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Editor's Note

Partial Fatty Acid Oxidation (pFOX) Inhibition: A New Therapy for Chronic Stable Angina

Key words: partial fatty acid oxidation (pFOX), chronic stable angina

Introduction

I recently attended a session on partial fatty acid oxidation (pFOX) inhibition as an alternative approach using a metabolically active drug in the treatment of patients with chronic stable angina. I suspect that many are not familiar with this type of therapy, which, in my opinion, may prove very useful to those of us who take care of patients who have persistent chronic stable angina despite sound medical therapy including revascularization.

Energy for Cardiac Contraction under Resting Nonischemic Conditions

To summarize briefly, energy for cardiac contraction and relaxation is derived from adenosine triphosphate (ATP) breakdown, and ATP is derived from the oxidation of fatty acids and carbohydrates. Under resting nonischemic conditions when hypoxia is not present, a large percentage of the energy required for ATP synthesis comes from fatty acids. It is not important for the heart to use glucose as an efficient energy source to drive myocardial function.

Energy for Cardiac Contraction during Myocardial Ischemia

In humans, fatty acid levels increase during ischemia and serve as an even greater source of cardiac energy than they do under resting nonischemic conditions. As a result, myocardial oxygen consumption is increased, resulting in a vicious cycle in which myocardial blood flow is decreased, as it is during myocardial ischemia. If carbohydrate oxidation is activated reciprocally, myocardial oxygen consumption is reduced as the contraction of the heart is maintained.

Effects of pFOX Inhibition on Energy Source for Cardiac Contraction during Myocardial Ischemia

In the animal laboratory, a pFOX inhibitor directly inhibits fatty acid oxidation of ischemic myocytes. This, in turn, results in a reduction in the inhibition of pyruvate dehydrogenase. More pyruvate dehydrogenase is then available to facilitate glucose oxidation. More acetyl-coenzyme A is then available to enter into the Krebs citric acid cycle, thus improving myocardial efficiency by optimizing myocardial energy metabolism utilizing glucose. Thus, when pyruvate dehydrogenase activity is high, glucose oxidation is stimulated; when it is low, fatty acid oxidation is stimulated. Animal models of cardiac ischemia suggest an 11% increased yield of ATP for a given rate of myocardial oxygen consumption when the source of fuel is switched from fatty acids to carbohydrates. When this happens, cardiac work can be increased or maintained as myocardial oxygen consumption is decreased, in contrast to the effects of beta blockade in which myocardial oxygen consumption is decreased, but cardiac work is also decreased.

Thus, in my opinion, the pFOX inhibitors are a unique new category of drugs that provide additional therapy to current treatment of patients with chronic stable angina pectoris. According to several studies, pFOX inhibitors do not affect hemodynamics, that is, heart rate, coronary vasodilation, or hypotension.

Clinical Trials of pFOX Inhibition

Ranolazine is not a new drug and is well known to be a partial inhibitor of fatty acid oxidation, thus, a pFOX inhibitor. Ranolazine does what one would expect, that is, it shifts ATP production away from fatty acid oxidation towards carbohydrate oxidation. Myocardial oxygen demand is then reduced without decreasing cardiac work. A further benefit is that glycolysis continues to be coupled to pyruvate oxidation and thus lactate accumulation is minimized, as is lactic acidosis.

Two clinical trials of the pFOX inhibitor ranolazine have been performed and presented at national meetings. In MARISA (Monotherapy Assessment of Ranolazine in Stable Angina), a double-blind randomized trial of 168 patients, subjects were withdrawn from any other anti-angina drugs and then randomized to different doses of ranolazine and placebo;

results were quite interesting. The pFOX inhibitor, ranolazine, had no effect on resting or exercise blood pressures or on heart rate compared with placebo, but it did increase exercise duration, time to angina, and time to 1 mm ST-segment depression compared with placebo. In my view, this trial was a study to illustrate a proof of principle—that pFOX inhibition was effective therapy for myocardial ischemia compared with placebo in patients with stable angina pectoris.

However, as everyone treating these patients well knows, the real world of management will include beta blockers, probably nitrates, and possibly calcium antagonists.

Thus, a second trial of the pFOX inhibitor ranolazine was carried out. In CARISA (Combination Assessment of Ranolazine in Stable Angina), patients received low-dose atenolol, low-dose diltiazem, or low-dose amlodipine. Ranolazine b.i.d. was administered to 823 patients with chronic angina on anti-angina therapy as outlined above. Minimal effects on resting and exercise heart rate and blood pressure were observed. The major result was that at 12 weeks, ranolazine at peak dose significantly increased exercise duration, time to angina, and time to ST-segment depression in patients who were taking background anti-angina therapy as outlined above.

In clinical trials of ranolazine, the QTc interval was increased 5–6 ms and theoretically could result in torsades de pointes. Thus, patients with prolonged QTc prior to therapy must be monitored regularly. Ranolazine is metabolized principally by CYP4503A4, so should not be used with drugs that inhibit that enzyme system.

Summary

During myocardial ischemia, fatty acids are the principal source of energy, increasing myocardial oxygen consumption and making a decrease in coronary blood flow less well tolerated. Increasing glucose oxidation during myocardial ischemia may improve cardiac efficiency. The pFOX inhibitors have the potential to accomplish this.

In 2003, I think we can look forward to learning more about this class of compounds called pFOX inhibitors. Perhaps they will provide us alternative therapies in our patients who have persistent chronic stable angina pectoris despite aggressive medical therapy and/or revascularization. It seems to me that this is an increasing problem, and it is particularly common in older patients who want to remain active, but whose chronic stable angina interferes with that lifestyle.

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Selected readings

1. Schofield RS, Hill JA: Role of metabolically active drugs in the management of ischemic heart disease. *Am J Cardiovasc Drugs* 2001;1:23–35
2. Schofield RS, Hill JA: The use of ranolazine in cardiovascular disease. *Expert Opin Investig Drugs* 2002;11(1):117–123