TRIAL OF AN ORAL DIURETIC, HYDROCHLOROTHIAZIDE

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Hydrochlorothiazide has been introduced as an oral diuretic agent with a potency considered greater than that of any other oral agent, and has been submitted to clinical trial by various observers.[1-10] In general its efficacy has been confirmed, although there is disagreement concerning the loss of potassium which it induces,[11] and its potency compared with other diuretics. In the present study the effect of a relatively large single oral dose, 250 mg., is compared with that of 2 c.c. of a parenteral mercurial, mersalyl, in the same patients. This oral dose was chosen after preliminary trials with single doses increasing from 50 to 250 mg. had indicated increasing effect until at the higher figure a water diuresis equivalent to that of 2 c.c. of mersalyl was obtained.

Methods

Eleven patients kept at bed rest in hospital were studied. All were suffering from chronic congestive heart failure—due in 1 to essential hypertension, in 3 to constrictive pericarditis, in 3 to rheumatic valvular disease, and in 4 to African cardiomyopathy. All were on digitalis therapy and a low-salt diet (approx. 400 mg. per day) and initially were closely observed after a state of equilibrium in congestive heart failure had been achieved. This observation period lasted for a minimum of 1 week. The blood urea and serum concentrations of sodium, potassium and chloride were determined and the urine examined before the beginning and at the end of the trial. The height of the jugular venous pulse and the degree of oedema and hepatomegaly were assessed daily from the beginning of the period of close observation. From the first day of the trial, daily 24-hour volumes of urine were collected; their content of sodium, potassium and chloride were estimated in 9 of the patients. At the end of the first 24-hour period, 2 c.c. of mersalyl was injected, and at the end of the 4th period 250 mg. of hydrochlorothiazide was given by mouth. The mersalyl was repeated at the end of the 8th period, i.e. 1 week after the first injection, and hydrochlorothiazide was repeated at the end of the 11th period, 1 week after its first administration. This weekly administration of each drug in turn was continued for a varying time (Table I). Results were calculated for mersalyl by obtaining for each patient the ratio of the sums of outputs of water, sodium, potassium and chloride respectively in the 24-hour periods preceding the mersalyl injections to the sums of outputs in the 24-hour period succeeding the injections. Results for hydrochlorothiazide were obtained similarly. In all tests, as described above, the drugs were given alternately. As the trial lasted for a varying number of weeks in different patients, the mean ratios for the whole series were calculated not from the individual patient-ratios, but from all tests considered together.

Results

On this regime the patients showed no change in blood-urea or serum-electrolyte concentrations, the initial values of which were all normal, and in no patient was there any abnormal urinary finding after the trial. In all the patients there was gradual improvement as regards the heart failure. Other patients not in this series with less severe and less chronic heart failure have shown the same picture of rapid recovery when treated with digitalis and hydrochlorothiazide that is seen when parenteral mersalyl is used as the diuretic. No toxic effects were observed.

The results of excretion measurements are set out in Tables I - IV.

Urine volume. From Table I it is apparent that among the different patients there was a wide range of response to mersalyl and to hydrochlorothiazide, one patient, with constrictive pericarditis (case 1) showing a more than 5-fold increase in urine output after both drugs, and one patient (case 9) showing no response to mersalyl at all. It is possible that the slightly lower 24-hour volumes preceding hydrochlorothiazide compared with the volumes preceding mersalyl may have prejudiced the results against hydrochlorothiazide; but the distribution of the individual patients' tests relating volumes before mersalyl to volumes after mersalyl, and similarly for hydrochlorothiazide, showed a complete scatter, so that this factor cannot be considered to be operating. That the giving of mersalyl as the initial diuretic made no difference to the results is shown by the fact that if the first mersalyl result was ignored in calculating the before-after ratios, no significant difference was observed. This can be explained by the relatively refractory heart failure in all these patients, so that their clinical state varied only slowly. The ratios for all tests of urine-volume output are similar for mersalyl and hydrochlorothiazide, 1 : 1·77 and 1 : 1·61.

Sodium and chloride outputs. The saluretic effects of the drugs is shown by their high before-after administration ratios, appreciably higher than their urine-volume ratios and of the same order for sodium as for chloride. Both with mersalyl and with hydrochlorothiazide the difference between the outputs of these two substances is not statistically significant ($p > 0·2$). Moyer *et al.*[7] on the other hand considered on their figures that the primary effect seemed to be on chloride excretion, there being nearly always a greater increase in chloride than in sodium excretion. The same variation in response to the drugs is seen with sodium and chloride as it is with water; patient E.D. (case 1) produced a before-after ratio with hydrochlorothiazide of 1 : 52·6 for chloride, and 1 : 36·9 for sodium. The equivalent figures for patient N.N. (case 3), who showed the least response, are 1 : 1·42 and 1 : 1·39.

Potassium. The excretion of potassium is considerably less promoted by both drugs than the excretion of sodium and chloride. Although at this dose there is a potassium excretion of 1·59 times the control level after hydrochlorothiazide, this before-after ratio is not significantly greater than the ratio 1 : 1·14 for mersalyl ($p = 0·1$).

TABLE I. URINE VOLUME SUMS, IN C.C.

Patient	No. of Tests		Periods		Periods		Before/After Ratios	
	Mers.	Hyd.	Before Mers.	After Mers.	Before Hyd.	After Hyd.	Mers.	Hyd.
							1:	1:
1. E.D. ..	4	4	1,790	9,930	1,160	8,965	5·55	7·73
2. M.C. ..	2	2	1,710	3,570	1,620	4,590	2·09	2·83
3. N.N. ..	3	2	4,510	6,230	2,200	2,680	1·38	1·22
4. M.N. ..	4	3	5,010	9,540	3,900	6,830	1·90	1·75
5. M.Ng. ..	5	5	7,500	13,400	6,180	8,830	1·79	1·43
6. J.X. ..	4	3	3,360	7,300	3,480	3,500	2·17	1·01
7. B.S. ..	10	9	14,640	23,810	11,600	17,410	1·63	1·50
8. J.M. ..	6	5	7,510	15,630	7,170	11,220	2·08	1·56
9. S.H. ..	3	3	5,760	5,700	4,320	6,180	0·99	1·43
10. J.Mz. ..	4	3	7,560	10,620	5,400	6,600	1·40	1·22
11. A.N. ..	4	5	4,460	7,430	5,560	8,070	1·67	1·45
Totals ..	49	44	63,810	113,160	52,590	84,875		
Ratio:			1:	1·77	1:	1·61		

TABLE II. SODIUM OUTPUT SUMS, IN MILLI-EQUIVALENTS

Patient	No. of Tests		Periods		Periods		Before/After Ratios	
	Mers.	Hyd.	Before Mers.	After Mers.	Before Hyd.	After Hyd.	Mers.	Hyd.
							1:	1:
1. E.D. ..	4	4	126	1,006	21	775	8·00	36·90
2. M.C. ..	2	2	51	246	28	424	4·82	15·14
3. N.N. ..	3	2	364	619	189	263	1·70	1·39
4. M.N. ..	2	1	106	465	115	209	4·39	1·82
5. M.Ng. ..	5	5	470	1,367	246	647	2·90	2·63
6. J.X. ..	4	3	255	756	138	313	2·97	2·27
7. B.S. ..	9	9	605	1,823	271	949	3·01	3·50
8. J.M. ..	4	4	410	1,054	172	610	2·57	3·55
11. A.N. ..	4	5	155	553	146	383	3·57	2·62
Totals ..	37	35	2,542	7,889	1,326	4,573		
Ratio:			1:	3·1	1:	3·45		

TABLE III. POTASSIUM OUTPUT SUMS, IN MILLI-EQUIVALENTS

Patient	No. of Tests		Periods		Periods		Before/After Ratios	
	Mers.	Hyd.	Before Mers.	After Mers.	Before Hyd.	After Hyd.	Mers.	Hyd.
							1:	1:
1. E.D. ..	4	4	117	182	33	295	1·56	8·93
2. M.C. ..	2	2	89	122	78	196	1·38	2·51
3. N.N. ..	3	2	148	119	92	74	0·80	0·80
4. M.N. ..	2	1	109	117	148	63	1·07	0·43
5. M.Ng. ..	5	5	218	250	181	236	1·15	1·30
6. J.X. ..	4	3	173	155	130	165	0·89	1·27
7. B.S. ..	10	9	453	616	325	496	1·36	1·53
8. J.M. ..	4	4	177	176	162	305	1·00	1·88
11. A.N. ..	4	5	198	174	177	279	0·88	1·57
Totals ..	38	35	1,682	1,911	1,325	2,109		
Ratio:			1:	1·14	1:	1·59		

TABLE IV. CHLORIDE OUTPUT SUMS, IN MILLI-EQUIVALENTS

Patient	No. of Tests		Periods		Periods		Before/After Ratios	
	Mers.	Hyd.	Before Mers.	After Mers.	Before Hyd.	After Hyd.	Mers.	Hyd.
							1:	1:
1. E.D. ..	3	4	58	932	19	1,000	16·07	52·63
2. M.C. ..	2	2	87	378	31	587	4·34	18·93
3. N.N. ..	3	2	420	645	186	264	1·54	1·42
4. M.N. ..	2	1	138	363	156	239	2·63	1·53
5. M.Ng. ..	5	5	606	1,314	268	812	2·17	3·03
6. J.X. ..	3	2	279	571	176	367	2·04	2·07
7. B.S. ..	10	9	586	1,579	347	1,136	2·69	3·28
8. J.M. ..	4	4	324	1,109	240	717	3·42	2·99
11. A.N. ..	4	5	224	639	118	427	2·85	3·53
Totals ..	36	34	2,722	7,530	1,541	5,549		
Ratio			1:	2·77	1:	3·60		

Discussion

The results show that this single oral dose, 250 mg., of hydrochlorothiazide produces a diuresis of water, sodium, potassium and chloride similar to that of 2 c.c. of parenteral mersalyl, and that the potassium excretion is minor. The mean increase of potassium excreted over control values was 22 mEq. in the 24 hours following administration. This figure would certainly be greater in more responsive patients, as is indicated by the dose-response curve of Moyer *et al.*, where the figure is about 65 mEq. The dose of hydrochlorothiazide used in this study is higher than that used in trials by others[4-6] but is comparable to the 200 mg. dose used by Moyer *et al.* Since it appears to lie at the peak of the dose-response curve of Moyer *et al.*, it is probably optimal for single dose administration. The amounts used by others have been designed for daily maintenance therapy and are therefore not comparable with a dose designed for single administration. Various authors[1,3,5] have reported that maintenance can be achieved with between 25 and 100 mg. a day.

SUMMARY

A single oral dose of 250 mg. of hydrochlorothiazide was tested alternately with a single parenteral dose of 2 c.c. of mersalyl in a series of patients with chronic heart failure.

The two drugs produced similar diureses of water, sodium, potassium and chloride. Those of sodium and chloride were marked, that of potassium, minor. Toxic effects were not observed.

It is concluded that a single oral dose of 250 mg. of hydrochlorothiazide forms a substitute for a single parenteral dose of 2 c.c. of mersalyl.

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