Clinical Evaluation of Chlorothiazide

By WALTER M. KIRKENDALL, M.D.

CHLOROTHIAZIDE, commercially available as Diuril, was introduced to the general medical profession January 1, 1958. It had been available to clinical investigators during the previous year. In this span it has won wide acceptance as an oral diuretic and antihypertensive agent. These comments should be considered in the light of this relatively brief experience.

The chemical structure of chlorothiazide is shown in figure 1. Chlorothiazide, acetazolamide, and sulfanilamide all have the sulfamyl group. As a result of this structural similarity, chlorothiazide, like sulfanilamide and acetazolamide, is an inhibitor of the enzyme, carbonic anhydrase. However, the ability of chlorothiazide to inhibit carbonic anhydrase plays only a small role in the drug's long-term action.1

Chlorothiazide is rapidly absorbed from the gastrointestinal tract and is well tolerated intravenously.2 It is rapidly excreted by the kidneys, both by glomerular filtration and by tubular excretion. Approximately 30 to 50 per cent of the oral dose is excreted in 24 hours and over 90 per cent of the intravenous dose in 6 hours. Following oral ingestion, the drug is active for 6 to 12 hours and after intravenous administration for 2 to 4 hours.

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DIURETIC ACTION

The most noteworthy action of chlorothiazide is its ability to increase the urinary excretion of sodium, potassium, chloride, and water.3 This increase may occur immediately after intravenous injection (table 1). The initial excretion of these electrolytes is accompanied by the diuresis of bicarbonate. After 24 hours bicarbonate excretion falls and the principal electrolytes excreted are sodium, potassium, and chloride. Figure 2 shows the effect of chlorothiazide on the excretion of water and electrolytes and on the composition of the blood. Immediately after the administration of 1 Gm. of chlorothiazide there was prompt weight loss, increased urinary output, a large increase in sodium, potassium, and chloride excretion. On the first day, bicarbonate excretion was elevated and the pH of the urine relatively alkaline. By the ninth day of therapy there was still a brisk diuresis of water, sodium, and chloride but little increase of potassium excretion over control levels. Bicarbonate excretion was much lower. There was a relatively constant serum sodium level, a slight fall in serum potassium, and no change in serum chlorides during this period. Carbon dioxide content of the serum had increased 3 mEq./L. during the study. During the posttreatment period, there was a prompt increase in body weight, a sharp retention of sodium and chloride, and a less remarkable retention of potassium. Serum electrolytes either returned toward normal or had stayed normal during the study.

Long-term effects of chlorothiazide on body electrolytes in nonedematous patients have
been either a mild, long-term deficit or no change in exchangeable pools of sodium, potassium, and chloride.\(^4\) Initially there is a tremendous loss of these elements. However, most of the deficits are replenished from the diet or from other electrolyte pools in the body. We have measured exchangeable electrolytes a number of times over 1- to 2-month periods in 5 patients receiving chlorothiazide, but our results are not conclusive. There is a tendency for initial electrolyte depletion to cease as therapy is continued. Although we usually detected some decrease in body electrolytes, the changes were small and tended to get smaller as treatment continued. Clinical effectiveness was maintained.

The mechanism of the diuretic action of chlorothiazide is not known. It is postulated that the drug interferes with sodium or chloride reabsorption in the proximal convoluted tubule of the kidney.\(^1\) As a result of this interference, these electrolytes, plus water, are swept through the remaining portion of the nephron. Potassium may be exchanged for some of the sodium in the distal portions of the kidney. When the sodium ion is being avidly retained by the body, potassium is a relatively more important excretory product.

True tolerance to this drug does not seem to develop. There appears to be a level of depletion beyond which chlorothiazide is not active; if additional salt is given, it is excreted promptly. If one gives an extremely large dose of sodium chloride, the drug's effect may be overwhelmed and all the ingested salt will not be excreted.

When used as a diuretic agent in patients with edema, a 1-Gm. dose of chlorothiazide is about as effective as 2 ml. of meralluride (MERCUHYDRIN) given intramuscularly. The effectiveness varies from patient to patient. In our experience it has a wider range of use than the parenteral mercurials. FORD et al.\(^5\) have shown that chlorothiazide is a much

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**TABLE 1.—Onset of Action of Chlorothiazide in Man**

<table>
<thead>
<tr>
<th>Min. in col.</th>
<th>Urine flow</th>
<th>Renal clearance (ml./min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>46</td>
<td>4.3</td>
<td>Na 0.9 Cl 1.10 K 11.4</td>
</tr>
<tr>
<td>Chlorothiazide, 250 mg. I.V.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4.9</td>
<td>1.2 1.47 14.5</td>
</tr>
<tr>
<td>3</td>
<td>6.0</td>
<td>4.3 2.66 26.1</td>
</tr>
<tr>
<td>3</td>
<td>8.0</td>
<td>4.9 3.64 39.2</td>
</tr>
<tr>
<td>4</td>
<td>6.5</td>
<td>5.5 5.46 40.8</td>
</tr>
<tr>
<td>22</td>
<td>5.1</td>
<td>4.0 3.76 32.7</td>
</tr>
<tr>
<td>24</td>
<td>6.2</td>
<td>3.7 3.98 36.9</td>
</tr>
</tbody>
</table>

Since the transit time from the kidney to the bladder is at least 2 to 3 minutes at these urine flow rates, the suggestive increase in flow and all clearances at 3 minutes and the definite increase at 6 minutes indicates that chlorothiazide acts immediately.

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**Fig. 1.** Structural formulas. Chlorothiazide has a heterocyclic and a benzene ring, the sulfamyl (H\(_2\)N\(_2\)SO\(_2\)) group being on the benzene ring. Dihydrochlorothiazide (Esidrex) is a derivative of chlorothiazide, which is approximately 10 times as effective as a saluretic agent. This new compound has the double bond in the heterocyclic ring saturated by 2 hydrogen atoms.

**Sulfanilamide**

This figure shows the structure of sulfanilamide, a compound used in the treatment of edema. It is a derivative of chlorothiazide and is effective in similar conditions.
more potent diuretic than any other currently available oral diuretic agent. [This includes aminometramide (Mictine), chloromerodrin (Neohydrin), acetazolamide (Diamox), amisomadrine (Rolicton).]

In responsive patients the drug will continue to act until the body is free of edema. Figure 3 shows the weight loss of a patient with congestive heart failure after administration of chlorothiazide and maintenance of dry weight with a standard daily dose.

The diuretic action of chlorothiazide can be enhanced by the use of currently available carbonic anhydrase inhibitors such as acetazolamide. In addition, its action can be potentiated by mercurial diuretics and at times there appears to be a synergistic effect between chlorothiazide and the mercurials. The chlorothiazide effect may be enhanced by drugs that compete with it for excretory enzyme systems, such as paraaminophipprurate and by drugs that interfere with this excretory mechanism, such as probenecid (Benemid).

Chlorothiazide, alone or in conjunction with digitalis, is effective in removing the edema from over 80 per cent of our patients with congestive heart failure. It is of substantial benefit in removing edema from over half the patients with the nephrotic syndrome, and it is equally effective in edematous patients with cirrhosis of the liver. It usually relieves premenstrual edema, and salt and water accumulation caused by steroid therapy. I have found it of considerable value in the control of localized collections of fluid, such as hypertensive encephalopathy. It has also been beneficial in such conditions as malignant exophthalmus.

Since this drug acts chiefly on the kidneys, its usefulness is limited if kidney function is poor. Nevertheless, it will help remove edema in persons with moderate to severe azotemia. It is not unusual to have an increase in blood urea nitrogen after the use of this drug in patients with uremia. This may be related to the mild depression in glomerular filtration rate and renal plasma flow reported by Cosby and Cullen and observed by us.

Chlorothiazide is indicated in the treatment of generalized edema if kidney and liver function and electrolytes are relatively nor-
normal. It may be used in the face of these abnormalities if adequate precautions are taken.

Most patients with edema return to dry body weight with doses of 0.5 to 1 Gm. of chlorothiazide, daily or less frequently. At this dose, severe electrolyte disturbances are less common than with higher doses. Patients with initial potassium depletion and those who lose relatively large amounts of potassium (especially those on low-sodium diets) should have oral repletion of this ion with from 1 to 6 Gm. of a potassium salt daily. Larger amounts of chlorothiazide probably should be used for only short periods, although patients may tolerate 4 Gm. a day for as long as 3 months.9

Antihypertensive Action

In 1948 Megibow and his associates10 demonstrated that hypertension could be reduced by accelerated sodium depletion with mercurials. Nevertheless, at first chlorothiazide was not considered to be a hypotensive agent. Blood pressure lowering was not observed in laboratory animals. Soon after its introduction several investigators found that this drug often caused hypotension in hypertensive patients. A lively interest in the treatment of the hypertensive patient with chlorothiazide and other diuretics has developed.

Although a decrease in cardiac output after the acute administration of chlorothiazide has been observed,11 this is not thought to be the chief reason for its ability to reduce blood pressure. Peripheral resistance is lowered also. The following hypotheses have been presented to explain the hypotensive effect: (1) chronic depletion of the plasma volume, (2) mild sodium depletion, (3) redistribution of sodium and potassium within the compartments of the body, (4) the mild metabolic alkalosis which develops, (5) a direct effect of the drug on the central nervous system, or (6) on peripheral blood vessels. Most workers favor salt depletion or electrolyte redistribution, since other diuretics can produce the same effect and it can be prevented by adding salt to the diet.

The usual dose of chlorothiazide will not do much to "normal" blood pressure. Although there is a tendency for blood pressure to fall, it usually does not fall to hypotensive levels. Chlorothiazide alone will lower blood pressure in many hypertensive subjects but only about 10 to 15 mm. Hg mean pressure. Such a response is shown in figure 4. This fall in pressure, when it occurs, comes within
the first 1 to 2 days, is maximal within a week and is not necessarily orthostatic. There is a tendency to return to pretreatment level by the end of the first week after therapy is terminated. It may occur in patients with hypertension from any cause, including toxemia of pregnancy.

Chlorothiazide enhances the effect of Rauwolfia preparations, hydralazine, and veratrum alkaloids. The most spectacular results are seen when chlorothiazide is given with a ganglionic-blocking drug. A fall in mean supine pressure occurs but there is a more striking enhancement of the orthostatic drop. In figure 5, this orthostatic drop is shown when a blocking agent was administered with chlorothiazide in a patient who had had a lumbar-dorsal sympathectomy. The mean supine pressure was reduced only about 15 mm. Hg but the orthostatic pressure fell to levels incompatible with activity. Figure 6 shows a sharp fall in standing pressure in a patient with severe hypertension after the institution of chlorothiazide therapy, even though the dose of the blocking agent was decreased. Similar results occur in the sympathectomized patient without the addition of ganglionic blockers. As Sellers and his group\textsuperscript{12} have reported, this is true also of adrenalectomized hypertensive patients.

We now have observed 6 hypertensive patients for 16 to 18 months and 40 patients for over 12 months who have had a good initial response to chlorothiazide therapy. Of these, the majority have continued to benefit from the drug. In many, objective signs of severe hypertensive disease have abated. Four have had myocardial infarcts during chlorothiazide therapy; and 2 of these died of rupture of the heart. Three patients, including 1 who had a myocardial rupture, died with progressive hypertensive disease. The remainder generally have looked and felt better than they did before we began chlorothiazide therapy.

Most of our patients are treated with 0.5 to 1 Gm. of chlorothiazide daily, for we have had very little success with intermittent therapy in hypertension. We advise that their intake of sodium chloride be about 4 Gm. of salt a day. All patients on ganglionic-blocking agents are regulated with the aid of home blood pressure measurements and thus are controlled more easily and sent home earlier with safety.

When a patient is receiving a ganglionic-blocking drug and we wish to start chlorothiazide, we usually put him in the hospital or observe him very closely in our out-patient clinic. The dose of ganglionic-blocking drug is cut in half the day he starts therapy and necessary adjustments are made to keep the blood pressure within the desired range thereafter.

If a patient has not been treated with hypertensive agents and we wish to prescribe ganglionic-blocking drugs with chlorothiazide, we advise him to enter the hospital. Although these drugs may be started in the clinic, it is more convenient for both patient and physician, safer, and probably less expensive to have this period of close observation. Our usual plan is to prescribe chlorothiazide alone for 3 days. After breakfast on the fourth day, we give one oral dose of a ganglionic-blocking agent [2.5 mg. mecamylamine (Inver- sine), 20 mg. chlorisondamine (Reolid), 20 mg. trimethidinium (Ostensin) or 25 mg. pentolinium (Ansolysen), the ratio between...
TABLE 2.—Frequently Observed Side Effects of Chlorothiazide Therapy

<table>
<thead>
<tr>
<th>Hypokalemia</th>
<th>Hyponatremia</th>
<th>Hyponatremia</th>
<th>Hypochloremia</th>
<th>Metabolic alkalosis</th>
<th>Hyperuricemia</th>
<th>Azotemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and epigastric pain</td>
<td>Cardiac arrhythmias (digitalis intoxication)</td>
<td>Orthostatic hypotension</td>
<td>Weakness</td>
<td>Usually when given with ganglionic-blocking drugs or low salt diets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin rashess</td>
<td>Hepatic coma (only in patients with severe liver disease)</td>
<td>Paresthesias of hands and feet</td>
<td>Myocardial infarction</td>
<td>Iodine depletion (2 cases observed)</td>
<td>Metabolic acidosis (1 case reported)</td>
<td>Cholestatic jaundice (1 case reported)</td>
</tr>
</tbody>
</table>

† Weight loss

These drugs being roughly 1:8:8:10 and observe the response with hourly blood pressure measurements. If orthostatic hypotension (below 130/90 mm Hg) has not occurred by evening, we repeat the dose at 6:00 p.m. and continue the blood pressure measurements. If the patient's response is satisfactory, he is given 3 doses (after breakfast, at 2:00 p.m. and at bedtime) of the blocking agent on the fifth and sixth days. If the sitting pressure falls below 140/90 mm Hg during this period, the next dose of the blocking agent is withheld or cut in half. After the sixth day, increases in dose of blocking agent ordinarily are indicated to keep the pressure within the desired range. When the patient leaves the hospital on the fifteenth day, he usually is taking the equivalent of 20 mg. of mecamylamine in divided doses. Subsequent adjustments of dosage are made after an out-clinic visit 2 weeks later, although the patient himself is instructed to change the dose of the ganglionic-blocking drug to maintain optimal blood pressure lowering. We strive to keep sitting blood pressures in the range of 140/90 mm. Hg in patients without azotemia, although this is not always possible because of orthostatic hypotension with symptoms. If reserpine is used as a third drug, we start this (maximal dose 0.5 mg.) on the first day of therapy. If hydralazine (Apresoline) is employed as an adjunct, it is begun on the twelfth day in a dose of 10 to 25 mg. twice daily. We gradually increase this for 2 weeks after the patient leaves the hospital, to a total of 200 mg. (less frequently 400 mg.) in 4 divided doses. Such a program avoids the introduction of hydralazine while we are evaluating the patient's initial response to the blocking drug.

It is our custom to measure the blood urea nitrogen and serum potassium before and in the first week after beginning chlorothiazide therapy, repeating these tests after 3 and 6 weeks of therapy and thereafter at 12-week intervals. Approximately 6 months after the institution of therapy, we measure the serum uric acid, serum sodium and carbon dioxide content, or sooner if the patient does not appear to be doing well. We do not routinely give potassium supplements if the patient is receiving 1 Gm. or less of chlorothiazide daily and is eating well. If the serum potassium falls below 3.5 mEq./L. we supplement the diet with potassium salts each day. We have recognized no symptoms caused by potassium depletion in our hypertensive patients. Arrhythmias frequently do develop in our digitalized cardiac patients who have a considerable diuresis after chlorothiazide. It is possible that subtle changes occur in our hypertensive patients who have low serum potassium levels.

**Side Effects and Toxic Reactions**

Besides potassium depletion, the side effects and toxic reactions shown in tables 2 and 3 have been reported. Sodium and chloride lowering have been noted. They may become important in some patients with edema but are seldom a problem in most of our hypertensive patients. The mild metabolic alkalosis which develops regularly does not appear harmful. We have ignored it.
CLINICAL EVALUATION OF CHLOROTHIAZIDE

Just as this drug may deplete, it may also disturb excretory mechanisms of the body as well. The occasional rise of nonprotein nitrogen probably is secondary to the known decrease in glomerular filtration rate. The transient increase in serum uric acid may be secondary to the drug's effect on enzyme systems in the proximal convoluted tubules of the kidneys. Neither of these forms of retention has been a problem in the management of patients except in those with very poor renal function. Usually the elevations disappear during therapy or very shortly after stopping the drug. One hesitates, however, to continue long-term treatment with chlorothiazide in the face of significant elevations of either of these values.

Nausea and epigastric pain are a problem in some patients but this is seldom severe enough to interrupt therapy. They may be responsible in part for the weight loss sometimes seen in nonedematous patients given chlorothiazide for long periods.

The orthostatic hypotension and weakness are almost always associated with the administration of ganglionic-blocking drugs but occasionally occur in patients with extremely low salt diets.

I have listed weight loss as a questionable side effect of chlorothiazide therapy, since in our group of hypertensive patients approximately one half have had a weight loss of 10 pounds after 6 months or more. We have not controlled other variables that might have caused patients to lose weight, but I have put this suggestion on the table primarily because the weight loss has been great in some patients in whom obesity was not a problem and whose calories were not restricted.

A toxic effect of chlorothiazide has been a maculopapular skin rash, which we have seen 4 times during the treatment of approximately 350 patients.

In some patients with liver disease, chlorothiazide precipitated hepatic coma or the triad of confusion, flapping tremor, and abnormal electroencephalographic changes. Whether potassium loss is of primary importance is not known. Electrolyte imbalance is probably not the sole cause, since this state can be prevented by the administration of broad spectrum antibiotics such as Neomycin.14

Paresthesias of the hands and feet have been reported15 but are not a major problem. The last 4 items are very difficult to assess. Wilkins16 has suggested that myocardial infarction might be a complication of chlorothiazide therapy but he points out the difficulty of ascribing such vascular episodes to chlorothiazide. Although we have observed myocardial infarction, all patients had been severely ill with hypertension before the infarction and undoubtedly were poor risks. While theoretically the decrease in plasma volume might increase the likelihood of thrombosis, this has not been proved. The reduction of pressure, the decrease of cardiac work, the removal of edema and the increase in activity which most patients achieved should more than offset this risk.

The possibility of iodine depletion raises some interesting points. Certainly there are fundamental theoretical objections to the use of a drug that depletes the body of one or more of its elements. Although it is not proved unequivocally that the action of chlorothiazide is necessarily dependent on its ability to deplete the body of electrolytes and other materials, the possibility and probability exist. Thus, one should remember that other materials might be swept from the body as a result of interference with reabsorptive enzyme systems or secondary to the osmotic diuresis, which must occur in each nephron unit. It is possible, as with the mercurial diuretics, that certain water soluble vitamins might be swept from the body when water diuresis is brisk. Such materials as iodide, which may act much like chloride, may be carried through the kidney if chloride diuresis is pronounced. We have observed 2 patients who had an average increase in 24-hour uptake of radioiodine of over 30 per cent after 3 weeks of chlorothiazide therapy. This has not been a problem in long-term management of our patients, however, since we have found no significant increase in the uptake of radioiodine in 10 patients who received the drug for over 1 year.
Metabolic acidosis has been reported in 1 patient. This appears to be a very rare complication and perhaps occurs with only significant or unusual degrees of renal failure.

A patient who developed a skin rash after chlorothiazide also developed a cholestatic type of jaundice similar to the type seen following the use of methyltestosterone and chlorpromazine. No other such complication has been reported.

**Summary**

In the 2 years chlorothiazide has been available, it has been demonstrated to have many of the characteristics of the ideal diuretic agent. It has become an important drug in the treatment of patients with edema and hypertension. Experience has indicated that the side effects and toxic reactions are not severe nor do they prohibit long-term use of the drug. In the vast majority of patients, clinical effectiveness has persisted for the duration of the study, up to 2 years in some and more than a year in many.

Chlorothiazide is a new type of powerful diuretic agent. Surely other similar compounds will be introduced. For these reasons, it is especially important that we understand its mechanism of action and shortcomings. Interest in the pharmacology of chlorothiazide already has brought us new information about certain fundamental problems of kidney function and systemic arterial hypertension.

**Summario in Interlingua**

In le 2 annos del disponibilitate de chlorothiazido, illo se ha private dotate de multes del caracteristicas del agente diuretic ideal. Illo ha devenite un importante droga in le tractamento de patientes con edema e hypertension. Le experientia ha monstrate que le effectos lateral e le reactiones toxic non es sever e non prohibi le uso prolongate del droga. In le majoritate del patientes, le efficacia clinica ha perdurate le periodo del studio, i.e. usque a 2 annos in certes e plus que un anno in multes.

Chlorothiazido es un nove typo de diuretic potente. Certo, altere simile compositos va esser introducite. Pro iste rationes il es specialmente importante que nos comprende su mecanismo de action e su disadvantages. Le interesse in le pharmacologia de chlorothiazido ha jam produce pro nos nove informaciones relative a certe problemas fundamental de function renal e de hypertension arterial in le circulation systemic.

**REFERENCES**

rial hypertension, including patients previously subjected to sympathectomy and adrenalectomy. Circulation 18: 779, 1958.


Since the initiating factor in acute rheumatic fever is infection by the Group A streptococcus, the authors attempted to alter the course of established rheumatic fever by eradicating the original inciting agent with penicillin. Forty-nine patients with acute rheumatic fever received an intensive 6-week period of penicillin treatment. The course of this group was compared with that of 48 patients who were not given antibiotics. All patients initially were treated with similar courses of aspirin for relief of symptoms. At the end of the 6-week period both treated and control patients were given 1,200,000 units of benzathine penicillin every 5 weeks for 1 year. Observations during the first 6 weeks of the illness in these patients showed no significant differences between the treated and control groups in regard to the acute clinical, laboratory, and electrocardiographic manifestations of the disease. Studies a year later, however, indicated a probable statistically significant reduction in the incidence of valvular heart disease in the penicillin-treated group. The difference between the effects of penicillin on the acute-phase manifestations of rheumatic fever and on the endocardial lesions suggests that these lesions may differ pathogenetically and also that the living streptococcus may continue to play a significant role in the development of valvular heart disease even after the symptoms of rheumatic fever have appeared. On the basis of these observations it is concluded that an intensive course of penicillin in addition to symptomatic therapy may be important in the treatment of acute rheumatic fever to reduce the incidence of later valvular damage.

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