

Trimetazidine: a metabolic agent for the treatment of stable angina

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It has been recently demonstrated that trimetazidine, known for years to be an effective antianginal agent, shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. By decreasing fatty acid oxidation, trimetazidine stimulates glucose utilization, restoring coupling between glycolysis and carbohydrate oxidation and leading to adenosine triphosphate production with lesser oxygen consumption. The antianginal properties of this agent are independent of haemodynamic changes, and dramatically improve recovery of mechanical function after ischaemia. Several studies have tested the efficacy of trimetazidine and have demonstrated this agent to be at least as effective as and better tolerated than haemodynamic agents. In stable effort angina, trimetazidine improves exercise tolerance and elevates the ischaemic threshold to an extent comparable with beta-blockers and calcium channel blockers. The combination of trimetazidine and a beta-blocker appears more effective than the combination of nitrates and a beta-blocker, and the addition of trimetazidine improves symptoms in patients resistant to diltiazem. The cardioprotective effects of trimetazidine have been recently confirmed in human ischaemia–reperfusion, including patients

undergoing percutaneous coronary artery revascularization and bypass surgery with cardioplegic arrest. A new modified-release (MR) formulation of trimetazidine will shortly be introduced. A twice-daily regimen of these new MR tablets has been shown to be bioequivalent to the thrice-daily regimen of the previous formulation, and has been clinically tested in patients with stable angina pectoris resistant to beta-blockers. In a multicentre, international, double-blind, randomized, placebo-controlled study, the addition of trimetazidine MR tablets twice daily to atenolol 50 mg significantly prolonged the time to 1 mm ST depression and the time to onset of angina, with a favourable safety profile. The clinical safety of this new formulation has been confirmed in a double-blind, placebo-controlled study enrolling 234 elderly patients treated for 1 year. Safety and efficacy of trimetazidine MR promise to expand the role of metabolic agents for the treatment of ischaemic heart disease.

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Introduction

According to the classic pathogenetic view, myocardial ischaemia is caused by an imbalance between myocardial metabolic demands and myocardial blood supply. Such an imbalance may result either from an increase in cardiac work that is not accompanied by a parallel increase in coronary blood flow, or from a primary reduction in coronary blood flow. Actually, in many patients both mechanisms contribute to the development of ischaemia, and a combination of drugs that supposedly have different mechanisms of action is often prescribed in order to prevent adverse events and improve quality of life.

When abnormal coronary vasomotion contributes to the ischaemic attacks, nitrates are the first line of treatment.

They lower coronary smooth muscle tone, dilate coronary epicardial vessels and prevent coronary vasospasm. Beta-blockers are most effective in reducing cardiac work and myocardial oxygen consumption. Agents from this class lower heart rate and aortic pressure, depress myocardial contractility, and are the most prescribed drugs worldwide for long-term treatment of effort angina. Calcium channel blockers are a complex family of drugs that includes substances with prominent coronary vasodilating effects, with marked negative inotropic and chronotropic effects, and with intermediate characteristics. With appropriate selection, these agents can be used in effort angina as well as in angina due to abnormal coronary vasomotion.

Medical treatment based on these 'haemodynamic' agents improves symptoms and quality of life in many patients with angina pectoris. No conclusive evidence is yet available that these agents reduce the rate of major cardiac events and prolong patient survival. Moreover, many patients with stable angina pectoris receive multiple

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prescriptions for agents with similar mechanisms of action and show no evidence of beneficial effects in this regard^[1-4].

Trimetazidine, which has been known for years to be an effective antianginal agent, markedly departs from this scenario because it does not interfere with coronary blood flow regulation or with the determinants of myocardial oxygen consumption^[5].

Trimetazidine: mechanism of action

It has recently been demonstrated that, by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase, trimetazidine alters energy metabolism via inhibitory effects on fatty acid oxidation, thus favouring glucose oxidation^[6]. On the basis of this recent observation, trimetazidine is regarded as the prototype of a new class of antianginal agents: the 3-ketoacyl coenzyme A thiolase inhibitors.

The benefits of increased glycolytic substrate utilization are attributed to a number of mechanisms. The number of moles of adenosine triphosphatase (ATP) produced per mole of carbon oxidized is approximately 29% higher for free fatty acids relative to glucose, but the number of moles of ATP produced per mole of oxygen consumed is 12% higher for glucose than for free fatty acid oxidation. Thus, in normal conditions, it is more efficient for the myocardium to utilize free fatty acids, but during ischaemia glucose is a better substrate^[7].

By decreasing fatty acid oxidation and stimulating glucose utilization, trimetazidine restores coupling between glycolysis and carbohydrate oxidation, and leads to ATP production with less oxygen consumption. By stimulating membrane phospholipid turnover during ischaemia and reperfusion, trimetazidine redirects fatty acids toward phospholipids^[8].

Cellular effects of trimetazidine in ischaemia-reperfusion

In rabbit hearts undergoing a sequence of ischaemia-reperfusion, trimetazidine inhibited neutrophil accumulation without adverse effects on vascular permeability^[9]. Experimental studies have also shown that trimetazidine protects myocardial cells from reperfusion injury, attenuates intracellular acidosis during ischaemia, and accelerates restoration of phosphorylation at reperfusion. Addition of trimetazidine to a cardioplegic solution limits ATP depletion, attenuates intracellular acidosis, and accelerates metabolic recovery at reperfusion^[10].

In patients undergoing coronary artery bypass surgery, the addition of trimetazidine to the cardioplegic solution was associated with a reduction in biochemical markers of cell damage and lipid peroxidation^[11]. In animal studies, the anti-ischaemic properties of trimetazidine are associated with a reduction in infarct size^[12,13] and with a dramatic recovery of mechanical function after ischaemia^[14].

The hypothesis that trimetazidine has a direct cytoprotective action has been confirmed by observations in patients undergoing percutaneous transluminal coronary angioplasty, in which intracoronary trimetazidine markedly attenuated ECG signs of ischaemia during balloon inflation^[15].

Trimetazidine: clinical efficacy

The efficacy of trimetazidine as an antianginal drug has been assessed in randomized, placebo-controlled studies, both as 'solo' treatment and in combination with beta-blockers and calcium channel blockers.

In patients with chronic angina, trimetazidine increases work capacity and delays the appearance of symptoms and ECG changes during exercise^[16-18]. The benefits observed after acute administration are maintained in chronic treatment with trimetazidine, which is well tolerated by patients^[19].

Comparison studies have shown that the efficacy of trimetazidine in chronic angina is comparable to that of nifedipine and propranolol, with the additional bonus, in prolonged trimetazidine treatment, of a lower incidence of side effects^[20-23]. Given the absence of effects on heart rate and blood pressure, trimetazidine appears to be the ideal agent for combination therapy with classic 'haemodynamic' drugs in chronic treatment of angina pectoris. In patients who were already receiving nifedipine or propranolol, the addition of trimetazidine significantly improved clinical status and reduced the number of ischaemic episodes per week. These clinical effects were associated with a prolongation of the exercise time and a delay in the appearance of ischaemic symptoms and diagnostic ST-segment changes. Side effects were significantly less frequent in patients receiving trimetazidine than in patients receiving nifedipine or propranolol^[20-23].

Evidence in support of the hypothesis that the mechanism of action of trimetazidine is distinct from the 'haemodynamic' effects of beta-blockers and that the benefit from the metabolic approach may be additive to the benefit of haemodynamic agents was gained from a multicentre, randomized, double-blind study, in which addition of trimetazidine to propranolol was compared with addition of nitrates to propranolol^[24]. That study was performed in patients with chronic effort angina and documented coronary artery disease, and concluded that the combination of trimetazidine with propranolol was more effective and better tolerated than the combination of nitrates with propranolol.

Similar evidence was obtained in recent double-blind, randomized studies performed in patients with angina uncontrolled by diltiazem^[25,26]. These studies showed that addition of trimetazidine significantly reduced the number of ischaemic attacks, prolonged exercise time and time to onset of angina, and increased the maximum work at peak exercise. These beneficial effects were obtained without adverse haemodynamic changes or increased incidence of side effects.

All of these clinical benefits were recently confirmed in a randomized, double-blind, placebo-controlled, multicentre

study conducted in Poland^[27], which proved the efficacy and acceptability of trimetazidine in patients with angina uncontrolled by metoprolol alone.

Clinical development and future applications of trimetazidine

Years of experience have identified the clinical efficacy and favourable safety profile as distinctive characteristics of trimetazidine, and have built a reputation for this drug as the ideal treatment for chronic angina. Recent studies have identified certain subgroups of patients, including diabetic and elderly patients, as experiencing particular benefit from trimetazidine administration. This strong reputation and positive perception is expected to be further enhanced by the development of a slow-release formulation termed Vastarel 35 mg MR (modified release) that is expected to become commercially available in the near future (Les Laboratoires Servier, Neuilly-sur-Seine, France).

The pharmacokinetic profile of the 35 mg MR tablets administered twice a day compares favourably with the classic 20 mg tablets administered three times a day, ensuring higher trough concentrations and lower peak concentrations (data on file, Les Laboratoires Servier).

The efficacy and safety of the new formulation have been assessed in a multicentre, international, double-blind, randomized, placebo-controlled study performed in two parallel groups of 120 angina patients receiving trimetazidine 35 mg MR or placebo in addition to atenolol. In patients receiving the active drug, a significant prolongation of the time to onset of angina and of the time to 1 mm ST-segment depression was observed. The incidence of adverse events was similar between the groups, and no significant effect on laboratory tests was observed in the active group as compared with the patients receiving placebo over a 6-month treatment period (data on file, Les Laboratoires Servier).

The clinical safety of trimetazidine MR 35 mg has also been confirmed in a more fragile population – elderly patients with chronic angina – treated for 1 year. The results of that double-blind, placebo-controlled study confirmed the long-term safety of trimetazidine 35 mg MR; no difference was observed between the active and the placebo groups in the incidence of adverse events or in other safety parameters, including biochemistry, haematology and ECG parameters, and vital signs (data on file, Les Laboratoires Servier).

Conclusion

Long-term management of ischaemic heart disease remains a difficult challenge for the clinical cardiologist. Macrovascular and microvascular disease limit the efficacy of revascularization procedures, and increase early and late complications in patients managed medically. Classic haemodynamic agents do not provide optimal results and are often poorly tolerated. Correction of the alterations in

cardiac metabolism that are associated with the ischaemia-reperfusion sequence may represent an innovative and effective therapeutic approach in the management of ischaemic heart disease.

Trimetazidine 20 mg three times a day has been proved to be effective and well tolerated in several patient populations, including high-risk subgroups such as diabetic persons, the elderly and patients with ventricular dysfunction^[26–28]. The introduction of trimetazidine 35 mg MR tablets promises to enhance further the reputation of this drug, given its favourable pharmacokinetic profile, improved patient compliance, and preliminary clinical experience in elderly patients and in patients who are refractory to beta-blocker therapy.

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