The Mode of Action and Use of Chlorothiazide and Related Compounds

By John H. Laragh, M.D.

The development of chlorothiazide has proved to be one of the most significant advances in clinical medicine in the past decade. No attempt will be made to annotate the vast literature, which confirms its remarkable therapeutic efficacy. Rather, the purpose of this discussion is to consider in more detail certain pharmacologic properties of chlorothiazide that not only permit better treatment, but also allow fuller understanding of the diseases associated with abnormal salt and water retention. In treatment of congestive heart failure, for example, the study of the effects of diuretic agents can yield important information about the mechanisms involved in salt and water balance, upset of which may result in the formation of edema. Accordingly, the main objectives of this discussion are (1) to consider some controlled studies that provide information concerning the mode and site of action of chlorothiazide and its derivatives, as compared with other types of diuretic agents, and (2) the application of these findings in the treatment of various states of edema and hypertension.

Pharmacologic Considerations

Absorption, Fate and Excretion

Chlorothiazide is rapidly absorbed in man, and after a single oral dose a peak blood level is reached in 1 to 3 hours.1,2 About half of the oral dose appears in the urine within 6 hours in man2 and dogs.3 Certain patients with advanced congestive heart failure or renal or hepatic disease may exhibit impaired renal excretion.2 The volume of distribution of the compound is similar to that of mannitol3 (extracellular fluid). In nephrectomized dogs, some 40 per cent of an intravenous dose is excreted in the bile and another 10 per cent into the intestine.4 Normally, the compound is excreted rapidly by the kidney, largely by a process of tubular secretion, so that 90 per cent of an intravenous dose of 0.5 Gm. appears in the urine in 2 hours.2 Chlorothiazide is cleared from the renal circulation three and one-half times as fast as creatinine (used for the measurement of glomerular filtration rate), and it can be cleared by the kidney at a rate approaching that of the renal plasma flow (para-aminobipurate clearance).5 Beyer3 noted that chlorothiazide competes with probenecid for renal tubular transport. The rate of tubular secretion of chlorothiazide can be reduced by probenecid without reducing its diuretic properties.

Effect on the Renal Excretion of Electrolytes and Water

Chlorothiazide increases the renal excretion of sodium, potassium, chloride, and bicarbonate ions.1,3,5 The main action of the compound is to inhibit tubular reabsorptive mechanisms, for the observed effects on electrolyte excretion can be shown to occur in the presence of a decreased glomerular filtration rate.5 In vitro, chlorothiazide inhibits carbonic anhydrase, a property that led to its discovery.6 However, this action is difficult to demonstrate in man, or even after rela-
Table 1

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Chlorothiazide</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCl (Normal dogs)</td>
<td>.68</td>
<td>.64</td>
</tr>
<tr>
<td>(Sodium-depleted dogs)</td>
<td>.72</td>
<td>.74</td>
</tr>
<tr>
<td>KHCO₃ (Normal dogs)</td>
<td>.32</td>
<td>.34</td>
</tr>
<tr>
<td>(Sodium-depleted dogs)</td>
<td>.22</td>
<td>.29</td>
</tr>
</tbody>
</table>

The control represents the average of two 40-minute control periods. The chlorothiazide data are averaged from two consecutive 40-minute experimental periods for all animals studied.

Continuous administration, potassium depletion develops frequently. The effect of chlorothiazide on calcium excretion has not been established, but, like mercurial agents, this drug can increase the excretion of magnesium.

Renal clearance studies have been carried out by us in normal dogs in an effort to characterize the effect of chlorothiazide on the excretion of potassium and other electrolytes. These experiments, summarized in figure 1, provide a general profile of the effects of the compound on electrolyte excretion. Trained unanesthetized dogs, maintained on oral potassium chloride (KCl supplements of 10 Gm. daily) were given infusions of KCl, 0.45 mEq./min. for 220 minutes. After 160 minutes, 2 mg./Kg. of chlorothiazide were given intravenously as a priming dose, and 3 mg./Kg./hr. were added to the infusion. Next, these experiments were repeated in the same dogs, using equimolar KHCO₃ infusion instead of KCl. Such paired studies were done again in these dogs after sodium chloride depletion had been produced by peritoneal dialysis. The anion being infused was the predominant anion excreted during all of these studies (fig. 1 and table 1). After chlorothiazide administration, the relative rates of Cl and HCO₃ excretion were not altered, i.e., no evidence of a selective inhibition of anion reabsorption by the drug (and thus no evidence

* A recent report indicates that a variety of sulfonamide diuretics reduce urine calcium. (Lichtwitz, A., Parlier, R., deSèze, S., Hico, D., and Miravet, L., La Semaines des Hôpitaux 44: 2350, 1961.)

Circulation, Volume XXVI, July 1962
for selective carbonic anhydrase inhibition was noted). But, administration of chlorothiazide did change the proportion of sodium to potassium excreted. In the nonsodium-depleted dogs, chlorothiazide increased sodium excretion to a relatively greater extent than potassium excretion during the potassium salt infusions. After sodium chloride depletion, however, sodium excretion increased only slightly from control values, whereas potassium output was increased to the same extent as before NaCl depletion. These data illustrate that, after NaCl depletion, the kidney excretes relatively more potassium and less sodium in response to chlorothiazide. This situation is perhaps an experimental counterpart of the potassium depletion so often observed after prolonged chlorothiazide administration in man. Apparently, chlorothiazide acts directly to block sodium reabsorption and only indirectly to cause potassium loss. Thus, potassium depletion from chlorothiazide administration may occur pari passu, as a result of the continuing diversion of more sodium to the distal tubular site for potassium secretion. This effect would be intensified as sodium depletion progresses, because the distal tubular ion exchange mechanism of K⁺ for Na⁺ then is more active (perhaps stimulated by aldosterone) and secretes more potassium in order to conserve more sodium. Potassium loss, therefore, may be a natural consequence of the action of chlorothiazide to block sodium reabsorption proximal to the site of K⁺ secretion.

If this postulation is correct, the various active derivatives of chlorothiazide may have the potentiality for causing potassium depletion in direct proportion to their capacity to block proximal sodium reabsorption. This has actually been the experience to date; a number of potent derivatives of chlorothiazide (see below) have the capacity to cause excessive potassium excretion. In this same connection, Gantt and Synex recently have found that adrenalectomized rats, given hydrochlorothiazide, do not exhibit potassium diuresis unless replacement therapy with a sodium-retaining hormone is given. Therefore, the increased aldosterone production of sodium depletion may be involved in promoting potassium loss. These findings explain the effectiveness of the aldosterone antagonists, which, in small doses, block the potassium loss of the chlorothiazides and also account for the observation that potassium depletion is uncommon in patients receiving diets unrestricted in sodium.

Effects of Chlorothiazide on Renal Excretion of Electrolytes Compared with Other Types of Diuretics

Certain differences in the pattern of excretion of electrolytes produced by chlorothiazide, as compared with other types of diuretic agents, are presented in figure 1. Typical carbonic anhydrase inhibitors, such as acetazolamide (Diamox), induce natriuresis by reducing Na⁺ for H⁺ exchange; these compounds produce a sizable increase in bicarbonate and an associated suppression of chloride excretion. Chlorothiazide and its derivatives have been termed the chloruretic sulfonamides to distinguish them from the classical carbonic anhydrase inhibitors. This term can be misleading, however, because the main action of chlorothiazide-type compounds may be inhibition of sodium rather than of chloride reabsorption.

Also shown in figure 1 is the observation that the natriuretic effect of chlorothiazide is potentiated by KHCO₃ as compared with KCl in the sodium-depleted dogs. The augmentation of chlorothiazide natriuresis by KHCO₃ may have the same basis as the potentiation observed when chlorothiazide is combined with acetazolamide, since the latter compound also increases the amount of bicarbonate in the urine.

In contrast to chlorothiazide, mercurial diuretics produce a selective increase in chloride excretion, and diuresis is enhanced by the production of hyperchloremic acidosis, utilizing either NH₄Cl or acetazolamide. However, acetazolamide therapy should be discontinued 1 to 3 days prior to the mercurial injection, possibly because mercurial agents are less effective during the bicarbonate diuresis induced by carbonic inhibitors. When given
intravenously, mercurial diuretics usually do not increase potassium excretion.5 Also, intravenous mercurial diuresis can block the kaliuretic action of chlorothiazide.5 With more prolonged administration mercurial agents may, at times, produce potassium depletion. But, unlike chlorothiazide, the potassium deficiency associated with mercurial diuretic therapy is much slower to develop and occurs in only a minority of instances.14 These observations support the proposal that mercurial diuretics act in part to inhibit, specifically, renal tubular secretion of potassium.11

Renal Site of Action of Chlorothiazide as Compared with Mercurial Diuretics

The effects of intravenous chlorothiazide were observed in normal subjects during a maintained water diuresis.8 Following chlorothiazide, the urine flow and total solute output increased, but the free water clearance either did not change or decreased. By contrast, mercurial, given under similar circumstances, produced a comparable increase in urine flow but a lesser rise in solute output, resulting in either an unchanged or an increased excretion of free water. These findings suggest that mercurial diuretics act* largely in the proximal tubule to block the isosmotic reabsorption of NaCl, whereas chlorothiazide appears to act both in the proximal tubule and in a more distal portion of the nephron to inhibit reabsorption of NaCl without water (i.e., "selective" reabsorption at the site of free water formation). These observations may explain the effectiveness of chlorothiazide

*Evidence has recently been presented which indicates that the mercurial diuretics might act to block isosmotic electrolyte reabsorption in a late distal segment of the tubule. (Goldstein, M. H., Levitt, M. F., Hauser, D., and Polimeros, D.: Effects of mercurial diuretics on solute and water excretion in hydrated man: Comments on site of action. J. Clin. Invest. 40: 731, 1961). Also, in a most comprehensive study, Earley, L. E., Kahn, M., and Orloff, J., (The effect of infusions of chlorothiazide on urinary dilution and concentration in the dog. J. Clin. Invest. 40: 857, 1961) have confirmed the action of chlorothiazide to reduce free water formation and have also shown that it may increase T H2O findings that point to a major distal tubular action for the compound.

either alone or in combination with mercurial agents in patients resistant to mercurial diuretics. The concept that mercurial agents act proximally, while chlorothiazide acts in both the proximal and distal portions of the nephron, has gained additional support from studies made with the stopped-flow technic.15

Hemodynamic Effects

Chlorothiazide produces an average fall in glomerular filtration rate of 20 per cent when given intravenously to normal subjects.5 The effect appears before any appreciable salt and water depletion occurs, and is not associated with a change in arterial blood pressure. The depression of glomerular filtration rate persists in both hypertensive16 and normal17 subjects maintained for periods of from 4 days to several weeks on chlorothiazide, although in such instances fluid and electrolyte depletion become contributing factors. Crosley and associates18 found that the reduction in glomerular filtration, after intravenous chlorothiazide, is associated with a similar fall in renal blood flow. They concluded that the changes in renal circulation result from a significant reduction in cardiac output (and cardiac work) which, in turn, they considered was caused by venous pooling and decreased venous return. No change in arterial pressure or pulse rate was noted. Other carbonic anhydrase inhibitors produced similar hemodynamic changes. While this study adequately describes the acute effects of administration of chlorothiazide, the extent to which these effects are responsible for the antihypertensive action that occurs with more prolonged administration is not yet clear. Blood levels of chlorothiazide achieved in these acute studies are higher than would be expected with the usual maintenance dosage. Again, sodium, potassium, and water depletion associated with more prolonged administration may be more important in producing the antihypertensive effect.

Fries19 has observed a reduced cardiac output, right atrial pressure, arterial pressure, plasma volume, and extracellular fluid volume in hypertensive patients after 3 days of chloro-

Circulation, Volume XXVI, July 1962
CHLOROTHIAZIDE

V. H. Wilkins, M.D.
W. R. Tuckman, M.D.
L. D. Holmes, M.D.

thiazide therapy. He attributed the initial hypotensive action to the reduced plasma volume of sodium depletion, but could not explain persistence of the effect weeks or months later, when plasma and extracellular fluid volumes had returned toward pretreatment values. Hypovolemia with increased vasoconstriction also was offered as an explanation for the reported chlorothiazide-induced sensitivity of hypertensive patients to ganglion-blocking agents. However, the hypotensive effect was early reported to persist despite sodium repletion. Because the reduced blood pressure persists after the exchangeable sodium returns to normal, Conway and Lauwers have related the hypotensive effect to a fall in total-body, largely cellular, water. Aleksandrow and his associates also could not relate the blood pressure lowering to a consistent reduction in either the cardiac output or the blood volume of hypertensive patients and attributed the effect to a reduced peripheral resistance, proposing that an observed reduction in sensitivity to infused norepinephrine arises from sodium depletion of arterioles. It is the author's view that, while depletion of electrolyte and water undoubtedly plays a role, the antihypertensive action must be referable in part to other factors because not only exchangeable sodium, but also the exchangeable potassium level tends to return to normal on continued therapy. The hypotensive action may be related to a more direct and immediate influence on the circulation.* This action could be associated with critical shifts in electrolyte and water distribution, such as suggested by Crosley and associates.

Other Metabolic Effects

Chronic administration of chlorothiazide results in hyperuricemia. This usually is asymptomatic, and episodes suggesting acute gout have been reported in only five patients. In acute renal clearance studies, chlorothiazide produces a uricosuric response, but the prolonged administration of 1 to 2 Gm. daily reduces the excretion of urate. One group proposes that the lower blood levels, associated with oral administration, block urate secretion by the renal tubule, while high concentrations, achieved with intravenous administration, also block tubular reabsorption with the secretory block then being masked. Therefore, chlorothiazide appears to resemble other uricosuric agents which, in low dosage, produce urate retention.

Interestingly, a hyperglycemic effect of chlorothiazide and its derivatives has been observed in patients with latent or overt diabetes mellitus. Six of 20 diabetic patients developed reversible hyperglycemia and glycosuria, when given standard doses of chlorothiazide or its derivatives. The effect did not occur in normal subjects, and apparently was not related to other therapy nor to the diuretic action of the drug. Since this hyperglycemic effect was observed in a minority of diabetic patients and was readily reversible, it probably is not an important contraindication to the use of sulfonamide diuretics in diabetes mellitus. However, the finding may prove useful in the further studies and in the early recognition of certain patients with diabetes mellitus.

It has been shown and amply confirmed that chlorothiazide and its derivatives are effective in the treatment of diabetes insipidus. Administration of 1.0 Gm. daily can reduce urine volume and polydipsia by about 50 per cent. It was originally sug-

gested\textsuperscript{31a} that these chloruretic sulfonamides acted by specifically opposing aldosterone. However, no good evidence has been provided to support this proposal. The antidiabetic effect only develops after sodium depletion, can be maintained by sodium deprivation alone, and can be produced with other types of diuretics.\textsuperscript{32, 33} It therefore seems likely that the reduced solute load of sodium depletion is critical in producing the effect. But, additional, more specific effects of chlorothiazides on glomerular filtration and also on water reabsorption may also be involved,—the latter effect perhaps being associated with the known action of these agents to inhibit sodium reabsorption in the diluting segment of the nephron. Whatever the mechanism, these diuretic agents appear useful in treating diabetes insipidus, especially of the nephrogenic type where hormonal therapy is ineffective.

**Effects of Excessive Administration**

Prolonged administration of chlorothiazide may cause disturbances that are consequences of its potent pharmacologic actions. Potassium depletion of some degree occurs in almost every patient given full dosage\textsuperscript{1} and may be seen after only 3 or 4 days of treatment. Some muscular weakness may be noted, but paralysis\textsuperscript{34} is rare. The plasma electrolytes reveal a lowered potassium and an elevated bicarbonate concentration. Depletion of sodium and fluid may contribute to muscular weakness and occasionally lead to prostration. Because chlorothiazide produces relatively greater excretion of solute and lesser excretion of free water than do other types of diuretics,\textsuperscript{5} hyponatremia is likely to develop and, at times, may be severe.\textsuperscript{1} A reversible elevation in blood urea nitrogen may appear even in patients without renal disease; this probably is referable to an induced reduction in glomerular filtration rate. Hyperuricemia may occur but only rarely is associated with episodes of acute gout. In susceptible subjects with renal disease, uremia may be precipitated, and in subjects with hepatic insufficiency, induced potassium deficiency can be associated with electroencephalographic abnormalities and hepatic coma.\textsuperscript{35} Mackie and associates\textsuperscript{36} demonstrated that chlorothiazide therapy may be followed by an increased concentration of blood ammonia, another factor in causing hepatic coma. The cause of hyperammoniemia during chlorothiazide administration to patients with liver disease remains unexplained. The condition also can be produced by carbonic anhydrase inhibitors such as acetazolamide,\textsuperscript{37} but has not been reported with mercurial diuretics. Impending coma during chlorothiazide therapy may be avoided\textsuperscript{36} by oral nonabsorbable broad-spectrum therapy.

**Side Effects and Toxicity**

In the large majority of instances, chlorothiazide is well tolerated orally. In my experience, gastrointestinal symptoms have been unusual and seem to be associated with administration of large single doses.

Considering its broad usage during the past 4 years, chlorothiazide has proved to be singularly free of serious toxicity. However, papular skin rashes,\textsuperscript{1} exfoliative dermatitis,\textsuperscript{38} purpura,\textsuperscript{39} thrombopenia and agranulocytosis,\textsuperscript{40-42} one instance of jaundice,\textsuperscript{43} and one of fatal acute glomerulonephritis\textsuperscript{44} have been recorded. These reports have been sufficiently uncommon to admit the possibility that some of the reactions were either coincidence or the result of other therapeutic agents. Important is the occurrence of acute pancreatitis\textsuperscript{45} in three women who had received chlorothiazide daily for several months. Two recovered with cessation of the drug. In the third instance, postmortem examination demonstrated the presence of severe hemorrhagic pancreatitis.\textsuperscript{*} Other workers\textsuperscript{46} believed that chlorothiazide-type diuretics induce a thrombophilic tend-

\textsuperscript{*}Further evidence that chlorothiazide may influence pancreatic function is provided by another report that the agent aggravated or precipitated development of diabetes mellitus (Hollis, W. C., J.A.M.A. 176: 145, 1961). Also, chlorothiazide produced an elevated serum amylase in 50 per cent of treated patients, and, in mice, caused inflammatory or necrotic lesions in the pancreas (Cornish, A. L., McClellan, J. T., and Johnston, D. H., New England J. Med., 265: 673, 1961).
ency in certain patients, although the mechanism of this effect remains obscure.

**Derivatives of Chlorothiazide**

A number of active derivatives (fig. 2) of chlorothiazide have been developed. Many of these compounds are more potent per unit weight than chlorothiazide but, when full dosages are compared, no convincing evidence that the derivatives are more active, as diuretic agents, than the parent compound has as yet been found. Further study is necessary because occasionally patients seem to respond better to one of the more potent derivatives. Yet, most evidence to date suggests that these derivatives probably are qualitatively similar to chlorothiazide. For example, in controlled renal clearance studies, dihydrochlorothiazide, while 10 to 20 times as potent by weight, produced effects entirely similar to chlorothiazide on glomerular filtration and on the excretion of electrolytes and water.47 Chronic administration of this compound also resulted in urate retention.48 The trichloromethyl derivative of chlorothiazide is notable because it is more than 100 times as active as chlorothiazide. The benzhydro derivative (fig. 2) is also potent and is said to be active for 3 to 18 hours after a single oral dose. Chlorthalidone19 bears little structural relation to the other members of the group (fig. 2). It contains a pthalimidine grouping instead of the usual thiazide grouping, and resembles chlorothiazide only in that the sulfamyl group with a halogen in the ortho position is retained. Physiologically, however, chlorthalidone resembles all the other compounds of this group; it is a weak carbonic anhydrase inhibitor in vitro, and in vivo it produces changes in electrolyte excretion similar to chlorothiazide. Chlorthalidone is the longest acting compound of the group. A single dose of 100 mg, is said to exert a diuretic action for 60 to 72 hours. Despite this feature, nocturia does not appear to have been a problem. It has been claimed that chlorthalidone does not depress glomerular filtration.49a A compound with such prolonged action might provide an advantage in the control of either edematous states or hypertension.49b

**Figure 2**

The structural formulae of some sulfonamide compounds are presented. At the top is the parent compound, sulfanilamide, which, in addition to its antimicrobial action, is a carbonic anhydrase inhibitor. Two representative sulfonamide compounds, one with antidiabetic activity (Orinase) and the other, primarily a carbonic anhydrase (Diamox), are also shown. Unlike the typical carbonic anhydrase inhibitors, chlorothiazide and its derivatives act mainly to inhibit sodium chloride reabsorption. All these sulfonamides have in common a configuration in which the sulfamyl group and a halogen are in the ortho position. The thiazide grouping does not appear essential for diuretic activity because in chlorthalidone (Hygroton), it has been replaced by a pthalimidine group. In parentheses below each compound, a recommended single oral dosage and its reported duration of action are presented.

**Therapeutic Application**

**General Principles**

The intelligent use of chlorothiazide and its derivatives in treatment of patients is wholly dependent on a thorough knowledge of the pharmacology of these compounds in relationship to other types of diuretics. With
a grasp of this fundamental information, appropriately individualized treatment is relatively simple. Nevertheless, in recent years, schedules of treatment, which usually are based on clinical experience, have been recommended for patients with heart failure or those with high blood pressure. Such "recipe" medicine is hazardous, because routine therapeutic programs tend to be widely accepted and utilized without consideration of the basic pharmacology of the drugs involved. When unexpected reactions develop, the physician may be ill-equipped to adjust the therapeutic regimen. The diuretic or antihypertensive potency of a drug is difficult, or impossible, to quantitate by testing relatively small numbers of ambulatory patients for short periods of time. The degree and nature of the disease process, as well as the state of hydration, acid-base balance, cardiac output, activity, emotion, other drugs and the diet, all contribute to produce great variation in patient responsiveness. Because of these shortcomings of drug assays in human subjects, a true appraisal of the relative merit and toxicity of the newer derivatives of chlorothiazide (which have been developed faster than they can be properly evaluated) has been difficult to obtain. These new derivatives may offer definite advantages, but, until more precise and detailed information is available, the newer drugs should be employed cautiously and with a healthy skepticism of the claims made for their superiority over older compounds of the group.

At present chlorothiazide, or a derivative, is the diuretic agent of choice, because of rapid action, potency, and ease of administration. Since many diuretic agents with different effects on electrolyte metabolism are now available, a base line evaluation of the status of renal function and electrolyte balance must be obtained. Unfortunately, serious derangements of electrolyte metabolism, azotemia, or both can exist without symptoms and can interfere with the diuretic response. With suitable treatment, almost all these derangements can be compensated, at least in part; so it is imperative that the total situation be appraised before therapy is begun. Thus, attention to nonspecific measures which correct an impaired renal circulation, such as digitalization, will enhance the response to a diuretic.

**Dosage and Administration**

In the administration of chlorothiazide and its derivatives, certain principles are well established. Because potassium depletion develops readily and can occur, at times, after only 3 or 4 days, chlorothiazide should not be given in full dosage (2 Gm./day) except on an intermittent basis. Maximum diuresis may not appear until the second day, so that a program of 3 to 4 consecutive days of treatment, followed by 2 to 4 days without treatment, seems reasonable. In patients with heart failure, 250 mg., given every 3 hours, produces a greater diuresis than 500 mg., every 6 hours. One or two 250-mg. tablets, given at 3-hour intervals in early morning, appears to be a minimal initial dosage. The amount may then be doubled and the dosage schedule increased to four times daily, if necessary. A maximal diuretic response usually occurs with 2 Gm. daily (500 mg. four times a day), but up to 8 Gm. per day has been given without untoward effect. This higher dosage is rarely needed, and often 1.0 Gm./day suffices. Intravenously, 500 mg. can be injected without difficulty, but this route rarely is necessary.

Potassium supplements (KCl 3 to 6 Gm. daily) may be needed, but this therapy in itself can be hazardous in sodium-depleted subjects. Increased fruit intake may obviate the need for potassium supplements. Hypokalemia is most apt to occur in sodium-depleted subjects where the natriuretic response is reduced. The hazards of potassium depletion are often compounded because many patients under treatment with chlorothiazide concurrently receive digitalis or adrenal corticosteroids. Sudden onset of a serious cardiac arrhythmia in a potassium-depleted subject receiving digitalis is an important possibility under these circumstances. As indicated above, chlorothiazide manifests little or no carbonic anhydrase activity at
usual dosages, and this probably explains the marked, and at times dramatic, potentiation of diuresis which may be observed when a thiazide is combined with acetazolamide for 24 to 48 hours. This combination should be used judiciously, however, because most severe potassium depletion may ensue. Mercurial diuretics not only can block the kaliuresis, but also can augment the natriuresis of chlorothiazide in acute experiments, leading to a more ideal type of diuresis, but this combination probably is not suitable for long-term administration. Potassium loss during prolonged chlorothiazide therapy can be blocked by combined administration of relatively small doses of spirolactones (aldosterone inhibitors). Therefore, if cost is not a factor, the combined use of a chlorothiazide compound with a spirolactone could be recommended almost routinely for patients requiring long-term chlorothiazide therapy.

In the most resistant patients, chlorothiazide may be combined not only with mercurial agents, carbonic anhydrase inhibitors, or spirolactones, but also with corticosteroids, such as prednisone. Possibly these glucocorticoids, as well as the theophylline compounds, aid diuresis by increasing glomerular filtration.

Chlorothiazide and its derivatives may produce hyponatremia by promoting excretion of salt in excess of water. Therefore, in edematous subjects, who are also hyponatremic, mercurial diuretics, which can increase free water excretion, may be preferred. Because of the dangers of potassium depletion and of hyperammoniemia in patients with severe liver disease, an intermittent dosage program, supplemented, if necessary, by a low-protein diet, potassium salts and a non-absorbable antibiotic may be needed. Urate retention from chlorothiazide is usually asymptomatic; the concurrent use of a uricosuric agent may be worthwhile, but such a regimen has not been critically tested.

In treatment of hypertension, chlorothiazide appears to be effective at considerably smaller dosages than are required to achieve a maximal diuretic effect. Therefore, the danger of significant potassium depletion is lessened. A longer acting derivative, such as chlorthalidone, may conceivably produce a more sustained (and presumably more beneficial) hypotensive effect, but further study is necessary. An initial dosage of 125 mg. of chlorothiazide three times a day, an average of 250 mg. and a maximum of 500 mg. two or three times a day has been recommended.

**Summary**

Chlorothiazide acts to inhibit renal tubular reabsorption of electrolytes. Experimental data are presented which indicate that, under various conditions, anion reabsorption is depressed unselectively so that the pre-existing ratio (Cl/HCO₃⁻) is not changed during chlorothiazide diuresis. The data suggest that chlorothiazide acts primarily to block sodium ion reabsorption.

Chlorothiazide diuresis is potentiated experimentally by KHCO₃ and clinically by acetazolamide, organomercurials, or spirolactone. The latter two can also operate to block the potassium wastage of chlorothiazide.

Increased potassium excretion caused by chlorothiazide is viewed as a consequence of the activity of the drug in blocking sodium reabsorption proximal to the site of potassium secretion. According to this concept, all chlorothiazide-type compounds will cause potassium depletion in proportion to their capacity to block proximal sodium reabsorption by diverting more sodium distally to the site of potassium secretion.

Unlike mercurial agents, chlorothiazide either depressor or does not change excretion of free water during a water diuresis. These data suggest that chlorothiazide acts both in the proximal and distal portions of the nephron, while mercurial agents may act largely in the proximal tubule.

The different mode of action of chlorothiazide on tubular reabsorption of electrolytes, as compared with other diuretic agents (acetazolamide, organomercurials, spirolactone), affords evidence that a number of discrete tubular transport mechanisms participate in the regulation of electrolyte and water bal-
ance and provide a rational basis for combined use of various types of diuretic agents in treating edematous patients.

The nature of the antihypertensive action of chlorothiazide has not yet been elucidated. The effect may be related to electrolyte and fluid depletion, but evidence for a more direct action on the circulation is reviewed.

Other aspects of the pharmacology of chlorothiazide and its derivatives are considered, and the application of this information in treatment of states of edema or hypertension is discussed.

References


22. DUSTAN, H. P., CUMMING, G. R., CORCORAN, A. C., AND PAGE, I. H.: A mechanism of chlorothiaz-
CHLOROTHIAZIDE


The Mode of Action and Use of Chlorothiazide and Related Compounds

JOHN H. LARAGH

Circulation. 1962;26:121-132
doi: 10.1161/01.CIR.26.1.121

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/26/1/121

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/