EARLY OBSERVATIONS ON THE DIURETIC EFFECT OF ORAL CHLOROTHIAZIDE

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It is well known that digitalis and mercurial diuretics are the two most potent agents in the treatment of heart failure, and that mercurial compounds are particularly useful if the heart rhythm is regular. Up to the present time oral diuretics have compared unfavourably with parenteral therapy in increasing urinary output and lessening pulmonary congestion, especially when heart failure is severe. Aminometradine ("mictine") is less potent than mersalyl; its maximum effect is often delayed, and treatment may have to be limited because of gastro-intestinal intolerance (Platts and Hanley, 1956). Acetazolamide ("diamox") compares unfavourably with mersalyl, and it is doubtful if it serves any useful purpose in the treatment of patients with severe congestive heart failure (Relman *et al.*, 1954). Jose and Wood (1958) compared the diuretic action of mersalyl and amisometradine ("roliction") in 20 patients and found the oral diuretic to be less than half as potent. It is clear, therefore, that, should an oral diuretic become available that is equal to or better than the well-established drugs given intramuscularly, it would be of great use in therapeutics and of immense practical value. From our preliminary observations we believe that chlorothiazide ("saluric," "chlotride," "diuril") may well prove to be such a drug.

Chlorothiazide was first synthesized by Novello and Sprague (1957) and is designated chemically as 6-chloro-7-sulphamyl-1,2,4-benzothiadiazine-1,1-dioxide. It produces water diuresis in man by promoting the excretion of sodium and chloride in equimolar amounts. Its diuretic action is therefore similar to that of mercurial compounds.

The main objects of this paper are to record our early observations on the potency of chlorothiazide in water diuresis and to compare its efficacy with parenteral mercurial diuretics.

Methods

The effect of oral chlorothiazide on the urinary output was observed in 20 in-patients, all with clinical oedema or pulmonary congestion from heart failure. Seventeen were also given parenteral mercaptomerin ("thiomerin") or mersalyl. All the patients were confined to bed during the period of investigation and their ventricular rate was kept constant with or without digitalis. The 24-hour fluid intake and urinary output were recorded in fluid ounces. The fluid intake was inconstant, 30–50 oz. (852–1,420 ml.) in one day, and the sodium intake calculated as sodium did not exceed 0.7 g. daily.

We were aware of the spontaneous diuresis which may occur when a patient is first rested in bed, and that the initial diuresis in any patient with heart failure is usually better than the response obtained by later therapy. We therefore deliberately chose to use parenteral diuretics first in 16 cases. In 10 patients several injections were given

initially, and so the oral effect of subsequent chlorothiazide was thought to be of greater significance. In six patients mercurials were used only once or twice before instituting oral therapy. The dosage of mersalyl or mercaptomerin used was 2 ml. intramuscularly at varying intervals without preceding ammonium chloride. Chlorothiazide, 1 g., was given twice a day, at 10 a.m. and 2 p.m., for four consecutive days, followed by an interval of three to four days before a further course was started.

The diuresis was compared in units of two days. The mercurial diuretic was given on the first day only, and chlorothiazide was administered on each of the two days under consideration. In practice, parenteral diuretics are rarely given on consecutive days, whereas chlorothiazide may be so given. Evans and Paxon (1941) defined the diuretic index as "the excess of the daily output of urine over the fluid intake, both measured in ounces." We have used this as a basis in our study, but recorded the total diuretic index for two successive days because the mercurials often continue to be effective on the day following the injection. The serum electrolytes were estimated before and after treatment in 13 cases.

Results

The average diuretic index for every case was calculated from the number of two-day periods of treatment, and is recorded in Table I. The total number of two-day periods

TABLE I.—Average Diuretic Index (Per Two-day Period) in 20 Patients, Following Mercurial Diuretics and Chlorothiazide

Case No.	Age and Sex	Cause of Heart Failure	Parenteral Mercurials (2 ml. on 1st Day of Each 2-day Period)		Oral Chlorothiazide (1 g. b.d. on Both Days of Each 2-day Period)	
			No. of 2-day Periods	Average Diuretic Index	No. of 2-day Periods	Average Diuretic Index
1	58 F	R.H.D.	8	-18	6½	+42
2	68 F	C.A.D.	12	+10	10	+19
3*	65 M	C.A.D.	4	+12	3	+20
4	67 F	P.H.D.			3	+51
5	51 F	R.H.D.	23	+3	6½	+10
6	74 M	H.H.D.	19	+20	5½	+55
7	60 M	C.A.D., H.H.D.			6	+75
8	62 F	R.H.D.			2	+53
9	53 M	H.H.D.	1	+56	3½	+93
10	65 F	C.A.D.	1	+62	4	+45
11	59 F	R.H.D.	7	0	4	+72
11 (a)	59 F	R.H.D.			2	+124
12	54 M	P.H.D.	15	+22	4	+13
13	60 F	P.H.D.	6	-8	4	+14
14	62 M	C.A.D.	5	+10	2	+16
15	64 M	P.H.D.	3	+35	3	+29
16	67 M	R.H.D.	2	+68	4	+53
17	60 M	C.A.D.	2	+41	4	+28
18	68 M	C.A.D.	2	+24	5	+39
19	74 M	C.A.D., H.H.D.	2	+30	6	+28
20	58 M	R.H.D.	5	+49	4½	+66

C.A.D.=Coronary artery disease. H.H.D.=Hypertensive heart disease. P.H.D.=Pulmonary heart disease. R.H.D.=Rheumatic heart disease.

* Patient given mercurials after chlorothiazide.

of treatment is shown in each case—for example, Case 1 received eight two-day periods of therapy with mercurial diuretics and six and a half two-day periods (that is, 13 days) on chlorothiazide. In 16 of the 20 patients mercurial diuretics were given first. In the remaining four chlorothiazide was given initially for various reasons. Two patients (Cases 7 and 8) had been given mercurials at weekly intervals for over a year without clinical improvement, and this was the prime reason for their admission to hospital. One patient (Case 4) was inadvertently given the oral diuretic initially, and the diuresis and clinical improvement was such that she subsequently refused parenteral therapy. Prior to admission Case 3 developed a rash after mercaptomerin and it was therefore considered wise to start with the oral diuretic. Later it was found that mersalyl caused no such skin reaction.

Of the 17 patients given both forms of diuretic therapy, Case 11 showed the most satisfactory response to chloro-

thiazide, and this is illustrated in the Chart. During her first admission she had a higher average diuretic index following chlorothiazide (+72) than mercaptomerin (0), although the latter was given first in seven two-day periods. When readmitted she was given chlorothiazide initially for four successive days with an average diuretic index of +124.

It can be seen (Table I) that where mercurial diuretics were not given in hospital the average diuretic index on chlorothiazide was highly satisfactory in all three patients (Cases 4, 7, and 8). In the remaining 17 patients both types of diuretic agent were used and the average diuretic index was superior following chlorothiazide in 11. Mercurial diuretics were apparently superior in six patients (Cases 10,

Case 11. Action of initial mercaptomerin, seven two-day periods, compared with subsequent chlorothiazide, six two-day periods, shown by diuretic indices over two-day periods.

12, 15, 16, 17, and 19). It is clear that this could be attributable in five (Cases 10, 15, 16, 17, and 19) to the use of only one to three preliminary injections when considerable fluid retention was present. In Case 12 it would seem that the mercurial compound was superior, but when chlorothiazide treatment was started his clinical oedema had almost disappeared.

Six patients (Cases 9, 10, 16, 17, 18, and 19) were given only one or two mercurial injections initially, followed by chlorothiazide. We calculated the average of the diuretic indices obtained from all six patients following each form of therapy, and the findings are shown in Table II.

It was expected that this analysis would favour mercurial diuretics because of the satisfactory diuretic response usually obtained in early therapy. Actually the average diuretic

TABLE II.—Average Diuretic Index of Six Patients Given One or Two Mercurial Injections Initially

No. of Cases	Mercurials (10 × 2-day Periods)		Chlorothiazide (26½ × 2-day Periods)	
	Sum of Average Diuretic Indices	Average	Sum of Average Diuretic Indices	Average
6	281	+47	286	+48

indices obtained were almost identical. It is appreciated that the variability of diuresis obtained in these cases individually was such that in a larger series the average indices might not have been so similar.

In only five patients was chlorothiazide given initially, and included among these was the one patient (Case 11a) who was given chlorothiazide only on her second admission. The average of the diuretic indices of these five patients is shown in Table III. The average diuretic index is high

TABLE III.—Average Diuretic Index of Five Patients Given Chlorothiazide Initially

Chlorothiazide (16 × 2-day Periods)		
No. of Cases	Sum of Average Diuretic Indices	Average
5	323	+65

(+65). Only one of these patients received subsequent mercurials, and so a comparison of the diuretic agents cannot be made in these five cases. A relevant comparison can be made with the average diuretic index obtained following mercurials in those cases which were given only one or two injections initially, as shown in Table II (+47).

The average of the indices of 10 patients who were given more than two mercurial injections initially is shown in Table IV. It will be noted that the average index proved

TABLE IV.—Average Diuretic Index of 10 Patients Given More than Two Mercurial Injections Initially

No. of Cases	Mercurials (103 × 2-day Periods)		Chlorothiazide (50 × 2-day Periods)	
	Sum of Average Diuretic Indices	Average	Sum of Average Diuretic Indices	Average
10	123	+12	336	+34

to be higher in the chlorothiazide group. Some of these cases were showing a diminishing response to mercurials and may have been developing drug tolerance, but the subsequent effect of chlorothiazide was gratifying, as shown particularly in Cases 6 and 11 (Table I).

The average of the indices in the whole series of 20 patients, including all courses of treatment, is given in Table V. This shows that the number of two-day periods was

TABLE V.—Average Diuretic Index of all Patients

Mercurials (117 × 2-day Periods)			Chlorothiazide (92½ × 2-day Periods)		
No. of Cases	Sum of Average Diuretic Indices	Average	No. of Cases	Sum of Average Diuretic Indices	Average
17	416	+24	20	945	+47

approximately the same in both groups, and that the average diuretic index of 20 patients was higher in the chlorothiazide series (+47) than that of 17 patients treated with mercurial diuretics (+24). As a result of combined therapy the signs of pulmonary congestion and peripheral oedema disappeared in all our 20 patients.

The serum electrolytes were determined in 13 patients, and in these the serum sodium and chloride were not significantly altered. The serum potassium did not fall to below 3.3 mEq/l. in any of these patients. In five it fell to between 3.3 and 3.9 mEq/l. Symptoms of hypokalaemia did not develop in these.

Discussion

We are conscious of the inherent difficulties in a comparison of diuretic agents because of the many variables that are introduced into any such study. We have already mentioned the spontaneous diuresis that may occur in a patient following bed rest alone, with or without digitalis, and the advantage possessed by the initial diuretic agent. Obviously, it is difficult to assess the degree of fluid retention in any

patient at a given time, and the diuretic response to any drug must be influenced by this clinical state. In 16 of our patients any likely advantage in diuretic action was given to mercurials as they were given before chlorothiazide. It is evident from our results that a significant diuresis was obtained with subsequent chlorothiazide, and our preliminary observations suggest that this drug is at least as potent as parenteral mercurials, or more so. In the patients who were given chlorothiazide initially the diuretic response was excellent. Our study of this small series of patients has convinced us that chlorothiazide is the most potent oral diuretic now available. If subsequent trials confirm our findings we will have an efficient diuretic which has the merits of practicability and ease of administration. Our patients were grateful that a change had been made from repeated injections, particularly as most of them noticed that the effect was usually better. The practical advantage of the oral method in domiciliary practice is obvious. Toxic manifestations did not appear in a single case, and, in particular, no gastrointestinal disturbances occurred.

The most important side-effect of oral chlorothiazide is hypokalaemia (Bayliss *et al.*, 1958; Slater and Nabarro, 1958). In the dosage used by us the serum electrolyte levels were not markedly affected, but it is known that if continuous daily therapy is instituted hypokalaemia occurs. Further work on the electrolyte changes following prolonged treatment is necessary, as this would seem to be the only serious disadvantage to the use of chlorothiazide in general practice. None of our cases was given supplementary potassium, but it must be stressed that the dose of chlorothiazide never exceeded 2 g. in one day, and that it was never given for more than four consecutive days at intervals of three to four days. Only one patient received as much as 20 days of intermittent therapy. We do not therefore wish to imply that supplementary potassium is unnecessary during treatment with chlorothiazide, but it is possible that this can be avoided if its administration is interrupted by free periods according to the procedure we adopted.

Summary

Oral chlorothiazide was given in doses of 1 g. twice daily to 20 patients with heart failure. In 17 of these 2 ml. of a mercurial diuretic was given parenterally and in 16 it was given initially. To compare the value of these diuretic agents varying courses of intermittent therapy were used. The response obtained was measured as the diuretic index over a two-day period.

Chlorothiazide produced a good therapeutic effect in all cases, and our results suggest that it is as effective as the parenteral diuretics, or more so.

In the short and intermittent courses of treatment which we used only a slight fall in serum potassium was recorded in five patients. Toxic effects were not observed in any of our patients.

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TREATMENT OF HAY-FEVER WITH LOCAL HYDROCORTISONE HEMI- SUCCINATE SODIUM

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During recent years various analogues of hydrocortisone have been used by local application to the nasal mucosa in the treatment of hay-fever. Owing to the relative insolubility of the free alcohol and acetate derivatives, previous workers have used these substances either incorporated in a snuff or as nose-drops in weak concentration. Pennypacker (1954) used nose-drops containing the free alcohol of hydrocortisone dissolved in saline in a strength of 0.2 mg. per ml., which represents its maximum aqueous solubility; vasoconstrictors were also included. Herxheimer and McAllen (1956) employed hydrocortisone acetate dispersed in lactose and used as a snuff, the maximum daily dose being 15 mg. Godfrey *et al.* (1957) also used a snuff, but one containing prednisolone in a maximum daily dose of 2 mg.

The development of compounds of hydrocortisone which are highly soluble in water has introduced a new factor into its use as a local therapy. Such compounds are likely to enter the tissues more rapidly and in higher concentration than the less soluble ones. Any beneficial actions of hydrocortisone in its less soluble forms might be expected to occur with greater speed and lower total dosage with these new preparations. In the present study we describe the use of a highly soluble preparation used in nose-drops. This was hydrocortisone hemisuccinate sodium, which has appeared to be effective when used locally in ulcerative colitis, as described in a previous article (Truelove, 1957), in which is also included a brief review of its properties.

Procedure

Hydrocortisone hemisuccinate sodium suffers from a minor disadvantage for use in nose-drops in that it undergoes in aqueous solution a slow hydrolysis with the liberation of hydrocortisone itself, which is liable to precipitation because of its low solubility. The rate of hydrolysis is dependent upon the intensity of light, and the process can be slowed by keeping the solution in a dark glass bottle. Under these conditions the solution is reasonably stable for 48 hours.

The hemisuccinate was therefore supplied by Glaxo Laboratories in the form of tablets. Each tablet contained the equivalent of 2.5 mg. of free hydrocortisone. The nose-drops were prepared each day by the patient dissolving one or more, as ordered, of these tablets in 5 ml. of normal saline contained in a small dark glass bottle fitted with a nasal dropper. Each patient began by using two tablets to the bottle, yielding a concentration of 1 mg. of hydrocortisone per ml. Some patients who responded well to this initial concentration continued their treatment with one tablet in the bottle. Others, in whom the initial concentration was ineffective, used a higher concentration.

The patients began treatment by applying three drops in each nostril four times a day. The nasal droppers yield 1-minim (0.06-ml.) drops—that is, 15 drops per ml.—so that the patients received 2 ml. or less of the solution daily. In