Superiority of combined diltiazem and propranolol therapy for angina pectoris

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ABSTRACT Twenty-four patients with stable angina were evaluated in a 14 week crossover trial. A single-blind placebo period (baseline 1) was followed by two double-blind periods evaluating maximum tolerated doses of diltiazem (up to 360 mg daily) vs placebo. Over the next 1 to 4 weeks, propranolol was started and increased until clinically documented β-blockade was achieved (baseline 2). The final phase consisted of a pair of evaluation periods comparing propranolol plus the maximum tolerated dose of diltiazem to propranolol and placebo. The daily rate of angina attack was 1.6
during baseline, was unchanged during placebo therapy, but fell during treatment with diltiazem to 0.6 (p < .005). With the addition of diltiazem to propranolol, the angina rate was improved (0.3) compared with that with either propranolol alone (0.6) or propranolol and placebo (0.5) (p < .01). Total exercise duration during baseline 1 was 360 sec and increased to 497 sec with diltiazem, 481 sec with propranolol, and 527 sec with the combination of diltiazem and propranolol. Two patients with reduced ejection fractions developed congestive heart failure with propranolol. The combination of diltiazem and propranolol similarly resulted in congestive heart failure in one patient who had tolerated both drugs alone.


THE INTRODUCTION of the calcium-channel blockers provided an important addition to our armamentarium for the prophylactic treatment of stable exertional angina pectoris. Each of the three currently available drugs has been shown to be more effective than placebo.1-3 Yet the therapy for many patients remains incomplete: a significant number of patients remain symptomatic despite treatment with either the calcium-channel blockers or “conventional” therapy, i.e., β-blockers and the long-acting nitrates alone. Combination therapy has been used empirically in many patients, and several studies have objectively demonstrated the additional benefits of nifedipine4 or verapamil5-7 added to propranolol. As has been well stressed,8 the calcium-channel blockers have variable impact on coronary and peripheral vascular, myocardial, sinoatrial, and atrioventricular nodal tissues, and therefore may vary not only in their antianginal mechanisms but potentially in their interactions when used in combination with β-blockers.

This study was designed to assess the efficacy and safety of diltiazem in a dose of 360 mg daily alone and in combination with propranolol. Twenty-four patients with chronic stable angina and unrestricted left ventricular function were evaluated in a randomized placebo-controlled, crossover protocol.

Methods

Patient selection. Each patient met the following criteria before entry into the study: (1) a history of classic, stable angina pectoris, predominantly on effort, with an average of five angina attacks per week during the initial 2 week placebo washout period, and (2) demonstration of standard electrocardiographic manifestations of ischemia (horizontal or down-sloping ST segment depression of 1 mm or more during or immediately after exercise) on the preentry treadmill exercise tolerance test. A repeat exercise test was performed at the end of the placebo stabilization period (week 2). If the total exercise duration of the preentry and week 2 exercise tests varied by more than 2 min, a repeat exercise test was required 1 week later. If there were more than 2 min difference in total exercise duration between the second and third tests, the patient would be excluded from further participation; however, no patients had to be excluded for this reason.

Exclusion criteria were unstable angina, myocardial infarction within the preceding 3 months, concurrent significant diseases, inability to discontinue all other long-acting antianginal medications, or existence of conditions that might cause electrocardiographic changes that mimic ischemia. Evidence of im-
paired left ventricular function did not preclude participation in the study.

**Study design.** This was a 14-week, double crossover trial consisting of four phases (figure 1). β-Blockers and other antianginal medications were discontinued at least five half-lives before the initial phase, a 2 week single-blind placebo stabilization period ending with an exercise tolerance test (baseline 1). Two 2 week long double-blind periods then followed, evaluating the maximum tolerated dose of diltiazem (up to 360 mg daily) vs placebo. Down-titration of study medication was not performed at the end of the evaluation periods. After the first crossover evaluation periods, the propranolol dosage optimization phase was carried out. Patients were started on 20 mg of propranolol qid and were evaluated at weekly intervals with doses increased to 40, 60, and 80 mg qid. Weekly upward titration of propranolol was determined on the basis of presence or lack of blunted heart rate response to exercise. Heart rate was determined at rest and after walking up two flights of stairs. An increase in heart rate from rest to end-exercise of 20 beats/min or less defined adequate β-blockade. Upon achievement of clinical β-blockade, an exercise test was repeated (baseline 2).

The fourth and final phase again consisted of a pair of evaluation periods of 2 weeks each, during which time propranolol plus the maximum tolerated dose of diltiazem was compared with propranolol plus the maximum tolerated dose of placebo.

Exercise performance was assessed by a symptom-limited treadmill exercise testing using a modified Bruce protocol (stage \( \frac{1}{2} = 1.7 \) mph at 5% incline). Electrocardiographic leads V5, V4, and V6 were monitored continuously and a complete 12-lead electrocardiogram was recorded after each minute of exercise during the test as well as immediately and 1, 3, 5, and 8 min after termination. Blood pressure was recorded by a sphygmomanometer at rest and during the final minute of each stage of exercise. Patients were instructed to exercise to the degree of angina equal to that for which they would ordinarily discontinue activity and take a nitroglycerin tablet. The patients were instructed to exercise on subsequent examinations to the same level of angina experienced on the initial exercise tolerance test.

Symptomatic response was assessed by means of daily diaries in which patients recorded the number of anginal attacks, nitroglycerin consumption, and precipitating factors.

**Statistical methods.** The efficacy parameters of interest were (1) daily frequency of anginal attacks, (2) daily nitroglycerin consumption, and (3) time to termination of exercise, time to onset of angina, and time to onset of 1 mm ST segment depression.

A nonparametric two-period crossover analysis was performed twice, once with the data from weeks 4 and 6 and a second time with the data from the second pair of evaluation periods, weeks 8 and 10. The data from end week 2 (baseline 1) were subtracted from the data resulting from the first crossover, and the data from end propranolol titration (baseline 2) were subtracted from the data resulting from the second crossover. The nonparametric analysis was applied to these differences. Test procedures for hypotheses concerning residual effects of treatment, direct effects of treatment, and period effects were formulated in terms of Wilcoxon rank sum statistics. Residual effects were tested by applying the Wilcoxon rank sum test to the sums of the two intrapatient observations. If residual effects were not significant, direct effects, i.e., diltiazem vs placebo, were tested by applying the Wilcoxon rank sum test to the differences between the two intrapatient observations. If the residual effects were not significant, period effects were tested by applying the Wilcoxon rank sum test to the crossover differences.

To compare the two crossovers, two-way analyses of variance were performed to compare baseline 1 to placebo to diltiazem to baseline 2 to placebo plus propranolol to diltiazem plus propranolol. If the F test associated with treatment effects was significant at the .05 level, Duncan’s multiple comparison procedure was used to determine exactly which of the six treatments differed significantly.

The protocol was approved by the hospital’s Human Studies Committee. All patients gave informed consent.

**Results**

Twenty-four patients (23 men, one woman) satisfied the prerrandomization criteria and were enrolled into the study. Their ages were 49 to 70 years (mean 60). Eleven of the 24 had had a prior myocardial infarction, and 14 of the 24 had undergone coronary arteriography (one with one-vessel disease, three with two-vessel disease, and 10 with three-vessel disease). Three patients had not undergone cardiac catheterization and had not had myocardial infarction, yet had classic angina on exertion and electrocardiographic evidence of myocardial ischemia. Left ventricular ejection fraction ranged from 29% to 79% (mean 55%). No signs or symptoms of congestive heart failure were present at baseline. Before participation in the study all 24 patients had received β-blocking therapy, 17 of the 24 had had treatment with long-acting nitrates, and 10 had been treated with a calcium-channel blocker. All were at least partially symptomatic despite the above regimens.

All patients attained full-dose diltiazem therapy of 90 mg qid while in the study. No rebound of symptoms was noted despite the abrupt discontinuation of medications at the end of the evaluation periods. During the propranolol dosage optimization phase, the dosage of propranolol required to achieve clinically documented

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**FIGURE 1.** Study design. PLBO = placebo; DILT = diltiazem; PROP = propranolol; ETT = exercise tolerance test.
**β-blockade** was a mean of 276 mg with a range of 80 to 320 mg daily.

Of the 24 patients entering the protocol, four were dropped before the completion of the second pair of evaluation periods because of side effects (two with rash, two with congestive heart failure, see below). Data on efficacy included all 24 patients for the evaluation of monotherapy and 20 for the evaluation of combination therapy.

**Frequency of angina and nitroglycerin consumption.**
The number of episodes of angina occurring daily during the initial placebo stabilization phase was 1.6 ± 0.3 (mean ± SEM). This was unchanged during placebo therapy (1.6 ± 0.4) but fell significantly during treatment with diltiazem (0.6 ± 0.2). A parallel response was observed with nitroglycerin consumption: 0.8 ± 0.2 during the initial placebo phase and 0.8 ± 0.2 and 0.3 ± 0.1 with double-blind placebo and diltiazem treatment, respectively. During the second baseline period, i.e., the nonblinded propranolol dose titration phase, both daily rate of angina attack (0.6 ± 0.1) and nitroglycerin consumption (0.3 ± 0.1) were improved over the values with placebo. The addition of diltiazem resulted in a further decrease in rate of angina attack to 0.3 ± 0.1 and in nitroglycerin consumption to 0.08 ± 0.04. The addition of placebo to the β-blocker conferred little additional benefit, 0.5 ± 0.1 for angina frequency and 0.1 ± 0.04 for nitroglycerin consumption. These findings are graphically represented by figure 2. Each of the active forms of treatment were more effective than placebo alone. Nonparametric analysis of the changes from baseline indicated a statistical advantage for diltiazem over placebo in reducing angina and nitroglycerin consumption (both p < .005). Similarly, the improvement over propranolol alone was significantly better with the addition of diltiazem vs that with placebo for both daily rate of angina attack (p < .01) and nitroglycerin use (p < .025).

**Exercise tolerance.** Exercise parameters evaluated included time to onset of angina, time to occurrence of 1 mm ST depression, and total exercise duration. During the first crossover period, treatment with diltiazem resulted in a significant improvement in all three variables compared with placebo (table 1 and figure 3). The average change from baseline in time to angina was 147 vs 52 sec, time to 1 mm ST segment depression was 145 vs 45 sec, and total exercise duration was 138 vs 37 sec for diltiazem and placebo, respectively. All were significant at the p < .005 level.

Similarly, the change from baseline 2 was noted for diltiazem plus propranolol vs placebo plus propranol...
propranolol alone having the next greatest impact followed by diltiazem, which reduced resting and submaximal heart rate more than placebo (table 2). At peak exercise there was no difference in heart rate when patients were on diltiazem or placebo alone. Propranolol significantly blunted the heart rate at peak exercise, with a further reduction when diltiazem was added.

Changes in systolic blood pressure were secondary to propranolol therapy: at each level of exertion or at rest the systolic blood pressure was lower when patients were receiving propranolol than when they were receiving either diltiazem or placebo. There was no additional impact on systolic blood pressure when diltiazem was used either alone or in combination with the β-blocker.

Changes in heart rate × systolic blood pressure largely paralleled those of heart rate alone. At rest and at each submaximal stage of exercise, heart rate × systolic blood pressure was lowest during propranolol plus diltiazem treatment, followed in impact by propranolol alone, diltiazem alone, and placebo. At peak effort, however, the addition of diltiazem resulted in no further blunting of the rise in heart rate × systolic blood pressure over that obtained by propranolol alone.

**Adverse reactions.** The combination of diltiazem and propranolol was generally well tolerated. Table 3 lists the adverse reactions occurring during the various treatment regimens that were felt by the investigators to either be possibly or probably related to the medication. The only significant adverse reaction to diltiazem alone was a rash that resolved after discontinuation of therapy. One patient was noted to have first-degree atrioventricular block on his electrocardiogram. Similar first-degree block was noted intermittently on the baseline (placebo) electrocardiograms.

Another additional patient developed a rash necessitating discontinuation of medication while receiving propranolol. The other significant adverse effect during propranolol therapy was congestive heart failure, which occurred in two patients. The first, with three-vessel disease and a left ventricular ejection fraction of 30%, had tolerated 40 mg qid for several years without difficulty. When his dose was increased to 80 mg qid dyspnea on exertion occurred. These symptoms resolved with reduction in propranolol dosage to 60 mg qid and the addition of digoxin and a diuretic to his regimen. The patient continued in the protocol and had diltiazem added to the β-blocker without difficulty. The prior efficacy results do not include his data because of the change in his concomitant medications.

Nine of the 20 patients who completed the second crossover period were found to have had either no further increase (n = 1) in total exercise duration with combination therapy or an actual reduction (n = 8) in exercise capacity from either of the active medications alone. Of these, five of the eight had their maximal exercise capacity on diltiazem therapy alone, with a significant reduction with propranolol therapy either alone or in combination. Two of eight had better exercise tolerance on propranolol than either diltiazem alone or in combination, and another patient had better exercise duration on either diltiazem or propranolol than on their combination.

**Cardiovascular parameters.** A hierarchy of drug effect on heart rate was present at rest, during submaximal exercise, and at peak exertion: the combination of diltiazem and propranolol reduced resting, submaximal, and peak exercise heart rate to the greatest degree, with
TABLE 2
Hemodynamic responses to exercise

<table>
<thead>
<tr>
<th></th>
<th>Baseline 1</th>
<th>Placebo</th>
<th>Diltiazem</th>
<th>Baseline 2</th>
<th>Propranolol + placebo</th>
<th>Propranolol + diltiazem</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR Rest</td>
<td>81 ± 4</td>
<td>82 ± 2</td>
<td>76 ± 3</td>
<td>58 ± 1</td>
<td>62 ± 2</td>
<td>56 ± 2</td>
</tr>
<tr>
<td>End Bruce ½</td>
<td>110 ± 4</td>
<td>106 ± 3</td>
<td>97 ± 3</td>
<td>78 ± 2</td>
<td>79 ± 3</td>
<td>70 ± 2</td>
</tr>
<tr>
<td>End Bruce 1</td>
<td>120 ± 3</td>
<td>115 ± 3</td>
<td>111 ± 3</td>
<td>87 ± 2</td>
<td>88 ± 3</td>
<td>78 ± 2</td>
</tr>
<tr>
<td>Peak effort</td>
<td>128 ± 4</td>
<td>125 ± 4</td>
<td>126 ± 4</td>
<td>101 ± 3</td>
<td>99 ± 3</td>
<td>91 ± 4</td>
</tr>
<tr>
<td>SBP Rest</td>
<td>131 ± 3</td>
<td>133 ± 4</td>
<td>130 ± 3</td>
<td>126 ± 4</td>
<td>130 ± 4</td>
<td>123 ± 3</td>
</tr>
<tr>
<td>End Bruce ½</td>
<td>149 ± 5</td>
<td>151 ± 3</td>
<td>145 ± 4</td>
<td>136 ± 4</td>
<td>135 ± 3</td>
<td>131 ± 3</td>
</tr>
<tr>
<td>End Bruce 1</td>
<td>164 ± 5</td>
<td>164 ± 4</td>
<td>157 ± 5</td>
<td>142 ± 5</td>
<td>138 ± 4</td>
<td>134 ± 4</td>
</tr>
<tr>
<td>Peak effort</td>
<td>160 ± 4</td>
<td>168 ± 4</td>
<td>163 ± 6</td>
<td>146 ± 5</td>
<td>150 ± 4</td>
<td>144 ± 6</td>
</tr>
<tr>
<td>HR × SBP (×10³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>10.6 ± 0.4</td>
<td>11.1 ± 0.6</td>
<td>9.9 ± 0.5</td>
<td>7.5 ± 0.2</td>
<td>7.9 ± 0.3</td>
<td>6.7 ± 0.3</td>
</tr>
<tr>
<td>End Bruce ½</td>
<td>16.4 ± 0.7</td>
<td>15.9 ± 0.6</td>
<td>14.2 ± 0.7</td>
<td>10.7 ± 0.5</td>
<td>10.8 ± 0.4</td>
<td>9.2 ± 0.4</td>
</tr>
<tr>
<td>End Bruce 1</td>
<td>19.8 ± 0.8</td>
<td>18.4 ± 0.7</td>
<td>17.5 ± 0.8</td>
<td>12.4 ± 0.6</td>
<td>12.1 ± 0.5</td>
<td>10.5 ± 0.5</td>
</tr>
<tr>
<td>Peak effort</td>
<td>20.3 ± 0.9</td>
<td>19.9 ± 0.9</td>
<td>20.9 ± 1.1</td>
<td>15.1 ± 0.9</td>
<td>16.0 ± 1.1</td>
<td>14.3 ± 0.9</td>
</tr>
</tbody>
</table>

HR = heart rate; SBP = systolic blood pressure.

*p < .05 diltiazem vs placebo.

#p < .05 diltiazem plus propranolol vs propranolol.

however, the statistical significance of the results remained unchanged with or without his data.

The other patient who developed congestive heart failure on propranolol likewise did so on combination therapy. This patient had a reduced ejection fraction (29%) and inoperable three-vessel disease. He had tolerated 160 mg daily of propranolol without symptoms of congestive heart failure. His response to diltiazem alone was excellent: he noted a dramatically improved anginal threshold and more than doubled his exercise tolerance. During the propranolol titration phase, while receiving 160 mg daily, he developed pulmonary edema immediately after unaccustomed exertion and emotional upset. His symptoms quickly resolved with diuresis alone. Because of his severely limiting angina on prior therapy and the apparent precipitating event, he and his physician elected to continue with the protocol. After he tolerated 20 mg of propranolol qid for 1 month, diltiazem was again added to his regimen. Although low-dosage diltiazem was tolerated without difficulty, he redeveloped congestive heart failure on the combination of 80 mg of propranolol and 360 mg of diltiazem daily.

Discussion

Myocardial ischemia results from an imbalance between myocardial oxygen demand and myocardial blood supply. β-Adrenergic blocking drugs and calcium-channel blockers are effective in patients with stable angina pectoris by lowering myocardial oxygen demand. Thus they share similar abilities to reduce systemic blood pressure and contractility and, depending on the agent, can blunt the heart rate response to exercise.

Use of both a calcium-channel blocker and β-adrenergic blocker results in multiple and varied interactions. Calcium-channel blockers have both direct cardiac and vascular effects that can produce secondary reflex changes. For example, reflex adrenergic stimulation after vasodilatation induced by a calcium-channel blocker can profoundly modify the impact of the calcium-channel blocker on contractility. The additional use of a β-blocker blunts this reflex stimulation and may unmask the underlying negative inotropism of the calcium-channel blocker. 10

TABLE 3
Adverse reactions/complaints

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adverse reaction (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem</td>
<td>Constipation (2)</td>
</tr>
<tr>
<td></td>
<td>First-degree AV block (1)</td>
</tr>
<tr>
<td></td>
<td>Maculopapular rash (1)</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Congestive heart failure (2)</td>
</tr>
<tr>
<td></td>
<td>Fatigue (1)</td>
</tr>
<tr>
<td></td>
<td>Macular rash (1)</td>
</tr>
<tr>
<td>Placebo</td>
<td>Nausea (1)</td>
</tr>
<tr>
<td>Propranolol + diltiazem</td>
<td>Congestive heart failure (1)</td>
</tr>
<tr>
<td></td>
<td>First-degree AV block (1)</td>
</tr>
<tr>
<td></td>
<td>Sinus bradycardia (1)</td>
</tr>
</tbody>
</table>

AV = atrioventricular.
Diltiazem alone. Previous investigators have demonstrated the efficacy of low- and moderate-dose diltiazem in decreasing frequency of angina and improving exercise tolerance.1-11 At the initiation of this investigation, data on efficacy of high-dose (360 mg daily) diltiazem were not available. The first crossover period documented a significant reduction in frequency of angina and nitroglycerin consumption as well as improvement in all measures of exercise tolerance. These findings corroborate recently published data from other institutions on the 360 mg daily dose.12-14

Combination therapy. Two previous investigations of combined diltiazem-propranolol therapy have been published. Using a Latin square model, Kenny et al.13 studied 12 patients randomly receiving these drugs alone or in combination. Each agent produced the expected improvement over placebo. Although time to onset of angina improved further, the frequency of angina was not significantly decreased with combination therapy. Both the diltiazem and propranolol doses were fixed and relatively low (60 mg tid and 80 mg tid, respectively). Hung et al.19 used a similar protocol to evaluate 12 patients. Although the daily dose of propranolol was the same, the dose of diltiazem was twice as high, 360 mg daily. Despite this, the results were similar: patients had an improved exercise capacity on either drug but showed no further improvement with the combined therapy.

In contrast to the results of the above reports, our study did document a further improvement in rate of angina attack and nitroglycerin consumption as well as exercise duration. Our study involved twice as many patients, which increases the statistical power of the analysis and lessens the likelihood of a false-negative or so-called beta error. Although Hung et al.16 also used a 360 mg daily dose of diltiazem, the dose of propranolol was fixed at 240 mg daily. Our patients had doses individually titrated to achieve clinical β-blockade, analogous to common practices for ambulatory patients with angina.

Hemodynamics. Although prior investigations of the calcium-channel blockers have shown a blunted hemodynamic response to submaximal exercise, at peak exercise there generally is no difference from the response with placebo, a finding confirmed by our observations with diltiazem alone. In contrast, the addition of diltiazem to propranolol produced further lowering of heart rate beyond that obtained with propranolol alone at submaximal as well as peak exertion. Similar findings have been reported with diltiazem,16 lidoflazine,17 and verapamil.6 Although we found a lower double product at rest and submaximal exercise, sever-

al other investigators have reported a reduced heart rate × systolic blood pressure with combination therapy at peak exercise.6,15-17

Safety. The most significant adverse reaction was congestive heart failure. This occurred twice while patients were receiving propranolol therapy alone. In each instance the patient had previously tolerated similar doses of propranolol despite marked baseline left ventricular dysfunction.

There was a single occurrence of clinical congestive heart failure with the combination of diltiazem and low-dose propranolol. The combination of β-adrenergic blocker therapy and either verapamil7,18 or nifedipine19-21 has also been associated with heart failure. Although in isolated muscle strip preparations the calcium-channel blockers each manifest negative inotropic properties, the intact animal brings reflex adrenergic stimulation into play. Therapy with a β-adrenergic blocker blunts this reflex catacholamine response, potentially unmasking the negative inotropism of the calcium-channel blockers. In addition, the degree of underlying cardiac dysfunction probably affects the amount of myocardial depression.22 Being the weakest peripheral vasodilator of the three currently available agents, diltiazem appears to involve the least reflex catacholamine stimulation. Indeed, with diltiazem investigators have been unable to produce negative inotropy in an intact canine preparation.23,24

Conclusion. Our study has further independently confirmed the improvement in subjective and objective measures of angina with high-dose (360 mg/day) diltiazem therapy. We have demonstrated further that benefits resulted from the addition of diltiazem to treatment with a representative β-adrenergic blocker. Not all patients do better with more therapy — almost half of our patients either had no further benefit or showed a reduction in exercise tolerance with combination therapy. In general, the combination of diltiazem and propranolol was well tolerated. However, as with the other calcium-channel blockers, in the presence of reduced left ventricular function and β-adrenergic blockade there is the potential for congestive heart failure to develop. This potential adverse effect should not preclude the use of diltiazem with propranolol; indeed, many patients are being treated successfully with this combination even in the face of compromised left ventricular function. Instead, the prudent clinician must be alert for this adverse effect, as he or she would be with any new medication or combination of medications.

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