SOME ASPECTS OF DIURETIC ACTIVITY OF CYCLOPENTHIAZIDE AND EFFECT OF SPIRONOLACTONE ON THEM, COMPARED WITH MERSALYL

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(Received August 30, 1962)

Cyclopenthiazide, a new thiazide oral diuretic was compared by itself and in combination with spironolactone to intramuscular mersalyl in patients with edema using a rapid quantitative method for determining the efficacy of diuretic drugs. Diuretic efficacy of the thiazide drug, alone or in combination with the steriod was about 2/3rd that of mersalyl. Cyclopenthiazide affected adversely Na/K excretion ratio while addition of spironolactone brought it more or less in line with mersalyl.

Cyclopenthiazide is a comparatively newer drug belonging to the thiazide group of diuretics. We have been interested in evaluating one aspect of thiazide diuretics, namely, their efficacy when compared in maximally effective doses to that of an organic mercurial given by intramuscular injection. It was decided to gather similar information about this drug. The scope of the trial was extended so as to include the effect of addition of aldosterone antagonist spironolactone to cyclopenthiazide with the hope that it might increase the diuretic efficacy of and prevent the expected high excretion of potassium in urine with thiaizde diuretic or at least do the latter. The trial was carried out in 21 in-door patients admitted (in K.E M Hospital, Bombay) for edema due to varied pathological conditions.

METHODS

The method used was a slight modification of the one used by Gold *et al.*, 1960, 1961). In one of our recent publications (Mehta *et al.*, 1962) we have described the method with all the modifications. The method in short; patients with edema due to various conditions were hospitalized and received base regimen of bed-rest, low salt diet and digitalis if necessary. Effect of ceiling doses of each drug was observed on 24-hours loss of body weight in each patient. In the present study each patient received the following three treatments in three consecutive days. (i) Mersalyl, 2 ml by

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intramuscular injection; (ii) Cyclopenthiazide, 2 mg orally as a single dose, and (iii) a combination of 400 mg of spironolactone in combination with 2 mg of cyclopenthiazide again given at the same time. All drugs were given at approximately the same time of the day Daily body weight was recorded by one of us under precautions and routine described in our previous publication (Mehta *et al*, 1962). Weight losses of half lb or less were neglected.

Pertinent characteristics and diagnosis of patients in the study are given in Table I. In all, 21 patients were included in the trial. One of the patients (10) was readmitted after about 6 weeks and hence features again in the series as a separate patient (14). Two other patients were started on the trial but were dropped out of the series midway as deterioration of their clinical condition due to advanced stage of the disease warranted use of combination of therapeutic measures usually followed in such patients. Patient of any age, sex and diagnosis was taken in the study provided he or she had edema and was able to stand unaided so that accurate body weight could be obtained.

Diuretic efficacy of intramuscular mersalyl 2 ml, the standard drug, was taken as 100. Efficiencies of cyclopenthiazide and its combination with spironolactone were expressed in terms of that of mersalyl. An estimation of efficacy of cyclopenthiazide and spironolactone combination was made in terms of cyclopenthiazide alone. As explained in the previously mentioned publications, ratio of the 24-hr loss of body weight by the test-drug to that with standard drug gave an indication of the diuretic efficacy of test-drug in terms of the standard in that particular patient. Each efficacy ratio from the ndividual patient was converted into its logarithm and calculations for the average, confidence interval and 't' test for the significance of difference of means were done using logarithmic values. This was necessary as the distribution of efficacy of test-drug in terms of the standard when activity of the latter was taken as 100, would be on a logarithmic scale.

Efforts were made to obtain a correct 24-hr urine sample during the trial. After measuring the urine volume, an aliquot was analyzed for its sodium and potossium contents using a flame photometer. At times for some reason or other a 24-hr urine sample was not available. A comparison of the effects of three drugs on 'electrolyte excretion ratio' each patient was done. The 'ratio' was estimated for each drug in each patient from,

$$\frac{\text{Total 24-hr excretion of sodium}}{\text{Total 24-hr excretion of potassium}}$$

An analysis of individual electrolyte excretion ratios is given in Table IV. The number of these ratios with individual drug comparisons do not coincide

TABLE I

Characteristics of patients used in study

No.	*Initials*	*Sex*	*Age*	*Diagnosis*
1	T.S.	M	38	Hep. cirrh. with peripheral edema and ascites.
2	B.V.	M	40	Hyp., EH, RSR, congestive fai'ure.
3	I.D.	F	14	Nephrotic syndrome with peripheral edema.
4	N.M	M	23	Nephrotic syndrome with peripheral edema.
5	K.T.	M	50	Coronary heart disease, EH, RSR, congestive failure.
6	M.B.	F	13	Nephritic nephrotic syndrome with peripheral edema.
7	P.D.	F	20	Hep. cirrh. with peripheral edema and ascites.
8	L.A..	F	50	Hep. cirrh. with peripheral edema and ascites.
9	L.G	M	40	Hep. cirrh. with peripheral edema and ascites.
10	T.B.	M	50	Coronary heart disease, EH, RSR, congestive failure.
11	R.Z.	M	25	Hepatic cirrh. due to tuberculosis, with peripheral edema and ascites.
12	S.R.	M	44	Coronary heart disease, EH, RSR, congestive failure.
13	C.M.	M	42	Coronary heart disease, EH, RSR, congestive failure.
14	T.B.	M	50	Coronary heart disease, EH, RSR, congestive failure.
15	D.S.	M	34	Rheumatic, mitral stenosis, EH, auricular fibrillation, congestive failure.
16	V.D.	F	30	Rheumatic, mitral incompetence, EH, auricular fibrillation, congestive failure.
17	B.T	F	16	Dietary iron deficiency anemia with hypoproteinemia, EH, RSR, congestive failure.
18	S.B.	M	92	Bilateral basal bronchiectasis with corpulmonale.
19	C.M.	M	40	Hepatic cirrhosis with peripheral edema and ascites.
20	B.M.	M	40	Rheumatic, mitral stenosis; EH, RSR, congestive failure.
21	Y.V.	M	32	Rheumatic, mitral stenosis, EH, auricular fibrillation, congestive failure.

Hep. cirrh., hepatic cirrhosis; Hyp., hypertensive; EH., enlarged heart; RSR.; regular sinus rythm.

with the number of weight loss ratios in Table II, as in some patients the urine could not be collected or when the urine was available, weight loss ratios could not be obtained due to the 24-hr loss of body weight with one of the drug being less than half lb. A 't' test for significance of difference of electrolyte excretion ratios within patients was done for the three possible comparisons with the three drugs. In this way each patient acted as his own control.

RESULTS

Table II gives the order in which the drugs were given, 24-hr loss of body weight with each drug, and the logarithm of individual efficacy ratios. Table III gives the analysis of data from Table II and also retransformation of final logarithmic values into whole numbers. Diuretic efficacy of cyclopenthiazide when compared to mersalyl was about 2/3 that of latter, (Table III), confidence limits at P 0 05 were 42.8; 101.0. Addition of spironolactone did not affect the efficacy of cyclopenthiazide.

The effect of cyclopenthiazide on electrolyte excretion as compared to that of mersalyl was as expected from a fairly potent thiazide diuretic. In the majority of the patients cyclopenthiazide had a lower Na/K excretion ratio in urine than mersalyl. Addition of spironolactone even for a day changed the pattern of electrolyte excretion seen with cyclopenthiazide (Table IV). Even though spironolactone did not change the pattern to make it significantly different than cyclopenthiazide alone, it did produce sufficient change towards mersalyl values, so that there was significantly no difference between mersalyl and the combination on this score. The effects of mersalyl and cyclopenthiazide alone were significantly different.

DISCUSSION

When compared with cyclopenthiazide alone, the combination of spironolactone and cyclopenthiazide did not show any difference in diuretic efficacy. It probably was expected that spironolactone would not cause any increase in diuretic efficacy of concurrently given cyclopenthiazide in the present study for two reasons. Dose of cyclopenthiazide used was a true ceiling dose and no further effect could be expected by any procedure aimed at increasing its efficacy. Most of the current reports show that beneficial effect with this steroid is only seen after continuous administration for 2 to 3 days at least.

It is quite likely that spironolactone given 2 to 3 days previous to the administration of conventional diretics may be more useful than the single

TABLE II

Weight, losses and efficacy ratios with the drugs, mersalyl (M), cyclopenthiazide (C) and combination of cyclopenthiazide with spironolactone (S)

No.	Pattern	24-hr wt. loss in lbs with			Logarithm of rate of wt. losses X 100		
		M	C	S	C/M	S/M	S/C
1	CSM	3.0	5.5	5.0	2.22194	2.22194	1.95856
	,,	0.5	1.5	—	2.47712	—	—
2	SCM	3.0	5.5	6.0	2.26316	2.30103	2 03782
3	MCS	8.5	4.5	3.5	1.72346	1.61490	1.89098
	,,	1.5	1.0	1.0	1.82413	1.82413	2.00000
4	CMS	10.5	3.5	3.0	1.52244	1.45637	1.93298
	,,	3.0	1.5	3.5	1.69897	2.06707	2.36791
5	MSC	7.5	1.75	5.5	1.36736	1.86510	2.49734
	,,	3.25	2.0	—	—	1.78888	—
6	CSM	0.5	1.0	0.5	2.30103	2.00000	1.69897
	,,	2.5	0.5	1.5	1.30103	1.77815	2.47712
	,,	0.5	2.5	0.5	2.69897	2.00000	1.30103
7	SMC	6.0	0.5	2.0	0.91908	1.52244	2.60206
8	MCS	3.0	2.0	0.5	1.82413	1.22272	1.39794
	,,	6.5	—	1.5	—	1.36361	—
9	SCM	1.0	—	3.0	—	2.47712	—
	,,	2.5	0.5	1.0	1.30103	1.60206	2.30103
10	SMC	9.5	3.0	3.0	1.49969	1.49969	2.00000
	,,	7.0	1.5	3.5	1.33041	1.69897	2.36791
	,,	3.0	—	1.5	—	1.69897	—
11	CMS	1.5	2.0	1.75	2.12483	2.06707	1.94201
	,,	3.0	0.75	—	1·39794	—	—
12	MSC	7.0	5.0	0.5	1.85370	0.85126	1.00000
13	SMC	8.0	3.0	3.0	1.57403	1.57403	2.00000
	,,	3.0	1.0	—	1.52244	—	—
14	MCS	4.0	2.5	—	1.79588	—	—
15	SCM	5.5	8.0	6.0	2.16286	2:03782	1.87506
	,,	0.5	1.0	—	2.30103	—	—
16	CSM	8.0	7.0	7.0	1.94201	1.94201	2.00000
	,,	1.5	4.0	—	2.42602	—	—
17	MSC	2.0	—	5.0	—	2.39794	—
	,,	3.0	—	3.0	—	2.00000	—
18	SMC	8.5	1.5	3.0	1.24551	1.54777	2.30103
19	CMS	6.5	4.0	7.0	1.78888	2.02222	2.24304
	,,	1.5	4.0	2.5	2.42602	2.22194	1.79588
20	SCM	8.0	10.5	2.0	2.11826	1.39794	1.27875
21	CMS	10.0	3.0	3.5	1.47712	1.54407	2.06707
	,,	1.5	0.5	—	1.69897	—	—

Blank space (—) means either there was no weight loss or it was less than half lb, or again in weight.

TABLE III

Analysis of data from Table II. A comparison. Figures in brackets and underlined are whole numbers

	Cyclopenthiazide/Mersalyl	Combination Mersalyl	Combination Cyclopenthiazide
No. of ratios	32	31	25
Log. average	1.81783	1.79398	1.97338
(Average)	(65.7)	(62.2)	(94.1)
Log C.I. at 0.05P	1.63098 ; 2.00468	1.66050 ; 1.92706	1.80792 ; 2.13896
(C.I.)	*(42.8 ; 101.0)*	*(45.8 ; 84.6)*	*(64.7 ; 137.7)*
't' test for significant difference	2.36*	3.16*	0.16

* Significant at P 0.05

TABLE IV

Comparisons of differences of urinary sodium potassium excretion, ratios between the three drugs.

	Mersalyl-Cyclopent-thiazide.	Mersalyl-combination of cyclopenthiazide and spironoloctone	Combination spirono-lactone and cyclopen-thiazide-cyclopenthiazide.
No. of ratios compared	28	29	27
Average differance in ratios in favour of underlined	4.035	2.661	0.833
Range of differences	—6.39 to 25.01	—4.66 to 25.62	—2.89 to 6.80
't' test for significance of difference	3.09*	1.63	1.144

* Significant at P 0.05. Calculations for 't' tests were done by using the differences in Na/K excretion ratios of the pair of drugs under comparison.

day's administration tried here. One of the aims of using a combination of spironolactone and cyclopenthiazide was to see whether latter drug affected the urinary Na/K excretion ratio unfavourably and whether the addition of a spironolactone even for a day would prevent it.

The results obtained in this study gave complete support to these suppositions. Due to the nature of the study it was not possible to see the effect of continuous administration for several days of cyclopenthiazide to a patient on blood sodium and potassium level. But it is not difficult to visualize that if the drug causes a comparatively high excretion of potassium in one day, it is very likely that it would do the same if used for a week or more. Hence potassium supplements might have to be used whenever the expected treatment would be of more than a few days.

Lastly, to comment on the diuretic efficacy of cyclopenthiazide, it is shown here that the maximum effect with the tolerated doses of the drug would be of the order of 2/3rd that of mersalyl. It is very difficult to compare how it stands in comparison with other available thiazide diuretics as far as diuretic efficacy is concerned, as the methods used have been very different in other studies or in studies outside India where the reference drug was not mersalyl.

Our thanks are due to Ciba of India Limited, Bombay, for liberal supply of cyclopenthiazide (Navidrex*) and to Dr. G. Venning of G. D Searle & Co. High Wycombe, U. K., for the supply of spironolactone (Aldactone) used in this study.

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Hep. Cirrh., hepatic cirrhosis; Hyp., hypertensive; EH., enlarged heart; RSR., regular sinus rythm.