THE ROLE OF TRIMETAZIDINE IN ISCHEMIC CARDIOMYOPATHY

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Abstract

Abnormalities of myocardial energy metabolism appear as a common background of the two major cardiac disorders: ischemic heart disease (IHD) and heart failure (HF). Myocardial ischemia has been recently conceived as a multifaceted syndrome that can be precipitated by a number of mechanisms including metabolic abnormalities. HF is a progressive disorder characterised by a complex interaction of haemodynamic, neurohormonal and metabolic disturbances. HF may further promote metabolic changes, generating a vicious cycle. Thus, targeting cardiac metabolism in IHD patients may prevent the deterioration of left ventricular function, stopping the progression to HF. For these reasons, several studies have explored the potential benefits of trimetazidine (TMZ), an inhibitor of free fatty acids oxidation that shifts cardiac and muscle metabolism to glucose utilization.

Because of its mechanism of action, TMZ has been found to provide a cardioprotective effect in patients with angina, diabetes mellitus, and left ventricular (LV) dysfunction, and those undergoing revascularization procedures, without relevant side effects. In addition, the lack of interference with heart rate, arterial pressure, and most of frequent comorbidities, makes TMZ an attractive option for patients and clinicians as well. The impact of TMZ on long term mortality and morbidity in ischemic syndromes and in heart failure need to be conclusively confirmed in properly designed RCT.

Introduction

Ischemic heart disease (IHD) and heart failure (HF) are two major cardiac disorders whose prevalence is increasing, with a huge burden for global healthcare systems. Acute and chronic ischemic syndromes affect about 3 million males and 2.8 million females in Europe and have been traditionally attributed to coronary

atherosclerotic obstructions that may abruptly or progressively lead to vessel lumen occlusion [1]. It has recently been acknowledged that, beside atherosclerotic lesions, other mechanisms, such as endothelial dysfunction, microvascular disease, and vasospasm, either isolated or in combination with atheromatous plaques, may precipitate myocardial ischemia [2]. Therefore, IHD is a much more complex syndrome than obstructive atherosclerosis of the coronary arteries [3,4].Anti-ischemic strategies are focused on removal of the coronary obstruction and on pharmacological modulation of cardiac work and coronary blood flow. Unfortunately, stenosis focused strategies have a limited and transient impact on symptoms, and no impact on prognosis [[5], [6], [7]].

Recent advances in the understanding of IHD have called attention to strategies that target "alternative pathogenetic mechanisms", including modulators of cardiac energy metabolism [8]. Metabolic modulation may play a major role in acute ischemic events, [9,10], may impact on the results of interventions and may prevent the development of heart failure (HF) [[11], [12]].

Hence, inadequate cardiac energy production as the result of either insufficient substrate availability or insufficient cellular ATP production appears at the crossroad of both IHD and LV dysfunction/HF. Therefore, addressing cardiac metabolic issue in IHD may provide benefits by preventing the deterioration of LV function and stopping the progression to HF [13,14].

With the exception of calcium channel blockers in Prinz-Metal angina, no agent has been tested in angina patients when a flow-limiting stenosis was absent or had been removed, based on the reluctance of cardiologists in accepting a diagnosis of angina in the absence of a flow-limiting stenosis.

Based on these new concepts, drugs of proven clinical efficacy such as trimetazidine (TMZ), an inhibitor of free fatty acids (FFA) oxidation that shifts cardiac and muscle metabolism to glucose utilization resulting into a greater production of high-energy phosphate [13], deserve an objective re-evaluation of their clinical value.

BACKGROUND

Trimetazidine (TMZ) has been shown to partially inhibit free fatty acid oxidation by shifting substrate utilization from fatty acid to glucose. The aim of this study was to assess the effects of TMZ in patients with diabetes and ischemic cardiomyopathy.

METHODS

Sixteen patients with diabetes and ischemic hypokinetic cardiomyopathy (all males) on conventional therapy were randomized to receive either placebo or TMZ (20 mg 3 times per day), each arm lasting 15 days, and then again to receive either placebo or TMZ for 2 additional 6-month periods, according to a double-blind, crossover design. At the end of each period, all patients underwent exercise testing, 2-

dimensional echocardiography, and hyperinsulinemic/euglycemic clamp. Among the others, New York Heart Association class, ejection fraction, exercise time, fasting blood glucose, end-clamp M value (index of total body glucose disposal) and endothelin-1 levels were evaluated.

RESULTS

Both in the short and long term (completed by 13 patients), on TMZ compared to placebo, ejection fraction (47 ± 7 vs 41 ± 9 and 45 ± 8 vs 36 ± 8%, P < .001 for both) and M value (4.0 ± 1.8 vs 3.3 ± 1.6, P = .003, and 3.5 ± 1.5 vs 2.7 ± 1.6 mg/kg body weight/min, P < .01) increased, while fasting blood glucose (121 ± 30 vs 136 ± 40, P = .02 and 125 ± 36 vs 140 ± 43, P = .19) and endothelin-1 (8.8 ± 3.8 vs 10.9 ± 3.8, P < .001 and 6.2 ± 2.4 vs 9.2 ± 4.3 pg/mL, P = .03) decreased. In the short term, 10 patients decreased 1 class on the NYHA scale during treatment with TMZ (P = .019 vs placebo). Eight patients decreased 1 NYHA class while on long-term TMZ treatment, while on placebo 1 patient increased 1 NYHA class and none improved (P = .018 vs placebo).

CONCLUSIONS

In a short series of patients with diabetes and ischemic cardiomyopathy, TMZ improved left ventricular function, symptoms, glucose metabolism, and endothelial function. Shifting energy substrate preference away from fatty acid metabolism and toward glucose metabolism by TMZ appears an effective adjunctive treatment in patients with diabetes with postischemic cardiomyopathy.

Section snippets

Patients

We selected 16 consecutive male, white patients with type II diabetes (age 64 ± 7 years, range 52–76 years) and hypokinetic cardiomyopathy secondary to ischemic heart disease. Baseline ejection fraction (EF) was 40% ± 5%. Fourteen patients had had a previous myocardial infarction. Twelve of them had undergone maximal attainable revascularization, while the remaining 4 were either not amenable to revascularization (2 patients) or presented chronic coronary occlusions not suitable for

Results

All 16 recruited patients completed the short-term study. However, only 13 completed the long-term phase. All 3 patients who interrupted the study were on long-term TMZ: 1 died of injuries from a road traffic accident, while the remaining 2 patients dropped out because of nausea and epigastric distress. Figure 2, Figure 3, Figure 4 and Table II, Table IIIsummarize the main results.

Discussion

The results of the present study show that in patients with diabetes and postischemic hypokinetic cardiomyopathy, TMZ consistently improves patients' functional capacity

and left ventricular function. Additionally, for the first time the drug has been shown to improve overall glucose metabolism and endothelial function. These effects appear to be operative both in the short and long term.

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