SUMMARY We report the results of a multicenter trial in which nitrendipine, alone or in combination with a diuretic, a β-blocker, or both, was administered to 114 patients with severe hypertension (≥115 mm Hg). Nitrendipine was titrated in doses of 5 to 30 mg b.i.d. If blood pressure was not controlled with nitrendipine alone, hydrochlorothiazide or propranolol or both were added. After a mean of 29 days in the study, 96 (90%) of 107 patients reached the initial goal of therapy; in 44 (41%) given nitrendipine alone the mean decrease in supine blood pressure was 38/25 mm Hg. After a mean of 91 days, 69 (72%) of 96 patients achieved the final goal of therapy; in 24 (25%) patients given nitrendipine alone the mean supine blood pressure decrease from baseline was 49/33 mm Hg. Falls in blood pressure were comparable in the patients given drug combinations. Seventy-two of 114 patients given study drug(s) had adverse experiences; headache and edema were the most frequent complaints. Only four patients dropped out of the study because of adverse effects. Most abnormal laboratory values occurred when nitrendipine was given with hydrochlorothiazide or propranolol or both. Analysis of severely hypertensive patients followed up in our Virginia center revealed continued control of blood pressure after long-term follow-up (43 ± 3 [SD] months). Average supine blood pressure was reduced from 180/121 ± 21/5 to 140/90 ± 1679 (SD) mm Hg (p < 0.001). It was concluded that the calcium antagonist nitrendipine, alone or in combination with a diuretic or β-blocker or both, is effective in the treatment of severe hypertension. (Hypertension 11 [Suppl I]: I-225-I-228, 1988)

KEY WORDS • nitrendipine • refractory hypertension • resistant hypertension • diuretics • β-blockers

SUCCESSFUL long-term treatment of severe hypertension remains a difficult clinical problem. The literature concerning the treatment of hypertensive emergencies is extensive, but most reports are limited to either immediate or short-term therapy of markedly elevated blood pressure. There are relatively few published reports concerning the systematic evaluation of various treatment regimens. Monotherapy of severe hypertension is rarely achieved, and most severely hypertensive patients are given either two- or three-drug regimens. Besides providing additional efficacy, a second or third antihypertensive agent is frequently employed to blunt or nullify the counterregulatory mechanisms activated by the primary antihypertensive agent. Hence, polypharmacy for the treatment of severe hypertension is the rule rather than the exception.

Calcium antagonists have been demonstrated to be effective antihypertensive agents in a wide range of hypertensive states; however, most reports of treatment of severe hypertension have been limited to immediate or short-term effects. Clinical evaluations of long-term calcium antagonist therapy of severe hypertension frequently lack sufficient detail to compare the results with the effects of other antihypertensive medications. In the present report of a multicenter trial of the calcium antagonist nitrendipine in patients with severe hypertension, the results of nitrendipine therapy are presented after approximately 3 months of therapy in 114 patients in the multicenter trial and after 43 ± 3 months of therapy in patients treated at our site. An evaluation of the initial 3 months of therapy at our center (15 patients) was the subject of a preliminary report. The protocol allowed for the addition of a diuretic, a β-blocker, or both to achieve blood pressure control.

Subjects and Methods
This investigation was conducted at seven sites in the United States (see list at end of article) to assess the safety and efficacy of treatment with nitrendipine,
alone or combined with propranolol, hydrochlorothia-
zide, or both, for severe hypertension. Male and female
patients, 21 to 70 years of age, with severe hyperten-
sion were eligible to be enrolled in this open-label
investigation. Reduction of blood pressure was the
criterion for efficacy. Substantial flexibility was al-
lowed in study execution because of the severity of the
hypertension. Antihypertensive drugs were withdrawn
during a wash-out period lasting from 3 to 7 days,
depending on the severity of the patient’s hypertension
and the investigator’s clinical judgment. Up to three
visits could be scheduled during this period. All blood
pressures were determined three times, 2 minutes
apart, with the arithmetic mean recorded. The fifth
phase of Korotkoff sounds was recorded as the diastolic
pressure. Patients with supine diastolic blood pressure
(SDBP) of 115 mm Hg or higher at the end of the
baseline period (Visit 4) qualified for the investigation.

When used as the only treatment, nitrendipine was
titrated at doses of 5, 10, 20, and 30 mg twice daily,
usually at no less than 2-day intervals during the initial
2 to 5 weeks. If SDBP did not reach the initial goal of
therapy (≤100 mm Hg for patients with SDBP between
115 and 124 mm Hg and ≤105 mm Hg for patients with
a baseline SDBP ≥125 mm Hg) at a maximum dosage
of nitrendipine (30 mg b.i.d.), propranolol or hydro-
chlorothiazide or both were added in standard stepwise
practice as needed. Maximum daily doses of propran-
olol and hydrochlorothiazide were 120 and 150 mg,
respectively. Patients who did not meet the initial goal
of therapy could have nitrendipine increased to 40 mg
twice daily.

Blood pressures of patients who reached the initial
goal of therapy were titrated to the final goal (SDBP ≤
90 mm Hg) over a second 2- to 5-week period beginning
with Visit 9, which was the first study endpoint for
statistical analysis. Visits were scheduled at weekly
intervals or less frequently, according to the investi-
gator's clinical judgment. When SDBP of 90 mm Hg
or lower was reached, patients continued the regimen
they were receiving for at least 4 more weeks, with
biweekly visits ending at Visit 16. Patients were then
eligible for long-term extension of the protocol. All patients
given active drug were included in the safety
evaluation. Patient history, and complete physical
examinations and electrocardio-
graphic studies were also done at Visits 2, 9, 15, and
19, and brief examinations were conducted at all other
visits.

Results

Of 141 patients screened for this investigation 114
were found to be eligible based on the entry criteria.
Seven patients were excluded from the efficacy analyses
because they did not have data available at any of the
study end points. Seven patients did not differ in age, race, or blood pressure from the remaining
patients. The clinical characteristics of the 107 patients
with valid data available for efficacy analysis at Visit
9 are shown in Table 1. One patient was lost to
follow-up and one was dropped because of noncom-
pliance between Visits 9 and 14. Two patients withdrew
between Visits 9 and 16 due to adverse experiences.

Nitrendipine was titrated at 2-day intervals for most
patients, but at 1-day intervals for a few. Titration in a few patients was begun with 10 or 20 mg of
nitrendipine twice daily, based upon the clinical judg-
ment of the investigator. The first evaluation of data was at Visit 9 after a mean of 29 days of drug administra-
tion, and the final evaluation was after a mean of 91
days (Table 2). All changes in the supine and stand-
ing blood pressures were statistically significant.
Seventy-two percent of patients achieved normotension
(SDBP ≤ 90 mm Hg) after the final titration and after
a month of maintenance therapy (Table 3).

Seventy-two of the 114 patients given study medi-
cations had adverse experiences (Table 4). Sixty-two
had adverse experiences while taking nitrendipine
alone, but these appeared to be unrelated to dose. Two
of the 114 patients given study medications discon-
tinued participation due to adverse experiences. Two
more patients were recorded as choosing to withdraw
from the study, and both had had associated adverse
experiences. One patient was hospitalized with hyper-
osmolar syndrome after taking nitrendipine for 2½
months and hydrochlorothiazide for 1 month.

Twenty-one persons with normal baseline serum
potassium values had below normal values (<3.5

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>60 (56%)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>47 (44%)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>42 (39%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>58 (54%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7 (7%)</td>
<td></td>
</tr>
</tbody>
</table>

Percentages and ranges are shown in parentheses.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>52 ± 10 (31-74)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>90 ± 21 (50-165)</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168 ± 15 (94-193)</td>
<td></td>
</tr>
<tr>
<td>Duration of hypertension (yr)</td>
<td>13 ± 9 (1-40)</td>
<td></td>
</tr>
</tbody>
</table>

Results

<table>
<thead>
<tr>
<th>Blood pressure (mm Hg)</th>
<th>Initial titration</th>
<th>Final titration</th>
<th>After 4-wk maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 9</td>
<td>(Visit 9, n=107)</td>
<td>(Visit 14, n=100)</td>
<td>(Visit 16, n=96)</td>
</tr>
<tr>
<td>Supine Baseline</td>
<td>187.7/121.0</td>
<td>187.8/121.1</td>
<td>188.7/121.4</td>
</tr>
<tr>
<td>SE</td>
<td>2.1/0.8</td>
<td>2.2/0.9</td>
<td>2.2/0.9</td>
</tr>
<tr>
<td>Mean decrease</td>
<td>39.2/26.7*</td>
<td>45.5/32.3*</td>
<td>48.8/33.4*</td>
</tr>
<tr>
<td>SE</td>
<td>1.9/0.9</td>
<td>2.2/1.1</td>
<td>2.2/0.5</td>
</tr>
<tr>
<td>Standing Baseline</td>
<td>186.2/123.5</td>
<td>186.1/127.4</td>
<td>186.5/33.3</td>
</tr>
<tr>
<td>SE</td>
<td>2.0/1.0</td>
<td>2.1/1.0</td>
<td>2.1/0.9</td>
</tr>
<tr>
<td>Mean decrease</td>
<td>41.4/26.8*</td>
<td>47.6/32.3*</td>
<td>51.8/33.3*</td>
</tr>
<tr>
<td>SE</td>
<td>2.1/1.2</td>
<td>2.3/1.3</td>
<td>2.2/1.2</td>
</tr>
</tbody>
</table>

*p<0.0001 compared to baseline value.
TABLE 3. Severely Hypertensive Patients Achieving Goal of Therapy a

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Initial titration (Visit 9, n = 107)</th>
<th>Final titration (Visit 14, n = 100)</th>
<th>After 4-wk maintenance (Visit 16, n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTP alone</td>
<td>44 (85%)</td>
<td>22 (79%)</td>
<td>21 (88%)</td>
</tr>
<tr>
<td>NTP + HCTZ</td>
<td>24 (96%)</td>
<td>19 (90%)</td>
<td>17 (68%)</td>
</tr>
<tr>
<td>NTP + PRO</td>
<td>10 (83%)</td>
<td>12 (67%)</td>
<td>11 (65%)</td>
</tr>
<tr>
<td>NTP + HCTZ + PRO</td>
<td>18 (100%)</td>
<td>19 (70%)</td>
<td>20 (67%)</td>
</tr>
<tr>
<td>Goal achieved</td>
<td>96 (90%)</td>
<td>72 (72%)</td>
<td>69 (72%)</td>
</tr>
</tbody>
</table>

NTP = nitrendipine; HCTZ = hydrochlorothiazide; PRO = propranolol.

aGoal of therapy

- At visit 9: SDBP < 100 mm Hg for patients with SDBP between 115 and 124 mm Hg; SDBP < 105 mm Hg for patients with SDBP > 125 mm Hg.
- At visit 14: SDBP < 90 mm Hg.
- At visit 16: SDBP < 90 mm Hg.

mEq/L) at the last measurement. Seventeen of these patients were also receiving hydrochlorothiazide. Serum glucose first became abnormal (fasting blood sugar > 120 mg) with nitrendipine alone in two patients, with nitrendipine plus hydrochlorothiazide or propranolol in two, and with all three drugs in six. No consistent relationship of laboratory abnormalities could be attributed to nitrendipine administration.

Of the 12 patients who entered a long-term extension of the initial study at our Virginia center, eight remained in the protocol after an average of 43 ± 3 months. The mean supine blood pressure was reduced from 180/121 ± 21/5 to 140/90 ± 16/9 (± SD) mm Hg (p < 0.0001). Weight, pulse, and results of laboratory studies did not reveal any significant changes after nearly 3½ years of treatment (Table 5). Of the four patients who discontinued therapy during the long-term extension, two had possible drug-related side effects.

Discussion

Calcium antagonists appear to be particularly well suited for the treatment of severe hypertension due to their effectiveness and tolerability. Because of cardio-depression and effects on atrioventricular conduction, drugs of the verapamil type may not be appropriate for this purpose if there is a likelihood that /3-adrenergic blocking agents may also be needed. For this reason, dihydropyridines appear to be a particularly good choice for initial therapy. Of the dihydropyridines, nitrendipine seems to be advantageous for long-term management of severe hypertension because of its relatively long half-life. In the present investigation it was used in a twice-daily dosing regimen with good clinical results.

Most previous trials of nitrendipine in humans described the effects of immediate and short-term administration in patients with mild to moderate hypertension.4,17-21 One longer-term (6 months) study of patients with mild to moderate hypertension treated with nitrendipine in combination with metoprolol demonstrated that nitrendipine has a sustained antihypertensive effect.22 In our investigation of severely hypertensive patients with diastolic blood pressures of 115 mm Hg or higher, nitrendipine alone was effective therapy in 25% of patients. Nitrendipine combined with modest doses of diuretic, /3-blocker, or both was effective in controlling markedly elevated blood pressure in the majority of the patients. Using the relatively strict criterion (SDBP =< 90 mm Hg), 72% of the 96 patients completing the trial achieved the final goal of therapy. The fall in blood pressure from baseline was quite impressive, averaging 49 mm Hg systolic and 33 mm Hg diastolic. This degree of change could be expected to result in a substantial number of side effects purely due to the magnitude of the blood pressure decrease. Although adverse experiences were not infrequent (see Table 4), they were usually tolerable and diminished with continuation of therapy in the majority of patients. Of the 114 patients who were originally enrolled in the trial, only three discontinued therapy because of adverse experiences that could be attributed to the medication.

The eight patients who remained with the long-term protocol at our Virginia site showed no evidence of tolerance to therapy, and they continued to have excellent blood pressure control. In these patients, the initial supine blood pressure was 180/121 ± 21/5 mm Hg, and after 43 ± 3 months it had decreased and was maintained at 140/90 ± 16/9 mm Hg. These pa-
tients continue to tolerate their drug regimens well.

It was concluded from this multicenter investigation that nitrendipine alone or in combination with a diuretic, a β-adrenergic receptor blocking agent, or both, is effective therapy in severe hypertension. Side effects such as headache and edema, which occurred most frequently in patients receiving nitrendipine alone, were relatively well tolerated and could be treated with the addition of either the diuretic or β-blocking agent. Patients who remained in the study long term did not appear to have any loss of blood pressure control and they continued to tolerate the medication well.

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