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Review Article

Ranolazine: A review on its safety, efficacy and therapeutic indications and overview on analytical methods

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ABSTRACT

Myocardial ischemia is related to reduced ATP fluxes and energy supply leading to disturbances of intracellular ion stability in cardiac muscle cells. From current era, raised persistent (late) sodium current was recommended to contribute to disturbed ion stability by increasing intracellular sodium concentration following with elevation of intracellular calcium. The treatment of angina is specific with prevention of disease development by risk reduction.

The new anti-ischemic drug ranolazine is a specific late sodium current inhibitor which reduces sodium overload and enhances disturbed ion stability. This is related with symptomatic improvement of angina. Additionally, ranolazine shows anti-arrhythmic effects. Contraindications may occur in some cases or may remain unrelieved from anginal discomfort with conventional drug therapy. Among newer alternatives, ranolazine indirectly reduces the intracellular calcium overload associated with cardiac ischemia. It is known as a valid addition to traditional therapy. Recent reports showed some potential side effects of ranolazine in the arrhythmia therapy. This review offers an overview of the essential principles of ranolazine within the

treatment of myocardial ischemia and assessing its applications in the new field of anti-arrhythmic effects. The review also outlines the different analytical methods carried out for determination of ranolazine.

KEYWORDS: Ranolazine, Myocardial ischemia, Anti-arrhythmic, ATP fluxes, Drug therapy, Angina.

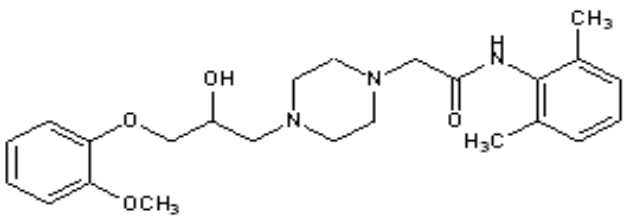
INTRODUCTION:

Cardiovascular disease is the main reason of death in the western world about more than one million deaths per year. In the United States, stable angina pectoris affects more than 9 million of population as a part of morbidity correlated with coronary artery disease. The condition is caused due to pathological instability of cardiac oxygen demand and supply. [1] Cardiac oxygen demand is analyzed by heart rate, contractility, left ventricular wall stress and systolic blood pressure. While myocardial oxygen supply is specifically dependent on coronary blood circulation and diastolic perfusion pressure. [2]

Chronic angina is a condition that reduces quality of life and affects 6.4 million Americans is related with reduced life anticipation. Current treatment that lessen angina frequency and increase the entrance at which myocardial ischemic symptoms become visible includes drugs, exercise conditioning. Several new drugs are being investigated for improvement in the treatment of chronic angina. [3]

Ranolazine, a piperazine derivative is a well-tolerated drug that specifically inhibits the late sodium current. Moreover, ranolazine has a favorable metabolic effect that does not affect heart rate/ blood pressure. Ranolazine was approved on January 2006. Ranolazine is currently accepted as a second-line drug in the treatment of chronic stable angina pectoris. This review will focus on effects of ranolazine, a drug that decreases angina symptoms, with a mechanism of action different from that of currently available therapies. [4,5]

Drug Profile:

Drug	Ranolazine
Structure	
IUPAC name	*N*-(2,6-dimethylphenyl)-2-[4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]piperazin-1-yl]acetamide
Molecular formula	$C_{24}H_{33}N_3O_4$
Molecular weight	427.5 g/mol
Solubility	Soluble in dichloromethane, methanol; sparingly soluble in tetrahydrofuran, ethanol, acetonitrile, acetone; slightly soluble in ethyl acetate, isopropanol, toluene, ethyl ether; very slightly soluble in water
Physical forms	White to off-white solid

Mechanism of Action:

The activity of ranolazine is to inhibit late sodium current therefore prevent sodium overload of the cell. As a result, ranolazine prevents reverse mode of sodium and calcium exchange, thus diastolic build up of calcium resulting in enhanced diastolic tone and improved coronary blood flow. [6,7]

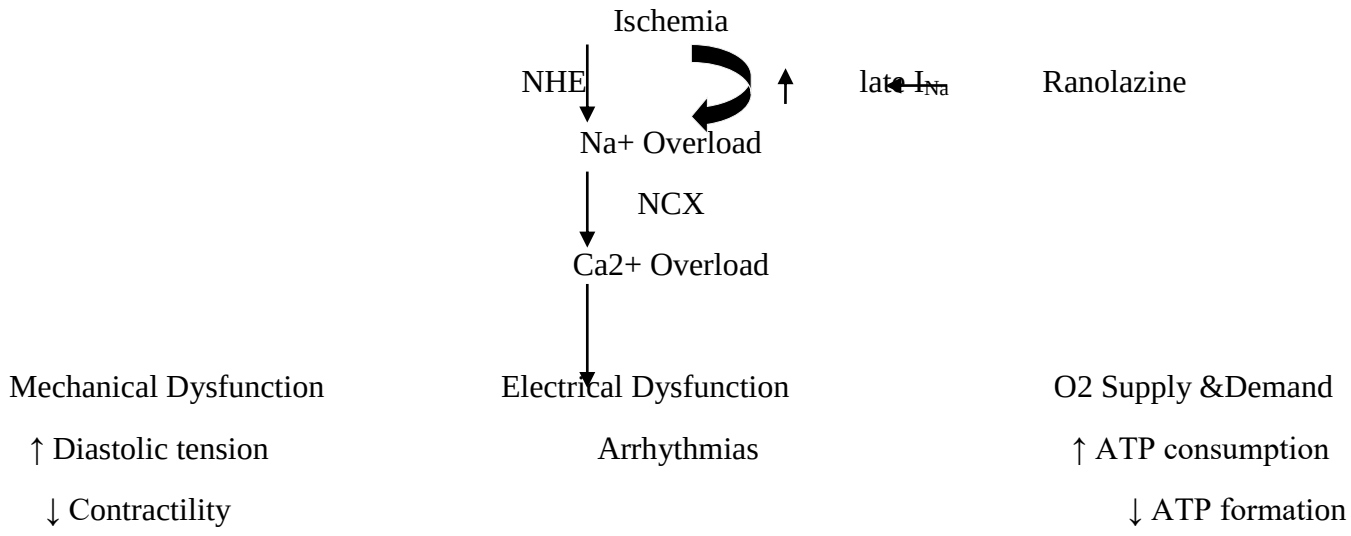


Fig. Activity of Ranolazine

Pharmacology:

- **Pharmacokinetics:**

Ranolazine is rapidly metabolized in the liver. Primarily it is metabolized through the Cytochrome P-450 3A enzyme (CYP3A) pathway and in the intestine. [8] More than 70% of the drug is excreted in the urine. This pharmacokinetic profile of ranolazine includes careful dose adjustments in patients who are older, whose weight is less than 60 kg and have mild-to-moderate renal deficiency or hepatic impairment, and in patients who are in New York Heart Association (NYHA) functional class III–IV. [9] Ranolazine is restricted in patients with severe renal dysfunction or hepatic impairment. The use of ranolazine has not been studied in patients who are undergoing renal transplant therapy. [10]

- **Pharmacodynamics:**

Ranolazine inhibits Na and K ion channel currents. Restriction of the late phase of sodium current entering during myocardial repolarization has been studied. In disease condition, increased sodium and calcium exchange due to increased late phase of the entering sodium current action activates increased cytosolic calcium concentration. [11] Intracellular calcium overload is believed to be harmful to the mechanism of reduced left ventricular relaxation caused by ischemia and reperfusion. Raised left ventricular diastolic pressure compromises cardiac blood flow. Eventually, calcium overload has several side effects on myocardial electrical activity predisposing to ventricular tachycardia. Meanwhile the mechanism of ranolazine has been studied in rats, as a result of late sodium ion channel inhibition improving myocardial perfection lack of data to support this mechanism in ischemia patients. [12,13]

Safety:

Ranolazine did not induce clinically significant changes in heart rate or blood pressure during rest or exercise. Overall, the side effects increase with higher doses. However, all the side effects occurred are mild to moderate in general arises after using the drug and reduces with reducing the dose or discontinuation of treatment. The

increase in adverse events seen with the 1500 mg dose is disproportionately larger than the increase in anti-anginal effect. [14] Orthostatic hypotension and blackout were observed in some patients taking ≥ 1000 mg ranolazine, most likely due to consequent use of other medications that are known to increase the plasma concentration of ranolazine. This can be prevented by starting ranolazine at a low dose of 500 mg and increasing the dose as needed. [15]

Ranolazine is metabolized in the liver, so that precaution should be taken in those who use other drugs or patients with hepatic dysfunction as this may cause accumulation of ranolazine. Moreover, ranolazine is excreted mainly by the kidneys and so careful dose titration is recommended in patients with renal impairment. It is completely inhibited in patients with severe renal impairment. Ranolazine should be used cautiously with drugs like calcium-channel blocker, as this might increase the absorption and subsequently the plasma concentration of ranolazine. [16]

Efficacy:

Several clinical trials tested for the efficacy ranolazine in the treatment of chronic angina. The result shows ranging from negative effects to benefits of ranolazine as an anti-anginal treatment. This range of effects caused due to different dosages used. [17] The efficacy of the formulation was analyzed by clinical trials. The efficacy of the extended formulation of ranolazine for treating acute coronary syndrome shows no benefit for ranolazine. Ranolazine increases the treadmill exercise performance similar to that observed with other anti-anginal drugs. The beneficial effects of ranolazine seemed to be limited i.e., it reduces angina episodes by nearly 1 per week. Based on the findings, it is safe to say that ranolazine is recommended for the therapy of chronic angina as the sole drug, or combined with other treatments. [18,19]

Drug Interaction:

Due to ranolazine dependence on CYP3A metabolic pathways, the co-administration of different drugs can affect its renal clearance. In specific patients, ketoconazole is a potent CYP3A inhibitor that can increase concentrations of ranolazine to more than 3 times than expected value. Hence, ketoconazole is prohibited in patients who are taking ranolazine therapy. Inhibitors of CYP3A, such as verapamil and diltiazem must be used with cautiously. [20,21] Simvastatin is a weak inhibitor of CYP3A, does not increase ranolazine levels. Macrolide antibiotics, human immunodeficiency virus protease inhibitors should be used with caution. Ranolazine has been shown to enhance serum digoxin levels by 1.5 times that leading to suggested that digoxin doses should be altered in patients who are taking both drugs treatment. [22]

Side effects:

The common side effects are nausea, dizziness, headache and constipation. Less than 2% of patients experience the side effects. In several conditions, the symptoms are mild, and they occur within the 1st few weeks of therapy. Some patients have to discontinue the drug, most patients can tolerate reduced dose. [23,24]

Overview on analytical methods for Ranolazine:

Chromatographic method:

HPLC chiefly utilizes a column (stationary phase), a pump that transfer the mobile phase through the column, and a detector that exhibits the retention time of the analyte. Retention time depends upon the interactions between the stationary phase and the solvents (analyte) used. The sample to be analyzed is injected in small volume to the mobile phase and is restricted by specific chemical or physical interactions with the stationary phase. [25,26]

Sr. No.	Drug	Method	Description	References
1	Ranolazine	HPLC	Column- C18 Kromasil (4.6x 250mm, 5µm) Mobile phase- Methanol: Triethylamine 0.5% pH-6 with O-phosphoric acid (75:25) Wavelength- 271 nm Retention time- 3.71 min.	27
2	Ranolazine	RP-HPLC	Column-Inertsil ODS C18 Mobile phase- Buffer: Acetonitrile pH adjusted with triethylamine (60:40) Wavelength- 224	28
3	Ranolazine	RP-HPLC	Column- Hypersil BDS C18 (150 x 4.6mm, 5µm) Mobile phase- Disodium hydrogen orthophosphate buffer of pH 7: Acetonitrile (55:45) Wavelength- 205 nm Retention time- 7.6 min	29
4	Ranolazine	HPLC	Column- Agilent ZORBAX C18 Mobile phase- Acetonitrile: 0.1% Formic acid (90:10) Wavelength-273 nm	30
5	Ranolazine	RP-HPLC	Column- ODS C18 (250 x 4.6mm) Mobile phase- Acetonitrile: Methanol: THF (40:50:10) Wavelength- 269 nm Retention time- 4.1 min.	31
6	Ranolazine	RP-HPLC	Column- C8 (250 x 4.6mm, 5µm) Mobile phase- Ammonium acetate buffer: Acetonitrile (50:50) Wavelength- 220 nm Retention time- 9 min.	32
7	Ranolazine	HPLC	Column- Phenomenex Gemini C18 (100 x 4.6mm,3 µm) Mobile phase-Triethylamine buffer pH 6 adjusted with O-phosphoric acid: Acetonitrile (60:40) Wavelength- 273 nm Retention time- 5.08 min.	33

UV spectroscopic method:

First order derivative spectroscopic method and area under curve method was developed for the determination of Ranolazine. [34]

Sr. No.	Drug	Method	Description	Reference
1	Ranolazine in bulk and pharmaceutical formulation	UV method	Wavelength- 272 nm Linearity – 10-100 µg/ml Solvent-Methanol	35

2	Ranolazine in bulk and pharmaceutical dosage form	First order derivative spectroscopy	Wavelength- 271 nm Linearity – 20-100 µg/ml Solvent- 0.2% O-phosphoric acid	36
3	Ranolazine in API and tablet form	Area under curve method	Wavelength- 261 nm Linearity -75-200 µg/ml Solvent-Distilled water	37

CONCLUSION:

Chronic angina pectoris remains a major health problem in spite of multiple developing medical treatments. The adverse effects of conventional antianginal drugs can lead to morbidity and contribute to noncompliance with therapeutic administration. Ranolazine does not show many of the side effects. It is a potential alternative to conventional treatment. The safety, efficacy and tolerability of the drug have been studied in clinical trials. Patients with chronic angina appear to obtain beneficial clinical and symptomatic effects from ranolazine and reductions in ischemia. Ranolazine may be an effective anti-anginal treatment for millions of individuals who have chronic angina.

The efficacy of conventional therapies for chronic stable angina in several conditions novel compounds with different properties is required. This can happen for the treatment of those patients who are contraindicated to beta-blockers, nitrates, or calcium channel blockers. Ranolazine is a late sodium current inhibitor that carries out its action specifically on ischemic myocardiocytes without affect normal resting myocardiocytes. Several clinical trials pointed out the efficacy of ranolazine as antianginal drug. These studies also reported a favorable safety profile and highlighted that ranolazine controls angina symptoms and improves exercise tolerance without affecting heart rate or blood pressure. Its unique mechanism of action has shown several other studies, analyzing other applications of ranolazine. The analytical methods used for ranolazine was found to be safe and efficient.

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