and Dronedarone in the Management of Paroxysmal Atrial Fibrillation: Mechanistic and Therapeutic Synergism (HARMONY) trial, 134 patients with paroxysmal AF and implanted pacemakers were randomized to ranolazine 750 mg BID, dronedarone 150 mg BID, dronedarone 225 mg BID, combination therapy, or placebo. This moderate dose of ranolazine combined with the reduced-dose dronedarone (which is currently available as 400 mg) was hypothesized to have complementary electrophysiological properties with a potential increased safety and tolerability profile. After 12 weeks of treatment, a significant 59% reduction (P=0.008) in AF burden was observed in the combination therapy group (ranolazine 750 mg BID/dronedarone 225 mg BID) compared with placebo. No significant reduction in AF burden was noted in the placebo, either drug alone, or combination therapy with dronedarone 150 mg BID groups [13].

In other trial 173 consecutive patients (68 ± 10 years, 54% male) with recent-onset (<48-hour duration) AF who were eligible for pharmacologic cardioversion were enrolled. Patients were randomized to intravenous amiodarone, or amiodarone plus a single oral dose of ranolazine [14]. Mean left atrial diameter did not significantly differ between groups. The combination therapy group compared with the amiodarone only group showed significantly shorter time to conversion (8.6 ± 2.8 hours vs 19.4 ± 4.4 hours, P < 0.0001) and higher conversion rate at 24 hours (98% vs 58%, P < 0.001). Left ventricular ejection fraction did not markedly vary between the two groups and ranged within moderately reduced values. No serious clinically evident adverse effects were observed in any of the patients receiving either amiodarone or the combination treatment.

Recent meta-analysis of 484 initially identified studies, 8 randomized controlled trials (RCTs) on the use of ranolazine for prevention and cardioversion of AF have yielded conflicting results [15]. The analysis of RCTs showed that ranolazine significantly reduced the incidence of AF compared to the control group in various clinical settings, such as after cardiac surgery, in acute coronary syndromes, and post-electrical cardioversion of AF (relative risk [RR] 0.67, 95% confidence interval [CI] 0.52-0.87, Z = 3.06, P =.002). Furthermore, a higher conversion rate of AF from the combined use of it and amiodarone compared to amiodarone alone (RR 1.23, 95% CI 1.08-1.40, Z = 3.07, P =.002) was clear, with conversion time significantly shorter in ranolazine plus amiodarone compared to the amiodarone group (weighted mean difference [WMD] = -10.38 hours, 95% CI -18.18 to -2.57, Z = 2.61, P =.009). Thus, this meta-analysis suggests that ranolazine may be effective in AF prevention, whereas it potentiates and accelerates the conversion effect of amiodarone of recent-onset AF. Larger RCTs with long-term follow-up in diverse clinical settings are needed to further clarify the impact of ranolazine on AF therapy.

Its perspective to use of ranolazine in ventricular arrhythmia treatment. 59 patients with symptomatic premature ventricular contraction (PVCs) were identified from full-disclosure Holters. Doses of 500 and 1,000 mg offlabel ranolazine, daily, were given to 34 and 66% patients, respectively, and repeat Holters were performed prospectively during mean followup of 3.1 months. The mean age of the patients was 63 years, 60% were males, mean left ventricular ejection fraction was 60%, with 34% having coronary artery disease, 73% were hypertensive, 24% had type 2 diabetic, and 34% were on beta blockers. Upon repeat Holters at a mean of 3.1 months after initiating ranolazine, 95% (56/59) of the patients had their PVC count reduced as follows: 24% (14/59) had more than 90% decrease, 34% (20/59) had 71 to 90% decrease, and 17% (10/59) had 50 to 70% decrease. In the entire group, ranolazine reduced PVCs by 71% (mean: 13,329 to 3,837; $p < 0.001$). Ventricular bigeminy was reduced by 80% (4,168 to 851; $p < 0.001$), ventricular coupletswere reduced by 78% (374 to 81; $p < 0.001$), and ventricular tachycardiawas reduced by 91% (56 to 5; $p < 0.001$). The PVC reduction was dose dependent. Off-label ranolazine offers an effective and safe pharmacologic treatment for symptomatic triggered PVCs. A large, prospective randomized study is needed [16].

In a substudy of the MERLIN-TIMI 36 trial, Holter electrocardiographic monitoring showed that the patients who received ranolazine in addition to the standard therapy

showed significant reduction in ventricular tachycardia (VT) lasting ≥8 beats compared with placebo at 24 hours (2.3% vs 3.4%; RR: 0.67, 95% CI: 0.50-0.90, *P*= 0.008) and 48 hours (3.1% vs 4.7%; RR: 0.65; 95% CI: 0.51-0.84, *P* < 0.001) after randomization [7]. An ongoing randomized trial, the Ranolazine Implantable Cardioverter-Defibrillator (RAID) trial, is currently evaluating the efficacy of ranolazine on top of standard therapy in reducing ventricular arrhythmia and death in patients with ICDs.

In a head-to-head study, ranolazine was found to be as effective as sotalol and lidocaine in the prevention of ischemia/reperfusion induced arrhythmias in anesthetized rats (*P* = 0.01 in sotalol group vs control, *P* = 0.10 in lidocaine group vs control, and *P* = 0.048 in ranolazine group vs control) [17]. When combined with dronedarone in low doses, ranolazine led to blunting of ischemia-induced T-wave heterogeneity and VT vulnerability in Yorkshire pigs [18].

4. Conclusion

Ranolazine, although approved as a second-line antianginal medicine, is not approved for use as an antiarrhythmic but has a potential antiarrhythmic role in the prevention as well as management of atrial and ventricular arrhythmias.

5. References

1. Roger VL. Epidemiology of myocardial infarction. Med Clin North Am. 2007; 91:537-552.
2. Nichols M, Townsend N, Scarborough P. Cardiovascular disease in Europe 2014: epidemiological update. Eur Heart J 2014; 35: 2929.
3. Writing Group Members, Mozaffarian D, Benjamin EJ. Executive Summary: Heart Disease and Stroke Statistics - 2016 Update: A Report From the American Heart Association. Circulation. 2016; 133:447-454.
4. Rayner-Hartley E, Sedlak T, Ranolazine. A Contemporary Review. Journal of the American Heart Association. 2016; 5: e003196.
5. Fihn SD, Gardin JM, Abrams J. ACCF/AHA/ACP/AATS/ PCNA/ SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons.Circulation. 2012; 126:354-471.
6. Montalescot G, Sechtem U, Achenbach S. ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013; 34:2949–3003.
7. Scirica BM, Morrow DA, Hod H. Effect of ranolazine, an antianginal agent with novel electrophysiological properties, on the incidence of arrhythmias in patients with non ST-segment elevation acute coronary syndrome: results from the Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) randomized controlled trial. Circulation. 2007; 116:1647-1652.
8. Hale SL, Shydrock JC, Belardinelli L, Sweeney M, Klon er RA. Late sodium current inhibition as a new cardioprotective approach. J Mol Cell Cardiol. 2008; 44:954–967.
9. Gupta L, Khera S, Kolte D, Aronow WS, Isai S. Antiarrh ythmic properties of ranolazine: a review of the current evidence. Int J Cardiol. 2015; 187:66-74.
10. Letienne R, Vie B, Puech A, Vieu S, Le Grand B, John GW. Evidence that ranolazine behaves as a weak beta1- and beta2-adrenoceptor antagonist in the rat cardiovascular system. Naunyn Schmiedebergs Arch Pharmacol. 2001; 363:464-471.
11. Shryock JC, Song Y, Rajamani S, Antzelevitch C, Belard inelli L. The arrhythmogenic consequences of increasing late INa in the cardiomyocyte. Cardiovasc Res. 2013; 99:600-611.
12. Koskinas KC, Fragakis N, Katritsis D, Skeberis V, Vassil ikos V. Ranolazine enhances the efficacy of amiodarone for conversion of recent-onset atrial fibrillation. Europace. 2014; 16:973-979.
13. Reiffel JA, Camm AJ, Belardinelli L, Zeng D, Karwatow ska-Prokopczuk E, Olmsted A, Zareba W, Rosero S, Kowey P. HARMONY Investigators. The HARMONY Trial: combined ranolazine and dronedarone in the management of paroxysmal atrial fibrillation: mechanistic and therapeutic synergism. Circ Arrhythm Electrophysiol. 2015; 8:1048-1056.
14. Tsanaxidis N, Aidonidis I, Hatzifthimeou A. Ranolazine added to amiodarone facilitates earlier conversion of atrial fibrillation compared to amiodarone-single therapy. Pacing Clin. Electrophysiol, 2017. doi: 10.1111/pace.13048.
15. Gonq M, Zhanq Z, Fraqakis N. Role of ranolazine in the prevention and treatment of atrial fibrillation: A meta-analysis of randomized clinical trials. Heart Rhythm. 2017; 14:3-11.
16. Murray GL. Ranolazine is an Effective and Safe Treatment of Adults with Symptomatic Premature Ventricular Contractions due to Triggered Ectopy. Int. J Angiol. 2016; 25(4):247-251.
17. Kloner RA, Dow JS, Bhandari A. First direct comparison of the late sodium current blocker ranolazine to established antiarrhythmic agents in an ischemia/reperfusion model. J Cardiovasc Pharmacol Ther. 2011; 16:192-196.
18. Verrier RL, Pagotto VPF, Kanas AF. Low doses of ranolazine and dronedarone in combination exert potent protection against atrial fibrillation and vulnerability to ventricular arrhythmias during acute myocardial ischemia. Heart Rhythm. 2013; 10:121-127.