Once- and Twice-daily Nitrendipine in Patients with Hypertension and Noninsulin-dependent Diabetes

Timothy C. Fagan, M.D., Edward B. Nelson, M.D., Kenneth C. Lasseter, M.D., James Crook, M.D., John Morledge, M.D., and Kenneth A. Conrad, M.D.

One hundred and six patients with uncomplicated mild to moderate essential hypertension received nitrendipine 10 mg twice a day or 20 mg once a day in a double-blind, randomized design. At the end of the dosing interval, supine and standing blood pressures were lowered 6/4 and 6/3 mm Hg respectively with the former regimen, and 2/3 mm Hg with the latter. In 10 patients, blood pressure variability through the dosing interval was not increased by nitrendipine 10 mg twice daily, but in another 10, 20 mg daily increased the variability by 28% compared to placebo. Significantly more patients had adverse effects with 20 mg daily than 10 mg twice daily; and both regimens caused more side effects than placebo. In 20 patients, serum glucose levels did not change significantly during treatment with nitrendipine, but in 10 of those with noninsulin-dependent diabetes, the range of maximum plasma insulin in response to a high-carbohydrate meal was 7 times as great during treatment with nitrendipine as it was during treatment with placebo. Nitrendipine lowers blood pressure when given once or twice daily, but twice-daily administration appears to be better tolerated.
(Pharmacotherapy 1986;6(3):128–136

Nitrendipine is an investigational, dihydropyridine, calcium-channel–blocking agent with arterial vasodilating properties. Our multicenter study was designed to compare the efficacy and safety of nitrendipine 20 mg/day divided into 1 or 2 daily doses as antihypertensive monotherapy in patients with uncomplicated mild to moderate essential hypertension. A daily dose of 20 mg was chosen because preliminary studies suggested that it was generally well tolerated and produced a measurable antihypertensive effect. A secondary objective was to examine the time course of blood pressure from the end of one dosing interval through the first 9 hours of the next dosing interval in a subgroup of 20 patients. A third objective was to examine the effects of nitrendipine on the response of plasma insulin and serum glucose levels to a standard meal containing a high percentage of its calories as simple carbohydrates in the same subgroup of 20 patients, 10 with and 10 without noninsulin-dependent diabetes mellitus.

From the Departments of Medicine and Pharmacology (Dr. Fagan, Dr. Conrad), University of Arizona College of Medicine, Tucson; Department of Medicine, Baylor College of Medicine, Houston, Texas (Dr. Nelson); Clinical Pharmacology Associates, Inc., Miami, Florida (Dr. Lasseter); Department of Medicine, Medical College of Wisconsin V.A. Medical Center, Milwaukee (Dr. Crook); and Jackson Clinic and Foundation, Madison, Wisconsin (Dr. Morledge).

Address reprint requests to Timothy C. Fagan, M.D., General Internal Medicine Section, University of Arizona College of Medicine, Arizona Health Sciences Center, 1501 North Campbell Avenue, Tucson, AZ 85724.

This work was supported in part by a grant from Miles Pharmaceuticals, West Haven, CT.

This paper was presented in part at the cardiovascular pharmacotherapy international symposium, Geneva, Switzerland, April 1985.

Methods

Patient Enrollment

One hundred and six men and women age 21 to 70 years, were selected from the outpatient clinics at the 5 participating institutions. Patients were excluded for clinical evidence of class III or IV congestive heart failure, myocardial infarction within the past 3 months, major arrhythmia or conduction disturbance, significant disease of any major organ system, presence of any malignancy, psychosis, drug or alcohol dependence, and pregnancy or child-bearing potential. No patient had evidence of secondary hypertension on physical examination or by labora-

tory evaluation. Some had previously had more extensive work-ups to rule out secondary hypertension, but this was not required for entrance into the study. No patient had evidence of significant end-organ damage, that is, no grade III or IV retinopathy, no evidence of congestive heart failure or cardiomegaly on physical examination or chest radiograph, and no serum creatinine level greater than 1.8.

Noninsulin-dependent diabetes mellitus (NIDDM) was neither an exclusion nor inclusion criterion for the study, and was specifically documented only at the University of Arizona. The disease was defined as a fasting serum glucose greater than 139 mg/dl; absence of NIDDM was defined as a fasting serum glucose of less than 111 mg/dl. Of the 20 patients studied at the University of Arizona, 10 had NIDDM by this definition and 10 did not. No patient with NIDDM had evidence of gastrointestinal dysfunction or orthostatic hypotension, and thus were considered not to have an autonomic neuropathy.

Informed consent was obtained according to procedures and using forms approved by the institutional review boards at each institution. Each patient had a medical history, physical examination, electrocardiogram, chest radiograph, complete blood count, urinalysis, and 20-item serum chemistry panel. No attempt was made to alter salt intake or any other aspect of the patients' diets.

Measurements and Assays

The same procedure was followed at each of the 5 centers with regard to evaluating efficacy and safety. Blood pressure was measured by a mercury sphygmomanometer or aneroid sphygmomanometer calibrated with a mercury column. In each patient, blood pressure was measured in the same arm at every visit. Phases I and V of Korotkoff's sounds were considered to represent systolic and diastolic blood pressures respectively. Blood pressure was measured once after 5 minutes in the supine position and once after 1 minute in the standing position. All blood pressures were measured at the end of the dosing interval, that is, just prior to the morning dose, in order to assure that antihypertensive efficacy was present at that time, when one would expect the least drug effect.

To determine glucose and insulin levels, blood was drawn into one tube without anticoagulant and into one tube with edetate (EDTA). The tubes were placed on ice, and serum and plasma were separated from the cells in a refrigerated centrifuge. The samples were stored at −80°C until assayed. Glucose was assayed on a Beckman autoanalyzer by a standard glucose oxidase method, and insulin was analyzed by radioimmunoassay according to the method of Zaharko and Beck.[1]

Compliance was assessed by tablet count at each visit. Patients who returned tablets indicating that they had not taken 2 or more days' worth of the prescribed medication were dropped from the study.

Adverse effects were assessed by nondirective questioning at each visit without suggesting particular symptoms; for example, "Have you had any problems since the last visit?" In addition, blood and urine tests and electrocardiograms were repeated at intervals.

General Study Design

All antihypertensive medications were tapered over a period of 2 weeks. Placebo was then administered in a single-blind fashion for 2 weeks, and supine diastolic blood pressure was documented to be between 90 and 114 mm Hg and varying by no more than 14 mm Hg on 2 consecutive visits. Blood pressure and heart rate were measured weekly prior to active drug therapy; after 1, 3, and 5 weeks of active drug therapy; and after 3 days off therapy. Nitrendipine was administered as regular tablets (nonsustained-release) daily at 8 AM, and nitrendipine or placebo (for the once-daily regimen) was administered at 8 PM.

Patients whose supine diastolic blood pressure exceeded 114 mm Hg with nitrendipine alone could be given hydrochlorothiazide or dropped from the study, but were excluded from analysis of antihypertensive efficacy in either case. After 5 weeks of treatment, nitrendipine was stopped abruptly and the patients were seen again 3 days later while not taking antihypertensive medications. At the final visit they had blood pressure, heart rate, and weight determinations, and a final physical examination. If the electrocardiogram or any part of the laboratory evaluation at the last visit during active drug therapy was abnormal, the appropriate test was repeated at this final visit.

At the University of Arizona the patients remained in the clinic after the morning dose of study drug on 2 occasions — at the end of placebo treatment and after 3 weeks of treatment with nitrendipine. Supine and standing blood pressures and heart rate were recorded 4 times at half-hourly intervals beginning one-half hour before the morning dose of study drug, and then at hourly intervals until 9 hours after administration. One and one-half hours after the study drug was ingested (placebo on the first occasion and nitrendipine 10 or 20 mg on the second), each patient consumed a standard breakfast of french toast with syrup and margarine, milk, juice, and a decaffeinated hot beverage; a total of 1058 calories of which 748 were derived from carbohydrates. Blood samples for glucose and insulin were drawn before and 0.5, 1, 2, 3, 4, and 5 hours after the meal.

Randomization and Statistics

Randomization codes were generated in blocks of 4 for each institution, and the patients were assigned to receive either nitrendipine 20 mg once daily or 10 mg twice daily in a double-blind design. Three patients with NIDDM and seven without NIDDM received the latter regimen. Three patients with

NIDDM continued unchanged doses of oral hypoglycemic agents throughout the study.

Results were analyzed by multivariate analysis of variance with repeated measurements, Fisher's exact test, and Wilcoxson rank sum tests as appropriate. The mean values of blood pressure for all visits during nitrendipine therapy were compared to values at the last visit while taking placebo (week 0) by analysis of variance. Statistical significance was taken as a less than 5% likelihood of occurring by chance for the physiologic variables. Because so many laboratory values were tested, the chance that at least one would falsely appear to be significant at the 5% level was high, so the 1% level of statistical significance was chosen for these. The mean blood pressure values for each group at each point in time through the 9.5-hour observation periods were calculated and each mean was used as a single value. From these single values at each time point, a mean, standard deviation, and coefficient of variation were calculated for each blood pressure value for each regimen.

Results

Ten patients were not included in the efficacy analysis. Six did not complete the study, five due to side effects. Four patients completed the study but were not evaluable because two received hydrochlorothiazide and two had significant deviations from the protocol. Demographic characteristics and blood pressure and heart rate at entry (last placebo visit) of the 2 groups are shown in Table 1 for the 96 patients who were included in the efficacy analysis. There were no significant differences between the groups in any variable.

Effects on Blood Pressure and Heart Rate

Effects of once- and twice-daily nitrendipine on blood pressure and heart rate in the supine and standing positions are shown in Figure 1. All blood pressure values were lowered during treatment with nitrendipine 10 mg twice daily: 6/4 mm Hg supine and 6/3 mm Hg standing ($p < 0.001$). Supine heart rate was not affected, but standing heart rate was increased 1 beat per minute ($p < 0.05$). Treatment with nitrendipine 20 mg once daily reduced both supine and standing diastolic pressures by 3 mm Hg ($p < 0.01$). No changes in supine or standing, systolic or diastolic blood pressures were statistically different between the regimens, however.

For all 20 patients enrolled at the University of Arizona, the effects of placebo and nitrendipine 10 and 20 mg on supine and standing blood pressures and heart rate, from 0.5 hour before through 9 hours after a dose, at the end of 3 weeks of treatment with nitrendipine, are shown in Figures 2 and 3. After 3 weeks, both supine and standing blood pressures were reduced by nitrendipine 10 mg twice daily (all values $p < 0.02$). Nitrendipine 20 mg once daily showed a statistically significant effect only on supine systolic blood pressure. Blood pressure obviously decreased after the meal during placebo treatment, and a parallel decrease occurred with nitrendipine.

Compared with placebo, blood pressure variability through the day was increased 4% by nitrendipine 10 mg twice a day (Table 2). Nitrendipine 20 mg once daily increased the variability of blood pressure by 28% compared to placebo.

Effects on Blood Glucose and Insulin

Mean levels of glucose and insulin ± 1 standard deviation are shown in Table 3. Overall, changes in blood glucose during nitrendipine therapy were small (mean maximal increase for diabetics, 4%; for nondiabetics, 0%). No nondiabetic patient developed a diabetic glucose tolerance profile while receiving nitrendipine, but individual diabetic and nondiabetic patients had increases in maximum blood glucose of up to 15%.

Changes in meal-induced maximum levels of plasma insulin between placebo and nitrendipine were

Table 1. Comparison of the Groups at Entry into the Study

Variables	10 mg Twice a Day	20 mg Daily
Number	49	47
Age (yrs)[a]	49.1 ± 11.2	51.0 ± 10.3
Male:Female	37:12	38:9
White:black	43:6	41:6
Weight (kg)[a]	87.1 ± 16.1	91.4 ± 16.5
Duration of hypertension (mo)[a]	112.7 ± 100.1	87.5 ± 63.4
Supine blood pressure		
Systolic (mm Hg)[a]	149.2 ± 14.5	147.5 ± 12.2
Diastolic (mm Hg)[a]	98.1 ± 4.9	98.1 ± 5.5
Heart rate (bpm)[a]	73.0 ± 8.8	75.6 ± 10.6
Standing blood pressure		
Systolic (mm Hg)[a]	146.9 ± 16.1	145.2 ± 10.5
Diastolic (mm Hg)[a]	98.9 ± 6.1	98.8 ± 5.3
Heart rate (bpm)[a]	80.4 ± 9.3	82.1 ± 11.5

[a]Values are mean ± 1 standard deviation.

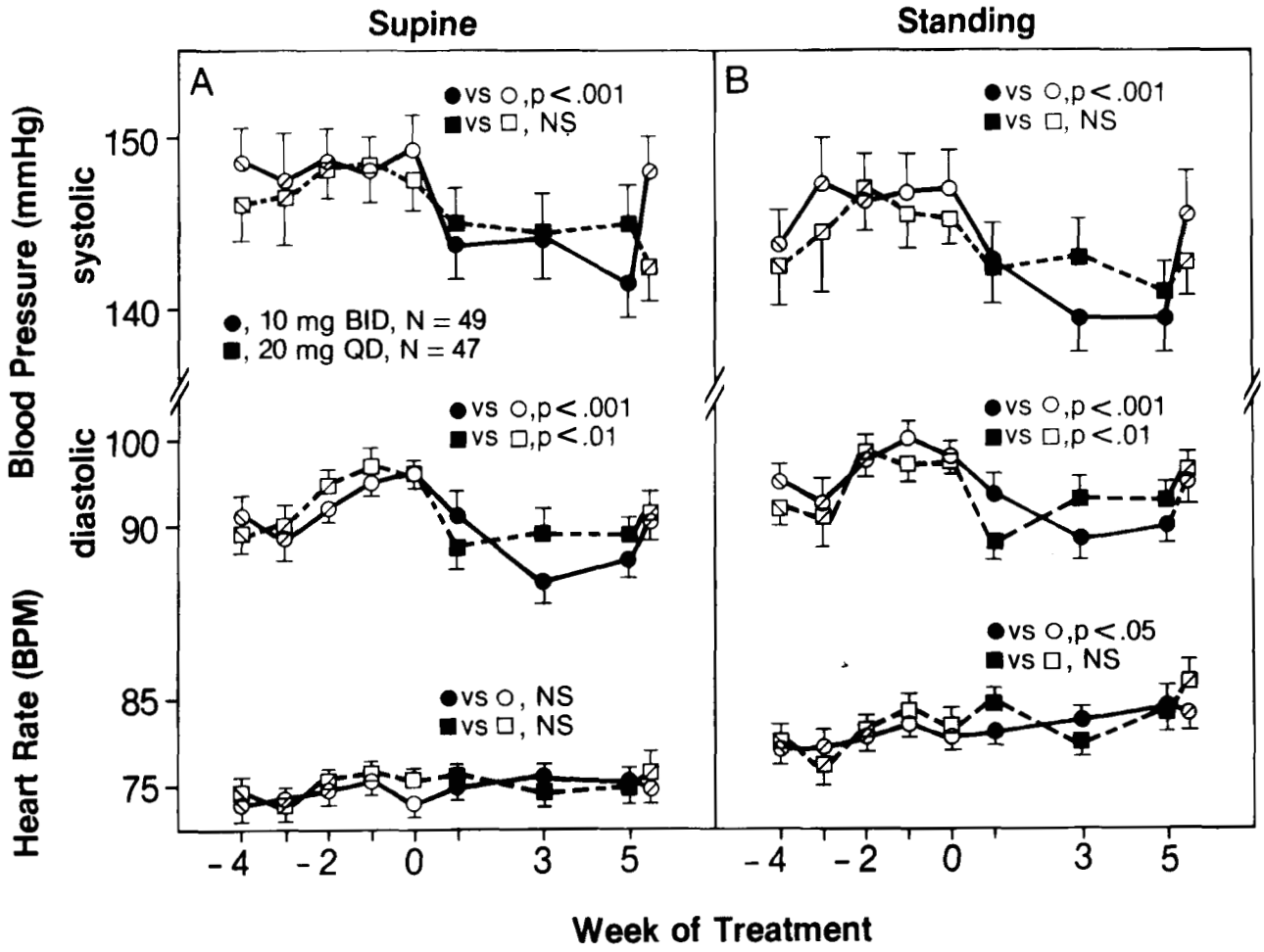

Figure 1. Heart rate and blood pressure effects of previous antihypertensive drug treatment, ○, □, (week −4); no treatment, ○, □, (weeks −3, −2, and follow-up); placebo treatment, ○, □, (weeks −1 and 0); and nitrendipine 10 mg twice daily, ● (N = 49) or 20 mg daily, ■ (N = 47). Mean values ± SEM are shown.

highly variable (Figure 4). Five patients experienced at least a 9-fold higher level on the day they received placebo. Five patients had at least a 58% reduction on the day they received nitrendipine compared to their highest level on the placebo day. Ten patients had increases in maximum plasma insulin of 87% or less or decreases of 42% or less on the day that they received nitrendipine compared to the day they received placebo. There was no difference among the 3 groups with regard to sex, age, weight, dosing regimen, or fasting insulin, but four of the five patients with a decrease in the maximum level were nondiabetic. Two of the three diabetic patients receiving oral hypoglycemic agents had no change in maximum plasma insulin, and one had an increase.

Other Effects

Adverse experiences are summarized in Table 4. The most common side effects associated with nitrendipine were headache, flushing, palpitations, and edema. During active treatment, significantly more patients had adverse effects with the once-daily regimen ($p < 0.01$); 75% of patients receiving 20 mg once daily and 39% receiving 10 mg twice daily had at least 1 side effect. Two patients taking 20 mg daily and three receiving 10 mg twice a day dropped out due to side effects: one each with headache, impotence, dizziness, and a sensation of "heart racing," and two with unspecified reactions.

Mean weight decreased in both groups: 0.46 kg ($p < 0.05$) dosed once daily; 0.41 kg (NS) dosed twice daily. On physical examination, the only significant change was edema of the extremities. At the 1% level of significance, the only change on the electrocardiogram was in QT_c, which increased by 0.01 second from the screening visit when some patients were receiving other antihypertensive drugs, to the end of treatment with nitrendipine in patients receiving 20 mg once daily. There was no difference between the regimens in any electrocardiographic val-

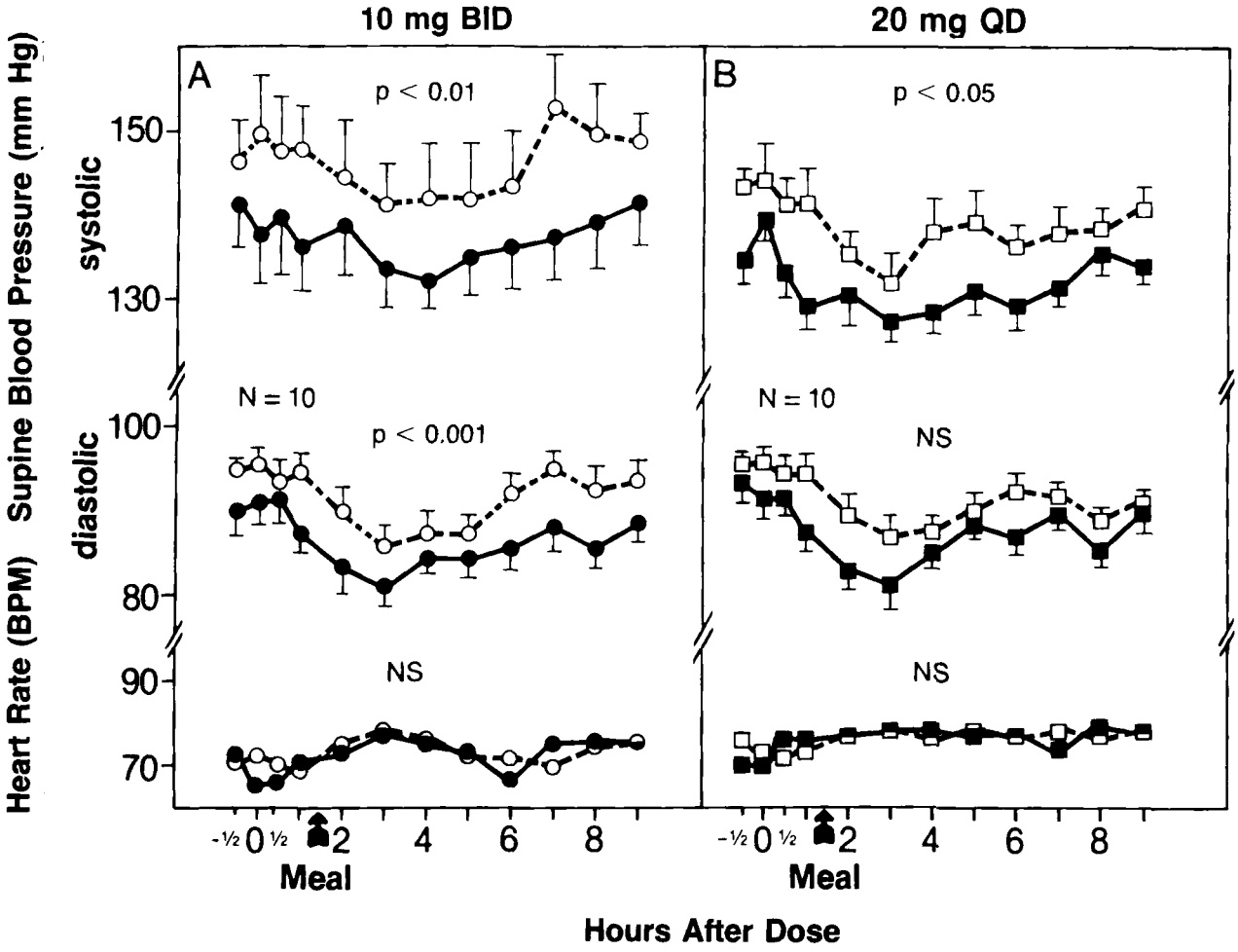

Figure 2. Time course of supine blood pressure and heart rate during treatment with placebo (○, □) and after 3 weeks of treatment with nitrendipine 10 mg twice daily (●) (N = 10, panel A), and 20 mg daily (■) (N = 10, panel B). Mean values ± SEM are shown at hourly or half-hourly intervals from one-half hour before until 9 hours after the morning dose of study drug. The standard high-carbohydrate meal was ingested 1.5 hours after the morning dose of study drug.

ue at the 1% level of significance, and there were no clinically significant differences.

The patients receiving nitrendipine 20 mg once daily had a decrease in red blood cell mean corpuscular volume from 90.5 to 89.8 ($p < 0.01$) from the end of placebo treatment to the end of nitrendipine treatment. In the group receiving 10 mg twice a day, blood urea nitrogen increased from 13.9 to 15.4 ($p < 0.01$) and total cholesterol increased from 208 to 219 mg/dl ($p < 0.001$). No significant changes occurred in either group in total or differential white blood cell count, red blood cell count, hemoglobin, hematocrit, mean corpuscular hemoglobin, or mean corpuscular hemoglobin concentration; urinary specific gravity, pH, protein, glucose, white blood cell count, red blood cell count, casts, or crystals; serum glucose, creatinine, sodium, potassium, chloride, bicarbonate, calcium, phosphate, uric acid, alkaline phosphatase, lactate dehydrogenase, serum glutanic oxaloacetic and pyruvic transaminase, creatine phosphokinase, total bilirubin, total protein, albumin, or triglycerides.

Discussion

Nitrendipine was previously shown to be effective in treatment of essential hypertension as monotherapy[2-5] as well as in combination with hydrochlorothiazide[4] and metoprolol.[6] Our study demonstrated that diastolic blood pressure is significantly lowered at the end of the dosing interval by nitrendipine 20 mg/day administered in either 1 or 2 daily doses. It is reasonable to assume that if blood pressure is significantly lowered at the end of the dosing interval when the drug effect should be least, it will also be lowered throughout the dosing interval. In fact, all blood pressure values were numerically lower at the end of the dosing interval and throughout the first 9 hours of the next interval in the smaller group of patients studied at the University of Arizona. The

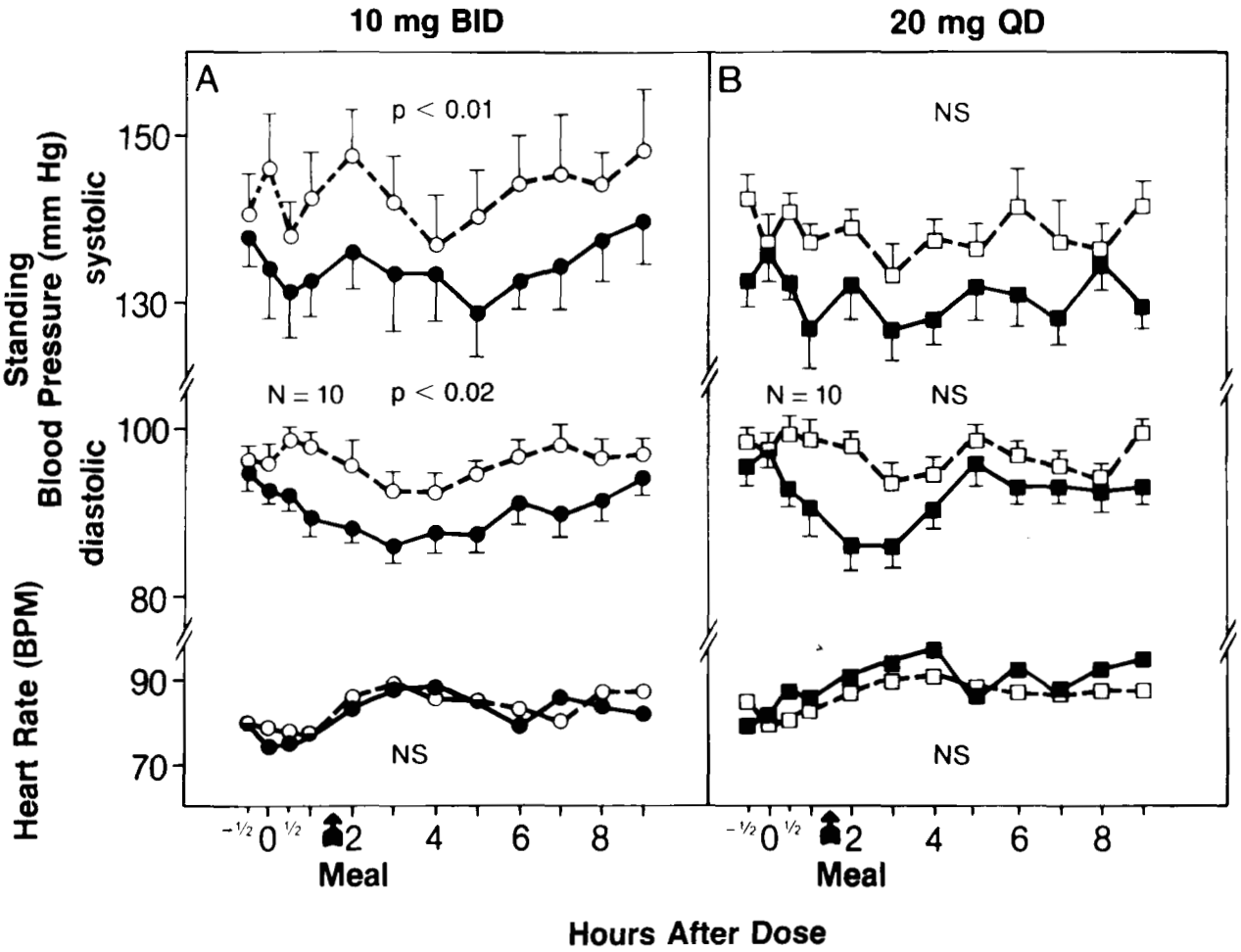

Figure 3. Time course of standing blood pressure and heart rate during treatment with placebo (○, □) and after 3 weeks of treatment with nitrendipine 10 mg twice daily (●) (N = 10, panel A), and 20 mg daily (■) (N = 10, panel B). Mean values ± SEM are shown at hourly or half-hourly intervals from one-half hour before until 9 hours after the morning dose of study drug. The standard high-carbohydrate meal was ingested 1.5 hours after the morning dose of study drug.

power of statistical tests in the subgroup was less, and even though the numeric lowering of blood pressure was similar in this subgroup to that in the entire group, statistical significance was not achieved with nitrendipine 20 mg once daily except in supine systolic blood pressure. The fact that the measured lowering of blood pressure was small may be due to 3 potential factors: (1) the weekly assessment of blood pressure was made at the end of the dosing interval, measuring the minimum effect of nitrendipine during that interval; (2) the dose of nitrendipine was relatively small, and larger doses in a similar patient population have produced a greater reduction in arterial pressure[5]; (3) the magnitude of blood pressure reduction is related directly to pretreatment blood pressure for many antihypertensive drugs, including propranolol,[7] minoxidil,[8] and nifedipine.[9] Most of the patients participating in this study had mild hypertension, which may have minimized the magnitude of the reduction in blood pressure.

While no statistically significant difference existed between the responses of blood pressure in the 2 treatments, blood pressure was lowered to a numerically greater extent with twice-daily therapy. Compared to placebo, twice-daily nitrendipine controlled blood pressure smoothly with no clinically significant increase in variability throughout the dosing interval. The 28% increase in blood pressure variability with the once-daily regimen may be of clinical significance.

The plasma half-life of nitrendipine shows wide interpatient variation, and values in healthy subjects have varied more than 4-fold in individual studies and showed an overall range of 1–22 hours.[10,11] Since the half-life is so variable, it is difficult to estimate mean duration of antihypertensive effect from mean plasma half-life, and studies such as ours are necessary to establish the optimum dosing regimen for the average patient. Clinically, the regimen may need to be individualized, as with any drug.

Table 2. Comparison of 9-hour Blood Pressure Variability in 20 Patients (using coefficient of variation)

Blood Pressure	Placebo[a] (%)	10 mg Twice a Day[a] (%)	Placebo[b] (%)	20 mg Daily[b] (%)
Supine				
Systolic	2.5	2.1	2.5	2.7
Diastolic	3.7	3.7	3.4	4.2
Standing				
Systolic	2.5	2.3	2.0	2.3
Diastolic	2.1	3.1	2.2	3.8
Mean all BP	2.7	2.8	2.5	3.2

[a]N = 10.
[b]N = 10.

Table 3. Serum Glucose and Plasma Insulin Values in 20 Patients After a Standard Meal

Time (hrs)	0	0.5	1	2	3	4	5
Serum glucose (mg/100 ml)							
Diabetics (N = 10)							
Placebo	159±60	256±47	262±77	235±12	198±103	168±89	146±74
Nitrendipine	161±60	259±66	274±73	238±92	190±90	161±78	132±71
Nondiabetics (N = 10)							
Placebo	81±10	132±38	111±34	101±24	96±23	82±21	78±18
Nitrendipine	83±12	120±30	125±35	107±26	97±23	91±21	83±16
Plasma insulin (μu/ml)							
Diabetics (N = 10)							
Placebo	14±17	44±67	35±42	29±36	19±22	21±32	22±38
Nitrendipine	17±21	184±435	39±42	87±133	39±50	29±32	18±20
Nondiabetics (N = 10)							
Placebo	8±6	93±94	66±72	43±28	28±24	21±17	12±9
Nitrendipine	16±17	88±77	56±42	75±125	45±52	48±80	25±38

Values are mean ± standard deviation.
There were no statistically significant differences in serum glucose or plasma insulin values between treatments with placebo and nitrendipine in either diabetics or nondiabetics at any time.

The decrease in blood pressure and increase in heart rate after the meal were probably due to splanchnic vasodilation, and are similar to previously reported effects of a meal in hypertensive patients.[12] This effect of the meal interfered with our ability to assess whether or not, during long-term treatment with nitrendipine, changes in blood pressure were due to the drug during the first few hours after a dose.

The calcium-channel blockers nifedipine,[13] diltiazem,[13] and verapamil[13,14] all inhibit insulin release from pancreatic islet cells in vitro. In one study, oral nifedipine inhibited insulin release in both nondiabetic patients and those with noninsulin-dependent diabetes, while impairing glucose tolerance in diabetic patients but paradoxically lowering blood glucose levels in nondiabetic patients.[15] In another study of healthy volunteers, intravenous verapamil inhibited insulin release due to administration of glucose or sulfonylurea and increased levels of serum glucose.[16] In a third study, both intravenous and oral verapamil improved glucose tolerance without affecting insulin release in patients with noninsulin-dependent diabetes.[17] Thus the effects of calcium-channel blockers on plasma insulin and glucose appear to depend upon the specific drug involved, whether or not the patient has preexisting glucose intolerance, and probably upon other undetermined factors as well.

The explanation for the large interpatient variation in insulin response to the high-carbohydrate meal in our patients is unclear. Nitrendipine may inhibit insulin release and also antagonise insulin effects. Although it appears unlikely, it is also possible that random variation accounted for the nearly 7-fold increase in the range of maximum postprandial plasma insulin levels in the diabetic patients, from 6–218 μu/ml with placebo to 11–1411 μu/ml with nitrendipine. Overall, changes in blood glucose levels with nitrendipine were small and did not appear to be significant either statistically or clinically. The possibility exists, however, that glucose metabolism could be significantly deranged in an occasional patient, due either to impaired insulin release or peripheral antagonism of insulin effect, or both.

The slight decrease in weight in combination with development of edema in 8% of patients suggested

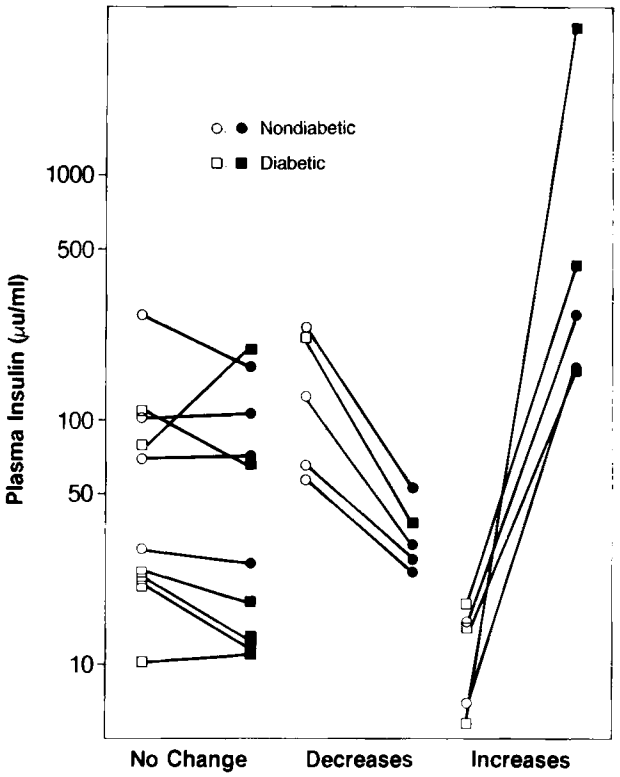

Figure 4. Maximum plasma insulin after the standard meal during treatment with placebo (open symbols) and during treatment with nitrendipine (solid symbols) in diabetics (□, ■) (N = 10) and nondiabetics (○, ●) (N = 10). The decreases column refers to patients with >58% decrease in maximum plasma insulin. The increases column refers to patients with >900% increase in maximum plasma insulin.

that, as with nifedipine, the edema probably represented redistribution rather than retention of fluid. The minimal change in QT_c from the screening visit to the end of treatment with nitrendipine 20 mg once daily may have been due to withdrawal of previous antihypertensive drugs, and was of no clinical significance. The minor changes in laboratory values with the 2 regimens were of questionable clinical significance, with the possible exception of the increase in total cholesterol, which averaged 3.4% for all patients who received nitrendipine. Without knowing the relative changes in high- and low-density lipoprotein cholesterol, the clinical significance is difficult to assess.

The high overall rate of reported side effects was probably due to several factors. First, patients expect side effects in any study employing new medication, but subtraction of the rate of adverse effects with placebo from the rate with nitrendipine still yielded an overall rate of 37%. A second factor was the dosage regimen; the rate of side effects was nearly twice as great with once-daily therapy. Finally, many of the adverse effects were mild or relatively inconsequential and easily tolerated, and less than 5% of patients dropped out because of them. Thus although the reported overall rate of adverse effects was high, the rate of significant adverse effects was low, and nitrendipine appears to be well tolerated, particularly when given twice a day. Combination therapy with beta blockers should decrease the frequency of headache and palpitations, and concurrent use of diuretics may decrease the prevalence of edema, the 3 most common adverse effects of nitrendipine in this study.

Table 4. Adverse Effects

Symptom or Sign	P_{10}	N_{10}	$N\text{-}P_{10}$	P_{20}	N_{20}	$N\text{-}P_{20}$	$N\text{-}P_T$
Headache	8	10	2	8	21	13	15
Flushing	1	3	2	1	11	10	12
Palpitations	0	7	2	1	3	2	9
Edema	0	2	2	0	6	6	8
Fatigue	0	4	4	1	2	1	5
Sexual Dysfunction	0	2	2	0	2	2	4
Dizziness	1	3	2	2	3	1	3
Nausea	0	2	2	0	1	1	3
Dropout due to side effects	0	3	3	0	2	2	5
Any adverse effect	8 (15%)	21 (39%)	13 (24%)	13 (25%)	39[a] (75%)	26 (50%)	39 (37%)

P_{10} = number of patients with each side effect in 54 patients treated with placebo.
N_{10} = number of patients with each side effect in 54 patients treated with nitrendipine 10 mg twice daily.
$N\text{-}P_{10}$ = number of patients who had the adverse effect during treatment with nitrendipine 10 mg twice daily in excess of the number of patients who had the adverse effect during placebo treatment.
P_{20} = number of patients with each side effect in 52 patients treated with placebo.
N_{20} = number of patients with each side effect in 52 patients treated with nitrendipine 20 mg daily.
$N\text{-}P_{20}$ = number of patients who had the adverse effect during treatment with nitrendipine 20 daily in excess of the number of patients who had the adverse effect during placebo treatment.
$N\text{-}P_T$ = Total number of patients who had the adverse effect during treatment with either nitrendipine regimen in excess of the number of patients who had the adverse effect during placebo treatment.
[a] $p < 0.01$ compared to N_{10}.

Both nitrendipine regimens significantly lowered arterial blood pressure, but the degree of lowering was small, possibly due to the relatively small dose, the timing of blood pressure measurements relative to the dose, and the low initial blood pressures of the patients. Although the reduction in blood pressure was modest, this is often all that is required in patients with mild hypertension.

Although there were no statistically significant differences between the regimens in lowering blood pressure, the reductions were numerically greater with the twice-daily regimen. Also, the variability in blood pressure tended to be less through the first 9 hours of the dosing interval with that regimen, and significantly more side effects occurred with the once-daily schedule. Nitrendipine is effective in lowering blood pressure on a once- or twice-daily regimen, but twice daily appears to be better tolerated.

Acknowledgments

We thank David Burkholder, Ph.D. for help with conducting the study and comments on the interpretation, and Janet Mar, R.N. for assistance with the clinical aspects.

References

1. **Zaharko DS, Beck LV.** Studies of a simplified plasma insulin immunoassay using cellulose powder. Diabetes 1968;17:444–57.
2. **Hansson L, Andren L, Orö L, Ryman T.** Pharmacokinetic and pharmacodynamic parameters in patients treated with nitrendipine. Hypertension 1983;5(suppl II):25–8.
3. **Vlachakis ND, Vanov SK, Taylor RJ, Pun EFC.** Controlled comparison of nitrendipine and placebo in treatment of hypertension. In: Scriabine A, Vanov SK, Deck K, eds. Nitrendipine. Baltimore, Munich: Urban & Schwarzenberg, 1984:443–50.
4. **Black HR, Vlachakis N.** Once and twice daily nitrendipine therapy in essential hypertension. In: Scriabine A, Vanov SK, Deck K, eds. Nitrendipine. Baltimore, Munich: Urban & Schwarzenberg, 1984:509–18.
5. **Fagan TC, Sternlieb C, Vlachakis N, Deedwania PC, Mehta JL.** Efficacy and safety comparison of nitrendipine and hydralazine as antihypertensive monotherapy. J Cardiovasc Pharmacol 1984;6(suppl 7):1109–13.
6. **Orö L, Ryman T.** A long-term study of the combined antihypertensive action of nitrendipine and metoprolol. In: Scriabine A, Vanov SK, Deck K, eds. Nitrendipine. Baltimore, Munich: Urban & Schwarzenberg, 1984:527–34.
7. **Fagan TC, Walle T, Corns-Hurwitz R, et al.** Time course of development of the antihypertensive effect of propranolol. Hypertension 1983; 5:852–7.
8. **Shen D, O'Malley K, Gibaldi M, McNay JL.** Pharmacodynamics of minoxidil as a guide for individualizing dosage regimens in hypertension. Clin Pharmacol Ther 1975;17:593–8.
9. **Bertel I, Conen D, Radü EW, et al.** Nifedipine in hypertensive emergencies. Br Med J 1983;286:19–21.
10. **Aronoff GR.** Pharmacokinetics of nitrendipine in patients with renal failure: comparison to normal subjects. J Cardiovasc Pharmacol 1984;6(suppl 7):974–6.
11. **Lasseter KC, Shamblen EC, Murdoch AA, et al.** Steady-state pharmacokinetics of nitrendipine in hepatic insufficiency. J Cardiovasc Pharmacol 1984;6(suppl 7):977–81.
12. **Fagan TC, Conrad KA, Mar JH, Nelson L.** Effects of meals on hemodynamics: implications for antihypertensive drug studies. Clin Pharmacol Ther 1986; in press.
13. **Yamaguchi I, Akimoto Y, Nakajima H, Kiyomata A.** Effect of diltiazem on insulin secretion. I. Experiments in vitro. Jpn J Pharmacol 1977;27:679–87.
14. **Davis G, Somers G, Van Obbershen E, Malaisse WJ.** Calcium antagonists and islet function. I. Inhibition of insulin release by verapamil. Diabetes 1975;24:247–51.
15. **Giugliano D, Torella R, Caciapuoti F, Gentile S, Verza M, Varrichio M.** Impairment of insulin secretion in man by nifedipine. Eur J Clin Pharmacol 1980;18:395–8.
16. **De Marinis L, Barbarino A.** Calcium antagonists and hormone release. I. Effects of verapamil on insulin release in normal subjects and patients with islet cell tumor. Metabolism 1980;29:599–604.
17. **Röjdmark S, Andersson DE.** Influence of verapamil on glucose tolerance. Acta Med Scand 1984;Suppl 681:37–42.