Effects of Withdrawing Diuretic Therapy on Blood Pressure in Mild Hypertension
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SUMMARY A 1-year double-blind placebo-controlled study on the effects of diuretic withdrawal was conducted on a group of 62 previously well-controlled, mildly hypertensive patients. Data were collected on blood pressure (BP), biochemical laboratory values, and subjective reports of side-effects. Twenty-six percent of placebo subjects and 3% of the active treatment subjects reached preset criteria for the return of hypertension (reverters). The average systolic and diastolic pressures of all placebo-treated patients who did not revert showed statistically significant increases. BP control was quickly reestablished in reverters by restarting diuretic therapy. No substantial differences in side-effects were reported between the groups, and laboratory changes were those consistent with known metabolic effects of thiazide and thiazide-like diuretics. This study showed a much lower reversion rate after treatment withdrawal than previously reported by other investigators. It also showed significant increases in BP of placebo patients who did not revert. Long-term diuretic therapy retains its effectiveness in responsive mild hypertensive patients, potentially offering protection against the increased risks of mortality and morbidity associated with even slight elevations of BP. Withdrawal of diuretics cannot be recommended for patients with mild hypertension without use of other equally effective interventions to maintain optimum BP control. (Hypertension 5: 539—544, 1983)

KEY WORDS • placebo therapy • return of hypertension • side-effects • laboratory values • diuretic efficacy

SEVERAL earlier studies reported changes in blood pressure (BP) and considered the possibility that BP might remain in the normal range when antihypertensive treatment is discontinued after a prolonged period of control. The results reported have been inconsistent, and they have been difficult to interpret due to differences in patient selection, levels of BP, drugs used, and study designs.

The VA Cooperative Study Group on hypertension reviewed earlier reports and presented its own findings from withdrawal of effective therapy in a double-blind placebo-controlled trial. Patients had to maintain an average diastolic pressure less than 90 mm Hg for six visits during the first six months, and thereafter pressures had to remain consistently less than 95 mm Hg. Seventy percent of these individuals with previously controlled BP reverted, requiring reuse of antihypertensive medication during the 18-month observation period.

Boyle et al. reported the results of withdrawing treatment from 20 patients controlled on thiazides only. Eighteen (90%) were returned to treatment after 1 to 132 weeks (mean, 31 weeks). Others have shown that some patients with hypertension previously controlled with diuretics alone have remained normotensive for prolonged periods after withdrawal of drugs. Because of this, and because of the discrepancies in previous studies, a new trial was designed to study the effects of diuretic withdrawal on blood pressure, laboratory values, and side-effects. This study attempted to correct for discrepancies in previous reports by: 1) using a community-based patient population, initially screened, selected, and treated in a standardized way; 2) limiting the patient group to those with mild hypertension (90–104 mm Hg diastolic BP) who have been on treatment for at least 5 years; 3) requiring these patients to have been under good control for at least the previous year on diuretics only; 4) using a randomized double-blind, placebo-controlled design; and 5) setting clearly stated criteria for patient selection, exclusion, and return to therapy. Changes in BP, symptoms, and selected blood chemistries were monitored for 1 year after withdrawal of diuretics.
Methods

Subject Selection and Randomization

The National Hypertension Detection and Follow-up Program (HDFP), its selection process, participant characteristics, study design, and results have been described elsewhere.9,10 After completion of the HDFP, 88 participants with mild hypertension (DBP 90-104 mm Hg) from the Salt Lake City Clinical Center were recruited for the present study. Selection and exclusion criteria are presented in table 1. Written informed consent to participate was obtained from 62; 26 declined because they preferred to have their BP managed by their private physicians, were unwilling to accept possible assignment to the placebo group, or failed to meet blood pressure criteria for selection. The 62 who consented were randomly assigned in a double-blind manner to receive either the same diuretic they started on at the beginning of the HDFP, or a physically identical placebo. Of these, 54 (87%) were taking chlorthalidone, seven (11%) were taking hydrochlorothiazide, and one (2%) was taking triamterene at the start of the study. All pretrial regimens had been in use for at least the last 12 months of the HDFP. None of the participants in this trial was taking potassium supplements, uricosuric drugs, or allopurinol. Other characteristics of the participants are presented in table 2.

Blood Pressure Measurement and Visit Protocol

Blood pressures were measured in the right arm after the participant had been seated for at least 5 minutes. Four measurements were taken at each visit at least 30 seconds apart, two each using a standard and a random zero mercury manometer (Hawkesley, England) and an appropriately sized cuff. The random zero device conceals the true zero point of the mercury column until the reading is completed to avoid digit preferences in BP readings.11 The average of the two random zero measurements (the 2nd and 4th) was taken as the official reading for each visit. The diastolic pressure was read as the 5th phase of the Korotkov sounds. Standing blood pressures were obtained if participants complained of orthostatic dizziness, or if the seated diastolic pressure was below 60 mm Hg.

Participants were seen in the clinic at 4- to 6-week intervals as long as the diastolic pressure was 90 mm Hg or less. If the diastolic reading at any visit was 95 mm Hg or higher, a revisit was scheduled for 2 weeks and this frequency was maintained until the diastolic pressure dropped below 95 mm Hg, or until the participant met one of the criteria for removal from the trial (table 1). At each visit, participants were weighed and questioned about their feelings of well-being, major changes in their diet and physical activity, symptoms suggestive of diuretic-induced side-effects, possible effects of diuretic withdrawal, and use of other drugs.

| TABLE 1. Criteria for Participant Selection, Exclusion, and Removal from the Trial |
|---------------------------------|-----------------|-----------------|-----------------|
| **Participant status**          | **Criteria**    | **Exclusion**   |
| **Selection**                   |                 |                 |
| An average DBP of 90 mm Hg or less at an eligibility visit plus the 2 preceding visits |                 | History of major cardiovascular events, such as stroke, myocardial infarction, transient ischemic attack, congestive heart failure, renal failure, and severe angina pectoris |
| No DBP above 95 mm Hg at any of the above 3 visits |                 | Evidence by valid count of unused medication on more than two occasions during the preceding 12 months, of less than 80% or more than 110% of prescribed usage |
| An average DBP of 90 mm Hg or less for all visits during the preceding 12 months |                 | Inability or unwillingness to attend clinic at least once every 4 to 6 weeks |
| Only antihypertensive medication used during the preceding 12 months was a diuretic |                 | |
| **Exclusion**                   |                 |                 |
| History of major cardiovascular events, such as stroke, myocardial infarction, transient ischemic attack, congestive heart failure, renal failure, and severe angina pectoris |                 | |
| Evidence by valid count of unused medication on more than two occasions during the preceding 12 months, of less than 80% or more than 110% of prescribed usage |                 | |
| Inability or unwillingness to attend clinic at least once every 4 to 6 weeks |                 | |

| TABLE 2. Characteristics of Participants at Entry into the Withdrawal Study |
|-----------------|-----------------|-----------------|
| **Characteristic** | **Placebo** | **Active** | **Total** |
| **Total number** | 31 | 31 | 62 |
| Sex (no.)        |     |     |     |
| Male             | 12  | 19  | 31  |
| Female           | 19  | 12  | 31  |
| Race (no.)       |     |     |     |
| Black            | 1   | 0   | 1   |
| Non Black        | 30  | 31  | 61  |
| **Mean age (yrs)** | 60.8 | 59.8 | 60.3 |
| **Age distribution (yrs)** |     |     |     |
| 30-39            | 1   | 0   | 1   |
| 40-49            | 2   | 6   | 8   |
| 50-59            | 10  | 6   | 16  |
| 60-69            | 13  | 14  | 27  |
| 70+              | 5   | 5   | 10  |
| Mean HDFP intake BP (mm Hg)* |     |     |     |
| Systolic         | 154.2 | 152.3 | 153.2 |
| Diastolic        | 99.3  | 99.2  | 99.2 |
| Mean pretrial BP (mm Hg)† |     |     |     |
| Systolic         | 124.3 | 124.4 | 124.3 |
| Diastolic        | 77.8  | 77.7  | 77.8 |
| PreHDFP history of hypertension | 13  | 17  | 30  |
| On antihypertensive treatment at HDFP intake | 4   | 6   | 10   |

*Mean of the first three BP determinations.
†Mean of the last two HDFP determinations, plus the first trial visit value.
No special counseling was provided on weight control, reducing salt intake, or abstinence from smoking.

"Removals" in this trial are defined as those participants whose blinded treatment was discontinued for any reason, not only those who met one or more criterion for reversion. Follow-up continued whenever possible, even for participants removed from the study. Those who met blood pressure criteria for removal (reverters) were given their pretrial medication at the same dose-level in use at the end of the HDFP study and prior to randomization into this study. Participants removed at their own request were treated the same way. Those removed by their private physicians for blood pressure elevation or for other reasons were encouraged to follow their physician's advice and return periodically for BP measurements.

**Laboratory Studies**

Laboratory studies were performed at the start of the trial, at 3 months, and at 6 months. Routine laboratory tests were done on 4-hour fasting serum samples and included glucose, calcium, sodium, potassium, chloride, inorganic phosphate, urea nitrogen, creatinine, uric acid, cholesterol, triglyceride, high density lipoprotein, low density lipoprotein, total protein, albumin, total bilirubin, alkaline phosphatase, SGOT, and HCO3 determinations. A 1-hour postglucose challenge test (100 g) was performed at the second laboratory examination.

**Data Analysis**

Differences in blood pressure change between the two groups were examined for by two methods. The mean blood pressures of the two groups were calculated and compared using the two-tailed Student's t-test. Reversion to a hypertensive level was compared between groups by the corrected chi square test. Laboratory data were analyzed by use of the Student's t-test to compare means of the various measurements between groups.

**Results**

**Morbidity, Mortality, and Dropouts**

Fifty-nine of the original 62 enrollees completed the 1-year follow-up. The three who did not complete the study included one patient in the active treatment group who died from cardiac arrest, and two dropouts from the placebo group. One of the placebo dropouts developed a myocardial infarction and refused follow-up, and one refused to keep clinic appointments. One participant in the active treatment group had a transient ischemic attack (TIA).

**Removals and Reversions**

Eleven participants in the placebo group were removed. These included eight of the 31 (26%) who met one of the blood pressure criteria for reversion, one who developed isolated systolic hypertension, and two who were removed at their own request.

Four participants in the active treatment group were removed. One of the 31 (3%) met criteria for reversion and three were removed for other reasons: one for the TIA mentioned above, one for the complaint of sexual dysfunction, and one for persistently elevated blood sugar.

**Changes in Blood Pressure**

A total of nine reverted to elevated blood pressure; eight from the placebo group and one from the active treatment group. This difference in reversion between the two groups was statistically significant ($p = 0.03$). Six of the reverters were female; three were male. The average time to reversion was 27 weeks, with a range of 15 to 48 weeks.

The change in blood pressure of both groups was evaluated in two ways: 1) by comparing the mean pretrial pressure with the mean pressure throughout the trial up to the time of removal, reversion, or the final visit, whichever came first; and 2) by subtracting the mean pretrial blood pressure from the mean of the last two visits prior to removal, reversion, or the final visit (table 3). Both methods of comparison showed significant increases in the systolic and diastolic pressures of the placebo group over the active treatment group. Blood pressure increases were even higher for reverters compared to the total placebo group (fig. 1).

During the HDFP study, diuretic therapy had produced average decreases of 29 mm Hg systolic and 21 mm Hg diastolic from pretreatment BP levels (table 2). Over the 1-year withdrawal period of this study, the placebo patients regained 21 mm Hg systolic and 7 mm Hg diastolic pressure. The reverters as a subgroup regained 24 mm Hg systolic and 14 mm Hg diastolic over their pretrial BP levels. Figure 2 shows the mean systolic and diastolic BP values recorded each month.
FIGURE 1. Comparison of the change in blood pressure in reverters vs the total active and placebo treatment groups. \( \Delta BP \) = the mean blood pressure of the last two visits prior to removal, reversion, or the final visit minus the mean pretrial blood pressure. *\( p = \) probability from the two-tailed Student's \( t \) test.

during the trial for the active treatment group and the placebo group nonreverters.

Other Differences Between Reverters and Nonreverters

Differences were sought that would distinguish reverters from nonreverters. Slight differences were found in age, mean preHDFP, and mean pretrial blood pressures when reverters were compared with the total placebo and active treatment groups. Reverters were slightly older and had slightly higher preHDFP blood pressures, but none of these differences was statistically significant. The ratio of male to female reverters reflected the sex ratio of the placebo group as a whole.

Effect of Resuming Treatment

Elevated pressures in all reverters returned to normotensive levels within 1 month of restarting the pretrial medication at the dose-level previously used. The single case of isolated systolic hypertension in the placebo group also responded with a drop from 211 to 156 mm Hg within 1 month.

Changes in Laboratory Values

Laboratory values obtained at the first trial visit and at 3 and 6 months were compared for both groups (table 4). Only those participants who remained on their assigned treatment were included in each comparison, and only quantifiable values were analyzed for triglyceride and high and low density lipoprotein. The mean values for each parameter in both treatment groups were analyzed.

Significantly higher values were measured in the placebo group for second and third serum potassium, and second and third serum chloride concentrations. Significantly lower values were measured in the placebo group for first serum sodium, second and third serum uric acid, and third serum creatinine concentrations. Significant differences were not found for fasting or 1-hour post-load glucose, cholesterol, triglyceride, or high or low density lipoprotein. One active treatment participant, not included in the analysis, was removed by his private physician for persistently elevated fasting and 1-hour post-load glucose values.
Table 4. Comparison of Laboratory Values

| Measurement                  | Placebo | Active | ρ*  
|------------------------------|---------|--------|-----
|                              | Lab     | No.*   | X   | Lab | No.* | X   | p  
| Fasting glucose (mg/dl)      | 1       | 30     | 84.3| 1   | 28   | 99.4| 0.29  
|                              | 2       | 24     | 80.4| 2   | 29   | 91.3| 0.58  
|                              | 3       | 20     | 92.1| 3   | 29   | 97.5| 0.63  
| One-hour postload glucose   | 2       | 21     | 161.6| 2 | 27 | 183.1| 0.31  
| Potassium (mEq/liter)        | 1       | 30     | 3.56| 1 | 28 | 3.77| 0.11  
|                              | 2       | 24     | 4.31| 2 | 30  | 3.56| 2 x 10^-9  
|                              | 3       | 20     | 4.38| 3 | 29  | 3.77| 2 x 10^-5  
| Chloride (mEq/liter)        | 1       | 30     | 101.5| 1 | 28 | 105.2| 2 x 10^-3  
| Sodium (mEq/liter)          | 1       | 30     | 136.5| 1 | 28 | 139.9| 0.003  
| Creatinine (mg/dl)          | 1       | 28     | 1.14| 1 | 30 | 1.16| 0.75  
|                              | 2       | 24     | 1.15| 2 | 30 | 1.22| 0.26  
|                              | 3       | 20     | 1.12| 3 | 29 | 1.27| 0.05  
| Urea nitrogen (mg/dl)       | 1       | 30     | 16.7| 1 | 28 | 15.8| 0.51  
| Cholesterol (mg/dl)         | 1       | 27     | 255.2| 1 | 30 | 243.3| 0.56  
|                              | 2       | 23     | 245.8| 2 | 30 | 236.8| 0.51  
|                              | 3       | 19     | 259.3| 3 | 29 | 245.1| 0.66  
| Triglyceride (mg/dl)        | 1       | 27     | 203.4| 1 | 30 | 189.3| 0.63  
|                              | 2       | 23     | 245.8| 2 | 30 | 236.8| 0.51  
|                              | 3       | 19     | 259.3| 3 | 29 | 245.1| 0.66  
| High density lipoprotein (mg/dl) | 1     | 30     | 51.4| 1 | 27 | 49.0| 0.62  
| Low density lipoprotein (mg/dl) | 2     | 24     | 57.8| 2 | 30 | 55.7| 0.82  
|                              | 3       | 20     | 54.5| 3 | 38 | 44.1| 0.19  
| Uric acid (mg/dl)           | 1       | 28     | 6.98| 1 | 30 | 7.09| 0.78  
|                              | 2       | 24     | 5.87| 2 | 30 | 7.35| 1 x 10^-4  
|                              | 3       | 20     | 5.86| 3 | 29 | 7.29| 3 x 10^-5  

*The number of determinations for each mean value.  
†Probability from the two-tailed Student’s t test.

Side-Effects and Treatment Group Assessment

Standardized questions were asked at each visit about side-effects and feeling of well-being. Reports of side-effects were assessed at each visit and classified as either unlikely, possibly due to, or probably due to the difficulty in quantitating "symptoms made applica-

tion of statistical tests inappropi-ate. There was no substantial difference in feeling of well-being or frequency of side-effects between the two groups.

Discussion

Reversion vs Generalized Blood Pressure Increase in Placebos

After replacing pretrial diuretic treatment with placebo, 26% (8 of 31) of the participants reached protocol criteria for blood pressure reversion within 1 year.

Three percent (1 of 31) of the actively treated participants reverted. This apparently lower reversion rate compared to earlier reports occurred in spite of the lower blood pressure criteria for reversion used in this study. Whether the number of reversions is actually lower, or whether the time course of blood pressure increase is only slower in mild hypertensives, cannot be determined from this trial due to its 1-year length. A lower reversion rate for this study group was expected because of lower pretreatment pressures compared to the VA Cooperative Study Group,1 the groups followed by Boyle et al.,2 Thurm and Smith,3 and Perry and Schroeder.4

Results of this study suggest that effective, long-term diuretic therapy can modify the course of hypertension in some patients. This is in agreement with the results of trials previously cited. The only patient characteristics that could be linked with blood pressure reversion appeared to be age and level of pretreatment blood pressure.
The observed increases in systolic and diastolic blood pressure in the placebo nonreverters may be of greater long-term importance than the seemingly low reversion rate of only 26%. These increases occurred early after treatment withdrawal (fig. 2) and reached high levels of statistical significance even without isolating reverters as a separate subgroup (fig. 1).

While the mean BP values for placebo patients did not reach pre-HDFP levels, they did regain over 70% of the diuretic-induced decrease in systolic pressure, and one-third of the decrease in diastolic pressure in 1 year. Reverters regained an average of 80% of the decrease in systolic pressure, and two-thirds of the decrease in diastolic pressure. These increases in pressure may not seem excessive in terms of the final BP values, but the results of the HDFP suggest that differences of 4 to 6 mm Hg in diastolic pressure may have significant adverse effects on long-term mortality and morbidity for large numbers of mildly hypertensive patients.

Effectiveness of Long-Term Diuretic Treatment

In contrast to the blood pressure increases in the placebo group, the active treatment group, with the exception of one participant, showed no loss of blood pressure control over the year. The effectiveness of simple, often low-dose diuretic therapy has continued after a period of 7 to 8 years.

Conclusions

A 1-year trial of withdrawal of diuretic treatment in previously well-controlled mild hypertensives revealed that only 26% reverted to hypertensive levels of DBP. This reversion rate was substantially lower than that reported in earlier studies using patients with more severe blood pressure elevations. There appears to be no dependable way, in mild hypertensives, to distinguish reverters from nonreverters in advance. However, from this study and the work of others, the likelihood of reversion apparently increases with the level of the pretreatment blood pressure. Clinically and statistically significant increases in blood pressure occurred in the placebo group, even though individual reversion by protocol criteria may not have occurred.

Blood chemistry changes observed were those due to known metabolic effects of thiazide and thiazide-like diuretics. Significant differences were not detected for cholesterol, triglyceride, or high or low density lipoprotein. The spectrum of reported side-effects was consistent with the known effects of diuretic drugs, and the difference between the groups in their overall subjective feeling of well-being was not significant.

Even though only 26% of the participants on placebo reverted to DBP considered elevated, there was significant increase in the average systolic and diastolic BP of those on placebo who did not revert. Because of this gradual BP rise in placebo-treated nonreverters, we cannot assert that reverters and nonreverters are two separate groups. The BP response of our placebo group may be, as suggested by Thurm and Smith, a continuum that is artificially separated by the point in time, and the duration of our analysis. Among compliant active treatment participants, there was no increase in DBP. Therefore, we cannot recommend withdrawal of diuretics in well-controlled mild hypertensives for any but those severely affected by adverse metabolic or subjective side-effects. Since cardiovascular complications relate directly to the graded risk of increasing BP, even a small increase in DBP that does not exceed an arbitrary criterion for reversion can be clinically adverse to individuals. It seems unlikely that even mild hypertensives will go for prolonged periods without increasing the risk for cardiovascular complications unless there are effective interventions to provide optimum individual BP control.

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