Increased Exercise Tolerance and Reduced Electrocardiographic Ischemia with Diltiazem in Patients with Stable Angina Pectoris

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SUMMARY Diltiazem is a calcium slow-channel blocking drug that may be effective in the treatment of chronic stable angina pectoris. To evaluate the therapeutic efficacy 3 hours after a single oral dose of 120 mg, 12 men with chronic stable angina pectoris performed a maximal exercise test on a bicycle ergometer after ingesting either placebo or diltiazem administered in a double-blind fashion. During submaximal exercise at a fixed work load, diltiazem decreased the average heart rate response from 119 ± 17 to 107 ± 14 beats/min (p < 0.01), systolic blood pressure from 182 ± 15 to 175 ± 15 mm Hg (p < 0.05) and the rate-pressure product from 21.8 ± 4.2 to 18.8 ± 3.2 × 10³ units (p < 0.01). The average submaximal work load at which significant ST-segment depression (0.1 mV) first appeared was increased from 355 ± 142 to 525 ± 143 seconds (p < 0.01) after diltiazem. At peak exercise after diltiazem, the average depth of ST-segment depression in any one lead and the extent of myocardial ischemia observed in all 12 ECG leads were decreased (p < 0.01), even though the average work load was increased by 29% (p < 0.01). Peak heart rate, systolic blood pressure and rate-pressure product were similar with placebo and diltiazem. The plasma diltiazem concentration was 139 ± 29 ng/ml 3 hours after ingestion and was significantly (p < 0.05) related to the increased time to the onset of important ST-segment depression (r = 0.65) and to the decrease in the extent of myocardial ischemia observed in all 12 ECG leads (r = −0.61) compared with placebo. Thus, diltiazem is effective in treating chronic stable angina pectoris. It decreases myocardial oxygen requirements during upright exercise and appears to increase myocardial oxygen delivery.

THE EFFECTIVENESS of diltiazem, a calcium slow-channel blocking drug, in the prevention of coronary spasm is well documented.1-3 It decreases systemic arteriolar resistance, increases coronary artery blood flow and has a negative chronotropic effect.4-6 These properties have justified its study in the treatment of exertional angina in patients with fixed coronary artery stenoses.7-11 Repeat oral-dose studies of diltiazem show an increase in the time to the onset of angina or to significant ST-segment depression during standard multistage exercise testing.7-9 Both the total daily dose and schedule appear to influence the drug’s efficacy and ability to reduce indexes of myocardial oxygen demand during exercise. Hassock and Bruce7 found a greater effect using 60 mg four times daily than smaller doses and with a schedule of 30 mg four times daily vs 60 mg three times daily. Single-dose studies10, 11 with 60 and 90 mg of diltiazem have not shown a significant decrease in the indexes of myocardial oxygen demand during exercise.

Therefore, in the present study, we compared, after 3 hours, the effects of a single oral dose of 120 mg of diltiazem vs placebo on the time to the onset of significant ST-segment depression (0.1 mV) and to peak exercise; the indexes of myocardial oxygen consumption at a fixed submaximal work load, at the onset of significant ST-segment depression and at peak exercise; and the extent of electrocardiographic ischemia at peak exercise. Finally, when diltiazem resulted in significant improvements in the above mentioned variables, correlations were determined with the plasma diltiazem concentration measured 3 hours after ingestion.

Methods

Patient Population

Twelve men, mean age 58 years (range 45-64 years), who were treated for chronic stable angina pectoris formed the study group. None of the patients had rest angina. Two patients had had a previous inferior wall myocardial infarction. Each patient had ≥ 0.1 mV of horizontal or downsloping ST-segment depression for 0.08 second after the J point on multistage bicycle ergometer testing. Coronary angiography, performed in 10 patients, revealed significant fixed stenoses ≥ 70% of at least one major artery. Three patients had one-, five two- and two three-vessel disease. Five patients had an abnormal left ventricular contraction pattern. Patients who had severe hypertension, intraventricular conduction disturbances, significant ventricular dysrhythmia and hepatic or renal dysfunction were excluded. The purpose of the study and possible side effects of diltiazem were explained, and each patient gave informed consent.

Experimental Protocol

A baseline multistage bicycle ergometer exercise test was used to familiarize participants with the laboratory conditions. After at least 48 hours, the patients returned to the laboratory in the morning on two occasions separated by 3-7 days. In the intervening period, the patients took isosorbide dinitrate until 24 hours
before the second test. Each patient received a single oral dose of 120 mg of diltiazem or an identical placebo. The multistage exercise test was conducted 3 hours later. Treatment with diltiazem or placebo was performed under randomized double-blind conditions.

The exercise tests were performed on a Siemens-Elema model 380 bicycle ergometer. The initial work load was started at 30 W and was increased in 30-W increments every 3 minutes until progressive angina pectoris or fatigue. Exercise tolerance and work load for this standardized test are expressed in terms of exercise duration in seconds. The 12-lead ECG was recorded on a six-channel Mingograf-Elema Schonander recorder (model 61) each minute and during the last 10 seconds of the test. Simultaneous arterial blood pressure measurements were obtained by sphygmomanometry. The heart rate, systolic blood pressure and rate-pressure product were studied at rest, at the onset of exercise, and in the 10 seconds preceding the termination of the test. The ST segment was measured using a seven-power magnifying glass calibrated in tenths of a millimeter and by an investigator with no knowledge of the treatment received. At peak exercise, the ST segment was evaluated in each ECG lead. The amount of ST-segment depression in three consecutive complexes for each lead was averaged and the sum of the averaged beats was used to determine the extent of electrocardiographic ischemia. After exercise, a venous blood sample was withdrawn in a heparinized tube and rapidly centrifuged. The plasma was stored at −30°C and diltiazem blood concentrations were then determined for each patient using the fluoroscopic method of Rovei et al.14

Statistical Analysis

Statistical comparisons of differences between placebo and diltiazem treatments were made using either the t test for paired data or a repeated-measures analysis of variance with the Tukey test15,16 when more than two comparisons were made. The statistical procedure used is indicated in the tables. Linear correlations were calculated between plasma diltiazem concentrations and selected exercise test variables.

Results

At rest, there was no significant difference in heart rate (66 ± 15 vs 72 ± 18 beats/min), systolic blood pressure (125 ± 11 vs 133 ± 17 mm Hg), diastolic blood pressure (77 ± 14 vs 82 ± 14 mm Hg) and the rate-pressure product (8.4 ± 2.4 vs 9.6 ± 2.6) between placebo and diltiazem.

Submaximal Exercise

The average exercise duration at the onset of ST-segment depression (0.1 mV) was 355 ± 142 seconds 3 hours after placebo. With diltiazem, this same work load was accomplished without significant ST-segment depression and at a lower heart rate (107 vs 119 beats/min, p < 0.01), systolic blood pressure (175 vs 182 mm Hg, p < 0.05), and rate-pressure product (18.8 vs 21.8 × 10−3 units, p < 0.01) compared with placebo (table 1, fig. 1). The diastolic blood pressure was not significantly different between diltiazem and placebo. The exercise duration at which significant ST-segment depression first occurred in any lead after diltiazem was greater than that after placebo (525 vs 355 seconds, p < 0.01). At this higher workload, the average heart rate (129 vs 119 beats/min, p < 0.01), systolic blood pressure (194 vs 182 mm Hg, p < 0.01), and rate-pressure product (25.1 vs 21.8 × 10−3 units, p < 0.01) were greater with diltiazem than placebo.

Peak Exercise

The time to peak exercise was 29% greater with diltiazem than placebo (580 vs 475 seconds, p < 0.01) (table 2).

![FIGURE 1. Indexes of myocardial oxygen demand are lowered with diltiazem at exercise work loads that induced ECG myocardial ischemia with placebo and increased with diltiazem at the onset of significant ST-segment depression.](image-url)
systolic and diastolic blood pressures and rate-pressure product were similar with diltiazem and placebo. However, the maximum depth of ST-segment depression in any one lead was less with diltiazem than with placebo (1.5 vs 2.0 mm, \( p < 0.05 \)) and the extent of ST-segment depression in all 12 ECG leads was lower (3.7 vs 6.9 mm, \( p < 0.01 \)). Patients 4, 7, 9, 10 and 11 showed a negative chronotropic effects of diltiazem at peak exercise; all five achieved a higher work load with a similar or lower peak heart rate response. In the nine men who had improved peak exercise tolerance after diltiazem, the systolic blood pressure response was the same or less in five, compared with placebo. With placebo, the exercise test was terminated in seven patients due to angina pectoris, while no patient had angina pectoris with diltiazem. All had significant exercise-induced ST-segment depression.

The average plasma concentration of diltiazem was 139 ± 29 ng/ml 3 hours after the single 120-mg oral dose. The plasma diltiazem concentration was significantly related (fig. 2) to the increase in time to the onset of significant ECG ischemia with diltiazem vs...
placebo ($r = 0.65$, $p < 0.05$) and to the decrease in the sum of ST-segment depressions in all 12 leads ($r = -0.61$, $p < 0.05$). The correlation between the plasma diltiazem concentration and the decrease in the rate-pressure product at a fixed submaximal work load with diltiazem vs placebo was not significant ($r = -0.51$). No significant correlation was found between plasma diltiazem concentration and the increase in peak exercise time with diltiazem.

**Discussion**

The present study confirms previous reports$^7$-$^{10}$ that demonstrated that diltiazem can increase exercise tolerance and time to the onset of significant ST-segment depression in patients with fixed coronary artery stenoses. Our results show that 3 hours after a single 120-mg dose of diltiazem, the extent of myocardial ischemia at peak exercise is decreased even though a higher work load can be accomplished. The causes are complex but appear to be related to reduced myocardial oxygen demand and, possibly, improved myocardial perfusion.

**Exercise at a Fixed Work Load**

Three hours after diltiazem, we observed a reduction in heart rate, systolic blood pressure, rate-pressure product and ECG evidence of myocardial ischemia during exercise at a fixed submaximal work load. A significant decrease in the indexes of myocardial oxygen demand was not found in the studies using a single dose of 60$^3$ or 90 mg,$^9$ and repeat dose studies showed little or no effect at doses of less than 240 mg/day.$^7$-$^9$ A lower rate-pressure product at a constant work load in patients with chronic stable angina pectoris has also been reported for other slow-channel calcium inhibitors such as verapamil$^7$ and nifedipine,$^8$-$^{10}$ although with nifedipine there was either a reduction in systolic blood pressure alone$^{18,19}$ or combined with a small decrease in heart rate.$^{20}$

The differing results obtained in exercise studies of slow-channel calcium inhibitors may be due to different dose levels and schedules used in the individual studies or to the specific action of each drug. The average 3-hour plasma diltiazem concentration reported in the present study is within the range of clinically effective drug levels.$^{13}$ The importance of the quantity of the oral dose can be surmised from the data of Hossack and Bruce,$^7$ who found a progressive increase in exercise capacity with larger and more frequent doses (four times daily vs three times daily). Peak plasma diltiazem levels are dose-related and are reached in 3–4 hours,$^{21}$ with maximal hemodynamic responses occurring 2–3 hours after oral ingestion.$^{21}$

The lower heart rate response during submaximal exercise after diltiazem ingestion is not unlike the exercise response observed in patients taking $\beta$ blockers.$^{21}$ There is a dose-related suppression of sinoatrial node activity with calcium-channel blockers.$^6$ However, unlike diltiazem, the more potent vasodilator and reflex $\beta$-adrenergic response of nifedipine$^{24}$ can reduce or abolish this negative chronotropic effect.$^{18-20}$

**Indirect Evidence for Improved Myocardial Oxygen Supply**

Diltiazem delayed the onset of exercise-induced ST-segment depression (355 to 525 seconds). The rate-pressure product at this threshold was higher than with placebo, which might be attributable to a depression of myocardial contractility, a smaller increase in ventricular volumes, or an improved myocardial perfusion. The negative inotropic effect of diltiazem is reported to be minor,$^{25,26}$ and less than that with nifedipine$^{27}$ or verapamil.$^{27,28}$ A smaller ischemia-induced increase in

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**Table 2. Peak Exercise Data 3 Hours after a Single Oral Dose of 120 mg of Diltiazem or Placebo**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Exercise work load (seconds)</th>
<th>Heart rate (beats/min)</th>
<th>Blood pressure (mm Hg)</th>
<th>Rate-pressure product ($\times 10^{-3}$ units)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>P</td>
<td>D</td>
<td>P</td>
<td>D</td>
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<tr>
<td>1</td>
<td>180</td>
<td>300</td>
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<td>2</td>
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<td>12</td>
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<tr>
<td>Mean</td>
<td>475</td>
<td>580</td>
<td>132</td>
<td>137</td>
</tr>
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</table>

$^{6}p < 0.01$, $t$ test for paired data.

Abbreviations: P = placebo; D = diltiazem.
TABLE 2. (Continued)

<table>
<thead>
<tr>
<th>Maximum depth of ST-segment depression in any lead (mm)</th>
<th>Σ ST-segment depression in all 12 leads (mm)</th>
<th>Plasma diltiazem concentration (ng/ml)</th>
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<tbody>
<tr>
<td>P</td>
<td>D</td>
<td>P</td>
</tr>
<tr>
<td>1.6</td>
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<tr>
<td>2.0</td>
<td>1.5*</td>
<td>6.9</td>
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<tr>
<td>±0.4</td>
<td>±0.4</td>
<td>±3.2</td>
</tr>
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</table>

ventricular volume and a relatively higher ejection fraction was found when verapamil was compared with placebo during exercise at a constant absolute work load. Diltiazem has been reported to have a similar effect; however, it is not yet known if ventricular volume remains lower with diltiazem at the onset of exercise-induced ECG ischemia. Also, the coronary vasodilator effect of diltiazem can improve blood flow to marginally ischemic zones in animals. In humans, diltiazem results in an increase in total coronary flow at rest. Lichtlen et al. showed that nifedipine increases myocardial blood flow to poststenotic regions during pacing-induced ischemia. Fox et al., using 16-lead ECG mapping, recorded a smaller zone of exercise-induced ST-segment depression with nifedipine and propranolol compared with propranolol alone. If diltiazem improves regional myocardial perfusion to ischemic areas during exercise, it could explain our finding of less myocardial ischemia determined electrocardiographically during peak exercise at a higher work load and a similar rate-pressure product.

However, calcium slow-channel blocking drugs have a potential for affecting several different sites within cell membranes or in the cell. Diltiazem may have a direct electrophysiologic effect on stabilizing ischemic cell function, thereby reducing the extent of exercise-induced ST-segment depression. That diltiazem decreases the extent of exercise-induced ST-segment depression may be related to increased myocardial blood flow to the ischemic myocardium or to stabilization of myocardial function or to both. In either case, this finding was significantly related to the plasma diltiazem levels attained despite the relatively small group of patients studied.

References

12. Chaitman BR, Bourassa MG, Wagniart P, Corbana F, Ferguson RJ:
Improved efficiency of treadmill testing using a multiple lead ECG system and basic hemodynamic exercise response. Circulation 57: 71, 1978


33. Fox K, Jonathon A, Selwyn A: Administration simultanée à haute dose de nifédipine et de propranolol à des malades atteints d’angine de poitrine. Le Concours Médical 102 (suppl): 97, 1980

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doi: 10.1161/01.CIR.66.1.23

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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