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Review

Role of Ranolazine in cardiovascular disease and diabetes: Exploring beyond angina

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ABSTRACT

Ranolazine was FDA approved for chronic angina in 2006. Since then, there has been extensive research involving this drug. The mechanism of action, debatable at the time of approval, has been demonstrated. Ranolazine acts via inhibition of late sodium channel current in the myocardium. This acts by lowering abnormally high cytosolic calcium levels. Other possible clinical applications of Ranolazine have also been explored. Out of many lines of investigation, its effects in atrial fibrillation, especially post-CABG and recurrent atrial fibrillation show promise. It has also shown definite HbA1c lowering effects when used in diabetics with coronary artery disease. Other possible indications for the drug include pulmonary arterial hypertension, diastolic dysfunction and chemotherapy-induced cardiotoxicity. This review aims to summarize major research regarding Ranolazine in potential applications beyond chronic angina. There are few dedicated large, randomized, phase III trials exploring the newer effects of Ranolazine. There are a few such trials underway, but more are needed.

1. Introduction

Out of the 85.6 million Americans suffering from cardiovascular disease, chronic angina affects 8.2 million people [1]. Current therapeutic modalities include drugs (nitrates, beta-blockers, and calcium channel blockers), reconditioning (exercise) and revascularization of diseased coronary arteries. Among recently approved drugs, Ranolazine exerts effects via a completely different mechanism of action. Originally approved by FDA in 2006 for use in stable angina, this novel drug is showing promise in clinical situations apart from angina. This review is an attempt to summarize existing evidence and the emerging role of Ranolazine in applications beyond stable angina. A number of trials have been completed, while more are still ongoing. The results of these may point to new uses to this already familiar drug.

1.1. Ranolazine—pharmacology

Ranolazine ($C_{24}H_{33}N_3O_4$, PubChem CID: 56959 [2]) is a piperazine derivative approved by the FDA in 2006 for chronic angina [3]. It is available in the USA as extended release tablets of 500 or 1000 mg to be taken orally [4]. Typical doses are 500 to 1000 mg twice daily. Plasma concentration peaks 2 to 5 h after oral administration, and food has no effect on its pharmacokinetics [2]. It is metabolized extensively by hepatic cytochrome (CYP3A4 and CYP2D6) enzymes. The metabolites are primarily excreted via urine while only 5% of the drug is excreted unchanged. The elimination half life is just under 2 h for non-extended release preparations [5].

1.2. Ranolazine—mechanism of action

Cardiac myocytes are sensitive to ischemia. An imbalance between oxygen demand and supply triggers a disturbance in ion balance in myocardial cells. In response to ischemia, there is impaired inactivation and thus prolonged opening of late Na^+ channels. While fast Na^+ channels which are responsible for the upstroke (phase 0) of the action potential, late Na^+ channels play a role in repolarization of the cardiac myocyte [6,7]. Increased opening of late I_{Na} channels leads to an increase in cytosolic Na^+. This increased cytosolic Na^+ is exchanged via the Na^+–Ca^{+2} exchanger, leading to rise in Ca^{+2} levels intracellularly. As a result, LV relaxation is impaired and LV wall tension during diastole is increased. This impairs coronary blood flow to the already ischemic myocardium, further worsening ischemia [8]. Increased myocardial cytosolic Ca^{+2} also destabilizes the cell membrane, leading to increased excitability and predisposing to arrhythmias [9].

Ranolazine acts by blocking late sodium channels [8]. The rise of Na^+ and thus Ca^{+2} is blocked at the outset and there is no downstream rise in cytosolic Ca^{+2} concentrations. Both mechanical effects (impaired

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diastolic relaxation, worsened coronary blood flow, ischemia, angina) and electrical effects (arrhythmias) are thus inhibited by Ranolazine. LV wall tension is relieved, coronary blood flow is improved, and ischemia relieved. This is how Ranolazine is hypothesized to improve angina. Similarly, acting on the right ventricle (RV), it lowers RV wall tension and improves coronary blood flow. This effect is seen in pulmonary artery hypertension (PAH) where Ranolazine has demonstrated benefits.

By preventing the rise of intracellular Ca^{+2}, Ranolazine improves membrane stability and is the suspected mechanism in controlling or preventing arrhythmias (Fig. 1).

The I_{Na} blocking action of Ranolazine is not confined to cardiac myocytes. Dhalla et al. [10] postulated that Ranolazine blocks Na + channels in pancreatic islets alpha cells, thus inhibiting glucagon release. They put forward the hypothesis that this leads Ranolazine to exert antidiabetic actions, via a mechanism not very different from its anti-anginal action. However, Ranolazine has also been found to cause beta-cell preservation [11]. It has also been found to recruit muscle microvasculature, increasing endothelial surface area and allowing better tissue delivery of insulin [12]. These factors combined comprise the current understanding of the glycemic effects of Ranolazine.

The late potassium current is involved in myocyte repolarization. Ranolazine also inhibits the late rectifier K^+ current. This effect is evident at therapeutic concentrations and results in prolongation of the ventricular action potential [13]. Changes to the action potential duration are antagonized by late I_{Na} blockade. These antagonistic effects result in net a prolongation of QTc interval by 2 to 6 ms [14]. This mechanism could contribute to the antiarrhythmic actions of Ranolazine by supplementing the sodium channel blockade.

Evidence of beta-1 and beta-2 antagonist activity of Ranolazine has been shown in animal models [15]. However, the significance of this finding and how it is applicable in a clinical scenario needs further investigation.

A completely different mechanism of action for Ranolazine was initially proposed, via modulation of metabolic pathways in myocytes. It was found that Ranolazine shifted metabolic trends in myocardium from fatty acid to glucose utilization. This is more efficient in terms of oxygen utilization and reduces lactate production [16]. It was hypothesized that this would reduce myocardial oxygen demand and thus relieve ischemia and hence angina. However this effect has been demonstrated only in rats and occurs at concentrations too high to be reached therapeutically in humans [17].

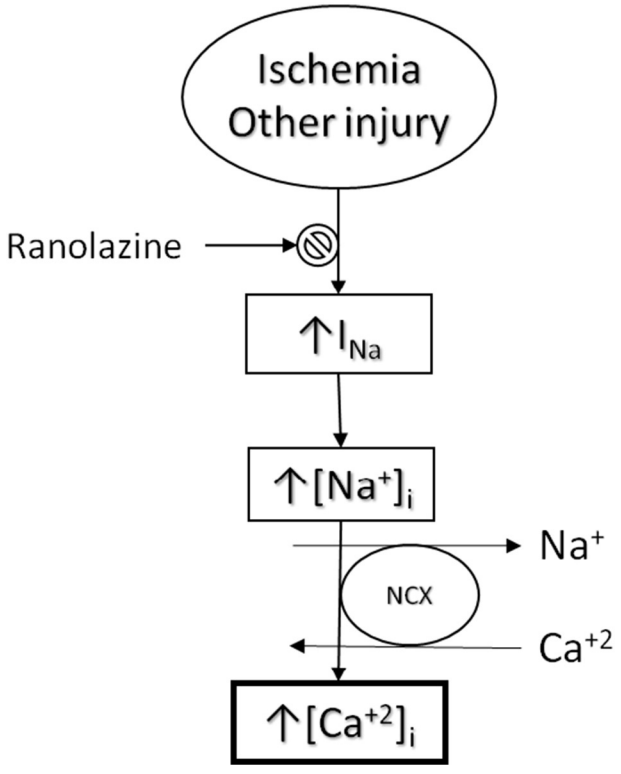

Fig. 1. Mechanism of action of Ranolazine. Ranolazine blocks opening of sodium channels, thus preventing rise of $[Na^+]_i$. (I_{Na} = Sodium current, $[Na^+]_i$ = Intracellular sodium concentration, $[Ca^{+2}]_I$ = Intracellular Calcium concentration).

2. Ranolazine in angina

Chronic stable angina pectoris is currently a problem in about 8 million North Americans and is a huge burden on the society both in terms of quality of life and monetary expenses. A subsection of patients with angina who do not respond to the first line of treatment are termed refractory. Standard therapy, i.e. beta-blockers, calcium channel blockers and nitrates cannot provide adequate relief for these patients, leaving the field open for newer drugs. Ranolazine is one such drug, which added to standard therapy, shows symptom relief in patients with refractory angina, increased exercise duration, reduced NTG consumption [18–22] and reduced ACS related admissions [23]. The drug has received FDA approval for use in refractory angina. Since approval, new evidence has shown benefit of this drug in other conditions as well.

3. Expanding roles of Ranolazine

Apart from angina, other areas where Ranolazine has been investigated include cardiac arrhythmias, incomplete revascularization, diastolic dysfunction, pulmonary hypertension, drug-related cardiotoxicity and diabetes. None of these indications are FDA approved, but research is underway. A few trials primarily targeting angina [19,24] were sufficiently powered to investigate effects on blood sugar, in addition to dedicated trials focusing on one or more of these endpoints as primary outcomes.

3.1. Ranolazine in arrhythmias

A number of conditions increase the I_{Na}, resulting increased intracellular calcium level. This leads to electrical instability in the myocardium, in the form of prolonged action potential duration [25]. Ranolazine, by blocking the I_{Na}, prevents this calcium overload, and exerts an antiarrhythmic effect. The reduction of calcium overload effects the myocardium, stabilizing the membrane and reducing excitability. Investigation into this effect is described below.

3.1.1. Ranolazine in atrial fibrillation

The RAFAELLO trial [26] investigated 241 patients in atrial fibrillation (AF) who underwent electrical cardioversion (ECV). They randomized patients after ECV to either placebo or Ranolazine in a range of doses (375 mg bid, 500 mg bid or 750 mg bid). These patients were monitored by EKG transmitted over phone. Ranolazine was well tolerated, and showed a 35% reduction in incidence of AF. This effect was observed only in the 500 mg and 750 mg doses, and not at 375 mg bid dosage. The investigators suggested testing Ranolazine for AF in a larger phase III trial.

Fragakis et al. [27] conducted a pilot study with 51 patients in AF testing the synergistic effects of amiodarone with Ranolazine. Finding favorable results, Koskinas et al. [28] conducted a trial with 121 patients with the aim of testing Ranolazine as an additive therapy to amiodarone in AF. Out of 121 enrolled patients with new-onset AF put on amiodarone infusion, about half were randomized into an additive Ranolazine therapy arm. Patients who received both amiodarone and Ranolazine had higher rates of conversion to sinus rhythm and shorter time to conversion. Patients who had large LA size were more likely to convert to sinus rhythm. Modest QT prolongation was observed but no arrhythmias were reported in the trial.

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