Comparison of Propranolol and Hydrochlorothiazide for the Initial Treatment of Hypertension

II. Results of Long-term Therapy

Veterans Administration Cooperative Study Group on Antihypertensive Agents

• As described in the preceding communication, either propranolol hydrochloride or hydrochlorothiazide were randomly allocated in a double-blind manner to 683 patients with initial diastolic BP in the range of 95 to 114 mm Hg. Of this number, 394 entered the long-term treatment phase. During the subsequent 12 months of long-term treatment, hydrochlorothiazide was more effective than propranolol in controlling BP (mean reductions, −17.5/−13.1 mm Hg with hydrochlorothiazide compared with −8.3/−11.3 with propranolol. After treatment with hydrochlorothiazide, a greater percentage of patients achieved the goal diastolic BP of less than 90 mm Hg (65.5% compared with 52.8% taking propranolol). Also during treatment, fewer patients receiving hydrochlorothiazide required termination as compared with those receiving propranolol; comparative dosage requirements were lower; additional titration during long-term treatment was required less often, and BP remained lower after withdrawal of the active drugs. However, biochemical abnormalities were greater with hydrochlorothiazide. Although not statistically significant, the antihypertensive effects of hydrochlorothiazide were greater in blacks than in whites. Whites, on the other hand, had a greater response to propranolol than blacks, although it was still less than the response of the whites to hydrochlorothiazide.

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THIS study was designed to determine the degree of BP lowering that can be achieved with propranolol hydrochloride as compared with hydrochlorothiazide and to examine the dosage distribution of each drug required to achieve control of BP. These questions have clinical relevance because of recommendations that propranolol replace thiazide diuretics as the primary treatment for hypertension.[1,2] This recommendation involves mostly theoretical considerations based either on renin profiling[1,3] or on supposedly adverse biochemical effects of thiazides as compared with the possibly beneficial antiarrhythmic effects of the β-blockers.[2]

In a prior cooperative study carried out by our group, propranolol alone controlled the BP in 52% of the patients with mild hypertension.[4]

See also p 1996.

However, no comparison was made with diuretic alone. The present study is designed to compare the two single entities. The short-term responses to these two agents are presented separately in THE JOURNAL (p 1996). The present report is concerned with a comparison of the long-term effectiveness of propranolol and hydrochlorothiazide during 12 months of continuous treatment. Data also are presented concerning BP and other indices before treatment and during a final placebo period.

SUBJECTS AND METHODS

The design of the prerandomization and early postrandomization (titration) period of the study are described in the preceding communication. Briefly, this consisted of a prerandomization placebo period of four weeks' duration to obtain baseline data and to determine eligibility defined as an average diastolic BP at two consecutive visits in the range of 95 to 114 mm Hg and pill counts of the placebo within a designated acceptable range with respect to compliance. Consenting, eligible patients were randomly assigned in a double-blind fashion to either propranolol hydrochloride, 80 mg daily, or hydrochlorothiazide, 50 mg daily, both given in equal twice-daily divided doses. Doses of propranolol hydrochloride were titrated to as high as 640 mg per day, or until the diastolic BP fell below 90 mm Hg or there were side effects. Doses of hydrochlorothiazide were titrated similarly up to a level of 200 mg daily. A maximum of seven clinic visits one to two weeks apart were permitted to complete the titration of dosage. To enter the long-term treatment phase of the study the patient had to achieve an average diastolic BP during the last two consecutive visits of the acute titration phase below 100 mm Hg and at least 6 mm Hg less than the baseline average. The long-term treatment phase consisted of 48 weeks of continuous treatment.

Additional titration of dosage was permitted during the long-term treatment period if all of the following conditions were present: (1) diastolic BP was 90 mm Hg or higher; (2) patient had been com-

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pliant as evidenced by pill counts (return of 20% or less of prescribed number of tablets); (3) dose level had been changed less than three months previously; (4) patient had not yet passed the ninth week of the long-term treatment period; (5) there were no severe side effects; and (6) the maximum permitted dose level had not yet been reached. If the dose had been titrated without producing additional antihypertensive effects, hydrochlorothiazide administration was dropped to the level where no further fall had occurred with subsequent increases of dose. Also, if severe dose-related side effects or serious hypotensive symptoms developed, the dose could be reduced to the next lower level after consulting with the chairman of the study.

Patients were terminated from the study if the diastolic BP was greater than 119 mm Hg on any single visit. Patients with diastolic BP between 105 and 119 mm Hg who had been previously controlled or had finished their initial dosage titration were seen again in one week. If the diastolic BP was still greater than 104 mm Hg the patient was terminated from the study after dose tapering. Patients with two successive visits at which diastolic BP was greater than the pretreatment average also were terminated.

The 48-week interval during the long-term treatment period was subdivided into 12 visits at intervals of four weeks. This was followed by two weekly visits for dose tapering and two further weekly visits for the final placebo period. Tapering was carried out using blister packs containing both active drug and placebo tablets so that the patient was not aware of when his dosage was being reduced. Tapering was carried out to protect the patient against potential complications that may result from the sudden discontinuation of a β-blocker.

Laboratory studies, including the standard urinalysis, complete blood cell count, and blood chemistries determined by automated analyzers, were carried out just before the beginning of the dosage titration phase, after completing dosage titration, midway and at the end of the 12-month long-term treatment phase, and at the end of the two weeks final placebo phase. The ECG and x-ray film of the chest also were taken at the beginning and end of the long-term treatment phase. The ECG was repeated at the end of the final placebo phase. Special tests included plasma renin activity studies, which were carried out in five hospitals, and blood glucose tolerance testing determined in two hospitals. The results of these tests will be reported separately.

A sample size of 300 patients randomized to each regimen, propranolol or hydrochlorothiazide, was considered sufficient to detect a 20% difference in the proportion of patients successfully completing the long-term treatment period. The criteria for effectiveness were the absolute number and percent of patients entering the long-term treatment phase who in the seated position achieved a diastolic BP of 90 mm Hg or less at the end of the long-term treatment period. Student's t test, χ^2 analysis of variance (ANOVA), and regression analyses were used to assess statistically significant differences ($P<.05$) between groups of data.

The mean age of the patients entering the long-term treatment phase was 49.2 years for the propranolol group and 50.2 years for the patients receiving hydrochlorothiazide. The racial distribution was 52% blacks and 48% whites. There was no significant difference in the black-white ratio of patients receiving propranolol compared with hydrochlorothiazide-treated patients. The percentage of patients receiving hydrochlorothiazide was slightly greater, being 53.8% as compared with 46.2% taking propranolol. This was due to the greater number of terminations in the group receiving propranolol during the earlier titration phase of the study.

RESULTS

Of 906 patients who entered the prerandomization placebo phase of the study, 683 were randomized. However, only 491 of these entered the study early enough to be eligible for long-term treatment. Of this number, 394 completed the dose titration phase of the study and met the criteria for entering the long-term treatment phase. Among the 394 patients who entered the long-term treatment phase, 302 completed the 12 month follow-up, while 92 were terminated for the reasons described herein.

Changes in BP

The pretreatment baseline diastolic BP averaged 101.5 mm Hg in patients who entered the long-term treatment phase and was not significantly different in the two drug groups. The changes in BP from the prerandomization baseline period in the 302 patients who completed the long-term treatment period averaged −8.3/−11.3 mm Hg with propranolol and −17.5/−13.1 mm Hg with hydrochlorothiazide. The reductions were significantly greater with hydrochlorothiazide than with propranolol for both the systolic ($P<.001$) and diastolic ($P<.001$) BP.

The average diastolic BP at the end of the preceding titration period was less than the average at the end of long-term treatment in both treatment groups, the rise being greater with propranolol than with hydrochlorothiazide. The mean elevations were +7.0/+3.5 mm Hg with propranolol and +1.8/+1.0 mm Hg with hydrochlorothiazide. The differences between hydrochlorothiazide and propranolol with respect to these changes was significant ($P<.001$) for both the systolic and diastolic differences. During the long-term treatment phase, 28 patients were terminated because their diastolic BP rose above the levels defined as terminating criteria. Twenty-five of these patients had been randomized to propranolol, while three had been receiving hydrochlorothiazide ($P<.01$).

The percentage of patients whose diastolic BP was controlled below 90 mm Hg during the long-term treatment phase was 52.8% in the propranolol group and 65.5% in the patients receiving hydrochlorothiazide ($P<.03$). In addition, an estimate was made of the ability of either drug to arrest progression of the hypertension by comparing the diastolic BP during the prerandomization period and the diastolic BP at the end of posttreatment or final placebo period, which followed the long-term treatment phase. A rise of diastolic BP during the final placebo period as compared with the level present in the prerandomization baseline phase may represent possible evidence of progression of the underlying hypertension during treatment. The diastolic BP was higher in the posttreatment placebo period than in the prerandomization phase in 32% of the patients receiving propranolol compared with 10% of those receiving hydrochlorothiazide. Thus, BP increased above baseline three times more frequently after withdrawal of propranolol treatment than after discontinuing hydrochlorothiazide administration.

Race

Because there seemed to be racial trends with regard to responses to the two drugs, it was considered essential to analyze the changes by race as well as by drug. It was possible that the greater response to hydrochlorothiazide detailed previously could have been influenced by racial differences in responsiveness. At the end of the

Table 1.—Changes in BP During and After the Long-term Treatment Period, by Race*

	Average BP, mm Hg							
	B				W			
Phase of Study	n	Propranolol Hydrochloride	n	Hydrochlorothiazide	n	Propranolol	n	Hydrochlorothiazide
Systolic BP								
Long-term treatment phase	57	...	95	...	68	...	82	...
Prerandomization	...	141.4	...	147.6	...	147.4	...	145.6
Long-term treatment	...	135.7	...	127.7	...	136.8	...	130.9
Change	...	−5.6	...	−19.9	...	−10.6	...	−14.7
Posttreatment placebo phase	112†	...	137	...	94	...	113	...
Prerandomization	...	142.1	...	148.6	...	147.8	...	147.0
Final placebo	...	143.0	...	140.2	...	146.5	...	138.5
Change	...	+0.8	...	−8.4	...	−1.3	...	−8.5
Diastolic BP								
Long-term treatment phase	57	...	95	...	68	...	82	...
Prerandomization	...	100.2	...	101.9	...	102.9	...	101.1
Long-term treatment	...	88.9	...	87.9	...	91.2	...	89.1
Change	...	−11.3	...	−14.0	...	−11.5	...	−12.0
Posttreatment placebo phase	112	...	137	...	94	...	113	...
Prerandomization	...	100.2	...	101.7	...	102.4	...	101.6
Final placebo	...	98.0	...	94.8	...	99.1	...	94.0
Change	...	−2.2	...	−6.9	...	−3.3	...	−7.6

*Prerandomization BP represents average BP for at least two visits of that phase. Long-term treatment and posttreatment placebo phase BPS represent BP at last visit of each phase.

†Also includes patients terminated in initial titration period (phase A).

Table 2.—Changes in BP During Long-term Treatment Period Compared With Short-term Titration Phase

	Average BP, mm Hg								Significance of Difference (*P*)		
	B				W						
Phase of Study	n	Propranolol Hydrochloride	n	Hydrochlorothiazide	n	Propranolol	n	Hydrochlorothiazide	Race	Drug	Race × Drug
Systolic BP*	57		95		68		82				
Short-term titration	...	128.1	...	126.1	...	130.2	...	128.7	...	...	...
Long-term treatment	...	135.8	...	127.7	...	136.8	...	130.9	...	...	...
Change	...	+7.7	...	+1.6	...	+6.6	...	+2.2	NS	<.001	NS
Diastolic BP	57		95		68		82				
Short-term titration	...	85.7	...	86.4	...	85.9	...	88.6	...	...	...
Long-term treatment	...	88.9	...	87.9	...	91.2	...	89.1	...	...	...
Change	...	+3.2	...	+1.5	...	+5.3	...	+0.5	NS	<.001	NS

*Short-term titration phase and long-term treatment phase BPs represent BP at last visit of each phase.

long-term treatment phase, the number of blacks still in the trial was 152 and the number of whites was 150, that is, the number in each group was essentially equal. However, the racial distribution was unequal within each drug group (Table 1), necessitating the use of ANOVA in the analysis to separate drug effects from race effect.

After treatment with propranolol the average change in systolic BP from prerandomization baseline was −5.6 mm Hg in blacks and −10.6 mm Hg in whites (Table 1). With hydrochlorothiazide, the systolic BP change averaged −19.9 mm Hg in blacks and −14.7 mm Hg in whites. An analysis of variance to attribute these differences to a pure race effect, pure drug effect, and effect of differential racial response within each treatment group showed that differences between the two drug groups and the differential response were both highly significant. Both racial groups without regard to treatment exhibited a drop in systolic BP. However, the reductions were greater with hydrochlorothiazide than with propranolol in both racial groups, although whites responded better to propranolol than did blacks, and the reverse with hydrochlorothiazide. These racial differences, however, were not significant.

A similar analysis of changes in diastolic BP showed that hydrochlorothiazide treatment resulted in a significantly greater lowering of diastolic BP than propranolol. No racial effect was shown, however, both racial groups having a similar fall in diastolic pressure without regard to drug. Both whites and blacks responded more to hydrochlorothiazide treatment than to propranolol treatment, and the race-by-drug interaction was not significant.

The mean levels of BP at the end of the long-term treatment period were compared with those obtained during the short-term titration phase to compare short-term with long-term treatment effects by drug and race (Table 2). Both systolic and diastolic BP were somewhat higher in both races and with both drugs at the end of the long-term treatment phase. The mean elevations with propranolol averaged 7.6/3.2 mm Hg in blacks and

Significance of Difference (P)		
Race	Drug	Race × Drug
...	...	...
...	...	...
...	...	...
NS	<.001	<.001
...	...	...
...	...	...
...	...	...
NS	<.001	NS
...	...	...
...	...	...
...	...	...
NS	=.03	NS
...	...	...
...	...	...
...	...	...
NS	<.001	NS

6.6/5.3 in whites. With hydrochlorothiazide, the mean increases were 1.5/1.5 mm Hg in blacks and 2.2/0.5 mm Hg in whites. The increases in BP over time were significantly less with hydrochlorothiazide than with propranolol ($P<.001$). Racial differences and race-by-drug interactions with respect to these change in BP were not significant.

Heart Rate

There was a marked reduction in heart rate in the group taking propranolol as compared with the prerandomization heart rates, which averaged 77.0 beats per minute before treatment and 60.9 beats per minute on entering the long-term treatment period after drug titration. On the other hand, heart rate rose slightly after hydrochlorothiazide administration, averaging 76.6 before treatment and 79.5 after titration. The difference between the two drugs was highly significant ($P<.001$). These changes were maintained during long-term treatment. At the end of the long-term treatment period, the reduction in heart rate compared with baseline averaged 16.2 beats per minute with propranolol and 0.8 beats per minute with hydrochlorothiazide. At the end of the study after the final two-week placebo period, heart rate rose from propranolol treatment levels to a mean value of 0.23 beats per minute above pretreatment baseline, while with hydrochlorothiazide the average fell to 3.30 beats per minute less than baseline. The difference between the two drugs was significant ($P<.001$).

Body Weight

Average body weight was greater for the patients taking propranolol than for those receiving hydrochlorothiazide. Compared with baseline, the patients receiving propranolol gained an average of 1.69 kg compared with a loss averaging 1.97 kg in the group treated with hydrochlorothiazide ($P<.001$). This significant difference may have been due at least in part to reduction in extracellular fluid volume maintained by the hydrochlorothiazide. There was no significant difference in weight changes between blacks and whites. In the final placebo period, the average body weight in the propranolol group as compared with pretreatment baseline increased by 0.99 kg and in the hydrochlorothiazide group remained under the baseline average by 0.46 kg.

Terminations

Ninety-two of 394 patients were terminated during the long-term treatment period, 47 for administrative reasons and 45 for medical causes. Administrative reasons for termination included 14 patients receiving propranolol and 18 receiving hydrochlorothiazide who stopped treatment or failed to return, three patients receiving each drug who moved, two in each group who withdrew consent, and one patient receiving propranolol and three treated with hydrochlorothiazide who stopped their drug use because of unrelated intercurrent illnesses.

More terminations owing to medical causes occurred in the propranolol group as compared with the patients receiving hydrochlorothiazide. There were 46 medical terminations, of which 35 were associated with propranolol and 11 with hydrochlorothiazide ($P<.001$), that is, medical terminations were approximately three times as frequent with propranolol as with hydrochlorothiazide. The difference was due primarily to elevation of diastolic BP beyond acceptable limits in patients treated with propranolol. During the long-term treatment period, patients were terminated if their diastolic BP was either greater than 104 mm Hg or greater than their pretreatment diastolic BP on two successive visits, or if the diastolic BP was greater than 119 mm Hg on any single visit. Among patients treated with propranolol, 25 were terminated because of elevated diastolic BP compared with three patients in the hydrochlorothiazide group, that is, terminations owing to unsatisfactory control of diastolic BP were nearly nine times as high in the patients treated with propranolol compared with those receiving hydrochlorothiazide.

Seven of the eight terminations related to side effects also were associated with propranolol. There were three patients with bronchitis and wheezing and one patient each with syncope, impotence, depression, or hallucinations, compared with one patient receiving hydrochlorothiazide who complained of muscle cramping. Myocardial infarction was diagnosed or suspected in two patients receiving hydrochlorothiazide and two receiving propranolol. Stroke occurred in three patients taking hydrochlorothiazide. Cancer developed in three patients all receiving hydrochlorothiazide. The incidence of these morbid events was too low to draw any conclusions as to possible drug influences.

Adverse Reactions

All of the patient's complaints were reported, and those that were not present during the prerandomization period were considered as possible side effects of the drug used. The results were analyzed by calculating the fraction of visits for which a given new complaint was either volunteered or elicited. Some of the complaints were noted in a significantly higher frequency with one drug than with the other. However, because of the large variety of complaints it was probable that some correlated "significantly" by chance alone.

The various complaints are listed in Table 3. The following complaints were associated significantly with the patients treated with hydrochlorothiazide as compared with those taking propranolol: tachycardia, diarrhea, constipation, impotence, tinnitus, dry mouth, lumbar pain, loss of libido, edema, and numbness and tingling. The complaints associated signifi-

cantly more with propranolol than with hydrochlorothiazide were indigestion, insomnia, vivid dreams, depression, hallucinations, blurred vision, and swelling of the hands. Many of these complaints had a low incidence and some were bizarre, such as edema significantly associated with the diuretic. The most frequent complaints that were noted in 1% or more of patient visits were insomnia, swelling of the hands, and vivid dreams, which were associated significantly with propranolol, whereas diarrhea, impotence, constipation, and numbness were associated with hydrochlorothiazide. All of these complaints were relatively infrequent, however, none being noted in more than 3% of patient visits.

Table 3.—Complaints Not Present During Prerandomization Period Present During Treatment*

Complaint	Fraction of Visits Present: Propranolol Hydrochloride	Fraction of Visits Present: Hydrochlorothiazide	Significance of Difference (P)
Propranolol-associated			
Insomnia	0.0260	0.0103	<.001
Swelling of hands	0.0260	0.0103	<.001
Vivid dreams	0.0188	0.0095	<.001
Depression	0.0072	0.0040	<.004
Hallucinations	0.0029	0.0002	<.01
Indigestion	0.0013	0.0000	<.013
Blurred vision	0.0008	0.0000	<.017
Hydrochlorothiazide-associated			
Diarrhea	0.0152	0.0970	=.020
Impotence	0.0203	0.0291	<.006
Constipation	0.0068	0.0164	<.001
Numbness	0.0064	0.0150	<.001
Lumbar pain	0.0034	0.0077	=.005
Loss of libido	0.0003	0.0065	<.001
Edema	0.0000	0.0055	<.001
Tinnitus	0.0000	0.0055	<.001
Numbness, tingling	0.0005	0.0031	<.001
Dry mouth	0.0005	0.0031	=.001
Tachycardia	0.0000	0.0012	=.02

*Complaints present during treatment significantly more often with one drug than with the other.

Blood Chemistries

The changes in blood chemistries from the pretreatment levels are shown in Table 4. Significant changes in mean values after propranolol administration included a slight rise in serum potassium concentration, fasting blood glucose level, and calcium level. Serum cholesterol levels averaged 4% higher than control and triglyceride values rose 25% above the baseline level. During long-term treatment with hydrochlorothiazide the average uric acid concentration increased 21% as compared with the pretreatment value, the serum potassium level decreased 13%, and the serum urea nitrogen level increased 17%. All of these changes were significant. Fasting glucose values increased slightly, but the change was not significant. Serum cholesterol and triglyceride levels surprisingly decreased slightly but not significantly.

Compared with short-term treatment (Table 5), the changes in blood chemistry findings occurring with the passage of time were generally small and not clinically important. With propranolol, the average changes at the end of long-term treatment as compared with short-term treatment were a decrease of 6% in serum urea nitrogen levels and of 2% in potassium levels. Serum triglyceride levels rose further, the increase averaging 6%. With hydrochlorothiazide, there was no further change during long-term treatment except for slight increase in potassium values and fall in creatinine levels as compared with the early phase of treatment. Serum triglyceride levels decreased 17%, but the change was not significant (P=.07).

During long-term treatment, no patients in the group treated with propranolol exhibited a serum potassium level below 3.5 mEq/L. In the patients treated with hydrochlorothiazide, 41% exhibited levels below 3.5 mEq/L, of whom 6% were below 3.0 mEq/L. In both treatment periods, uric acid levels of 10 mg/dL developed in approximately 12% of the patients treated with hydrochlorothiazide, as opposed to none in the group treated with propranolol. Fasting blood glucose levels of 150 mg/dL or above occurred in 6% of the patients receiving hydrochlorothiazide and in 4% of those receiving propranolol. These percentages represent an increase above pretreatment baseline of 3% for the patients treated with hydrochlorothiazide and no change for the propranolol group. There was no significant change from pretreatment baseline in the percentage of patients with cholesterol levels of 300 mg/dL or higher in the patients treated with either propranolol or hydrochlorothiazide. The percentage of patients exhibiting elevated triglyceride levels of 300 to 399 mg/dL rose from 4.2% in the pretreatment period to 8.6% in the titration phase to 11.7% in the long-term treatment period. The percent increases with hydrochlorothiazide were from 3.8% during the pretreatment phase to 5.5% and 5.8% in the titration and long-term treatment period, respectively.

Dosage Requirements

After the initial titration of dosage and during the long-term treatment period, 37.6% of the patients treated with propranolol and 20.9% of patients receiving hydrochlorothiazide required further increases of dosage (P<.015). By contrast, only 0.8% of patients receiving propranolol and 4.0% of those taking hydrochlorothiazide had their doses reduced, the total number of these being too small to achieve significance. These differences probably reflected the lower percentage of patients controlled with propranolol as compared with hydrochlorothiazide.

COMMENT

As described in the preceding article, the baseline characteristics of the patients assigned to each regimen were similar. Because of fewer patients attaining goal BP with propranolol as compared with hydrochlorothiazide, more patients taking propranolol were terminated in the initial titration phase than was the case with hydrochlorothiazide. As a result, at the beginning of the long-

Table 4.—Changes in Blood Chemistries*

Blood Test	Propranolol Hydrochloride n	Pretreatment Mean	Mean Change	P	Hydrochlorothiazide n	Pretreatment Mean	Mean Change	P	Difference Between Drugs (P)
Uric acid, mg/dL	122	6.58	0.10	NS	174	6.47	1.37	<.001	<.001
Potassium, mEq/L	121	4.23	0.17	<.001	174	4.20	−0.56	<.001	<.001
Creatinine, mg/dL	123	1.18	0.01	NS	173	1.18	0.03	NS	NS
Urea nitrogen, mg/dL	120	14.1	0.43	NS	175	14.3	2.5	<.001	<.001
Fasting glucose, mg/dL	119	99.6	6.4	<.001	174	101.7	4.7	<.05	NS
Cholesterol, mg/dL	121	222.3	8.7	=.02	167	226.2	−3.0	NS	NS
Triglycerides, mg/dL	118	166.9	42.2	<.01	170	186.7	−3.3	NS	<.05
Calcium, mg/dL	131	9.27	0.34	<.001	100	9.46	−0.13	<.05	<.001

*During long-term treatment period compared with pretreatment period.

Table 5.—Changes in Blood Chemistries*

Blood Test	Propranolol Hydrochloride n	Short-term Mean	Mean Change	P	Hydrochlorothiazide n	Short-term Mean	Mean Change	P	Difference Between Drugs (P)
Uric acid, mg/dL	107	6.71	0.0	NS	152	8.05	−0.15	NS	NS
Potassium, mEq/L	105	4.49	−0.10	<.02	154	3.50	0.03	NS	<.02
Creatinine, mg/dL	107	1.19	−0.01	NS	154	1.24	−0.04	<.03	NS
Urea nitrogen, mg/dL	104	15.32	−0.86	<.02	155	17.02	−0.28	NS	NS
Fasting glucose, mg/dL	103	103.6	3.13	NS	153	106.0	0.60	NS	NS
Cholesterol, mg/dL	103	217.0	0.5	NS	147	231.0	−7.7	<.02	NS
Triglycerides, mg/dL	102	197.7	11.7	NS	147	219.6	−37.6	=.07	NS
Calcium, mg/dL	121	9.64	−0.03	NS	89	9.37	−0.02	NS	NS

*During long-term treatment period compared with short-term treatment period.

term treatment phase the number of patients receiving each drug was slightly different, with 182 patients receiving propranolol and 212 taking hydrochlorothiazide. Since the difference was due to the selective loss of propranolol nonresponders, the effect should be to influence the results in the long-term treatment period in favor of propranolol as compared with hydrochlorothiazide. However, it seems. likely that this influence, if any, was small and probably did not significantly affect the results.

By the end of the long-term treatment period an additional greater number of patients were terminated in the group receiving propranolol. The greater number of terminations was due primarily to the lesser effectiveness of propranolol to control the diastolic BP within acceptable limits. Therefore, by the time of completion of the long-term treatment period, there were 29% more patients remaining in the hydrochlorothiazide group than in the group receiving propranolol. However, the BP differences between the two regimens still were large despite elimination of the patients unresponsive to propranolol and probably could not be ascribed to the differences in sample size resulting from attrition. The differences would have been even greater if the BP of the terminated patients also had been included.

The greater antihypertensive effectiveness of hydrochlorothiazide as compared with propranolol was evidenced by several criteria. The reductions of BP, both systolic and diastolic, were significantly greater with hydrochlorothiazide. The difference was most marked with respect to systolic BP ($P<.001$). The difference in the degree of fall in diastolic BP between the two drugs was not great ($P=.03$). This was partly due to the fact that propranolol was associated with a greater reduction of diastolic than of systolic BP. This effect of propranolol may be due at least in part to the slowing of heart rate, which, by lengthening the diastolic runoff period, contributes to the lowering of diastolic BP. After hydrochlorothiazide treatment, however, the systolic fall was greater than the diastolic.

Evidence of the more sustained effectiveness of hydrochlorothiazide is provided by the comparison with the BP at the end of the initial titration period. Compared with this short-term treatment period, both systolic and diastolic BP rose significantly higher during the long-term treatment period in more patients receiving propranolol than in those receiving hydrochlorothiazide. Further evidence of the lesser effectiveness of propranolol is provided by the cases terminated because of increased diastolic BP. Eighty-six percent of the terminations due to this cause had been receiving propranolol.

The dosage requirement also was less with hydrochlorothiazide than with propranolol. Three times more patients responded to a low dose of hydrochlorothiazide (25 mg twice daily) as responded to a low dose of propranolol (40 mg twice daily), although the percentage of patients receiving the highest doses used in the titration procedure was essentially the same with the two drugs. However, the number of patients requiring increased doses during the long-term treatment phase was nearly twice as high in the propranolol group of patients as in those receiving hydrochlorothiazide.

Additional evidence of the lesser antihypertensive effectiveness of propranolol as compared with hydrochlorothiazide is shown by the percentage of patients whose diastolic BP was

controlled below 90 mm Hg. This goal was achieved in 65.5% with hydrochlorothiazide and in 52.8% with propranolol, a significant difference. Inclusion of the 26 losses among patients receiving propranolol *v* three treated with hydrochlorothiazide because of the development of increased BP would make the difference even greater. Finally, after discontinuation of treatment with both drugs at the end of trial, diastolic BP rose above the pretreatment placebo level three times more frequently with propranolol than with hydrochlorothiazide. Therefore, by several different indices of effectiveness, propranolol alone was less active as an antihypertensive agent than was hydrochlorothiazide alone. The mean reduction of BP, both systolic and diastolic, was significantly less; significantly fewer patients had their diastolic BP controlled; considerably more patients had to be removed because of increased diastolic BP in the propranolol group than in the patients receiving hydrochlorothiazide; fewer patients were controlled on low doses of propranolol than on the lower dose of hydrochlorothiazide; almost twice as many patients in the propranolol group as compared with hydrochlorothiazide required increases in dosage during the long-term treatment period, and after discontinuation of treatment the number of patients whose diastolic BP rose above the pretreatment baseline level was three times greater in the patients taking propranolol than was the case in the group receiving hydrochlorothiazide.

Other investigators have not found such clear differences in the antihypertensive effectiveness of diuretic as compared with β-blockers. Berglund and Andersson,[5] in a randomized trial of six years' duration, found no significant difference in BP response between 40 and 80 mg per day of propranolol hydrochloride and 2.5 to 5.0 mg per day of bendroflumethiazide. Paterson and Dollery[6] carried out a crossover trial in 11 patients with mild hypertension in which they compared 80 and 240 mg per day of propranolol with hydrochlorothiazide 50 mg daily. The BP was consistently lower with the diuretic, but probably because of the small sample size the difference was not significant. Also, the daily dose of hydrochlorothiazide was only one fourth the maximum dose used in the present study. Seedat[7] gave atenolol, 100 mg daily, in a crossover trial with chlorthalidone, 25 mg daily, to 24 black South Africans. Atenolol had no more effect than placebo on BP, while chlorthalidone was associated with a small but not significant reduction. The reason that the reduction was small with the diuretic may have been due to the rather small dose of chlorthalidone used in his study. The relatively poor effect of the β-blockers in black patients is consistent with our experience.

Few cardiovascular complications and no deaths related to cardiovascular disease occurred during the long-term treatment period. In a prior Veterans Administration trial[4] comparing various regimens, in the treatment of mild hypertension, including propranolol plus hydrochlorothiazide and reserpine plus hydrochlorothiazide, there were two cardiovascular deaths associated with propranolol plus hydrochlorothiazide, compared with none with reserpine plus hydrochlorothiazide. In the six-year trial of Berglund and Andersson[5] on propranolol *v* thiazide diuretic, there were three deaths associated with propranolol as compared with one with the diuretic. Although the number of events is too small to draw any definite conclusions, these studies do not support the opinion that propranolol is more protective against cardiovascular deaths than is thiazide. However, there is evidence that β-adrenergic blocking agents are effective in the prevention of sudden death following recovery from myocardial infarction.[8,9]

Side effects sufficiently serious to terminate the patient from the trial occurred in a ratio of 7 to 2, propranolol compared with hydrochlorothiazide. Certain biochemical side effects, particularly hypokalemia, were considerably higher with hydrochlorothiazide than with propranolol. The unusually high incidence of hypokalemia may have been related to the dose of hydrochlorothiazide, which ranged between 50 and 200 mg per day. Nonterminating complaints were somewhat more numerous in patients treated with hydrochlorothiazide than in the group receiving propranolol. Their importance and their relationship to the drug, however, is questionable. For example, impotence and loss of libido together was complained of in 0.0203 of all patient visits with propranolol and 0.0350 in those taking hydrochlorothiazide. The difference, which was significant, involved only 1.5% more patient visits in the hydrochlorothiazide than in the propranolol group. Considering the difficulty in obtaining reliable information from the patient and with the increased opportunity for chance association when a wide variety of complaints are being itemized, the nonterminating side effects data is probably the least reliable of any of the results reported herein.

The British Medical Research Council trial[10] has reported on adverse reactions to propranolol and to diuretic in approximately 10,000 patients with mild to moderate hypertension. Impotence was complained of in 16.2% of men receiving the diuretic, 13.8% receiving propranolol, and 8.9% taking placebo. However, approximately three times as many patients were terminated because of impotence in the diuretic group as compared with patients taking propranolol. This is considerably higher than was observed in the present trial. In the study by Berglund and Andersson,[5] subjective side effects were equally distributed between propranolol and diuretic. The incidence of gout and diabetes mellitus also were the same in both groups. With the exception of the British trial, it seems that both drugs were well tolerated, with slightly but not markedly more complaints of impotence with hydrochlorothiazide than with propranolol.

The data suggested but did not conclusively demonstrate a racial difference in responsiveness to the two drugs. The mean reduction in BP with propranolol was greater in whites than in blacks, while with hydrochlorothiazide the greatest mean reduction was greater in blacks. However, the reductions in diastolic BP with hydrochlorothiazide were greater than with propranolol in either race, and the differences between the drugs by race were not significant and could not account for the lesser effect of propranolol as compared with hydrochlorothiazide. Seedat[7] also found that a diuretic was more effective than a β-blocker in blacks. Hypertensive blacks tend to have higher plasma volumes and lower plasma renin

activity than white hypertensive persons.[11-13] According to Laragh,[1] such "low renin" or "volume dependent" hypertension will respond better to diuretics than to β-adrenergic blocking drugs, which was actually the case in both Seedat's[7] and the present study. However, while renin profiling may be informative in revealing general trends, most investigators have not found it to be a reliable guide for treating individual patients. Renin profiling[14,15] was carried out in the present trial, and the results will be reported in another communication.

Other possible mechanisms for the black-white difference in responsiveness to hydrochlorothiazide and propranolol have been discussed in the preceding article. One of the most striking racial differences found in the present study was the presence of a considerably reduced potassium excretion,[16] probably reflecting a diminished dietary intake in blacks as compared with whites.

The changes in BP secondary to treatment were similar during the acute titration phase and the long-term phase. The decrements of systolic and diastolic BP were essentially of the same degree acutely and over the long term. The fall of BP was greater with hydrochlorothiazides than with propranolol at both times, and the effectiveness of hydrochlorothiazide seemed to be greater in blacks than in whites both acutely and in the long term.

After propranolol treatment, serum triglyceride levels increased by 25% in the present study. This is similar to the increases reported by other investigators.[17,18] Propranolol also has been reported to reduce serum high-density-lipoprotein cholosterol levels, but to produce no significant change in total cholesterol levels.[18] We also observed little change in total serum cholesterol levels in the present study. Our results, however, are at variance with other investigators with respect to the lipidemic effects of thiazide diuretics. While no significant changes were found in serum cholesterol or triglyceride concentrations after hydrochlorothiazide treatment, most others have observed increases in both.[19-21] The reason for the discrepancy is not clear. Systematic technical errors did not seem to be involved because the determinations were carried out separately in each hospital using an autoanalyzer method. The European Working Party on High Blood Pressure in the Elderly also did not find an increase in total serum cholesterol levels during long-term treatment with hydrochlorothiazide in combination with triamterene.[22] Thus, the increase in total cholesterol does not seem to be a consistent accompaniment of thiazide treatment.

Fewer patients responded to propranolol than to hydrochlorothiazide despite the fact that the dosage was titrated to higher levels in the group receiving propranolol. Responders to the lower dose range of propranolol were less than was the case for the lower dose range of hydrochlorothiazide. Combined with the greater cost of propranolol, it is apparent that the expense of treating most patients with propranolol considerably exceeds that of using hydrochlorothiazide.

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