Efficacy of Vastarel MR on silent and symptomatic myocardial ischemia

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Abstract

Despite advances in the medical treatment of myocardial ischemia, a large proportion of patients with coronary artery disease suffer from angina and have silent episodes of myocardial ischemia. Chronic repetitive ischemic episodes may lead to ischemic cardiomyopathy. Trimetazidine, the 3-ketoacyl coenzyme A thiolase inhibitor, is a metabolically active agent that is effective, whether alone or in combination with standard therapy, in reducing myocardial ischemia. It has been shown to reduce daily episodes of both silent and symptomatic myocardial ischemia. These effects, together with those of trimetazidine on myocardial energy production, are likely to reduce the progression of ventricular dysfunction in patients with ischemic cardiomyopathy.
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Keywords: Ischemic cardiomyopathy, myocardial energy, silent myocardial ischemia, symptomatic myocardial ischemia, trimetazidine

Introduction

Despite treatment with hemodynamic drugs, angina remains a significant health problem for many patients with ischemic heart disease. It has long been known that hemodynamic anti-ischemic drugs do not have a significant additive effect, whereas the combination of hemodynamic agents with drugs that improve cardiac metabolism is an effective treatment for myocardial ischemia. The ''metabolic'' antianginal drugs that partially inhibit fatty acid metabolism induce a shift from utilization of free fatty acids towards utilization of glucose, thereby increasing energy production for a given amount of oxygen. Trimetazidine, the most effective among the cardiometabolic drugs, has been shown to have significant anti-ischemic effect without any influence on hemodynamic parameters.

The mechanism of action of trimetazidine has been well established experimentally and is related to the inhibition of the enzyme, long-chain 3-ketoacyl coenzyme A thiolase, which is a crucial enzyme in the β-oxidation pathway [1]. This inhibition decreases the utilization of free fatty acids as a source of energy for the myocardium. It has been shown that inhibition of free fatty acid oxidation with trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation and increases the oxidation of pyruvate formed from glucose, glycogen, and lactate, restoring coupling between glycolysis and carbohydrate oxidation, and leading to the production of ATP with the consumption of less oxygen [2].

Effect of trimetazidine on symptomatic ischemia

Several clinical trials have demonstrated the potential benefits of trimetazidine in ischemic heart disease.

In stable effort angina, trimetazidine improves exercise tolerance and increases the ischemic threshold to the same extent as β-blockers or calcium antagonists [3,4]. When given in combination with β-blockers,

trimetazidine has a greater anti-ischemic effect than nitrates and calcium antagonists [5]. The Trimetazidine in Poland (TRIMPOL) II trial [6], a large, randomized, controlled trial, enrolled 426 patients with stable angina who were allocated randomly to groups receiving either trimetazidine or placebo in addition to metoprolol. This study demonstrated an improvement in time to ST-segment depression in exercise tolerance tests, total exercise workload, mean nitrate consumption, and frequency of angina in patients who received trimetazidine.

A meta-analysis of 12 double-blind, randomized, controlled clinical trials of trimetazidine in the treatment of stable angina [7] showed that trimetazidine was associated with significant reductions in the number of weekly angina attacks, and improved the time to 1 mm ST-segment depression and the total work at peak exercise. Overall, this meta-analysis confirmed that trimetazidine is an effective antianginal agent when used alone or in combination with traditional hemodynamic agents.

A Cochrane Review of trimetazidine in stable angina [8] included 23 studies involving 1378 patients. Compared with placebo, trimetazidine significantly reduced the number of weekly angina attacks and the weekly consumption of glyceryl trinitrate tablets. There was also an improvement in the exercise time to 1 mm ST-segment depression.

In a multinational, randomized, double-blind, placebo-controlled study [9], a new slow-release (modified-release [MR]) formulation of trimetazidine has been shown to improve both symptoms and myocardial ischemia significantly. Patients with stable angina received atenolol 50 mg per day and trimetazidine MR 35 mg or placebo. The primary endpoint, time to 1 mm ST-segment depression, was increased significantly with trimetazidine compared with placebo.

A larger open clinical trial enrolled 906 patients with stable angina. All patients were required to have experienced at least three angina attacks per week for more than 6 months despite traditional angina treatment with long-lasting nitrates, β-blockers, or calcium antagonists. After 2 months of treatment with trimetazidine MR 35 mg twice a day, there was a significant ($P < 0.0001$) decrease (67%) in the number of angina attacks per week and a significant decrease (71%) in the number of short-acting nitrates taken per week ($P < 0.0001$) in the treated group [10].

Recent findings suggest that the modified-release formulation of trimetazidine could be more effective than immediate-release with respect to relief of angina. In an Indian multicenter prospective study of 279 patients with uncontrolled stable angina, the immediate-release trimetazidine formulation was substituted with twice-daily trimetazidine MR, which reduced the mean frequency of angina by four attacks per week and the consumption of glyceryl trinitrate by 3.6 tablets per week [11].

Effect of trimetazidine on silent ischemia

Silent myocardial ischemia, defined as objective documentation of myocardial ischemia in the absence of angina or anginal equivalents, is often diagnosed in patients with known or unknown ischemic heart disease, with prevalence rates ranging from 9 to 57% [12] and with considerable differences in specific subgroups of patients such as those with diabetes or the elderly [2].

Treatment of repetitive episodes of silent myocardial ischemia in patients with coronary artery disease is a primary goal because these episodes may cause the progression of coronary artery disease to ischemic cardiomyopathy. Trimetazidine has been demonstrated to be an effective option for reducing the incidence of symptomatic ischemia and silent myocardial ischemia in diabetic individuals with coronary artery disease. In a study by Marazzi et al [13], 6 months of administration of trimetazidine to 15 diabetic patients receiving standard antianginal therapy, in addition to significantly reducing the number of episodes of transient myocardial ischemia, also (*Figure 1*) significantly reduced the number of episodes of silent myocardial ischemia with respect to placebo, and the total silent ischemic burden compared with placebo.

Silent myocardial ischemia after infarction is associated with stunned or hibernating myocardium, left ventricular dysfunction, and an adverse prognosis. Surgical revascularization is the optimal treatment for dysfunctional but viable myocardium; however, it is not always feasible. Trimetazidine acts on chronically hibernating myocardium by diminishing the effects of ischemia and thus improving contractile

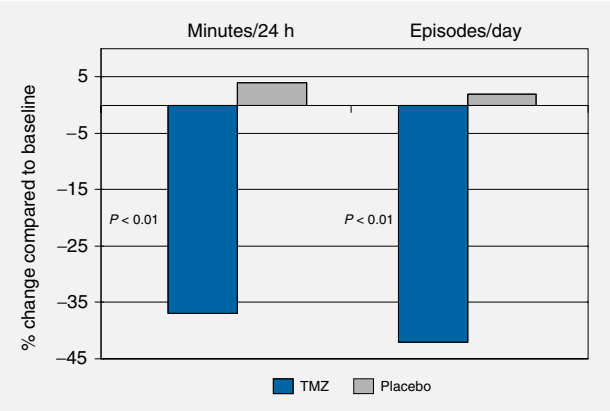

Figure 1. Effect of trimetazidine added to standard antianginal therapy on total silent ischemic burden and episodes of silent myocardial ischemia in patients with coronary artery disease.

function by correcting the imbalance between energy and function. Belardinelli and Purcaro [14], using low-dose dobutamine echocardiography, demonstrated a significant improvement in the rest and peak systolic wall thickening score index and ejection fraction in 38 patients with left ventricular dysfunction and multivessel left coronary artery disease who were treated with trimetazidine for 2 months. Similar results have been observed when the contractile response of the left ventricle was evaluated by means of gated single photon emission computed tomography. El-Kadi et al [15] demonstrated improvements in stress and rest perfusion scores, and in systolic wall thickness, in patients who received 24 months of treatment with trimetazidine.

More recently, our group demonstrated that the adjunct of trimetazidine to standard treatment in patients with type 2 diabetes, coronary artery disease, and reduced left ventricular function improved the left ventricular systolic and diastolic function of chronically dysfunctional myocardium [16].

Summary

Trimetazidine is an effective drug in the metabolic management of both symptomatic and silent ischemia. It shifts metabolism away from a preference for fatty acids toward more carbohydrate oxidation, ameliorating the energy–function imbalance of the myocardial cells. This can lead to a reduction in the number of episodes of refractory angina and improve contractile function of the hibernating myocardium, slowing the progression of cardiac failure. ■

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