

Comparison of Prazosin with Hydralazine in Patients Receiving Hydrochlorothiazide

A Randomized, Double-blind Clinical Trial

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SUMMARY The antihypertensive efficacy and the incidence of side effects of prazosin and hydralazine were compared in a randomized, double-blind trial in 232 adult male hypertensives who could not be controlled with hydrochlorothiazide alone. There were no significant differences between regimens in the percentage of patients who attained goal blood pressure (reduction of diastolic blood pressure to below 90 mm Hg and at least 5 mm less than the baseline randomization pressure), effect on pulse rate or the incidence or reasons for terminations. Absolute reduction of blood pressure was similar for both drugs except for sitting systolic pressure at 3 and 6 months, when prazosin effected a 3.7- and 3.6-mm Hg greater response ($p < 0.05$). Orthostatic dizziness ($p < 0.005$), sexual dysfunction ($p < 0.02$), and nightmares ($p < 0.02$) were more frequent with prazosin than with hydralazine; nevertheless, patient compliance was similar for both drugs. An unexpected finding was the lack of pulse rate increase associated with hydralazine, particularly in older patients.

HYDRALAZINE AND PRAZOSIN are generally considered as alternative choices within the same levels of stepped-care management of hypertension. The successful combination of either of these drugs with diuretic and β -adrenergic inhibitory compounds has provided a rationale for more widespread use.¹⁻¹⁰

The antihypertensive mechanisms of hydralazine are not well established.¹ Although prazosin inhibits phosphodiesterase,¹¹ it is not known if this action is clinically important. The antihypertensive properties of the medication are attributable primarily to blockade of postsynaptic α -adrenergic receptors (α_1) of the vascular smooth muscle.^{9, 10} Both medications decrease total peripheral resistance and increase vascular cyclic AMP.^{1, 9-11} Neither one manifests central, vagal, β -adrenergic receptor, neuronal or ganglionic blocking activity.^{1, 9, 10} Prazosin differs from hydralazine in that it dilates capacitance as well as resistance vessels,¹² and by an apparent lack of induction of marked tachycardia and hyperreninemia.^{9, 10, 13, 14}

No large scale, double-blind systematic studies have compared the antihypertensive efficacy of hydralazine and prazosin. The available data, however, suggest that while the drugs are of similar potency, the incidence of side effects, some of them necessitating withdrawal, may be more pronounced with hydralazine.¹⁵⁻¹⁷

The purpose of this study was to compare the antihypertensive efficacy and the incidence of side effects of prazosin and hydralazine through a randomized, double-blind clinical trial in patients whose blood

pressure was not successfully controlled with hydrochlorothiazide alone.

Methods

Objectives of the Study

The study was designed to determine (1) the antihypertensive efficacy of prazosin compared with hydralazine (both given in addition to hydrochlorothiazide) on the basis of the percentage of patients in each group who at the 5-month and 6-month postrandomization visits attained an average reduction of sitting diastolic pressure to below 90 mm Hg and at least 5 mm less than the baseline randomization pressure, and the mean changes in blood pressure between the randomization visit (hydrochlorothiazide alone) and the average of the 5-month and 6-month postrandomization visits (hydrochlorothiazide plus either prazosin or hydralazine); (2) the acceptability of both regimens over a 6-month experience based on the incidence of toxic reactions and side effects; and (3) the degree of chronotropic effect upon the heart of both regimens as measured by the change in pulse rate at the same levels of blood pressure response.

Selection of Patients

Male patients, 21-74 years of age, whose average diastolic pressure at two successive clinic visits was 95-114 mm Hg, were recruited from the admitting room, outpatient clinics and hospital. Patients were excluded from the study if they had severe complications of hypertension, serious systemic disease or conditions that would contraindicate the drug regimens used. A complete list of exclusions is presented in appendix A. Patients receiving antihypertensive therapy were allowed to enter the study, provided the diastolic blood pressure was 95-114 mm Hg after medication was discontinued for 4 weeks.

The blood pressures were measured at all visits after the patients lay undisturbed in a quiet room for 10-15 minutes. Three readings were taken in the right arm in

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the sitting position at 1-minute intervals using a standard mercury sphygmomanometer. The average of these three readings was recorded, followed by the pulse rate counted for 1 minute. A large cuff was used when the circumference of the arm exceeded 32 cm. On the visit when hydrochlorothiazide was started, the randomization visit, the 4- or 6-week postrandomization visit and the last study visit, the blood pressure average was similarly determined in the supine position and in the erect position after standing 2 minutes, followed by counting the pulse for 1 minute.

The measurements used throughout the study to determine therapeutic decisions and end points were the average of three diastolic fifth-phase (Korotkoff) readings in the right arm in the sitting position.

Prerandomization Trial Period

The nature of the study was explained to the patient and a signed informed consent was obtained.* A history and physical examination were performed. Laboratory studies included chest roentgenogram, ECG, CBC, urinalysis, fasting serum sugar, SGOT, alkaline phosphatase, and serum determinations of potassium, uric acid, cholesterol, triglycerides, creatinine and antinuclear antibody. At all visits, a checklist of the known or suspected side effects of the drugs was reviewed with the patient.

If the patient's diastolic blood pressure was in the range of 95–114 mm Hg and there were no exclusion factors, he was given placebo capsules and was instructed to take them three times daily. He was further instructed to return the remaining capsules at each clinic visit, and pill counts were made to test compliance. Compliance was recorded as satisfactory if the patient took from 10% less to 10 pills more than the exact prescribed number of each medication.

The patients were allowed a maximum of four biweekly visits to qualify for hydrochlorothiazide treatment or were dropped from the study. Within this "placebo period," if the diastolic blood pressure averaged 95–114 mm Hg without a pill count violation on two successive clinic visits, the patient was placed on hydrochlorothiazide, 25 mg three times daily, and continued on placebo. Two weeks later, if the average of three diastolic blood pressure readings was 90–114 mm Hg and the pulse rate below 95 beats/min without pill count violation, the patient was randomized; otherwise he was excluded from the study. The average pressure of the randomization visit was designated as the baseline pressure for the patient.

Postrandomization Period

In substitution of the placebo look-alike capsules, patients were randomly assigned in a double-blind fashion to one capsule three times daily of "Zarpine," the code name for the capsules that contained either prazosin or hydralazine. Hydrochlorothiazide was

continued at the same dose. Zarpine No. 1 contained either 1 mg of prazosin or 10 mg of hydralazine, Zarpine No. 2 either 2 mg of prazosin or 25 mg of hydralazine, and Zarpine No. 3 either 5 mg of prazosin or 50 mg of hydralazine.

The patients were seen biweekly for the first four visits after randomization and then every 4 weeks for the final four visits of the postrandomization period. If the pill count indicated that the patient had taken at least 80% of the expected dose, the dose of Zarpine was increased from No. 1 to No. 2 and then to No. 3, with the purpose of achieving goal blood pressure, defined as a sitting diastolic pressure less than 90 mm Hg and 5 mm Hg below the baseline pressure for the patient. If hypotensive symptoms developed or if the heart rate was greater than 99 beats/min, the strength of the Zarpine capsules was decreased to the next lower strength, or if on the weakest strength, decreased to twice daily, to once daily and then discontinued if symptoms persisted.

Laboratory tests performed at prerandomization were repeated at 4, 12 and 24 weeks after randomization. ECGs were obtained at the initial study visit, at randomization and 12 and 24 weeks later.

Patients were terminated from the study and placed on appropriate antihypertensive treatment if they developed severe complications of hypertension, conditions that would interdict the drug regimens used, inadequate control of hypertension, or failed to comply with clinic appointments without proper excuse. Appendix B is a complete list of reasons for termination.

Statistical Methods

The chi-square test was used for comparison of the discrete variables between the two drug regimens, the paired *t* test for individual changes in continuous variables, and the two-sample *t* test for comparison of continuous variables between the two regimens.

Results

Three hundred ninety-two patients were entered into the study at the six participating hospitals; 232 were eventually properly randomized, 111 to prazosin and 121 to hydralazine.

Prerandomization Losses

One hundred sixty patients were excluded before randomization for reasons specified in the protocol. Fifty-five (34%) were excluded because either blood pressure or pulse rate was out of the acceptable range; 21 of these responded to hydrochlorothiazide alone with a diastolic blood pressure below the acceptable lower limit of 90 mm Hg. Seventy-one (44%) were excluded because they were noncompliant, 13 (8%) at their own request, and the remaining 21 (13%) for miscellaneous reasons.

Baseline Data

The baseline data at randomization of the 232 patients randomized and of the 198 patients who com-

*The study was approved by the Human Use Committee at each hospital and conformed to the Helsinki declaration.

TABLE 1. *Baseline Data at Randomization*

	All randomized		Completed study	
	Prazosin	Hydralazine	Prazosin	Hydralazine
n	111	121	92	106
Sitting pulse (beats/min)	77.5	†80.5	77.5	79.9
Standing pulse (beats/min)	82.6	*84.9	82.1	84.2
Sitting DP (mm Hg)	100.2	98.9	99.6	98.7
Standing DP (mm Hg)	100.5	99.5	100.0	99.4
Sitting SP (mm Hg)	137.3	137.6	137.6	137.3
Standing SP (mm Hg)	135.1	137.3	135.3	137.3
Weight (kg)	84.1	86.3	83.5	85.3
Serum K (mEq/l)	3.76	3.72	3.75	3.72
Uric acid (mg/dl)	8.05	7.91	8.12	7.84
Creatinine (mg/dl)	1.20	1.14	1.19	1.14
Cholesterol (mg/dl)	230.5	228.8	228.9	222.7
Glucose (mg/dl)	110.0	112.8	107.7	112.9
Triglycerides (mg/dl)	177.4	183.1	177.0	178.9
Age (years)	50.7	52.4	51.5	52.1
Race				
White (%)	50	60	50	59
Black (%)	50	40	50	41

Significance between regimens:

* $p < 0.1$.† $p < 0.01$.

Abbreviations: DP = diastolic pressure; SP = systolic pressure.

pleted 6 months of treatment are shown in table 1. At randomization, the sitting pulse was significantly different between both groups ($p < 0.01$), while it was borderline ($p = 0.06$) for the standing pulse. None of the other differences in this table are significant.

Postrandomization Losses

Thirty-four patients were lost after randomization, 19 were receiving prazosin and 15 hydralazine. The principal reasons for postrandomization loss were failure to return to the clinic in 13 instances and at the patient's own request in five. Other causes were angina pectoris in four patients (three of whom were taking hydralazine), blood pressure exceeding protocol criteria in three patients using prazosin, and miscellaneous reasons in nine patients. Only one patient was dropped for rapid heart rate; he was receiving prazosin.

The records of the 13 patients who failed to return to the clinic and of the five who requested to be discontinued from the study were examined in detail retrospectively. Eleven had been randomized to prazosin and seven to hydralazine. Eleven were lost within the first 2 months after randomization, five of whom had only one or no postrandomization visit. No drug-related reason could account for discontinuing treatment except for one patient, who had discontinued prazosin for 1 week to undergo a prostatectomy. Upon resumption of the same dosage, he had an episode of syncope and thereafter refused to take the drug. This was the only "first-dose" effect observed during the study. Including this patient, two patients

were lost because of dizziness and both were on prazosin.

Effects on Blood Pressure

The antihypertensive effects of the two drug regimens in the patients who completed 6 months on treatment are shown in table 2. The 1- and 3-month blood pressure figures correspond to the readings of those clinic visits, but the 6-month figures represent the average of the 5- and 6-month clinic readings. The greatest difference between regimens in attainment of goal blood pressure was at 6 months, when it was 44.6% of prazosin-treated patients and 39.6% of hydralazine-treated patients. Even then, the difference was not significant ($p > 0.05$). The mean reductions in sitting systolic and diastolic pressures after starting prazosin were 6.7/6.7 mm Hg at 1 month, 9.6/9.7 mm Hg at 3 months, and 8.7/8.9 mm Hg at 6 months. For hydralazine, the corresponding figures were 5.0/6.4 mm Hg at 1 month, 5.9/8.8 mm Hg at 3 months, and 5.1/8.2 mm Hg at 6 months. These are significant decrements from baseline pressures for both drugs at all periods ($p < 0.001$); however, between drugs, the only significant differences are in systolic pressure at the third and sixth months in favor of prazosin ($p < 0.05$). For standing blood pressures, all reductions from baseline are also significant for both drugs ($p < 0.001$), but between drugs, the only difference that approaches significance is the systolic blood pressure at 1 month, which is in favor of prazosin ($p = 0.055$).

The racial composition of the patient samples at

TABLE 2. *Blood Pressure Effects*

	Prazosin	Hydralazine
n	92	106
Attained goal blood pressure		
1 month	34.8%	32.1%
3 months	48.9%	47.2%
6 months	44.6%	39.6%
Mean blood pressure reduction from baseline (mm Hg)*		
Sitting		
1 month:		
Systolic	6.7 ± 1.2	5.0 ± 1.2
Diastolic	6.7 ± 0.7	6.4 ± 0.7
3 months:		
Systolic	9.6 ± 1.3 ‡	5.9 ± 1.2
Diastolic	9.7 ± 0.8	8.8 ± 0.8
6 months:		
Systolic	8.7 ± 1.2 †	5.1 ± 1.0
Diastolic	8.9 ± 0.7	8.2 ± 0.7
Standing		
1 month:		
n	86	97
Systolic	7.7 ± 1.2 †	4.3 ± 1.3
Diastolic	7.8 ± 0.8	6.4 ± 0.7
6 months:		
n	91	104
Systolic	10.4 ± 1.4	7.3 ± 1.3
Diastolic	9.5 ± 0.9	8.3 ± 0.8

*Values are mean ± SEM.
 Significance between regimens:
 †*p* < 0.1.
 ‡*p* < 0.05.

randomization (*p* = 0.09) and upon completion of the study (*p* = 0.18) was not significantly different between regimens (table 1). Nevertheless, because of the possibility that the relatively higher proportion of blacks in the prazosin-treated patients may have affected blood pressure response adversely in this group, an analysis of blood pressure distribution and responses by race was performed. There was no significant difference in the baseline average diastolic blood pressure between whites and blacks of both groups. Furthermore, the percentage of blacks who attained goal blood pressure (41.3%) with prazosin was almost the same as for those who received hydralazine (41.9%). Therefore, there is no basis to suspect that the racial composition of the samples may have influenced the blood pressure response.

Drug Dosage

The patients at each dosage level were grouped according to whether they reached goal blood pressure at 6 months (table 3). The average dose at 6 months for all prazosin-treated patients was 10.6 mg/day; for the hydralazine-treated patients the corresponding average dose was 115.6 mg/day. The average daily dose of the patients on prazosin who reached goal

blood pressure was 8.5 mg/day, compared with 12.5 mg/day for those who did not. In the case of hydralazine, the average daily dose for those patients who reached goal blood pressure was 94.3 mg/day, compared with 129.5 mg/day for those who did not. For both drugs a larger proportion of patients received the highest dosage among those who did not reach goal blood pressure than among those who did, reflecting the effort made in the clinics to achieve goal blood pressure. However, 12 patients who received prazosin and 13 who received hydralazine, although they did not attain goal blood pressure, were not at the maximal dosage at the end of the study. Twelve had attained goal pressure previously, but a blood pressure reading higher than usual nudged the 5-6-month average over the goal; in nine the clinic was reluctant to increase the dosage because of pill count violations, and in the four others there were a considerable number of side effects. The reasons for failure to increase dosage were not noticeably different between the drugs.

Side Effects

The analyses of side effects were done both by adding elicited and volunteered side effects and by assessing them separately for each category, but there was no remarkable difference between these two approaches. Table 4 shows the percentage incidence of the sum of elicited and/or volunteered post-randomization side effects.

The data were analyzed counting all patients with postrandomization side effects and also excluding those who had the concerned side effect before randomization. The average percentage of clinic visits at which side effects were noted and the number of side effects manifested at two consecutive clinic visits were also analyzed. Orthostatic dizziness (*p* < 0.005), nightmares (*p* < 0.02), sexual dysfunction (*p* < 0.02), and possibly lethargy (*p* < 0.08) were more frequent with prazosin than with hydralazine on one or more of these analyses.

The incidence of these side effects on a month-by-month basis is shown in table 5. Patients treated with prazosin had a significantly higher incidence of side effects than those treated with hydralazine during the first month, but between the first and third months, only the incidence of orthostatic dizziness remained significantly higher. Between the third and sixth months, more patients continued to complain of these side effects with prazosin than with hydralazine, but the differences were less notable.

Despite the differences in side effects, patient compliance, determined according to pill counts, was similar for both drugs at 1, 3 and 6 months. For prazosin, 66.3% of the patients were compliant at 1 month, 68.5% at 3 months and 68.5% at 6 months. For hydralazine, 76.4% were compliant at 1 month, 69.8% at 3 months, and 74.5% at 6 months.

Effect on Pulse Rate

Pulse rates during the study are shown in table 6. As shown in table 1 the sitting pulse rate was significantly

TABLE 3. Number of Patients by Dosage and Goal Attainment at 6 Months

Prazosin				Hydralazine			
mg/day	Total	Goal blood pressure		mg/day	Total	Goal blood pressure	
		Yes	No			Yes	No
1	3	2	1	10	1	0	1
2	2	2	0	20	3	3	0
3	15	11	4	30	16	10	6
6	17	10	7	75	16	10	6
15	55	16	39	150	70	19	51
Total	92	41 (44.6%)	51	Total	106	42 (39.6%)	64

different between the groups before taking hydrochlorothiazide; for the patients eventually randomized to prazosin, the average pre-hydrochlorothiazide pulse was 74.5 beats/min and for patients eventually randomized to hydralazine it was 77.4 beats/min ($p < 0.05$). This difference was present before randomization, so is attributable to chance variation. Pulse rate also increased significantly during treatment with hydrochlorothiazide, by 3 beats/min in the group later randomized to prazosin ($p < 0.05$) and by 2.5 beats/min in the group later randomized to hydralazine ($p < 0.05$). However, after randomization, the changes in average pulse rates were not significant for either drug or between drugs at any period.

On the assumption that pulse rate changes would be more noticeable in the standing position, the pertinent data were analyzed. Standing pulses were available for the periods indicated on the numbers of patients shown in parentheses in the table. There was an in-

crease in standing pulse rate 1 month after randomization in patients who received prazosin ($p < 0.05$), but the other differences were not significant within or between regimens.

Other Changes

No significant differences were noted between regimens in serum potassium, uric acid, creatinine, cholesterol, sugar and triglycerides from randomization as compared to 6 months after randomization. However, body weight increased an average of 0.5 kg in the group treated with prazosin and decreased an average of 0.6 kg in the group treated with hydralazine ($p = 0.009$). This difference might have been influenced by regression toward the mean, because although there was no significant difference between the initial average weights of both groups, the figure was higher for the hydralazine-treated group than for the prazosin-treated group (table 1).

TABLE 4. Percentage Incidence of Postrandomization Patient Side Effects Elicited or Volunteered

Side effects	By patients, all postrandom.		By patients, new only		By avg. % of visits		At 2 consec. visits	
	P	H	P	H	P	H	P	H
Anorexia	5.4	4.7	2.3	4.8	1.7	0.9	5.4	* 1.0
Weakness	34.8	34.9	31.3	32.3	12.9	9.1	16.3	12.3
Orthostatic dizziness	47.8	‡ 26.4	37.8	† 22.4	17.7	‡ 8.1	22.8	‡ 9.4
Lethargy	37.0	* 25.5	31.7	20.8	14.0	* 8.1	16.3	8.5
Headaches	40.2	39.6	31.9	31.2	12.2	12.2	13.0	16.0
Dyspnea on effort	47.8	41.5	39.0	32.9	17.5	15.0	21.7	22.6
Angina	12.0	8.5	9.0	5.9	2.3	4.1	2.2	4.7
Palpitations	28.3	27.4	17.7	18.5	9.5	11.9	14.1	15.1
Skin rash	8.7	10.4	6.7	6.1	2.7	3.9	3.3	5.7
Arthritis	25.0	18.9	20.0	17.0	9.5	6.4	9.8	9.4
Sexual dysfunction	32.6	† 19.8	27.7	17.8	13.9	† 5.7	16.3	* 8.5
Depression	14.1	9.4	10.2	7.7	5.2	3.0	8.7	3.8
Nightmares	19.6	† 7.5	17.8	† 6.8	5.1	2.3	8.7	* 2.8
Ulcer symptoms	14.1	11.3	12.4	10.0	2.0	3.4	1.0	4.7
Other	53.3	53.8	46.7	44.4	14.0	15.6	17.4	16.0

Significance between regimens:

* $p < 0.1$.

† $p < 0.05$.

‡ $p < 0.01$.

Abbreviations: P = prazosin; H = hydralazine.

TABLE 5. Percentage Incidence of Postrandomization Patient Side Effects per Month

Side effects	During month 1		Months 1-3		Months 3-6	
	P	H	P	H	P	H
Orthostatic dizziness	31	† 17	28	‡ 13	25	* 15
Lethargy	23	† 12	22	16	21	* 11
Sexual dysfunction	21	‡ 7	20	11	19	11
Nightmares	10	† 3	10	5	11	* 4

Significance between regimens:

**p* < 0.1.

†*p* < 0.05

‡*p* < 0.01.

Abbreviations: P = prazosin; H = hydralazine.

Discussion

No significant differences in antihypertensive efficacy were found between prazosin and hydralazine, with either drug given in addition to hydrochlorothiazide, except for a 3.7- and 3.6-mm Hg greater decrement for prazosin in sitting systolic pressure 3 and 6 months, respectively, after starting treatment.

The dosage could have affected these results. In the patients who reached goal blood pressure, the average dose of prazosin was 8.5 mg/day, compared with the average dose of 94.3 mg/day of hydralazine. This indicates an approximate 1:11 ratio by weight of these drugs for similar blood-pressure-lowering effectiveness. This is lower than the 1:20 to 1:30 ratio reported in other studies,¹⁶⁻¹⁹ and may have been due to the maximal level of 150 mg/day established for hydralazine titration in the present study. However, this dosage approximates closely the recommended daily maximum for this drug. The titration to maximum dosage to achieve goal blood pressure was vigorously pursued in this study.

Orthostatic dizziness, sexual dysfunction, nightmares, and possibly, lethargy were more frequently associated with prazosin than with hydralazine. Side effects were evaluated in this study through a checklist questionnaire, a method prone to inductive responses after repeated exposures. Because there was no placebo-treated group, we could not differentiate the real side effects from the false-positive responses. The side effects observed in this study are valid as to the

comparison of incidences between regimens but not as to the absolute incidence of side effects for each drug.

The observation that prazosin-treated patients complained more of orthostatic dizziness than those treated with hydralazine during the first month of therapy is consistent with the published reports that this side effect appears early during the course of treatment. However, the complaint of orthostatic dizziness by patients receiving prazosin persisted throughout the 6 months of the study, indicating that it may be appropriate to watch for orthostatic dizziness and adjust dosage accordingly in prazosin-thiazide-treated patients during at least the first 6 months of treatment rather than just early after starting treatment.

The greater frequency of nightmares and sexual dysfunction with prazosin than with hydralazine was unexpected. These symptoms and others, such as lethargy, hallucinations, irritability, depression and vivid dreams, have been reported to be rare with prazosin.^{10, 14, 17, 18, 20} Although in the rat brain prazosin increases norepinephrine turnover and depletes serotonin,²¹ there is little evidence to support a central action of this drug when administered in antihypertensive doses.²² Nevertheless, the central nervous system side effects of prazosin may be a reflection of these changes.¹⁴

The side effects observed in this study are in contrast to the published reports that as a substitute for hydralazine, prazosin appears to cause fewer troublesome side effects.^{10, 17, 20, 21, 24} However, our patients were selected for absence of congestive heart

TABLE 6. Average Pulse Rates (beats/min) During the Study

n	Before HCTZ	Sitting				
		At random.	Drug	1 mo.	3 mo.	6 mo.
92	74.5	†77.5	Prazosin	79.1	78.7	78.2
	*					
106	77.4	†79.9	Hydralazine	81.0	80.7	80.2
Standing						
(number of patients in parentheses)						
		82.1 (92)	Prazosin	86.0 (86)†		83.8 (91)
		84.2 (105)	Hydralazine	85.9 (97)		84.4 (104)

*Significance between regimens: *p* < 0.05.

†Significance within regimens: *p* < 0.05.

Abbreviations: HCTZ = hydrochlorothiazide.

failure, angina pectoris and history of myocardial infarction, all of which might predispose toward recognized hydralazine side effects such as angina, palpitations and dyspnea on effort. Nevertheless, neither these symptoms nor headache, which is another recognized hydralazine side effect, was more frequent with hydralazine than with prazosin. Despite the differences in side effects, no significant difference in compliance or in the incidence or reasons for termination was observed.

The finding that the only significant increase was in standing pulse rate 1 month after randomization in the patients taking prazosin ($p < 0.05$) was surprising, particularly in the case of hydralazine, which is known to cause reflex tachycardia in patients not treated with β -blocking drugs. It was no less surprising that hydrochlorothiazide alone produced a slight but significant increase in pulse rate in both groups before the administration of the test drugs.

These findings were unexpected, so the clinics were requested to read blindly the heart rates in the ECGs that had been recorded at the corresponding visits. The results corroborated the previous findings in that there was a significant increase in heart rate after hydrochlorothiazide administration in the group later randomized to hydralazine ($p < 0.05$), but no other significant differences within and between drugs subsequently.

Perhaps the prior increase in pulse rate associated with hydrochlorothiazide may have blunted the reflex tachycardia that would be expected from the use of the test drugs. This possibility cannot be proved, because both groups received hydrochlorothiazide before the test drugs. Another possibility is that the response to reflex sympathetic stimulation may be less marked in middle-aged and elderly patients, as were entered into this study. This possibility was substantiated by the comparison of pulse rate responses in the patients younger than 50 years vs those 50 years and older (table 7). No significant pulse rate differences were noted in the older group for both drugs. However, in patients younger than 50 years of age, significant pulse rate increases were noted at 1 month in patients taking

hydralazine ($p < 0.05$), and at 6 months in patients taking prazosin ($p < 0.05$). The increase in pulse rate at 1 month in patients taking hydralazine compared with those taking prazosin was also significant ($p < 0.01$).

The advantages and disadvantages of either hydralazine or prazosin must be considered. The results of this study suggest that the differences between these drugs may render one preferable to the other in individual cases, according to the specific circumstances.

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TABLE 7. Comparison of Pulse Rates (beats/min) Between Patients Age 50 Years or Older and Those Younger Than 50 Years

Drug	n	Random.	1 mo.	3 mo.	6 mo.
Younger than 50 years					
Prazosin	31	76.5	78.2	80.5†	79.7§
		*	†		
Hydralazine	31	81.0	84.8§	80.7	82.0
50 years or older					
Prazosin	61	77.9	79.6	77.8	77.4
Hydralazine	75	79.4	79.4	80.7	79.5

Significance between regimens:

* $p < 0.05$.

† $p < 0.01$.

Significance of changes from randomization within regimens:

‡ $p < 0.1$.

§ $p < 0.05$.

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APPENDIX A. Conditions Requiring Exclusion from the Study

- (1) Surgically curable hypertension
- (2) Congestive heart failure within the last 3 months
- (3) Atrioventricular block greater than first degree
- (4) Atrial fibrillation
- (5) Angina pectoris or history of myocardial infarction
- (6) History of cerebral hemorrhage or hypertensive encephalopathy
- (7) History of dissecting aneurysm
- (8) Serum creatinine above 2.0 mg/dl
- (9) Average sitting heart rate above 94 beats/min at two successive prerandomization visits
- (10) Lupus erythematosus, scleroderma, polyarteritis nodosa, dermatomyositis
- (11) Active liver disease or cirrhosis
- (12) Intolerance to thiazides or hydralazine
- (13) Positive fluorescent ANA test
- (14) Grade III or IV hypertensive retinopathy
- (15) Poor risks for reliability such as addicts, psychopaths, poorly motivated patients, etc.
- (16) Inability to return to clinics

APPENDIX B. Reasons for Termination from the Study

- (1) Diastolic blood pressure > 104 mm Hg on two consecutive visits 2 weeks apart or > 114 mm Hg on two consecutive visits 1 week apart on maximal dose of medication
- (2) Hypotensive symptoms persisting after reduction of Zarpine No. 1 to once daily
- (3) Heart rate > 99 beats/min persisting after reduction of Zarpine No. 1 to once daily, or on two consecutive visits in a symptomatic patient
- (4) Angina pectoris or myocardial infarction
- (5) Congestive heart failure
- (6) Atrioventricular block greater than first degree
- (7) Grade III or IV hypertensive retinopathy
- (8) Cerebral hemorrhage, subarachnoid hemorrhage, cerebral thrombosis, or hypertensive encephalopathy
- (9) Dissecting aneurysm
- (10) Pulmonary embolism or infarction
- (11) Arthritis or dermatitis associated with lupus cells in the blood or positive fluorescent ANA test
- (12) Thrombocytopenic purpura or agranulocytosis
- (13) Serum creatinine greater than 2.0 mg/dl and 50% higher than the baseline
- (14) Failure to meet clinic appointments without legitimate excuse