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Review

Ranolazine: Drug overview and possible role in primary microvascular angina management ☆

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ABSTRACT

Ranolazine is a novel well-tolerated anti-ischemic drug, which selectively inhibits late sodium current and exerts metabolic properties without any hemodynamic effect. Ranolazine has been approved as a second-line medical treatment for symptomatic stable coronary artery disease. Primary microvascular angina (MVA) is suspected when angina symptoms occur in patients with demonstrated myocardial ischemia, absence of myocardial disease and normal coronary artery angiography. Recent clinical data suggest that MVA represents a complex entity, which has been increasingly recognized as a significant cause of morbidity. High variability and low response to traditional anti-anginal treatment characterize primary MVA. Despite the fact that clinical and preclinical evidence provides information regarding ranolazine usefulness in primary MVA management, only three recent small randomized trials have investigated this issue. By selecting peer-reviewed literature in *Pubmed* and *Cochrane Library*, this review provides an overview on ranolazine pharmacology and efficacy, focusing on recent evidence suggesting its usefulness in management of primary MVA.

1. Introduction

Ranolazine is a novel well-tolerated anti-ischemic drug, which selectively inhibits late sodium current, it has metabolic properties and does not exert any hemodynamic effect. Ranolazine has been approved as a second-line medical treatment for symptomatic stable CAD.

The annual incidence of chronic stable angina in the USA increases with age and varies with both sex, and ethnic origin, and is much more prevalent than acute myocardial infarction [1].

Microvascular angina (MVA) is a complex entity, which has been increasingly recognized as a significant cause of morbidity, especially in middle-aged post-menopausal women [2,3]. Primary MVA is usually diagnosed when angina symptoms occur in patients with demonstrated myocardial ischemia, absence of heart disease and normal coronary artery angiography [4]. Epidemiological data on microvascular (MVA) angina are missing. Nonetheless, recent clinical data suggest that MVA and vasospastic angina account for up to two-thirds of patients symptomatic for stable angina but without significant coronary stenosis on angiography. MVA prevalence is higher in women [2]. High variability as well as low response to traditional anti-anginal treatment characterize primary MVA [4,5]. Hence, the quest for further anti-anginal drugs that may be used in addition to standard therapy, either in patients intolerant to first-line agents or in patients with persistent and refractory angina, still represents an open issue.

This review provides an overview on ranolazine pharmacology and efficacy focusing on recent evidence regarding its possible usefulness in management of primary MVA.

2. Study selection

Relevant peer-reviewed literature was selected in *Pubmed* and *Cochrane Library* using terms 'ranolazine', 'microvascular angina', 'cardiac syndrome X', and 'stable coronary artery disease'. The search was limited to English language publications, without date limitation. Furthermore, European Medicines Agency (EMA) product information papers were included [6].

3. Clinical pharmacology

3.1. Mechanisms of ischemia

Myocardial ischemia is characterized by impaired energy supply to various proteins relevant to the contraction–relaxation cycle of the cardiac myocyte. It results in disruption of intracellular sodium and calcium homoeostasis (Fig. 1). Fast inward sodium current may be altered during ischemia, which enhances late opening of the sodium channel following depolarisation. This is known as late sodium current

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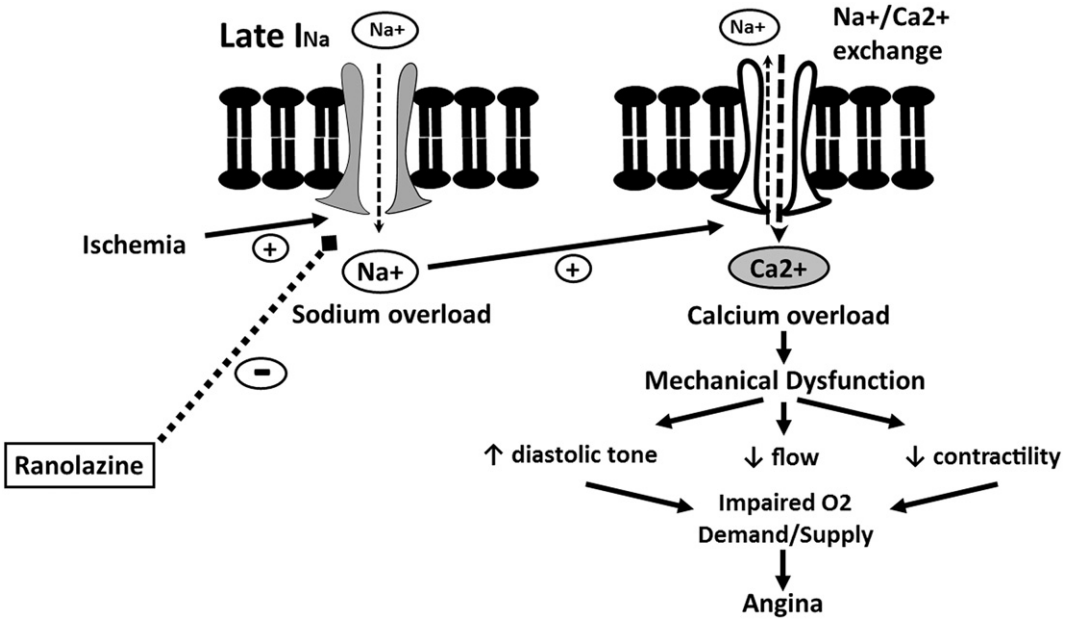

Fig. 1. Disrupted intracellular sodium and calcium homoeostasis during ischemia and suggested ranolazine anti-ischemic action. Energy impairment during ischemia, results in disruption of intracellular sodium and calcium homoeostasis. Enhanced late sodium current (late Ina) which represents a major source for increased intracellular sodium during ischemia by reversing the direction of the Na^+–Ca^{2+} transporter efflux. Consequently, calcium-activate contractile proteins during diastole lead to mechanical dysfunction, augmented energy consumption and increased micro-circulatory resistance, which contribute to energy imbalance in the ischemic myocardium. Ranolazine prevents calcium overload inhibiting late Ina in ischemic cardiac myocytes during cardiac repolarization. As a consequence, ranolazine is thought to exert anti-ischemic and antianginal action by improving the mechanical dysfunction and coronary blood flow without exerting any hemodynamic effect. + means promotion; − means inhibition.

(late Ina) which represents a major source for increased intracellular sodium during ischemia [7]. Similarly, intracellular calcium overload during myocardial ischemia, results from energy lack for active calcium efflux via Na^+–Ca^{2+} exchange. These two mechanisms result in increased intracellular sodium reversing the direction of the Na^+–Ca^{2+} transporter. Consequently, elevated diastolic calcium levels activate contractile proteins even during diastole. Such mechanical dysfunction leads to increased myocardial diastolic tone, augmented energy consumption and increased micro-circulatory resistance, which contribute to further energy balance disruption of the ischemic myocardium [8].

3.2. Pharmacodynamics

Ranolazine is N-(2,6-dimethylphenyl)-4(2-hydroxy-3-[2-methoxyphenoxy]-propyl)-1-piperazine acetamide dihydrochloride. Ranolazine exerts anti-anginal and anti-ischemic effects without consequence on heart rate or blood pressure, but its specific mechanism of action has not yet been fully elucidated (Fig. 1). According to preclinical data, ranolazine inhibits the late phase of the inward sodium channel (late I_{Na}) in ischemic cardiac myocytes during cardiac repolarization. It exerts a concentration, voltage and frequency-dependent inhibition of late I_{Na} [9]. Reduced intracellular sodium concentration prevents intracellular calcium overload, possibly improving mechanical dysfunction and coronary blood flow [10,11]. In other words, ranolazine is thought to reduce ischemia and subsequent angina symptoms by improving the diastolic function [12], through prevention of intracellular sodium and calcium imbalance. At higher concentrations, ranolazine inhibits the rapid delayed rectifier potassium current (I_{Kr}), thus prolonging the QT interval [9].

Furthermore, ranolazine improves glycometabolic homeostasis. Despite the lack of clear evidence, ranolazine has been shown to improve endothelial function in rats enhancing insulin function [13]. Those preclinical data seem to be confirmed by a sub-analysis of the MERLIN-TIMI 36 trial [14] and CARISA trial [15], which demonstrated a significant reduction in HbA1c and recurrent ischemia in patients with diabetes mellitus as well as a reduced progression toward diabetes. Last but not least, recent findings suggest that ranolazine may have some additional anti-inflammatory or antioxidant effects [16], possibly providing additional explanations to endothelial function improvement in patients with type two diabetes [17] or stable CAD [18].

3.3. Pharmacokinetics

Ranolazine pharmacokinetics is detailed in Table 1. Nonetheless, a few aspects deserve particular attention. Immediate-release (IR) ranolazine was firstly investigated but the short half-life and highly variable interindividual absorption of this formulation led to the development of the currently approved extended-release formulation (ER) [6]. Ranolazine undergoes an extensive hepatic metabolism by the cytochrome P450 (CYP) [6,19]. Age and gender do not influence ranolazine pharmacokinetics, but it should be used with caution in patients ≥75 years of age, related mainly to impaired renal function [6].

3.4. Tolerability and precautions

Data on both short-term [20,21] and long-term [22–24] tolerability demonstrated that ER ranolazine is a well-tolerated drug. Most of the adverse events ranged from mild to moderate severity [6,25]. The most frequent dose-related adverse events (mainly with dose beyond

Table 1
Pharmacokinetics characteristics of ranolazine [6,19].

Parameters	Value
Bioavailability	35%–55% Interindividual variability for IR
Peak plasma concentration	2–6 h (oral dose)
Steady state	About 3 days
Half-life at steady state	About 7 h 6–22 h metabolites with undefined activity
Metabolism	P-glycoprotein substrate Extensive hepatic (CYP3A4 ≫ CYP2D6)
Protein bound	About 62%
Excreted	Urine (75%) Feces (about 20%) 5–7% as unchanged drug