Efficacy of Nadolol Alone and Combined with Bendroflumethiazide and Hydralazine for Systemic Hypertension

VETERANS ADMINISTRATION COOPERATIVE STUDY GROUP
ON ANTIHYPERTENSIVE AGENTS

Nadolol (N) titrated from 80 to 240 mg or bendroflumethiazide (B) 5 to 10 mg, or the combination (B+N), were randomly assigned double-blind to 365 men with pretreatment diastolic blood pressures (BP) of 95 to 114 mm Hg. After 12 weeks of treatment, a diastolic BP of <90 mm Hg was achieved in 49% who received N, 46% who received B and 85% who received B+N. With N, the diastolic BP decreased more in whites than in blacks; with B, this racial trend was reversed. Side effects were infrequent; the most common were impotence, lethargy, weakness and postural dizziness, which occurred more often with B than with N. Addition of hydralazine, 25 to 100 mg twice daily, controlled diastolic BP at a level of <90 mm Hg in approximately 60% of those previously uncontrolled. N, and especially B+N, provided an efficacious once-daily treatment for systemic hypertension, and addition of hydralazine was effective in most nonresponders.
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Beta-adrenergic blocking agents differ with respect to cardioselectivity, intrinsic sympathomimetic activity and membrane-stabilizing effects.[1] Nadolol (N) does not exhibit any of these properties,[2,3] but it has 2 characteristics that are important for the treatment of systemic hypertension. The first is long duration of action. This permits once-daily dosage with a consequent gain in compliance. The second is that in contrast to other beta-adrenergic blocking agents, nadolol is not associated with a decrease in renal blood flow,[4,5] a desirable feature especially in patients with hypertension.

The present study assesses the relative effectiveness of 3 regimens: N alone, bendroflumethiazide (B) alone[6,7] and B+N combined. In addition, the effectiveness of adding hydralazine was assessed in patients whose blood pressure (BP) was not controlled with one or the other of these regimens.

Methods

Four hundred eighty men, aged 20 to 69 years, were evaluated for randomization out of 809 patients screened, of whom 365 were eventually randomized (Fig. 1). The untreated sitting diastolic BP (Korotkoff phase V) had to be 95 to 114 mm Hg inclusive. Patients were excluded who had major cardiovascular complications, serious systemic diseases or who had preexisting conditions that would interdict the use of the test drugs (see Appendix A).

Prerandomization placebo period: The nature of the study was explained to the patient and written informed consent was obtained. In the patients who met the age and diastolic BP criteria for entry and had no exclusion factors, antihypertensive therapy, if any, was discontinued for at least 2 weeks up to a maximum of 8 weeks, depending on the type of drug taken. A history was taken that included volunteered complaints, and a physical examination was performed. The following laboratory studies were obtained: a chest x-ray (if not taken within the previous 3 months), an electrocardiogram, complete blood cell count, urinalysis, serum potassium fasting blood glucose, uric acid, cholesterol, triglycerides, creatine, alkaline phosphatase, serum glutamic oxaloacetic transaminase, fluorescent antinuclear antibodies and serum bilirubin.

Systolic and diastolic (Korotkoff, phase V) BP readings were taken 3 times in the sitting position at each clinic visit and once in the standing position. Readings were taken in the right arm using a standard mercury sphygmomanometer. The median of 3 determinations of BP with the patient sitting was used for analysis. The patient qualified for randomization if the median diastolic BP on 2 successive weekly visits was 95 to 114 mm Hg and if 80 to 110% of the prescribed number of tablets had been taken as estimated by pill counts. A maximum of 4 weekly visits was allowed to fulfill these requirements. The patient was excluded from the study at any clinic visit if the diastolic BP was >119 mm Hg. Patients were also

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Address for reprints: Edward D. Freis, MD, Senior Medical Investigator, Veterans Administration Medical Center, 50 Irving Street, N.W., Washington, D.C. 20422.

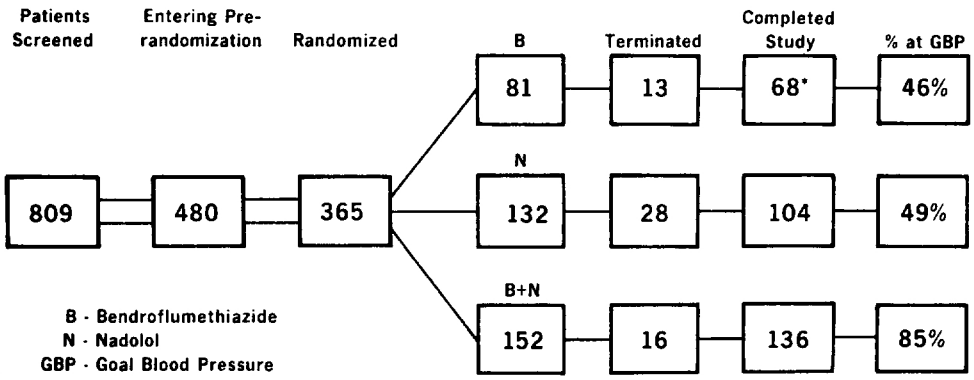

FIGURE 1. Flow chart of phase A showing numbers of patients screened, entering prerandomization and randomized double-blind to the 3 regimens of bendroflumethiazide, nadolol and the combined drugs. Also shown are the number terminated, completing the trial and the percentage controlled at diastolic blood pressure <90 mm Hg. Phase B (hydralazine) is not shown.

terminated if the diastolic BP was <95 mm Hg or >114 mm Hg on each of the 2 successive visits.

The patient was given 2 bottles that contained placebos and was instructed to take 1 tablet daily from each. He also was requested to return the bottle of remaining tablets to the clinic each visit. A check list of known side effects associated with the administered drugs was reviewed at each visit before as well as after randomization.

One hundred fifteen patients were dropped during the prerandomization phase: 62 because the diastolic BP was below the acceptable range (<95 mm Hg) and 7 because the diastolic BP was above the acceptable range (>114 mm Hg); 30 patients were noncompliant, of whom 20 failed to return to the clinic; and 16 patients were dropped for miscellaneous reasons.

Postrandomization period (phase A): Of the 365 patients who were randomized into the study, 308 completed phase A. Recruitment goals were met or exceeded in most of the clinics; the hospital with the lowest number of randomizations achieved 94% of its quota.

The study was a randomized, double-blind trial in which patients were assigned to 1 or 3 regimens: B plus placebo of N (81 patients), N plus placebo of B (132 patients) or B+N (152 patients). The reason for the unequal randomization is as follows: the patients eligible for entering phase B (addition of hydralazine) were those whose diastolic BP failed to decrease to <90 mm Hg on N alone, B alone or the combination of B+N. We estimated that the combination would be the most effective in reducing BP and, therefore, would provide fewer patients eligible to receive hydralazine. Consequently, more patients were randomized to the 2-drug regimen so as to provide approximately equal numbers of eligibles for entry into phase B.

It was estimated that for phase A only, in order to provide 90% power and a type I error of alpha = 0.05/2 for the 2 comparisons, a sample size of 60 patients per group would be needed. This was based on the assumption that 50% of patients receiving B or N and 80% receiving the combination would attain the goal diastolic BP of <90 mm Hg. However, larger sample sizes were chosen because of the need to provide sufficient patients for entry into phase B. With an additional allowance for dropouts the number of patients required for randomization was estimated to be 350, or 50 patients per hospital.

The patients were assigned to the 3 treatment groups using simple randomization in a ratio of 3:5:6. The randomization was blocked after every 14 patients within each hospital and also across hospitals, i.e., each 2 consecutive patients across 7 hospitals equalled the block of 14. More patients were randomized to N than to B to gain more experience with the former drug.

The placebos, which appeared identical to the active drugs, were used to maintain the double-blind nature. The initial dose were 80 mg of N and 5 mg of B, each given once daily before breakfast in the morning. Patients were seen in 1 week and were managed as follows: If the diastolic BP was >75 mm Hg, B or its placebo was increased to 10 mg, which dose was continued througout the study; if the diastolic BP fell to ≤75 mm Hg, the patient was removed from the trial. N was titrated

TABLE I Baseline Characteristics of 365 Randomized Patients

	Bendroflu-methiazide (B)	Nadolol (N)	B+N
No. of pts	81	132	152
Age (yr)	50.9 ± 1.1	49.4 ± 1.0	51.1 ± 0.8
Black	65%	62%	57%
White	35%	38%	43%
Weight (kg)	196.7 ± 4.1	197.8 ± 3.7	192.0 ± 2.7
Blood pressure (mm Hg) (Standing)			
Systolic	146.7 ± 1.7	145.5 ± 1.4	148.9 ± 1.4
Diastolic	103.7 ± 0.8	103.3 ± 0.6	104.9 ± 0.6
Blood Pressure (mm Hg) (Sitting)			
Systolic	146.9 ± 1.6	144.7 ± 1.2	148.4 ± 1.3
Diastolic	101.8 ± 0.6	101.3 ± 0.4	101.8 ± 0.4
Heart rate (beats/min)	77.1 ± 1.1	76.2 ± 0.9	76.4 ± 0.9
Uric acid (mg/dl)	6.0 ± 0.2	6.4 ± 0.1	6.2 ± 0.2
Serum potassium (mEq/liter)	4.2 ± 0.0	4.2 ± 0.0	4.3 ± 0.0
Creatinine (mg/dl)	1.2 ± 0.0	1.1 ± 0.0	1.2 ± 0.0
Fasting blood sugar (mg/dl)	99 ± 2.0	100 ± 2.0	97 ± 1.0
Cholesterol (mg/dl)	233 ± 7.0	220 ± 4.0	223 ± 4.0
Triglycerides (mg/dl)	171 ± 14.0	176 ± 11.0*	147 ± 8.0*

* Significance of difference <0.05.
Values are mean ± standard error of the mean.

TABLE II Mean Changes in Sitting Blood Pressure (BP) and Heart Rate in Blacks and Whites After 12 Weeks of Treatment

Variable	Bendro	Nadolol	Combination	Significance
Number (blacks/whites)	68 (42/36)	104 (61/43)	136 (75/61)	
Attained goal blood pressure	46%	49%	85%	B–C‡, N–C‡
Blacks	46%	31%	84%	B–C‡, N–C‡
Whites	46%	77%	85%	B–N†, B–C‡
p Value	NS	<0.001	NS	
Baseline systolic BP (mm Hg)	146.8 ± 1.7	144.1 ± 1.4	147.7 ± 1.3	
Blacks (178)	148.6 ± 2.2	145.1 ± 1.8	149.6 ± 1.9	
Whites (130)	143.8 ± 2.6	142.7 ± 2.1	145.5 ± 1.9	
Change systolic BP (mm Hg)	−17.4 ± 1.7	−10.5 ± 1.6	−25.3 ± 1.4	B–N†, B–C‡, N–C
Blacks	−19.9 ± 2.4	−5.8 ± 2.1	−27.3 ± 2.1	B–N‡, B–C*, N–C†
Whites	−13.3 ± 2.0	−17.2 ± 2.3	−22.9 ± 1.7	N–C*, B–C‡
Baseline diastolic BP (mm Hg)	101.0 ± 0.6	101.4 ± 0.4	101.6 ± 0.4	
Blacks (178)	101.2 ± 0.8	101.2 ± 0.5	101.9 ± 0.6	
Whites (130)	100.5 ± 0.8	101.6 ± 0.7	101.2 ± 0.6	
Change diastolic BP (mm Hg)	−11.6 ± 1.2	−12.1 ± 0.8	−17.9 ± 0.7	B–C‡, N–C‡
Blacks	−12.4 ± 1.5	−9.6 ± 0.9	−18.1 ± 1.0	B–C‡, N–C‡
Whites	−10.2 ± 1.7	−15.6 ± 1.2	−17.7 ± 0.8	B–N†, B–C‡
Baseline pulse rate (beats/min)	76.3 ± 1.1	75.7 ± 1.0	75.4 ± 0.8	
Change pulse rate (beats/min)	0.8 ± 1.4	−16.1 ± 1.0	−15.8 ± 0.8	B–N‡, B–C‡

* $p < 0.05$.
† $p < 0.01$.
‡ $p < 0.001$.
B–N = significance of the difference between bendroflumethiazide (B) and nadolol (N); B–C = significance of the difference between B and combination (C); N–C = significance of the difference between N and C; NS = not significant.

as necessary biweekly until goal diastolic BP, defined as <90 mm Hg, was achieved. The once-daily doses of N or its placebo were increased from 80 to 160 to 240 mg. After attaining goal diastolic BP, each regimen was then continued at the same dosage until the 12th week after randomization. If the diastolic BP was >119 mm Hg at any clinic visit or >104 mm Hg at 2 successive clinic visits during this phase of the study, the patient was terminated from the study. These patients were removed from the trial and were treated openly. They did not enter phase B. The duration of phase A was 12 weeks and included initially 4 visits at 1-week intervals followed by 4 biweekly visits.

Postrandomization period (phase B): The effects of adding hydralazine to the treatment regimens of patients who failed to achieve the goal diastolic BP of <90 mm Hg during phase A was assessed at completion of phase B. Hydralazine was added in an initial dose of 25 mg twice daily, but was increased to 50 mg and then 100 mg twice daily until either the diastolic BP fell to <90 mm Hg or intolerable side effects supervened. The duration of phase B was 9 weeks. Patients were seen at 1 week for the first week only and then were scheduled for biweekly visits.

TABLE III Terminations During Phase A Treatment Period

Termination Cause	Bendro*	Nadolol	Combination
DBP elevated†	9	9	0
Dropouts	3	9	7
Lapse in treatment	0	4	3
Drug intolerance	0	2	4
Cardiovascular complication	1	1	1
All other	0	3	1
Total	13	28	16
No. randomized	81	132	152
Percent terminations	17	21	11

* Bendroflumethiazide, 5 to 10 mg/day.
† DBP >119 mm Hg at any visit, DBP 114–119 mm Hg on 2 successive weekly visits during titration or >104 mm Hg on 2 successive visits after maximum titration.
DBP = diastolic blood pressure.

Characteristics of randomized patients: The mean BP at the time of randomization was 146.7/101.6 mm Hg and did not differ significantly among the treatment groups (Table I). The mean age was 50.4 years. The racial distribution was 61% black and 39% white. There were no significant differences in these characteristics among treatment groups or in heart rate and the various blood chemistry values except triglycerides, which averaged lower ($p < 0.05$) in the group that received both drugs (Table I).

Statistical analysis of results was carried out using the 2-sample t test to compare mean values between independent samples. The comparison of percentages between independent samples was accomplished using the Z test based upon the normal distribution. Comparison of changes within patients was done using the paired t test.

Results

Changes in blood pressure during phase A: The percentage of patients who achieved goal BP (defined as a diastolic BP <90 mm Hg) at the last or 12th week of treatment was determined (Table II, Fig. 1). In the patients treated with N alone who either completed the 12-week treatment period or else were terminated because of elevated diastolic BP, 49% were controlled, 44%

TABLE IV Leading Side Effects in Phase A*

	% Complaining		
Complaint Any Visit	Bendro	Nadolol	Both Drugs
Weakness	3	0	1
Lethargy	6	2	6
Impotence	9	4	2
Postural dizziness	3	0	2
Insomnia	0	3	1

* Complaint made on at least 2 visits during Phase A but not during placebo baseline period.
Bendro = bendroflumethiazide.

were not controlled and 7% had to be terminated for elevated BP during the treatment period. With B, 46% were controlled, 43% were not controlled and 11% had to be terminated for BP above the acceptable range. The combination of the 2 drugs was significantly more effective ($p < 0.001$) than either of the single drug regimens, with 85% controlled, only 15% uncontrolled and no terminations because of high BP.

In the patients receiving N alone, 31% achieved goal BP with 80, 10% with 160 and 13% with 240 mg/day. In the group receiving the combination, which included 10 mg of B, 46% attained goal BP with the 80-mg dose of N, 29% with 160-mg dose and 10% with the 240-mg dose. Forty-three percent of the patients who responded to B alone did not achieve goal blood pressure immediately after taking the 10-mg dose, but required several more weeks before this dose decreased the diastolic BP to <90 mm Hg.

The average changes in BP, which includes only the patients who completed phase A of the trial, were as follows: of the 104 patients assigned to N, the BP averaged 144.1/101.4 during the prerandomization period and 133.6/89.3 mm Hg by the end of the 12-week treatment period, a reduction of 10.5/12.1 mm Hg (Table II). The average BP of the 68 patients who received B decreased from 146.8/101.0 mm Hg before randomization to 129.4/89.4 mm Hg at the end of the treatment period, a reduction of 17.4/11.6 mm Hg. The reduction in systolic but not diastolic BP was significantly greater with B than with N ($p < 0.01$). With the combination of B+N, the BP averaged 147.7/101.6 mm Hg before treatment and 122.4/83.7 mm Hg at the end of treatment, an average reduction of 25.3/17.9 mm Hg. The reductions in both systolic and diastolic BP were significantly greater with the combination than with either of the drugs given alone ($p < 0.001$/$p < 0.001$).

A racial difference was observed in the response to N (Table II). In white persons the average decrease in diastolic BP was 15.6 mm Hg, significantly ($p < 0.001$) greater than the 9.6 mm Hg average reduction attained in black persons. In the patients treated with N alone, 77% of whites achieved a diastolic BP <90 mm Hg, compared with only 31% of blacks ($p < 0.001$). By contrast, the diastolic BP response of the blacks to the thiazide diuretic was somewhat, but not significantly, greater than the response of the whites (12.4-mm Hg reduction in blacks and 10.2-mm Hg in whites). The greater reduction of systolic BP to B in blacks (19.9 mm Hg) compared with whites (>13.3 mm Hg) was almost significant ($p = 0.055$). There was essentially no racial difference in the response of diastolic BP to the combination of the 2 drugs, with average reductions of 17.7 mm Hg in whites and 18.1 mm Hg in blacks.

The degree of reduction of diastolic BP was correlated with the height of the baseline diastolic BP in that the higher the baseline diastolic BP, the greater the decrease. For example, in patients with a pretreatment diastolic BP of 95 to 99 mm Hg, the reduction of diastolic BP averaged 8.8 mm Hg with N, 8.2 mm Hg with B and 16.8 mm Hg with the combination. In contrast, the reductions of diastolic BP in patients with baseline levels of 110 to 114 mm Hg averaged 19.3 mm Hg with N, 23.5 mm Hg with B and 24.1 mm Hg with the combination. To assess the effects of age in the response to the various regimens, the patients were subdivided into 2 age groups, those age 50 years or less and those older than 50 years. The mean reductions in diastolic BP were almost identical in the 2 groups.

Pulse rate did not change significantly with B alone; the average pulse rate increased, but only by 0.8 beats/min. The average pulse rate decreased significantly from baseline, by 16.1 beats/min with N alone and by 15.8

TABLE V Changes in Serum Chemistry Values After 12 Weeks of Treatment

Serum Chemistry	Bendro	Nadolol	Both Drugs
Potassium (mEq/liter)			
No. of patients	68	99	134
Baseline	4.26 ± 0.05	4.26 ± 0.04	4.28 ± 0.03
Change	−0.57 ± 0.06†	0.08 ± 0.04	−0.44 ± 0.05†
Uric acid (mg/dl)			
No. of patients	63	97	126
Baseline	6.7 ± 0.2	6.4 ± 0.1	6.5 ± 0.1
Change	1.7 ± 0.2†	0.4 ± 0.1*	1.9 ± 0.1†
Fasting glucose			
Number of patients	67	97	133
Baseline	100.6 ± 2.0	103.0 ± 1.9	97.2 ± 1.3
Change	+6.1 ± 2.1†	+2.4 ± 1.8	+7.4 ± 1.1†
Cholesterol			
No. of patients	60	88	121
Baseline	234.9 ± 8.0	223.6 ± 5.0	227.2 ± 4.9
Change	11.5 ± 4.3†	−1.5 ± 3.9	3.5 ± 3.6
Triglycerides			
No. of patients	66	94	132
Baseline	169.6 ± 14.2	172.3 ± 11.6	149.3 ± 8.3
Change	34.6 ± 14.8*	38.7 ± 13.2*	67.8 ± 11.9†

Values are mean ± standard error of the mean.
Significant changes from baseline:
* $p < 0.01$.
† $p < 0.001$.
Bendro = bendroflumethiazide.

beats/min with the combination ($p < 0.001$). Body weight decreased on the B and B+N regimens. At the second visit after randomization, when most patients had received their maximal dose, the mean reductions were 3.0 and 2.8 pounds body weight, respectively, for B alone and for the B+N. Body weight did not change in the patients taking N alone.

Terminations: Thirteen (16%) of the randomized patients receiving B, 28 (21%) of those receiving N and 16 (11%) of those receiving both drugs were terminated from the study (Table III). Nine patients receiving each of the single drug regimens were terminated because of an elevated diastolic BP. None of the patients receiving both drugs were terminated for this reason. Two patients receiving N, 4 receiving both drugs and none receiving B were terminated because of suspected drug intolerance.

Side effects: The only complaints for each patient that were considered as possibly drug-related were those that were not manifest during the prerandomization placebo period. To be counted as a side effect, the complaint also had to be registered on more than 1 clinic visit during the drug treatment period. With these criteria, subjective side effects were relatively few (Table IV). The most frequently noted complaint was sexual impotence. This occurred with all regimens, but most frequently with B alone (9% of patients). Also, the complaints of weakness, lethargy and postural dizziness, while relatively infrequent were associated mostly with the thiazide-containing regimens. An exception was insomnia, which occurred in 3% of the patients receiving N, none receiving B and 1% of patients receiving B+N.

Serum chemistries: Changes in serum chemistries reflected primarily those usually associated with the thiazide diuretics (Table V). Serum potassium decreased significantly and serum uric acid increased significantly (both $p < 0.01$) with B and B+N, but they remained essentially unchanged with N alone. Fasting serum glucose increased by an average of 6.0 and 7.4 mg/dl on B and B+N, respectively, and remained essentially unchanged after treatment with N alone. There was no significant change in serum creatinine with any of these regimens.

Baseline triglyceride levels averaged 149.3 mg/dl in patients receiving the combination of drugs, compared with 169.6 and 172.3 mg/dl for the B and N groups, respectively. Serum triglycerides increased significantly, by 34.6 mg/dl (20%) with B, 38.7 mg/dl (23%) with N and 67.8 mg/dl (45%) with the combination of drugs. Serum cholesterol increased 11.5 mg/dl (4.9%) after B alone. Serum cholesterol averaged 1.5 mg/dl lower in patients receiving N alone. With B+N, it increased 3.5 mg/dl (1%).

Changes during phase B, addition of hydralazine: The number of nonresponders (failure to achieve a diastolic BP <90 mm Hg) during phase A who entered phase B, when hydralazine was added, included 30 receiving B, 40 receiving N and 19 receiving the combined drugs (Table VI). The addition of hydralazine resulted in similar decreases in diastolic BP, averaging 7.5 mm Hg with either B or N alone and 7.7 mm Hg with the combination. The percentage of these previously uncontrolled patients who attained a diastolic BP of <90 mm Hg after the addition of hydralazine was 57% in the patients receiving B alone, 68% in the N-treated patients and 58% of those receiving the combination of these drugs. Thus, hydralazine was effective in more than half of the previously incompletely controlled patients. In contrast to the diuretic and beta blocker, there were no racial differences in the response to hydralazine. Heart rate increased by an average of 5.6, 2.4 and 4.1 beats/min after hydralazine was added to B, N and the combination, respectively (Table VI).

Terminations from the study because of side effects were few. One patient receiving hydralazine with B requested discontinuation because of impotence. Four patients receiving N with hydralazine and 1 patient receiving all 3 drugs were terminated because of headache. There were no other terminations associated with drug intolerance.

Discussion

In designing the trial, care was taken to minimize known sources of bias. The double-blind nature was maintained as much as possible, with each drug and its placebo identical in appearance. Possible carryover effects from the prior regimen that may occur with crossover designs were avoided by using parallel treatment groups. The randomization procedure was successful in preventing significant differences between treatment groups with respect to any of the important prerandomization characteristics. The sample size quotas were met on time and with no great differences in recruitment among the various hospitals. All of the randomized patients were tested for compliance, and on the basis of tablet counts, all ingested ≥80% of the placebos prescribed during the prerandomization period. The results reported, therefore, may be better than the general experience because identified noncompliant patients were excluded.

The 2 drugs given as single entities had approximately the same effectiveness. However, the combination of the 2 drugs was considerably more efficacious than either drug used alone. The percentage of patients whose diastolic BP was controlled <90 mm Hg (goal diastolic BP) was significantly greater with the combined drugs than with either agent used alone. In the group receiving the combination, 85% achieved goal diastolic BP, compared with 49% with N alone and 46% with B. This result is similar to that in a previous trial by our group.[8] In that study, propranolol alone was compared with propranolol plus hydrochlorothiazide in patients with mild hypertension. Propranolol controlled the diastolic BP in 52% of these patients, whereas with the combination, 81% attained goal diastolic BP. The impressive results using the combined drugs should not negate the fact that N alone controlled BP in half of the patients, indicating that it is a highly effective treatment for hypertension, although not as effective as the N-diuretic combination.

B produced a somewhat greater fall in systolic BP than N. This greater effect of the diuretic compared with the beta blocker on systolic BP was also found in

TABLE VI Mean Changes in Sitting Blood Pressure (BP) and Heart Rate After 9 Weeks of Added Hydralazine

Variable	Hydralazine, 25–100 mg b.i.d., plus			
	Bendro	Nadolol	Combination	Significance
No. of patients	30	40	19	
Systolic BP (mm Hg) prehydralazine	134.1 ± 1.5	143.0 ± 2.1	133.6 ± 2.4	B + H*, N + H†, B + N
Change systolic BP (mm Hg)	−4.3 ± 1.9	−7.7 ± 1.9	−6.9 ± 2.0	
Diastolic BP (mm Hg) prehydralazine	95.5 ± 1.0	94.9 ± 0.7	95.5 ± 1.0	B + H†, N + H†, B + N
Change diastolic BP (mm Hg)	−7.5 ± 1.0	− 7.5 ± 1.1	−7.7 ± 1.1	
Pulse rate beats/min prehydralazine	74.2 ± 1.9	59.8 ± 1.4	57.2 ± 1.6	B + H‡
Change pulse rate (beats/min)	5.6 ± 2.0	2.4 ± 1.4	4.1 ± 2.0	

* $p < 0.05$.
† $p < 0.001$.
‡ $p < 0.01$.
B + H = significance of change after adding hydralazine to bendroflumethiazide (Bendro); N + H = significance of change after adding hydralazine to nadolol; B + N + H = significance of change after adding hydralazine to the combination of B + N.

a previous study.[9] Although the reason has not been clarified, it seems likely that the reduction in plasma volume and tendency to a somewhat low cardiac output may be important factors.

Although the population was predominantly black, the randomized group included 142 white patients, which was sufficient to make valid black-white comparisons in responsiveness to the various treatments. N was significantly more effective as an antihypertensive agent in whites than in blacks. The reverse was found with B, which was somewhat, although not significantly, more effective in blacks than in whites. Similar black-white differences in the antihypertensive response to beta blockers and to diuretics were found in the Veterans Administration Cooperative Study comparing propranolol with hydrochlorothiazide.[9] Seedat[10] also observed that a diuretic was more effective than a beta blocker in blacks.[10] Hypertensive blacks are said to exhibit higher plasma volumes and lower plasma renin activities than hypertensive whites,[11,12] although other investigators have disputed these claims.[13,14] Laragh postulated that patients with high plasma volumes have a "volume-dependent" hypertension that will respond to reduction of extracellular and plasma volume with diuretics, while those with high plasma renin activity and low plasma volumes should respond to beta blockers.[15]

Few side effects were noted with either drug in this trial. The most frequent complaints were impotence, lethargy, weakness and postural dizziness. These side effects were encountered more often with B than with N, although they were uncommon with both drugs. In the prior trial of propranolol versus hydrochlorothiazide,[9] subjective side effects also were uncommon. The most frequent hydrochlorothiazide-associated complaints in that study were diarrhea, impotence, constipation and numbness, and the most frequent side effects among propranolol-treated patients were insomnia, swelling of the hands and vivid dreams. However, as in the present trial, the number of possibly drug-related complaints was relatively small.

Addition of hydralazine to the patients who failed to reach goal diastolic BP with B, N or both resulted in a similar decrement of blood pressure in each of the 3 treatment groups. The average additional reduction was about 7.5 mm Hg in all 3 treatment groups. This response is similar to that achieved in a previous Veterans Administration Cooperative Study.[16] In the latter study, hydralazine was added to the regimen of patients who failed to achieve a diastolic BP of <90 mm Hg with hydrochlorothiazide alone. These patients had an additional average decrease in diastolic BP of 8.8 mm Hg 3 months after adding hydralazine. Although these reductions may seem small, the BP had already been reduced, although not to goal levels, by the original therapy. Furthermore, the lower the level of BP the less will be the reduction following an antihypertensive drug. For example, in phase A of the present trial the reduction in diastolic BP after B averaged 8.2 mm Hg in patients with pretreatment baseline levels of 95 to 99 mm Hg, 11.6 mm Hg with 100 to 104 mm Hg diastolic BP prerandomization and 18.6 mm Hg with entry diastolic BP of 105 to 114 mm Hg. If the diastolic BP had not already been partially reduced by the initial treatment, the decrease associated with hydralazine might have been considerably greater.

Side effects during hydralazine administration were not impressive. The most frequent side effect was moderately severe to severe headache, which occurred in 4 patients receiving N and 1 receiving the combination. Headache of this severity was not noted in the groups receiving hydralazine and B alone. Although the incidence of headache was too low to make firm conclusions, these results suggest that thiazide diuretics may prevent hydralazine-induced headache, possibly by reducing plasma and extracellular volume. Except for headache, the side effects complained of most frequently during hydralazine treatment were the same as those present before the drug, including lethargy, weakness and impotence.

Elevation of serum triglyceride levels after either thiazide diuretics of beta blockers have been noted previously by other investigators.[17,18] The increase was especially marked after the combined drugs, when the increase averaged 47% above baseline values. The clinical importance of this change is not clear, however,

because of the role of triglycerides in the pathogenesis of atherosclerosis is not well defined. Serum cholesterol increased modestly after B but not after N. These observations with respect to serum cholesterol are also similar to those reported by others.[17,19]

In conclusion, as judged by the results of this trial, N appears to be a safe and effective antihypertensive agent. Its long action permits once-daily dosage, which should facilitate compliance and offer an advantage over shorter-acting beta-adrenergic blocking drugs. The present results suggest that approximately half of the patients with mild and moderate hypertension will achieve a diastolic BP of <90 mm Hg with N alone, a further one-third with the addition of B and 10% more with the addition of hydralazine. Thus, approximately 85% of patients can be controlled by a relatively simple step-care regimen involving once-daily doses of 1 or 2 agents, with the third drug, hydralazine, reserved for the small percentage of nonresponders. Also, because of the differing racial response to these 2 agents, it would appear advisable to initiate treatment with B in blacks and with N in whites.

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Appendix

Exclusions

1. Known adverse reactions to hydrochlorothiazide, beta-blocking agents or hydralazine
2. Malignant hypertension including hypertensive neuroretinopathy
3. Hypertensive retinopathy (K–W scale) greater than grade II
4. Acute hypertensive encephalopathy
5. Cerebral or subarachnoid hemorrhage
6. Atherosclerotic stroke within the past six months
7. Myocardial infarction within 6 months or angina pectoris greater than New York Heart Association class II
8. Patients currently taking "digitalis-like" preparations
9. Patients with primary valvular heart disease (e.g., rheumatic or congenital)
10. Atrial fibrillation
11. Heart block greater than 1st degree or Wolff-Parkinson-White syndrome or, if not currently receiving beta-blocking agent, sinus bradycardia (<60 beats/min)
12. Patients with Raynaud's disease or symptomatic and objective peripheral vascular disease
13. Asthma
14. Cor pulmonale due to obstructive lung disease
    Obstructive lung disease with asthmatic wheezes
15. Diabetes requiring treatment other than diet
16. Collagen vascular disease
17. Surgically curable forms of hypertension—pheochromocytoma, primary aldosteronism, Cushing's disease or renovascular hypertension
18. History or evidence of psychiatrically documented nonsituational, clinically important mental depression
19. Malignancy including leukemia and lymphoma
20. Drug abuse, severe organic brain damage or severe alcohol abuse
21. Patients on adrenergic augmenting psychotropic drugs including monoamine oxidase inhibitors, amphetamine and its derivatives
22. Patients regularly using transcendental meditation, biofeedback relaxation and/or similar techniques
23. Serum creatinine >2.0 mg/dl
24. Congestive heart failure as evidenced by at least 2 of the following:
    A. Recent dyspnea or orthopnea not of pulmonary origin
    B. Ventricular diastolic gallop (S_3)
    C. Basal pulmonary rales
    D. Cardiothoracic ratio greater than 0.5 on x-ray
25. Patient unreliable
26. Patient unable or unwilling to participate or refuses to sign the informed consent

Participants

Co-Chairmen: Edward D. Freis, MD (Washington, D.C.) and J. R. Thomas, MD (Memphis, TN)

Principal Investigators: Frederick N. Talmers, MD (Allen Park, MI); William C. Cushman, MD (Jackson, MS); Harold Schnaper, MD (Birmingham, AL); Thomas J. White, MD (Memphis, TN); Orlando Fernandez, MD (Miami, FL); Eli A. Ramirez, MD (San Juan, PR); Ibrahim Khatri, MD (Washington, D.C.)

Nurses: Barbara Gregory, RN, and Madeline Metcalfe, RN (Washington, D.C.); Chris Grant, RN, and Julie Pawelak, RN (Allen Park, MI); Pauline Derrington, RN (Jackson, MS);

Anita McKnight, RN, Susan Reece, RN, and Kristina Grossman, RN (Memphis, TN); Mary H. Smith, RN, and Eileen Haran, RN (Miami, FL); Maria Natal, RN (San Juan, PR); William Hackett, RN, and Donald Quinn, PA (Birmingham, AL)

Biostatistician: Thomas J. Tosch, PhD

Forms Reviewers: Janice Ivie (Memphis, TN); Mary Ellen Vitek and Jane Foregger (Hines, IL)

Central Research Pharmacist: Larry Young, RPh

Operations Committee: Walter Kirkendall, MD, James C. Gunnels, MD, C. Mort Hawkins, DS

Consultants: Barry J. Materson, MD, John C. Alexander, MD, Joseph Meyer, PhD, Dionisio L. Caloza, Jr, MD

Hines Cooperative Studies Program Coordinating Center Human Rights Committee: Jennie McKoy; Patrick Moran; Mary Davidson, PhD, Kenneth Elmer, Rev. Martin Feldbush

Cooperative Studies Program Central Administration: James A. Hagans, MD, PhD, and Ping Huang, PhD (VA Central Office, Washington, D.C.); William G. Henderson, PhD, Janice Ivie, Mary Ellen Vitek (Cooperative Studies Program Coordinating Center, Hines, IL); Mike Sather, RPh, MS (Cooperative Studies Program Research Pharmacy Coordinating Center, Albuquerque, NM)

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