Trimetazidine and the metabolic profile of ischemia

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Abstract

Trimetazidine, a metabolic agent, acts at the cellular level to improve myocardial metabolism at the time of ischemia. A recent Cochrane Collaboration review of its use in stable angina has confirmed its effectiveness in reducing anginal attacks and nitrate consumption, at the same time as improving exercise performance with minimal adverse events. Additional reports identifying improved left ventricular function in cardiac failure suggest a potential prognostic role.
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The conventional management of stable angina focuses on reducing myocardial demand by means of drugs that reduce heart rate, blood pressure, and contractility [1]. There is no doubt that these drugs are very effective but, once the hemodynamic option has been maximized, the addition of agents with a similar mode of action has never been shown to improve symptoms. Indeed, adverse effects are often the consequence, and it is adverse effects that may limit the usefulness of hemodynamic agents; however, this should not be over emphasized. The most common dose-limiting adverse effects are cold peripheries, lethargy and ''heavy legs'' or a ''zombie'' feeling in patients receiving β-blockers, fluid retention in those receiving calcium antagonists, and headaches in individuals receiving oral nitrates or nicorandil. To circumvent these effects, suboptimal combination treatment is often used – for example, atenolol 50 mg plus amlodipine 5 mg daily, rather than atenolol 100 mg daily.

An alternative strategy is to address the metabolic causes or consequences of ischemia [2]. The normal heart derives 60–90% of its energy from the consumption of free fatty acids (FFAs), and the remainder from glucose and lactate. FFA metabolism yields more adenosine triphosphate (ATP) per gram, but requires more oxygen consumption to do so. When ischemia develops and there is a deficiency in oxygen delivery to the myocardium relative to the demand for ATP, glycolysis is activated in an attempt to generate ATP anaerobically. Glycogen stores are broken down, glucose uptake is increased, and instead of lactate consumption there is lactate production, which can be measured in the coronary sinus. As a consequence, the pH in the cell is reduced and calcium overload occurs, leading to contractile dysfunction [3].

Trimetazidine inhibits the enzyme of fatty acid β-oxidation, long-chain 3-ketoacyl coenzyme A thiolase (known as 3-KAT). Through the inhibition of myocardial fatty acid oxidation, glucose and pyruvate oxidation is increased (pyruvate dehydrogenase activity is increased) and lactate production is decreased at the time of effort- (or emotionally) induced ischaemia – that is, the supply–demand imbalance is restored, independently of hemodynamic actions. The evidence base for the effectiveness of trimetazidine in stable angina has been the subject of a recent Cochrane Collaboration review, but we also have increasing reports of its beneficial actions in patients with heart failure, who show improvements in symptoms, exercise performance, ejection fraction and, possibly, prognosis [4,5].

In the Cochrane review, the objective was to determine the efficacy and tolerability of trimetazidine in

Table 1. Summary of the effectiveness of trimetazidine in stable angina.

Comparison between trimetazidine and	Outcome	Superiority
Placebo	Angina: events per week	Trimetazidine
	Glyceryl trinitrate: use per week	Trimetazidine
	Time to 1-mm ST-segment depression on exertion	Trimetazidine
	Number of adverse events	Trimetazidine
Hemodynamic agent	Angina: events per week	Equal
	Glyceryl trinitrate: use per week	Equal
	Time to 1-mm ST-segment depression on exertion	Equal
	Number of adverse events	Trimetazidine

patients with stable angina. Selection criteria were for randomized trials comparing trimetazidine with placebo or with other antianginal drugs, in adults with stable angina. A total of 23 studies, involving 1378 patients, met the inclusion criteria. The findings are summarized in *Table I*. Compared with placebo, trimetazidine reduced the weekly angina attack rate by 40% (mean difference −1.44, 95% confidence interval [CI] −2.10 to −0.79; $P < 0.0001$) and nitrate consumption (−0.73, 95% CI −1.47 to −2.20; $P < 0.0001$). Objectively, trimetazidine improved exercise time to 1-mm ST-segment depression ($P = 0.0002$). The benefits occurred with trimetazidine as monotherapy and in combination. An important feature of all the studies was the low incidence of adverse effects – fewer than placebo!

This report demonstrated the efficacy of trimetazidine versus placebo and in addition to conventional haemodynamic agents in the treatment of stable angina. Trimetazidine is therefore an effective antianginal drug that with its minimal side effect profile it has an important role to play when side effects limit haemodynamic agents and in those vulnerable to adverse effects such as one elderly. It is therefore, at present, a drug for relief of symptoms and, with its minimal side-effect profile, it has an important part to play when side effects limit the usefulness of hemodynamic agents and in those patients who are vulnerable to adverse effects, such as the elderly [6].

The question of whether there are prognostic benefits needs to be addressed, given the evidence of an improved ejection fraction in patients with cardiac failure. In one study of 200 patients with ischemic left ventricular dysfunction as a result of multivessel coronary artery disease, 100 patients were placed on a regimen of trimetazidine in addition to conventional treatment and 100 received placebo [7]. Trimetazidine improved ischemic attacks clinically and also improved both exercise performance and perfusion judged using single photon emission computed tomography. Survival at 2 years was 92% among patients treated with trimetazidine and 62% among those treated with placebo. Clearly, this observation is of significance, given the poor prognosis in cardiac failure even when all the evidence-based medicine has been deployed.

Trimetazidine is therefore an effective, well tolerated treatment for stable angina, with a fascinating and potentially exciting potential in cardiac failure in which there is evidence of systolic dysfunction. ■

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