Atherosclerosis 226 (2013) 157–160

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Effect of ranolazine on arterial endothelial function in patients with type 2 diabetes mellitus

Priscilla Lamendola [a], Roberto Nerla [a], Dario Pitocco [b], Angelo Villano [a], Giuseppe Scavone [b], Alessandra Stazi [a], Giulio Russo [a], Antonino Di Franco [a], Alfonso Sestito [a], Giovanni Ghirlanda [b], Gaetano A. Lanza [a,*], Filippo Crea [a]

[a] Institute of Cardiology, Università Cattolica del Sacro Cuore, Rome, Italy
[b] Diabetes Unit, Institute of Internal Medicine, Università Cattolica del Sacro Cuore, Rome, Italy

ARTICLE INFO

Article history:
Received 13 September 2012
Received in revised form
16 October 2012
Accepted 22 October 2012
Available online 31 October 2012

Keywords:
Type 2 diabetes mellitus
Endothelial function
Ranolazine

ABSTRACT

Objective: To assess the effect of ranolazine on systemic vascular function in patients with type II diabetes mellitus (T2DM).
Methods: We randomized 30 consecutive T2DM patients with no evidence of cardiovascular disease and no insulin therapy to receive one of the following 3 forms of treatment in a blinded fashion: ranolazine, 375 mg bid for 3 weeks (group 1); ranolazine, 375 mg bid for 2 weeks, followed by placebo bid for 1 week (group 2); placebo bid for 3 weeks (group 3). Flow-mediated dilation (FMD) and nitrate-mediated dilation (NMD) of the right brachial artery were assessed at baseline and after 48 h, and 2 and 3 weeks.
Results: FMD and NMD were similar among groups at baseline. Compared to the basal value, FMD significantly improved after 2 weeks in group 1 and in group 2 ($p < 0.01$ for both), but not in group 3. At 3 weeks, FMD remained improved, compared to baseline, in group 1 ($p < 0.05$), whereas returned to basal values in group 2 ($p = 0.89$ vs. baseline). No changes in NMD were observed in any group.
Conclusions: In this controlled study, ranolazine was able to improve endothelial function in T2DM patients.

1. Introduction

Endothelial dysfunction plays a key role in the accelerated process of atherosclerosis in patients with type 2 diabetes mellitus (T2DM) [1,2]. Accordingly, assessment of endothelial function might represent a valid tool to select T2DM patients with increased cardiovascular risk, while improving endothelial function might delay atherosclerotic and cardiovascular disease events [3,4].

Several studies have shown beneficial effects of ACE-inhibitors, angiotensin II receptor blockers and statins on endothelial function in T2DM patients [5–7], whereas the evidence about a beneficial effect of anti-diabetic drugs is poor [8].

Ranolazine is a novel drug that reduces anginal symptoms in patients with ischemic heart disease [9,10]. Its clinical benefits seem to be related to a reduction of calcium overload in ischemic cardiomyocytes through inhibition of the late sodium current [11], with improvement of left ventricular relaxation [12]. Recent data, however, suggest that ranolazine might also have some pleiotropic effects, including anti-inflammatory and anti-oxidant properties [13]. Moreover, ranolazine was found to improve glycated hemoglobin in patients with T2DM [14,15] and a recent study suggested that it may improve endothelial function in peripheral microcirculation [16].

In this study we aimed at assessing whether ranolazine may improve endothelial function in systemic arterial vessels of patients with T2DM.

2. Methods

2.1. Study population

We enrolled 30 consecutive patients with a diagnosis of T2DM, according to the American Diabetes Association (ADA) guidelines, who presented at the Diabetic Care Unit of our University hospital for a follow-up clinical visit and fulfilled the following inclusion

* Corresponding author. Istituto di Cardiologia, Università Cattolica del Sacro Cuore, Largo A. Gemelli, 8, 00168 Roma, Italy. Tel.: +39 06 3015 4126; fax: +39 06 30 55 535.
E-mail addresses: g.a.lanza@rm.unicatt.it, g.a.lanza@inwind.it (G.A. Lanza).

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http://dx.doi.org/10.1016/j.atherosclerosis.2012.10.051

criteria: 1) no evidence of cardiovascular disease, according to clinical history, physical examination and standard electrocardiogram (ECG); 2) no evidence of acute or chronic inflammatory disease, as well as of hepatic or renal failure; 3) no insulin therapy; 4) glycated hemoglobin (Hb1Ac) <7.0%.

After basal clinical and laboratory assessment, patients were randomized, following a computer-generated table of random numbers, to one of the following treatments in a blinded fashion: 1) ranolazine (375 mg bid) for 3 weeks (Group 1, $n = 10$); 2) ranolazine (375 mg bid) for 2 weeks, followed by placebo for another week (Group 2, $n = 10$); 3) placebo (1 tablet bid) for 3 weeks (Group 3, $n = 10$). All other medications were left unchanged throughout the whole period of the study.

Co-authors involved in the preparation of anonymous drug packages and in the randomization process did not participate in the clinical assessment of patients. Cardiologists involved in the clinical and laboratory assessment of patients and/or analyses of data were blinded to the allocation treatment.

All patients underwent assessment of peripheral arterial dilator function at baseline and 48 h, 2 weeks and 3 weeks after starting treatment (see below). The local Ethics committee of our Institute approved the research protocol, which complies with the Declaration of Helsinki. All subjects were informed of the purpose and nature of the study and provided written, informed consent for participation.

2.2. Assessment of peripheral vascular function

Systemic endothelium-dependent vasodilation was assessed by measuring flow-mediated dilation (FMD), following a method described in detail elsewhere [17,18]. Shortly, after 10 min rest, images of the right brachial artery were obtained by a 10-MHz probe attached to a high-resolution ultrasound machine. A mechanical support maintained the probe in a fixed position throughout the whole examination. Brachial artery diameter was measured throughout the test using a totally automated system [17,18], which provides a diameter measurement every second. After obtaining basal measures, a forearm cuff, positioned 1 cm under the antecubital fossa, was inflated to 250 mm Hg and released after 5 min to elicit forearm reactive hyperemia. FMD was calculated as the maximum percent change of the brachial artery diameter during hyperemia compared to the basal diameter.

Fifteen minutes after recovery of brachial artery diameter to basal values, nitrate-mediated dilation (NMD) was assessed. To this aim, 25 μg of sublingual glyceryl trinitrate were given and NMD was measured as the maximum percent change in the next 5 min of the brachial artery diameter compared to the basal diameter.

2.3. Statistical analysis

All variables considered in the study showed a distribution not different from the normal one according to Kolmogorov–Smirnov test. Comparisons among groups of continuous variables were done by analysis of variance (ANOVA), whereas categorical variables were compared by χ^2 test. Two-way repeated measure ANOVA was applied to compare the effects of the different treatments on the outcome variables. In case of global statistical significance between- and within-groups comparisons were done by unpaired and paired *t*-test, respectively, with statistical results of multiple comparisons corrected by Bonferroni rule.

Data are reported as means ± SD, unless differently indicated. A two-tailed p value <0.05 was considered as statistically significant. Data were analyzed by the SPSS 17.0 statistical software (SPSS Italia, Florence, Italy).

3. Results

Table 1 shows the main clinical characteristics of the 3 groups of patients, whereas Table 2 shows brachial artery flow (basal and peak) velocities and FMD results in the 3 groups. There were no differences among groups with regard to age, gender, cardiovascular risk factors and drug therapy. No patient complained of any side effect related to the treatment.

At baseline, no differences were observed among groups both in basal and in peak flow velocity in the brachial artery; similarly, no differences in brachial artery flow velocity were observed among groups at each follow-up (FU) time-point.

At baseline FMD was similar in the 3 groups; no changes in FMD occurred in the 3 groups after 48 h from treatment onset. However, a significant improvement in FMD, as compared to baseline, was observed after 2 weeks in group 1 ($p < 0.01$) and in group 2 ($p < 0.05$), but not in group 3 ($p = 0.75$). As a result, FMD at 2 weeks was higher in group 1 and group 2 compared to group 3 ($p < 0.05$ for both), whereas there was no significant difference in FMD values between group 1 and group 2 ($p = 0.45$). The improvement, however, was maintained at 3-week FU only in Group 1 ($p < 0.05$) whereas it returned to baseline values in group 2 ($p = 0.89$) (Fig. 1).

There were no differences in NMD among groups at baseline (11.6 ± 1.3, 11.5 ± 1.3 and 12.2 ± 0.6% in groups 1, 2 and 3, respectively; $p = 0.32$). No changes in NMD were observed at follow-up in any group. NMD at 3 weeks was 11.8 ± 1.9, 11.6 ± 1.2 and 12.5 ± 0.7% in the 3 groups, respectively; $p = 0.33$).

4. Discussion

Ranolazine is a novel anti-ischemic drug that has recently been shown to reduce anginal symptoms in patients with stable angina and obstructive CAD [9,10].

It is believed that ranolazine mainly acts by reducing calcium overload in ischemic cardiomyocytes through inhibition of the late sodium current [11], which results in improvement of left ventricular diastolic function and of subendocardial perfusion [12].

In this study we show, for the first time, that ranolazine is able to improve arterial endothelial function in patients with T2DM. The mechanisms for this favorable effect cannot be derived from our

Table 1
Main clinical characteristics of patients enrolled in the study.

	Group 1 ($n = 10$)	Group 2 ($n = 10$)	Group 3 ($n = 10$)	p
Age (years)	60 ± 7	61 ± 9	64 ± 8	0.56
Gender (M/F)	7/3	8/2	7/3	0.84
BMI (Kg/m^2)	28 ± 2	30 ± 6	29 ± 4	0.72
HbA1C (%)	6.7 ± 0.3	6.9 ± 0.7	6.8 ± 0.6	0.77
Diabetes duration (years)	14 ± 7	14 ± 9	13 ± 3	0.94
Cardiovascular risk factors				
Family history of CVD	5 (50%)	5 (50%)	6 (60%)	0.87
Hypertension	6 (60%)	6 (60%)	7 (70%)	0.87
Hypercholesterolemia	5 (50%)	4 (40%)	6 (60%)	0.67
Active smoking	2 (20%)	1 (10%)	2 (20%)	0.79
Drug therapy				
β-blockers	4 (40%)	4 (40%)	5 (50%)	0.87
Calcium-channel blockers	1 (10%)	1 (10%)	1 (10%)	1.00
Antiaggregants	5 (50%)	5 (50%)	6 (60%)	0.87
ACE-inhibitors	3 (30%)	2 (20%)	3 (30%)	0.84
ARBs	4 (40%)	4 (40%)	4 (40%)	1.00
Statins	5 (50%)	3 (30%)	5 (50%)	0.60
Metformin	10 (100%)	10 (100%)	9 (90%)	0.36
Pioglitazone	1 (10%)	0 (0%)	1(10%)	0.59
Sulfonylureas	5 (50%)	6 (60%)	4 (40%)	0.67

ACE = angiotensin-converting enzyme; ARBs = angiotensin-II receptor blockers; BMI = body mass index; CVD = cardiovascular disease; HbA1C = glycated hemoglobin.