Is Low-Dose Hydrochlorothiazide Effective?
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SUMMARY In a double-blind crossover study, 13 patients with pretreatment diastolic blood pressure between 95 and 109 mm Hg received nadolol, 80 mg/day, plus placebo of hydrochlorothiazide and nadolol, plus three different doses of active hydrochlorothiazide. Patients remained on each active regimen for 3 weeks, with an intervening placebo period of 2 to 4 weeks. With 12.5 mg of hydrochlorothiazide daily plus nadolol, there was no greater reduction of blood pressure than with nadolol alone. A dose of 25 mg of hydrochlorothiazide was associated with a significantly greater decrease in systolic but not diastolic pressure, as compared with nadolol alone. A significantly greater reduction in both systolic and diastolic blood pressure was obtained only with the 50 mg/day dose of hydrochlorothiazide. Extension to 6 weeks of treatment with 12.5 mg/day failed to lower the blood pressure more than the level seen at 3 weeks. These results suggest that in combination with nadolol, 12.5 mg of hydrochlorothiazide per day has no significant antihypertensive effect. There was no evidence of a flat dose-response curve in the daily dose range of 12.5 to 50 mg. For most patients, a dose of 50 mg of hydrochlorothiazide was required to lower both systolic and diastolic blood pressure significantly below the level obtained with nadolol alone. (Hypertension 8 [Suppl II]: II-135-II-139, 1986)

KEY WORDS • diuretics • hypertension • dosage

ALTHOUGH diuretics remain the cornerstone of antihypertensive therapy, they have come under increased attack in recent years, primarily because of hypokalemia and the fear that this side effect may contribute to myocardial infarction and sudden death. Two approaches have been utilized to minimize these assumed risks. One is to treat the hypokalemia with potassium supplements and potassium-sparing diuretics. The other is to reduce the dose of the diuretic to a level at which biochemical side effects will be minimal. Reduced doses of diuretics, particularly chlorothalidone,1,2 have been suggested by several authors who favor the addition of a second drug instead of raising the dose of the diuretic. With respect to hydrochlorothiazide, other investigators have claimed that doses as small as 12.5 mg/day were as effective as 25 or 50 mg/day.3 When used in combination with enalapril, doses of hydrochlorothiazide as small as 6.25 mg/day were reported to be as effective as the more standard, larger doses.4 Other studies, however, indicate that the dose-response curve for hydrochlorothiazide is not flat until the dose reaches 50 mg/day or higher.4-7

Because of the importance of diuretics in the treatment of hypertension and the conflicting information regarding the optimal dosage, we conducted the present study to reinvestigate the relationship between dosage and effectiveness in patients with hypertension.

Methods
The study group consisted of 13 men with uncomplicated hypertension whose diastolic blood pressure without treatment was in the range of 95 to 109 mm Hg. Their mean age (± SD) was 56 ± 12 years. Twelve were black, and 1 was white. Fully informed consent was obtained in every case. If a patient was receiving antihypertensive drugs at the time of initial screening, these drugs were withdrawn. All patients were given a placebo of nadolol and hydrochlorothiazide during the first period of the study (pretreatment placebo period) and were seen again 2 and 4 weeks later (Figure 1). For a patient to be eligible to enter the next phase of the trial, the average diastolic blood pressure during the second and fourth weeks of the pretreatment placebo period had to be in the range of 95 to 109 mm Hg. If the average diastolic pressure was not in this range, the pretreatment period was extended for an additional week, and the average pressure during the fourth and fifth weeks was used to determine eligibility. The average blood pressure for the second
Figure 1. Flow chart showing the design of the trial. The pretreatment placebo period was of 4 to 6 weeks’ duration. Each active drug regimen was followed by 3 weeks, and the intervening placebo periods were of 2 to 4 weeks’ duration. The various regimens were assigned in random order. HCTZ = hydrochlorothiazide.

Conventional statistical methods were used for the calculations of mean values, standard errors, and standard deviations. The significance of differences between paired observations was estimated with Student’s t test. Values of p < 0.05 were considered significant.

Results

Blood pressure changes after 2 and 3 weeks of treatment are presented in Figures 2 and 3. Systolic and diastolic changes are shown separately for each treatment regimen. After 2 and 3 weeks of treatment with 12.5 mg of hydrochlorothiazide plus 80 mg of nadolol, average reductions in blood pressure from the placebo baseline value were 11.3/5.0 and 11.7/8.9 mm Hg, respectively. These changes were not significantly different from the reductions recorded after 80 mg of nadolol plus hydrochlorothiazide placebo (11.1/7.7 after 2 weeks and 11.7/10.3 after 3 weeks). The 25-mg dose of hydrochlorothiazide also failed to lower diastolic blood pressure more than the nadolol control; the average reductions being 20.8/8.5 at 2 weeks and 19.8/9.8 at 3 weeks. Unlike the 12.5-mg dose of hydrochlorothiazide, the 25-mg dose did result in a significant fall in systolic pressure (p < 0.05). With the 50-mg dose, the reduction in pressure at 2 and 3 weeks was 24.5/14.8 and 22.9/13.4 mm Hg, respectively. Systolic pressure was significantly reduced at 2 and 3 weeks, as compared with the reductions obtained with nadolol alone. Diastolic pressure after the 50-mg dose of hydrochlorothiazide was significantly reduced at 2 weeks, and the reduction approached significance at 3 weeks.

The time required for diuretics to exert their full antihypertensive effect is a controversial issue. In the present study blood pressure changes were not significantly different after 2 or 3 weeks of treatment. To rule out the possibility of a longer term antihypertensive response, a subgroup of seven patients remained on the regimen of 12.5 mg of hydrochlorothiazide plus 80 mg of nadolol for an additional 6 weeks. As shown in Figure 4, there was no further reduction of blood pressure from 3 to 6 weeks with this combination.

The pulse rate decreased with all regimens, ranging from —13.4 beats/min with nadolol plus 12.5 mg of

and fourth or fifth week of the pretreatment placebo period was 157/102 ± 19.5/4.4 mm Hg.

Subjects were assigned, in a double-blind fashion, to one of the four following regimens: 1) 50 mg of hydrochlorothiazide plus 80 mg of nadolol once daily, 2) 25 mg of hydrochlorothiazide plus 80 mg of nadolol once daily, 3) 12.5 mg of hydrochlorothiazide plus 80 mg of nadolol once daily, or 4) placebo hydrochlorothiazide plus 80 mg of nadolol once daily. The order of administration was determined in such a manner that all possible sequences of the four regimens could be administered in a double-blind manner.

Each treatment phase was of 3 weeks’ duration (see Figure 1). Clinic visits were scheduled for the second and third weeks. The blood pressure measurements for Weeks 2 and 3 of each treatment were averaged separately. The placebo periods between the treatment periods were 2 weeks in duration. If the diastolic pressure at the end of the intervening 2-week placebo period had risen to within 4 mm Hg or less of the baseline value (before random assignment), the patient entered the next treatment phase. If the blood pressure remained below this level after 2 weeks, the placebo period was extended for an additional 2 weeks, and if it was still below the acceptable level, the patient was eliminated from the trial.

At each clinic visit the patient was asked whether he had experienced any unusual symptoms or discomfort during the interval since the last visit. He was also questioned about specific side effects, including fatigue, faintness, weakness, and impotence. After the subject had rested for at least 10 minutes in a quiet room, the blood pressure was recorded three times in the lying, sitting, and standing positions by the nurse. The median of the three readings recorded in each position was taken as representing the pressure for a particular visit. Heart rate and body weight were also recorded at each visit.

Laboratory studies included plasma potassium, uric acid, creatinine, cholesterol, and bicarbonate measurements and urinalysis. These values were determined at the end of each treatment and each placebo phase.

Conventional statistical methods were used for the calculations of mean values, standard errors, and standard deviations. The significance of differences between paired observations was estimated with Student’s t test. Values of p < 0.05 were considered significant.
hydrochlorothiazide to –7.4 beats/min with nadolol plus 50 mg of hydrochlorothiazide.

Small (not significant) decreases in serum potassium were seen with all doses of hydrochlorothiazide except the 50-mg dose, which was associated with a significant decrease (0.23 mEq/L). In no case did the serum potassium fall below 3.5 mEq/L. Serum uric acid rose significantly with all diuretic regimens. The elevations were 0.45, 1.60, and 1.48 mg/dl with 12.5, 25, and 50 mg of hydrochlorothiazide, respectively. The 25-mg and 50-mg regimens were associated with minor elevations in blood urea nitrogen and serum glucose, which were clinically unimportant but statistically significant for the 25-mg combination (p < 0.01 and 0.025, respectively). There were no significant changes in serum calcium, creatinine, or cholesterol.

Six patients were dropped from the study. In three of the six the diastolic pressure failed to return to within 4 mm Hg of the established baseline diastolic pressure during the interim placebo period. Two of the six were noncompliant, as judged by pill counts (see below), and one suffered a cerebrovascular accident during the study.

Side effects, which were infrequent, included impotence and nasal stuffiness. No patient was dropped from the study because of side effects.

Compliance, monitored by pill counts, was in general excellent. Patients whose pill counts fell below 80% on two consecutive occasions were eliminated from the study.

**Discussion**

The small doses of hydrochlorothiazide were tested in combination with a β-adrenergic blocking drug, because advocates of small doses of diuretics generally...
recommend that they be used as an adjunct to enhance the activity of another antihypertensive agent. With both drugs used together, the chances of controlling hypertension with small doses of the diuretic will be much greater than if the diuretic is given alone. Nadolol was chosen because it has been shown to be highly effective, especially in combination with a diuretic. Nadolol also offers the convenience of a once-daily dose.

Used in combination with nadolol, the smallest daily dose of hydrochlorothiazide that significantly lowered diastolic blood pressure, as compared with nadolol alone, was 50 mg. However, both the 25-mg and 50-mg doses of hydrochlorothiazide lowered systolic pressure significantly. Other studies have shown that the thiazide diuretics have a greater effect on systolic than on diastolic pressure. This effect may be secondary to the reduction in extracellular volume and cardiac output that occurs with the administration of diuretics.

Small doses of diuretics have been found to be effective by other research groups. One of the first was Bengtsson et al., who found that a reduction in chlorthalidone from 50 mg daily to three times per week resulted in no change in diastolic blood pressure, although systolic pressure was moderately increased. Materson et al. found that 25, 50, and 75 mg of chlorthalidone per day resulted in similar falls in blood pressure. The reduction was smaller, however, with 12.5 mg per day than with the larger doses. Similarly, Tweeddale et al. found no difference in the antihypertensive effectiveness of 25, 50, 100, and 200 mg of chlorthalidone daily. Chlorthalidone has a longer duration of action than hydrochlorothiazide and is probably more effective, milligram for milligram. Thus, the results obtained with small doses of hydrochlorothiazide are not comparable to those obtained with similar doses of chlorthalidone.

The search for the smallest effective dose of diuretics has been motivated by the truism that the smaller the dose, the fewer the side effects. This rationale is generally accepted. The controversy, however, concerns the minimal effective dose of hydrochlorothiazide. Degnbol et al. determined the effects of daily doses of 25, 50, 75, and 100 mg, with each dose given for a 6-week period in a crossover design without intervening placebo periods. They reported a fall of 11 mm Hg in mean blood pressure after the 25-mg dose. With the higher doses, the fall in pressure was linearly related to the dose, but the greatest reduction occurred with the 25-mg dose.

Three groups of investigators have reported on the effects of very small doses of hydrochlorothiazide. Berglund and Anderson found average blood pressure reductions of 4/1 mm Hg with 12.5 mg daily, 4/2 mm Hg with 25 mg, and 5/3 mm Hg with 50 mg. These responses seem unusually small, especially for the higher doses. For example, in the Veterans Administration study of ticrynafen versus hydrochlorothiazide a dose of 50 mg of hydrochlorothiazide reduced the average blood pressure by 16/10 mm Hg. The difference was not due to racial effects, because 72% of the patients were white.

MacGregor et al. measured the effects of small doses of hydrochlorothiazide added to acebutolol. The mean fall in blood pressure was about 15% with each dose of hydrochlorothiazide (12.5, 25, and 50 mg daily). The reason for the discrepancy between their results and ours is not clear. The design of our study differed from theirs in that we incorporated an intervening placebo period between each active drug phase. This placebo period could be extended until the diastolic blood pressure returned to within 4 mm Hg of the baseline control value; if this condition was not met, the patient was eliminated from the trial. A second and perhaps more important difference is that we incorporated a control of β-blocker with the placebo dose of hydrochlorothiazide, whereas MacGregor et al. did not assess the effects of the β-blocker separately. A third difference between the two studies is that we utilized the standard auscultatory method for measuring blood pressure, MacGregor et al. used a semiautomatic ultrasonic method (Arteriosonde).

Andren et al., the third group advocating very low doses of hydrochlorothiazide, added doses of 6.25, 12.5, or 25 mg of the diuretic to enalapril, 10 mg or 40 mg. They found significant reductions in blood pressure in all groups, but there were no significant differences among the groups. This double-blind randomized study used parallel treatment groups instead of a crossover design. Again, our study differed in that we incorporated a control regimen containing the second drug plus placebo hydrochlorothiazide, which could be used for comparison with the addition of small doses of the diuretic.

Reports of the effectiveness of small doses of diuretics have led to the concept that the dose-response curve for the antihypertensive effects of diuretics is essentially flat from very small doses to high doses. Other data, however, indicate a dose-related response even in the high-dose range of hydrochlorothiazide. For example, in the Veterans Administration study of propranolol alone versus hydrochlorothiazide alone, 50% of the thiazide responders (diastolic pressure <90 mm Hg) had hypertension controlled with the initial dose of 25 mg twice daily. However, in 30% hypertension was not controlled until the dose was increased to 50 mg twice daily, and 20% required 100 mg twice daily. Although such high doses are not recommended in routine practice, the data nevertheless demonstrate that increased doses lead to greater antihypertensive effectiveness even up to high doses. Another investigator reporting that the dose-response curve is not flat, even at moderate doses, is Pederson, who found that 25 mg of hydrochlorothiazide twice daily failed to control blood pressure in 15 of 20 patients with mild hypertension. A dose of 50 mg twice daily lowered the pressure an additional 8/7 mm Hg. In patients with diastolic pressure between 110 and 115 mm Hg a dose of 25 mg of hydrochlorothiazide proved inadequate. A further reduction in pressure was obtained when the dose was increased to 50 mg daily. With doses of 50 mg per
day or less, biochemical side effects were minimal in the above studies.

It would appear from the present study that very low doses of diuretics are ineffective in many patients and therefore cannot be relied on in the effort to avoid biochemical side effects. The problem is to strike an optimal balance between antihypertensive effectiveness and side effects. The present results indicate that a 12.5-mg dose of hydrochlorothiazide is significantly less effective than higher doses and is too low to provide adequate antihypertensive activity in most patients, even when combined with a second drug. Nevertheless, since responsiveness to diuretics varies over a wide range, it is possible that individual patients will respond to very small doses. Our data are inconsistent with the concept that the dose-response curve for blood pressure versus dose is flat at doses of 12.5 mg and higher. The present results suggest that for most patients at least 25 mg/day of hydrochlorothiazide is required for the initial dose, which can be increased to 50 mg/day if needed.

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