THE ROLE OF TRIMETAZIDINE DRUG IN POST-MYOCARDIAL INFARCTION CONDITION

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ABSTRACT

The efficacy of trimetazidine, an anti-ischaemic agent, has been largely assessed and presented in the international literature through its metabolic effects, selective and specific fatty acid oxidation inhibition and lack of haemodynamic effects in stable angina pectoris. As such, trimetazidine has opened up a new class of metabolic agents that reduce fatty acid oxidation: the 3-KAT (3-ketoacyl-CoAthiolase) inhibitors.The aim of this review article is to demonstrate the cardioprotective benefits of trimetazidine, and how this can be translated into positive effects in the treatment of cardiac disorders. Trimetazidine has been assessed in several double-blind randomised studies as a treatment of ischaemic heart disease or as an agent given prior to or during percutaneous transluminal coronary angioplasty, coronary artery bypass grafting and thrombolysis to prevent or limit ischaemia/reperfusion damage in the heart. All these studies demonstrate that trimetazidine protects the heart from the deleterious consequences of ischaemia by switching cardiac metabolism from fatty acid oxidation to glucose oxidation. Study results cast no doubts on the value of the cardioprotective effects of trimetazidine and support the fact that trimetazidine has a direct anti-ischaemic effect on human myocardial cells. Trimetazidine has proven antianginal efficacy, and can be also used in other cardiac diseases with ischaemic signs.

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.

SECTION SNIPPETS

Efficacy of TMZ in chronic IHD (stable angina)

Several clinical studies, part of the development program of TMZ, have confirmed its effect to be similar to other anti-angina drugs, including β-blockers and calcium channel blockers. An interesting study, back in 1997 proved the superiority of the combination β-blocker with TMZ versus β-blocker with long-acting nitrate [15]. In this study TMZ was compared with isosorbide dinitrate, both in a combination with propranolol in a double blind controlled study including 53 angina patients. Exercise

EFFICACY OF TMZ IN ACUTE SYNDROMES

The GISSI study demonstrated the effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Its publication triggered a burst of enthusiasm among Cardiologists that were proposed for the first time with an effective therapy for acute myocardial infarction (AMI). The initial enthusiasm was however tempered by a growing awareness that myocardial reperfusion is a double-edged sword. Reperfusion injury is attributed to the burst of oxygen free radicals which cause lipid

Cardioprotection by TMZ during and after myocardial revascularization

Several studies have explored the potential benefits of TMZ in patients undergoing myocardial revascularization, either by coronary artery bypass grafting (CABG) or PCI. The ability of TMZ to reduce oxidative stress in cardiac surgery was tested in 24 patients undergoing on-pump CABG. TMZ was given for 2 weeks before surgery and blood samples were collected for measurement of the serum concentrations of major endogenous antioxidant enzyme systems [24]. The results showed that the levels of Efficacy of TMZ in diabetics with myocardial ischemic symptoms. In diabetic and pre- diabetic states a reduced glucose uptake and utilization coupled with a preferential FFA oxidation occur as a consequence of inadequate insulin receptor signalling due to either a state of insulin resistance or decreased insulin levels. In diabetic patients, the increased uptake and utilization of FFA both at rest and during stress and ischemia is responsible for the increased susceptibility to myocardial ischemia and to a greater decrease of myocardial performance

Trimetazidine is a metabolic agent of proven efficacy in improving myocardial ischemia and angina. A comparative international multicenter randomized trial, assessed anti-anginal anti ischemic efficacy and safety of Trimetazidine (60 mg/d) and Thiotriazoline (600 mg/d) in symptomatic patients with chronic ischemic heart disease receiving the first line therapy. The study assessed the efficacy of the two drugs on total exercise duration, time to 1-mm ST segment depression, the number of angina attacks and nitroglycerin tablets consumed amount. Both drugs have demonstrated clinical efficacy equal for all primary and secondary endpoints.

COVID-19 leads to disruption of the blood coagulation system, to thrombosis, hypercoagulability, as a result, to an increased risk of strokes and heart attacks. During COVID-19, endothelial dysfunction develops associated with NO deficiency with decrease in the level of SH compounds. Tiazotic acid (Thiotriazoline) has immunomodulatory, anti-inflammatory, antioxidant, anti-ischemic, cardio- and endothelioprotective, antiplatelet, hepatoprotective activity. Our studies conducted at the National Research Medical Center "University Clinic of ZSMU" with the participation of 57 patients (from 30 to 65 years old) with post-COVID syndrome, who received thiotriazol with basic therapy in either tablets (200 mg each) or suppositories Dalmaxin (0.2 g each) twice a day for 30 days. Inclusion criteria for the study were a positive PCR test for COVID-19; if the PCR test was negative, then the presence of IgM COVID-19 or IgG COVID-19 (with radiologically confirmed pneumonia). The following biochemical parameters were studied: C-reactive protein - by immunoturbodimetric method; D-dimer - by enzyme immunoassay; ferritin - by immunochemiluminescent method; endothelial NO-synthase (eNOS) - by ELISA method; alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), total bilirubin; international normalized ratio (INR) and determination of platelet aggregation. During treatment with thiotriazoline, significant increase in the eNOS content was recorded, which indicated the presence of endothelioprotective activity of the drug. Thiotriazoline significantly reduced the level of D-dimer in the blood of patients, and also led to the normalization of INR. The established effects testified to the presence of antiplatelet and fibrinolytic action of thiotriazoline and its ability to reduce the risks of heart attacks and strokes in post-COVID syndrome. Thiotriazoline led to an objective improvement in general clinical parameters in patients with post-COVID syndrome, complaints of palpitations disappeared, blood pressure stabilized.

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