Combination therapy with diltiazem and nifedipine in patients with effort angina pectoris

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ABSTRACT The antianginal effects of diltiazem and nifedipine alone and in combination were evaluated in a double-blind, randomized, placebo-controlled trial in 11 patients (nine men and two women, 57 ± 8 years old) with stable effort angina. Each patient received placebo, 30 mg of diltiazem, 10 mg of nifedipine, and 30 mg of diltiazem plus 10 mg of nifedipine four times daily for 1 week each. Antianginal efficacy was assessed by means of a treadmill exercise test. The exercise tolerance time was significantly prolonged from 235.1 ± 52 (placebo period) to 342.2 ± 101 sec by diltiazem (p < .01) and to 325.6 ± 73 sec by nifedipine (p < .01). The drug combination further prolonged exercise time to 451.1 ± 103 sec, which was significantly longer than the interval attained with either diltiazem (p < .01) or nifedipine (p < .01) alone. The plasma concentration of diltiazem was unaffected by the addition of nifedipine, whereas the plasma nifedipine concentration was significantly increased from 34.8 ± 11 to 106.4 ± 37 ng/ml (p < .001) by the concomitant administration of diltiazem. These data suggest that exercise tolerance in patients with effort angina is increased by the concomitant administration of diltiazem and nifedipine associated with an increase in the nifedipine plasma concentration. Circulation 77, No. 6, 1370–1375, 1988.

Calcium antagonists are a heterogenous group of compounds having different pharmacokinetic properties and pharmacodynamic effects.1 For example, nifedipine produces greater peripheral vasodilatation than either verapamil or diltiazem, whereas verapamil is more potent than the other two drugs in reducing myocardial contractility. Verapamil and diltiazem decrease atrioventricular conduction, whereas therapeutic doses of nifedipine do not.2,3

Several investigators have reported evidence of the existence of multiple binding sites for different subclasses of calcium antagonists.4,5 Recently, diltiazem was shown to potentiate the pharmacologic effects of dihydropyridine calcium antagonists such as nitrendipine6–8 and nimodipine.9 Therefore, if one calcium antagonist fails to produce a satisfactory clinical response, it would seem reasonable to try another agent of this class, or a combination. In this study, we investigated the antianginal effect of diltiazem and nifedi-
test, on a Marquette CASE exercise system, according to the Bruce protocol. The patients were instructed to indicate the point at which chest pain developed ("onset of chest pain"), and exercise was terminated when the chest pain became moderate. Heart rate and blood pressure were measured before, at 1 min intervals during, and 5 min after exercise. The pressure-rate product was calculated as an index of myocardial oxygen consumption. A 12-lead electrocardiogram was also recorded at 1 min intervals and electrocardiographic lead V5 was continuously monitored with an oscilloscope throughout the exercise test and automatically analyzed. For assessment of the clinical utility of each treatment, the following variables were measured and compared: (1) exercise tolerance time, (2) time to onset of chest pain, (3) time to 1 mm ST depression, (4) magnitude of ST depression at corresponding exercise levels during the drug and placebo periods (corresponding exercise levels were those during different treatment regimens in which the shortest exercise duration was recorded).

Blood samples were taken just before each exercise test. The diltiazem plasma concentration was determined by high-performance liquid chromatography (HPLC) by use of a Hypersil 5-ODS column eluted with a mixture of acetonitrile and 1% triethylamine, pH 3 (3:7), and ultraviolet detection (240 nm) after cyclohexane extraction for each sample. The nifedipine plasma concentration was also determined by HPLC by a modified method of Sadanaga et al.10

Statistics. A one-way analysis of variance for repeated measures was used to determine if there were significant differences in the group mean values. If analysis of variance indicated a significant difference, a two-tailed paired Student's t test was then applied to the data. Differences were considered significant at the p < .05 level. All values were expressed as the mean ± 1 SD.

Results

Exercise testing variables (table 1)

Exercise tolerance time (figure 1). Compared with placebo, which resulted in a mean exercise tolerance time of 235.1 ± 52 sec, diltiazem prolonged exercise time to 342.3 ± 101 sec (p < .01) and nifedipine prolonged it to 325.6 ± 73 sec (p < .01). The combination of both drugs further prolonged the mean exercise tolerance time to 451.1 ± 103 sec, which was significantly better than the results achieved with either diltiazem (p < .01) or nifedipine (p < .01) alone.

Time to onset of chest pain. The time to onset of chest pain was prolonged from 150.5 ± 61 sec in the placebo period to 221.3 ± 69 sec (p < .01) with diltiazem and to 236.5 ± 74 sec (p < .01) with nifedipine. The combination therapy further prolonged time to onset of chest pain to 340.5 ± 104 sec, which again was significantly better than the results with either diltiazem (p < .01) or nifedipine (p < .01) monotherapy.

Time to 1 mm ST depression. The time to 1 mm ST depression was also prolonged by diltiazem (p < .05) and nifedipine (p < .05), but was more significantly prolonged by the combination treatment (p < .01).

Magnitude of ST depression at corresponding exercise level in the drug and placebo periods. The magnitude of ST depression with combination therapy was 0.78 ± 0.5 mm, which was significantly smaller than that measured after diltiazem (p < .05) or nifedipine (p < .05) monotherapy.

Plasma concentration (figure 2). The plasma concentration of diltiazem was 66.3 ± 28 ng/ml when it was administered alone and 66.2 ± 18 ng/ml when it was administered concomitantly with nifedipine; the difference was not significant. On the other hand, the plasma concentration of nifedipine increased in all patients when nifedipine was administered concomitantly with diltiazem from 34.8 ± 11 ng/ml during monotherapy to 106.4 ± 37 ng/ml during combination therapy (p < .001).

Hemodynamic effects (table 2)

Rest. The resting heart rate was decreased slightly but not significantly by diltiazem and was increased (p < .05) by nifedipine. When diltiazem and nifedipine were given concomitantly, the resting heart rate showed no statistically significant change in comparison with nifedipine alone. Systolic blood pressure was lowered by both diltiazem (not significant) and nifedipine (p < .01), and was reduced even more (p < .05 relative to nifedipine monotherapy) when the two drugs were given concomitantly. The pressure-rate product did not change significantly during any treatment periods.

| TABLE 1 |
| Exercise tolerance time, time to onset of chest pain, time to 1 mm ST depression, and magnitude of ST depression with the four treatment regimens |

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>D, 30 mg</th>
<th>N, 10 mg</th>
<th>D, 30 mg, plus N, 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETT (sec)</td>
<td>235.1 ± 52</td>
<td>342.3 ± 101&lt;sup&gt;B&lt;/sup&gt;</td>
<td>325.6 ± 73&lt;sup&gt;B&lt;/sup&gt;</td>
<td>451.1 ± 103&lt;sup&gt;C,E&lt;/sup&gt;</td>
</tr>
<tr>
<td>T1 (sec)</td>
<td>150.5 ± 61</td>
<td>221.3 ± 69&lt;sup&gt;B&lt;/sup&gt;</td>
<td>236.5 ± 74&lt;sup&gt;B&lt;/sup&gt;</td>
<td>340.5 ± 104&lt;sup&gt;C,E&lt;/sup&gt;</td>
</tr>
<tr>
<td>T2 (sec)</td>
<td>181.5 ± 64</td>
<td>256.0 ± 69&lt;sup&gt;A&lt;/sup&gt;</td>
<td>254.3 ± 65&lt;sup&gt;A&lt;/sup&gt;</td>
<td>320.2 ± 88&lt;sup&gt;B,D&lt;/sup&gt;</td>
</tr>
<tr>
<td>mST ↓ (mm)</td>
<td>1.90 ± 0.6</td>
<td>1.33 ± 0.6&lt;sup&gt;A&lt;/sup&gt;</td>
<td>1.13 ± 0.4&lt;sup&gt;A&lt;/sup&gt;</td>
<td>0.78 ± 0.5&lt;sup&gt;C,D&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

D = diltiazem; N = nifedipine; ETT = exercise tolerance time; T1 = onset of chest pain; T2 = onset of 1 mm ST depression; mST ↓ = magnitude of ST depression at the corresponding exercise level.

<sup>A</sup>p < .05; <sup>B</sup>p < .01; <sup>C</sup>p < .001 compared with placebo; <sup>D</sup>p < .05; <sup>E</sup>p < .01 compared with diltiazem and nifedipine monotherapy.

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FIGURE 1. Exercise tolerance time during each of the four treatments. The exercise tolerance time was significantly prolonged by diltiazem and nifedipine in comparison with placebo, and was prolonged more by the concomitant administration of diltiazem and nifedipine than by either drug given alone. D = diltiazem; N = nifedipine.

Maximal exercise. The maximal heart rate increased slightly with drug therapy, together with a prolongation of exercise tolerance time from 107.8 ± 10/min during the placebo period to 113.2 ± 13/min after diltiazem and 115.4 ± 13/min after nifedipine. Although neither of these increases was significant, the combined drug treatment did significantly increase the heart rate to 126.2 ± 15/min (p < .01 relative to placebo and diltiazem and nifedipine monotherapy). The systolic blood pressure showed no statistically significant changes. The pressure-rate product increased slightly with each treatment and was highest during combination therapy, but these changes also were not statistically significant.

TABLE 2
Heart rate, systolic blood pressure, and pressure-rate product at rest and maximal exercise with the four treatment regimens

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>D, 30 mg</th>
<th>N, 10 mg</th>
<th>D, 30 mg, plus N, 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rest</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>69.7 ± 6</td>
<td>67.5 ± 10</td>
<td>75.8 ± 10</td>
<td>76.3 ± 11</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>141.8 ± 16</td>
<td>133.6 ± 16</td>
<td>122.4 ± 16</td>
<td>116.0 ± 15</td>
</tr>
<tr>
<td>PRP (beats/min·mm Hg·10⁻²)</td>
<td>102.1 ± 19</td>
<td>95.1 ± 19</td>
<td>97.7 ± 23</td>
<td>90.7 ± 18</td>
</tr>
<tr>
<td><strong>Maximal exercise</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>107.8 ± 10</td>
<td>113.2 ± 13</td>
<td>115.4 ± 13</td>
<td>126.2 ± 15</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>167.3 ± 22</td>
<td>163.5 ± 21</td>
<td>158.7 ± 23</td>
<td>157.3 ± 24</td>
</tr>
<tr>
<td>PRP (beats/min·mm Hg·10⁻²)</td>
<td>177.3 ± 33</td>
<td>188.9 ± 42</td>
<td>179.9 ± 37</td>
<td>197.2 ± 44</td>
</tr>
</tbody>
</table>

D = diltiazem; N = nifedipine; HR = heart rate; SBP = systolic blood pressure; PRP = pressure-rate product.

*p < .05; **p < .01 compared with placebo; †p < .05; ‡p < .01 compared with diltiazem monotherapy; ††p < .05; ‡‡p < .01 compared with nifedipine monotherapy.
Side effects. No clinical complications occurred during any of the treatments, and no adverse reactions were reported.

Discussion

Calcium antagonists have been in clinical use for more than a decade and are widely used in the treatment of various cardiovascular disorders, such as angina pectoris due to either coronary spasm or coronary atherosclerosis, systemic hypertension, supraventricular tachycardia, and hypertrophic cardiomyopathy. Diltiazem\textsuperscript{11, 12} and nifedipine\textsuperscript{13, 14} have been shown to be effective antianginal agents in patients with chronic stable effort angina. Several clinical trials have indicated that treatment with these drugs is associated with a reduced number of anginal episodes, diminished nitroglycerin consumption, and improved exercise tolerance. There are many physiologic mechanisms responsible for the clinical efficacy of calcium antagonists in coronary artery disease. Like other antianginal agents, calcium antagonists reduce the myocardial oxygen demand by decreasing heart rate and/or blood pressure, and they also have a well-documented direct inhibitory effect on coronary vessel tone. In patients with effort angina pectoris, calcium antagonists are often given concomitantly with other drugs,\textsuperscript{15–18} especially β-blockers. In our study, the concomitant administration of diltiazem and nifedipine was expected to neutralize certain problems that occur with their use individually, e.g., diltiazem suppresses the tachycardia caused by pronounced sympathetic activation with nifedipine. We postulated that this combination therapy would be beneficial, particularly in patients with disorders for which β-blockers are considered to be contraindicated, such as vasospastic angina, diabetes mellitus, bronchial asthma, and atherosclerosis obliterans.

Our results indicate that combination therapy with diltiazem and nifedipine significantly increases exercise tolerance in patients with effort angina. Moreover, the plasma concentration of nifedipine increases about threefold with concomitant administration of diltiazem. It is not clear whether the superiority of the combination treatment derived mainly from an additive effect of diltiazem or an augmentation of nifedipine's effect due to its increased plasma concentration. However, since the effects of nifedipine are known to be dose dependent,\textsuperscript{14, 19, 20} the elevated plasma concentration of the drug during combination therapy probably contributed importantly to the enhanced effectiveness.

Drug interactions with the calcium antagonists. Calcium antagonists have been noted to interact with a variety of other drugs.\textsuperscript{21, 22} It has been reported that both verapamil\textsuperscript{23, 24} and diltiazem\textsuperscript{25–27} decrease the renal clearance of digoxin and increase its plasma level. Pedersen et al.\textsuperscript{23} demonstrated that verapamil induces a 60% to 75% increase in the serum digoxin concentration. Yoshida et al.\textsuperscript{25} reported that diltiazem increases the plasma digoxin concentration in healthy subjects by producing a 24% decrease in total digoxin clearance. A clinically relevant interaction between verapamil and prazosin was reported recently by Elliott et al.\textsuperscript{28} who found that combined administration resulted in an increased peak plasma concentration and a greater area under the concentration-time curve for prazosin.

Farringer et al.\textsuperscript{29} reported that the plasma concentration of quinidine was lower when nifedipine was added than when quinidine was given alone and that this decrease was associated with a reduced pharmacodynamic effect. Interactions between theophylline and verapamil,\textsuperscript{30} cyclosporin and diltiazem,\textsuperscript{31} and propranolol and diltiazem\textsuperscript{32} have also been reported. However, whether or not the altered drug metabolism that results from the addition of a calcium antagonist produces any appreciable clinical effects is unclear at present.

Mechanisms of the interaction of diltiazem and nifedipine. The mechanisms of drug interactions with calcium antagonists are not well understood, including those of the interaction between diltiazem and nifedipine seen in this study. Etoh et al.\textsuperscript{32} reported an increase in the plasma concentration of propranolol on its coadministration with diltiazem, and speculated that this interaction involved a diminished first-pass metabolic clearance of propranolol secondary to an increase in hepatic blood flow induced by diltiazem. However, this proposed mechanism does not explain the increased plasma level of nifedipine associated with concomitant administration of diltiazem. Such a mechanism would also raise the diltiazem plasma concentration, since nifedipine is a stronger vasodilator than diltiazem and diltiazem undergoes more extensive first-pass metabolism than does nifedipine (their bioavailabilities are 42%\textsuperscript{33} and 55% to 63%,\textsuperscript{34, 35} respectively). Therefore, a different or additional mechanism is required to explain this specific interaction.

Recently, studies in vitro have demonstrated that both diltiazem and verapamil are competitive inhibitors of cytochrome P-450–dependent biotransformation of aminopyrine.\textsuperscript{36} Studies in vivo have also demonstrated that diltiazem inhibits oxidative drug metabolism.\textsuperscript{37, 38} This inhibition can potentiate drug interaction when calcium antagonists are used in combination with other liver-metabolized agents. Oxidation to the pharmacologically inactive pyridine deriva-
tive is the primary step in the biotransformation of nifedipine; thus, it is logical to propose that the interaction of nifedipine with diltiazem is a result of inhibition of hepatic oxidation.

Clinical implications and summary. Carver et al. described a female patient with variant angina who had persistent chest pain despite vigorous therapy with maximally tolerable doses of oral and transcutaneous nitrates, nifedipine (40 mg every 6 hr), or diltiazem (60 mg every 6 hr). When the two calcium antagonists were given in combination, the chest pain disappeared and there were no ST-T wave changes noted during 24 hr electrocardiographic monitoring. On the other hand, Prida et al. reported that combination treatment with diltiazem and nifedipine was associated with a high incidence of side effects such as dizziness, edema, and headache. These results were considered to be partly caused by the increased nifedipine plasma concentration due to drug interaction with diltiazem. Thus, although some drug interactions might be clinically beneficial, side effects must be carefully monitored when calcium antagonists are used in combination with other drugs because of the potential for unexpected elevation of the plasma concentrations of combined drugs.

In summary, the results of this study indicate that, in patients with effort angina, exercise tolerance is increased by the concomitant administration of diltiazem and nifedipine. This effect appears to be partly a consequence of an increase in the nifedipine plasma concentration as an expression of drug interaction. We believe this to be the first report of a clinically useful interaction, specifically in terms of therapy for effort angina, between these two agents.

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