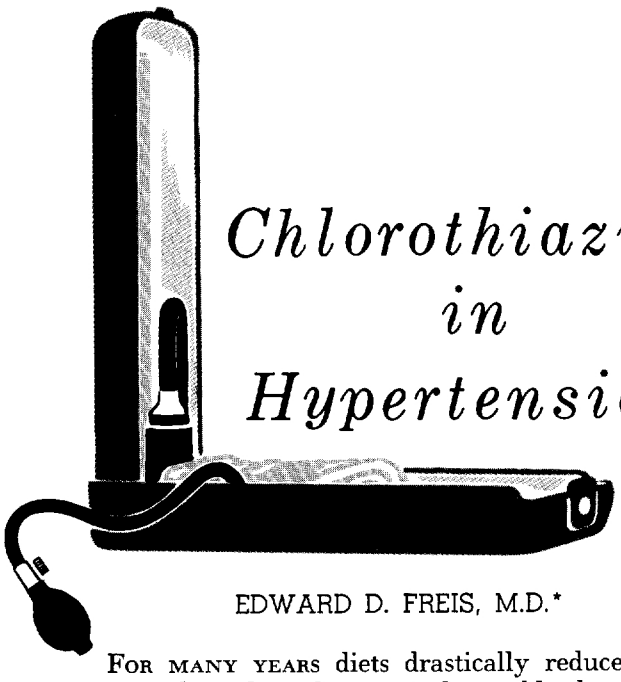

Chlorothiazide in Hypertension

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FOR MANY YEARS diets drastically reduced in salt content have been known to lower blood pressure in hypertensive patients. Attempts have been made to duplicate the antihypertensive effects of low sodium diets with use of diuretic agents to increase the renal elimination of salt. In the past these attempts were not successful because oral preparations lacked sufficient potency. Significant enhancement of the antihypertensive effects of ganglionic blocking agents could be demonstrated after parenteral administration of mercurial diuretics. The requirement for daily injections to maintain the effect, however, excluded this procedure as a practical treatment method in hypertension.

antihypertensive effectiveness

Two years ago, Novello and Sprague discovered that chlorothiazide (Diuril®) had a potent salt-depleting or saluretic effect in animals, an observation soon confirmed in edematous patients by Ford and others. Although the drug is related chemically to carbonic anhydrase inhibitors, such as acetazoleamide (Diamox®), its action in this regard is weak. Fortunately, it has instead a remarkable ability to block renal tubular reabsorption of both chloride and sodium, as well as of potassium. The loss of both sodium and chloride in the urine after a dose of 1 to 1.5 gm. per day orally is ordinarily as great as after an optimal dose of mercurial parenterally. There are, in addition, no evidence of tolerance and few side effects, except those which are directly attributable to diuretic action.

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The compound was only moderately effective when used alone. In ten hospitalized hypertensive patients given 500 mg. three times daily for six days, reduction of mean pressure averaged 16 per cent. However, in 73 patients in whom chlorothiazide, 500 mg. twice daily, was added to treatment regimens that included such drugs as Rauwolfia, Rauwolfia-hydralazine (Apresoline®), Veratrum viride, or the ganglionic blocking agents, reduction of mean pressure $\left(\frac{systolic + diastolic}{2}\right)$ averaged 27 per cent. Average pretreatment blood pressure for the 73 patients was 211/126 mm. of mercury. After therapy with chlorothiazide plus other agents, it was 153/98 mm. Furthermore, the latter average allowed for the fact that ganglionic blocking drugs were discontinued in 19 of 32 patients (but with continuation of reserpine and/or hydralazine) and reduced to approximately one-half the previous dose in the remainder.

side reactions and toxic effects

The advantages of chlorothiazide, particularly in general practice, are simple dosage schedule and relative absence of discomforting side effects. This does not imply, however, that the drug is innocuous. As will be seen later, chlorothiazide can produce serious toxic effects under certain circumstances. Nevertheless, in the average case of hypertension uncomplicated by renal or cardiac failure, no significant toxicity was noted with a standard dose of 500 mg. of chlorothiazide on arising and 500 mg. at bedtime. No potassium supplements have been used in these uncomplicated cases; and, except for occasional transient episodes of nausea or weakness early in the course of treatment, patients have experienced no difficulties.

Patients with congestive heart failure, however, not infrequently exhibit toxic manifestations after chlorothiazide administration. They lose more potassium in the urine than normally, an effect enhanced by chlorothiazide. If the drug is given continuously, as it must be to maintain antihypertensive effect, significant hypopotassemia can result. In patients who are also receiving digitalis, low plasma potassium levels provide the substrate for development of digitalis intoxication. Frequently there are extrasystoles, bigeminy, A-V block, and various arrhythmias secondary to the combined effect of hypopotassemia and digitalis.

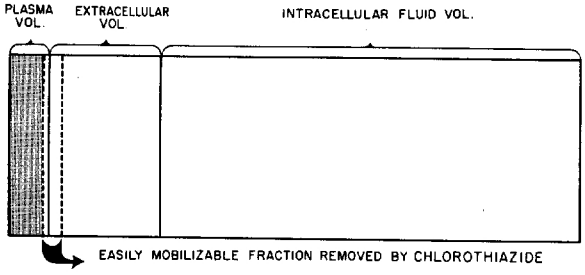
Because of the frequency of digitalis intoxication, I have adopted certain policies in treatment of hypertensive patients with congestive heart failure. If hypertension is mild, that is, with diastolic pressure below 105 mm., digitalis is continued and chlorothiazide,

1 gm., is given twice weekly principally for diuretic effect. However, if the diastolic pressure is elevated above 105 mm., chlorothiazide is given daily in the usual dosage along with Rauwolfia, and also, if necessary, a ganglionic blocking agent to reduce blood pressure. If pressure is well controlled, digitalis usually can be discontinued without return of congestive signs and symptoms. Occasionally, a patient requires both antihypertensive drugs and digitalis, in which case dosage of the latter should be carefully adjusted and potassium supplements may be needed. Normotensive patients in whom hypertension develops as a complication of steroid therapy should not receive chlorothiazide, since adrenal corticosteroids also produce potassium diuresis and severe hypopotassemia can result.

Patients with severe renal disease cannot readily adjust to the electrolyte-depleting effects of chlorothiazide. In a "salt-losing" type of nephritis, serious hyponatremia can develop with the additional stimulation of chlorothiazide. Rapid reduction of blood pressure in advanced renal disease can precipitate further elevation of the blood urea nitrogen level. Apparently these patients often require an elevated arteriolar pressure head to maintain adequate glomerular filtration. Therefore, when patients with serious renal impairment are given chlorothiazide, the blood urea nitrogen or nonprotein nitrogen should be measured frequently and dosage reduced or withdrawn if there is significant elevation in either of these levels.

Chlorothiazide is a potent saluretic agent which considerably enhances the antihypertensive effects of other agents or procedures capable of reducing blood pressure. In patients who have undergone sympathectomy or in those who are being treated with ganglionic blocking drugs, blood pressure reduction may be profound. If, in addition, the patient has atherosclerosis of the cerebral or coronary blood vessels, the resultant severe hypotension could possibly cause a cerebral or coronary artery thrombosis. Even in uncomplicated cases, ganglionic blocking agents should be cut in half when chlorothiazide is administered, then readjusted as necessary. In atherosclerotic patients, even greater caution is indicated. Blood pressure readings obtained during office examination may be considerably higher than those obtained at home. For this reason, and also because of changing dosage requirements, I insist upon frequent home recordings of blood pressure in patients who are receiving ganglionic blocking agents.

EFFECT OF CHLOROTHIAZIDE ON THE BODY FLUID SPACES IN NONEDEMATOUS PATIENTS



mechanism of antihypertensive effect

The mechanism by which chlorothiazide reduces blood pressure has not been established. However, most evidence suggests that it is associated with depletion of body salt and resultant diminution in plasma and extracellular fluid volumes. Even in nonedematous hypertensive patients, there is urinary loss of approximately 250 to 300 mEq. of sodium and chloride and lesser amounts of potassium. This loss of body stores of salt occurs primarily during the first 48 hours after daily oral administration of the drug. Thereafter, excretion and intake tend to balance so that little further salt depletion occurs despite continuation of the drug. However, restoration of the initial salt loss is prevented. Thus, a new equilibrium is established in which moderate depletion of sodium and chloride is maintained for as long as the drug is given.

The salt loss seems to be derived almost entirely from the extracellular fluid space including the plasma volume. Measurement of these spaces before and after chlorothiazide therapy indicates loss of isotonic extracellular fluid roughly comparable to the extent of salt loss, that is, about two liters. Of this amount, plasma volume fraction averages about 300 ml. (fig. 1).

As a result of the loss of extracellular water and salt in equal proportions, concentrations of sodium and chloride in the serum are seldom significantly reduced. For reasons as yet unexplained, serum potassium concentrations often decline, but in the absence of congestive heart failure or excessive corticosteroid administration, seldom to abnormally low levels. With extracellular fluid loss there is loss in body weight.

In general, reduction of extracellular fluid volume is maintained for as long as adequate dosages of the drug, 500 mg. twice daily, are continued. An increase in extracellular fluid volume can almost always be demonstrated within 48 hours after discontinuation, even when the drug has been taken for many months. Concurrently, the blood pressure returns to pretreatment levels. In addition, if sufficient salt is given to restore the body weight, blood pressure will rise significantly despite the continual administration of chlorothiazide. As much as 25 gm. of salt may be required

to do this in some instances. Furthermore, mercurials given parenterally produce the same degree of salt loss, extracellular fluid volume depletion, and blood pressure reduction. For these reasons, I believe that the antihypertensive effects of chlorothiazide probably are secondary to the drug's salt-depleting effect. Probably diets low in sodium, such as the rice diet, parenterally administered mercurials, and chlorothiazide all act to reduce blood pressure through this same mechanism. However, Hollander, Chobanian, and Wilkins are of the opinion that chlorothiazide acts primarily through some other unknown mechanism.

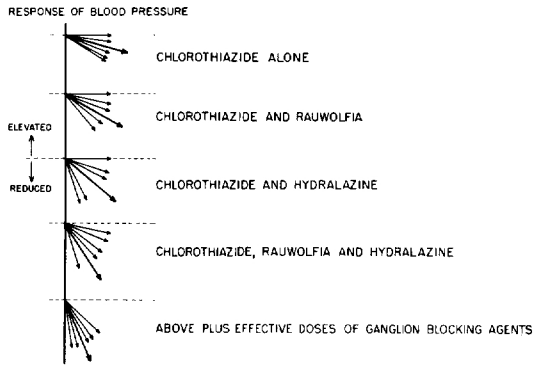
Although the mode of hypotensive action of chlorothiazide is still not completely clarified, reduction in plasma and extracellular fluid volume is probably entirely responsible for the pronounced reactivity to ganglionic blocking agents and sympathectomy produced by the drug. In the presence of ganglionic blockade, reductions in blood volume of as little as 200 to 400 ml. have a profound effect on blood pressure. The effect of extracellular fluid volume on tissue pressure also influences response to ganglionic blocking drugs. Chlorothiazide alone does not reduce blood pressure in normotensive individuals.

dosage administration

In uncomplicated hypertension, the type usually seen in office practice, chlorothiazide alone, 500 mg. twice daily, may be given for a week. If pressure reduction is inadequate, Rauwolfia may be added. Recommended dosages are Serpasil®, 0.25 mg., or Rauwiloid®, two mg., four times daily for two weeks, followed by a maintenance dose of Serpasil, 0.25 mg., or Rauwiloid, two mg., once daily. If response is inadequate, hydralazine (Apresoline®) may be added in a dose of 25 mg. three times daily and increased gradually, if necessary, to but not beyond 50 mg. per dose. All three drugs may be required in some cases. I have found that combination of chlorothiazide and hydralazine in dosages not to exceed 150 mg. per day is often effective, well tolerated, and free of serious toxic effects. This combination probably is the treatment of choice for mild and moderate hypertension, since the potential danger of emotional depression from long administration of Rauwolfia alkaloids is avoided.

In more severe cases a ganglionic blocking drug may be needed. If so, dosage of the blocking agent can be regulated most effectively in the hospital or, at least, with frequent recording of blood pressure in the home by the patient or a member of his family. Initial dosages should be low, Ansolysen® ten mg., Ecolid® ten

SPECTRUM OF BLOOD PRESSURE RESPONSES TO CHLOROTHIAZIDE IN VARIOUS HYPERTENSIVE PATIENTS



to twelve mg., or Inversine® 1.25 mg. every eight hours, and should be increased gradually. Response of blood pressure in the erect position should be used as a guide to further dosage. Because of the increased responsiveness induced by chlorothiazide, dosages often can be kept small enough to avoid disturbing side effects. However, the usual precautions in regard to the use of ganglionic blocking agents, including use of laxatives to prevent constipation, are still required.

Most patients are more responsive to combinations of agents than to individual drugs. A certain average response is to be anticipated with a specific agent or combination of agents in a large group of patients with hypertension. However, among individuals in the group, there may be variations from almost no response to extreme reduction of blood pressure. The relative spectra of responsiveness to be expected from chlorothiazide alone and in combination with other agents are depicted schematically above.

The introduction of chlorothiazide represents another step toward the objective of ultimate control of hypertension. The drug's principal value seems to be enhancement of the antihypertensive effects of other agents. It has the advantages of simplicity of administration and relative freedom from annoying side effects, but it is potent, and, hence, potentially toxic if not used with good judgment and discrimination.

suggested reading

FORD, R. V., et al.: Clinical and Laboratory Observations on Chlorothiazide, An Orally Effective Nonmercurial Diuretic Agent, Arch. Int. Med. 100:582 (Oct.) 1957.
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