Evaluation of 3-benzylthiomethyl chlorothiazide
A new oral diuretic

A clinical evaluation is presented of the relative diuretic effectiveness of benzylthiomethyl chlorothiazide and hydrochlorothiazide in 17 edematous patients. Comparing single 100 mg. doses of each drug, benzylthiomethyl chlorothiazide is about 85 per cent as effective as hydrochlorothiazide.

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This study was undertaken to compare clinically the diuretic response resulting from benzylthiomethyl chlorothiazide, a newer substituted benzothiadiazine, with that obtained from chlorothiazide. The effect of each agent on body weight, urine volume, and urine sodium and potassium contents was observed. Patients received, in random order, one of these drugs or a placebo on each day of a consecutive 3 day period. All subjects were hospitalized; all had fluid retention meriting diuretic therapy. Seventeen patients were studied (7 had organic heart disease with congestive heart failure, 5 hepatic cirrhosis, 2 the nephrotic syndrome associated with diabetic nephropathy, 2 lymphoblastoma, and one idiopathic cyclical edema).

Methods

A single oral dose of either 100 mg. hydrochlorothiazide or 100 mg. benzylthiomethyl chlorothiazide, or a placebo tablet of identical size and shape, was given to each patient at 7:00 A.M. The amount of drug and the frequency of its administration were chosen for comparability rather than for maximal diuretic effectiveness. The composition of any tablet used was known neither by the physician giving it nor by the subject receiving it. The order of administration of the three substances during the 3 day period was randomized to compensate for any effect that one agent might have on the action of a second given the following morning.

Each patient was given any additional necessary medication and had the same diet prescribed for at least 5 days prior to and during the 3 days of administration of the diuretic drugs, so that these factors would not affect this comparative study. Two subjects received a regular hospital diet, 5 a 200 mg. sodium diet, and 10 an 800 mg. sodium diet daily. Seven patients were maintained on 0.1 Gm. digitalis daily. One patient received 1 Gm. potassium chloride 3 times each day.

Twenty-four hour urine collections were divided into the first 6 hours after the drug was given (7:00 A.M. to 1:00 P.M.) and the

Diuretic drugs supplied were 3-benzylthiomethyl chlorothiazide (3-benzylthiomethyl-6-chloro-7-sulfamyl-1,2,4,-benzothiadiazine-1, 1-dioxide) as P-1393 by Chas. Pfizer & Co., Inc., and hydrochlorothiazide (6-chloro-7-sulfamyl-3, 4-dihydro-1,2,4-benzothiadiazine-1, 1-dioxide) as Hydrodiuril by Merck Sharp & Dohme Research Laboratories.

Table I. *Urine volume, sodium and potassium excretion after a placebo, benzylthiomethyl chlorothiazide, and hydrochlorothiazide*

Patient No.	*Diagnosis*	*Drug given*	*0 to 6 hours*			*6 to 24 hours*		
			Urine volume (ml.)	*Sodium content (mEq.)*	*Potassium content (mEq.)*	*Urine volume (ml.)*	*Sodium content (mEq.)*	*Potassium content (mEq.)*
1	Heart failure	Placebo	256	1.2	7.6	550	2.8	24.4
		BTM*	310	0.7	24.4	653	9.5	54.6
		Hydro†	132	11.1	2.0	580	8.8	48.0
2	Lymphoma	Placebo	440	3.6	16.7	560	3.8	22.2
		BTM	470	3.1	14.1	753	6.5	35.5
		Hydro	610	7.2	26.7	400	3.1	15.4
3	Hepatic cirrhosis	Placebo	280	3.2	14.8	210	1.4	7.7
		BTM	74	0.7	4.4	375	2.6	16.6
		Hydro	420	19.8	24.6	810	24.1	47.5
4	Hepatic cirrhosis	Placebo	340	2.6	24.8	400	3.0	25.7
		BTM	160	1.3	13.3	460	3.5	34.1
		Hydro	295	2.2	14.8	440	2.9	20.1
5	Heart failure	Placebo	170	1.7	15.3	400	4.5	40.6
		BTM	550	56.4	32.9	725	6.6	46.6
		Hydro	490	5.8	43.5	980	13.3	94.0
6	Heart failure	Placebo	160	6.8	15.1	1,210	11.1	53.7
		BTM	85	2.1	7.3	1,470	16.5	62.8
		Hydro	210	10.3	19.0	1,600	39.0	68.0
7	Lymphoma	Placebo	46	3.3	8.7	540	72.7	78.0
		BTM	130	19.5	21.4	415	63.1	62.2
		Hydro	95	13.7	16.5	200	38.3	32.7
8	Hepatic cirrhosis	Placebo	190	14.7	13.4	390	32.4	36.3
		BTM	170	26.6	13.8	720	129.6	56.7
		Hydro	320	73.5	28.0	860	203.2	48.0
9	Hepatic cirrhosis	Placebo	510	36.8	14.5	230	29.3	9.4
		BTM	260	19.9	19.9	375	24.1	16.8
		Hydro	440	62.3	13.5	585	49.8	35.1
10	Diabetic nephropathy	Placebo	235	5.9	12.0	1,160	12.8	74.6
		BTM	310	12.3	20.7	1,250	24.9	104.9
		Hydro	480	20.9	63.5	1,955	47.7	134.8
11	Heart failure	Placebo	510	2.8	25.0	1,375	8.4	63.3
		BTM	780	10.2	55.1	774	82.1	10.6
		Hydro	168	3.3	23.5	1,124	17.5	103.4
12	Heart failure	Placebo	280	14.6	6.9	940	7.0	23.9
		BTM	218	2.0	18.7	950	9.8	65.0
		Hydro	580	52.6	60.3	1,980	101.3	105.0
13	Hepatic cirrhosis	Placebo	555	74.9	26.0	378	34.9	28.7
		BTM	400	50.7	29.6	688	49.4	38.5
		Hydro	48	5.8	2.9	510	30.2	34.4
14	Heart failure	Placebo	165	3.1	16.8	980	75.7	98.0
		BTM	230	11.9	23.0	135	5.8	16.5
		Hydro	200	15.0	20.0	740	29.0	68.5

Table I
Continued

Patient No.	Diagnosis	Drug given	0 to 6 hours			6 to 24 hours		
			Urine volume (ml.)	Sodium content (mEq.)	Potassium content (mEq.)	Urine volume (ml.)	Sodium content (mEq.)	Potassium content (mEq.)
15	Cyclical edema	Placebo	410	7.5	11.3	1,500	22.8	87.7
		BTM	705	40.2	32.3	855	30.6	43.3
		Hydro	1,318	65.9	27.6	1,230	113.7	55.9
16	Heart failure	Placebo	700	37.7	9.2	588	57.4	14.5
		BTM	410	55.4	12.7	1,350	109.9	39.3
		Hydro	715	62.4	26.1	380	17.1	6.2
17	Diabetic nephropathy	Placebo	645	17.8	32.3	1,950	17.0	73.0
		BTM	1,540	91.8	42.7	2,400	133.4	90.2
		Hydro	1,550	89.9	62.0	1,930	48.3	65.4
Mean		Placebo	346±70	14.0±4.7	15.9±1.7	785±46	23.4± 5.9	44.8±6.7
±		BTM	402±29	23.8±6.3	22.7±3.1	848±41	41.6±11.0	46.7±6.2
S.E.M.‡		Hydro	475±39	30.7±7.1	27.9±4.5	959±45	46.3±12.3	57.8±8.5

*BTM, 100 mg. benzylthiomethyl chlorothiazide.
†Hydro, 100 mg. hydrochlorothiazide.
‡S.E.M. = Standard error of mean.

subsequent 18 hours (1:00 P.M. to 7:00 A.M. the following morning). Body weight was recorded at 7:00 A.M. each day, after voiding and prior to administration of drug. Urine volumes were measured and sodium and potassium contents determined by flame photometry.

Results

Calculated mean urine volumes and mean sodium and potassium excretions of all patients following administration of each diuretic agent and the placebo are shown in Fig. 1. Values determined for individual patients are shown in Table I. In comparison with the mean 24 hour urinary output observed with the placebo (1,131 ml.), benzylthiomethyl chlorothiazide increased mean urine volume by 119 ml., whereas hydrochlorothiazide induced a 303 ml. increase in the same period of time. The diuresis resulting from both hydrochlorothiazide and benzylthiomethyl chlorothiazide was greater within the first 6 hours than in the following 18 hours. The mean 24-hour weight loss was 1.04 pounds after benzylthiomethyl chlorothiazide, 1.12 pounds after hydrochlorothiazide, and 0.58 pound after placebo.

Hydrochlorothiazide caused more natriuresis and kaliuresis than did benzylthiomethyl chlorothiazide in the doses used. In the first 6 hours it increased mean sodium excretion 119 per cent and potassium excretion 76 per cent above control values. The accompanying increase in urine volume was 37 per cent. In the subsequent 18 hours sodium output increased 98 per cent, potassium 29 per cent, and urine volume 22 per cent. During the entire 24 hours after hydrochlorothiazide was given the total sodium excretion was 103 per cent greater, total potassium 41 per cent greater, and urine volume 27 per cent greater than the mean values during the 24 hours following placebo administration.

During the first 6 hours after benzylthiomethyl chlorothiazide was given, sodium

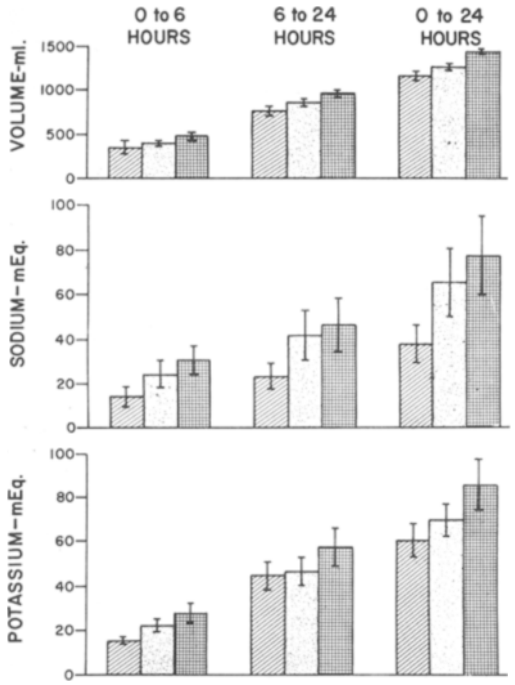

Fig. 1. The mean total urine volume, sodium, and potassium excreted in the first 6 hour period (on the left), the subsequent 18 hour period (in the center), and the entire 24 hour period (on the right) after a placebo tablet (diagonal line column), 100 mg. 3-benzylthiomethyl chlorothiazide (white column), and 100 mg. hydrochlorothiazide (column of squares). Vertical lines represent range of standard error of the mean.

excretion rose 70 per cent, potassium output 46 per cent, and urine volume 16 per cent above the mean control values. The next 18 hours showed a sodium increase of 78 per cent, potassium of 4 per cent, and a volume rise of 8 per cent. In the entire 24 hours after benzylthiomethyl chlorothiazide administration, total sodium excretion increased 75 per cent, total potassium 14 per cent, and urine volume 12 per cent above the mean levels found when the placebo was given.

These percentages are not absolute values as they are derived from means which, as shown in Fig. 1, have considerable ranges of standard error. They do afford a relative comparison of the two diuretic agents, however. If one directly compares the efficacy of these diuretic drugs, it is found that in the first 6 hours after benzylthiomethyl chlorothiazide administration, sodium excretion was 77 per cent of that seen after hydrochlorothiazide, potassium was 81 per cent, and urine volume was 85 per cent. During the subsequent 18 hours the comparable figure for sodium excretion was 90 per cent, potassium 81 per cent, and urine volume 88 per cent. In the entire 24 hour period after benzylthiomethyl chlorothiazide was given there was 85 per cent as much sodium, 81 per cent as much potassium, and 87 per cent of the volume of urine excreted as there was after hydrochlorothiazide administration.

Individual patients showed varying responses to these agents. Nine patients exhibited greater volume diuresis with hydrochlorothiazide; in 2 of these benzylthiomethyl chlorothiazide had less effect than the placebo. Five subjects showed a greater diuretic response with benzylthiomethyl chlorothiazide; in 3 of these hydrochlorothiazide effected less response than the placebo. Three patients had little increase in urine volume after receiving either drug. Eleven patients demonstrated a greater natriuretic and kaliuretic effect of hydrochlorothiazide; in 3 of these there was less sodium and potassium excretion after benzylthiomethyl chlorothiazide than after the placebo. Four subjects eliminated more sodium and potassium after receiving benzylthiomethyl chlorothiazide; 2 of these excreted less sodium and potassium after hydrochlorothiazide than after the placebo. Two patients were relatively unresponsive, in respect to excretion of these ions, to the administration of both drugs. It should be emphasized that there was no correlation between the effectiveness of a particular agent and a specific disease process. No side effects from these drugs were observed in any of these patients.

Discussion

Administration of a placebo provides a control day during each 3 day period and allows evaluation of the effect of hydrochlorothiazide and benzylthiomethyl chlorothiazide on urine volume and electrolyte

excretion in each patient in relation to that seen when no diuretic agent is given. Since hydrochlorothiazide is a drug of known diuretic potency, it serves as a standard against which to judge benzylthiomethyl chlorothiazide.[1,2] On a weight basis hydrochlorothiazide is 10 to 12 times as potent a diuretic agent as chlorothiazide; however, it is only one ninth as potent a carbonic anhydrase inhibitor.[3] Its greater diuretic potency is due to a greater mercury-like effect. Benzylthiomethyl chlorothiazide also shows an electrolyte excretion pattern analogous to that of the mercurial diuretics.*

In evaluating a diuretic agent the most significant factor is its natriuretic effect, since sodium is the principal ionic constituent of expanded extracellular volume. Sodium loss is necessary for the mobilization of edema fluid. On the other hand, potassium loss is not desirable. A specific danger of potassium loss is the potentiation of digitalis toxicity. This has been reported during chlorothiazide therapy.[4] The optimal objectives of diuretic therapy therefore are maximal sodium loss accompanied by minimal potassium loss.

From the data presented here, based on dosage levels employed and the conditions of this study, hydrochlorothiazide causes a greater increase in urine volume and more natriuresis and kaliuresis than does benzylthiomethyl chlorothiazide. However, benzylthiomethyl chlorothiazide is nearly as effective in its natriuretic and diuretic actions, being about 85 per cent as potent as is hydrochlorothiazide. The kaliuretic effect of benzylthiomethyl chlorothiazide was slightly less, although of similar magnitude, being 81 per cent of that caused by hydrochlorothiazide. In so far as these electrolytes are concerned, it appears that these drugs induce comparable excretory patterns.

*Based on information supplied by Dr. D. G. Iezzoni, Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

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