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Original Investigations

Persistence of Normal BP After Withdrawal of Drug Treatment in Mild Hypertension

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• **Antihypertensive therapy was discontinued in 24 patients with mild hypertension whose BPs had been well controlled with diuretics alone. Eleven patients (46%) maintained normal diastolic BPs (≤90 mm Hg) for six months after stopping treatment and five patients (21%) for 12 months. All patients who remained normotensive for six to 12 months had mean diastolic BPs of 82 mm Hg or less during treatment. There was no significant correlation between maintenance of normotension and any of the following: pretreatment BP, presence of target-organ damage, duration of known hypertension, family history of hypertension, heart rate, body weight, weight gain after stopping diuretic therapy, 24-hour urinary sodium and potassium excretion, serum electrolyte values or renin profile. This study demonstrates that hypertension may be favorably modified, sometimes for many months, by effective antihypertensive treatment.**

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It is generally assumed that once antihypertensive drug treatment is begun patients will require continuous therapy for the remainder of their lifetimes. There is evidence, however, that some patients who are hypertensive may remain normotensive for months to years after antihypertensive therapy has been discontinued.[1-5] For example, the Veterans Administration Cooperative Study[5] found that 32% of patients with mild hypertension maintained normal BPs for at least 23 weeks after discontinuing treatment. By contrast, patients with moderate and severe hypertension showed rapid return of BP to hypertensive levels. With recent studies[6-9] demonstrating the potential benefit of BP control in persons with mild hypertension, the desirability of avoiding continuous drug treatment in large population groups has become increasingly important. Evidence that BP may remain normal after stopping antihypertensive treatment suggests that, in selected patients, such an approach may provide a useful alternative to lifelong drug treatment.

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At present, little information is available to help identify the patients most likely to remain normotensive after discontinuing treatment. This report describes the BP responses to withdrawal of therapy in patients with diuretic-controlled mild hypertension and examines the value of various clinical features in predicting the response of BP after withdrawal of therapy.

MATERIALS AND METHODS

Twenty-six male patients entered the drug reduction trial. The criteria for entry were as follows:

1. Patients had mild hypertension demonstrated by an average diastolic BP (DBP) between 90 and 109 mm Hg prior to treatment. In 15 of the patients this was demonstrated by readings taken on three to five pretreatment visits, several days to weeks apart. In the remaining 11 patients BP was measured at only two visits prior to initiating treatment, but at each of these visits the DBP reading was in the range of 90 to 109 mm Hg.
2. Subsequent to meeting the above screening criteria the patients must have received antihypertensive drug treatment with control of the average DBP to 90 mm Hg or less for at least 12 months preceding drug therapy withdrawal. Treatment consisted of diuretics alone, either 50 mg of hydrochlorothiazide once or twice daily, or 40 mg of furosemide twice daily, for the three months prior to drug withdrawal.
3. Patients had to be free of major cardiovascular complications such as stroke or myocardial infarction, and other serious illness such as cirrhosis, insulin-dependent diabetes, or renal disease with serum creatinine levels greater than 1.7 mg/dL.

These are the demographic features of the patients who entered the trial. The mean body weight was 84.9 kg. The mean duration of known hypertension was 4.6 years. The mean duration of continuous clinic treatment was 35 months. The average pretreatment BP was 152.3/101.4 mm Hg and the average BP during the last 12 months of treatment was 123.6/82.0 mm Hg. The mean serum creatinine level was 1.1 mg/dL. Left ventricular hypertrophy was found in ten patients by ECG and/or roentgenograms.

Drug withdrawal was initiated by substituting a placebo for the active diuretic. The initial follow-up visit was two weeks after substitution of placebo; patients returned thereafter at intervals of one to four weeks depending on their BP level. The trial period was one year, or less if any of the criteria listed below for return of hypertension were noted. Informed consent was obtained from all participants prior to study.

Placebo was discontinued and active medication was begun if any of the following criteria for termination were met: (1) DBP greater than 114 mm Hg on any visit; (2) DBP greater than 99 mm Hg on any two visits; (3) DBP greater than 94 mm Hg on any three visits; (4) average DBP for six months prior to six- or 12-month follow-up visit greater than 90 mm Hg; (5) occurrence of any cardiovascular

Blood Pressure Changes After Discontinuing Diuretic Therapy							
		Pretherapy BP, mm Hg		Average BP During Final Year of Therapy, mm Hg		Average of Last 3 BP Readings, mm Hg	
	No.	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
			After Six Months				
Return of hypertension	12	152±14	102±5	126±9	84±4	143±9*	94±3*
Persistent normotension	11	153±13	101±4	121±3	79±3	130±6†	84±3†
P value	. . .	NS	NS	NS	<.01	<.001	<.001
			After 12 Months				
Return of hypertension	17	153±13	102±5	125±8	83±5	145±11*	94±3*
Persistent normotension	5	153±12	101±3	120±2	78±4	135±5†	84±6†
P value	. . .	NS	NS	NS	<.05	NS	<.001

*Average BP of last three visits prior to termination from study.
†Average BP of last three visits of indicated drug withdrawal period.

complication or medical illness previously noted as reason for exclusion from the trial.

Blood pressures were recorded by the hypertension clinic nurse practitioners according to American Heart Association standards.[10] Phase V or disappearance of Korotkoff's sounds was considered to represent DBP. Heart rate and body weight were recorded at each visit.

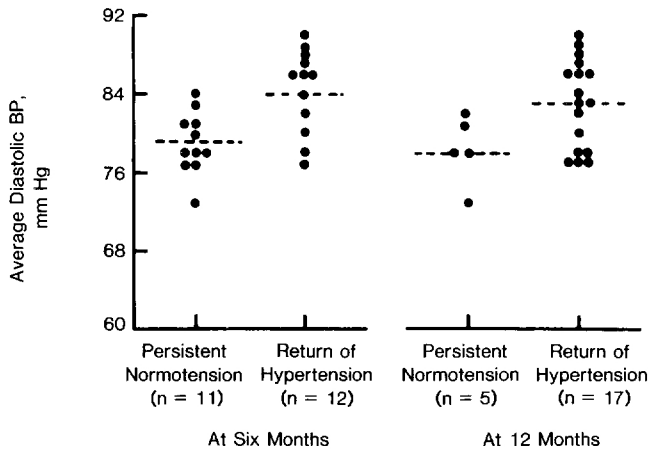
Serum chemistry values were determined at 0, 4, and 28 weeks into the trial using standard automated methods. Blood samples were obtained for plasma renin activity (PRA) at least four weeks after withdrawal of diuretic therapy. A "renin profile"[11] was obtained by comparing a random morning PRA value with sodium intake as determined from a 24-hour urine sodium sample collected the previous day. The 24-hour urinary creatinine and potassium levels were also analyzed. Blood for "stimulated" PRA[12] was obtained after patients received 40 mg of furosemide intravenously and maintained upright posture for 30 minutes. Plasma renin activity was measured by radioimmunoassay according to the method of Sealey et al.[13] Two-tailed Student's *t* test for unpaired observations was used for statistical analysis.

RESULTS

Among the 26 patients who originally entered the trial, three were dropped within six months and one after 11 months for reasons unrelated to BP increases. Two patients failed to keep clinic appointments; a supraventricular tachycardia developed in a third after four months of drug therapy withdrawal, despite an average DBP of 81 mm Hg. The fourth patient was removed from the study after 11 months of receiving placebo because of symptoms of cor pulmonale and signs of failure of the right ventricle. The patient had no evidence of left ventricular hypertrophy and DBP averaged 89 mm Hg at his last three clinic visits. Reinstitution of diuretic therapy resulted in resolution of his symptoms.

Of the 24 patients receiving follow-up, 11 (46%) remained normotensive for six months off treatment while 12 met at least one criterion for return of hypertension (Table). In four patients hypertension returned within three months, while in eight patients three to six months elapsed before there was a return of elevated DBP. After 12 months of follow-up, five of 24 patients (21%) remained normotensive (Table).

The patients remaining normotensive for six or 12 months had a significantly ($P<.001$) lower DBP during therapy than patients who exhibited return of hypertension. All patients who remained normotensive for 12 months had DBPs of 82 mm Hg or less during treatment (Figure). The DBP rose somewhat in patients who remained normotensive but, as expected, the rise was significantly less than in those who had a return of hypertension (5 ± 6 *v* 11 ± 5 mm Hg; $P<.05$).



Relationship between average diastolic BP during last year of diuretic treatment and persistence of normotensive BP at six and 12 months after withdrawing treatment. Dashed lines represent mean values.

Pretreatment levels of BP were similar for both the group that remained normotensive and for those whose BPs returned to hypertensive levels by six and 12 months following drug withdrawal.

The prevalence of target-organ damage[14] as manifested by left ventricular hypertrophy and serum creatinine level was not significantly different in patients with persistent normotension and those with return of hypertension. Clinical variables, such as age, duration of known hypertension, duration of therapy, or family history of hypertension, also showed no significant differences between the two groups at six months' follow-up. The patients with persistent normotension for 12 months tended to be younger (46 ± 12 *v* 55 ± 8 years; $P<.05$) and had a shorter duration of effective therapy (23 ± 12 *v* 37 ± 9 months; $P<.02$) than patients who exhibited return of hypertension.

Heart rates during and after diuretic treatment were similar in both groups at six and 12 months. Body weight and body weight changes before or during the study showed no correlation with BP response after withdrawing treatment. Weight gain two weeks after stopping treatment averaged 1.5 ± 2.2 kg in those with return of hypertension and 1.7 ± 2.2 kg in those who remained normotensive for 12 months.

Serum chemistry values also showed no significant difference between the two groups either before or after stopping

treatment. The 24-hour urinary sodium excretion (195 ± 114 *v* 194 ± 88 mEq/day) and potassium excretion (63 ± 24 *v* 56 ± 21 mEq/day) were similar in patients who were persistently normotensive and those with return of hypertension. Only two patients had 24-hour urine sodium levels less than 85 mEq; one remained normotensive one year after treatment, the other became hypertensive five months after treatment was discontinued. Renin profiles were similar in patients with persistent normotension and those with return of hypertension at both six or 12 months of follow-up. In both groups combined, 52% were classified as low-renin hypertensives, 33% as normal-renin hypertensives, and 14% as high-renin hypertensives. Renin responses to furosemide and upright posture were similar in patients who remained normotensive for six months in comparison with those with return of hypertension. However, in patients who remained normotensive for 12 months, renin stimulation resulted in a significantly increased response in comparison with those who became hypertensive (231% ± 100% increase from baseline *v* 79% ± 92% increase; $P<.05$), despite similar baseline values.

Because 11 patients in the trial were diagnosed as being hypertensive after only two elevated pretreatment BPs, we considered the possibility that some patients with persistent normotension after stopping therapy may have been initially misdiagnosed, ie, they may have demonstrated initial BP elevation that spontaneously returned to normal over time. However, all five patients who remained normotensive for 12 months after drug withdrawal exhibited diastolic hypertension during three or more pretreatment clinic visits. Their mean pretreatment DBPs ranged from 98 to 105 mm Hg, or 11 to 25 mm Hg higher than their DBP at 12 months off therapy.

COMMENT

Prior studies on the long-term effects of stopping antihypertensive therapy agree that some patients remain normotensive for periods of months to years without drug treatment. In 1967, Thrum and Smith[4] reported that 36% of 69 patients with essential hypertension maintained normal BPs for five months after discontinuing treatment and 23% remained normotensive for at least ten months. These patients had a mean pretreatment BP of 122 mm Hg and they received various therapeutic regimens that included chlorthalidone, methyldopa, hydralazine hydrochloride, and rauwolfia serpentina. Patients with relatively low pretreatment BPs and minimal evidence of target-organ damage maintained the lowest BPs after withdrawal of therapy.

The Veterans Administration Cooperative Study Group[5] analyzed BP responses after stopping treatment in 60 patients with mild to moderate essential hypertension. Thirty-two percent of patients with pretreatment DBPs less than 107 mm Hg remained normotensive at 23 weeks of follow-up and 15% remained normotensive for the full 72 weeks of the study. The best predictor of continued normotension after stopping therapy was a pretreatment DBP less than 107 mm Hg. Youth also was correlated with persistence of normotension, but less closely so.

Studies by Dustan et al[2] and Perry et al[3] found a much lower incidence of persistent normotension, 3% and 5%, respectively, after discontinuing therapy. However, the majority of the patients in these studies had severe hypertension and, in some cases, secondary forms of hypertension.

In general, these earlier studies suggested that patients with mild hypertension and minimal cardiovascular disease were most likely to remain normotensive after discontinuing an effective course of therapy. In view of this evidence, we designed the present study to include only patients with uncomplicated, mild hypertension. The results indicate that 46% of patients who were previously treated remained normotensive for six months after discontinuing diuretic therapy, while 21% remained normotensive for one year.

The patients who remained normotensive for six or 12 months after stopping treatment had significantly lower DBPs (average, 5 mm Hg) during therapy than those with return of hypertension. The five patients who remained normotensive for 12 months also exhibited an average DBP during treatment that was 82 mm Hg or less. A DBP during treatment of 82 mm Hg or less did not guarantee persistent normotension, however, since six additional patients with treatment BPs of 82 mm Hg or less demonstrated return of hypertension.

The presence of target-organ damage as indicated by the ECG, chest roentgenogram, or serum creatinine level was not helpful in predicting the BP response after stopping treatment. Patients who remained normotensive for 12 months after discontinuing treatment tended to be younger than those with return of hypertension and had a shorter mean duration of treatment in the hypertension clinic. Whether these differences are of clinical significance is uncertain. The only laboratory finding that correlated significantly with BP response after diuretic withdrawal was the PRA response to furosemide and upright posture. The patients who remained normotensive for 12 months after diuretic withdrawal tended to have greater PRA increases in response to furosemide stimulation than those with return of hypertension. Classification by renin profiling, however, demonstrated no significant differences between the two groups.

Of 24 patients completing follow-up, two had cardiovascular events requiring removal from the study. In one patient recurrent supraventricular tachycardia developed while the patient was still normotensive four months following withdrawal of treatment; in the other patient mild cor pulmonale developed while the patient was still normotensive 11 months following withdrawal of treatment. It is unlikely that BP changes secondary to diuretic withdrawal played an important role in either complication.

The mechanism by which long-term BP levels are modified by antihypertensive agents is unknown. Earlier investigators[4] hypothesized that just as baroreceptors show an "upward resetting" in response to induced, acute hypertension in animals,[15] antihypertensive treatment could result in "downward resetting," thereby accounting for the persistence of lower BP after discontinuation of therapy. Abnormalities of the baroreceptor reflex have been found in humans with essential hypertension, but most evidence suggests that baroreceptor reflex mechanisms do not play a major role in long-term BP regulation.[16]

It is possible that hydrochlorothiazide and related diuretics produce long-term functional changes that persist after withdrawal of diuretic treatment. Although hemodynamic and fluid balance changes during therapy have been studied well,[17,18] there are few studies documenting corresponding variations after diuretic therapy has been stopped. In 1959, Wilson and Freis[17] studied eight patients with moderate to severe hypertension in whom plasma and extracellular fluid (ECF) volumes rose above pretreatment control values one week after stopping diuretic therapy. Their BPs also rose, albeit more slowly, and did not reach control levels by one week.

Tarazi et al[19] measured plasma and ECF volumes weekly for one month after discontinuing hydrochlorothiazide treatment in eight patients who were hypertensive. The

highest values of plasma volume and weight were attained one week after therapy was discontinued. The PRA decreased 72% from treated levels one week after stopping therapy and did not change significantly thereafter. The increase in BP occurred much more slowly than the prompt rebound of plasma volume, body weight, and PRA, as mean BP increased only 6/2 mm Hg after one week, but rose 20/11 mm Hg at four weeks. Pretreatment BPs were not recorded, however.

In the present study, similar weight gain was noted two weeks after diuretic withdrawal in patients who remained normotensive as well as patients whose BPs returned to elevated levels. The consistent finding in all of these studies that weight, ECF, and plasma volumes return to control levels without parallel increase in BP suggests that acute body fluid changes alone are not responsible for the BP response to discontinuing diuretic therapy. Whether diuretics have a persistent effect, even after withdrawal, on vasoactive hormone levels, effector-receptor relationships, renal function, or circulatory dynamics is not known. The importance of the statistically significant differences in age, duration of therapy, and stimulated PRA values between groups at 12 months' follow-up is difficult to assess because of the small size of the normotensive group.

Variables that we were unable to quantitate could have influenced the long-term BP responses following drug treatment. During the course of clinic follow-up, patients may have made changes in their life-style or eating habits; changes in sodium and caloric intake being the most important of these factors. However, the similarly high urinary sodium excretion before and after treatment and the absence of significant weight differences in the two groups suggest that these two factors did not play an important role.

The five patients who remained normotensive for 12 months had at least three separate, pretreatment DBP readings greater than 90 mm Hg and yet their DBPs averaged 17 mm Hg lower than pretreatment values 12 months after withdrawal of diuretic treatment. It therefore seems unlikely that the DBP in these patients reverted to normal solely as a result of habituation or regression toward the mean,[20] although this possibility cannot be ruled out.[21]

These data support earlier findings[4,5] that a small percentage of patients with mild hypertension may not require continuous, lifelong antihypertensive drug therapy for BP control. Since more than 20 million patients in the United States have mild hypertension, the potential savings in drug costs and side effects from even a 5% to 10% "remission" rate is sizable. Blood pressure levels during treatment had the most predictive value in distinguishing those who remained normotensive from those who showed return of hypertension, as five of 11 patients (45%) with DBP of 82 mm Hg or less during treatment maintained normal BP for one year after stopping treatment. Conversely, a DBP greater than 82 mm Hg during treatment was consistently associated with eventual return of hypertension. Thus, a trial period off diuretic therapy may be appropriate for patients who are mildly hypertensive whose BPs have been well controlled for at least one year. Physicians and patients must understand the need for continued surveillance so that medication can be reinstituted if BP rises. Further studies are needed to verify the long-term efficacy of attempted drug withdrawal, to identify clinical features predictive of patients most likely to benefit, and to uncover the mechanisms behind the maintenance of normal BP in this form of drug "step-down."

Walter Flamenbaum, MD, of the Veterans Administration Medical Center, Boston, carried out the determinations of plasma renin activity, urine sodium levels and "renin profiling." James Burris, MD, Marlene J. Smith, RN, and Leticia Corpus, RN, assisted in recruiting and following up the patients in this study.

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