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EDITORIAL

Glyco-metabolic Effects of Ranolazine: A truly Multifaceted Drug?

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ABSTRACT

Ranolazine (R) is a non-haemodynamic anti-anginal agent used as adjunctive therapy in patients with chronic coronary heart disease (CHD) whose symptoms are unadequately controlled by conventional treatment. R decreases calcium overload in the ischemic myocytes through the inhibition of late sodium channel current in the myocardium; induces myocardial relaxation and improves myocardial blood flow. In addition to its anti-anginal effect, other possible clinical applications of R have also been explored, including treatment of atrial arrhythmias, chronic heart failure and diabetes. With regard to diabetes R has been shown to significantly improve glycemic control in diabetic patients with CHD in post-hoc analyses of large-scale clinical trials. Moreover reduction of glycated hemoglobin and fasting serum glucose levels have been also observed prospectively in small clinical trials conducted on diabetic subjects without CHD by using R alone or in combination with other oral glucose-lowering drugs. Lastly, R improved insulin resistance in non-diabetic overweight/obese patients with CHD. Hypothetical mechanisms of this metabolic action are: inhibition of secretion of glucagon from pancreatic islets, preservation of beta cells and increase of insulin delivery to tissues. In light of these observations R appear to be a potential multifaceted drug that offers the opportunity to treat glyco-metabolic disorders alone or in association to CHD. However, prospective studies are too small to be conclusive and new trials are needed to clarify which is the exact role of R in the treatment of glyco-metabolic disorders.

Key words: Ranolazine, Diabetes; Angina; Insulin resistance

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INTRODUCTION

Ranolazine (R) is an antianginal drug that reduces symptoms and improves exercise performance in patients with stable coronary heart disease (CHD) without affecting heart rate or blood pressure[1]. The clinical efficacy and safety profile of R, in monotherapy or in association with other antianginal drugs, established in several prospective randomized controlled trials (RCTs)[2-4] led to its approvation in the United States in 2006, for use in patients still symptomatic despite treatment with β-blockers, calcium antagonists, or nitrates. Since 2013 European Society of Cardiology guidelines

recommended R for second-line symptomatic treatment of angina, without evidence of benefits on prognosis (Class of recommendation IIa and Level of Evidence B)[5]. R reduces myocardial ischemia by improving sodium-calcium homeostasis via inhibition of the late phase of the inward sodium current (late INa) during cardiac repolarization[6]. Blockage of late INa current induces a favorable cascade of events that explains the anti-ischemic property of R: decrease of intracellular Na^+ and Ca^{+2} levels; improvement of myocardial relaxation and diastolic function; improvement of myocardial blood flow[7].

Recent evidences support a potential role for R in other areas, including arrhythmias, heart failure with preserved ejection fraction and glucose metabolism[8,9]. With regard to glucose metabolism and in particular diabetes, available data suggest two distinct pattern of interaction between R and diabetes: (1) Antiaginal effects of R are enhanced in presence of diabetes; (2) R directly improves glycemic control in subjects with type 2 diabetes mellitus (T2DM). Targeting diabetes is an important goal in CHD patients given the strong epidemiological link existing between these two conditions. Diabetes is a powerful predictor of CHD and myocardial infarction development; patients with diabetes have 2- to 4-fold greater risk of developing CHD than non-diabetic patients[10]. Moreover, patients with CHD and T2DM have more extensive disease[11] and worse outcomes[12] than those without T2DM. T2DM and CHD, while separate disease processes, have overlapping metabolic pathophysiology[13]: factors typically involved in diabetes such as hyperglycemia, dyslipidemia and insulin resistance, contribute to atherogenic changes like endothelial and smooth muscle cells dysfunction, impaired platelet function and abnormal coagulation. As a consequence of this common pathophysiological ground, in the last few years some drugs originally developed for treating diabetes showed to improve the outcome of subjects with heart disease[14]. Conversely, some drugs used for treating cardiovascular conditions have shown antidiabetic proprieties[15,16]. Therefore the possibility to develop multifaceted drugs treating both conditions appears to be concrete. Such potential multifaceted drugs are of great interest because they may represent a therapeutic simplification, by reducing the daily amount of drugs taken by patients and, ultimately, improving their compliance. In the case of R, when administered to patients with both CHD and diabetes, it may exert its effects by acting at different levels: at clinical level, by improving angina and reducing glycemia; at pathophysiological level, by improving diabetes and counteracting some diabetes-related factors involved in the progression of the atherosclerotic process. This review summarizes laboratory and clinical findings supporting the hypothesis that R is a truly multifaceted drug.

ANTIANGINAL EFFECT OF RANOLAZINE IN PATIENTS WITH CHD AND DIABETES

Overall, available data indicate that R is more effective as anti-ischemic drug in presence of diabetes, though results of different studies are not univocal to this regard. The first comparative study was the subgroup analysis of the CARISA trial, that included 823 patients of whom 189 were diabetic. Authors demonstrated that R decreased angina frequency to a similar degree in patients with and without diabetes[17]. Conversely, further studies conducted on patients with CHD in different clinical conditions, evidenced that the anti-ischemic effects of R were more pronounced among diabetic compared to non-diabetic patients. In the Metabolic Efficiency With Ranolazine for Less Ischemia in Non–ST-Elevation Acute Coronary Syndromes-Thrombolysis In Myocardial Infarction36 (MERLIN TIMI-36) trial, R reduced recurrent ischemia at 12 months by 25% in patients with diabetes, compared with 13% among all trial participants[18]. In the Type 2 Diabetes Evaluation in Patients with Chronic Stable Angina (TERISA) trial, which enrolled only diabetic subjects with CHD, R significantly reduced the number of angina episodes over 8 weeks of follow-up[19]. Interestingly, in this study the anti-ischemic effect of R was greater in patients with higher baseline $HbA1_c$. In the Ranolazine in Patients with Incomplete Revascularization after Percutaneous Coronary Intervention (RIVER-PCI) trial, including 2,604 patients with CHD (36.9% of whom with diabetes) and incomplete revascularization, patients with glycated hemoglobin ($HbA1_c$) $\geq$ 7.5% had a significant reduction in angina burden, which was not observed in patients with $HbA1_c < 7.5\%$[20]. Mechanisms underlying this finding remain to be determined. A possible explanation is that the levels of sodium channels blocked by R are higher in diabetic subjects. Koval *et al*[21] demonstrated that cardiomyocytes exposed ex vivo to high glucose, or isolated from hearts of diabetic animals have up-regulated phosphorylated Ca^{2+}/calmodulin-dependent protein kinase 2, a kinase known to phosphorylate the cardiac sodium channel resulting in an increased late INa current.

GLYCOMETABOLIC EFFECT OF RANOLAZINE IN DIABETIC PATIENTS WITH OR WITHOUT CHD

R has been shown to exert direct glycometabolic actions. Basically, evidences showing these favourable effects of R come from two types of sources. Firstly, from post-hoc analyses of multicenter RCTs designed to investigate anti-ischemic effects of R. Secondly from few small prospective trials directly addressing the effects of R on glycemic control in T2DM patients without CHD.

In the CARISA trial, enrolling patients with CHD and chronic angina, after three weeks of treatment R, 750 and 1000 mg, reduced $HbA1_c$ vs. placebo by 0.48 ± 0.18% (p = 0.008) and 0.70 ± 0.18% (p = 0.0002), respectively[17]. Results of CARISA have been confirmed in patients with acute coronary syndrome who were randomized to R or placebo in the MERLIN TIMI 36) trial[18]. Among T2DM subjects treated with R, $HbA1_c$ declined from 7.5% to 6.9% ($p < 0.001$). In addition, patients with T2DM treated with R were more likely to achieve A1C < 7.0% as compared with placebo-treated patients. Interestingly, R reduced the incidence of new fasting glucose >110 mg/dl in patients without T2DM at baseline compared to placebo (31.8% versus 41.2%; p = 0.003). In a secondary analysis of RIVER-PCI trial, Faranoff *et al*[22] reported the efficacy of R in lowering $HbA1_c$ especially in patients with poor glucose control and that this efficacy was greater at 6 months than at 12 months.

In the interpretation of data coming from post hoc analysis some important limitations need to be taken into account: among them the most important being that such studies were not designed to evaluated the effect on glycemic parameters; additionally, patients were often on other blood glucose lowering medications and there was an high treatment heterogeneity. Evidences coming from post hoc analysis were followed by some prospective trials directly addressing the effects of R on glycemic control in diabetic patients without CHD. Eckel *et al*[23] conducted a randomized, double blind placebo-controlled study including 465 patients with T2DM, in which R was the only blood glucose lowering drug administered. The primary endpoint of the study was a change in $HbA1_c$ at 24 weeks. Authors registered a greater reduction in $HbA1_c$ at week 24 from baseline in subjects taking ranolazine monotherapy with a placebo-

corrected least squares[LS] mean difference of -0.56%. The number of subjects achieving an $HbA1_c$ < 7.0% at week 24 was greater in the ranolazine group (25.6% placebo and 41.2% ranolazine; p 0.0004). Pettus *et al*[24] evaluated the efficacy of R (1gr/daily) as adjunct therapy to either metformine or glimepiride in 2 double-blind studies versus placebo. Again the primary study endpoint was change in HbA1c from baseline. The authors found that the administration of R-glimepiride reduced significantly $HbA1_c$ compared to placebo-glimepiride with a LS mean change from baseline of −0.51% (95% CI 0.71, 0.32). The effect on $HbA1_c$ was less pronounced in the R-metformine group compared to placebo-metformin, LS mean = −0.11% (95% CI−0.31, 0.1). In addition compared to baseline, R decreased fasting glucagon levels in the metformine group and post-prandial glucagon levels in both groups. Similarly to what observed by Eckel *et al*, in this trial, a greater proportion of subjects taking R ended the study with $HbA1_c$ < 7.0 % compared to placebo.

Regarding the safety issue, R showed a safe profile with no episodes of severe or symptomatic hypoglycaemia occurrence in these two clinical trials.

Our group for the first time evaluated the effects R on insulin resistance in subjects with CHD and metabolic syndrome in a small pilot study. We administered R or other antianginal drugs to 40 obese/overweight non-diabetic patients with already diagnosed CHD, previous revascularization and residual ischemia at ergometric test. After 12 weeks follow-up insulin resistance, assessed by homeostasis model assessment insulin resistance index, significantly decreased in the group taking R compared to control group[25].

PROPOSED MECHANISMS OF ANTI-DIABETIC EFFECTS OF RANOLAZINE

Mechanisms by which R affects glucose metabolism are complex and still not completely understood. It is possible that its glucose lowering effect results from actions played at several sites. In summary, proposed mechanisms are: (a) activity on pancreatic islet α cells causing the reduction in glucagon release; (b) preservation of pancreatic β cells; (c) reduction of insulin resistance by increasing insulin delivery to tissues in particular at skeletal muscle level.

(a) Inibition of glucagon release

This is the most documented mechanism of action for R and consists in the suppression of glucagon secretion from pancreatic α cells through inhibition of the Nav1.3 isoform of these cells[26]. Plasma glucagon levels are increased under both fasting and postprandial states in diabetes[27]. This hyperglucagonemia increases hepatic glucose production and contribute significantly to diabetic hyperglycemia[28]. Huang *et al*[29] observed that pancreatic α-cells of diabetic mice, with chronic hyperglucagonemia, had increased INa current, action potential duration, amplitude, and firing frequency, and increased glucagon content. R significantly reduced the veratridine-induced increase in glucagon secretion in a concentration-dependent manner and decreased blood fasting glucose and glucagon levels, postprandial hyperglucagonemia and $HbA1_c$ in diabetic rats[26].

(b) Preservation of β-cells

This hypothesis is based on the unique observation of Ning *et al* [30] who investigated the effects of R on mice with diabetes caused by streptozotocin-mediated pancreatic β-cell mass depletion. They found that 8-week treatment with R 20 mg/kg twice daily, preserved islet morphology and β-cell mass and decreased the rate of apoptosis in the islets. At the same time, treated mices presented lower levels of fasting plasma glucose and $HbA1_c$ and increased insulin secretion induced by glucose injection compared with mices treated with vehicle,

(c) Reduction of insulin resistance

This hypothesis rely on the observation that R elicits insulin delivery to tissues through the induction of skeletal muscle vasodilatation. In anesthetized pigs, intracoronary or intrafemoral ranolazine bolus exerted a marked, 2- to 3-minute dilatory effect that was more persistent than nitroglycerin, without inducing significant hemodynamic changes[31]. In an experimental rat model, Fu *et al*[32] observed that R exerted endothelial-indipendent vasodilatory effects leading to the recruitment of muscle microvasculature by increasing microvascular perfusion, and to the expansion of microvascular endothelial surface. These effects were associated with increased muscle delivery and action of insulin. Direct action at muscle level could also be involved in the reduction of insulin resistance induced by R. The addition of 10μ of ranolazine to murine myoblastic cells during proliferation, stimulated myogenesis, reduced pro-oxidant inflammation/oxidative condition and activated a calcium signaling pathway[33].

CONCLUSIONS

Patients with CHD and diabetes or metabolic syndrome are those with greater expected benefit from R administration because of the greater antianginal efficacy of R in the presence of high blood glucose levels and because R potentially exerts actions beyond the angina relief by counteracting atherogenic factors, such as hyperglycemia and insulin resistance, that are involved in the progression of atherosclerosis. However, the question whether these effects of R on pathophysiological pathways translate into prognostical benefits still remains unanswered. In our opinion, new studies investigating whether starting R in patients with CHD and glycometabolic disorders can help to slow down atherosclerosis progression and improve the outcome of CHD in comparison to other therapeutical approaches would be warrant.

Despite its demonstrated propriety of lowering $HbA1_c$, studies using R as a direct oral glucose- lowering agent in T2DM subjects without CHD are still preliminary and conclusion cannot be drawn as recently underlined by the meta-analysis of Zeng *et al*[34]. In particular the effect size produced by R in diabetic patients when used in monotherapy or in association with other glucose-lowering drugs remains unclear. Therefore, further multicentric trials are required to elucidate the exact role of R in treating glycometabolic disordes.

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