Invited review

The role of trimetazidine in patients subjected to surgical revascularization

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Abstract

In recent years methods interfering with cellular metabolism to prevent and treat heart diseases have become available. Metabolic treatment involves the use of drugs to improve the function of cardiomyocytes. Trimetazidine (TMZ) is one of the drugs in this group. The ESC 2006 guidelines on the management of patients with stable angina indicated the efficacy of metabolic treatment in improving the physical efficiency and decreasing the recurrence of pain. The available data suggest that a combined therapy of TMZ and haemodynamic drugs is an effective antianginal treatment that significantly reduces the risk of pain recurrence. The most recent studies also suggest that TMZ might be highly effective in patients subjected to surgical revascularization. However, as there have only been a few studies so far, and most of them included a very small number of patients, this treatment cannot be recommended until large, randomized trials are performed. On the other hand, TMZ can be considered as an alternative, additional treatment in patients subjected to cardiac surgery.

Key words: surgical revascularization, ischaemia-reperfusion injury, metabolic treatment, trimetazidine.

Introduction

Recent evidence suggests an important, but too rarely used, method of interfering with cellular metabolism as part of the prevention and treatment of cardiovascular diseases. The term 'metabolic treatment' has been used for some time to denote a therapy that uses drugs to improve the function of cardiomyocytes [1, 2].

Trimetazidine (TMZ), as a representative of this group, inhibits beta-oxidation of fatty acids. Its main effect is to selectively inhibit 3-ketoacyl coenzyme A thiolase (3-KAT), the last enzyme participating in the beta-oxidation of long-chain fatty acids (FFA – *free fatty acids*). This leads to the inhibition of FFA oxidation and a secondary increase in glucose oxidation. TMZ also causes an increase in pyruvate dehydrogenase (PDH) activity, enabling the restoration of the coupling of glycolysis and glucose oxidation impaired during ischaemia. The result is a reduction in hydrogen ion

production, intracellular acidosis and calcium ion accumulation. This effect of TMZ prevents ATP deficiency. It also limits the accumulation of sodium and calcium in the cytoplasm of cardiomyocytes, reduces the formation of free oxygen radicals and inhibits neutrophil infiltration. An important aspect of the drug's activity is its effect on increasing the mechanical resistance of the sarcolemma during reperfusion. This mechanism might play a special role in acute coronary syndromes as it limits the necrotic area in patients with myocardial infarction. There are studies suggesting that TMZ affects the restoration of ischaemia-impaired mitochondrial function and the sites of TMZ binding to the mitochondrial membrane have been identified, confirming the anti-ischaemic properties of the drug. There have also been reports on the effect of TMZ on the metabolism and release of endothelin-1 (ET-1), a peptide substance synthesised in the endothelium which causes a progression in heart remodelling and hemodynamic impairment. Another possible mechanism of action of TMZ is the inhibition of apoptosis in cardiomyocytes. This has been confirmed among others by the study by Argaud et al., in which the authors show that administering TMZ 10 min before ischaemia significantly protects the myocardium from ischaemia-reperfusion injury, including inhibition of apoptosis in the cardiomyocytes (associated with the caspase-3 pathway). Similar results were obtained in the study by Ruixing et al. [3-6].

Another drug from the same group is ranolazine (RS 43285) or (N1-(2,6-dimethylphenyl)-2-[4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]piperazin-1-yl] acetamide) that inhibits fatty acid oxidation, especially during reperfusion [3]. Ranolazine has therefore been used in patients with angina pectoris, reducing the angina attack rate and delaying the occurrence of pain during exercise tests. However, the mechanisms underlying the anti-anginal and anti-ischaemic effects of ranolazine are not completely clear. Recently, investigations of the electrophysiological effects of ranolazine have found that it blocks the late cardiac sodium current (I_{NaL}). Accumulation of intracellular sodium induced by ischaemia results in calcium overload in myocardial cells, leading to mechanical dysfunction. It has been suggested that by blocking the sodium channel (I_{NaL}), ranolazine might prevent this sodium-induced calcium overload, and thereby attenuate ischaemia [3, 7].

Current role of metabolic treatment

Ischaemic heart disease (IHD) and its complications remain the leading cause of mortality in Poland, Europe and the United States of America [8, 9]. The available data show that in Poland over 800 thousand men and 700 thousand women have IHD. More than 100 thousand of these people suffer myocardial infarction every year [9]. The European Society of Cardiology (ESC) guidelines for stable IHD were published in June 2006 and comment on the management of angina pectoris [8]. Apart from emphasising the key role of statins and increasing the importance of angiotensin-converting enzyme inhibitors (ACEIs), they recommended new groups of drugs to treat IHD by reducing its clinical symptoms, including substances that open the potassium channels (nicorandil) and sinus node inhibitors (ivabradine) and metabolic drugs (TMZ/ranolazine). TMZ was indicated for the first time as an agent that should be considered as an addition to the main therapy or as replacement agents in case of intolerance to standard treatment aimed at reducing symptoms (IIB recommendations) [8].

Metabolic treatment has been introduced in the standard management of stable angina as a result of many completed clinical trials, mostly TMZ trials (since 1994). The studies have shown that TMZ is a highly efficient anti-ischaemic drug which has no direct effect on the hemodynamic parameters of the cardiovascular system. It has been shown to reduce the rate of angina episodes and nitroglycerin dosage, and significantly extends the duration of physical exercise without anginal pain or significant ST depression. Recently, there are more and more studies suggesting its possible role in patients with acute coronary syndrome (ACS), heart failure (especially as a result of ischaemia) and cardiomyopathies. As a consequence of its action in stable angina, TMZ may also play a role in patients subjected to surgical revascularization [10, 11].

TMZ in patients subjected to surgical revascularization

There are still only a few studies suggesting the role of TMZ in patients subjected to CABG (*coronary artery bypass grafting*). However, according to its confirmed anti-ischaemic and anti-anginal role in stable IHD, with a well-known mechanism of activity, the application of TMZ in patients undergoing surgical revascularization seems to be completely justified. On the other hand, according to the rules of EBM (*Evidence Based Medicine*), large randomized studies should be performed to confirm this thesis and previous research [12, 13].

In the first study on this point (1992) Fabiani et al. evaluated the role of TMZ in the prevention of disadvantageous effects of ischaemia-reperfusion injury in patients subjected to cardiac surgery. 19 patients – 10 in TMZ and 9 in the control group – who underwent surgical revascularization were included in the study. Pretreatment was started 3 weeks before the surgery with 1 tablet (20 mg) t.i.d. and the same drug was added to the cardioplegic solutions (TMZ: 10^{-6} M). Metabolic measurements showed that the increase of malondialdehyde

measured in the coronary sinus 20 min after reperfusion was significantly (p=0.014) less in the TMZ group (from 1.60±0.11 to 1.79±0.2 µmol/L) than in the placebo group (from 1.17±0.11 to 2.84±0.58 µmol/L). Myosin was present 4 h after surgery in all patients in the placebo group and in 5 of the 10 of the TMZ group (p=0.036). The obtained outcomes showed that patients pretreated with TMZ had better ventricular function, as assessed by the stroke work index (SWI), which was significantly (p=0.01) higher in the TMZ group (0.0391±0.0029 g/min/m^2/beat) than in the placebo group (0.0282±0.0026 g/min/m^2/beat). The authors for the first time concluded that TMZ seems to reduce ischaemia-reperfusion injury during cardiac surgery; moreover, pretreatment with TMZ allows the patient to face the operation with better ventricular function [14]. Similar results were obtained in the experimental study by Aussedat et al. (1993), and El Banani et al. (2000), where the authors confirmed its role as an addiction to the cardioplegic solution, in decreasing ischaemia-reperfusion injury [15, 16].

In the second study on this point (1996), the results obtained by the authors were definitely less favourable. In the randomized, double-blind, placebo-controlled study of Vedrinne et al., the authors assessed the cardioprotective effects of TMZ on left ventricular function after CABG. Forty patients undergoing elective CABG, receiving either TMZ or a placebo (PCB), were included in the study. The serial measurements of fractional area change (FAC), percent of systolic wall thickening (SWT) and malondialdehyde (MDA) production were performed in all patients. There were no differences regarding the number of vessels revascularized, duration of aortic clamping or bypass time. The authors showed that FAC increased by 12% in both groups 20 min after aortic unclamping ($p<0.05$) and remained above the initial value at the sixth postoperative hour. SWT was 23.8±1.6%, 25.4±1.9%, then 21.6±.5% in the TMZ group and 22.8±1.6%, 23.8±1.4%, then 22.3±1.6% in the PCB group, after induction of anaesthesia and one and 6 h after aortic unclamping ($p>0.05$). MDA increased by 24% in the PCB group and 25% in the TMZ group 20 min after aortic unclamping ($p<0.01$). Lactate levels were lower in the TMZ group ($p<0.05$). Compared to the placebo group, patients from the TMZ group also received less intravenous calcium before aortic clamping ($p<0.02$) and less calcium channel entry blocking drugs in the early phase after aortic unclamping ($p<0.01$). The authors concluded that in patients with good preoperative ejection fraction undergoing CABG, TMZ did not demonstrate clinically significant cardioprotective effects on left ventricular performance and lipid peroxidation compared to placebo. However, this study also had many limitations, especially concerning the number of patients and inclusion criteria; therefore the obtained results should be confirmed in further studies, as was emphasized in commentaries after the publication of the original paper [17].

The cardioprotective role of TMZ was observed 3 years later (1999) in the important study by Tunerir et al., where the authors evaluated potential myocardial protection by TMZ by measurement of troponin T (TnT) during coronary bypass operations. Thirty randomized patients who underwent CABG were included in this double-blind, placebo-controlled study. The TMZ group was composed of 15 patients and the placebo group of 15 patients in New York Heart Association (NYHA) class III or IV. Pretreatment was started 3 weeks preoperatively with TMZ (60 mg orally per day) or placebo. The preoperative serum concentration of TnT was 0 to 0.39 ng/mL in all patients. The mean TnT levels were measured 5 min after completion of cardiopulmonary bypass (1.5±0.3 ng/mL) and 12 (1.4±0.1 ng/mL), 24 (0.9±0.1 ng/mL) and 48 h postoperatively (0.1±0.1 ng/mL) in the TMZ group. TnT levels in the placebo group measured at the same time points were 4.4±0.4, 4.8±0.7, 2.8±0.4 and 0.7±0.1 ng/mL. In the TMZ group, TnT levels were significantly lower than those of the placebo group ($p<0.001$). The authors concluded that pretreatment with TMZ significantly reduces ischaemic-reperfusion damage during CABG [18].

Kuralay et al. (1999) evaluated the effect of TMZ and diltiazem on persistent myocardial ischaemia after CABG. Sixty patients were divided into 3 groups of 20 each and followed up for 12 months. Patients in all 3 groups received acetylsalicylic acid 100 mg/day, those in group 1 also had TMZ 60 mg/day, and those in group 2 had diltiazem 90 mg/day. The authors observed that ischaemic episodes had resolved at 27 weeks in group 1, at 35 weeks in group 2 and at 51 weeks in group 3 ($p<0.05$). Perfusion defects (on the basis of cardiac scintigraphy) had resolved in the TMZ group at 6 months. At 12 months, perfusion defects had resolved in the diltiazem group but not in the group receiving only acetylsalicylic acid ($p<0.05$). At these doses, TMZ and diltiazem were effective in decreasing silent myocardial ischaemia following CABG, but TMZ appeared to be superior to diltiazem at 6 months on 24-h ambulatory electrocardiogram monitoring and myocardial scintigraphy [19].

At the same time, studies concerning the influence of TMZ in patients subjected to cardiac revascularization were conducted in the Department of Cardiac Surgery of the Medical University of Lodz in Poland. In the retrospective study, Banach et al. evaluated the effect of TMZ on the haemodynamic parameters of the heart and postoperative prognosis. 140 patients were included in the study, 70 in the placebo group and 70 in the TMZ group (60 mg orally per day), and the therapy was used for at least

2 months before and after cardiac surgery. The following variables were evaluated during the study: mean time of aortic clamping, postoperative levels of creatine kinase isoenzyme MB (CK-MB), early postoperative ejection fraction (EF), postoperative arrhythmias occurrence, mean time of intensive care unit (ICU) stay and length of hospitalization. The mean number of coronary grafts was similar in both groups – 3.03±0.82 and 3.36±0.64 in the TMZ and placebo groups, respectively. Analyzing the number of postoperative arrhythmias, the authors did not observe significant differences, but the occurrence of atrial fibrillation was significantly less frequent in the TMZ compared to the placebo group ($p<0.05$). The preoperative ejection fraction was similar in both groups; however, in the postoperative period the authors found a significant increase of EF in the TMZ group ($p<0.05$), compared both with the preoperative values and with postoperative values of the control group. Differences in early mortality in both groups were not observed. The authors concluded that the administration of TMZ before and after cardiac surgery might influence postoperative haemodynamic parameters and complications. These outcomes were especially interesting because in the above-mentioned study by Tunerir et al., the authors did not observe an influence of TMZ on postoperative haemodynamic parameters [20].

The effective role of TMZ in patients following revascularization (PCI – *percutaneous coronary intervention* or CABG) was also studied by Ruzyllo et al. The aim of the study was to assess the efficacy of TMZ in the subpopulation of patients with a history of PCI or CABG, who were included in the TRIMPOL II study (*TRIMetazidine in POLand*). A subgroup of 94 patients with a history of revascularization for IHD was retrospectively analysed from the TRIMPOL II study. These patients were still symptomatic after 6 months despite treatment with metoprolol (50 mg b.i.d.). All patients were randomized to receive either TMZ (20 mg t.i.d.) or placebo for 12 weeks, on top of the beta-blocker. Exercise test parameters, clinical efficacy and safety were assessed. On the basis of obtained results the authors showed that compared to placebo, the 12-week treatment with TMZ significantly improved: time to 1 mm ST segment depression (385.1±144.6 s vs. 465.0±143.8 s, $p<0.01$), exercise test duration (466.9±144.8 s vs. 524.4±131.5 s, $p=0.048$), total workload (9.0±2.4 m.e vs. 10.1±2.4 m.e, $p=0.035$) as well as time to onset of angina (433.6±164 s vs. 508.1±132.4 s, $p=0.031$). Weekly number of angina attacks and nitrate consumption were significantly reduced in the TMZ group when compared to placebo. The authors concluded that TMZ provides anti-anginal efficacy in post-revascularized patients with recurrent angina despite monotherapy with metoprolol [21].

All above findings were confirmed in the study by Iskesen et al. (2006) that investigated the effect of preoperative use of trimetazidine on the reduction of oxidative stress during CABG. 24 patients were included in the study, 12 in the control group and 12 in the research group. Pretreatment began two weeks before CABG with TMZ (60 mg/day), whereas the control group did not receive any medication. Serial blood samples were collected before and after CABG for measurement of the serum concentrations of major endogenous antioxidant enzyme systems. The authors showed that postoperative levels of antioxidant enzymes were significantly different between the groups ($p<0.05$), although there were no significant differences in the hemodynamic values. The authors concluded that pretreatment with TMZ alleviates malondialdehyde production and preserves endogenous antioxidant capacity during CABG [22].

In conclusions after the publication of the ESC guidelines in June 2006 [8], there is no doubt that TMZ can be used in patients with stable IHD, because it is very efficient, improves physical performance and reduces the incidence of pain. Furthermore, haemodynamic drugs are a more efficacious anti-anginal treatment when used concomitantly with TMZ and there is less risk of pain recurrence.

On the basis of available studies we can say that metabolic treatment with TMZ might also be very effective in patients subjected to cardiac surgery (CABG), reducing the risk of ischaemia-reperfusion injury and risk of recurrent angina and improving the postoperative patients' condition. However, as there have been only a few studies so far, and most of them included a very small number of patients, this therapy cannot be recommended until large, randomized, preferably multicentre trials are performed. On the other hand, TMZ can obviously be considered as an alternative, additional treatment in patients subjected to cardiac surgery [23, 24].

References

1. Banach M. The role of trimetazidine in the treatment of heart diseases. Poznan, Poland: Termedia Publishing House, 2006.
2. Pekcetin C, Ergur BU, Kiray M, et al. The protective effects of trimetazidine on testicular ischemia and reperfusion injury in rats. Pediatr Surg Int 2007; 23: 1113-8.
3. Banach M, Goch A, Rysz J, Rosano G. The role of metabolic treatment with trimetazidine in patients after acute myocardial infarction. J Cardiovasc Pharmacol 2008; 51: (in press).
4. Argaud L, Gomez L, Gateau-Roesch O, et al. Trimetazidine inhibits mitochondrial permeability transition pore opening and prevents lethal ischemia-reperfusion injury. J Mol Cell Cardiol 2005; 39: 893-9.
5. Ruixing Y, Wenwu L, Al-Ghazali R. Trimetazidine inhibits cardiomyocyte apoptosis in a rabbit model of ischemia-reperfusion. Transl Res 2007; 149: 152-60.
6. Banach M, Barylski M, Goch JH. Is metabolic treatment a standing element of ischemic heart disease therapy? Geriatr Pol 2006; 2: 235-49.

7. Abrams J, Jones CA, Kirkpatrick P. Ranolazine. Nat Rev Drug Discov 2006; 5: 453-4.
8. Fox K, Garcia MA, Ardissino D, et al. Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology; ESC Committee for Practice Guidelines (CPG). Guidelines on the management of stable angina pectoris: executive summary: the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 2006; 27: 1341-81.
9. Steinhubl SR. Risk stratifying the acute coronary syndrome patient: a focus on treatable risk. Rev Cardiovasc Med 2007; 8 (Suppl 3): S3-8.
10. Danchin N. Clinical benefits of a metabolic approach with trimetazidine in revascularized patients with angina. Am J Cardiol 2006; 98 (5A): 8J-13J.
11. Di Napoli P, Taccardi AA, Barsotti A. Long term cardioprotective action of trimetazidine and potential effect on the inflammatory process in patients with ischaemic dilated cardiomyopathy. Heart 2005; 91: 161-5.
12. Banach M. Perspective application of metabolic treatment (trimetazidine) in patients with left ventricle dysfunction. Przew Lek 2006; 7: 40-51.
13. Danchin N. Recent advances in cardioprotection during myocardial revascularization procedures: Benefit of a metabolic intervention. Eur Heart J 2001; (Suppl. 3): 021-025.
14. Fabiani JN, Ponzio O, Emerit I, et al. Cardioprotective effect of trimetazidine during coronary artery graft surgery. J Cardiovasc Surg (Torino) 1992; 33: 486-91.
15. Aussedat J, Ray A, Kay L, Verdys M, Harpey C, Rossi A. Improvement of long-term preservation of isolated arrested rat heart: beneficial effect of the antiischemic agent trimetazidine. J Cardiovasc Pharmacol 1993; 21: 128-35.
16. El Banani H, Bernard M, Baetz D, et al. Changes in intracellular sodium and pH during ischaemia-reperfusion are attenuated by trimetazidine. Comparison between low- and zero-flow ischaemia. Cardiovasc Res 2000; 47: 688-96.
17. Vedrinne JM, Vedrinne C, Bompard D, Lehot JJ, Boissel JP, Champsaur G. Myocardial protection during coronary artery bypass graft surgery: a randomized, double-blind, placebo-controlled study with trimetazidine. Anesth Analg 1996; 82: 712-8.
18. Tünerir B, Colak O, Alataşş O, Beşoğul Y, Kural T, Aslan R. Measurement of troponin T to detect cardioprotective effect of trimetazidine during coronary artery bypass grafting. Ann Thorac Surg 1999; 68: 2173-6.
19. Kuralay E, Demirkilic U, Ozal E, Uzun M, Tatar H. Myocardial ischemia after coronary bypass: Comparison of trimetazidine and diltiazem. Asian Cardiovasc Thorac Ann 1999; 7: 84-9.
20. Banach M, Rysz J, Zasłonka J, et al. The cardioprotective effect of trimetazidine in patients undergoing surgical revascularization. Russ Med J 2005; 13: 1269-71.
21. Ruzyllo W, Szwed H, Sadowski Z, et al. Efficacy of trimetazidine in patients with recurrent angina: a subgroup analysis of the TRIMPOL II study. Curr Med Res Opin 2004; 20: 1447-54.
22. Iskesen I, Saribulbul O, Cerrahoglu M, Var A, Nazli Y, Sirin H. Trimetazidine reduces oxidative stress in cardiac surgery. Circ J 2006; 70: 1169-73.
23. Kowalski J, Barylski M, Banach M, et al. Neutrophil superoxide anion generation during atorvastatin and fluvastatin therapy used in coronary heart disease primary prevention. J Cardiovasc Pharmacol 2006; 48: 143-7.
24. Lemos PA, Hoye A, Serruys PW. Recurrent angina after revascularization: an emerging problem for the clinician. Coron Artery Dis 2004; 15 (Suppl. 1): S11-5.