Clinical Pharmacology of Diuretic Agents with Special Reference to Chlorothiazide (Diuril*)

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The factors responsible for congestive heart failure as a clinical syndrome may be multiple. Although decreased cardiac output relative to inflow produces a moderate increase in venous pressure, there is a concomitant decrease in renal blood flow which may contribute to a decreased renal excretion of sodium. There is also a decrease in hepatic inactivation (? due to congestion) of adrenal cortical sodium-retaining hormone. Sodium retention produces at least a transient hypertonicity of the blood which may stimulate hypothalamic osmo-receptors, resulting in increased antidiuretic hormone secretion. Subsequent water retention produces a marked increase in venous pressure to further the development of edema. Thus, the rational therapeutic approach to the problem of congestive heart failure includes the exhibition of agents to increase cardiac output and increase renal blood flow, decrease venous pressure, decrease hepatic failure to inactivate steroids, decrease antidiuretic hormone activity, and decrease the abnormal renal retention of sodium. However, it is the renal retention of (or failure to excrete) sodium that assumes a major role in the pathogenesis of edema and it is this factor that concerns us therapeutically as we discuss diuretic agents. The purpose of this report is to describe the clinical pharmacology of diuretics with special attention to chlorothiazide (Diuril*).

Materials and Methods

A. Pharmacologic Investigations of Chlorothiazide. Ten men between the ages of 41 and 67 with controlled congestive heart failure were the subjects of a previous pilot study. They were maintained on a metabolic ward and were fed a diet containing 50 mEq. of sodium and given 3000 ml. of distilled water to drink daily. This study showed that the effective dose of chlorothiazide lay between 1000 and 2000 mg. In the control state and during the administration of the dosages determined by the pilot study, observations were made of the urinary excretion products in six periods per 24 hours — three consecutive two-hour periods and three consecutive six-hour periods. These included the excretion rates of sodium, potassium, ammonia, chloride, bicarbonate, titratable acidity, total solute, phosphorus, pH, and water.

Ten observations on the 24 hour excretion rate of sodium were made at each dose (1000 and 2000 mg.) and the data (increase in sodium excretion on the day of the drug over the control day) subjected to an analysis of variance. This analysis compares the dosage response curve of chlorothiazide with that of a standard diuretic, meralluride (Mercuhydrin), according to techniques previously described. These data can then be used to determine the “potency estimation” of chlorothiazide compared to meralluride (Mercuhydrin) as well as other diuretics.

*Supplied by Merck Sharp & Dohme Research Laboratories, West Point, Pa.
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To determine whether renal tolerance to chlorothiazide occurred, an edematous person who had been eating a low sodium (35 mEq.) diet for several years was given 500 mg. of the drug daily and the daily weight loss observed over a 15 day period.

One patient was given the drug at a dose of 1000 mg. at 6 A.M. and 6 P.M. on one day to compare the increase in sodium excretion obtained after giving the drug twice daily with that obtained after a single dose.

Another patient was given a dose of 2000 mg. intravenously over a 60-minute period and the increase in sodium excretion compared with that obtained after the same dose was given orally.

B. Clinical Therapeutics. Observations over a period of 18 months for chronic toxicity and beneficial results have been made on 200 patients. Their dosages of chlorothiazide varied from 500 to 2000 mg. daily. Some of these patients were receiving antihypertensive agents in conjunction with chlorothiazide.

C. Comparison of Chlorothiazide with Other Diuretics. Reference has been made in this paper to other publications in order to present a comparison of chlorothiazide with other diuretics.

Results

A. Pharmacologic Investigations of Chlorothiazide.

1. Electrolyte Excretion Effects. The data presented graphically in Figure 1 indicate the excretion rates for various observed moieties fol-
lowing the oral administration of chlorothiazide 2000 mg. The greatest responses were seen during the second two-hour period following the oral administration of the drug, with persistence of the response at a lower level for at least 12 hours and return to control levels during the third six-hour period (18 hours after the drug). The response was characterized by an increase in all moieties observed with the exception of ammonia, which showed a compensatory decrease during the period of drug response and a slight increase at the end of the 24-hour period. Quantitative differences in responses proportional to the dose were observed, but there were no significant qualitative differences in the electrolyte relationships. The greatest responses in excretion rates were observed in sodium and chloride. The magnitude of the increase in potassium excretion was about one-third (or less) that of sodium (and chloride). Ammonia excretion was depressed. Bicarbonate excretion increased from one-tenth to one-fourth that of the chloride excretion. The peak excretion rate was observed at the second 2-hour period, but the total excretion of bicarbonate over a 24-hour period was small. Phosphate excretion was not altered significantly. The pH of the urine increased significantly immediately and began to fall four hours after the drug was administered.

2. Dose-Response Relationships. The pilot study indicated that the effective dose lay between 1000 and 2000 mg.; hence repeated observations were made at these two doses. A dose of 4000 mg. produced no toxic effects but demonstrated no additional diuretic effectiveness (Fig. 2). Since the subjects of the bioassay were given a constant diet containing 50 mEq. of sodium, the control excretion in the urine was approximately 90 per cent of the dietary sodium (about 45 mEq.). The average increase in the 24-hour urinary sodium was 44 mEq. after the
1000 mg. dose and 104 mEq. after the 2000 mg. dose (Fig. 3). When these increases are compared to those following the administration of a standard parenteral mercurial diuretic agent meralluride (Mercuhydrin) by an analysis of variance, the dose response curves are found to be highly significant and parallel (P < 0.001), so that a calculation of "potency estimation" can be made.**

3. Comparative Potency of Chlorothiazide. When potency of chlorothiazide is compared with other diuretics (1), it appears that a dose of 40 mg. of mercury equivalent of diglucomethoxane (Mersiben) (1 cc., I.M.) produces an increase in sodium excretion that is equivalent to 1562 mg. of chlorothiazide administered orally, or 1 cc. of intramuscular meralluride (Mercuhydrin) is equivalent to 1119 mg. of oral chlorothiazide and 1 cc. of mercaptomerin (Thiomerin) administered parenterally is equivalent to 671 mg. of oral chlorothiazide. Four tablets (40 mg. mercury equivalent) of chloromerodrin (Neohydrin) administered orally are equivalent in natriuretic potency to 560 mg. of chlorothiazide.

4. Repetitive Effectiveness of Therapy. The persistence of diuresis as manifest by weight loss accompanying the continuous twice daily administration of chlorothiazide is well demonstrated (Fig. 4). This feature has further substantiating evidence in the group of chronically treated outpatients described below.

5. Effectiveness of Fractional Dosages of Chlorothiazide. In a patient who received the drug at a dose of 1000 mg. twice within a 24-hour period, the excretion pattern for sodium was repeated after the second dose in a fashion similar to that following the first dose but at a higher level, and the total increase in sodium excretion per 24 hours was greater.

![Dose-response curves for chlorothiazide (Diuril) versus meralluride (Mercuhydrin) for determination of comparative potency. The increase in sodium excretion plotted against the dose (in logarithmic order) for a standard diuretic (Mercuhydrin) intramuscularly administered and chlorothiazide orally administered permits a direct reading of potency (dotted line).](image-url)
than after a single dose of 2000 mg., indicating the advantages of fractional doses. There was no increase in the degree of natriuresis associated with four fractional cases.

6. Oral vs. Intravenous Administration of Chlorothiazide. Comparison of the enhanced sodium excretion in one patient following intravenous and oral administration of chlorothiazide 2000 mg., indicates that the latter is the more effective method for clinical use (Fig. 5). This is compatible with data showing that the drug is almost totally excreted within six hours following intravenous administration, whereas with the oral dose, one-half is excreted in 24 hours and excretion is completed in 48 hours.

B. Clinical Therapeutics.

1. Recommended Dosage Schedule. From personal experience in over 200 patients treated over a period of 18 months, I believe it best to administer two doses daily — one after breakfast and one after lunch. This is to avoid or decrease nocturnal diuresis. If the degree of edema is not dangerous, a daily dose of 500 mg. only after lunch might be started and increased slowly over a three to 10 day period to 500 mg. after breakfast and lunch, then to 1000 mg. after breakfast and lunch if necessary. A small group of patients may be sensitive to drastic diuresis and complain bitterly of weakness if the large doses are used initially. It must be remembered, also, that the hypertensive patient receiving, concurrently, a ganglionic blocking agent will experience a greater degree of orthostatic hypotension when this diuretic agent is added to the therapeutic regimen.

The prolonged outpatient use of chlorothiazide in congestive heart failure has fallen, roughly, into three categories. One-fourth of the patients have been stabilized and maintained edema-free with 500 mg.
diuretic syndrome. If and may have been followed by over 200 patients for more than one year without evidence of serious toxicity specifically attributable to chlorothiazide.

2. Chronic Toxicity. The long-term (18 months) use of this drug in over 200 patients has been remarkably free of serious toxic reactions. Four electrolyte imbalance states have been classified: (1) chronic diurional hyponatremia, (2) hypochloremic alkalosis, (3) "salt depletion" syndrome, and (4) potassium deficiency. Complaints of weakness have been observed in 20 per cent of the patients receiving large doses of chlorothiazide as opposed to 25 per cent in patients receiving 2 cc. of meralluride (Mercuhydrin) intramuscularly. It is only in hospitalized patients on strict sodium restriction that we have observed hypochloremic alkalosis (treatment discussed below) and only in the very far advanced problem of myocardial degeneration have we observed diurional hyponatremia. It is to be noted that these reactions are not peculiar to chlorothiazide but may be observed with mercurial diuretics as well. Clinically significant hypokalemia has been observed in only one patient, a 45 year old man with cirrhosis and ascites. He did not experience diuresis with chlorothiazide but continued to receive the drug inadvertently for a seven-day period. It is quite true that patients receiving chlorothiazide daily for extended periods of time will demonstrate a 15 to 30 per cent reduction in the serum potassium level but these patients do not present a truly significant clinical syndrome of hypokalemia.

Another complication of diuretic therapy is potassium deficiency. This may precipitate digitalis toxicity. Clinically, extreme muscle weakness, cardiac irregularities and abdominal distention are clues that should lead to the diagnosis. Ingestion of 6 to 8 ounces of orange juice on the day of diuretic therapy is usually adequate insurance against this complication. Should the complication occur, oral potassium chloride in dosages of 2 to 5 grams daily is indicated.

Ultimately, failure to respond to diuretics will be due to progressive impairment of glomerular filtration (secondary to decreased cardiac output) to such a degree that little sodium is filtered. Then virtually all of the sodium is reabsorbed, even after maximal tubular depression with diuretics. However, failure of diuresis may ensue because of an electrolyte imbalance which disrupts the normal biochemical architecture. This is usually a complication of too vigorous diuretic measures and too rigid salt restriction or progressive myocardial degeneration.

Chronic dilutional hyponatremia is one of the most serious metabolic derangements and is apparently unrelated to treatment unless concurrent primary renal disease is present. Under the latter circumstances, if fluids of low sodium content are given in excess of the kidney's ability to excrete water, dilutional hyponatremia results. The syndrome results from extreme dilution of extracellular fluid. Presumably excessive anti-diuretic hormone activity may also cause this syndrome. In the absence of severe primary renal disease in patients with heart failure, the syndrome is indicative of severe myocardial impairment. Serum sodium and serum chloride are low although total body sodium is excessive.
Hypochloremic alkalosis and "salt depletion" syndrome occur as a complication of vigorous therapy with saluretic agents and rigid dietary salt restriction. In hypochloremic alkalosis, the main deficit is chloride. In "salt depletion" syndrome, it is sodium. Clinically, there are lassitude, apathy, anorexia, oliguria and diuretic fastness in both. Hypochloremic alkalosis is also usually indicative of severe myocardial disease. It is difficult to produce this syndrome in normal subjects or in patients with only mild heart failure, even with vigorous daily diuretic administration. Therapy of hypochloremic alkalosis is directed at replacement of the appropriate electrolyte, using oral ammonium chloride. For this purpose at least 2 grams (30 grains) should be given every four hours. It is best to give the drug after a meal in order to avoid nausea and vomiting. Hypochloremic alkalosis can easily be avoided if ammonium chloride is given to predisposed individuals concurrently with the administration of diuretics that produce chloruresis.

The sodium deficit in patients with hyponatremia may be calculated from the serum sodium values, and replacement can be based on such calculations. Calculations may be based on extracellular (including intravascular) fluid sodium concentrations using 5% sodium chloride for replacement purposes. Thus 20 per cent of body weight (kilograms) is the approximate volume of the extracellular fluid. The plasma sodium

**FIGURE 5:** Although intravenous administration of chlorothiazide is associated with a slightly more rapid onset of increased sodium excretion, the total excretion is less than that following oral administration (2000 mg.). (Ford, et al, Arch. of Int. Med. 100:582, 1957.)
concentration is about the same as the extravascular, extracellular fluid sodium concentration. Therefore, normal plasma sodium (140 mEq.L.) minus the measured plasma sodium (milliequivalents) to correct the hyponatremia in the extracellular fluid compartment. One milliequivalent of sodium chloride equals 0.85 cc. of 5 per cent salt. Thus:

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\text{Body Wt. (Kgms.)} \times 0.20 \times (140 - \text{patients plasma sodium in mEq.}) \times 0.85\text{cc. of 5 per cent sodium chloride to be administered.}
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This salt should be given slowly by intravenous infusion over a period of two hours or more. It is important to restrict fluids (especially water) while the 5 per cent salt is being given and for some time thereafter. Otherwise the plasma sodium will be diluted again, the blood volume increased and the heart failure aggravated. After 12 hours, thus allowing adequate time for equilibrium and stability to occur, the plasma sodium concentration should again be determined. The process must then be repeated if hyponatremia continues. It is an error in our opinion to attempt to bring sodium levels entirely to normal. Furthermore, only if the sodium level is below 125 mEq. is corrective therapy with 5 per cent salt indicated and then only if the clinical symptoms demand it (severe oliguria, extreme weakness and lethargy, and cerebral symptoms). Otherwise, a liberalized salt intake will suffice. After the syndrome is corrected, the patient is then treated as a severe cardiac employing bed rest, digitalis and diuretics as before.

In summary, most of the complications of diuretic therapy may be avoided by (1) observation of the patient, (2) the use of these drugs only when indicated, and (3) full realization of their pharmacologic attributes.

**COMPARATIVE ELECTROLYTE EXCRETION EFFECTS OF VARIOUS DIURETICS**

![Bar graph showing comparative electrolyte excretion effects of various diuretics](image)

**FIGURE 6:** The electrolyte excretion patterns of five diuretic groups may be differentiated on the basis of the effects on sodium, potassium, chloride, and bicarbonate. Although other ions are influenced in varying degrees by the five different diuretics, the greatest change which is common to all is observed in sodium excretion.
C. **Comparison of Chlorothiazide with Other Diuretics.**

1. Pharmacodynamics of Five Classes of Diuretics. Chlorothiazide differs from other diuretic agents both in its chemical structure and its pharmacodynamic effect on the excretion of various electrolytes (Fig. 6).¹

The urinary electrolyte excretion pattern following the intramuscular administration of meralluride (Mercuhydrin) is typical of the patterns produced by the other mercurial diuretics. The onset of drug action occurs within two hours and lasts for 12 to 18 hours. There is a predominant augmentation of sodium and chloride excretion (Fig. 6) without significant alteration in potassium excretion. During the period of greatest sodium loss (two to six hours), ammonia excretion is slightly depressed. Bicarbonate excretion is suppressed during the period of greatest chloruretic response, but rises to normal or above normal when this period is over. Phosphate excretion is similar to that of bicarbonate. Continuous daily therapy is repetitively effective in the absence of biochemical dysequilibrium.

The oral administration of acetazoleamide (Diamox) produces a urinary electrolyte excretion pattern typical of the carbonic anhydrase inhibitors (Fig. 6). The predominant effect is the augmentation of the excretion of sodium with an almost equal effect on potassium and bicarbonate excretion. The onset of drug action occurs within six hours, and persists for six to 12 hours. During the period of greatest bicarbonate loss, chloride excretion is suppressed, but increases as the rate of bicarbonate excretion. The onset of drug action occurs within six hours, and significantly altered. Drug “tolerance” appearing on the second day of continuous therapy prevents repetitive effectiveness and demands an interrupted dosage schedule.

Aminometradine (Mictine) and its isomer aminoisometradine (Rolicon) produce an increased sodium and chloride excretion (Fig. 6). These aminouracils act within two to four hours; their duration of action is approximately 12 hours. There is no significant effect on potassium, bicarbonate, ammonia or phosphate excretion. Drug “tolerance” appearing on the second day of continuous therapy prevents repetitive effectiveness and demands an interrupted dosage schedule.

Oral administration of chlorothiazide (Diuril) causes a significant increase in sodium and chloride excretion which appears within two hours and lasts for approximately 12 hours (Fig. 6). Potassium excretion increases about one-third as much as sodium. Ammonia excretion is not altered (or slightly depressed) during the period of natriuresis, but increases during the ensuing 12 hours. This is probably a compensatory renal mechanism to conserve sodium. The excretion of phosphate is not significantly altered. Bicarbonate excretion is about one-fourth that of chloride excretion. Continuous daily therapy is repetitively effective in the absence of biochemical dysequilibrium.

Another chemically different diuretic is a new triazine compound. Chlorazanil (Daquin), when orally administered, augments sodium and chloride excretion (Fig. 6). The excretion rate of potassium is increased to about one-third that of sodium excretion. Ammonia excretion is suppressed during the period of greatest natriuresis, but increases in the following twelve hour period. The concentration of solutes is less than that
seen with comparably potent natriuretic agents suggesting that there is possibly a primary effect on water excretion. There is no significant alteration in phosphate excretion. Bicarbonate excretion is increased to about one-fourth that of chloride. Continuous daily therapy is repetitively effective unless there is biochemical imbalance.

These five classes of diuretics present differing electrolyte excretion patterns suggesting that their mechanisms of action are different although the principle action of each is the augmentation of the urinary excretion of sodium. This information may be of clinical importance in the intelligent selection of a diuretic to satisfy particular therapeutic needs in congestive heart failure with varied complicating situations. More precisely, these electrolyte excretion effects may be correlated with changes in the biochemical architecture occurring following the continuous administration of the diuretic agents. Thus, one may predict that the continuous loss of sodium and chloride will be associated with a tendency to the development of hypochloremic alkalosis and the low salt syndrome (mercurials and chlorothiazide). The continuous loss of bicarbonate (especially in the patient with poor or borderline renal compensation) may lead to a significant metabolic acidosis (with carbonic anhy-
drase inhibitors). The continuous loss of potassium (chlorothiazide and carbonic anhydrase inhibitors) may aggravate a pre-existing hypokalemia, e.g., cirrhosis, etc.

2. Comparative Potency of Various Diuretics. Figure 7 shows the relative potency of various diuretic agents by comparing the increase in sodium excretion produced after administration of the maximum single dose which is tolerated clinically in over 75 per cent of the patients. That is, this dose is toxic (usually gastrointestinal) in less than 25 per cent of the patients tested. Thus, chlorothiazide is equipotent to meralluride and more potent than chloromerodin, aminometradine, acetazoleamide, and chlorazanil.

To summarize the clinical application of diuretic therapy on the basis of drug tolerance, biochemical changes associated with continuous use, and finally potency, two groups of agents seem to be superior—mercurials and chlorothiazide. Since convenience of administration and economy must frequently be considered in the selection of a diuretic agent and since the oral administration of chlorothiazide is roughly equipotent with meralluride intramuscularly, chlorothiazide appears to be the current drug of choice.

SUMMARY

1. The clinical syndrome of congestive heart failure may be logically and effectively treated with diuretics although their use is not directed at the primary derangement.

2. Chlorothiazide therapy in congestive heart failure produces a significant loss of sodium and chloride via the kidney in almost physiologic proportions. It is effective orally in initiating therapy for edema and the maintenance of the edema-free state. The dose varies from 500 mg. to 2000 mg. daily. Adverse side reactions are minimal and not peculiar to this drug but are shared with any potent diuretic.

3. Comparison of chlorothiazide with mercurials, aminouracils, carbonic anhydrase inhibitors, and a triazine diuretic on the basis of potency, repetitive effectiveness, disturbances in biochemical architecture, and economy, indicates that chlorothiazide is the current diuretic of choice in congestive heart failure.

RESUMEN

1. El síndrome clínico de insuficiencia cardiaca congestiva puede ser tratado lógicamente y efectivamente por los diuréticos aunque su uso no se dirige hacia la afección primordial.

2. El tratamiento con la clorotiazida en la insuficiencia cardiaca congestiva produce una pérdida de sodio significante así como de cloro por la vía renal casi en proporciones fisiológicas. Es efectiva oralmente al iniciar el tratamiento de edema, así como para mantener un estado libre de edema. La dosis varía de 500 a 2,000 mg. diarios. Las reacciones adversas son mínimas y no son peculiares a la droga, sino las que son de esperarse en un diurético potente.

3. La comparación de la acción de la clorotiazida con los mercuriales, los aminoauracils, los inhibidores de la anhidrasa carbónica y la triacina, como diuréticos sobre de la base de potencia, efectividad en la reiteración de su uso, trastornos de la arquitectura bioquímica y economía indica que la clorotiazida es el diurético actual de elección en la insuficiencia cardiaca congestiva.

RESUMÉ

1. Le syndrome clinique de défaillance cardiaque peut être logiquement et efficacement traité par des diurétiques, bien que leur emploi ne soit pas dirigé contre l’altération première.

2. Le traitement par la chlorothiazide dans la défaillance cardiaque produit une perte marquée de sodium et de chlore par le rein presque dans les proportions physiologiques. Il est efficace par la bouche pour entreprendre le traitement de l’œdème et pour éviter son apparition. La dose varie entre 500 mg. et 2,000 mg. quotidiennement. Les réactions toxiques sont minimes et non pas particulières à ce produit mais telles qu’elles existent lorsqu’on utilise tout diurétique actif.

3. La comparaison de la chlorothiazide avec les diurétiques mercuriaux, les aminoauracils, les inhibiteurs à base d’anhydride carbonique et un diurétique triazine indique que, sur le plan de la puissance d’action, de l’efficacité en cas d’utilisation itérative, des modifications de l’architecture biochimique et de l’économie, la chlorothiazide est le diurétique courant électif dans la défaillance cardiaque.
ZUSAMMENFASSUNG

1. Das klinische Syndrom der Herzinsuffizienz mit Stauung kann folgerichtig und wirksam mit Diuretizis behandelt werden, obwohl deren Bebratisch nicht gegen die primäre Störung gerichtet ist.


REFERENCES