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A Dose-Ranging, Placebo-Controlled, Double-Blind Trial of Nisoldipine in Effort Angina: Duration and Extent of Antianginal Effects

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Maximal treadmill exercise testing at 1, 3 and 8 hours was used to assess the onset, duration and antianginal efficacy of the dihydropyridine slow channel calcium-blocking agent, nisoldipine, in an oral dose range of 5, 10 and 20 mg. A double-blind, randomized, placebo-controlled design was used involving 12 patients with stable effort angina. Exercise tolerance was significantly increased 3 hours after each dose, when the maximal beneficial effect occurred. The improvement was observed as early as 1 hour after the 10 and 20 mg dose, and persisted for 8 hours after the 20 mg dose. At 3 hours, the onset of an exercise-induced ST segment depression of 0.1 mV or greater was increased by 62 ($p < 0.05$), 75 ($p < 0.01$) and 117 seconds ($p < 0.01$) with the 5, 10 and 20 mg dose of nisoldipine, respectively, compared with placebo. Similarly, time to onset of angina was significantly increased. The sum of exercise-induced ST segment depression at peak exercise was significantly decreased ($p < 0.05$) from 8.7 ± 2.3 to 6.7 ± 1.8 and 6.4 ± 2.0 mm, respectively, after the 10 and 20 mg dose of nisoldipine. The rate-pressure product was significantly greater with nisoldipine than with placebo at the onset of ischemia and at peak exercise (22.8 ± 1.1 versus 20 ± 1.4 × 10^3 U for the 20 mg dose; $p < 0.01$).

Thus, nisoldipine is an effective antianginal agent with a rapid onset of action that improves exercise tolerance, increases angina threshold and persists for at least 8 hours after oral dosing.

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Several well designed studies have shown that slow channel calcium-blocking drugs are effective antianginal agents in the medical management of both obstructive (1–9) and vasospastic coronary artery disease (1–4,10–12). Within the dihydropyridine class of calcium channel blockers, nifedipine has been the prototypical agent whose beneficial cardiovascular effects in clinical and experimental myocardial ischemia have been extensively documented. The clinical efficacy of nifedipine as an antianginal drug when used alone (1–5,10–14) or in combination with a beta-receptor blocking agent (15–17) has also been demonstrated. Nifedipine has been shown to exert favorable effects on the myocardial oxygen demand and supply relation (14,15,18–20), thereby decreasing myocardial ischemia during exercise.

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Nisoldipine, a dihydropyridine slow channel calcium blocker, is structurally similar to nifedipine, and has been shown to have a longer-lasting antihypertensive action (21) and to be a more potent coronary vasodilator than nifedipine in animal studies (22–26). However, little is known of its effective oral dose in human beings, its efficacy as an antianginal drug and the duration of its cardiovascular effects. In this dose-ranging study, we compared the relative efficacy of a 5, 10 and 20 mg oral dose of nisoldipine on treadmill exercise test and hemodynamic variables. The onset and duration of action were determined by three maximal exercise tests performed at 1, 3 and 8 hours after oral drug ingestion.

Methods

Patients. Twelve patients, with a mean age of 58 years (range 46 to 66), with stable angina pectoris were studied. All had reproducible exercise-induced angina with an associated horizontal or downsloping ST segment depression of 0.1 mV or greater for at least 0.08 second after the J point at the baseline prerandomization exercise test. Ten

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patients were in Canadian Cardiovascular Society (27) angina class 2 and two were in functional class 3. Three patients had a previous myocardial infarction and one patient had prior coronary bypass surgery. Patients who had a history of predominant rest angina or ST segment elevation during an episode of chest pain were excluded from the study as were patients who had severe hypertension, valvular heart disease, congestive heart failure, intraventricular conduction disturbances or severe ventricular arrhythmias on the electrocardiogram at rest. All 12 patients had a fixed coronary stenosis (70% or greater narrowing of luminal diameter) at coronary angiography; 4 patients had one vessel disease, 4 had two vessel disease and the remaining 4 had three vessel disease. The left ventricular contraction pattern was normal in six patients. The other six patients had wall motion abnormalities: five had hypokinesia and one had anterolateral akinesia. The ejection fraction was less than 0.50 in one patient.

Exercise protocol. All cardiovascular medications were stopped at least 48 hours before the study with the exception of sublingual nitroglycerin. The patients refrained from smoking and drinking coffee or tea, and had not taken nitroglycerin within 8 hours of the exercise test. Each patient had had at least two exercise tests before entering the study and was familiar with the test environment.

The drugs were given orally at 8:00 AM and the exercise test was performed at 9:00 AM, 11:00 AM and 4:00 PM. A modified Naughton treadmill exercise protocol (28) was performed; 15 electrocardiographic leads were recorded during and after exercise as previously described (29,30). End points for terminating exercise were severe angina, dyspnea or extreme fatigue. Blood pressure, heart rate and the electrocardiogram were recorded each minute during exercise and for 10 minutes after exercise. The electrocardiogram was recorded every 20 seconds at the onset of junctional ST segment depression to determine as precisely as possible the onset of 0.1 mV of horizontal or downsloping ST segment depression.

Study protocol. This was a double-blind, placebo-controlled, randomized study comparing the short-term effects of a 5, 10 or 20 mg dose of oral nisoldipine on hemodynamic and treadmill exercise test variables. The exercise tests were performed at 1, 3 and 8 hours after oral drug ingestion, followed by a 48 to 72 hour washout period after each trial of drug therapy. The series of tests, involving 4 study days per patient, were completed within 2 weeks for each patient. Treatment codes were not known until after completion of the study. Informed consent was obtained from each patient before entry into the study.

Statistical analysis. The differences between the effects of placebo and the 5, 10 and 20 mg doses of oral nisoldipine at 1, 3 and 8 hours after ingestion were analyzed by a two-way analysis of variance. Intergroup differences were studied using a paired *t* test. All values are expressed as mean ± SEM. The data presented in the results are 3 hour data unless otherwise stated.

Results

No significant differences from baseline value were observed in heart rate, systolic blood pressure and rate-pressure product measured at 1, 3 or 8 hours after placebo ingestion. Similarly, the time to onset of 0.1 mV ST segment depression, time to onset of angina, peak exercise duration and extent of ST segment depression at peak exercise were not significantly different 1, 3 and 8 hours after placebo ingestion.

Rest. Three hours after placebo ingestion, the heart rate was 66 ± 3 beats/min. The heart rate response was similar (68 ± 3 beats/min) after the nisoldipine dose of 5 mg, but was significantly increased by 8 and 7 beats/min after the 10 and 20 mg dose, respectively ($p < 0.01$) (Table 1).

Systolic blood pressure was 130 ± 4 mm Hg after placebo ingestion, and decreased by 8 (p = NS), 11 ($p < 0.05$) and 14 mm Hg ($p < 0.01$) 3 hours after 5, 10 and 20 mg of nisoldipine, respectively. The systolic rate-pressure product after each dose of nisoldipine did not differ from that after placebo as a result of the directionally opposing change in systolic blood pressure and heart rate.

Submaximal exercise. Submaximal exercise heart rate (after 3 minutes of exercise) after placebo was 88 ± 4 beats/min and did not change significantly after 5, 10 or 20 mg of oral nisoldipine (89 ± 3, 92 ± 4 and 92 ± 3 beats/min, respectively).

Systolic blood pressure after placebo was 146 ± 5 mm Hg, and decreased by 7, 17 and 12 mm Hg after 5, 10 and 20 mg of nisoldipine, respectively (p = NS). As at rest, the directionally opposite changes in systolic blood pressure and heart rate resulted in no significant change in the rate-pressure product with all three drug doses compared with placebo.

Onset of ischemia. The time to onset of exercise-induced horizontal or downsloping ST segment depression of 0.1 mV or greater was significantly prolonged by all three doses of nisoldipine 3 hours after oral ingestion. The response was dose-related (Fig. 1). Compared with placebo, the increase in exercise time was greatest after the 20 mg dose (+117 seconds, $p < 0.01$), less with the 10 mg dose (+75 seconds, $p < 0.01$) and least with the 5 mg dose (+62 seconds, $p < 0.05$).

The rate-pressure product at the onset of ischemia was significantly greater only with the 20 mg dose of nisoldipine than with placebo (19.4×10^3 U ± 1.3 versus 16.2×10^3 U ± 0.8, $p < 0.01$). The increase was primarily related to increased heart rate with no significant change in systolic blood pressure.

Exercise-induced angina pectoris was abolished in two patients. In both, peak exercise duration was used to calculate mean exercise time to angina. The mean exercise time to angina was significantly increased at each drug dose

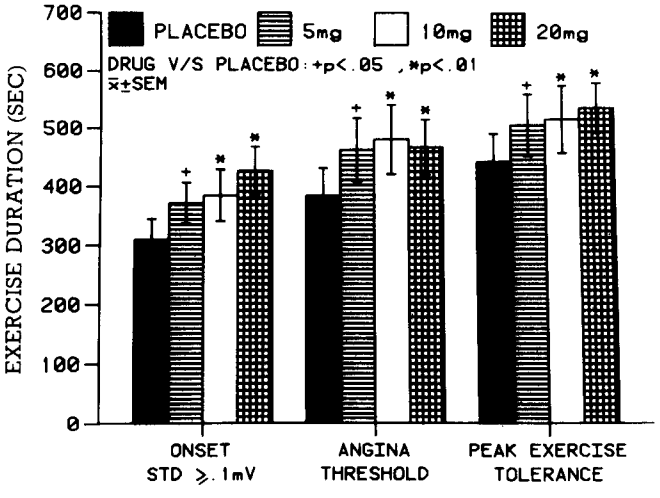
Table 1. Comparison of Nisoldipine, 5, 10 and 20 mg, With Placebo in 12 Patients at 3 Hours After Oral Ingestion

		Nisoldipine			Level of Significance (interdrug comparison)		
	Placebo	5 mg	10 mg	20 mg	5 to 10 mg	5 to 20 mg	10 to 20 mg
Heart rate (beats/min)							
At rest	66 ±3	68 ± 2	74 ± 4†	73 ± 3‡	<0.05	NS	NS
Submax. exercise	88 ± 4	89 ± 3	92 ± 4	92 ± 3	NS	NS	NS
Onset ST ≥ 0.1 mV	103 ± 4	109 ± 6*	113 ± 5†	121 ± 6‡	NS	0.01	0.01
Max. exercise	117 ± 6	130 ± 8*	131 ± 7‡	138 ± 5‡	NS	0.05	0.05
Systolic BP (mm Hg)							
At rest	130 ± 4	122 ± 4	119 ± 4*	116 ± 4†	NS	NS	NS
Submax. exercise	146 ± 5	139 ± 5	129 ± 9	134 ± 4	NS	NS	NS
Onset ST ≥ 0.1 mV	157 ± 4	157 ± 5	155 ± 6	159 ± 4	NS	NS	NS
Max. exercise	171 ± 5	170 ± 6	168 ± 6	168 ± 4	NS	NS	NS
Rate-pressure product ($\times 10^3$ U)							
At rest	8.5 ± 0.4	8.4 ± 0.3	8.9 ± 0.6	8.4 ± 0.4	NS	NS	NS
Submax. exercise	12.8 ± 0.7	12.3 ± 0.6	12.4 ± 0.5	12.2 ± 0.5	NS	NS	NS
Onset ST ≥ 0.1 mV	16.2 ± 0.8	17.1 ± 1.0	17.6 ± 1.0	19.4 ± 1.3†	NS	0.05	0.05
Max. exercise	20.0 ± 1.4	22.1 ± 1.7*	22.1 ± 1.5*	22.8 ± 1.1‡	NS	NS	NS
Max. Σ ST depression (mm)	8.7 ± 2.3	8.6 ± 2.4	6.7 ± 1.8*	6.4 ± 2.0*	0.05	0.05	NS
Time to onset ST depression ≥ 0.1 mV (seconds)	310 ± 35	372 ± 35*	385 ± 44‡	427 ± 41‡	NS	0.05	NS
Time to angina (seconds)	385 ± 47	463 ± 55*	481 ± 60†	467 ± 48‡	NS	NS	NS
Max. work load (seconds)	442 ± 48	505 ± 54*	515 ± 59‡	535 ± 44†	NS	NS	NS

Values are mean ± SEM. Placebo vs. drug: *p < 0.05; †p < 0.01; ‡p < 0.001. BP = blood pressure; Max. = maximal; NS = not significant; Submax. = submaximal; Σ = sum.

compared with placebo, the increase being 78 (p < 0.05), 96 (p < 0.01) and 82 seconds (p < 0.01) with the 5, 10 and 20 mg dose, respectively.

Figure 1. The time to onset of exercise-induced ST segment depression (STD) of 0.1 mV or greater, angina threshold and peak exercise work load were significantly increased 3 hours after nisoldipine ingestion. The increase was significant in each dose range. V/S = versus.



The rate-pressure product at angina threshold was increased by each drug dose. The increase was significant only at 3 hours and was 2.1 × 10^3 (p < 0.05), 2.6 × 10^3 (p < 0.05) and 1.9 × 10^3 U (p < 0.05) with the 5, 10 and 20 mg dose of nisoldipine.

Maximal exercise. Peak exercise tolerance was prolonged by each drug. The response was dose-related with the 20 mg dose resulting in the greatest increase in exercise duration of 93 seconds (p < 0.01); the 5 and 10 mg dose produced an increase of 63 (p < 0.05) and 73 (p < 0.01) seconds, respectively (Fig. 2).

The relative tachycardia induced by nisoldipine at rest was maintained throughout the exercise period, with an average heart rate increase of 13, 14 and 18 beats/min (p < 0.01) for the 5, 10 and 20 mg dose, respectively. Systolic blood pressure was unchanged compared with that of placebo. Consequently, the respective increase in rate-pressure product of 2.1 × 10^3 (p < 0.05), 2.1 × 10^3 (p < 0.05) and 2.8 × 10^3 U (p < 0.01) at peak exercise for the 5, 10 and 20 mg dose was mainly due to the increase in heart rate (Table 1). The augmentation of heart rate and rate-pressure product at peak exercise was associated with an increased work performance.

The sum of ST segment depression in the 15 electrocar-

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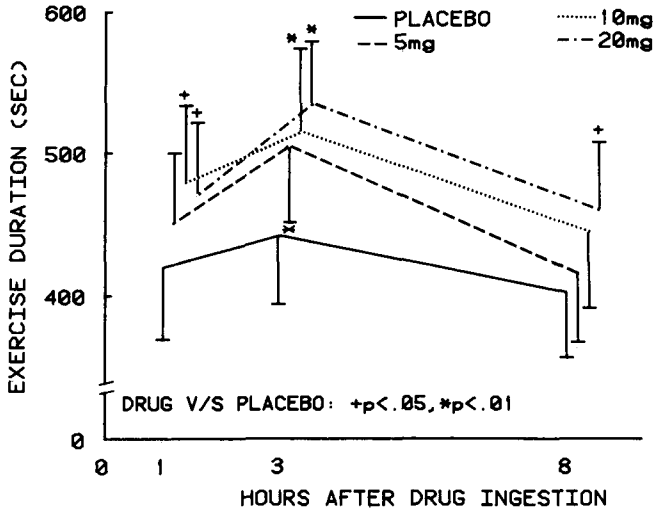


Figure 2. The maximal increase in exercise tolerance (exercise duration) occurred at 3 hours. The benefit was dose-related and occurred as early as 1 hour after 10 to 20 mg of nisoldipine and persisted for 8 hours after 20 mg of nisoldipine administration. V/S = versus.

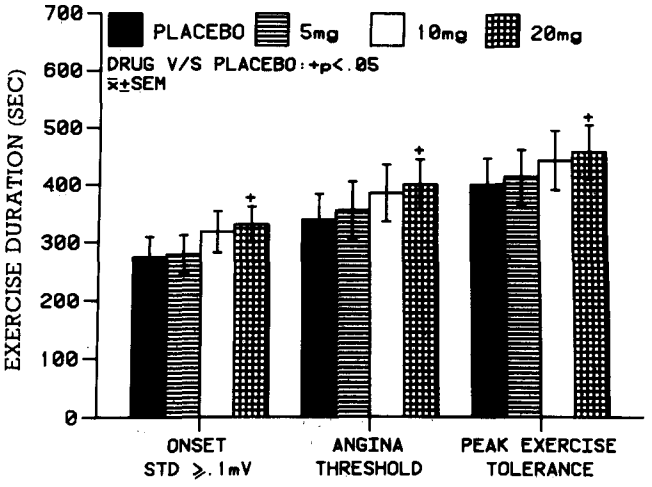
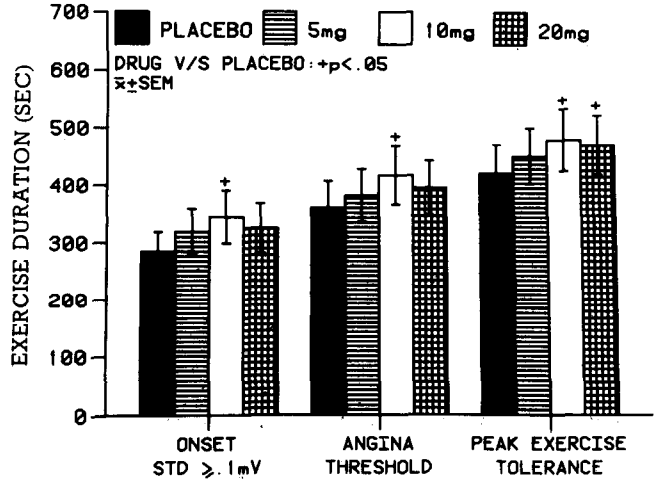


Figure 4. Eight hours after nisoldipine administration, only the 20 mg dose had a persistent beneficial antianginal effect. $\bar{x}$ ± SEM = mean ± standard error of the mean; other abbreviations as in Figure 3.

diographic leads at peak exercise was significantly less after the administration of 10 and 20 mg of nisoldipine than with placebo ($p < 0.05$) (Table 1). However, 3 hours after the drug was taken, conversion to a negative electrocardiogram (ST segment depression <0.1 mV in any lead) did not occur in any patient.

Temporal drug effect. The effect of the 5 mg dose of nisoldipine on heart rate, systolic blood pressure and rate-pressure product at rest was not significantly different from the effect of placebo 1, 3 and 8 hours after drug ingestion.

Figure 3. One hour after nisoldipine administration, the time to onset of exercise-induced ST segment depression (STD) of 0.1 mV or greater and angina threshold were significantly increased after the 10 mg dose. Peak exercise tolerance (exercise duration) was significantly ($p < 0.05$) improved by the 10 and 20 mg dose. V/S = versus.



The 10 mg dose of nisoldipine significantly increased heart rate compared with placebo to a similar degree 1 and 3 hours after administration although the effect was largely dissipated at 8 hours. The significant increase in heart rate and decrease in systolic blood pressure observed at 3 hours after the 20 mg dose of nisoldipine remained significantly different from the values with placebo 8 hours after drug administration although the magnitude of change was less marked.

Improvement in peak exercise duration was maximal at 3 hours for each dose of nisoldipine (Fig. 2) and was dose-related, with the 20 mg dose producing the greatest benefit. The onset of action occurred as early as 1 hour (Fig. 3) after drug ingestion and lasted for 8 hours after the 20 mg dose was ingested (Fig. 4). The 5 mg dose was ineffective at 1 and 8 hours.

In contrast to the 3 hour results, the sum of ST segment depression in the 15 electrocardiographic leads at peak exercise was similar to values with placebo at 1 and 8 hours for each dose of nisoldipine.

Discussion

Nisoldipine, a new dihydropyridine slow channel calcium blocker, has been shown in experimental animals (23–26) to have a longer duration of antihypertensive action and to be a more potent coronary vasodilator with less negative inotropic properties than its structural analog, nifedipine. Thus, nisoldipine may have the potential to be a useful antianginal agent. However, there is little documentation of either its clinical efficacy as an antianginal agent in human beings or its effective oral dose and duration of action.

Effect on test exercise variables. In this placebo-controlled, double-blind, randomized study, we have shown

that after oral administration of a single dose, nisoldipine produced a significant improvement in exercise tolerance in patients with stable effort angina and angiographically documented obstructive coronary artery disease. The improvement in exercise tolerance was indicated not only by a significant prolongation of the time to onset of angina and abolition of exercise-induced angina in two patients, but also by a significant increase in peak exercise capacity and a delayed appearance of electrocardiographic signs of myocardial ischemia. The salutary effects on exercise test variables were noted as early as 1 hour after oral administration of a single 10 or 20 mg dose; no significant effects were noted with the 5 mg dose. Maximal drug efficacy was noted at 3 hours after drug ingestion in a dose-related manner with the 20 mg dose having the most beneficial effect. Improvement in exercise variables were significant for 8 hours after the 20 mg dose only.

Hemodynamic effect. The hemodynamic effects included an 11% increase in heart rate at rest, similar to that previously reported (22). The tachycardia effect was evident as early as 1 hour and still present at 3 hours but not observed at 8 hours after drug ingestion. Systolic blood pressure decreased by approximately 10%, within the range of previously reported values (22). The decrease was noted at 3 hours and persisted to 8 hours for the 20 mg dose, supporting previous observations in dogs of an antihypertensive effect lasting up to 12 hours after oral drug usage (21). The decrease in blood pressure was not evident during exercise even when there was a persistent tachycardia effect.

The hemodynamic effect as well as the improvement in exercise variables at 8 hours after a 20 mg dose of nisoldipine are in contrast to previously reported effects of a 20 mg dose of nifedipine using a similar protocol (5) in which the latter produced no discernible benefit at 8 hours after oral dosing. This may be a clinically significant observation, in that nisoldipine may require less frequent dosing to maintain a beneficial antianginal effect. Comparison of the two drugs in the same patient group would be of interest. The results of this short-term dose study may not be extrapolated to long-term therapy in which the possibilities of drug accumulation, tolerance and interactions may play a role.

Antianginal mechanism. High-dose nisoldipine decreased systolic blood pressure and increased heart rate without changing rest or submaximal rate-pressure product. The constancy of the rate-pressure product, an indirect measure of myocardial oxygen demand (31), at rest and during submaximal exercise suggests that reduction of myocardial oxygen demand is not the only mechanism of action of this drug. The delayed appearance of myocardial ischemia and prolonged exercise capacity (Fig. 1), both accompanied by a higher rate-pressure product, suggests that the predominant antianginal mechanism of nisoldipine may be to increase coronary blood flow to potentially ischemic myocardium. This hypothesis is supported by the fact that electrocardiographic manifestations of exercise-induced myocardial ischemia were significantly decreased at higher peak work loads, and by other data which have shown an increase in total as well as collateral coronary blood flow to ischemic myocardium in experimental animals pretreated with nisoldipine (22,26). The mechanisms of action are similar to nifedipine (18–20), although nisoldipine is reported to be a more potent and selective coronary vasodilator (22,23,26).

Clinical implications. Nisoldipine is an effective antianginal drug. Longer-term studies are required to document its long-term efficacy and safety and to evaluate its beneficial effects relative to beta-receptor blockers and other slow channel calcium blockers. It would appear from this short-term dose study that 10 to 20 mg of nisoldipine may be necessary to produce an "optimal" antianginal effect and that the drug will not require more than two or three doses daily. The antianginal benefit of nisoldipine would most likely be potentiated by the use of beta-adrenergic blocking drugs that would blunt the reflex tachycardia induced by this dihydropyridine derivative.

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