Reprinted from The Journal of the American Medical Association
January 11, 1958, Vol. 166

TREATMENT OF ESSENTIAL HYPERTENSION WITH CHLOROTHIAZIDE (DIURIL)

ITS USE ALONE AND COMBINED WITH OTHER ANTIHYPERTENSIVE AGENTS

Edward D. Freis, M.D., Annemarie Wanko, M.D., Ilse M. Wilson, M.D.
and
Alvin E. Parrish, M.D., Washington, D. C.

Ten hypertensive patients were hospitalized on a constant intake of sodium chloride until their blood pressure levels had stabilized. Chlorothiazide in amounts of 1.5 Gm. per day reduced the systolic blood pressure in all. The average reduction was 18.7%; it took place within two or three days and was maintained to the end of a six-day period of medication. When it was withdrawn the blood pressure returned to its former level. Chlorothiazide (maintenance dose, 0.5 Gm. twice daily) added to the regimen of 73 ambulatory hypertensive patients who were receiving other antihypertensive drugs as well caused an additional reduction of blood pressure. In some patients it was possible to withdraw all other antihypertensive medication and to maintain the patient on chlorothiazide alone. Most of the patients noted a diuresis the first day or two after treatment with chlorothiazide. It exaggerated postural hypotension when that sign was already present, and reduction of the dosages of ganglion-blocking agents was necessary when chlorothiazide treatment was begun, in order to prevent postural collapse. Chlorothiazide also enhanced the antihypertensive activity of hydralazine, Veratrum, and reserpine. Side-effects were mild and infrequent and were promptly obviated by temporary withdrawal of the drug.

Chlorothiazide (Diuril) was synthesized by Novello and Sprague, who also reported on its diuretic properties.[1] Pharmacological studies in animals revealed that the orally administered drug produced a marked increase in the urinary excretion of sodium, potassium, and chloride.[2] No evidence of tolerance developed on continued administration. Ford and Moyer and their co-workers confirmed in man that chlorothiazide was a potent diuretic and saluretic agent.[3] Trials of orally given chlorothiazide in this clinic in hypertensive patients indicated that the drug potentiated markedly the action of various antihypertensive agents, resulting in improved blood pressure control, greater ease of dosage adjustment of antihypertensive drugs, and a considerable improvement in the incidence of side-effects due to the ability to reduce the dosage or discontinue use of ganglionic blocking agents.[4] This report presents these results in greater detail.

Antihypertensive Effect When Used Alone

The antihypertensive effect of chlorothiazide was measured under carefully controlled conditions in 10 previously untreated hypertensive patients. These were hospitalized and placed on a diet containing 1.25 Gm. of salt daily and in addition were given 3 Gm. of sodium chloride in tablet form. This provided a constant salt intake of approximately 4 Gm. daily regardless of any vagaries in the patient's appetite. After the blood pressure level had stabilized, recordings were taken twice daily by one of us for an additional six days. The patients then were given chlorothiazide, 1.5 Gm. in three divided dosages daily, for an additional six days.

Some reduction of blood pressure level occurred in every case (table 1). The average reduction in systolic blood pressure was 18.7% and in diastolic 13.9%. The fall to the new level occurred over a period of two to three days. In five of these patients chlorothiazide was then withdrawn. The blood pressure returned to the control level over a period of one to four days in all of these cases. There was a diuresis the first two days of treatment, and consequent weight loss varying between 1 and 7 lb. (0.5 and 3.2 kg.) (average 3.8 lb. [1.7 kg.]). No other side-effects were encountered.

From the Veterans Administration Hospital and Georgetown and George Washington University Schools of Medicine.

Use in Combination with Other Antihypertensive Agents

Chlorothiazide was added to the treatment regimen of 73 hypertensive patients. These patients had for the most part moderately severe cases. Prior to any treatment the pathological changes in the optic fundi had been classified as follows: grade 1, 11 cases; grade 2, 38; grade 3, 12; and grade 4, 2 cases.[5] Thirty-three patients were being treated with ganglionic blocking agents either alone or with reserpine and/or hydralazine, 19 were receiving the Veratrum alkaloids, some with and some without adjunctive medications, and 21 were taking reserpine alone or in combination with hydralazine (table 2).

The average period of observation prior to the administration of chlorothiazide was two years. The average period of observation after chlorothiazide was added was three and one-half months, with a range of one to eight months. Fifty-six of the patients were recording their blood pressure levels at home. The home and clinic readings were averaged together in calculating the changes. In almost all cases chlorothiazide was administered in a dose of 0.5 Gm. three times daily for three days, followed by 0.5 Gm. twice daily thereafter. In one patient the maintenance dose was 0.75 Gm. daily, and in two it was 1.5 Gm.

TABLE 1.—*Antihypertensive Effects of Chlorothiazide Alone in Ten Hypertensive Patients*

Blood Pressure Levels	Av.	Range
Pretreatment, mm.Hg	175/108	140/94 to 187/127
Post-treatment, mm.Hg	136/93	129/78 to 162/104
% decrease in systolic	—18.7	(—10 to —37)
% decrease in diastolic	—13.9	(— 5 to —20)
% decrease in mean*	—16.9	(— 9 to —25)

* Mean blood pressure $= \frac{\text{systolic} + \text{diastolic}}{2}$

The average reduction of blood pressure level for the entire group for the two-month period preceding the use of chlorothiazide was 11%. After the addition of chlorothiazide, the average reduction was 27%. Thus, the additional fall of blood pressure level after addition of chlorothiazide averaged 16%. Prior to any treatment the mean, control, "basal" systolic pressure for the entire group was 211 and the diastolic was 126 mm. Hg. After combined therapy including chlorothiazide the mean systolic was 153 and the diastolic 98 mm. Hg.

TABLE 2.—*Addition of Chlorothiazide to Other Antihypertensive Regimens*

Antihypertensive Regimen	No. of Patients	Av. Pretreatment Blood Pressure, Mm. Hg		% Decrease in Blood Pressure Level		
		Systolic	Diastolic	Before Chlorothiazide	After Chlorothiazide	Difference
Ganglionic blocker alone	10	225	135	12.5	28.7	16.2
with reserpine	12	214	130	9.6	25.7	16.1
with reserpine & hydralazine	8	236	134	20.9	34.8	13.9
with hydralazine	3	203	115	7.5	18.3	10.8
Veratrum alone	5	210	120	9.7	25.4	15.7
with reserpine	12	208	122	6.8	22.6	15.8
with reserpine & hydralazine	2	240	152	15.6	32.9	17.3
Reserpine	7	175	120	12.3	26.2	13.9
Reserpine & hydralazine	14	198	118	8.9	28.3	19.4
Total	73					
Mean		211	126	11.0	27.0	16.0

In the patients taking ganglionic blocking agents (pentolinium tartrate [Ansolysen], mecamylamine [Inversine], and chlorisondamine [Ecolid], the dosages of the blocking agent could be reduced in 13 and eliminated entirely in 19 others, providing that administration of reserpine and/or hydralazine was continued or substituted.

All other medicaments except chlorothiazide were withdrawn in 32 patients. After discontinuation of therapy with other drugs, the blood pressure level has not risen in 10 cases over a period of one to one and one-half months of observation. In 22 there has been a rise of 10% or more in the diastolic, and in six of the latter the elevation has approached pretreatment or control levels.

Treatment of Sympathectomized Patients

Five additional hypertensive patients had undergone lumbodorsal splanchnicectomy six months to three years previously. All of these patients responded with significant additional reductions of blood pressure level, averaging —21%, when on therapy with chlorothiazide alone. The uniform sensitivity of splanchnicectomized patients to the hypotensive effects of chlorothiazide has been noted also by Hollander and Wilkins.[6]

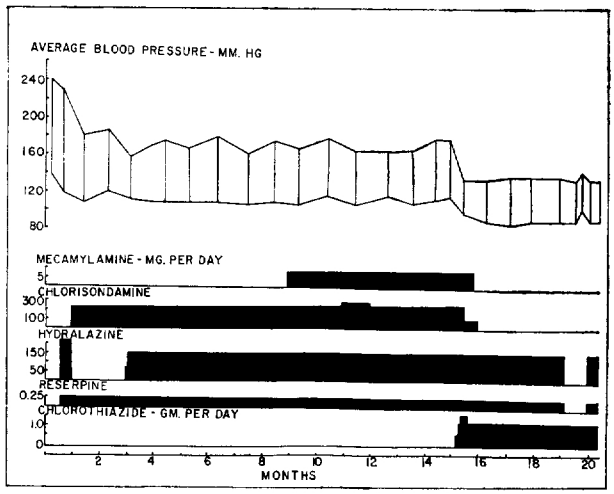

Chart of 32-year-old male with essential hypertension. Note prompt fall of blood pressure level after administration of chlorothiazide, persisting after withdrawal of blocking agents. After discontinuation of reserpine and hydralazine therapy the diastolic average rose from 90 to 105 mm. Hg, but subsided when these antihypertensive agents were administered again.

Treatment of Normotensive Subjects

Fifteen hospitalized normotensive patients in the inactive phases of a variety of conditions, including peptic ulcer, diabetes mellitus, osteoarthritis, and convalescent pneumonia, were placed under the same controlled-salt-intake regimen as the 10 hypertensive patients who were given chlorothiazide alone. In contrast to the hypertensive patients, after administration of chlorothiazide none of the normotensive subjects exhibited a reduction of "mean" arterial pressure level greater than 10%. The average decrease of blood pressure level for the group as a whole after, as compared with before, chlorothiazide therapy was only 1%.

Side-effects

Most of the patients noted a diuresis the first day or two after treatment with chlorothiazide. Weight loss varied from 1 to 8%, but averaged only 2.6 lb. (1.3 kg.) in nonedematous cases. In most of these the weight loss was regained after one to two months of treatment, despite continued reduction of blood pressure level.

Six patients complained of nausea and four of weakness during the first month of treatment. Discontinuation of the drug for one day, however, promptly cleared these symptoms. Chlorothiazide tended to exaggerate postural hypotension if that sign was already present, but the drug did not produce postural hypotension. Reduction of the dosages of ganglionic blocking agents was necessary when chlorothiazide treatment was begun, in order to prevent postural collapse.

Most patients looked and felt exceedingly well while taking the drug. When the ganglionic blocking agents and/or reserpine could be discontinued there usually was a pronounced increase in mental and physical vigor.

Other Observations

Two hospitalized hypertensive patients were placed on the previously described regimen supplying 4.25 Gm. of salt per day and then given chlorothiazide, 1.5 Gm. daily. The mean blood pressure level fell 15 and 18% respectively. After six days and with the dosage of chlorothiazide maintained, the salt intake was elevated to 11.25 Gm. daily by raising the dosages of salt tablets. After two days the blood pressure level rose 9% in one case and to pretreatment control levels in the other. The return of elevated blood pressure level was accompanied by a rise of serum sodium levels from 144 to 151 mEq. per liter in one case and from 142 to 152 mEq. per liter in the other. Serum potassium level also rose from 4.3 to 5.3 and from 4.9 to 5.2 mEq. per liter respectively.

The serum levels of sodium, potassium, and chloride have been followed in 24 patients. In no instance was there a fall to below the normal range. However, decreases varying from 5 to 8 mEq. for sodium and 8 to 12 mEq. for chloride were seen in 14 patients. Serum potassium decreases varied from 0.8 to 1.5 mEq. in 18 of the patients. Serum potassium levels were as low as 3.0 mEq. per liter in a few patients after continuous treatment with chlorothiazide.

The electrocardiogram has shown no specific changes after chlorothiazide therapy except for a decrease in left ventricular hypertrophy pattern in 5 of 17 patients studied before and after administration of the drug. The signs and symptoms associated with congestive heart failure were improved uniformly after chlorothiazide therapy.

Comment

The advantages of chlorothiazide were (1) significant antihypertensive effect in a high percentage of patients, particularly when combined with other agents, (2) absence of significant side-effects or toxicity in the dosages used, (3) absence of tolerance (at least thus far), and (4) effectiveness with simple "rule-of-thumb" oral dosage schedules. Salt was not severely restricted in the diet of any of these patients, but most were moderately restricted (avoidance of salt shaker and heavily salted foods).

When the reduction of blood pressure level achieved with chlorothiazide therapy alone was insufficient, reserpine, hydralazine, or Veratrum could be added, often with additional hypotensive effects. In the present study the dose of reserpine seldom exceeded 0.25 mg. per day, of hydralazine 150 mg. per day, and the dosage of Veratrum always was maintained below the emetic level. In the few cases which required ganglionic blocking agents the dosages of the latter were far less than were required formerly.

It is interesting but perhaps premature to speculate on the mechanism of the antihypertensive action of chlorothiazide. Studies reported in detail elsewhere indicate that chlorothiazide is a more effective saluretic agent than other known diuretics in nonedematous patients and that the drug often reduces plasma volume and radiosodium space.[7] In addition, the preliminary observations in two patients indicate that an excess of salt will overcome the antihypertensive effects of chlorothiazide in the dosages used. These bits of evidence suggest that the antihypertensive effect of the drug is secondary to the salt-depleting action. Hollander and Wilkins [6] have suggested that chlorothiazide in addition may have a direct hypotensive action not necessarily dependent on its saluretic effect.

It seems highly significant that the blood pressure levels of normotensive subjects were not reduced by chlorothiazide therapy. No other antihypertensive agent has shown such specificity. These various observations again point toward the importance of salt metabolism in the etiology of hypertension, although much further work will be required to clarify such relationships.

The low serum potassium levels developing in some patients suggest the need for potassium supplements. Our experience to date does not indicate that such supplements are needed. However, it is important to point out that the maintenance doses have been given twice daily, on arising and at bedtime. Thus the diuretic effect has largely worn off by dinner time, permitting body distribution of ingested potassium prior to the next dose, which was at bedtime.

Although no signs of electrolyte depletion were observed in this series, it is conceivable that under certain circumstances serious electrolyte disturb-

ances could occur. Injudicious elevation of dosages beyond the range used here, or continued administration of the drug in combination with diets very low in sodium or in the face of extrarenal salt loss such as may occur during protracted vomiting, diarrhea, or fever, might well lead to severe electrolyte imbalance. Finally, it should be stressed that eight months is not a long enough period to determine the effectiveness of any therapy for hypertension or to rule out the possibility of delayed and as yet unsuspected toxic reactions.

Summary and Conclusions

Chlorothiazide, a new orally effective diuretic and saluretic agent, was found to produce a significant reduction of blood pressure level in hypertensive but not in normotensive patients. The drug also potentiated the action of other antihypertensive agents and increased the hypotensive response resulting from splanchnicectomy. The dosages of ganglionic blocking agents were reduced or in many cases eliminated.

In the doses used disturbing side-effects were infrequent, mild, and transient. Dosage adjustment consisted of 0.5 Gm. three times daily for three days, followed by a maintenance dose of 0.5 Gm. twice daily in the majority of the cases.

The mode of action of chlorothiazide is different from that of other antihypertensive drugs and may be secondary to the salt-depleting effect. On the basis of the evidence available at present, the drug appears to represent an important new development in the chemotherapy of hypertension; however, a longer period of observation will be required to fully evaluate its effectiveness and freedom from serious toxic reactions.

2650 Wisconsin Ave. N. W. (7) (Dr. Freis).

This study was supported in part by a grant from the U. S. Public Health Service, National Heart Institute, and by Merck Sharp & Dohme, Division of Merck & Co., Inc., Philadelphia.

The chlorothiazide used in this study was supplied as Diuril through Dr. John R. Beem of Merck Sharp & Dohme.

References

1. Novello, F. C., and Sprague, J. M.: Benzothiadiazine Dioxides as Novel Diuretics, Communications to the Editor, J. Am. Chem. Soc. **79**:2028-2029 (April 20) 1957.

2. Baer, J. E.; Leidy, L.; and Brooks, A. V.: Physiological Disposition of Chlorothiazide (6-chloro-7-sulfamyl-1, 2, 4-benzothiadiazine-1, 1-dioxide), Saluretic-Diuretic Agent, abstracted, Fed. Proc. **16**:278 (March, pt. 1) 1957. Beyer, K. H.; Baer, J. E.; Russo, H. F.; and Haimbach, A. S.: Chlorothiazide (6-chloro-7-sulfamyl-1, 2, 4-benzothiadiazine-1, 1-dioxide): Enhancement of Sodium Chloride Excretion, abstracted, ibid. **16**:282 (March, pt. 1) 1957.

3. Ford, R. V.; Moyer, J. H.; Handley, C.; and Spurr, C. L.: Chlorothiazide (Diuril), Orally Effective Nonmercurial Diuretic Agent, M. Rec. & Ann. **51**:376-378 (April) 1957. Moyer, J. H.; Ford, R. V.; and Spurr, C. L.: Pharmacodynamics of Chlorothiazide (Diuril), Orally Effective Nonmercurial Diuretic Agent, Proc. Soc. Exper. Biol. & Med. **95**:529-531 (July) 1957.

4. Freis, E. D., and Wilson, I. M.: Potentiating Effect of Chlorothiazide (Diuril) in Combination with Antihypertensive Agents: Preliminary Report, M. Ann. District of Columbia **26**:468 (Sept.) 1957. Freis, E. D.; Wilson, I. M.; and Parrish, A. E.: Enhancement of Antihypertensive Activity with Chlorothiazide, abstracted, Circulation **16**:882 (Nov.) 1957.

5. Keith, N. M.; Wagner, H. P.; and Barker, N. W.: Some Different Types of Essential Hypertension: Their Course and Prognosis, Am. J. M. Sc. **197**:332-343 (March) 1939.

6. Hollander, W., and Wilkins, R. W.: Chlorothiazide: New Type of Drug for Treatment of Hypertension, Boston M. Quart. **8**:69-75 (Sept.) 1957.

7. Freis, E. D.; Wanko, A.; Wilson, I. M.; and Schnaper, H. W.: Antihypertensive Action of Chlorothiazide, Ann. N. Y. Acad. Sc., to be published.

Printed in U. S. A.