OBSERVATIONS ON A NEW BENZOTHIADIAZINE DIURETIC—TRICHLORMETHIAZIDE*

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The introduction of the benzothiadiazine diuretics has had a marked influence on the treatment of patients with oedema. Modifications of the original molecule have resulted in preparations which, in the main, vary quantitatively in potency but not qualitatively. This paper presents the effects observed of a recently developed derivative, trichlormethiazide (3-dichloro-methyl-6-chloro-7-sulfamyl-3, 4-dihydro-1, 2, 4-benzothiadiazine-1, 1-dioxide) (Fig. 1), on urinary electrolyte excretion in normal subjects and on patients with fluid retention.

Normal Subjects

Three healthy male medical students were studied. They were placed on a standard hospital diet for 11 days. During the first 4 days (control period) the 24-hour excretion of water, sodium, potassium, chloride, bicarbonate, and the pH of the urine was measured as well as the weight of each subject. During the next 7 days, trichlormethiazide was given in doses of 4 mg. *b.d.* Three grams of potassium chloride were administered in divided doses daily during the last 3 days of this period. Measurements of weight, urine volume, and electrolyte content

TABLE I. EFFECT OF TREATMENT IN HEALTHY SUBJECTS*

	Subject 1			
		mEq		
Days	*Urinary vol. ml.*	*Na*	*K*	*Cl*
1 - 4 contro	1,345	164	85	187
5	2,800	338	986	380
6	1,810	236	131·9	240
7	1,770	159	126·6	206
8	800	65·4	75·5	88·5
9	940	71·5	110·1	83
10	1,670	210	266	266
11	1,960	160	115	225

* Effect of 4 mg. of trichlormethiazide twice daily on urinary volume, sodium, potassium and chloride excretion in 3 healthy subjects after a control period of 4 days. Three g. of potassium chloride were given daily for the last 3 days.

* Trichlormethiazide ('fluitran') was made available for study through Dr. M. Tonkin, Medical Director, Scherag (Pty.) Ltd.

** Final year medical students.

TABLE I. (CONTD.) EFFECT OF TREATMENT IN HEALTHY SUBJECTS

Subject 2

Days	Urinary vol. ml.	mEq Na	mEq K	mEq Cl
1 - 4 control	1,510	150	82	176
5	1,700	185	136	178
6	1,650	152	118	208
7	2,220	182	134	229
8	1,830	209	75	211
9	1,680	147	88·5	188
10	1,140	111	83	163
11	870	121	78	166

Subject 3

Days	Urinary vol. ml.	mEq Na	mEq K	mEq Cl
1 - 4 control	1,251	180	76	236
5	1,530	345·1	81·5	306
6	1,000	138·6	80·6	186
7	1,770	71·3	112·7	204
8	1,050	106·3	109·2	131
9	1,050	43·5	61	64·2
10	730	93·5	74·5	93·5
11	900	133	65	151

TABLE II. EFFECT OF TREATMENT IN HEALTHY SUBJECTS—(CONTD.)*

Days	Na : K Subjects 1	2	3	Na : Cl Subjects 1	2	3
1 - 4 control	1·92	1·83	2·36	·88	·88	·76
5	3·43	1·36	4·24	·89	·67	1·16
6	1·79	1·30	1·71	·99	·74	·73
7	1·26	1·36	·64	·78	·80	·35
8	·86	2·79	·98	·74	1·00	·81
9	·66	1·66	·72	·87	·78	·68
10	·79	1·33	1·26	·79	·68	1·00
11	1·15	1·55	2·04	·75	·73	·88

* Na : K and Na :Cl urinary excretion ratios before and during the administration of 4 mg. of trichlormethiazide twice daily to 3 healthy subjects.

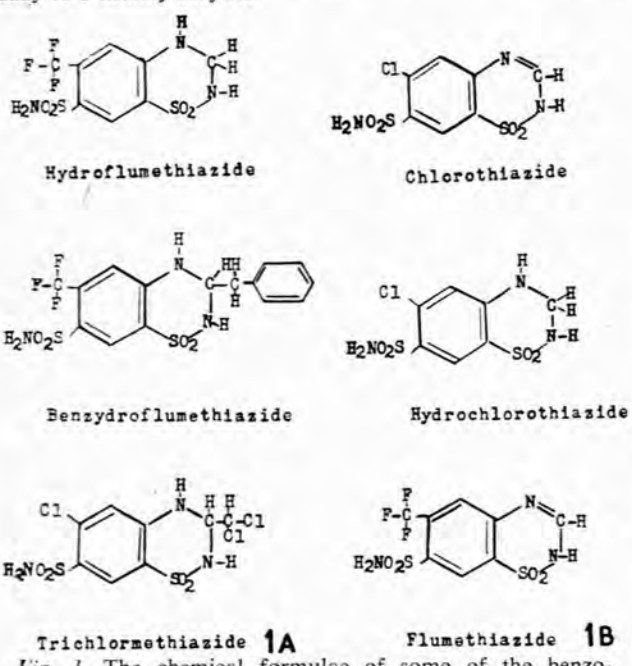

Fig. 1. The chemical formulae of some of the benzothiadiazine diuretics are shown. These are all substitutes at position 3 of chlorothiazide or flumethiazide.

were continued throughout the study, the urine being collected and preserved with toluene and thymol. The results are shown in Tables I and II and Fig. 2.

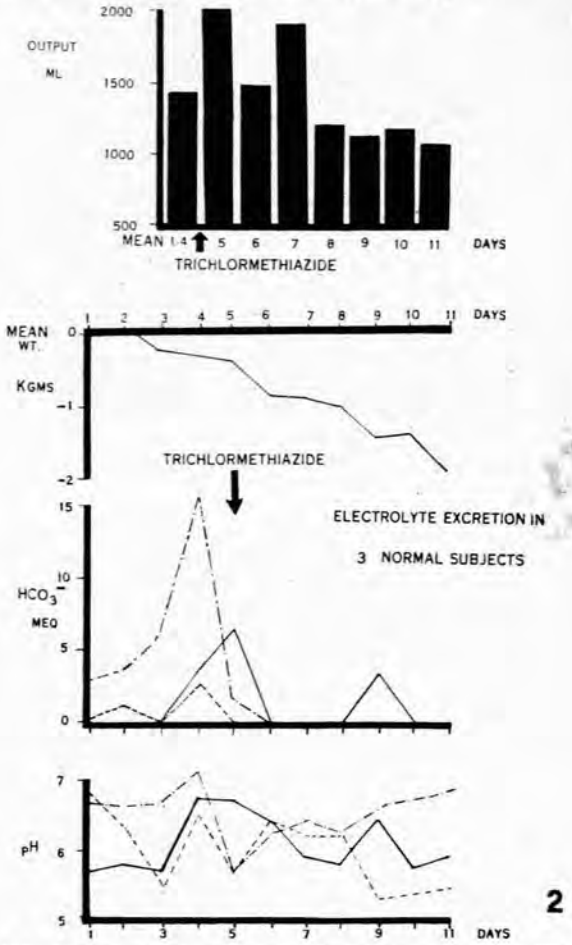

Fig. 2. The effect of 4 mg. of trichlormethiazide twice daily on body weight, bicarbonate excretion, and urinary volume is shown.

In 2 other healthy subjects the time of onset and duration of action of trichlormethiazide were studied. Urine was collected as above in periods from 8 a.m. - 2 p.m., 2 p.m. - 8 p.m. and 8 p.m. - 8 a.m. over 3 days while on a standard hospital diet. Trichlormethiazide (8 mg.) was then given and the effect on urine volume and electrolyte excretion observed for a further 60 hours. The results are shown in Figs. 3 and 4.

Patients with Fluid Retention

17 patients with fluid retention (9 with cardiac failure, 1 with the nephrotic syndrome, and 1 with steroid-induced oedema) were treated with 4 mg. of trichlormethiazide twice daily. Two patients had gross oedema, 9 mild oedema, and 6 had left ventricular failure without manifest oedema. Potassium supplements were not given during the 10 or 11 days of observation. In the patients with cardiac failure, specific treatment, excluding other diuretics, was given if indicated. Daily weight and frequent blood-electrolyte levels were recorded in each patient

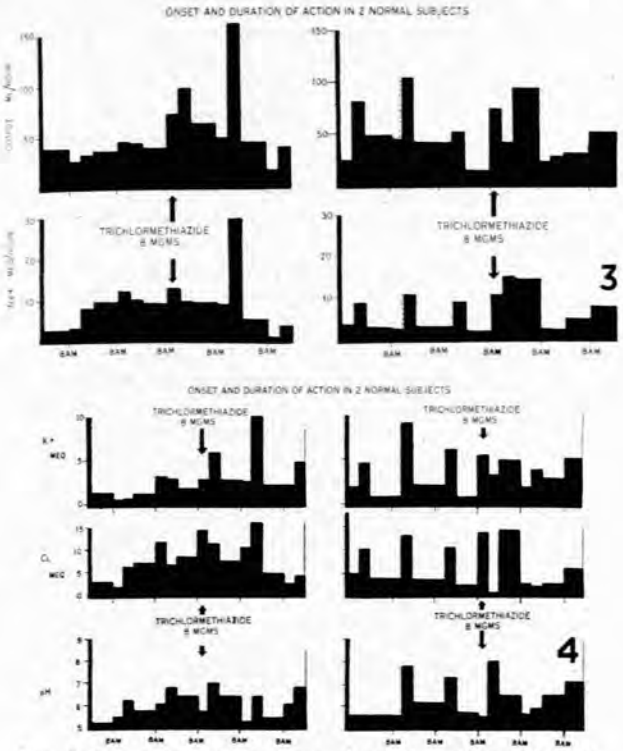

Fig. 3. The effect of an 8 mg. dose of trichlormethiazide on urinary output and sodium excretion in respect of its onset and duration of action is shown.

Fig. 4. The effect of an 8 mg. dose of trichlormethiazide on potassium, chloride, and urinary pH in respect of its onset and duration of action is shown.

during the course of treatment. The mean cumulative weight change and the mean serum-potassium change are shown in Fig. 5. There was no demonstrable alteration in the other blood electrolytes or urea. Table III shows the effects of trichlormethiazide on the urinary excretion of electrolytes in a patient with oedema.

TABLE III. EFFECT OF TREATMENT IN A PATIENT WITH OEDEMA*

		m.Eq.			
Days	*Urinary vol. ml.*	*Na*	*K*	*Cl*	*pH*
1 - 2 control	1,205	180	33	164	6·3
3	1,840	200	34·8	214	6·4
4	1,190	212	40·2	214	6·4
5	1,410	184	38·4	190	6·0
6	—	—	—	—	—
7	1,430	105	58·5	177	4·9
8	2,290	284	91·6	334	5·7
9	1,280	174	67·5	200	5·2
10	1,430	124	89·3	183	5·2

* Effect of 4 mg. of trichlormethiazide twice daily on urinary volume, sodium, potassium, chloride and pH in a patient with fluid retention.

DISCUSSION

The benzothiadiazines exert their effect, to a large extent, at the proximal convoluted tubule where they inhibit the reabsorption of a portion of the filtered sodium. This results in an osmotic diuresis. Moreover, there is an effect on the distal convoluted tubule of variable degree resulting

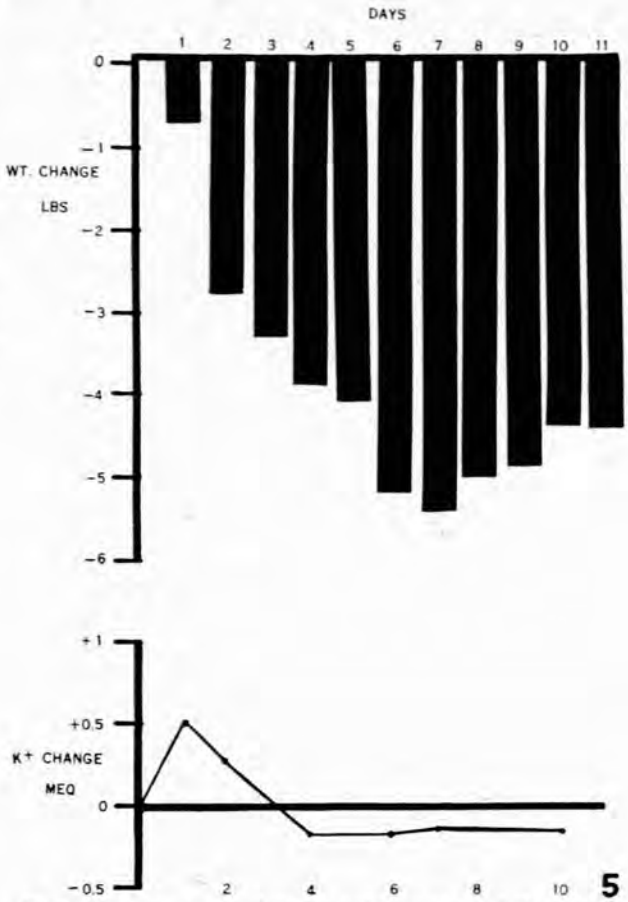

Fig. 5. The mean cumulative weight change and the mean serum potassium level is shown over 11 days of treatment with trichlormethiazide in 17 patients with fluid retention.

from the inhibition of carbonic anhydrase. The more recent derivatives have, however, little carbonic-anhydrase-inhibiting effect. As the molecule of chlorothiazide has been manipulated, so has the effective dose of the derivatives decreased and it has been suggested that this increased activity may be due to an increased solubility of the drug in the lipoid of the cell membrane.[1] A more specific interference with energy production in the cell is not, however, excluded, and possible differences in electrolyte excretion produced by the different preparations may result from this.

The administration of 4 mg. of trichlormethiazide twice daily to 3 normal subjects resulted in an increase in urine volume, sodium, and chloride excretion and, to a lesser extent, potassium. Urinary pH and bicarbonate excretion were not altered to any considerable extent. In 2 subjects the ratio of sodium to chloride excretion in the urine increased temporarily and then decreased when compared with control levels. In the same subjects similar changes were noted in the sodium: potassium ratio. The results are consistent with a primary action on sodium reabsorption and secondary osmotic diuresis. The absence of an increase in urine pH or bicarbonate excretion suggests little if any carbonic-anhydrase-inhibiting effect of the drug and is similar to that reported as occurring with

the 3-benzyl derivatives[2] and to a lesser extent with hydroflumethiazide.[3] The secondary retention of sodium observed after a few days suggests that a compensatory mechanism to restore body sodium began to exert an effect. This may be due to increased secretion of aldosterone as evidenced by a decrease in the sodium-potassium ratio and is to be expected in normal subjects depleted of water and sodium.[4] It is unlikely that other diuretics with similar modes of action would differ in this respect.

There was no marked increase in the absolute amount of potassium excreted, except in one subject in which a greater urinary excretion was seen to follow the administration of potassium supplements. Similar observations, that trichlormethiazide and bendroflumethiazide tend to cause less potassium loss than chlorothiazide, hydrochlorthiazide, flumethiazide and hydroflumethiazide, have been made by Bernstein.[5] A greater carbonic-anhydrase-inhibiting effect of the latter substances may account for this.

A single dose of 8 mg. of trichlormethiazide was found to exert an action within 6 hours of administration. The effect continued for 24 - 36 hours and was observed to abolish the normal diurnal rhythm of water and electrolyte excretion in the urine (subject 2, Figs. 2 and 3). It has also been stated that there is a continued water diuresis without electrolyte loss following cessation of continuous therapy of 7 days duration.[6] This has been associated with a decrease in serum osmolarity produced by the previous treatment. It would appear then that trichlormethiazide has a long duration of action and may be better given in intermittent courses with continued diuretic effect both during and for a period after stopping the drug. If administered in this manner, hyponatraemia, which presumably may develop on continuous therapy, would not occur.

Satisfactory diuresis was observed in the 17 patients treated with trichlormethiazide. There was a mean cumulative weight loss of 5½ lb. in these patients in 1 week. Comparisons with other diuretics cannot be made accurately with this heterogenous group of patients. The diuresis observed was satisfactory while the rate of clinical improvement was similar to the expected results with other diuretics, and Ford[7] has shown that 5 mg. of trichlormethiazide is equivalent to 2 ml. meralluride in natriuretic effect. In some patients the weight increased after a week, and was unassociated with signs of fluid retention. It is considered likely that this resulted from an increase in food intake and consequent increase in actual body solids. Although during the period of treatment there was no drop in the mean serum-potassium level, in some patients a small decrease was observed. Thus, although potassium depletion may be less likely to occur with this than with previous preparations, as judged by comparative urinary excretion, it may still be necessary to supplement potassium intake. During the period of observation no significant change in other blood electrolytes or the blood urea was observed, although in subsequent patients on high dosage a rise in blood urea has been observed in some. As with the other benzothiadiazine derivatives, it is likely that in patients with renal insufficiency, worsening of kidney function may occur with vigorous sodium depletion. Care should be exercised in these cases. Similarly, an increase in the serum uric-acid level may occur with trichlormethiazide as with any of the benzothiadiazines.

The LD_{50} dose of trichlormethiazide is given as 2·8 g./kg. in mice. Hydrochlorothiazide has a similar LD_{50} dose, but, because of the larger dose necessary to produce a diuretic effect, the therapeutic ratio is not as high as for trichlormethiazide.[8] This may be of advantage in that toxic effects would be less likely to occur with the smaller dose required when using trichlormethiazide. However, the therapeutic ratio is still considerable with the other benzothiadiazines and well within the toxic dose. Idiosyncrasies are independent of dose and may occur with either. In this series of subjects and in other patients treated concomitantly, no side-effects, toxic effects, or idiosyncrasies were observed.

SUMMARY AND CONCLUSIONS

The effects of trichlormethiazide, a benzothiadiazine derivative, were observed in 5 normal subjects and in 17 patients with fluid retention.

Increased excretion of sodium, chloride, water, and to a lesser extent potassium, was observed after administration of 4 mg. twice daily to normal subjects. The effect was measurable within 6 hours and persisted for 24 - 36 hours.

In the patients with fluid retention a satisfactory diuretic response was observed. Potassium depletion was slight and may be less than that reported for other benzothiadiazine derivatives.

No side-effects, toxic effects, or idiosyncrasies to the drug were noted.

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