The Additive Antianginal Action of Oral Nifedipine in Patients Receiving Propranolol
Magnitude and Duration of Effect

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SUMMARY Ten men with stable angina not completely relieved by full doses of propranolol (mean 218 mg/day) were administered an oral dose of 10 mg of nifedipine or placebo on alternate mornings in a double-blind fashion. Patients had been trained in a protocol that precipitated angina after 3–6 minutes of bicycle exercise. On test days, with propranolol continued, bicycle exercise to angina or fatigue was performed before nifedipine or placebo administration, and hourly thereafter for 8 hours. Mean exercise duration was greater 1 hour after nifedipine than after placebo by 123 seconds (372 ± 21 vs 249 ± 16 seconds, p < 0.001). By the fifth hour, the increase in exercise time was reduced to 93 seconds (p < 0.001), and a significant, though further diminished, difference of 57 seconds was still present at 8 hours (p < 0.01). Nifedipine lowered resting systolic blood pressure by 20 mm Hg (p < 0.001) without appreciably changing heart rate. We conclude that nifedipine is a very effective and reasonably long-acting antianginal supplement to propranolol.

IN THE ABSENCE of specific contraindications, β adrenoreceptor blocking drugs are usually prescribed for patients with significant limitations in exercise tolerance due to angina pectoris. While β blockers are generally effective in improving exercise tolerance, the improvement is frequently only partial. If so, a second drug will often be added to the therapeutic regimen. Nifedipine is a potent coronary and systemic arterial vasodilator, and double-blind studies have shown that it is an effective antianginal agent. The combination of a β blocker with a vasodilator (usually one of the long-acting nitrates) to achieve maximal symptomatic improvement in chronic angina pectoris has been accepted for many years. Many patients, however, do not tolerate nitrates, and the best studied long-acting nitrate, isosorbide dinitrate, has a duration of action of only about 4 hours. In an effort to find a more potent antianginal supplement to β blockers without the side effects and short duration of action of isosorbide dinitrate, we investigated the efficacy of oral nifedipine in patients who, although receiving optimal doses of propranolol, continued to be limited by angina pectoris. In addition to endeavoring to document a supplemental effect to that of propranolol, we were particularly interested in determining whether the duration of the effect justifies the recommended interval of 6–8 hours between doses.

Patients and Methods

Patients

Ten men with classic exertional angina pectoris were studied. In addition to reproducible provocation of typical angina during bicycle exercise, each patient had one or more objective indicators or ischemic heart disease (table 1). None of the patients had hypertension or evidence of congestive heart failure. Eight patients had undergone cardiac catheterization (table 1), and none showed abnormal global left ventricular function. No patient suffered from any other condition contraindicating β-blocker therapy. Since these patients were also to undergo evaluation of the effect of other vasodilators, including isosorbide dinitrate, patients with nitrates-induced headache by history or after a test dose were not accepted for study. None of the 10 patients had ever received nifedipine.

Training

The patients were trained on an upright, mechanically braked bicycle ergometer (Jonas-Ögland) according to the exercise protocol of Redwood et al., in which the work level is increased by 20 W every 3 minutes, and the starting level is chosen so that angina is precipitated between the third and sixth minutes of exercise. Training to the point of stable performance (appearance of angina at a constant time ± 30 seconds) required at least 10 and usually 15–20 exercise bouts to angina. These bouts were conducted at hourly intervals, usually three or four per session, with several sessions per week over 2–3 weeks. During this time, the patient became thoroughly familiar with the laboratory and the physician, learned to signal at the exact onset of angina, and achieved a degree of physical conditioning. Between the beginning and the end of the training period there was almost invariably an improvement of at least 3 minutes (one 20-W level) in exercise capacity.

Beta-blocker Therapy

Before assessing the effect of nifedipine, we endeavored to ensure that each patient was receiving optimal therapy with propranolol. Eight of the 10 patients were already receiving propranolol before entering the study. Five of these patients had had some subjective clinical improvement from the drug, and they fulfilled the commonly accepted clinical criteria for effective β-blocker therapy of resting pulse of 55–60 beats/min and heart rate during exercise to angina not exceeding 100 beats/min. These patients con-
continued to take their usual dose of propranolol for the study. In the three other patients already receiving propranolol, resting pulse was greater than 60 beats/min, and their dose was titrated up by at least 120 mg/day. Each showed some degree of increase in bicycle exercise tolerance, and in two the resting pulse fell to less than 60 beats/min. Two patients were not receiving β blockers when first examined. Both were treated with progressively increasing doses of propranolol. Each exhibited some improvement in bicycle exercise time, and the final dose of propranolol was selected after a higher dose was shown to be no more effective. The daily dose of propranolol for each patient is listed in table 1. The mean dose was 218 mg/day. Clinical and bicycle exercise–induced angina pectoris continued to be present in all patients despite β-blocker therapy.

**Study Design**

The study was carried out over 2 days. The patient reported to the exercise laboratory at 8:00 a.m. after his usual morning dose of propranolol. After a 15–30-minute rest, he performed a control exercise bout, beginning at the starting work level established during the training phase (table 1) and continuing to the point of angina. He was then given a capsule that contained a placebo or 10 mg of nifedipine. The dispensing order of the placebo and nifedipine was random and double blind. The patient then exercised to angina or extreme leg fatigue once hourly for 8 hours after drug administration.

A modified lead V₅ ECG was monitored continuously. Heart rate was measured using a 10-second ECG printout at rest and seven- to 10-beat printouts during exercise. Blood pressure was measured using a wall-mounted mercury sphygmomanometer. Resting heart rate and blood pressure were recorded after the patient had been sitting on the bicycle for 5 minutes. Special care was taken in determining resting blood pressure and at least three measurements were performed to assure that an accurate and stable value was recorded. Heart rate was measured at the end of each minute of exercise, while blood pressure was measured at the end of every third minute. The patient pedaled at a constant rate of 50 rpm and signaled the onset of angina. He then continued pedaling for 15–20 seconds while an ECG strip and blood pressure were recorded at peak exercise. During exercise bouts in which the patient was not limited by chest pain, he was prodded to exert maximal effort. Blood pressure and ECG were recorded just before the patient was forced to stop because of extreme fatigue.

In general, because exercise was stopped shortly after the onset of angina, the intensity of the pain was less than that experienced by the patient in the course of his usual daily activities. In no case did the chest pain last for more than several minutes after exercise, nor were there any adverse effects from the exercise, such as arrhythmias or hypotension. The only persisting side effect from the repeated exercise bouts was leg muscle soreness in patients who exercised to fatigue after nifedipine. Although all tests were performed on an outpatient basis, as a precautionary measure patients were connected to an ECG monitor and kept in easy chairs in the cardiac observation unit during the waiting periods between tests for the first 3 hours after capsule administration.

The exercise laboratory temperature was kept constant at 24°C. Two patients smoked occasionally, but not on test mornings. Aside from propranolol, no patient was receiving any medication except for two patients who were receiving chronic therapy with oral isosorbide dinitrate. On the study days, the morning dose was omitted and neither patient had received this drug within 12 hours of the test procedure. Seven of the 10 patients were not bothered by hunger and completed the 8½-hour procedure without food, drinking water only. The other three patients had a light snack on both days after the fifth hour. All of the exercise tests in an individual patient were performed by one of two physicians who were involved with the patient from the training phase. A technician was not used, nor were any observers or other persons allowed in the laboratory during the exercise bouts. For three of the 10 patients the two test days were consecutive. For three patients the test days were two days apart, for two days apart, and for two patients five days apart. Six of the patients had received nifedipine on the second day. Despite the extensive training period, two of the 10 patients demonstrated inconstant performance as manifested by improvement in control exercise tolerance during the study phase. These patients were retrained at a higher starting level and subsequently completed the two study days on a second randomization of drug administration. An eleventh patient also demonstrated improvement in control exercise performance. During attempts to retrain him at a higher level, he became angina-free on propranolol alone, and was dropped from the study.

The degree of physician blinding was only partial because of the marked differences in exercise perform-

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Angio.</th>
<th>Ischemic event</th>
<th>Stress test ↓ ST (mm)</th>
<th>Starting exercise level (W)</th>
<th>Propranolol dose (mg/day)</th>
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<td>56</td>
<td>1</td>
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<td>160*</td>
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<td>120*</td>
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<td>2</td>
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<td>2</td>
<td>80</td>
<td>120*</td>
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<tr>
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<td>62</td>
<td>3</td>
<td>MI</td>
<td>1</td>
<td>360</td>
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<tr>
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<td>43</td>
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<tr>
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<tr>
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<td>42</td>
<td>2</td>
<td>None</td>
<td>1</td>
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</tr>
</tbody>
</table>

*Long-term isosorbide dinitrate.
†After coronary bypass surgery.

Abbreviations: 1 VD, 2 VD and 3 VD = one-, two- and three-vessel disease; Ac. isch. = acute ischemia (acute chest pain with transient T-wave inversion, but no enzyme rise); MI = myocardial infarction.
ance between placebo and nifedipine days, which became obvious in most patients by the first or second exercise test. Often, a noticeable drop in blood pressure indicated that an active drug had been given even before the exercise 1 hour after capsule administration. Mitigating against an observer bias in favor of nifedipine was the fact that randomization included single-dose evaluations of verapamil and isosorbide dinitrate on other days. Thus, while the physician often had a good idea as to whether a placebo or active agent had been given, he did not know whether the active agent was nifedipine or one of the other drugs. The study was performed without drug company assistance. Commercially available nifedipine capsules were used, and these were placed in opaque gelatin capsules.

The study was explained to each patient, who then gave informed consent. The study protocol was approved by the hospital committee for research involving human subjects.

The difference between the effects of placebo and nifedipine was analyzed by an additive two-way analysis of variance with time and individual patients as factors. The significance of the difference at each hour was tested by the appropriate \( t \) test.

**Results**

**Exercise Time to Angina (table 2)**

Exercise time to angina after placebo was relatively constant over the 8-hour observation period. There was a trend toward slight but steady decline in performance, from a mean of 255 ± 16 seconds at the morning control exercise to 220 ± 15 seconds at the final late afternoon exercise (NS). The mean control exercise time was 240 ± 17 seconds. This rose markedly, to 372 ± 21 seconds, 1 hour after nifedipine, a value significantly greater than the 249 ± 15 seconds 1 hour after placebo (\( p < 0.001 \)). The significant improvement in mean exercise tolerance persisted for the full 8 hours, although there was a gradual diminution of the increase after the second hour. By the eighth hour after nifedipine, exercise time was 277 ± 26 seconds, vs 220 ± 15 seconds after placebo (\( p < 0.01 \)).

Five of the 10 patients showed maximum or near-maximum improvement by the first hour after nifedipine. Four others showed marked improvement by 1 hour, but the best performance was after 2 hours. Patient 6 showed slight improvement at 1 hour, marked improvement by the second hour, and best performance 3 hours after nifedipine. Seven of the 10 patients exercised until stopped by fatigue rather than angina during one or more of the hourly exercise bouts. Some bouts of exercise were terminated mainly by fatigue but with the appearance of marked ST depression or mild angina immediately after stopping. The amount of increased exercise tolerance varied from almost none in patient 8, to close to 4 minutes more than control with fatigue as the reason for stopping in patient 10. There was considerable individual variation with respect to duration of action. The length of time after nifedipine during which exercise duration was at least 1 minute greater than at the corresponding time after placebo was 8 hours in three patients, 7 hours in two, and 6 hours, 5 hours, 4 hours, and 3 hours in one patient each. Patient 8 showed no improvement after nifedipine.

Figure 1 depicts the overall group improvement in exercise tolerance after nifedipine. It takes into account the progressive increase in work load after every 3 minutes of exercise. Accordingly, since the mean starting work load was 75 W, and the increases were

| Table 2. Exercise Time (Seconds) to Angina or Fatigue After Nifedipine and After Placebo |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                | Control         | 1               | 2               | 3               | 4               | 5               | 6               | 7               | 8               | Hour after drug administration |
| Pt N P                         | 1               | 2               | 3               | 4               | 5               | 6               | 7               | 8               | 9               | 10               |
| 1 265 298                      | 422 *           | 290            | 290            | 409            | 255            | 309            | 229            | 268            | 238            | 249            |
| 2 250 250                      | 360 *           | 240            | 240            | 295 *          | 243            | 290 *          | 250            | 390 *          | 248            | 309            |
| 3 324 272                      | 460 *           | 261            | 261            | 274            | 352            | 278            | 375 *          | 313            | 377            |
| 4 261 187                      | 416            | 320            | 458            | 336            | 476            | 346            | 459            | 353            | 431            |
| 5 261 302                      | 416            | 320            | 458            | 336            | 476            | 346            | 459            | 353            | 431            |
| 6 252 334                      | 300            | 300            | 420 *          | 297            | 445 *          | 295            | 422 *          | 270            | 360 *          |
| 7 262 191                      | 430 *           | 220            | 410 *          | 254            | 422 *          | 214            | 422 *          | 262            | 422 *          |
| 8 266 283                      | 272            | 259            | 228            | 244            | 207            | 256            | 225            | 249            | NA             |
| Mean 240 255                   | 372            | 249            | 246            | 426            | 242            | 354            | 251            | 331            | 238            |
| ± SEM 17 ± 16 ± 21 ± 22 ± 12 ± 16 ± 27 ± 17 ± 25 ± 17 ± 28 ± 15 ± 28 ± 15 ± 29 ± 15 ± 26 ± 15 |
| p 0.36 < 0.001 < 0.001 < 0.001 < 0.001 < 0.001 < 0.001 < 0.02 < 0.01 |

*In patients 4 and 5, a single exercise test was performed at 7½ hours and the value was used for both the seventh and eighth hours. Patient 8 developed a severe headache and was unable to exercise after the fourth hour.

*Fatigue.

*Fatigue and ischemia.

Abbreviations: P = placebo; N = nifedipine.
FIGURE 1. Mean exercise times for the 10 patients before and hourly after 10 mg of nifedipine and placebo.

FIGURE 2. Amount of exercise-induced ischemic ST-segment depression before and 2 hours after nifedipine in patient 6. The delay in the appearance of ST depression after nifedipine corresponds to the increase in exercise time. The graph depicts the effect of nifedipine on this one patient's exercise tolerance over the 8-hour period, with the benefit lasting for approximately 6 hours, from the second through the seventh hours.

FIGURE 3. The amount of exercise-induced ischemic ST-segment depression before and 1 hour after nifedipine in patient 3. The patient showed marked improvement in exercise tolerance after nifedipine through the fifth hour, with a lesser degree of benefit still evident by the eighth hour.

by 20 W per stage, the height allotted to each minute is increased by 25% every 3 minutes. According to this weighted framework, the relative increase in exercise tolerance was approximately 65% through the third hour after nifedipine and 50% after 4-5 hours, falling to 30% between the sixth and eighth hours.

Improvement in exercise tolerance after nifedipine was indicated not only by the delayed appearance of the subjective sensation of angina; in patients who developed ST depression during exercise, there was also a marked delay in the development of the ECG changes (figs. 2 and 3).

Blood Pressure (fig. 4)

Sitting, resting systolic blood pressure decreased within 1 hour after nifedipine, to a mean of 94 ± 3 mm Hg, vs 114 ± 5 mm Hg 1 hour after placebo (p < 0.001). The reduction in blood pressure diminished during the subsequent hours, but persisted until the eighth hour (p < 0.03). Systolic blood pressure at a submaximal work load (i.e., 3 minutes of exercise) was also lower for the first 2 hours after nifedipine (p
= 0.02). At peak exercise (onset of angina or extreme fatigue), there was no difference in blood pressure between exercise after nifedipine and after placebo, even though a higher work load was usually achieved after nifedipine.

Heart Rate (fig. 5)

Despite the somewhat stressful circumstances, mean sitting resting heart rate was approximately 60 beats/min, indicating a good degree of β blockade. Similarly, as a result of the propranolol therapy, mean heart rate at peak exercise rose only to approximately 95 beats/min. There was no clinically significant change in heart rate at any hour after nifedipine at rest, during exercise, or at angina, except for a slight increase in resting heart rate, from 57 ± 2 to 63 ± 2 beats/min (p < 0.01) 1 hour after drug administration.

Rate-Pressure Product (fig. 6)

The rate-pressure product at the hour of best exercise performance after nifedipine was compared with that at the same hour after placebo. The resting rate-pressure product was reduced by nifedipine, from 6599 ± 413 to 5979 ± 234 (p < 0.03), as was the rate-pressure at 3 minutes of exercise, from 11572 ± 761 to 10730 ± 582 (p < 0.06). There was no difference in rate-pressure at peak exercise (angina or fatigue) between nifedipine and placebo. The lower rate-pressure after nifedipine at rest and during submaximal exercise was due entirely to the fall in blood pressure.

Adverse Effects

Patient 8 complained of severe headache after nifedipine, and was unable to complete the day’s exercise beyond the fourth hour. The largest drop in systolic blood pressure was from 142 mm Hg to 98 mm Hg, while the lowest systolic blood pressure was in a pa-

tient who went from 100 mm Hg to 86 mm Hg. Neither of these patients experienced dizziness.

Discussion

Our results indicate a marked increase in exercise tolerance after oral administration of an acute dose of 10 mg of nifedipine in patients with angina receiving β-blocking drugs. Our study was specifically designed to measure the time course of the therapeutic effect, since the overall benefit derived from an antianginal agent administered prophylactically is related as much, if not more, to the duration of the effect as it is to its magnitude. We found a rapid onset of action, generally within 1 hour, and a mean duration of near-maximum effect of 4–5 hours. A reduced, though significant, effect was still present for the group at 8 hours. These data are compatible with pharmacologic studies showing rapid and complete absorption of nifedipine after oral administration with a plasma half-life of 5 hours.13, 17

The duration of action of the antianginal effect varied from patient to patient, ranging from 3 to 8 hours, and there was generally considerable diminution of the beneficial effect in the later hours even in the patients with a long duration of action. Since the recommended dose range of nifedipine is 10–40 mg,12, 17 use of an acute dose higher than the 10 mg we used might have demonstrated a greater benefit and a longer duration of action. However, Moskowitz et al.,3 Guiney et al.,6 and Prempree and Tabatznik18 compared 10- and 20-mg doses of nifedipine and found little or no additional benefit from the larger dose. Lynch et al.5 and Mueller and Chahine4 found a slight advantage of the 20-mg dose, although the latter questioned whether the benefit was not outweighed by the increased side effects. Although our results suggest that nifedipine every 4 or 6 hours might provide a reasonably constant optimal level of antianginal effect for most patients, such a conclusion must be regarded with caution. The consid-
Although there was clearly an additional antianginal effect of nifedipine beyond that of propranolol alone, we did not test our patients on nifedipine alone, and thus cannot compare the relative benefits of nifedipine and propranolol. Various protocols have been tried to compare the antianginal efficacy of nifedipine to that of β blockers. Lynch et al.\textsuperscript{5} found propranolol to be superior to nifedipine; de Ponti et al.\textsuperscript{10} found nifedipine superior to propranolol; Ekelund and Oro\textsuperscript{4} concluded that the two drugs were relatively similar in potency. We cannot even be sure that the effect of nifedipine by itself might not have been just as great as that of the propranolol-nifedipine combination, although several studies\textsuperscript{3, 5} found that the effect of nifedipine and a β blocker in combination was greater than the antianginal effect of either drug alone. A weakness of the cited studies\textsuperscript{4, 5, 10} is that they generally used a fixed dose of a β blocker, making no particular effort to be sure that individual patients were being given their best possible dose. We feel that our demonstration of a supplemental effect of nifedipine in the symptomatic patient already receiving an individualized optimal dose of a β blocker is particularly relevant to the usual clinical situation, where, in the absence of a specific contraindication, an attempt is usually made to first control the anginal patient on β-blocker therapy alone. We also wished to avoid the ethical problem of having to discontinue propranolol in patients with angina already receiving it or to withhold it from symptomatic patients during the training period.

Immediate exacerbation of ischemia has been reported after administration of nifedipine,\textsuperscript{20, 21} and symptomatic hypotension has been described from the combination of nifedipine with a β blocker.\textsuperscript{22} Myocardial depression is at least a theoretical risk due to the combined negative inotropic effects of nifedipine\textsuperscript{13, 17} and propranolol. We did not encounter any of these adverse effects, although in the small number of patients we studied, absence of these relatively rare phenomena by no means refutes their existence. In fact, we observed near-syncope due to hypotension precipitated by 10 mg of nifedipine in a patient receiving only 20 mg of propranolol twice daily.

Regarding the mechanism of action of nifedipine, our observations are limited by the fact that all of our patients were receiving propranolol. The therapeutic effect of nifedipine was accompanied by a significant fall in blood pressure with no change in heart rate. Nifedipine lowered the rate-pressure product at rest and at submaximal exercise, while at peak, symptom-limited exercise, the greater amount of exercise it permitted occurred at a rate-pressure product no different from that achieved after placebo. These findings are in agreement with those of other investigators\textsuperscript{5, 8} and are compatible with a predominantly peripheral mechanism of action of nifedipine, i.e., reduced oxygen demand due to lowered blood pressure.\textsuperscript{23} Nevertheless, since we do not feel that the rate-pressure product estimation of myocardial oxygen demand necessarily takes into account all the relevant determinants, we
cannot rule out a direct coronary mechanism due to vasodilation of even diseased coronary arteries and increased coronary blood flow\textsuperscript{23, 24} or a change in myocardial metabolism.\textsuperscript{2}

Acknowledgment

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