ABSTRACT

Coronary heart disease (CHD) is the leading cause of death of men and women in the United States and it consumes a hefty portion of healthcare expenditures. Optimal treatment of CHD should be individualized based upon concurrent medications and medical conditions and may include lifestyle changes, and pharmacological and/or surgical therapy. Traditional pharmacologic approaches for treating ischemic heart disease have either increased oxygen supply to the heart muscle or decreased oxygen demand of the muscle by increasing coronary blood flow and reducing heart rate, cardiac contractility, arterial blood pressure, and afterload on the left ventricle. The organic nitrates are effective antianginal therapy; however, their long-term use is associated with tolerance issues. Calcium-channel blockers are safe and well-tolerated agents useful in patients with effort angina, particularly in those with concurrent hypertension. Data suggest that short-acting dihydropyridines should not be used in CHD patients. Beta blockers are considered treatment of choice in the management of CHD in the postinfarct and overt heart failure settings. Hypotheses supporting the anti-ischemic properties of angiotensin-converting enzyme inhibitors are reviewed. Novel therapies decrease anginal symptoms via modulation of myocardial energy substrate metabolism and include carnitine derivatives, antioxidants, and direct inhibitors of fatty acid beta-oxidation. The efficacy and tolerability of fatty acid oxidation inhibitors, trimetazidine and ranolazine, have been demonstrated in controlled clinical trials. These novel agents may prove to be particularly useful in patients on maximal dosages of traditional agents, for those who cannot tolerate hemodynamic-based therapy, or are not candidates for revascularization. New agents utilizing the nonhemodynamic mechanism of action for the management of angina offer promise in controlling the frequency of anginal attacks and improving exercise tolerance in CHD patients. (Adv Stud Med. 2004;4(6B):S472-S478)

IN SEARCH OF CARDIOPROTECTION: A REVIEW OF POTENTIAL AGENTS

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ABSTRACT

Coronary heart disease (CHD) is the leading cause of death of men and women in the United States and it consumes a hefty portion of healthcare expenditures. Optimal treatment of CHD should be individualized based upon concurrent medications and medical conditions and may include lifestyle changes, and pharmacological and/or surgical therapy. Traditional pharmacologic approaches for treating ischemic heart disease have either increased oxygen supply to the heart muscle or decreased oxygen demand of the muscle by increasing coronary blood flow and reducing heart rate, cardiac contractility, arterial blood pressure, and afterload on the left ventricle. The organic nitrates are effective antianginal therapy; however, their long-term use is associated with tolerance issues. Calcium-channel blockers are safe and well-tolerated agents useful in patients with effort angina, particularly in those with concurrent hypertension. Data suggest that short-acting dihydropyridines should not be used in CHD patients. Beta blockers are considered treatment of choice in the management of CHD in the postinfarct and overt heart failure settings. Hypotheses supporting the anti-ischemic properties of angiotensin-converting enzyme inhibitors are reviewed. Novel therapies decrease anginal symptoms via modulation of myocardial energy substrate metabolism and include carnitine derivatives, antioxidants, and direct inhibitors of fatty acid beta-oxidation. The efficacy and tolerability of fatty acid oxidation inhibitors, trimetazidine and ranolazine, have been demonstrated in controlled clinical trials. These novel agents may prove to be particularly useful in patients on maximal dosages of traditional agents, for those who cannot tolerate hemodynamic-based therapy, or are not candidates for revascularization. New agents utilizing the nonhemodynamic mechanism of action for the management of angina offer promise in controlling the frequency of anginal attacks and improving exercise tolerance in CHD patients. (Adv Stud Med. 2004;4(6B):S472-S478)

In the classification of coronary heart disease (CHD) are acute myocardial ischemia and acute coronary syndrome, which describes the condition of patients with acute myocardial infarction or unstable angina. CHD affects 6.4% of the US population and carries a substantial socioeconomic impact. Angina affects about 6.8 million Americans (3.5% of the US population), and stable angina affects 400,000 Americans. Accounting for 54% of the more than 900,000 deaths per year due to cardiovascular disease (CVD), CHD is the single largest killer of American males and females (Figure 1). In 2004, CHD is projected to cost $133.2 billion.

Treatment of CHD may include lifestyle changes, pharmacologic therapy, and/or surgical therapy. Efforts aimed at improving the prognosis of patients with CHD are evidenced by the growing incidence of cardiac revascularization procedures over the past 2 decades. However, up to one fourth (26%) of patients 1 year postrevascularization still experience anginal attacks, including patients who receive...
antianginal pharmacotherapy. Therefore, further efforts directed toward improvement in the management of CHD are clinically meaningful.

Traditionally, pharmacologic approaches for treating ischemic heart disease have either increased the oxygen supply to the heart muscle or decreased the oxygen demand of the muscle. These agents work by increasing coronary blood flow and reducing heart rate, cardiac contractility, arterial blood pressure, and afterload on the left ventricle. Novel therapies utilizing a different mechanism of action decrease anginal symptoms via optimization of myocardial energy metabolism. This paper reviews the rationale for pharmacologic agents, both traditional hemodynamic and novel metabolic agents, used in the treatment of myocardial ischemia.

**CARDIAC METABOLISM IN ISCHEMIA AND THERAPEUTIC IMPLICATIONS**

The healthy well-oxygenated heart derives energy, namely adenosine triphosphate (ATP), from 2 types of fuel: fatty acids (about two thirds of total) and carbohydrate (in the form of glucose and lactate). Lipid oxidation inhibits the oxidation of glucose and lactate in the myocardium, and pharmacologic inhibition of cardiac fatty acid oxidation results in a rapid increase in the oxidation of glucose and lactate. The healthy heart is built for stress and increases myocardial oxygen uptake and the oxidation of fatty acids, glucose, and lactate as needed to support the work demand. Patients with CHD frequently are unable to increase myocardial blood flow to meet the tissue requirement for oxygen, thus resulting in demand-induced ischemia and impairment of the aerobic formation of ATP. This impairment results in activation of nonoxidative glycolysis and a change from myocardial uptake of lactate to production of lactate. The decrease in ATP and increase in lactate disrupts the cellular homeostasis by producing an acidic intracellular environment that contributes to contractile dysfunction in the ischemic myocardium.

Traditional hemodynamic-based antianginal agents provide relief from anginal attacks via a reduction in ATP requirements by decreasing heart rate, cardiac contractility, and/or afterload or by increasing the aerobic formation of ATP by increasing coronary blood flow. An alternative novel mechanism for alleviation of anginal symptoms is to alter the metabolism of the ischemic heart. The stressed heart consumes fatty acids as fuel; this inhibits the oxidation of glucose and stimulates lactate production. In addition, fatty acids are less "oxygen efficient" than glucose, and the heart produces more ATP per unit of oxygen consumed using glucose compared to fatty acids. Inhibition of fatty acid oxidation works to shift the metabolism of the heart to use more glucose and fewer fatty acids during stress. This shift results in a greater ratio of ATP synthesis to oxygen consumption, a reduction in lactate production, normalization of intracellular pH, and sequential improvement in symptoms for the stable angina patient.

**REVIEW OF TRADITIONAL THERAPIES**

**NITROGLYCERIN**

The efficacy of nitroglycerin in relieving angina and preventing subsequent attacks was reported over 100 years ago, and today, nitroglycerin is the most frequently prescribed medication for treating anginal attacks. The organic nitrates are prodrugs that liberate nitric oxide (NO) upon biotransformation. NO has been shown to reduce blood pressure and afterload during ischemia and acts in a similar manner to beta

**Figure 1. Percentage Breakdown of Deaths from Cardiovascular Disease**

blockers and calcium antagonists by unloading the ventricle. NO also reduces platelet adhesion and aggregation and is involved in the control of endothelial function and vascular growth.

Available in an array of formulations allowing for individualization of treatment strategies, nitrates are used to treat an ongoing anginal attack and to provide prophylaxis of angina. Although logic dictates that nitrates plus a negative chronotropic agent would improve efficacy, limited data support the combination of nitrates with other antianginal medications. Therefore, monotherapy should be maximized prior to the addition of other agents.

Long-term administration of nitrates is associated with a loss of hemodynamic and antianginal effects. The exact mechanism of nitrate tolerance has not been fully elucidated but evidence suggests that the 4 following events may play a role: depletion of reduced sulfhydryl groups necessary for bio-transformation of nitrates, release of vasoconstrictor hormones with nitrate administration, expansion of plasma volume, and increased free-radical production by the endothelium. Although superior to continuous therapy in controlling anginal attacks, intermittent therapy with nitrates is not without complication and is associated with rebound myocardial ischemia during nitrate-free periods.

**Calcium-Channel Blockers**

Three distinct structural classes represent the calcium-channel blockers that block calcium entry into the myocardial and smooth-muscle cells resulting in relaxation of musculature and dilation of vasculature (Table 1). All of the calcium-channel blockers, regardless of class, have demonstrated efficacy in the reduction of silent and overt ischemia. These agents reduce myocardial oxygen demand by slowing the heart rate, decreasing contractility, and reducing afterload. Additionally, oxygen delivery is improved by the dilation of coronary arteries.

Due to effects on contractility, caution is advised when prescribing negative inotropic agents, including calcium-channel blockers, in patients with impaired left ventricular function. Members of the dihydropyridine class appear less likely to have this effect than other calcium-channel blockers and are therefore safer in such patients. The safety of calcium-channel blockers in patients with CHD is controversial and has been debated extensively. Review of these analyses suggests that short-acting dihydropyridines should not be used in CHD patients. Overall, the calcium-channel blockers are safe and well-tolerated agents that are useful in patients with effort angina, particularly in those with concurrent hypertension.

**Beta Blockers**

Beta blockers have demonstrated efficacy in reducing the frequency of ischemic episodes and the rate of cardiac events in patients with stable ischemia. Beta blockers reduce myocardial oxygen demand by inhibition of receptors on the myocardium that decrease the heart rate and force of contraction. Beta blockers should be considered the first treatment of choice in the management of CHD patients with chronic stable effort angina in the postinfarct and overt heart failure settings.

Some beta blockers are cardioselective, such as acebutolol, atenolol, betaxolol, carvedilol, and metoprolol and mainly block beta 1 cardiac receptors; however, all beta blockers become nonselective at higher dosages, making them generally contraindicated in patients with asthma. Safety concerns with beta-blocker therapy, such as bronchospasm, impotence, and impairment of exercise ability, make the individualization of antianginal pharmacotherapy important.

<table>
<thead>
<tr>
<th>Calcium-Channel Blocker</th>
<th>Heart Rate</th>
<th>Myocardial Contractility</th>
<th>Cardiac Output/ Index</th>
<th>Peripheral Vascular Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenylalkylamines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>±</td>
<td>↓↓</td>
<td>±</td>
<td>↓↓</td>
</tr>
<tr>
<td>Benzothiazepines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diltiazem</td>
<td>0-↓</td>
<td>0-↓</td>
<td>0-↑</td>
<td>↓↓(dose related)</td>
</tr>
<tr>
<td>Dihydropyridines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine</td>
<td>±</td>
<td>0-↓</td>
<td>↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>Felodipine</td>
<td>↑↑</td>
<td>0-↓</td>
<td>↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>Isradipine</td>
<td>↑↑</td>
<td>↓</td>
<td>↑</td>
<td>↓↑</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>↑↑</td>
<td>0-↓</td>
<td>↑↑</td>
<td>↓↑</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>0-↑</td>
<td>0-↓</td>
<td>↑↑</td>
<td>↓↑</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>No data</td>
<td>0-↓</td>
<td>No data</td>
<td>↓↓(dose related)</td>
</tr>
</tbody>
</table>

† † † or † † † † = pronounced effect; † † or † † † = moderate effect; † or ↓ = slight effect; ± = negligible.

Data from Killion.
ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

It has been suggested that angiotensin-converting enzyme (ACE) inhibitors have general cardiovascular protective benefits. The antihypertensive effects of these agents is well established, and these agents are now used in a variety of cardiovascular disorders, including heart failure. A link to the fibrinolytic system and the implication of the renin-angiotensin system’s involvement in the pathogenesis of atherosclerotic coronary artery disease (CAD) has provided theoretical evidence that ACE inhibitors provide beneficial effects on vascular wall damage. Clinical evidence coupled with epidemiologic and genetic links have supported a potential role for ACE inhibitors in reducing the risk for ischemic events in a wide range of high-risk patients. The exact mechanisms of antiatherogenic activity of ACE inhibitors is not fully understood, but a variety of hypotheses have been proposed (Table 2). The reduction in acute ischemic events with ACE inhibitors follows a 6- to 12-month time lag and suggests that the anti-ischemic activity of these agents is independent of the antihypertensive effects.

Further study is ongoing to determine if the anti-ischemic effects of ACE inhibitors observed in high-risk patients can be transferred to a population at lower risk for events. Additionally, investigations into the anti-ischemic properties of angiotensin receptor blockers are ongoing and may provide important treatment alternatives for patients unable to tolerate side effects of ACE inhibitors, such as cough.

REVIEW OF NOVEL METABOLIC THERAPIES

ANTIOXIDANTS

Antiatherosclerosis benefits of antioxidant therapy, such as with vitamins C and E, are plausible, yet their efficacy in reducing CVD remains unproven. Theoretical support for the efficacy of these agents is based on the antioxidant’s ability to inhibit the conversion of low-density lipoprotein (LDL) to oxidized LDL or to impede the actions of oxidized LDL, which has an underlying role in the formation and rupture of atherosclerotic plaque formation. Antioxidants have anti-inflammatory properties and may act to reduce the formation of plaques and improve stabilization of plaques. Also, antioxidants may relieve oxidant stress in the systemic arteries associated with endothelial dysfunction and angina.

The benefits of antioxidants in CVD have been suggested in several large observational studies conducted in healthy men and women receiving high doses of vitamin E. However, the utility of vitamins C and E in CAD remains inconclusive as results of clinical studies have failed to confirm the beneficial effects of antioxidant supplementation on CAD. It has been suggested that these studies were limited by the dose and type of vitamin E administered and that future study should include the more potent antioxidant vitamin E, alpha-tocotrienol vitamin E, to address the issue of this antioxidant’s utility in CAD.

FATTY ACID OXIDATION INHIBITORS

In an effort to optimize the energy metabolism of the ischemic heart, the inhibition of fatty acid oxidation has been studied as a novel method for intervention. During ischemic conditions, high rates of fatty acid oxidation cause a marked decrease in glucose oxidation. The inhibition of fatty acid oxidation allows for a metabolic shift to an increase in glucose oxidation, less lactate production, and a more optimal intracellular pH during demand-induced ischemia. In addition, the myocardium derives more ATP per unit of oxygen consumed from glucose oxidation than from fatty acid oxidation. Partial inhibition of myocardial fatty acid oxidation in healthy men and women receiving high doses of vitamin E.

Table 2. Potential Mechanisms of Protective Effects of Angiotensin-converting Enzyme Inhibition on Ischemic Events

- Improvement of endothelial function
- Inhibition of the breakdown of bradykinin
- Release of nitric oxide and prostacyclin
- Inhibition of vascular muscle cell growth and proliferation
- Decrease of macrophage migration and function
- Inhibition of low-density lipoprotein oxidation
- Enhancement of endogenous fibrinolysis
- Inhibition of plasminogen activator inhibitor type 1
- Increase of tissue-type plasminogen activator
- Inhibition of platelet aggregation
- Inhibition of sympathetic activity
- Reduction of blood pressure
- Reduction of left ventricular mass

oxidation during ischemia improved contractile function in preclinical studies and has been shown to reduce the symptoms of angina in CHD patients.

**CARNITINE PALMITYL TRANSFERASE I INHIBITORS**

Carnitine palmitoyl transferase I (CPT I) inhibitors drive a metabolic switch from fatty acid oxidation to glucose oxidation in the ischemic state by inhibiting fatty acid uptake by the mitochondria. CPT I inhibitors, oxfenicine and perhexiline, are associated with anti-ischemic efficacy and subsequent improvement of cardiac functioning; however, their long-term use is confounded by cardiac hypertrophy in animal studies. In addition, high serum concentrations of perhexiline are associated with neuropathy and hepatotoxicity.

**CARNITINE DERIVATIVES**

L-carnitine plays an important role in cardiac metabolism. The oxidation of fatty acids requires the translocation of fatty acids into the inner mitochondrial space via transport mediated by L-carnitine. In addition, L-carnitine assists in the regulation of pyruvate oxidation. The administration of L-carnitine or propionyl L-carnitine, an L-carnitine analog, results in an increase in the oxidation of glucose. Preclinical and clinical studies have demonstrated the anti-ischemic cardioprotective benefits of L-carnitine and propionyl L-carnitine. In small studies involving patients with CAD, both agents have demonstrated a reduction in ST segment depression and left ventricular end-diastolic pressure during stress testing.

**DIRECT FATTY ACID BETA-OXIDATION INHIBITORS**

Direct fatty acid beta-oxidation inhibitors include trimetazidine and ranolazine. Trimetazidine. Trimetazidine is an antianginal drug that is widely used outside of North America. It is an inhibitor of the fatty acid beta-oxidation enzyme long-chain 3-ketoacyl-CoA thiolase. Double-blind placebo-controlled trials in chronic stable angina demonstrated that trimetazidine monotherapy (20 mg 3 times daily) was associated with reduced frequency of angina episodes, reduced need for nitroglycerin, and improved exercise time to onset of angina or time to 1-mm ST segment depression. Beneficial effects were independent of hemodynamic effects (fall in blood pressure or bradycardia). Therefore, clinical improvement associated with trimetazidine was due to direct effects on the myocardium rather than a reduction in myocardial oxygen demand. Additionally, the combination of trimetazidine and traditional antianginal therapy with beta blockers or calcium-channel blockers demonstrated beneficial effects. Overall, trimetazidine has been shown to be well tolerated and safe.

Ranolazine. Antianginal efficacy of ranolazine has been demonstrated in patients with chronic stable angina, and, similar to trimetazidine, this clinical benefit was independent of direct hemodynamic effects. The efficacy of sustained-release ranolazine has been demonstrated in 2 randomized, double-blind, placebo-controlled studies.

In the Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) study, ranolazine monotherapy (500, 1000, or 1500 mg twice daily) in patients with angina demonstrated significant increases in exercise duration, time to onset of angina, and time to 1-mm ST segment depression at peak and trough compared to placebo. An increased incidence of
dizziness, nausea, asthenia, and constipation was observed with ranolazine, mostly at the 1500-mg dose level, compared with placebo.

The efficacy of ranolazine combined with traditional antianginal therapy was recently demonstrated in the Combination Assessment of Ranolazine in Stable Angina (CARISA) study. Patients with chronic angina who experienced angina and ischemia while on atenolol, amlodipine, or diltiazem were randomized to receive ranolazine (750 or 1000 mg twice daily) or matching placebo. The addition of ranolazine to standard antianginal therapy was associated with an increase in exercise capacity and additional relief from angina compared to placebo (Figure 2). At the completion of the double-blind portion of the CARISA study, patients were allowed to enroll in an open-label extension study in order to obtain long-term follow-up information. With a 1-year survival rate of 98.4% and a 2-year rate of 95.9%, no evidence of long-term survival consequences have been observed with ranolazine therapy in a population of patients with severe chronic angina.

CONCLUSIONS

Traditional antianginal therapies provide successful treatment by either increasing coronary blood flow or by reducing the consumption of oxygen by lowering the workload of the heart. Although minimizing the number of medications prescribed for the management of angina is ideal, about 50% of stable angina patients who are taking optimal dosages of traditional therapy continue to experience further angina episodes. Data supporting or refuting the efficacy of combining traditional antianginal therapies has been published. Some studies have demonstrated benefit of combining traditional agents, whereas others reported no benefit from adding a calcium-channel blocker to beta-blocker therapy.

Novel metabolic therapies for the treatment of chronic stable angina offer advantages over traditional therapies in that they potentially increase the mechanical efficiency of the left ventricle but do not adversely affect hemodynamics. The institution of a fatty acid oxidation inhibitors, such as ranolazine and trimetazidine, may prove to be particularly useful in patients on maximal dosages of traditional agents or for those who cannot tolerate hemodynamic-based therapy. In addition, ranolazine and trimetazidine provide an effective and safe treatment alternative for CHD patients who are not candidates for revascularization.

New agents utilizing a nonhemodynamic mechanism of action for the management of angina offer promise in controlling the frequency of anginal attacks in CHD patients. Individualization of therapy is important and should take into account the patient’s concurrent medications and medical conditions.

REFERENCES


