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Response of Angina and Ischemia to Long-Term Treatment in Patients With Chronic Stable Angina: A Double-Blind Randomized Individualized Dosing Trial of Nifedipine, Propranolol and Their Combination

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Seventy-four patients with chronic stable mild angina, mild coronary artery disease (83% had one- or two-vessel disease) and normal left ventricular function were studied to measure the response of treadmill exercise performance and painful and silent ischemia in the ambulatory setting to randomly assigned treatment with nifedipine or propranolol and their combination; titration to maximal tolerated dosages was performed in double-blind manner.

At 3 months both nifedipine and propranolol reduced the weekly angina rate ($p < 0.05$); during treadmill exercise testing, increases ($p < 0.05$) were noted in time to angina and total exercise time and decreases in maximal ST depression at the end of exercise. There were no differences between the responses to nifedipine and propranolol and no significant additional changes were seen after another 3 months of therapy. The combination of nifedipine and propranolol reduced the number of patients with angina on exercise treadmill testing from 64% to 38% ($p < 0.05$).

During ambulatory electrocardiographic monitoring before treatment, there were 1.4 ± 2.4 (mean ± SD) episodes/24 h of painful ischemia and a very low silent ischemia frequency: mean 1.1 ± 2.7 episodes/24 h, mean duration 16 ± 25 min/24 h. Treatment with propranolol and nifedipine resulted in reduction of episodes and duration of painful and painless ischemia; approximately 77% of patients were free of all ischemic episodes.

It is concluded that patients with chronic stable mild angina have a low incidence of silent ischemia. Nifedipine or propranolol alone, titrated to individualized maximally tolerated dosages, are equally effective in long-term control of painful and painless ischemia, anginal episodes and exercise-induced ischemia. Combination therapy further reduced only exercise-induced angina and maximal exercise-induced ST depression.

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The efficacy of beta-adrenergic blocking agents, calcium channel blocking agents and their combination in the treatment of patients with chronic stable angina pectoris is well established. Reduction of anginal symptoms and nitroglycerin consumption during daily activity has been documented, as have improved performance on exercise testing and reduced ST segment depression on ambulatory electrocardiographic (ECG) monitoring (1–23). However, the studies of nifedipine combined with a beta-blocker have predominantly involved patients with severe angina (6–18) and short-term observations of efficacy ranging from immediate responses to responses after 6 weeks of oral therapy with an occasional longer study of 8 to 15 weeks (8,14,18). Many patients with such severe angina now undergo some form of myocardial revascularization (24).

The efficacy of pharmacologic agents in the long-term treatment of *milder* angina has not been clearly documented. Moreover, only a few studies of long-term efficacy of medical treatment of angina, especially with regimens involving combination therapy, have been of sufficient duration to resemble actual clinical usage. In addition, studies are lacking on the optimal dosage and sequence of administration of these medications in combination. Although the many fixed dose studies have shown these agents to be effective in reducing ischemia, there is no documentation of their efficacy in treating patients with milder symptoms at individually titrated dosages either alone or in combination over a long term, as is common in clinical practice. Because more information in these areas is needed (25), these factors were considered in the design of this study, which was initiated in 1984 to evaluate the long-term response of symptoms and signs of ischemia in patients with chronic mild angina to treatment with nifedipine, propranolol and their combination.

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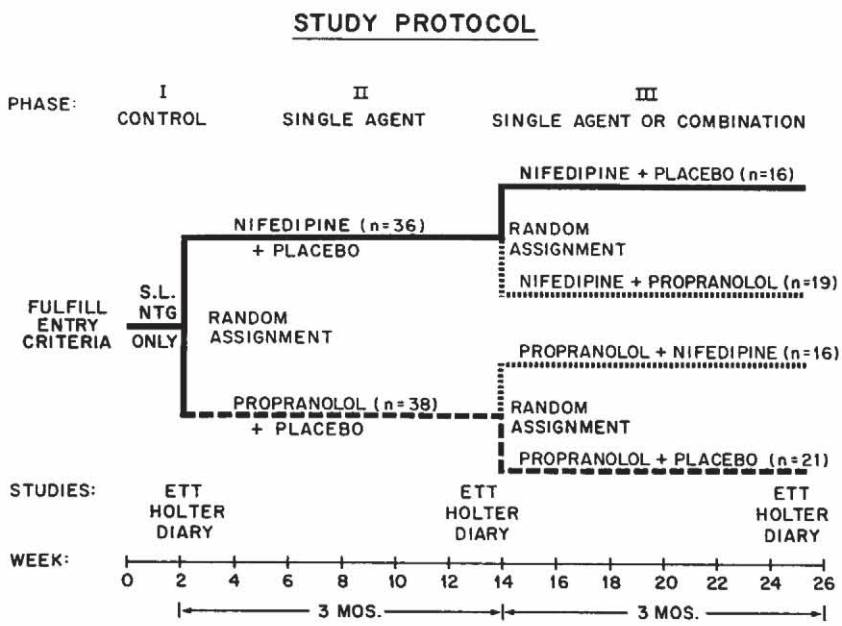

Figure 1. Protocol design. After fulfilling entry criteria, patients discontinued use of all prophylactic antianginal medications and took only sublingual (S.L.) nitroglycerin (NTG) for 2 weeks (phase I). After exercise treadmill testing (ETT), ambulatory electrocardiographic monitoring and review of the angina diary, patients were randomly assigned to 3 months of treatment with either nifedipine or propranolol (phase II). The measurements were repeated and the patients randomized to either continued treatment with the same drug or treatment with both drugs for another 3 months (phase III), after which the measurements were repeated. All drug titrations were performed in double-blind fashion and all patients underwent a second titration at the start of phase III.

Methods

Patient selection. The study was performed at the Los Angeles County and University of Southern California Medical Center; patient enrollment was begun in April 1984 and ended in November 1987. Patients were recruited from among those being evaluated for exertional angina. They were selected on the basis of 1) a history of chronic stable angina that was mild enough for them to tolerate a 2-week (control) period with only sublingual nitroglycerin and with no prophylactic antianginal medications. Angina was defined as the presence of a dull, pressurelike pain or discomfort in the precordium that was reproducibly brought on by exertion or emotional upset. The patients had to have at least three episodes of angina/week and <50% variability in the weekly angina frequency for the 2 months before enrollment in the study. 2) Documented coronary artery disease. All but two patients had coronary arteriograms that demonstrated ≥70% stenosis in at least one major coronary artery. The other two patients had a well documented myocardial infarction (by history of pain, classic ECG changes and serum enzyme determinations) and a positive exercise treadmill test for myocardial ischemia. Patients were not enrolled if they had a myocardial infarction or coronary revascularization procedure within the previous 3 months or if they had insulin-requiring diabetes, bronchospastic lung disease or other diseases with symptoms that could be confused with angina pectoris. Patients were also excluded if they had a left bundle branch block, left ventricular hypertrophy, digoxin therapy, treatment with antiarrhythmic agents or any condition or medication that would interfere with interpretation of ST segment changes on the exercise ECG.

The study protocol was approved by the Institutional Review Board and informed written consent was obtained from all patients who participated in this study.

Drug administration. During the 2-week control period (phase I), patients received only sublingual nitroglycerin, 0.4 mg. The angina diaries were reviewed and symptom-limited treadmill exercise testing and 24-h ambulatory ECG monitoring were performed. The patients were then randomized to treatment with either nifedipine or propranolol at the beginning of phase II (Fig. 1). Beginning with 10 mg of nifedipine or 20 mg of propranolol, titration to the *maximal tolerated dose* of medication was performed in double-blind fashion; each patient received two preparations at all times, one of which was a placebo during phase II. At each titration visit, blood pressure and heart rate were measured just before medication and at 15-min intervals for 1 h. If the dose was tolerated without excessive symptoms, change in blood pressure (>20 mm Hg decrease) or heart rate (to <50 beats/min), the patient was instructed to continue to take that dose four times a day. The dose was increased at intervals of 3 to 4 days, as tolerated, to a maximum of 30 mg of nifedipine (120 mg/day) or 80 mg of propranolol (320 mg/day). Pill counts were used to evaluate compliance with the prescribed medications and at least 85% compliance was required for continued participation in the study.

After 3 months of treatment, each patient was again randomized to either continuation of the same single drug plus placebo or to substitution of the other drug for the placebo at the beginning of phase III (Fig. 1). In all patients, dose titration to the maximal tolerated dose was again performed in double-blind fashion at the start of phase III; neither the investigators nor the patient knew whether the placebo from phase II was being retitrated or whether the other active drug had been substituted for the placebo.

Angina diaries. Each patient was given a pocket-sized diary at the start of the study and was instructed to record the time of each anginal episode and the severity of the

episode by checking a box for mild, moderate or severe intensity. Patients were also asked to note the number of nitroglycerin tablets taken, if any, for each episode.

Ambulatory ECG monitoring. Each patient had a 24-h ambulatory (ECG) recording at the end of phase I (control period), phase II and phase III. Patients were encouraged to continue their normal daily activities while wearing the recorder. A model 449B cassette recorder or model 445 reel to reel recorder (both Del Mar Avionics) was applied and standard lead V_5 and an inferior lead were recorded for 24 h; these are accurate in representing ST segment depression.

Analysis of ST segment depression was performed on the Trendsetter II system (Del Mar Avionics) for the cassettes and the Innovator (Del Mar Avionics) for the reel to reel tapes. The ST sample time was set to 60 ms after the J point with manual adjustment on the Innovator for each recording so that the computer measurement corresponded to the true level of ST depression at 0.08 s after the J point on the full disclosure printout of the ECG. Each episode of ST segment depression was defined as ≥1 mm depression from baseline for a duration of at least 1 min and at least 1 min after recovery from a previous episode. Each episode was counted only after confirmation of the changes on a full disclosure printout of the ECG. Correlation between an episode of angina and an episode of ST depression was established by comparing the ST change with the time recorded in the angina diary or that indicated on the tape when the patient pressed the event marker on the tape recorder. A delay of up to 15 min between ST depression and patient notation was considered a symptomatic episode because patients indicated that amount of delay frequently elapsed between the onset of angina and their noting the time in the diary or remembering to push the event marker.

Treadmill exercise testing. Each patient underwent symptom-limited treadmill exercise testing at the end of phase I (control period), phase II and phase III. The baseline for ST segment analysis was established as the level of ST segment observed after 30 s of hyperventilation in the standing position on the treadmill within 1 min before the start of exercise. The Balke-Ware protocol was used and was modified by a 2-min initial stage at 2 mph and 0% grade. Patients exercised to one or more of the following end points: 1) "moderate" angina, defined as the degree of severity of angina at which the patient usually stopped activity; 2) >2 mm ST segment depression; 3) greater than moderate dyspnea; 4) fatigue; 5) decrease in systolic blood pressure >10 mm Hg between any two measurements made at 1-min intervals; or 6) three or more consecutive premature ventricular complexes.

Statistics. The data are expressed as mean values ± SD. For nonnormally distributed samples, the median value is also reported. Analysis of covariance was used to compare the means of normally distributed values. A nonparametric Wilcoxon paired signed-rank test was used to compare the means of nonnormally distributed values. The chi-square test was used to compare the distribution of patients according to the presence or absence of events. A p value ≤ 0.05 was considered significant.

Table 1. Clinical Characteristics of 74 Patients

Age (yr) (mean ± SD)	54 ± 7
Male/female ratio	49/25
NYHA angina class	
I	3 (4%)
II	54 (73%)
III	17 (23%)
History	
Prior MI	46
CABG	10
PTCA	1
Hypertension	29
Coronary artery disease (≥70% stenosis)	
1 vessel	29 (40%)
2 vessel	31 (43%)
3 vessel	12 (17%)
LVEF (mean ± SD)	0.62 ± 0.13

CABG = coronary artery bypass grafting; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angioplasty.

Results

Patient characteristics (Table 1). There were no significant differences in the patient characteristics between the two groups. The patients' age averaged 54 years, left ventricular systolic function was normal in all and most had one- or two-vessel coronary disease.

Despite the double-blind titration, approximately equivalent daily dosages of nifedipine or propranolol were achieved in all groups except for the group that received a combination of nifedipine with propranolol subsequently added. This group tolerated a significantly lower dose of propranolol (Table 2).

Angina diary (Table 3). There was a significant reduction in angina frequency with both nifedipine and propranolol at the end of 3 months of treatment, and this response was sustained at 6 months. Treatment with the combination of nifedipine and propranolol for 3 months did not result in a significant further reduction of angina frequency or nitroglycerin consumption.

Table 2. Average Daily Dose of Study Medication

	Nifedipine (mg/day)	Propranolol (mg/day)
Single drug		
At 3 months	79.3 ± 32.9	250.8 ± 82.6
At 6 months	65.2 ± 25.9	251.4 ± 70
Combination therapy		
Nifedipine with propranolol added	79 ± 30.5	211.1 ± 77.5*
Propranolol with nifedipine added	84.9 ± 34.8	260 ± 83.8

*$p < 0.05$ versus other propranolol doses. All values are mean values ± SD.

Table 3. Effect of Treatment on Angina Frequency and Nitroglycerin Use

	Phase I (control)	Phase II (3 months)	Phase III (6 months)
Angina Frequency (episodes/week)			
Nifedipine	6.3 ± 4.3	4.3 ± 6.4*	2.7 ± 5.6*
Propranolol	7.1 ± 5.8	3.2 ± 6.1*	2 ± 2.3*
Nifedipine + propranolol			4.3 ± 7.9*
Propranolol + nifedipine			1.3 ± 1.7*
Nitroglycerin Use (tablets/week)			
Nifedipine	2 ± 5.7	1.7 ± 5.7	0.7 ± 1.6
Propranolol	3.3 ± 3.1	1 ± 1.3	0.7 ± 1.2
Nifedipine + propranolol			1.1 ± 2.2
Propranolol + nifedipine			0.3 ± 0.4

*$p < 0.05$ versus control.

Treadmill exercise testing. Nifedipine and propranolol treatment for 3 months resulted in significant increases of time to onset of angina and total exercise time (Fig. 2); these responses were sustained after an additional 3 months of treatment. For patients who received nifedipine alone for 3 months, time to onset of angina increased from 199 ± 96 to 286 ± 139 s and this increase was accompanied by an increase in total exercise time from 342 ± 127 to 433 ± 133 s ($p < 0.05$ for both). At 6 months the subset of patients who received nifedipine alone maintained this improvement, with time of onset of angina 304 ± 108 and total exercise time of 433 ± 132 s (both $p < 0.05$ vs. control). For propranolol alone, at 3 months, time to onset of angina increased from 255 ± 139 to 342 ± 116 s and total exercise time from 314 ± 157 to 421 ± 141 s ($p < 0.05$ for both). At 6 months the improvement was sustained at 346 ± 76 s for angina onset and 433 ± 159 s for total exercise time, ($p < 0.05$ vs. control for both). Nifedipine treatment did not alter the rate-pressure product significantly despite the increase in exercise times. However, after 3 months of treatment with propranolol there were significant decreases in rate-pressure product at the onset of angina (from 18,743 ± 5,570 to 13,494 ± 3,229) and at the end of exercise (from 21,237 ± 4,933 to 14,780 ± 3,277), that were also observed at 6 months (Fig. 2). The number of patients who terminated their exercise test because of angina was significantly reduced by administration of nifedipine (from 30 to 22 of 36 patients; $p = 0.04$) but not by propranolol (from 26 to 24 of 38 patients). The number of patients with >1 mm ST segment depression at the end of exercise was not reduced significantly by either nifedipine, (from 22 to 17 of 36 patients) or propranolol (from 28 to 22 of 38 patients).

With the combination of nifedipine and propranolol neither the time to onset of angina nor the total exercise time was significantly different from the value obtained with either drug alone. Treatment with the combination of nifedipine plus propranolol resulted in a time to angina onset of 330 ± 155 s and a total exercise time of 435 ± 144 s, neither of which was significantly different from the value obtained with single drug treatment. The rate-pressure product at the end of exercise was significantly reduced by combination therapy. There was also a significant difference in the number of patients who stopped exercise because of angina (Fig. 3); combination therapy reduced the number of patients who stopped because of angina to 38% compared with 64% with a single drug therapy ($p < 0.05$). There were fewer patients (5 of 19) in the group in which propranolol was added to initial nifedipine therapy who had angina during exercise than in the group in which nifedipine was added to initial propranolol therapy (9 of 17) ($p < 0.05$). The group with propranolol added to nifedipine also had fewer patients who continued to have >1 mm ST segment depression during exercise (3 of 19 vs. 6 of 17).

Twenty-four hour ambulatory ECG (Tables 4 and 5). Technically satisfactory 24-h recordings were available in 52 of the 74 patients. In the first 10 patients studied, our method of recording and analysis was still being developed and the studies were technically incomplete. In another 12 patients, one or another of the recordings was incomplete because of equipment problems or patient failure to keep the electrodes in place. The characteristics of the 52 patients with adequate

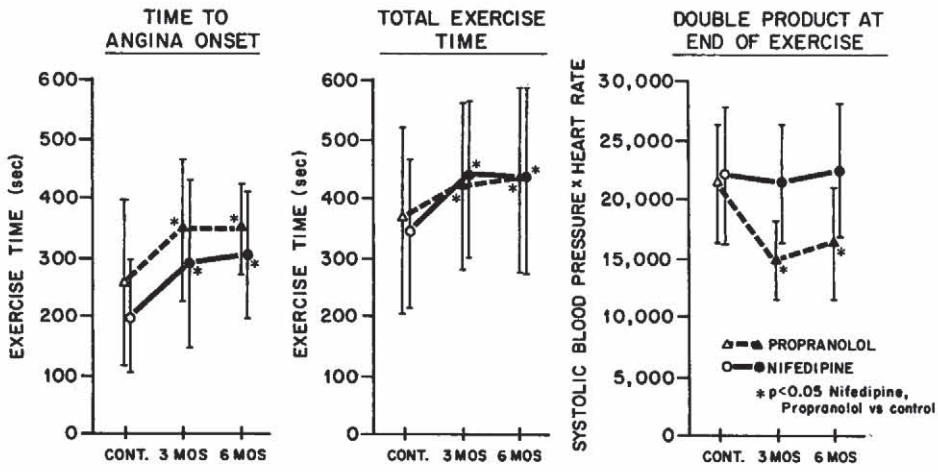

Figure 2. Exercise response to treatment with either nifedipine alone or propranolol alone for 3 and 6 months. Increase in time to onset of angina and total exercise time resulted from either treatment and was sustained at 6 months. Treatment with propranolol but not nifedipine reduced the rate-pressure (double) product at peak exercise. CONT. = control period.

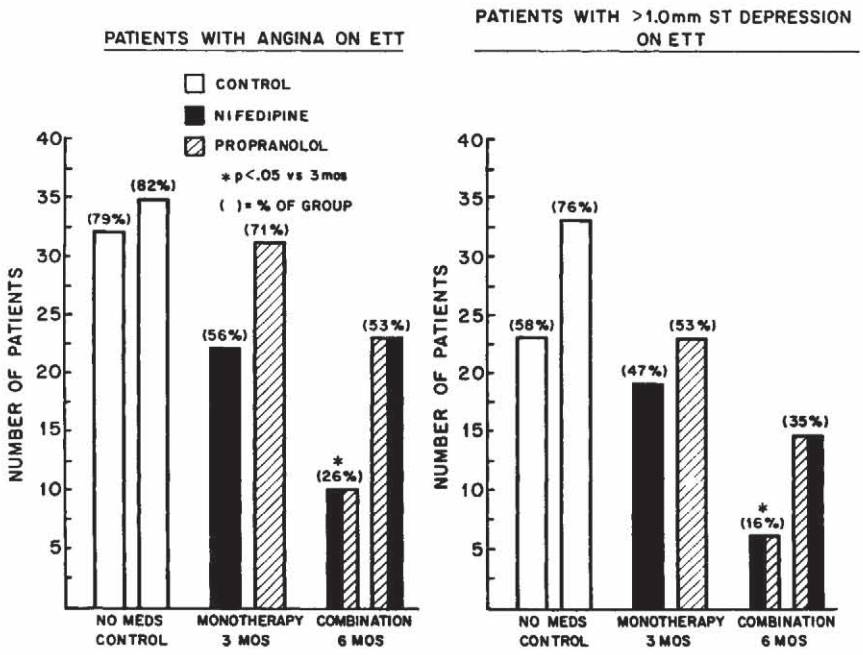

Figure 3. Response of angina and ST segment depression on exercise testing (ETT) to treatment. The group initially treated with nifedipine with subsequent addition of propranolol had a significantly smaller proportion of patients with angina and ≤1 mm of ST depression during exercise testing than did the groups receiving either drug alone or the group receiving nifedipine after treatment with propranolol. MEDS = medications.

records before treatment and at both 3 and 6 months of treatment did not differ from those of the entire cohort.

In the control phase a mean of 2.6 ± 3.9 total episodes/24 h of ST depression were observed (Table 4); these were nearly evenly distributed between painful and silent (or painless) episodes of ischemia. Silent ischemia without painful episodes occurred in 19% of patients. The mean duration of total ischemia, painful ischemia and silent ischemia is indicated in Table 5. The distribution of episodes was not normal for either total, painful or silent episodes; the medians were 1, 0, and 0 episodes/24 h, respectively, and distribution of duration of ischemia was similarly skewed toward absence of ischemia with medians of 3.5, 0 and 0 min/24 h for total, painful and silent ischemia, respectively. Of the 52 patients, 27 (52%) had no evidence of any ischemia, 33 (63%) had no painful ischemia and 29 (56%) had no silent ischemia on 24-h ambulatory ECG during the control phase.

The effect of 3 months of treatment with a single drug on the total number of episodes/24 h of ischemia, painful episodes and silent episodes was a significant reduction ($p < 0.05$ for all) (Table 4). In each category of ischemia, the distribution remained skewed with treatment. Silent ischemia without painful ischemia occurred in 12% of patients. Duration of ischemia/24 h also decreased in all categories (Table 5).

In response to treatment with nifedipine for 3 months, there was a decrease in the number of total, painful and silent episodes of ischemia; but the change was significant only for the reduction in the number of silent ischemic episodes. However, the decrease in the duration of ischemia was significant for each category (Table 5). Nifedipine increased the number of patients who were entirely free of both painful and silent ischemia and increased the number of patients with fewer episodes (Fig. 4; Table 4). In all, 65% had no ischemia, 81% had no painful ischemia on 24-h ECG and 77% had no silent ischemia.

Treatment with propranolol for 3 months also resulted in

Table 4. Episodes of Ischemia on Ambulatory ECG Monitoring (no./24 h)

	Total Episodes		Painful Episodes		Silent Episodes	
	Mean ± SD	Patients With None	Mean ± SD	Patients With None	Mean ± SD	Patients With None
Control period	2.6 ± 3.9	52%	1.4 ± 2.4	63%	1.1 ± 2.7	56%
3 months						
Single drug	0.7 ± 1.4*	71%*	0.4 ± 1.2*	85%*	0.3 ± 1.4*	81%*
Nifedipine	0.8 ± 1.4	65%	0.4 ± 1.1	81%	0.3 ± 0.8*	77%*
Propranolol	0.6 ± 1.5	77%	0.3 ± 1.2*	88%*	0.3 ± 0.7*	85%
6 months						
Single drug	0.7 ± 1.9*	77%	0.5 ± 1.8*	89%	0.2 ± 0.4	81%
Combination	0.5 ± 1.4*	85%	0.04 ± 0.4*†	96%	0.5 ± 1.3*	85%

*$p < 0.05$ versus control period; †$p < 0.05$ versus phase II (after 3 months of treatment with a single drug).

Table 5. Duration of Ischemia on Ambulatory ECG Monitoring (min/24 h)

	Total Episodes	Painful Episodes	Silent Episodes
Control period	33 ± 61	17 ± 51	16 ± 25
3 months			
Single drug	9 ± 22*	6 ± 20*	3 ± 11*
Nifedipine	16 ± 35*	7 ± 20	9 ± 31*
Propranolol	7 ± 21*	3 ± 14*	4 ± 14*
6 months			
Single drug	9 ± 34*	7 ± 34*	1 ± 3*
Combinaton	3 ± 10*	0.1 ± 0.6*†	3 ± 10*

*$p < 0.05$ versus control period; †$p < 0.05$ versus phase II (3 months). All values are mean ± SD.

a decrease in number of total, painful and silent episodes of ischemia (Table 4). The reduction in duration of all ischemia, as well as the duration of painful and painless ischemia, were significantly reduced by propranolol (Table 5). Propranolol treatment also increased the number of patients with no episodes of ischemia to 77% (Fig. 4; Table 4) and increased to 88% and 85%, respectively, the number who were free of painful or painless ischemia.

At the end of 6 months in the study, patients who were receiving the combination of nifedipine and propranolol maintained a decreased number of episodes and a shorter duration of total, painful and silent ischemia (Fig. 4; Tables 4 and 5) compared with observations in the control period. Continued treatment for the second 3 additional months with a single drug resulted in no further change in ischemia during ambulatory ECG monitoring. There was a small further reduction with combination treatment compared with treatment with a single drug in total episodes of ischemia and painful ischemia. Silent ischemia without painful episodes occurred in 12% of patients. Painful ischemia was nearly eliminated by combination treatment and the remaining ischemia was nearly all silent ischemia. At the end of 3 months of treatment with the combination of nifedipine and propranolol, 22 (85%) of the 26 patients had no episodes of ischemia, 96% had no episodes of painful ischemia and 85% had no episodes of silent ischemia during the 24 h of ambulatory ECG monitoring.

Cardiovascular events. During the 6-month study period, untoward cardiovascular events (death, nonfatal myocardial infarction, revascularization procedure) did not occur in any patient.

Discussion

Response to nifedipine and propranolol treatment. In this study, patients had a significant reduction in angina frequency with either nifedipine or propranolol treatment for up to 6 months; the responses to therapy were quite constant over 6 months. These were predominantly patients with mild angina based on their New York Heart Association angina class; most had one- or two-vessel coronary disease and all had normal left ventricular systolic pump function. Although a frequency of angina of 6.3 to 7.1 episodes/week seems high, it was recorded during the 2nd week of a 2-week period when all prophylactic antianginal medications had been withdrawn. Performance during exercise testing was also improved by either nifedipine or propranolol treatment, with an increase in time to onset of angina and total exercise time. Combination therapy produced additional benefit only as measured by a reduction in the number of patients having angina and >1 mm ST depression during exercise and a reduction in painful ischemia on ambulatory ECG monitoring. Silent ischemia was not very common before treatment and it responded to treatment with either nifedipine or propranolol alone and followed the same course as painful

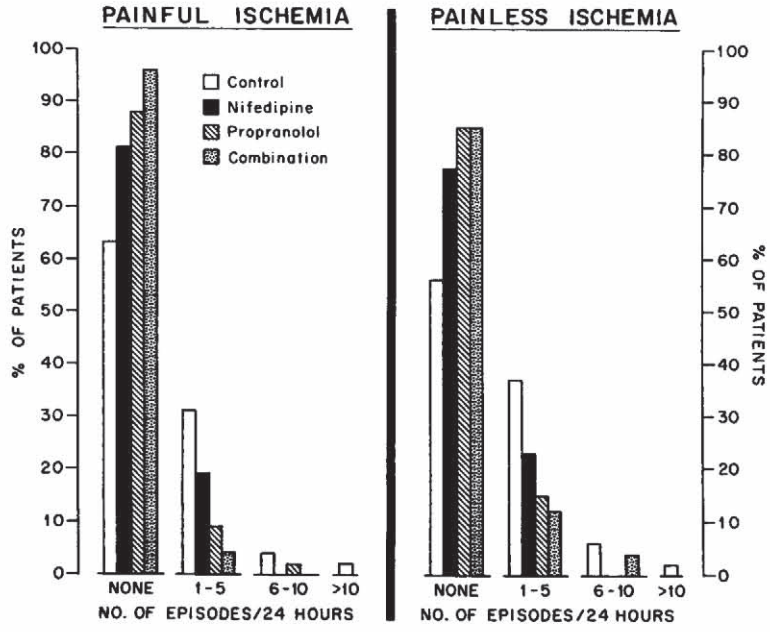

Figure 4. Changes with treatment in the distribution of patients according to the number of episodes of painful (**left panel**) or silent (**right panel**) myocardial ischemia on 24-h ambulatory electrocardiographic monitoring. Treatment increased the number of patients with no, or few, episodes of painful or silent ischemia.

ischemia. Although combination treatment was effective in reducing angina in the ambulatory setting, it was no more effective than a single drug in reducing silent ischemia.

Comparison with previous studies. Previous comparisons of the efficacy of calcium-channel blockers and beta-adrenergic blockers in the treatment of angina have evaluated fixed dose therapy after a period of usually 1 to 6 weeks and occasionally as long as 3.5 months (1–23). The present study clearly demonstrates that a decrease in angina frequency and an increase in both time to onset of angina and total exercise time resulted from treatment with either nifedipine alone or propranolol alone for 3 months. It further shows that over a long term this benefit is sustained after 6 months of treatment with either drug alone.

However, our study differed from previous investigations of nifedipine combined with propranolol in that fixed doses were not used and the drugs in all patients were titrated to their maximally tolerated dose in a manner analogous to a clinical strategy aimed at angina elimination. To our knowledge ours is the only efficacy study to include such a titration in a double-blind fashion in comparing nifedipine and propranolol and their combination. The paucity of data in this area has recently been noted (25). As expected, side effects were frequently observed and frequently precluded patients from achieving additional doses of medication. We also found that patients already receiving their maximally tolerated dose of nifedipine were generally not able to take as high a dose of propranolol as that taken by the other groups initially treated with propranolol. However, the nifedipine dose tolerated by those already receiving propranolol did not differ from the dose in patients who received nifedipine only. The deleterious effect of beta-blockers, especially in high doses when combined with verapamil (2), diltiazem (13) and nifedipine (16,20) in patients with left ventricular systolic dysfunction, is well described. However, in patients with stable angina and normal or mildly abnormal left ventricular function at rest, the addition of nifedipine to a beta-blocker may result in minimal or no change at rest and may prevent an exercise-induced decrease in ejection fraction (20,26). A prolongation of exercise duration has been observed in patients with angina when nifedipine is combined with propranolol (14) or metoprolol (17). In another study (8), in which results were similar to ours, an improvement in exercise tolerance in patients with severe angina was achieved when nifedipine was combined with a reduced dose of propranolol (one-half the dose required for full beta-blockade) even though a lesser response was achieved when the combination included the full dose of propranolol.

There appear to be no previous studies that have investigated the effects or significance of the dosing sequence when combination therapy is instituted. In our patients with essentially normal left ventricular systolic function and predominantly mild coronary disease (one- or two-vessel disease) who had propranolol added to nifedipine and whose dose of propranolol happened to be lower than that of the other group receiving combination therapy, a significant further reduction in symptoms and signs of ischemia on exercise was also observed. It is possible that concomitant administration of a beta-blocker with nifedipine may influence the effective level of nifedipine and that patients already receiving a maximal tolerated dose of nifedipine may therefore tolerate addition of propranolol poorly. Such a drug interaction was recently reported in studies of the combination of nifedipine with diltiazem (27,28).

Effect on hemodynamic variables. The hemodynamic alteration resulting from the combination of nifedipine and propranolol resembled that of propranolol alone. The rate-pressure product at the onset of angina and at the end of exercise, as well as the change from rest for both of these variables, was less in those patients who received propranolol either alone or in combination. The sequence of drug dosing was not important with regard to rate-pressure product because similar reduction was observed at peak exercise for either group treated with combination. A similar lack of effect on rate-pressure product was observed in a previous study (9) of patients with severe angina using fixed combinations of 30 mg/day of nifedipine and 240/day of propranolol and 60 mg/day of nifedipine and 480 mg/day of propranolol although a reduction in induced ST depression was achieved. Our study using treadmill testing suggests that a similar effect occurs with variable individualized dosing.

Effect on ischemia. Our study is also in agreement with previous studies in which the combination of nifedipine and propranolol resulted in improvement in markers of ischemia without a clear increase of exercise duration. The previous findings suggest that combination therapy using fixed dosages of nifedipine and propranolol, the latter at doses producing beta-blockade or at maximally tolerated dosages, may not be expected to increase exercise duration (7,11). However, results may be different when nifedipine is combined with other beta-blockers (17,26). In our study, treatment with maximally tolerated dosages of nifedipine and propranolol in combination resulted in further reduction of exercise-induced ST depression over that achieved by a single drug without an increase in exercise duration and also a reduction to near elimination of painful ST depression on ambulatory ECG monitoring. These results are encouraging for the clinical strategy of titrating medication dosage against symptoms.

Role of 24-h ECG monitoring. The low level of pretreatment ischemia detected on 24-h ambulatory ECG recordings in our study group is somewhat striking and has been observed (29–32) in other similar groups of patients with documented coronary disease who are asymptomatic or have mild angina. In particular, in a careful study (31) of ambulatory ECG monitoring in 42 patients, 79% of whom were in New York Heart Association class I or II (versus 77% in our study), a mean of 6.3 ± 0.45 total episodes of ischemia/24 h with a mean total duration of 55.2 ± 7.1 min was observed. The slightly milder coronary disease of our study patients (83% with one- or two-vessel disease vs. 53% in that report) may be related to the slightly lower total

number of episodes (3 ± 4.3/24 h) and duration (41 ± 69 min/24 h) of ischemia that we observed in our patients. These findings suggest that 1) a low frequency and duration of ischemia are related to both milder angina and lesser coronary disease; 2) in these patients, treatment with either nifedipine or propranolol controls silent ischemia when it controls painful ischemia; and 3) symptoms and severity of coronary disease are important factors to consider when comparing treatment responses of ischemia on ambulatory ECG studies.

Silent ischemia. It has also been suggested that in patients with no symptoms but with significant coronary disease, a significant percentage may be expected to have no evidence of ischemia on 24 h or even 48 h of ambulatory ECG monitoring (29). In one study, up to 40% of patients (56% of untreated patients) with chronic stable angina, a positive exercise test and angiographically documented coronary artery disease had no episodes of ischemia on 48 h of monitoring (31). Of the 52 patients we studied with 24-h ECG monitoring, 52% had no evidence of ischemia during the control phase and this percent increased to 71% and 77% at the end of 3 and 6 months, respectively, of treatment with a single drug. In our patients, during treatment with either nifedipine or propranolol, we observed a reduction of silent ischemia to a very low level of 0.3 ± 0.8 and 0.3 ± 0.7 episodes/24 h, respectively; the change with each drug was statistically significant. We found no significant further reduction below this low level with the combination of nifedipine and propranolol. The clinical significance of the persistence of such a low level of silent ischemia on ambulatory ECG monitoring in treated patients remains to be established. Furthermore, in our patients, silent ischemia occurred independently of painful ischemia in only a small percent of patients: 19% of patients in the control phase and 12% of patients after treatment with single drug or their combination.

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