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HYDROCHLOROTHIAZIDE IN THE TREATMENT OF CONGESTIVE HEART FAILURE

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INTRODUCTION:

The past two years has seen the introduction to the medical profession of a new class of potent oral diuretic agents, derived from the aromatic sulfonamides and belonging to a group known as benzothiadiazines. This major break-through in producing a non-toxic and highly active oral diuretic resulted in the development of chlorothiazide, 6-chloro, 7-sulfamyl, 1, 2, 4-benzothiadiazine-1, 1-dioxide.¹ Since then, a second and more powerful derivative, hydrochlorothiazide, has been synthesized and is designated as 6-chloro-7-sulfamyl-3, 4-dihydro-1, 2, 4-benzothiadiazine-1, 1-dioxide. Figure 1.

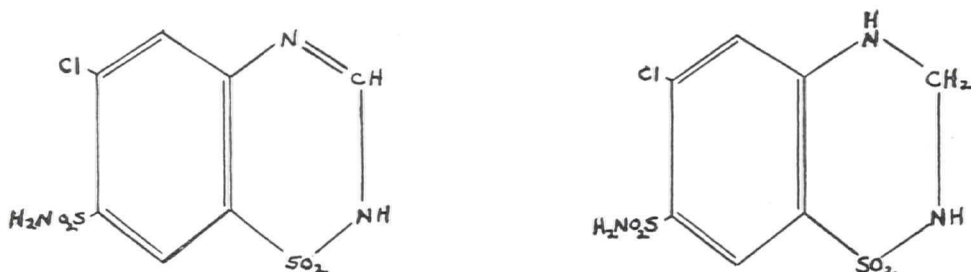


Figure 1

Both compounds are active saluretic agents, causing the excretion of large amounts of sodium, chloride and to a lesser extent, potassium. It is to this activity that they owe their effectiveness in the management of edema states, particularly congestive heart failure.

MODE OF ADMINISTRATION:

The comparable dose to 500 mgms. of chlorothiazide has not been concluded upon by the writers, but would appear to be somewhere between 50 and 100 mgms. The plan was to match 50 mgms. of hydrochlorothiazide to 500 mgms. of chlorothiazide. Some cases appeared to do as well on this program, but others required 150 mgms. of hydrochlorothiazide each day to equal 1,000 mgms. of chlorothiazide. It would appear that if the effects of hydrochlorothiazide are more prolonged,² a wider spacing of eight hours between doses might provide longer coverage and better diuretic effects. It also may be continued for long periods of extended therapy, the same as chlorothiazide, but caution must be used to avoid electrolyte depletion effects, as it does appear to depress chlorides more than chlorothiazide.

This drug may be administered intravenously in its lyohydrochlorothiazide form, 50 mgms. being diluted in 5 to 10 cc. of distilled water. This amount comes very close to equalling 2 cc. of mercaptomerin or meralluride in effectiveness.

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METHOD OF STUDY:

Thirty-two patients with congestive heart failure were treated with hydrochlorothiazide. Fourteen patients had arteriosclerotic heart disease and fourteen had rheumatic heart disease. Two patients had hypertensive heart disease, and there was one case each of congenital heart disease (probable atrial septal defect) and cor pulmonale.

The subjects were divided into three grades of congestive failure, as follows:
Table I

GRADE I: Patients with mild to moderate degrees of congestive heart failure, manifested usually by dyspnea, moist basilar rales, hepatic congestion and slight edema.

GRADE II: Patients with severe congestive failure, usually with marked edema and/or ascites.

GRADE III: Patients with severe congestive failure who had become resistant or refractive to previously used diuretic agents.

All patients were digitalized and the majority had received prior diuretic therapy, mercurials and/or chlorothiazide. One patient in grade I failure, and one in grade II, had received no previous diuretic. Grade I patients were maintained on 400 to 1,600 mgms. sodium diets as indicated, while those in grades II and III were maintained on the 400 mgms. sodium diet.

TABLE I

ETIOLOGY	GRADE I	GRADE II	GRADE III	TOTAL
ARTERIOSCLEROTIC	4 (1)	7 (2)	3	14
RHEUMATIC	3	10	1 (1)	14
HYPERTENSIVE	1	1	0	2
CONGENITAL	0	1	0	1
COR PULMONALE	0	1	0	1
TOTAL	8	20	4	32

() toxic changes

Twenty-four patients were hospitalized and the remaining eight were followed at one to four week intervals in the Out-Patient Department. A daily weight was obtained. Blood counts, urinalyses, BUN and serum electrolyte determinations once or twice weekly were obtained on all hospitalized patients. Clinic patients were checked with less regularity, though several maintained a daily weight chart at home.

RESULTS

GRADE I: Eight cases were classified as having grade I congestive failure, four with arteriosclerotic heart disease, three with rheumatic heart disease and one with hypertensive heart disease. Seven of the patients had been treated with previous diuretic programs, all with good response. When changed to hydrochlorothiazide, six of the seven responded equally well to this agent. One case (Case 1) demonstrated a superior response to a mercurial diuretic.

CASE 1: N.A. was a 71 year old white woman who had been followed in the Out-Patient Department since March 1957 with a diagnosis of rheumatic heart disease, aortic insufficiency and cardiac decompensation. She was maintained on a 1 gram salt diet, gitaligin 0.5 mgms. daily, and intermittent injections of mercurial diuretics.

She was admitted to the hospital on December 14, 1958, because of increasing dyspnea, palpitation and ankle edema of two weeks duration. Weight on admission was 106 pounds, and after four days of bedrest and her prior regime, her weight decreased to 104¼ pounds. Seventy mgms. of lyohydrodiuril was administered at this time with a loss of 1¼ pounds. Four days later an injection of 2 cc. of mercurhydrin resulted in a diuresis of 4¼ pounds. During this four day interval the patient showed no evidence of the delayed response to hydrochlorothiazide mentioned below.

One patient in this group not previously treated with diuretics showed a good response.

No toxicity was noted other than weakness in one case after three days of drug administration. This patient had an acute myocardial infraction and could not be weighed, but daily urinary output indicated a good diuresis and the serum chloride level fell to 84 mEq. This cleared promptly when the drug was discontinued.

GRADE II: There were 20 cases in this group, seven with arteriosclerotic heart disease, ten with rheumatic heart disease, and one case each of congenital heart disease, chronic cor pulmonale, and hypertensive heart disease.

One patient had not had previous treatment with diuretics and showed a good response. Of the remaining 19 cases, all had received previous diuretics with a satisfactory response, though the congestive heart failure was not completely controlled in all cases. Seventeen of the 19 cases showed a good response with a weight loss of one to 27 pounds after hydrochlorothiazide was started, the average being seven pounds. Thus, 18 of the 20 cases had a satisfactory diuretic response. Four patients previously maintained on chlorothiazide as the sole diuretic were felt to have an improved diuresis with hydrochlorothiazide.

CASE 2: A.D., a 73 year old woman with arteriosclerotic heart disease, chronic atrial fibrillation and chronic congestive heart failure was followed in the Out-Patient Department. Her passive congestion was incompletely controlled on a 1 gram salt diet, digitoxin 0.1 mgms. daily, diuril 500 mgms. twice daily three days each week and ammonium chloride. Hydrodiuril 50 mgms. b.i.d. was substituted for the diuril three days each week with a prompt loss of 6½ pounds, and considerable improvement in her hepatomegaly and edema, though still not at a dry weight.

In several cases, a prolonged diuresis with a delayed maximal response was noted, particularly following intravenous administration. This, to our knowledge, has not previously been reported.

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CASE 3: L.D. (Fig. I) a 46 year old white man, was admitted to the hospital on December 31, 1958. For two years prior to admission he had increasing dyspnea on exertion, cyanosis, ascites and pedal edema. There was a life-long history of bronchial asthma. Previous treatment included a low salt diet, digitalis and intermittent injections of mercurial diuretics.

Cardiac catheterization showed no evidence of a shunt. Diagnoses of chronic cor pulmonale, obstructive emphysema and congestive heart failure were made.

The patient was continued on digitoxin and a 1 gram salt diet. During the first week he diuresed 14 pounds with bedrest and two injections of mercaptomerin. On January 8, 1959, the patient weighed 202 $\frac{3}{4}$ pounds, and was given 50 mgms. of lyohydrochlorothiazide intravenously. The following morning he weighed 200 $\frac{1}{4}$ pounds, and on the day following — 192 $\frac{1}{2}$ pounds. The same intravenous dose was repeated, and over the next four day period, he diuresed an additional 13 pounds.

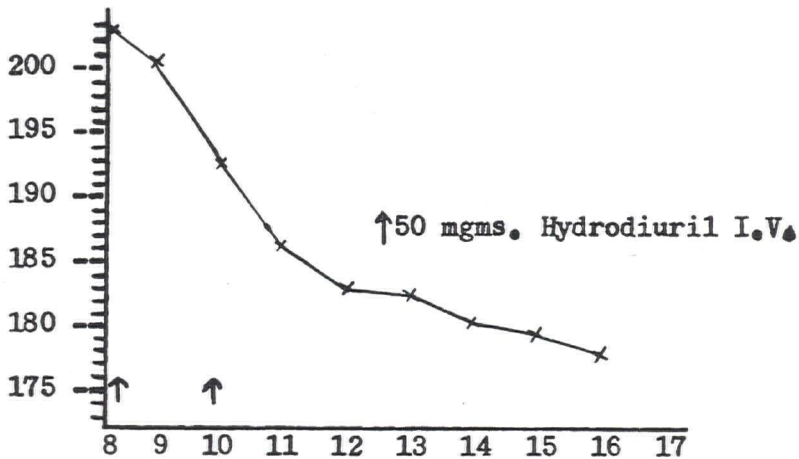


FIGURE I

Two patients in this group responded poorly to hydrochlorothiazide in a dose of 100 mgms. daily. A larger dose might have proven effective, though in our experience some effect can usually be obtained at this dosage level if the patient will respond at all to the drug.

Nausea and weakness occurred in one patient of this group who asked that the drug be discontinued. Serum electrolytes in this case were normal. Weakness and anorexia were noted by a second patient, but drug withdrawal was not necessary. Mild to moderate degrees of hypochloremia were not uncommon, but caused no untoward effects. No cases of hyponatremia or hypokalemia were noted in this series, but these complications have been observed by the authors since preparation of this report.

GRADE III: Four cases of severe, resistant congestive heart failure were given a trial of hydrochlorothiazide. Three were cases of advanced arteriosclerotic heart

disease and there was one case of rheumatic heart disease. All had developed refractoriness to mercurial diuretics and diuril, and showed no response to hydrochlorothiazide. Two patients subsequently showed some response to mercurial diuretics when started on large doses of triamcinolone.

No toxic effects directly attributable to hydrochlorothiazide were noted in these seriously ill patients. One case developed paroxysmal ventricular tachycardia twelve hours after receiving 50 mgms. of hydrodiuril intravenously. This converted readily during the administration of 40 mEq. of potassium in 500 cc. of 5% glucose in water. There were no other signs of possible digitalis toxicity while the serum electrolytes determined at the time showed only a mild hyponatremia (Na 127 mEq.). The relation to hydrochlorothiazide is conjectural.

COMMENT:

Hydrochlorothiazide, like chlorothiazide, causes a marked excretion of sodium, chloride and potassium in the urine, apparently due to a renal tubular blocking action on the reabsorption of these ions. Studies by Moyer and co-workers⁴ suggest that the primary action is on chloride excretion in contrast to chlorothiazide, which produces a relatively greater loss of sodium. The two drugs appear to cause approximately equal excretion of potassium. The saluretic effects are greater and more prolonged in the case of hydrochlorothiazide at a comparable oral dose.³ The latter effect was noted over a protracted period in one of the cases in this report (Case 3). Diuresis is apparently improved when acid salts, potassium chloride and/or ammonium chloride were used as adjunctive therapy in this series. It was somewhat less effective when serum chlorides were at slightly depressed levels and much less effective at moderately depressed levels, i.e. when serum chlorides were depressed after intensive or prolonged therapy below 97 mEq.

Hydrochlorothiazide is well tolerated orally and almost devoid of gastrointestinal side effects, even in the most advanced cases of congestive heart failure with severe visceral congestion. Like chlorothiazide, it remains consistently effective without evidence of drug tolerance and subsequent need of increasing dosage. Approximately two percent of our cases treated with chlorothiazide have developed a mild erythematous skin rash, while none were encountered in this series treated with hydrochlorothiazide. No adequate opportunity has been afforded to test the latter drug in a patient sensitive to chlorothiazide. Hydrochlorothiazide has not produced any toxic renal disturbance since its use was begun. Jaundice has not been reported to date, though this is a rare toxic complication with the use of chlorothiazide.

The greatest danger and toxic effect appears to be severe electrolyte depletion. Mild hypochloremia is a natural consequence of the use of either of these two agents, but if large doses are given over too long a period in salt depleted patients, severe hypochloremic alkalosis, "salt depletion syndrome", and severe hypokalemic effects may be produced. The adjunctive use of potassium chloride orally, and/or ammonium chloride can prevent severe hypokalemia, or hypochloremia, and in our opinion, should be used where heavy dosage of both drugs are employed, particularly over long periods. If severe liver impairment is present, as is so often the case in

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long-standing congestive heart failure, loss of potassium may already have occurred, and will be aggravated by this type of diuretic therapy. The depletion of potassium will lead to augmented digitalis effects with typical manifestations of digitalis intoxication, mild to severe, manifested often by unusual digitalis arrhythmias. The authors suspect one of the cases in this report was due to this effect.

It is recommended that regular serum electrolyte determinations be obtained where prolonged administration is used in advanced chronic congestive heart failure, particularly where hepatic or renal disease may be suspected, or known to exist, and to "spot check" others at the slightest suspicion of electrolyte depletion. The latter should be suspected if sudden oliguria, or failure to respond, occurs.

Hypochloremic alkalosis usually responds promptly to the use of ammonium chloride, and may be hastened by the combined use of a carbonic anhydrase inhibiting agent for several days.

Hydrochlorothiazide represents another significant advance in the diuretic management of congestive heart failure, and like chlorothiazide, approaches the effectiveness of parenterally administered mercurials.

SUMMARY:

Hydrochlorothiazide was administered to a series of thirty-two patients with congestive heart failure. It was a potent diuretic for the short or long term management of these cases, and can be administered by the oral or intravenous routes. Dosage and toxicity is discussed.

Drug material for this study was supplied by Merck Sharpe and Dohme, Research Laboratories, Division of Merck and Co., Inc., Philadelphia, Pennsylvania.

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