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Anti-anginal Drug Therapy in Stable Angina
The Need for Long-Term Outcome Studies

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At the recent Annual Meeting of the Canadian Cardiovascular Society in Montreal, a satellite symposium addressed the role of anti-anginal drug therapy in the management of stable angina. After concluding that surrogate endpoints (e.g., total exercise test duration or the time to the onset of angina) were inadequate to evaluate the long-term safety and efficacy of medical treatment, and providing a rationale for combination therapy with calcium and beta blocker therapy, the symposium concluded with the announcement of an important long-term clinical trial evaluating the effect of long-acting nifedipine on major cardiovascular event-free survival in patients with chronic angina.

Limitations of Surrogate Endpoint Trials in Stable Angina

Dr. François Charbonneau (Royal Victoria Hospital) opened the symposium by discussing the variety of endpoints used in previous studies to assess the relative value of anti-anginal medications. These include: (1) exercise stress test variables such as total exercise test duration, time to angina, time to 1 mm of ST segment depression, and maximal rate pressure product; (2) ambulatory ECG monitoring variables such as the total number of ischemic episodes, total duration of ischemia, heart rate at the onset of ischemia or angina, and circadian variation; and, (3) patient reported symptoms such as a change in Canadian Cardiovascular Society (CCS) anginal class, the number of episodes, and the number of sublingual nitroglycerin tablets utilized. However, these different measures of ischemia do not correlate strongly with one another. For example, in a substudy of the Angina and Silent Ischemia Study (ASIS), Borzak et al[1] found no correlation among the frequency of ischemic episodes by ambulatory ECG monitoring, exercise time to 1 mm ST segment depression, or the frequency of anginal episodes while patients were receiving placebo. Furthermore, for a given patient, the efficacy of each active medication (sustained release propranolol, diltiazem, or nifedipine) in reducing ambulatory ischemia (with or without symptoms) was not correlated with response in anginal symptoms or exercise test performance. Thus, efficacy for each clinical endpoint must be assessed separately when evaluating the impact of drug treatment. In addition, Dr. Charbonneau reminded the audience of the lesson learned regarding surrogate endpoints and pharmacologic treatments directed at such outcomes: patients with frequent premature ventricular beats (VPBs) post-infarction are at higher risk for subsequent mortality and yet suppression of VPBs with anti-arrhythmic therapy in the Cardiac Arrhythmia Suppression Trial (CAST)[2,3] led to a significantly greater mortality in the treatment

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as compared to placebo group. He concluded that surrogate endpoints are not the most appropriate measure to use in the evaluation of anti-anginal therapy and emphasized the need for large morbidity and mortality studies with these agents.

Anti-anginal Therapy in Stable Angina

Anti-anginal drug therapy reduces symptoms of angina via different mechanisms of action. The main classes include the organic nitrates (short or long acting), beta-blockers, and calcium channel blockers. In brief, nitrates and all calcium channel blockers are vasodilators and counteract vasospasm. Nitrates possess venous selectivity (resulting in reduced preload and intraventricular pressure), whereas calcium blockers are arterial vasodilators (resulting in coronary dilation and reduced afterload due to peripheral vasodilation). Calcium channel blockers are a heterogeneous group of drugs: dihydropyridines (e.g., nifedipine) possess varying degrees of vascular selectivity, whereas verapamil and diltiazem also impact upon the sinoatrial and atrioventricular nodes resulting in heart-rate lowering. In addition to decreasing myocardial oxygen demand, a reduction in heart rate prolongs the diastolic filling time and leads to enhanced myocardial blood (oxygen) supply. With its potentially rapid absorption, high peak plasma levels and therefore less predictable dose response, short acting nifedipine may lead to reflexogenic tachycardia and sympathetic activation. However, the longer acting forms (e.g., nifedipine gastro-intestinal Therapeutic System {GITS}) provide a constant, controlled rate of drug release that results in stable plasma levels over 24 hours, and this preparation of nifedipine has been demonstrated to reduce angina and ambulatory ischemia, and attenuate the circadian pattern of ischemia in patients with chronic stable angina.[4] Beta-blockers also reduce myocardial oxygen demands by reducing heart rate and contractility, and enhance oxygen delivery by prolonging diastolic perfusion time and potentially reversing coronary steal. The latter phenomenon may be explained by attenuation of metabolic vasodilation (and perhaps unopposed alpha-mediated vasoconstriction) in the myocardium.

Dr. Michael Baird (University of Ottawa Heart Institute) focused the next part of the symposium on the rationale and support for the use of combination therapy. In particular, he suggested that the combination of a beta-blocker and nifedipine therapy may be synergistic since the former offers heart rate reduction and the latter provides vasodilation. Further, by using lower doses of two different anti-anginal drugs, one could potentially avoid the adverse effects of higher doses of one drug used alone. While many double-blind placebo-controlled studies in patients with stable angina have demonstrated the efficacy of both beta- and calcium channel-blockers in the reduction of chest pain attacks, nitroglycerin use, and the improvement of exercise tolerance, few trials have compared the use of these 2 drug classes directly. Further, studies comparing the anti-anginal effects of combined versus monotherapy with either agent have been limited in sample size.

Three recently published trials (1 comparing beta- and calcium channel-blocker treatment[5] and 2 comparing combination with monotherapy[6-8]) were reviewed by Dr. Baird:

International Multicenter Angina Exercise (IMAGE) Study

This randomized study by Savonitto et al[8] was designed to investigate whether combination therapy with metoprolol and nifedipine provides greater anti-ischemic effect than does monotherapy in patients with stable angina. Two hundred and eighty patients were enrolled in a double-blind trial in 25 European centres, and received metoprolol (controlled release, 200 mg daily) or nifedipine (controlled release, 20 mg daily) for 6 weeks; placebo or the alternative drug was then added for a further 4 weeks. Exercise tests were performed at baseline, 6 and 10 weeks. At week 6, both metoprolol and nifedipine increased the mean exercise time to 1 mm ST segment depression in comparison with baseline (both $p<0.01$); metoprolol was more effective than nifedipine ($p<0.05$). At week 10, the groups randomized to combination therapy had a further increase in time to ST depression ($p<0.05$ vs. placebo). This short term study was not designed to evaluate clinical outcomes; 14 cardiovascular events occurred, and the incidence did not differ among treatment groups.

Angina Prognosis Study In Stockholm (APSIS)

This single-centre, randomized, double-blind study by Rehnqvist et al[5] compared the use of metoprolol (controlled release, 100-200 mg daily) and verapamil (slow release, 120-240 mg twice daily) in stable angina. Eight hundred and nine patients were followed for a median of 3.4 years. The combined primary outcome of mortality and nonfatal cardiovascular complications (including myocardial infarction, coronary revascularization, worsening angina with an indication for revascularization, stroke, and peripheral vascular events) occurred in 117 (29%) of 403 verapamil- and 125 (30.8%) of 406 metoprolol-treated patients ($p=0.23$; odds ratio 1.05; 95% confidence intervals: 0.78, 1.41).

Total Ischaemic Burden European Trial (TIBET)

This randomized, double-blind study by Dargie et al[7] compared the effects of atenolol, nifedipine, and their combination on exercise parameters, ambulatory ischemic activity, and clinical outcome in patients with mild, chronic stable angina. Six hundred and eighty-two patients from 69 centres in 9 countries received a placebo (washout) for 2 weeks followed by one of three treatments: (1) atenolol (50 mg twice daily); (2) nifedipine (slow release, 20-40 mg daily); or (3) atenolol plus nifedipine. Median follow-up was 2 years. Clinical endpoints included "hard" (cardiac mortality, myocardial infarction, and unstable angina) and "soft" [coronary revascularization, and treatment failure (persistent symptoms on high dose trial therapy plus prophylactic short-acting nitrate treatment)] outcomes. No differences were seen between the 3 treatment groups when comparing either "hard" + "soft" (atenolol 12.8%, nifedipine 11.2%, combination 8.5%; p=0.14) or "hard" endpoints (atenolol 20.8%, nifedipine 19.8%, combination 13.8%, p=0.32). While combination therapy appeared somewhat more favourable than either monotherapy in the reduction of "hard" endpoints, these data must be interpreted with great caution since TIBET did not have the statistical power to detect such a difference.

In a TIBET substudy, Fox et al[6] demonstrated that atenolol, nifedipine, and their combination were equally effective in markedly and significantly reducing all markers of reversible ischemia both during exercise testing (total exercise time, time to the development of angina and of 1 mm ST segment depression, maximum ST depression) and ambulatory monitoring (% of patients with ischemia during the 48 hour recording period) when compared with placebo. Based on these results, the investigators concluded that if the patient is symptomatically controlled, the routine practice of adding further agent(s) (to monotherapy) should await trials demonstrating improved prognostic outcome.

A Coronary disease Trial Investigating Outcome with Nifedipine GITS (ACTION)

In the final presentation of the symposium, Dr. John Parker (Mount Sinai Hospital, Toronto) introduced the ACTION study. ACTION is a multi-national, multi-centre randomized, double-blind, placebo-controlled trial designed to evaluate the effect of long acting nifedipine GITS (30-60 mg, once daily) on major cardiovascular event-free survival in patients with chronic symptomatic angina who are otherwise optimally treated. The study will randomize at least 6,000 patients over approximately 2 years with a follow-up period of at least 4 and a maximum of 6 years. The study will include patients who are: (1) ≥35 years of age; (2) in stable condition for ≥1 month while requiring oral treatment for symptomatic angina either to prevent or to treat anginal attacks; (3) have a left ventricular ejection fraction ≥40% (documented by two-dimensional echocardiography); and (4) on unchanged anti-anginal medication without calcium channel blockers during the past 2 weeks. Patients must have coronary artery disease defined by at least one of the following 4 criteria: (1) unequivocal myocardial infarction ≥3 months prior to the start of study medication; (2) coronary revascularization ≥3 months prior to the start of study medication; (3) angiographically documented coronary disease; (4) positive exercise test or perfusion defect on myocardial perfusion imaging.

The primary criterion for the evaluation of efficacy will be a combined endpoint consisting of the rate of: (1) death; (2) acute myocardial infarction; (3) emergency coronary angiography for refractory angina; (4) overt heart failure; (5) debilitating stroke; (6) peripheral revascularization. The sample size of approximately 6,000 patients will provide 80% power (two-tailed $p<0.05$) to detect a 14% relative reduction with nifedipine in the primary endpoint (assuming a 5.58 event rate/100 patient years in the placebo group). The ACTION study will hopefully be completed in 2003.

Conclusions

Current anti-anginal medical therapy in stable angina consists mainly of organic nitrates, beta-, and calcium channel-blockers. All have established clinical anti-anginal effects and from each class a large number of different compounds have been approved. How these drugs are used either alone or in combination varies and depends on side effects, individual symptomatic response, and physician preference. Evaluation of the efficacy of these agents has been limited to small studies, primarily focusing upon surrogate endpoints such as exercise test or ambulatory monitoring parameters, and symptoms. To date, large scale trials designed to evaluate the safety and efficacy of these agents in stable angina are lacking: the effect of long-acting nifedipine on major cardiovascular event-free survival will be evaluated in the upcoming ACTION study.

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