HYDROCHLOROTHIAZIDE (HYDRODIURIL)* IN THE MANAGEMENT OF CARDIAC ŒDEMA†

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HYDROCHLOROTHIAZIDE is a dihydro derivative of chlorothiazide. Chemically, hydrochlorothiazide differs from chlorothiazide in having no double bond in the heterocyclic ring (Fig. 1). This latest member of the benzodiazines has been found to have a diuretic action closely resembling that of chlorothiazide in dogs, but to be sufficiently more potent than chlorothiazide to warrant further clinical evaluation in man. Earlier observations in man have confirmed the diuretic action of hydrochlorothiazide and have shown it to be more potent than chlorothiazide.[1-3]

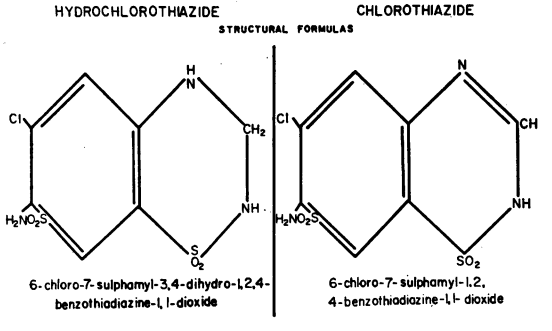

Fig. 1.—Structural formulæ of chlorothiazide and hydrochlorothiazide.

This study was undertaken to evaluate the diuretic effect of hydrochlorothiazide in patients in hospital with congestive heart failure, and also to study the effects of the drug in long-term treatment of ambulatory patients with chronic congestive heart failure. This report summarizes our experiences over the first three months of the study.

MATERIALS AND METHODS

The clinical material of the ambulatory group is presented in Table I. Thirty-one patients were studied, of whom 27 were observed in the cardiac clinic, and four in hospital during the period of study. Of these, 22 were men and 10 women, ranging in age from 42 to 87 years. Twenty patients had arteriosclerotic heart disease, six had rheumatic heart disease, four had hypertensive cardiovascular disease, and two had cor pulmonale.

Patients in Hospital

Four patients were admitted with classical signs and symptoms of congestive heart failure. In three cases, on admission, there was evidence of pulmonary congestion, enlargement of the liver and leg œdema, and in two of these cases there was also marked ascites with evidence suggesting some cardiac cirrhosis. The fourth patient had some pulmonary congestion, but no œdema.

The methods of investigation and the biochemical determinations were similar to those employed in the study of chlorothiazide and have already been described in detail.[4] In addition, in some instances serum calcium and magnesium were estimated by the Clark-Collip[5] and the titan-yellow[7] procedures, respectively.*

The patients were given diets containing 4-6 g. of sodium chloride; fluids were given *ad lib.*; the total fluid intake varied from 1 to 2 litres. All patients were digitalized. Whenever possible, a control period of two days was allowed before the hydrochlorothiazide was administered. In order to evaluate the dose response effect, dosage ranged from 50 to 800 mg. of hydrochlorothiazide, two or three times daily after meals. On the average, 100-200 mg. was administered in two doses – one after breakfast and another after supper. The duration of this study in in-patients varied from six to 30 days.

Ambulatory Patients

This group consisted of 27 patients who had been treated for chronic congestive failure in the cardiac clinic for periods ranging from six months to 14 years, with an average of 5.5 years (Table I). The majority of these patients had been previously treated with chlorothiazide, digitalis, ammonium chloride and mercurial injections parenterally, as required. The diet contained approximately 4-6 g. of sodium chloride daily. At the onset of this study, most of the patients were fairly well controlled and were quite comfortable, but on examination 19 had some residual signs of heart failure (Table I). Hydrochlorothiazide was administered in daily doses of 50-300 mg. However, it was soon observed that the optimal dose, particularly in the severer cases, was 100 mg. twice daily (Table I). If additional diuresis was required, the patient was instructed to increase the dose by 50-100 mg. for two days of each week and then to resume the usual dose. Injections of mercurial diuretics were given when the signs and symptoms of congestive heart failure could not be controlled by hydrochlorothiazide alone. Ammonium chloride, 60 grains (4 g.) daily, was given to many patients to prevent the occurrence of hypochloræmia with the prolonged use of hydrochlorothiazide. Treatment lasted from four to 12 weeks.

*Prepared by Merck, Sharp and Dohme under the trade name of Hydrodiurii.

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TABLE I.—RECORDS OF ALL THE AMBULATORY PATIENTS ATTENDING THE OUT-PATIENT CARDIAC CLINIC

Case (O.P.D.)	Diagnosis	Duration of failure	Degree of failure				Previous treatment			Present treatment			Duration of treatment	Weight		Date	Mg. mEq./l.	Na mEq./l.	K mEq./l.	Cl. mEq./l.	Ca. mg.%	P mg.%	B.U.N. mg.%	Notes
			Leg œdema	Ascites	Pulm. rales	Pleur. eff.	CT* mg. daily	2 c.c. M† i.m.	NH_4Cl	HC** mg. daily	2 c.c. M† i.m.	NH_4Cl		Bef. lb.	Aft. lb.								
J.A. 66, M.	A.S.H.D. Diabetes	2 yrs.	++	0	+	0	1000	2/wk.	+	100— —300	1/wk. 0	+	12 wks.	136	133	27 Nov. 1958 11 Dec. 1958 18 Dec. 1958 22 Jan. 1959 5 Feb. 1959 12 Feb. 1959	1.63 1.90 2.06 1.75 1.88	131.7 133.4 131.7 147.0 138.5 136.8	4.9 4.4 5.1 — 4.6 5.0	93.2 98.1 99.2 101.9 101.4 100.9	9.3 8.9 8.4	4.4 3.8 3.3	— 31.0 30.0 — 38.0 28.0	
J.B. 72, M.	A.S.H.D.	14 yrs.	+	0	0	0	500			200	0	0	12 wks.	153	154	27 Nov. 1958 15 Jan. 1959 29 Jan. 1959 12 Feb. 1959	1.80 2.23 1.94 1.97	130.0 140.2 138.5 138.5	5.1 5.2 4.9 5.2	93.2 94.7 100.9 101.4	— 9.6	3.5 —	27.0 — 30.0 22.0	
C.B. 73, F.	A.S.H.D. Diabetes	4 yrs.	0	0	0	0	500	0	0	100— —200	0	0	11 wks.	144	139	4 Dec. 1958 8 Jan. 1959 29 Jan. 1959 5 Feb. 1959	1.33 1.92 1.59 1.50	126.5 138.5 145.3 145.3	4.1 4.9 4.9 4.6	90.0 105.2 99.0 100.9	9.9	3.2 4.5	24.0 27.0 35.0 33.0	
F.B. 50, F.	R.H.D. 10 yrs.		0	0	+	0	500	occ.	0	100— —200	0	0	10 wks.	107	103	20 Nov. 1958 11 Dec. 1958 8 Jan. 1959 29 Jan. 1959 5 Feb. 1959 12 Feb. 1959	2.10 1.52 1.40 1.30 1.20 1.26	136.8 130.0 140.2 141.9 140.2 133.4	4.0 3.7 4.5 4.4 4.7 4.4	96.1 97.6 104.3 101.4 99.8 100.0	10.6 9.7 9.7	3.6 3.1 2.7	— 27.0 19.0 23.0 21.0 28.0	
C.C. 77, M.	A.S.H.D.	1 yr.	0	0	0	0	500	1/mo.	0	50— —100	0	0	10 wks.	170	163	11 Dec. 1958 8 Jan. 1959 5 Feb. 1959	1.85 2.15 1.72	131.7 138.5 138.5	4.7 4.9 4.6	104.7 94.7 101.4	11.3 8.5	3.6 3.8	27.0 26.0 34.0	
J.D. 70, M.	Cor pulmonale	2 yrs.	++	0	+	0	1000	1/2 wks.	+	200	0	+	12 wks.	182	174	27 Nov. 1958 18 Dec. 1958 15 Jan. 1959 29 Jan. 1959 12 Feb. 1959	1.83 1.95 1.58 1.61 1.54	135.1 130.0 133.4 138.5 136.8	4.0 4.3 4.5 4.4 4.2	90.8 86.1 94.7 96.6 95.7	— — 10.5	2.1 2.0 —	14.0 14.0 — 10.0 16.0	
J.E. 74, M.	R.H.D. H.C.V.D.	4 yrs.	++	0	+	0	1000	0	+ KCl	200	0	+	12 wks.	147	140	27 Nov. 1958 31 Dec. 1958 22 Jan. 1959 5 Feb. 1959	2.10 2.17 2.55 1.60	133.4 141.9 143.6 143.6	5.1 4.4 5.5 4.9	100.7 101.4 98.1 101.4	9.8 10.4 9.9	3.1 3.7 —	— 10.4 — 27.0	
D.E. 79, F.	A.S.H.D.	9 yrs.	±	0	0	0	500	1/wk.	0	100	0	0	6 wks.			31 Dec. 1958	1.60	133.4	5.4	97.1	10.0	3.6	16.0	
A.E. 74, M.	A.S.H.D. R.H.D. H.C.V.D.	3 yrs.														4 Dec. 1958	1.95	135.1	5.3	101.4	10.2	3.1	21.0	
G.F. 64, M.	H.C.V.D.	6 mos.	0	0	0	0	500— —1000	0	0	100	0	0	3 wks.	148	148	29 Jan. 1959	1.59	145.3	5.4	101.5			14.0	
C.G. 71, M.	R.H.D.	6 yrs.	0	0	0	0	500	1/mo.	0	100	0	0	13 wks.	149	144	20 Nov. 1958 18 Dec. 1958 29 Jan. 1959 12 Feb. 1959	2.03 1.77 1.72	136.8 133.4 141.9 147.0	4.9 5.1 5.2 4.4	100.9 98.1 100.0 94.7	10.2 —	3.0 3.0	19.0 22.0 21.0	
I.G. 70, F.	A.S.H.D. Diabetes	7 yrs.	+	0	0	0	500	1/wk.	+	200	0	+	11 wks.	136	135	4 Dec. 1958 18 Dec. 1958 31 Dec. 1958 15 Jan. 1959 5 Feb. 1959	2.41 1.98 1.96 2.04 1.82	136.8 138.5 131.7 141.9 140.2	5.1 4.7 4.7 5.2 5.2	98.1 94.2 99.5 100.4 98.1	10.8 11.6 12.1 11.5	4.0 4.4 4.7 —	— 20.0 — — 17.0	
D.H. 69, M.	A.S.H.D.* Hypo-pituitary	3 yrs.	+	0	0	0	500	1/wk.	0	100 200	0	0	12 wks.	147		20 Nov. 1958 11 Dec. 1958 8 Jan. 1959 29 Jan. 1959 12 Feb. 1959	1.84 1.71 1.60 1.68 1.54	138.5 130.0 133.4 140.2 133.4	4.5 4.6 5.0 4.4 4.4	100.4 94.2 99.0 99.5 100.9	— 11.0 9.5 —	3.2 4.08 3.00	— 27.0 — 21.0 27.0	
J.K. 79, M.	A.S.H.D.	4 yrs.	+	0	0	0	500	0	0	50	0	0	10 wks.	137	131	11 Dec. 1958 8 Jan. 1959	2.22 2.08	135.1 136.8	5.6 5.3	103.8 100.4	11.2 9.7	— 2.4	34.0 36.0	

TABLE I.—*(Continued)*

Case (O.P.D.)	Diagnosis	Duration of failure	Degree of failure				Previous treatment			Present treatment			Duration of treatment	Weight		Date	Mg. mEq./l.	Na mEq./l.	K mEq./l.	Cl. mEq./l.	Ca. mg.%	P mg.%	B.U.N. mg.%	Notes
			Leg œdema	Ascites	Pulm. rales	Pleur. eff.	CT* mg. daily	2 c.c. M† i.m.	NH_4Cl	HC** mg. daily	2 c.c. M† i.m.	NH_4Cl		Bef. lb.	Aft. lb.								
J.K. 64, M.	R.H.D. A.S., M.S., Diabetes	6 yrs.	+	0	+	0	500	1/mo.	+	100	0	+	11 wks.	116	115	4 Dec. 1958 18 Dec. 1958 8 Jan. 1959	1.82 1.62 2.15	131.7 135. 1 133.4	4.3 4.9 5.1	94.2 92.3 93.3	11.0 11.5 11.3	3.2 3.5 2.4	24.0 28.0 —	
A.L. 68, F.	A.S.H.D. Diabetes	5 yrs.	±	0	0	0	500	0	0	100	0	0	12 wks.	142	135	20 Nov. 1958 31 Dec. 1958 29 Jan. 1959	1.86 1.83 1.98	140.2 140.2 147.0	5.3 5.1 5.0	100.4 96.2 100.9	10.4 11.7	3.3 3.0	25.0 25.0 29.0	
A.L. 57, F.	H.C.V.D.	6 mos.	0	0	0	0	500	0	0	200	0	0	12 wks.	174	174	27 Nov. 1958 31 Dec. 1958 15 Jan. 1959 12 Feb. 1959	1.86 1.64 1.96	141.9 135.1 138.5 143.6	5.0 3.8 5.9 5.2	100.0 94.7 104.3 99.3	11.3 11.5 9.3	4.0 3.8 2.7	19.0 24.0 24.0 27.0	B.P. 220/110 → 180/80
L. 42, M.	A.S.H.D.	3 yrs.	0	0	0	0	1000	1/mo.	0	100	0	0	4 wks.	160	163	21 Jan. 1959	1.73	138.5	5.2	101.9	10.0	—	—	
R.M. 73, F.	A.S.H.D.	12 yrs.														27 Nov. 1958 15 Jan. 1959	1.60 2.18	126.5 133.4	4.5 5.3	89.9 101.4	10.5 10.3	2.9		
R.M. 87, M.	A.S.H.D.	3 yrs.	0	0	0	0	500	1/mo.	0	50— —100	0	0	10 wks.	168	160	18 Dec. 1958 29 Jan. 1959	1.56 1.35	135.1 147.0	3.5 4.4	101.9 105.7	11.0	4.0	31.0 31.0	
M. 68, M.	A.S.H.D.	6 mos.	±	0	0	0	1000	Occ.	+	100— —200	0	0	12 wks.	172	172	27 Nov. 1958 31 Dec. 1958 15 Jan. 1959	1.80 1.79 1.94	135.1 137.7 141.9	4.7 4.7 4.8	94.2 99.5 102.8	10.4 11.3 10.5	4.0 3.6 —	17.0 16.0 —	
I.M. 71, M.	H.C.V.D.	3 yrs.	++	0	+	0	500— —1000	0	+	200— —300	0	+	10 wks.	181	177	18 Dec. 1958 5 Feb. 1959	1.62 1.90	136.8 143.6	5.4 4.9	101.9 101.4	11.5	3.7	16.0 18.0	B.P. 160/100 → 148/90
P. 74, M.	A.S.H.D. Diabetes	3 yrs.	+	0	+	0	500 b.i.d.‡	1/mo.	0	100	0	0	4 wks.	150	144½	4 Dec. 1958 18 Dec. 1958	2.03 1.87	136.8 133.4	4.9 5.1	100.0 93.3	10.8 10.0	3.7 4.4	21.0 24.0	
R. 69, F.	A.S.H.D.	1 yr.	0	0	0	0	500	0	+	50— —100/wk.	0	+	4 wks.	142½	142½	15 Jan. 1959 12 Feb. 1959	1.94 1.66	135.1 143.6	5.1 4.7	97.1 98.1	10.2		 22.0	
C.S. 71, F.	H.C.V.D.	9 yrs.	+	0	0	+	1000	1/mo.	+	200— —300	0	+	12 wks.	148	141	27 Nov. 1958 11 Dec. 1958 8 Jan. 1959 29 Jan. 1959 12 Feb. 1959	1.85 1.90 1.66 1.60	130.0 133.4 138.5 138.5 140.2	4.7 5.3 4.4 4.6 4.6	95.1 94.2 99.0 101.4 99.8	9.4 10.1 9.5	3.7 2.7 2.6	24.0 21.0 24.0 27.0 21.0	B.P. 200/100 → 150/80
K.T. 74, M.	A.S.H.D.	1 yr.	+	0	0	0	500 1000	0	0	200	0	+	12 wks.	165½	164	27 Nov. 1958 31 Dec. 1958	1.90 1.68	131.7 135.1	4.3 5.4	100.0 112.9	9.4 10.0	3.9 3.6	33.0 29.0	
M.W. 63, M.	Cor pulmonale	10 yrs.	0	0	+	0	1000	0	+	100— —200	0	+	11 wks.	160	153	4 Dec. 1958 31 Dec. 1958 15 Jan. 1959	2.00 2.00 2.13	136.8 138.5 133.4	5.1 5.8 5.2	94.2 100.9 91.9	10.4 9.7 —	2.2 1.8 —	— 18.0 —	

*CT=chlorothiazide (Diuril).
**HC=hydrochlorothiazide (Hydrodiuril).
†M=meralluride (Mercuhydrin).
‡Plus chlormerodrin, 18.3 mg. t.i.d.

A.S.H.D.=arteriosclerotic heart disease.
A.S.=aortic stenosis.

R.H.D.=rheumatic heart disease.
H.C.V.D.=hypertensive cardiovascular disease.
M.S.=mitral stenosis.

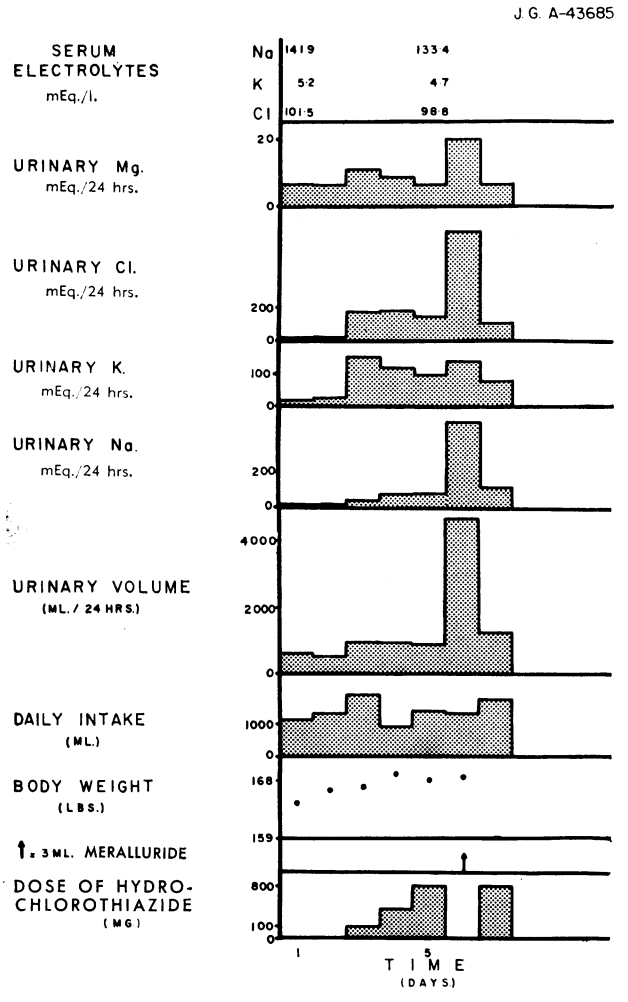

Fig. 2.—J.G., male, aged 54, rheumatic heart disease in very severe terminal heart failure. Note the magnitude of diuretic response obtained with 100-800 mg. of hydrochlorothiazide, as compared to 3 ml. of meralluride (Mercuhydrin) intramuscularly.

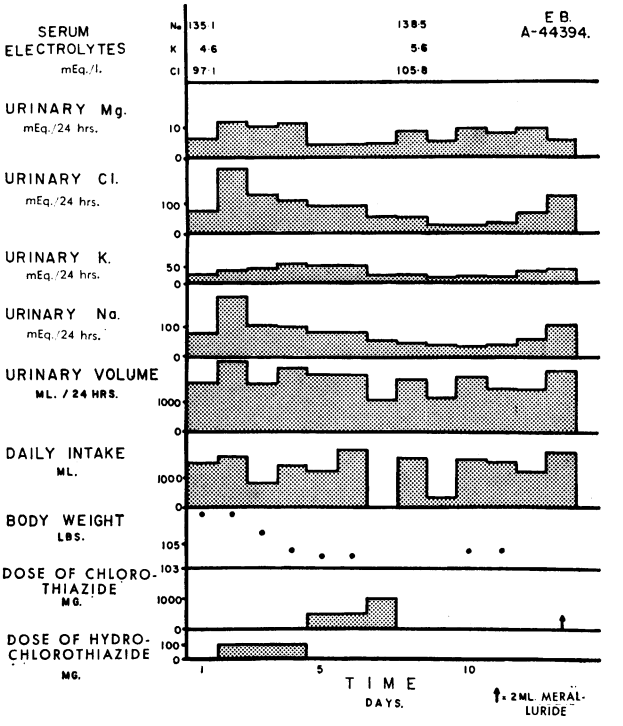

Fig. 3.—E.B., 54, with rheumatic and subacute bacterial endocarditis (Case 2). There is a prompt diuresis with increased excretion of electrolytes and associated weight reduction. Note that in the absence of œdema, the diuretic response decreases with further drug therapy, but response is still above control values.

RESULTS

The results of this study are tabulated in Table I for the ambulatory group and Figs. 2-5 for the in-patients. Hydrochlorothiazide, like its closely related analogue chlorothiazide, was useful in initiating a prompt diuresis and also in the long-term maintenance of the œdema-free state in patients with heart failure.

IN-PATIENTS

CASE REPORTS

CASE 1.—J.G., male, 54, had severe rheumatic heart disease, generalized anasarca, massive ascites and evidence suggesting cardiac cirrhosis. Hydrochlorothiazide (200 mg. per day) increased the 24-hour urinary volume from about 400 to 800 ml. Further increase of hydrochlorothiazide to 800 mg. a day produced no further urinary excretion or increase in excretion of sodium, potassium and chloride (Fig. 2). Three ml. of intramuscular Mercuhydrin (meralluride) the following day resulted in a massive diuresis of 4 litres. This patient was observed for a period of 40 days in the hospital, during which time a daily dose of hydrochlorothiazide was given without any significant clinical improvement or loss of œdema, although the urinary volume was increased over control values. Repeated use of 3 ml. of meralluride resulted in a further diuresis (1.2-4.5 litres), again with only slight clinical improvement. The ascites became so marked that 18 litres of fluid was removed over a period of ten days, in order to give the patient some relief. It was further observed that after a period of eight to ten days on hydrochlorothiazide, 200-400 mg. a day, the patient became very drowsy, lethargic and almost comatose. Upon cessation of therapy and the administration of potassium chloride because of hypokalæmia, there was a gradual return to normal. At this time the serum magnesium levels were reduced from 1.7 to 1.3 mEq./l., and 3 g. of magnesium sulfate was given intramuscularly in 24 hours. At a later date, after another course of hydrochlorothiazide therapy, the drowsiness reappeared and it was thought that the diuretic might have been responsible. At this time, the serum sodium level was 140 mEq./l., serum potassium 4.1 mEq./l., serum chloride 97.1 mEq./l., blood urea nitrogen (BUN) 31 mg. %, CO_2 34 mEq./l., and magnesium 1.6 mEq./l. The bromsulphalein (BSP) retention was 42%; cephalin flocculation, thymol turbidity and flocculation were also abnormal, and there was a marked reduction of the total proteins, with a slight reversal of the albumin/globulin ratio. The administration of glucose in water and cessation of all therapy led to a recovery in about five to six days.

CASE 2.—A.B., female, 54, with rheumatic and subacute bacterial endocarditis (Fig. 3). The patient had basal rales but no peripheral œdema. After a control period the effect of administration of 100 mg. of hydrochlorothiazide was compared with that of 500 and 1000 mg. of chlorothiazide and 2 ml. of meralluride intramuscularly. Hydrochlorothiazide led to a

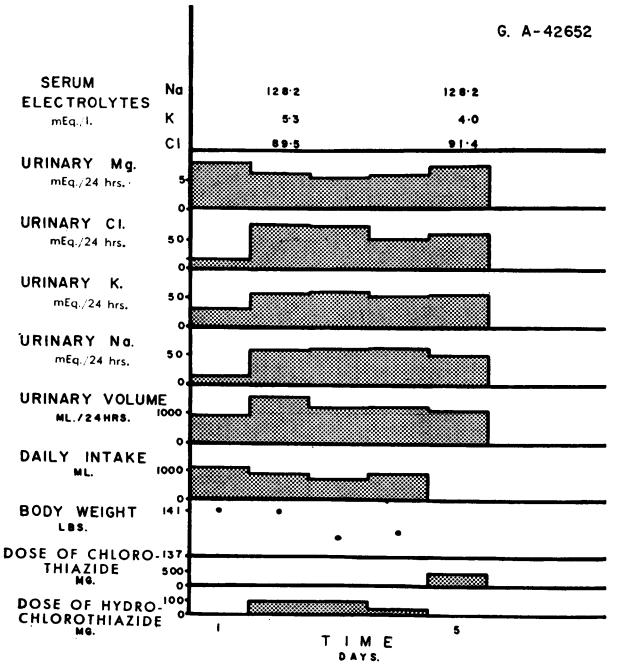

Fig. 4.—J.G., male, 62, with arteriosclerotic heart disease and severe heart failure (Case 3). The diuretic response to 50-100 mg. of hydrochlorothiazide equals the response to 500 mg. of chlorothiazide.

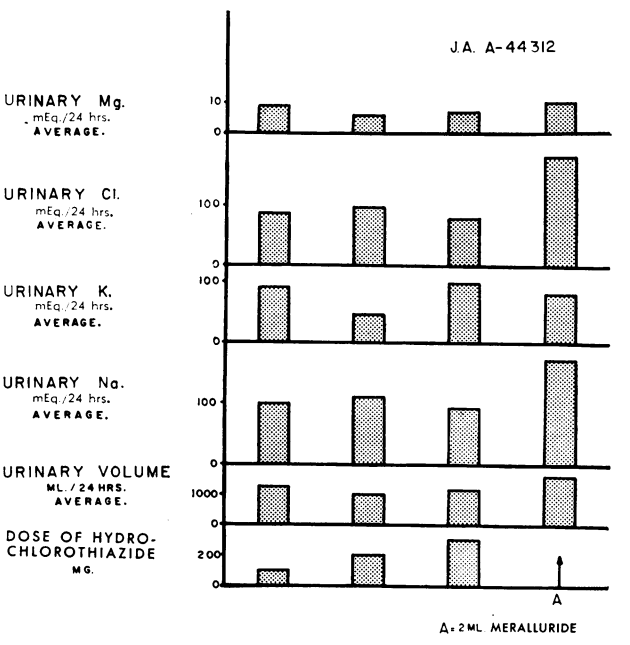

Fig. 5.—J.A., male, 66, with arteriosclerotic heart disease and massive œdema. The values charted are the average of three days of therapy with each dose of hydrochlorothiazide and three injections of meralluride. Note that the average daily response to 200 or 300 mg. of hydrochlorothiazide is no greater than after 100 mg.

prompt clinical improvement with weight reduction. The urine volume was increased, together with increased excretion of urine sodium, chloride, potassium and magnesium. After the initial diuresis, further therapy resulted in a smaller excretion of urine and electrolytes, but still greater than the control value (Fig. 3). In this case, the diuretic response to 100 mg. of hydrochlorothiazide was as great as after 500 mg. chlorothiazide or 2 ml. meralluride intramuscularly.

CASE 3.—J.G., male, 62, with arteriosclerotic heart disease, after a control period of two days showed a prompt diuresis with 100 mg. of hydrochlorothiazide (Fig. 4). This was associated with clinical improvement and reduction in weight. The diuretic response to 100 mg. of hydrochlorothiazide closely approximated the response to 50 mg. of the same drug and 500 mg. of chlorothiazide daily.

CASE 4.—J.A., male, 66, with arteriosclerotic heart disease, was admitted with generalized anasarca. Owing to the severity of his condition, a control period was not possible, and on the first day of admission 2 ml. of meralluride and 100 mg. of hydrochlorothiazide were administered. The continued use of hydrochlorothiazide produced further diuresis and loss of œdema. Fig. 5 shows the average 24-hour urine response to hydrochlorothiazide, 100-300 mg., as compared to 2 ml. of intramuscular meralluride. It appears that (1) the diuretic effect of 200-300 mg. of hydrochlorothiazide daily was no greater than that of 100 mg., and (2) 2 ml. of meralluride in the same patient produced a greater diuresis than 100-300 mg. of hydrochlorothiazide.

The above observations on in-patients show that hydrochlorothiazide produced a prompt diuresis which was associated with a marked increase in the 24-hour urine volume. As in the previous study with chlorothiazide,[4] no attempt was made to control the fluid intake and in every instance the 24-hour urine volume was significantly increased over control periods. This diuresis was always associated with a marked increase in the output of sodium, potassium and chloride. The pattern of electrolyte excretion was very similar to that effected with chlorothiazide. In general, the excretion of chlorides paralleled the excretion of sodium with a lesser excretion of potassium in the 24-hour urine specimens.

The maximum optimal dose in the in-patients varied between 100 and 200 mg. daily in two divided doses; diuresis was not enhanced by higher doses (up to 800 mg.). In some instances 50 mg. of hydrochlorothiazide was as effective as 100-300 mg. In attempts to compare the potencies of hydrochlorothiazide, chlorothiazide and parenteral meralluride in 2 ml. doses, 50-100 mg. of hydrochlorothiazide appeared to be as effective as 500 mg. of chlorothiazide and 2 ml. of intramuscular meralluride in some patients. In many instances, however, administration of 2-3 ml. of meralluride resulted in a massive diuresis which greatly exceeded the response to hydrochlorothiazide.

Ambulatory Patients

In the ambulatory group of patients with congestive heart failure (Table I), the administration of hydrochlorothiazide was effective both in initiating water diuresis and in the prolonged maintenance of the œdema-free state. Generally, the diuresis was most marked in patients with peripheral œdema at the onset of the study, and in these cases the initiation of the diuresis was associated with clinical improvement in the

patient. The œdema disappeared and the breathing of the patient improved.

At the onset of the study all the patients except one were maintained on 500-1000 mg. chlorothiazide daily, and a few still required mercurial diuretics (one injection weekly to one monthly). Hydrochlorothiazide was first given in a dose of 50 mg. daily and then 50 mg. twice daily, but after one to two weeks the optimal dose of 100 mg. was given twice daily (after breakfast and after supper). On this regimen only two cases required additional mercurial injections. When the daily dose of hydrochlorothiazide was not adequate and there was a slight return of leg œdema and rales, associated with a slight weight gain of 1-2 lb. over the previous week, the dose was increased to 200 mg. of hydrochlorothiazide for several days; either maintenance at this level or reduction to 100 mg. after two to three days produced increased diuresis. With such a treatment schedule, parenteral mercurial injections were required in two of 27 patients. In several of the patients, who did not return to the clinic for an additional supply of the drug, there was a prompt increase in the body weight, associated with leg œdema and pulmonary rales. Such cases again responded to the administration of hydrochlorothiazide, with prompt diuresis and clinical improvement. The prolonged daily use of this drug in patients for two to five months did not lead to development of a state of drug tolerance. In several instances where chlorothiazide alone failed to control the œdema, hydrochlorothiazide therapy also had to be supported by parenteral mercurial injections.

Electrolyte Studies

In the in-patients, administration of hydrochlorothiazide promptly increased excretion of sodium and chloride ions, and to a lesser extent, potassium ions. Sodium excretion was almost parallel to that of chloride; results were similar to those observed after chlorothiazide or meralluride. Serum electrolyte disturbances were minimal, mainly hypochloræmia and hyponatræmia; hypokalæmia was never encountered.

At the start of the study, serum sodium concentrations were 3-5 mEq./l. below normal in many patients, as a result of prolonged treatment with other diuretics, mainly chlorothiazide. Hydrochlorothiazide therapy in many instances either produced no change or actually caused return of the serum levels in the blood to normal values; in only a few cases did hyponatræmia persist. Similar observations were made with the serum chloride levels. In our experience, the administration of ammonium chloride to ten patients did not appear to alter the electrolyte pattern. In no instance was hypokalæmia present, and therefore it was never necessary to give supplemental potassium chloride orally.

Blood urea nitrogen levels taken at regular intervals showed no evidence of renal damage (Table I).

Results of serum calcium and inorganic phosphorus studies were always within normal limits.

Urinary and serum magnesium studies were carried out on all these patients as part of an overall study on the influence of diuretics on serum ions in patients with congestive failure, and these observations will be discussed in greater detail elsewhere. In general, it may be stated from the preliminary results that in many instances the urinary magnesium may increase after hydrochlorothiazide as well as after meralluride or chlorothiazide. Thus far, only three instances of hypomagnesæmia were encountered in this study and these cases will be presented at a later date.[7]

Side Effects

As in the case of chlorothiazide, the prolonged daily administration of hydrochlorothiazide seemed to be well tolerated by all patients, and in no instance was it found necessary to discontinue the drug because of any gastro-intestinal disturbances. The only complaints encountered were dryness of the mouth and occasional paræsthesiæ of the face and hands but these were never sufficiently severe to warrant discontinuation of therapy.

DISCUSSION

The above data clearly illustrate that hydrochlorothiazide is an effective oral diuretic which can be useful in initiating a prompt diuresis and in the long-term maintenance of patients with congestive heart failure. The observations also demonstrate that hydrochlorothiazide is many times more potent a diuretic agent than chlorothiazide, in confirmation of the earlier reports in animals and in man.[2-4]

Hydrochlorothiazide, although chemically related to chlorothiazide, has been shown by others to cause a larger excretion of chloride ion than sodium ion, suggesting that the two drugs may operate through different mechanisms. However, our data confirm the observations of others in dog and man that the excretion of sodium ion parallels chloride ion excretion. The exact mechanism(s) of action is not clearly understood, but it is believed to act on the renal tubule. In contrast to chlorothiazide, the excretion of potassium is much less than that of sodium or chloride ions. The absence of hypokalæmia in this study indicates that hydrochlorothiazide is a safer drug to use in the long-term management of patients with congestive failure.

The degree of diuretic response, as would be expected, was more pronounced in patients with the most peripheral œdema and was less marked when the patient was in the œdema-free state. The prolonged daily administration of the drug

to patients for the period of this study did not lead to development of a state of drug tolerance. The maximum clinical effect appeared to be achieved at a dose of 100-200 mg. daily in two divided doses. Very frequently, once the œdema-free state had been achieved, 50 mg. daily appeared to be sufficient in some cases, but doses above 200 mg. daily never resulted in any further clinical improvement. This fact was also confirmed during the study of the urinary excretion pattern in the in-patients. Comparison of the potency of hydrochlorothiazide with that of meralluride revealed that doses of 50-100 mg. of hydrochlorothiazide were equivalent to 1-2 ml. of the latter given intramuscularly. However, it should be pointed out that in many cases, especially those with very severe congestive heart failure, the use of hydrochlorothiazide or chlorothiazide may result in an increase in the 24-hour urine volume and an increase in the excretion of sodium, potassium and chloride ions, yet the clinical state does not appear to be altered significantly. In these patients, repeated use of 2-3 ml. of intramuscular meralluride frequently resulted in massive diuresis with some clinical improvement. Thus it is difficult to generalize on relative effectiveness but, broadly speaking, oral hydrochlorothiazide has been found to be as effective as intramuscular meralluride in the dosage described above. In only two patients of this present series has it been found necessary to supplement the diuretic regimen with parenteral mercurials. In those instances where some residual œdema was present at the time of the patient's weekly visit to the clinic, instead of meralluride being given, as was done previously, the dose of hydrochlorothiazide was raised for two to three days to 200 mg. daily and then followed by 50-100 mg. daily for the balance of the week. The degree of hypochloræmia was slight, and this was also present in ten of the patients given ammonium chloride along with the hydrochlorothiazide. The tendency for the hypochloræmia and hyponatræmia to be improved upon further treatment with hydrochlorothiazide must be attributed to the patient's better well-being and increased dietary intake of food containing salt. This improvement in electrolyte picture paralleled the clinical improvement of the patient. Preliminary observations in six patients with hypertension revealed that hydrochlorothiazide like chlorothiazide may lower blood pressure when used in combination with other drugs.

Caution should be exercised in its administration to patients with advanced liver cirrhosis, as this may lead to a state of coma, similar to that described after use of chlorothiazide.

CONCLUSIONS

The diuretic effect of hydrochlorothiazide has been studied in four in-patients and 27 ambulatory patients with congestive heart failure, for periods up to three months. Hydrochlorothiazide has been found to be more potent than chlorothiazide, and to cause fewer disturbances in serum electrolyte levels. In no instance was hypokalæmia encountered. In doses of 50-100 mg. hydrochlorothiazide daily, its action is equivalent to 1-2 ml. of intramuscular meralluride (Mercuhydrin).

Recommended dosage to initiate a diuresis is 100-200 mg. per two days, to be followed by 50-100 mg. daily for the long-term maintenance of the œdema-free state in patients with heart failure.

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RÉSUMÉ

Le personnel du département de médecine, du service cardio-vasculaire et des laboratoires de biochimie de l'hôpital général juif de Montréal a récemment mis à l'épreuve un nouveau diurétique dans l'œdème d'origine cardiaque. L'hydrochlorothiazide est le résultat d'une modification du chlorothiazide par laquelle la double liaison du noyau hétérocyclique est supprimée, conférant au dérivé des propriétés diurétiques supérieures à celles du produit souche. Quatre malades hospitalisés furent étudiés à fond au point de vue électrolytique alors qu'ils recevaient de l'hydrochlorothiazide; 27 malades de la clinique externe furent suivis d'aussi près que possible. De cette série, 20 sujets souffraient d'affection cardiaque artériosclérotique, six de maladie de cœur rhumatismale, quatre de maladie hypertensive cardio-vasculaire et deux de cœur pulmonaire. La durée des observations s'étendit jusqu'à trois mois.

Les résultats ont montré que l'hydrochlorothiazide est un diurétique plus puissant que le chlorothiazide et qui cause moins de perturbations électrolytiques. On a observé aucun cas d'hypokaliémie. Des doses de 50 à 100 mg. par jour produisent le même effet que 1 à 2 ml. de méralluride intramusculaire (Mercuhydrine). Les auteurs recommandent une dose d'attaque de 100 à 200 mg. aux deux jours afin d'amorcer la diurèse, suivie de doses quotidiennes de 50 à 100 mg. aussi longtemps qu'il est nécessaire afin d'éviter l'œdème de se reproduire chez les malades atteints de défaillance cardiaque.

SURGICAL MANAGEMENT OF COMPLICATED DIVERTICULITIS

Colcock (*New England J. Med.*, 259: 570, 1958) reviews the experience of the Lahey Clinic with diverticulitis of the sigmoid colon. Complications occur in about 30% — obstruction or perforation of the colon or fistula formation between colon and bladder or colon and vagina. Among 131 patients operated upon in a ten-year period, mortality was 1.5% (two cases). No deaths occurred in 69 cases subjected to a one-stage resection with a primary anastomosis.

Of this series of 131 patients, 40 (30.5%) had previously undergone one or more operative procedures without relief or with the development of postoperative complications. Surgery for diverticulitis should be performed before the development of complications; the affected portion of the colon must be completely resected. Primary anastomosis can then be carried out and the patient will be spared the possibility of a long and serious illness, often requiring multiple surgical procedures for correction.