Antianginal drugs that exert their anti-ischaemic effects primarily by altering myocardial metabolism have recently attracted attention. They have the potential to relieve symptoms in patients with refractory angina who are already on "optimal" medical therapy and have disease that is not amenable to revascularisation, making these drugs an attractive addition to therapy, particularly for the elderly population. In some cases, they may even be used as first-line treatment. These drugs increase glucose metabolism at the expense of free-fatty-acid metabolism, enhancing oxygen efficiency during myocardial ischaemia. Whilst they have been demonstrated to reduce ischaemia in several clinical trials, their use remains limited. This review aims to draw attention to these "metabolic" antianginal drugs while surveying the evidence supporting their use and mode of action. Four metabolic antianginal drugs are reviewed: perhexiline, trimetazidine, ranolazine, and etomoxir. We also discuss the metabolic actions of glucose–insulin–potassium and β-blockers and describe myocardial metabolism during normal and ischaemic conditions. The potential of these metabolic agents may extend beyond the treatment of ischaemia secondary to coronary artery disease. They offer significant promise for the treatment of symptoms occurring due to inoperable aortic stenosis, hypertrophic cardiomyopathy, and chronic heart failure.

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Review

Metabolic manipulation in ischaemic heart disease, a novel approach to treatment

Leong Leea,*, John Horowitzb, Michael Frenneauxa

a Wales Heart Research Institute, Heath Park, Cardiff, CF14 4XN, UK
b Department of Cardiology, University of Adelaide, Queen Elizabeth Hospital, Adelaide 5011, Australia

Received 11 August 2003; revised 11 February 2004; accepted 19 February 2004

KEYWORDS
Angina;
Metabolism;
Perhexiline;
Trimetazidine;
Ranolazine;
Etomoxir

Introduction

Considerable progress has been made over the last 25 years in expanding the therapeutic options available in ischaemic heart disease, including both pharmacological and interventional measures that improve symptoms and prognosis. However, many patients continue to experience intractable symptoms despite being on "optimal" medical therapy. In addition, an increasing number of patients, particularly elderly patients, are deemed to be unsuitable for coronary revascularisation.

A novel medical treatment would be particularly beneficial in relieving the significant morbidity that exists in this group.

The modes of action of most prophylactic antianginal agents involve haemodynamic changes, such as reduction in systemic vascular resistance, coronary vasodilatation, or negative inotropism, thus improving the imbalance in myocardial oxygen supply and demand. Recently, it has become apparent that certain antianginal treatments exert a primarily metabolic action and have little or no effect on coronary haemodynamics. These drugs have considerable potential as adjunctive therapy for angina, particularly in patients refractory to standard therapies, and may be a primary therapeutic option in certain circumstances. They generally do not adversely affect blood pressure, pulse rate, or left ventricular systolic function, offering a significant ad-
vantage in patients in whom conventional agents may induce symptomatic hypotension, inappropriate bradycardia, or worsening heart failure. The purpose of this review is to draw attention to some of these "metabolic" agents, while at the same time surveying the current level of evidence supporting their clinical use and mode of action. Two commonly used treatments for ischaemic heart disease that also exert metabolic effects have been included (β-blockers and glucose–insulin–potassium).

Myocardial metabolism

Under aerobic conditions the predominant substrate used by the normal adult human heart are free fatty acids (FFA), accounting for 60–90% of the energy generated (Fig. 1). Long-chain fatty acids (LCFA) are the major component of FFA utilisation. LCFA entry into myocardial cells is a complicated process facilitated by several enzymes. Following cellular uptake, LCFA entry into the mitochondria is facilitated by the enzymes carnitine-palmitoyl-transferase (CPT) I and II (Fig. 2). β-Oxidation then occurs, which yields acetyl-CoA. Acetyl-CoA enters the tricarboxylic acid cycle and eventually leads to the formation of ATP, which is critical for myocardial contraction and relaxation.

Carbohydrate metabolism, on the other hand, contributes only about 10–40% of energy generated by the healthy adult human heart. Glucose taken up by the myocardial cell is either stored as glycogen or converted into pyruvate by glycolysis. Pyruvate is then oxidised within the mitochondria by pyruvate dehydrogenase into acetyl-CoA.

Myocardial metabolic adaptations during ischaemia

In contrast to the adult heart, the foetal heart (which operates under hypoxic conditions) uses glucose as its predominant fuel. The switch to free fatty acids as the predominant substrate occurs in the early postnatal period. All metabolic adaptive mechanisms during ischaemia, whether physiologic or pharmaceutical, effectively recapitulate foetal energy metabolism by shifting substrate use towards glucose metabolism. The energetic advantages of incremental glucose utilisation arise from the fact that though fatty acid oxidation yields more ATP than glycolysis in aerobic conditions (in terms of ATP per gram of substrate), this is at the expense of greater oxygen consumption. Fatty acids require approximately 10–15% more oxygen to generate an equivalent amount of ATP when compared to glucose.

During subtotal ischaemia, the myocardium continues to derive a large proportion of its energy from oxidative metabolism. In moderate-to-severe ischaemia, there is increased utilisation by the myocardium of glucose as a substrate for energy production. Nevertheless, FFA oxidation continues to be the predominant substrate in the ischaemic heart (Fig. 3).

Apart from requiring a higher oxygen expenditure to generate energy than glucose metabolism, high levels of FFA uptake and catabolism during the ischaemic period may have detrimental effects on the myocardium. High rates of FFA oxidation suppress glucose oxidation through a direct inhibitory action on pyruvate dehydrogenase, thereby increasing lactate and proton accumulation in ischaemic cells. Increased lactate and proton content (and hence a fall in intracellular pH) is associated with a
reduction in the contractile function of myocardial segments. Cardiac efficiency is decreased because ATP is required not only to support contractile function, but increasingly to restore cellular ionic homeostasis. Furthermore, accumulation of LCFA intermediates during β-oxidation has previously been shown to reduce the ventricular arrhythmia threshold and induce diastolic dysfunction during ischaemia.

Physiologic, pathologic, or therapeutic suppression of FFA uptake and/or oxidation by any means stimulates an increase in myocardial glucose substrate utilisation. Therapeutic interventions aimed at a shift of myocardial substrate utilisation towards glucose metabolism may therefore be expected to offer considerable benefit in patients with ischaemic heart disease. Most of the currently available agents achieve this through suppression of FFA oxidation.

However, a theoretical downside exists to metabolic modulation by inhibiting FFA metabolism. Genetic abnormalities in fatty-acid oxidation, particularly involving acyl-CoA dehydrogenase (an enzyme involved in β-oxidation) have been implicated in causing dilated cardiomyopathy and arrhythmias in children. The mechanism appears to be due to accumulation of intermediary metabolites of free-fatty-acid metabolism (for example, long-chain acyl carnitines). It is also worth noting that in patients with idiopathic dilated cardiomyopathy there is a metabolic shift similar to that seen in ischaemic heart disease. Whether this represents an adaptive or maladaptive response in chronic heart failure remains to be determined.

"Metabolic" agents commonly used in clinical practice

β-Blockers

β-Blockers improve symptoms of angina and are an established, commonly prescribed treatment for ischaemic heart disease. Although their predominant mode of action is to reduce cardiac workload, some of the beneficial effects of β-blockers may reflect metabolic changes. Using radioactive FFA and glucose tracers, Wallhaus et al. demonstrated a 57% reduction in myocardial FFA uptake following treatment with carvedilol in patients with heart failure. However, in this relatively small study, neither mean myocardial uptake of labelled glucose tracers ([18F]-FDG) nor the rate of glucose utilisation increased significantly. While this may reflect a type 2 error, the demonstration of a marked fall in the ratio of myocardial FFA-to-glucose-utilisation does suggest a "metabolic shift" induced by carvedilol. While the au-
Acute administration of insulin, alone (in hyperglycaemic effects. Some coronary artery flow is required for GIK cellular necrosis may be independent of these metabolic effects of caradarvedilol and its therapeutic effects in heart failure.

Glucose—insulin—potassium (GIK)

Acute administration of insulin, alone (in hyperglycaemic diabetics) or together with glucose and potassium, has been widely postulated to induce potential beneficial effects in acute myocardial ischaemia by altering myocardial metabolism. The use of insulin in the presence of diabetes has been well established since the DIGAMI trial, which demonstrated a significant long-term mortality benefit in diabetic patients treated with insulin following myocardial infarction (MI). Though it is beyond the scope of this review to present all the evidence for the utility of GIK in non-diabetics during acute myocardial infarction, we have summarised some of the key studies investigating the utility of GIK in the acute ischaemic setting.

A meta-analysis by Fath-Ordoubadi and Beatt suggests that GIK infusion improves outcome postmyocardial infarction even in patients without diabetes mellitus. The observed improvements in mortality following GIK infusion post-MI appear to hold true even in the context of contemporary treatment with thrombolysis or percutaneous coronary intervention, as demonstrated by the ECLA study.

Two studies conducted in the post-MI setting, however, failed to demonstrate a significant short-term mortality benefit with GIK therapy. A Dutch study conducted in association with primary percutaneous coronary intervention suggested, on post hoc analysis, a reduction in mortality confined to patients without heart failure at presentation. While, in theory, this might reflect greater early access of GIK to the ischaemic zone (via collaterals), these results should be confirmed on a prospective basis. The negative Polish study used lower doses of GIK than other positive studies and a lower-risk cohort. It has therefore been suggested that higher-risk patients may derive greater benefit from GIK, particularly in the presence of collateral flow.

The mechanism of benefit of GIK infusion is thought to be due to increased glycolysis and reduced FFA uptake by myocardial cells. This has been purported to lead to lower myocardial oxygen requirement, a reduction in proton and free radical accumulation, and improved myocardial energetics. However, it remains possible that a component of the effects of insulin in reducing susceptibility to ischaemia-induced cellular necrosis may be independent of these metabolic effects. Some coronary artery flow is required for GIK to be delivered to the site of myocardial injury during acute MI. Previous studies have demonstrated that during MI, some flow to the infarcted regions persists, due primarily to collateralisation. Both the ECLA and Dutch study suggested that GIK was only beneficial when given in concert with reperfusion.

Anti-ischaemic drugs that act primarily by metabolic manipulation

Perhexiline

Perhexiline was a frequently prescribed antianginal agent in the 1970s. Early randomised controlled trials in patients with coronary artery disease demonstrated that it markedly relieved symptoms of angina, improved exercise tolerance, and increased the workload needed to induce ischaemia when used as monotherapy. More recently, randomised controlled trials have demonstrated that perhexiline exerts marked, incremental anti-ischaemic effects in patients receiving β-blockers or even "triple" prophylactic antianginal therapy.

Though originally designated as a calcium-channel blocker, it is clear that it has no significant calcium-channel blocking activity at therapeutic concentrations. Perhexiline is not negatively inotropic and does not alter systemic vascular resistance to a significant degree at plasma levels that are within therapeutic range. There is now increasing evidence that it acts by shifting myocardial substrate utilisation from fatty acids to carbohydrates through inhibition of CPT-1 and, to a lesser extent, CPT-2, resulting in increased glucose and lactate utilisation.

Perhexiline use declined dramatically in the early 1980s following reports of hepatotoxicity and peripheral neuropathy. These effects were later demonstrated to occur most commonly in patients who are "slow hydroxylators", bearers of a genetic variant of the cytochrome P-450 enzyme family. These patients are slow metabolisers of perhexiline due to saturation of hepatic metabolic pathways, which leads to accumulation of the drug and toxicity. The mechanism for toxicity appears to be due to phospholipid accumulation, which is a direct consequence of CPT-1 inhibition. Hence, this is a potential side effect of any drug that inhibits CPT-1, including amiodarone, which exhibits weak CPT-1-inhibitor properties. This is thought to be the mechanism responsible for the peripheral neuropathy and hepatitis occasionally seen with amiodarone use.

However, it has since been demonstrated that the risk of toxicity can be dramatically reduced by maintaining plasma concentrations between 150 to 600 ng/mL without compromising the efficacy of the drug. Indeed, during short-term therapy the risk of adverse effects is limited to nausea and dizziness associated with elevated plasma levels, and hypoglycaemia in diabetics. With long-term treatment, there is considerable risk of phospholipidosis-mediated hepatitis or peripheral neuropathy unless the drug is titrated according to plasma levels. Cole et al. confirmed the safety of perhexiline in a randomised, double-blind, crossover study following initiation of 100 mg of perhexiline twice daily with subsequent plasma-guided dose titration; none of the
patients developed major permanent adverse effects. They also confirmed the sustained clinical efficacy of perhexiline with this strategy by demonstrating a marked improvement in angina frequency and exercise capacity when perhexiline was added to “triple” prophylactic antianginal therapy.

These findings have led to resurgence in the use of perhexiline in some parts of the world, particularly Australia, for the treatment of refractory angina. However, its use in Europe remains limited. Perhexiline is currently available in most European countries on a named-patient basis, usually as adjunctive treatment for refractory angina in patients not suitable for, or awaiting, coronary intervention, but its use must be accompanied by serum level monitoring.

A recent study has suggested that in patients with chronic stable angina or unstable coronary syndromes, perhexiline may also increase the sensitivity of platelets to the antiaggregatory effects of nitric oxide. It is not yet clear whether this interaction of perhexiline with platelet function reflects changes in platelet CPT activity. This effect may be therapeutically important, especially in patients with unstable coronary syndromes.

In addition, the lack of significant negative inotropic effects of perhexiline, combined with its nonvasoactive properties, has raised its potential utility for angina occurring in the presence of systolic heart failure and/or aortic stenosis. One open-labelled study suggested an improvement in the symptomatic profile of elderly patients with inoperable aortic stenosis. A randomised, double-blind, controlled study investigating this further is presently underway.

Currently, the postulated therapeutic roles for perhexiline are as short-term therapy (less than 3 months duration) in patients with severe ischaemia awaiting coronary revascularisation or long-term therapy in patients with ischaemic symptoms refractory to other therapeutic measures.

Trimetazidine

Trimetazidine (1-[2,3,4-trimethoxybenzyl] piperazine dihydrochloride – a substituted piperazine compound similar to ranolazine) is a drug that has attracted considerable interest recently. It exhibits no significant negative inotropic or vasodilator properties either at rest or during dynamic exercise. Several clinical trials have demonstrated the potential benefits of trimetazidine in ischaemic heart disease. In two separate small studies, trimetazidine was found to increase systolic-thickening scores in ischaemic myocardial segments using dobutamine stress echocardiography. A larger, randomised, controlled trial conducted in Poland (TRIMPOL II) recruited 426 patients with stable angina who were randomised to either trimetazidine 20 mg three times a day or placebo in addition to metoprolol. This study demonstrated an improvement in time to ST-segment depression on exercise tolerance testing (ETT), total exercise workload, mean nitrate consumption, and angina frequency in patients randomised to receive trimetazidine. The drug had a favourable side-effect profile. A recent meta-analysis of 12 clinical trials of trimetazidine in stable angina demonstrated a significant reduction in anginal frequency, but only a nonsignificant trend towards prolongation of the duration of treadmill exercise.

However, a large, randomised, placebo-controlled trial recruiting 19,725 patients with acute myocardial infarction in centres across Europe did not demonstrate a short or long-term mortality benefit when intravenous trimetazidine was infused immediately post-MI for 48 h. Subgroup analysis demonstrated a trend towards reduced mortality that was nonsignificant by intention-to-treat but significant when analysed by protocol group (13.34% vs. 15.10%, $p = 0.027$). More recently, a small, double-blind, randomised, placebo-controlled study demonstrated improved exercise capacity and ST-segment depression during post-MI exercise testing.

While the potential clinical benefits of trimetazidine are established, the mechanism for its clinical effects is still debated. Initial work conducted in rat models demonstrated the profound inhibitory effects of trimetazidine on palmitoylcarnitine oxidation with no significant effect on pyruvate oxidation. Trimetazidine is a weak CPT-1 inhibitor, but this action is weaker than that of perhexiline or even amiodarone, which makes its unlikely that it would contribute significantly to the antianginal action of the drug. However, a derivative of trimetazidine, S-15176, has been shown to exert more potent CPT-1 inhibitory properties.

Kantor et al. demonstrated that trimetazidine reduces the rate of FFA oxidation, with a concomitant 210% increase in glucose oxidation rates during low-flow ischaemia. Their data also suggest that the likely route by which this is achieved is through the inhibition of the enzyme long-chain 3-ketoacyl coenzyme A thiolase (LC 3-KAT), which is a crucial enzyme in the β-oxidation pathway. In contrast, MacInnes et al. investigated the molecular target of trimetazidine in the β-oxidation pathway in crude and purified rat hearts and failed to demonstrate any inhibitory effects of trimetazidine on LC 3-KAT. They also did not demonstrate any significant inhibition of β-oxidation by trimetazidine at doses exceeding that which have previously been found to be clinically effective for angina. The authors concluded therefore that trimetazidine does not exert its antianginal effects via metabolic modulation, although they did confirm an improvement in the ischaemic myocardial function of rat hearts. In response to this study, Lopaschuk et al. submitted data demonstrating that the lack of LC 3-KAT inhibition in the study by MacInnes et al. may be related to the high substrate concentrations used in their experiments, leading to a reversal in the partial inhibitory action of trimetazidine on LC 3-KAT. They also confirmed their initial observations from the previous study. The molecular mechanism of trimetazidine therefore remains unresolved. However, it is likely that an induction of a metabolic shift represents the underlying mechanism for its antianginal effect.

The clinical efficacy of trimetazidine has been demonstrated in several clinical trials to date and it remains...
a potential treatment for the future. However, no randomised dose–response trials have been conducted on trimetazidine as of yet, which has led to uncertainty regarding its role, particularly in terms of its safety profile at higher doses. Its effect on the QT interval has not yet been determined at higher doses. A trial is currently underway to address this issue.

**Ranolazine**

Ranolazine, \((-\text{N-}(2,6\text{-dimethylphenyl})-4\{2\text{-hydroxy-3-(2-methoxyphenoxy)-propyl}\}-1\text{-piperazineacetamide}\) is a substituted piperazine compound similar to trimetazidine. On the basis of recently completed phase-3 clinical trials, it appears to offer considerable potential. Though the target enzyme by which it exerts its metabolic antianginal action has yet to be determined, ranolazine has been shown to stimulate glucose oxidation and to act as a partial fatty-acid-oxidation inhibitor (pFOX inhibitor). The term pFOX inhibitor was coined after it was observed that ranolazine only inhibits fatty-acid oxidation during the periods of elevated plasma FFA levels associated with myocardial ischaemia. As with trimetazidine, MacInnes et al. could not demonstrate any significant inhibition of LC 3-KAT by ranolazine. However, they did confirm the partial inhibition of β-oxidation by ranolazine in a dose-dependent manner. It seems likely that ranolazine exerts metabolic effects similar to those of trimetazidine and may even act via the same molecular route.

One of the first clinical trials conducted was a randomised, controlled, double-blind trial in 318 patients with chronic stable angina who were randomised to 30–120 mg three times a day of ranolazine or placebo. No difference was observed between the treatment groups with placebo on follow-up ETT in terms of time to 1-mm ST-segment depression or on reported weekly angina episodes. The authors therefore concluded that their data did not support previously conducted smaller studies, which demonstrated that ranolazine is superior to placebo in chronic stable angina. However, low doses of ranolazine were used (compared with subsequent studies), which probably accounts for the negative results.

More recently, two studies using far higher doses of ranolazine (up to 1500 mg twice daily) were conducted. The MARISA study (Monotherapy Assessment of Ranolazine in Stable Angina) is a randomised, double-blind, crossover study that evaluated 191 patients with chronic stable angina given ranolazine as monotherapy following withdrawal of all other antianginal drugs. During follow-up ETT, patients had a significantly longer time to angina and 1-mm ST-segment depression while on ranolazine than placebo.

The CARISA trial (Combination Assessment of Ranolazine in Stable Angina) studied 823 patients with chronic stable angina on background antianginal therapy of either a β-blocker or calcium-channel blocker who were randomised to either ranolazine (750 or 1000 mg twice daily) or placebo. At follow-up ETT, patients randomised to ranolazine had a significantly increased duration of exercise, time to onset of ST-segment depression, and time to angina, while also reporting fewer weekly angina episodes when compared to the placebo group. This benefit was observed regardless of baseline antianginal treatment. Ranolazine had no significant effect on blood pressure or heart rate, but there was a minor prolongation of QT interval in the ranolazine group. There were no cases of torsade de pointes, but this significant prolongation of QT was sufficient to raise concerns regarding routine use of the drug.

Both the MARISA and CARISA clinical trials offer encouraging data and indicate that ranolazine has a significant antianginal effect both as monotherapy and in combination with other antianginal agents. However, its long-term safety, particularly with relation to QT prolongation, remains to be established. Recently, the Food and Drug Administration of the United States have considered granting a restricted licence for its use, provided a study looking into ranolazine in the refractory angina population is conducted.

**Etomoxir**

Etomoxir has yet to be investigated in a randomised controlled trial but ex vivo work suggests that it has potential as an antianginal agent. It was initially introduced as a potential diabetic agent on the basis of its hypoglycaemic effects. It is a potent CPT-1 inhibitor that has been studied extensively in animal models of ischaemia, left ventricular hypertrophy, and left ventricular impairment. In palmitate-perfused ischaemic rat hearts, etomoxir reduced oxygen consumption during ischaemic recovery and also prevented depression of myocardial function. Turcani and Rupp perfused pressure-overloaded, hypertrophic, and failing rat hearts with etomoxir, leading to an improvement in indices of left ventricular dysfunction.

To date, only one clinical trial has looked at the potential benefits of etomoxir in the human heart. In this open-label, uncontrolled, pilot study conducted in 15 patients with New York Heart Association Class II–III heart failure, etomoxir 80 mg was administered daily. Following 3 months of open-label treatment, patients had improved left ventricular ejection fraction, cardiac output at peak exercise, and clinical status. However, there are currently no studies examining the long-term safety of etomoxir. As with all CPT-1 inhibitors, it has the potential to cause phospholipidosis. The potency of etomoxir has yet to be established.

**Conclusion**

"Metabolic" antianginal therapies induce a shift from free fatty acid towards predominantly glucose utilisation by the myocardium to increase ATP generation per unit oxygen consumption. Three such agents (trimetazidine, ranolazine, and perhexiline) have well-documented anti-ischaemic effects. However, perhexiline, the most
potent agent currently available, requires plasma-level monitoring to avert hepato-neuro-toxicity. Trimetazidine and ranolazine do not cause phospholipidosis due to their relatively weak CPT-1 inhibitor properties and seem to act further downstream in the FFA metabolic pathway. Plasma-level monitoring for these two agents is therefore not generally required. However, the long-term safety of both agents, in particular ranolazine, has yet to be established.

Aside from their more established roles as antianginal drugs in coronary artery disease, these agents, in theory, would also be beneficial to patients with angina secondary to hypertrophic cardiomyopathy and aortic stenosis due to their anti-ischaemic effects in the absence of vasodilatation. In addition, the potential for their use in chronic heart failure is gaining recognition as data emerge showing the improvement of myocardial function regaining the effects of these agents on mortality and hospitalisation rates due to coronary artery disease are required.

Future applications for this line of treatment show a great deal of promise and warrant additional research. In particular, large, randomised, controlled trials investigating the effects of these agents on mortality and hospitalisation rates due to coronary artery disease are required.

Acknowledgements

Dr. Lee is a Cardiology Research Fellow funded by the British Heart Foundation. Professor Frenneaux holds the British Heart Foundation Sir Thomas Lewis Chair of Cardiology.

References

10. Lopaschuk GD, Wambolt RB, Barr RL. An imbalance between glycolysis and glucose oxidation is a possible explanation for the detrimental effects of high levels of fatty acids during aerobic reperfusion of ischemic hearts. J Pharmacol Exp Ther 1993;264(1):135–44.


