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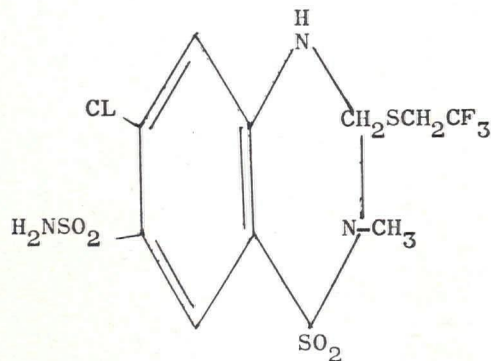
POLYTHIAZIDE IN THE TREATMENT OF CONGESTIVE HEART FAILURE

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THE INTRODUCTION of chlorothiazide and its analogues in the past few years have made available potent oral diuretics which approach the organic mercurial compounds in efficacy. These drugs have shifted the emphasis from parenteral mercury, particularly for the long term management of various derivatives, all appear to be effective and safe diuretics.

All of these compounds are active saluretic agents inhibiting tubular reabsorption of sodium, and causing increased excretion of chlorides. Potassium excretion is also significantly increased, but varies somewhat, depending on the particular analogue in use. Potency of these various analogues in the production of salt and water excretion together with a more prolonged action on single dose administration and a lessened tendency to kaliuresis is most desirable.

The present report deals with the evaluation of polythiazide** (P2525), (Fig. 1), the most recent thiazide compound to be used by us in the treatment of cardiac edema.



POLYTHIAZIDE

2-methyl-3-(2,2,2-trifluoroethylthiomethyl)-6-chloro-7-sulfamyl
3-4 dihydro-1,2,4-benzothiadiazine 1,1 dioxide

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**Supplied as Renese, Pfizer Laboratories, New York, New York.

METHOD OF STUDY

Fourteen cases of congestive heart failure were utilized in the evaluation, one of these was studied in the out-patient department and 13 cases were hospitalized patients. One of the cases was studied twice (2 different admissions). All cases were digitalized concomitantly but did not receive mercurials or other diuretics except the routine use of ammonium chloride or potassium chloride for acidifying purposes or as replacement therapy. Mercurials were used in several instances either before or after courses of polythiazide therapy for comparison purposes.

Serum electrolyte determinations (Na, K, Cl, HCO_3) were made during the control period and periodically in the course of polythiazide administration.

Nine patients had arteriosclerotic heart disease, 4 had chronic rheumatic heart disease, and 1 hypertensive heart disease. All patients exhibited edema, and were placed on bed rest and a 400 mgm. sodium diet. Daily weight and fluid intake and output were recorded.

Polythiazide was administered in a dose of 4 to 16 mgm. daily in single or divided doses. The course of treatment ranged from 2 days to 10 days continuous daily administration, the average being 5 to 7 days.

One out-patient received the drug over a 14 day period but only every other day for the last 7 days. Results: The diuretic response in 14 patients with 15 separate periods of treatment is summarized in Table I.

In 5 patients, twenty-four hour total urine volume collections were obtained prior to and during administration of polythiazide to evaluate the effect on excretion of sodium, potassium, chloride, and bicarbonate.

Case Discussion:

The cases ranged from mild heart failure to those resistant to diuretics. In the latter instances resistance was exclusive of electrolyte depletion as a related cause. There were two cases classified as mild congestive failure (Cases 7 and 12).

Case 7 received 8 mgms. daily in two divided doses (4 mgms. each) over a 4 day period. There was mild pulmonary congestion and minimal congestive hepatomegaly. Since the patient was an acute myocardial infarction he could not be weighed. The clinical response was good as evidenced by rapid improvement and by an increase in urine 24 hour volume over the four day period of drug administration. Electrolyte excretion studies showed a twofold increase in sodium and chloride and a four fold increase in potassium. A mild fall in serum potassium and a rather marked drop in serum chlorides occurred.

Case 12 had only a fair response, but received only 4 mgms. of drug as a single daily dose. Despite only a small weight loss, excretion studies indicated a four to five fold increase in sodium and chloride excretion. It is possible a 6 to 8 mgm. dose would have produced a greater edema weight loss. In this particular case, however, a mercurial was given (meralluride, 2 ml.) and no better response occurred.

There were nine cases of moderately severe congestive heart failure manifested by considerable hepatic congestion and ankle edema. They were not all in an early stage of this condition, some cases having been under previous therapy for considerable periods, but all were still responsive to diuretics — none were in a resistant

TABLE I

CASE	DIAGNOSIS	INITIAL WEIGHT (LBS.)	FINAL WEIGHT (LBS.)	TOTAL WEIGHT LOSS (LBS.)	NUMBER OF DAYS	REMARKS
1	ASHD	143	116 $\frac{1}{2}$	27 $\frac{1}{2}$	8	Excellent response; mild hypochloremic alkalosis; no hypokalemia
2	ASHD	201 $\frac{1}{2}$	150 $\frac{1}{2}$	51 $\frac{1}{2}$	9	Excellent response; mild hypochloremic alkalosis; no hypokalemia
3	ASHD	203 $\frac{3}{4}$	180	23 $\frac{3}{4}$	7	Excellent response; moderate hypokalemia and hypochloremic alkalosis
4	ASHD	173 $\frac{1}{2}$	152 $\frac{1}{2}$	21	6	Excellent response; moderate hypochloremic alkalosis
5	RHD	95 $\frac{1}{2}$	90 $\frac{1}{2}$	5	3	Good response; mild hypochloremic alkalosis; hypokalemia produced
6	RHD	116 $\frac{1}{2}$	109 $\frac{1}{2}$	7	5	Good response; mild hypochloremic alkalosis; mercaptomerin did no better
7	ASHD Acute Infarction				4	Not weighed; good response; mild hypochloremic alkalosis
8	RHD	144	140	4	5	Poor response; resistant to mercurial diuretics
9	ASHD	144	138	6	10	Fair response; resistant congestive failure; moderately severe hypochloremia
10	ASHD	131	128 $\frac{1}{2}$	2 $\frac{1}{2}$	2	Poor response
11	RHD	106 $\frac{1}{2}$	105 $\frac{1}{4}$	1 $\frac{1}{4}$	3	Poor response alone; good response in combination with mercury
12	ASHD	160 $\frac{3}{4}$	157 $\frac{1}{2}$	3 $\frac{1}{4}$	3	Fair response; response to mercury no better
13	ASHD	117	116	1	2	Poor response
14	HHD	300	277	23	14	Excellent response; OPD case
15 - 2nd admission of Case #1	ASHD	134 $\frac{1}{2}$	126 $\frac{1}{2}$	8	4	Excellent response; no hypochloremia

* ASHD - arteriosclerotic heart disease RHD - rheumatic heart disease
 HHD - hypertensive heart disease

stage. One of these cases had two separate hospital admissions and received two periods of therapy, (Case 1). There were six instances of excellent response in five cases treated. Two cases were classified as a good response and two cases responded poorly. One of the latter cases had been resistant to other diuretics and received 16 mgms. daily in two divided doses (Case 10). The other poor response occurred on a 4 mgm. single daily dose. In four of the six excellent responses, 6 or 8 mgms. was given in 24 hours as single or divided doses. The other two excellent responses occurred on only 4 mgms. as a single daily dose. The response to less than 6 mgms. in 24 hours gave poorer results in one case where the higher dose worked well. In this total group single daily doses seemed as effective as divided doses. In one case that showed an excellent response on 4 mgms. single daily dose — continued daily weight loss of edema fluid occurred when the drug was given as 4 mgm. every other day suggesting long continued activity. The daily loss was somewhat less on the in between days when the patient did not receive the drug (Case 14).

There were 3 cases classified as resistant to therapy. One (Case 9), responded in a fair manner losing six pounds in a 10 day period. This may well indicate a good result since this case had not responded as well to parenteral mercurials even after correction of hypochloremia. A single 8 mgm. daily dose was used. The second case responded poorly losing only four pounds during a five day course of therapy. A third (Case 11), was resistant to mercurials, and treatment with polythiazide alone gave no better response, but slightly more diuresis occurred when both drugs were given in combination.

Electrolyte excretion studies:

Daily twenty-four hour quantitative urine collections were made in five cases. There was a marked increase (2 to 5 fold) of sodium and chloride and an increase in potassium varying considerably from 1.5 times to 4 times the control excretion. However, in four of the five cases it was no greater than two times the control period. Two of the fourteen patients developed mild hypokalemia without clinical symptoms. Hypochloremic alkalosis occurred in most cases of a mild degree, but in one case (Case 9) was severe.

The following case illustrates an excellent result.

A. K., was a 68 year old man with arteriosclerotic heart disease and advanced congestive heart failure. On admission there was cardiomegaly with a protodiastolic gallop and distended neck veins. He had soft pitting edema extending to the thighs and sacrum as well as ascites, hepatomegaly, and pleural and interlobar fluid.

He lost no weight during a two day period during which he was digitalized. Polythiazide was administered in a dose of 8 mgms. daily for 3 days and then reduced to 4 mgms. daily for another 4 days. He lost a total of 26¼ pounds during this time after which he was felt to have achieved a "dry weight." Table II summarizes the results of the 24 hour urine excretion studies as well as the serum electrolyte response. No potassium or chloride supplements were administered during this time.

A.K. (Case #1) No. 902431			URINE					SERUM (MEQ/L)			
Day	Dosage (mg.)	Weight (lbs.)	Volume 24 hrs.	Sodium Meq/Vol	Potassium Meq/Vol	Chloride Meq/Vol	Bicarb. Meq/Vol	Sodium	Potassium	Chloride	Carbon Dioxide
Control	0	143	750	110	55	115	0	137	5.0	105	25.2
1	8	138	2100	222	45	192	0				
2	8	133½	3100	328	49	89	4	133	3.4	106	28.6
3	6	127	3900	401	78	292	0				
4	4	124	3720	272	78	232	0	132	4.3	99	28.6
5	4	121	3020	243	75	213	0				
6	4	119½	1130	89	30	73	14	130	4.2	100	25.2
7	4	116¾	1860	145	48	83	32	133	4.6	96	31.6

Table II

Case F.L. #67 97 54
 Hypertensive Heart Disease
 Congestive Heart Failure Group II

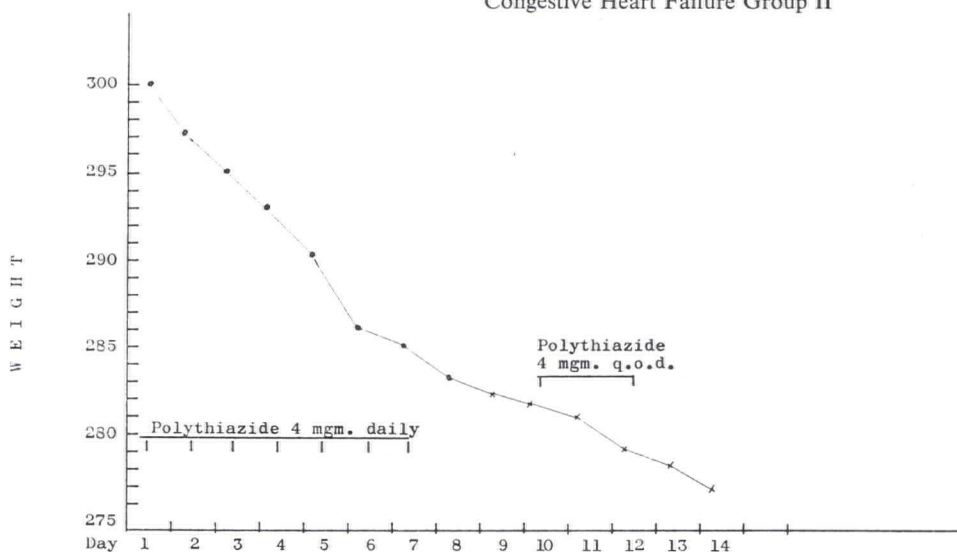


Table III

Table III illustrates an out-patient (Case #14) with an excellent response showing the effectiveness of a single daily dose and a continued daily edema weight loss when the drug was reduced to 4 mgms. every other day. It is believed that continued diuretic activity lasts beyond the twenty-four hour period though of a lessened degree as compared to daily administration.

Toxicity:

One patient developed a maculopapular rash that cleared promptly on omission of the drug without any serious sequelae. No serious intolerance was noted. The drug was easily taken and no local gastrointestinal disturbances noted. As is the case with other thiazide drugs hypochloremic alkalosis was the most frequent electrolyte disturbance. This was easily corrected by the administration of chloride replacement therapy.

DISCUSSION

Polythiazide was felt to be a good oral diuretic agent particularly effective by single daily dose administration; effective at least over a twenty-four hour period and probably longer. This seems to be its chief clinical advantage. It probably has no appreciable less potassium wastage than some of the other thiazide agents. It was well tolerated and gave very effective edema weight loss. No serious side effects were noted. One case of allergic sensitivity (maculopapular rash) occurred without serious sequelae. In one resistant case of congestive failure a surprising degree of

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diuretic activity occurred after failure of parenteral mercurials although a second case of refractory heart failure did not respond.

In clinical use of this material electrolyte depletion syndromes appear no less likely to occur and should be closely watched for their signs of development, particularly in the patient with advanced cardiac with hepatic cirrhosis and renal failure.

SUMMARY

A new benzothiadiazine derivative polythiazide-2-methyl-3-(2,2,2-trifluoroethylthiomethyl)-6-chloro-7-sulfamyl 3-4 dihydro-1,2,4-benzothiadiazine 1,1 dioxide, was given to 14 patients with varying degrees of congestive heart failure. Results indicate it to be an excellent oral diuretic of prolonged action. Rash allergic sensitivity may occur as with other benzothiadiazine analogues.

