

A comparison of the use of Aldactone and Aldactone A in the treatment of hepatic ascites

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EDITORIAL SYNOPSIS In eight patients with cirrhosis and stable ascites controlled on chlorothiazide and spironolactone, a small particle preparation of spironolactone (Aldactone A) was as effective, at one quarter the dosage, as conventional spironolactone (Aldactone). Plasma spironolactone metabolite levels and urinary excretion of spironolactone metabolite were equivalent with both preparations. The variable dosage requirement of spironolactone in patients with cirrhosis and ascites is discussed in relation to these observations.

The use of the aldosterone antagonist, spironolactone, in the treatment of oedema associated with secondary hyperaldosteronism is now well documented, and it is recognized that better results are obtained when a thiazide or mercurial diuretic is combined with spironolactone (Clowdus, Higgins, Rosevear, and Summerskill, 1960; Morrison and Chalmers, 1960; Shaldon, McLaren, and Sherlock, 1960). A major disadvantage has been the high cost of prescribing spironolactone and this has been exaggerated by the variable dose required to produce a satisfactory sodium diuresis. With the original preparation of spironolactone (Aldactone), the lowest effective dose for patients with cirrhosis and ascites was 400 mg. daily, but 20 to 40% of patients requiring spironolactone needed 800 to 1,200 mg. daily (Shaldon, 1961). No benefit was found by increasing the dose above 1,200 mg. daily (Shaldon and Sherlock, 1962). More recently a new preparation of spironolactone (Aldactone A), designed to preserve the small particle size of the original chemical spironolactone, has become available. This preparation is claimed to be effective in one quarter of the dosage of the older preparation, 'Aldactone' (Gantt, Gochman, and Dyniewicz, 1962). This communication describes a comparison of the use of the two preparations in eight patients with cirrhosis of the liver and ascites who required spironolactone therapy.

MATERIAL AND METHODS

In all patients ascites had been well controlled on maintenance diuretic therapy of chlorothiazide and spironolactone with salt restriction (22 mEq. sodium

daily). The duration of maintenance diuretic therapy was two months to two years (Table I). All patients were known to be completely resistant to chlorothiazide alone and to retain sodium on dietary salt restriction (22 mEq. sodium) without diuretic therapy. The comparison between Aldactone and Aldactone A was made during periods when the patients had been admitted to hospital for reassessment of diuretic requirements.

The patients were put to bed and received daily 22 mEq. dietary sodium, 75 mEq. dietary potassium, and 45 to 104 mEq. supplementary potassium as potassium effervescent tablets (Hadgraft, 1960) and 60 to 80 g. protein. The fluid intake was measured but not restricted and the patients were weighed daily. Heparinized blood was taken daily at 10 a.m., four hours after spironolactone was given orally. Twenty-four-hour urine collections were made from 6 a.m. to 6 a.m. Plasma and urine samples were analysed spectrofluorometrically (Gochman and Gantt, 1962) for the pharmacologically active spiro lactone 3 (3 oxo-17-hydroxy-4, 6 androstadien 17 α -yl) propionic acid γ lactone, which is the major metabolite of spironolactone. Twenty-four-hour urinary sodium and potassium levels were estimated using an E.E.L. flame photometer.

A control period of three days was allowed in all patients, although no patient had received diuretic therapy for at least four days before the start of the control period. After the control period, four patients (cases 1, 3, 5, 7) were given a three-day course of Aldactone at their previous maintenance dosage of 400 to 1,200 mg. (Tables I and II) and chlorothiazide, 2 g. daily. This was followed by a three-day course of Aldactone A, 100 to 300 mg. daily, and chlorothiazide, 2 g. daily. The dose of Aldactone A was one quarter of the Aldactone dose in each patient. In the other four patients (cases 2, 4, 6, 8) Aldactone A and chlorothiazide preceded the Aldactone and chlorothiazide combination, otherwise the procedures were identical. The Aldactone

TABLE I

CLINICAL DATA AND PREVIOUS DIURETIC REQUIREMENTS OF EIGHT PATIENTS WITH CIRRHOISIS AND CONTROLLED ASCITES

Case No.	Age	Sex	Aetiology of Cirrhosis	Ascites	
				Duration of Control	Maintenance Diuretic Therapy (and 22 mEq. Na intake)
1	42	M	Alcoholic	2 mth.	Chlorothiazide 2 g. Aldactone 400 mg. } 4 days per week
2	45	M	Cryptogenic	3 mth.	Chlorothiazide 2 g. Aldactone 400 mg. } 3 days per week
3	59	F	Cryptogenic	2 yr.	Chlorothiazide 2 g. Aldactone 800 mg. } 5 days per week
4	36	F	Cryptogenic	3 mth.	Chlorothiazide 2 g. Aldactone 800 mg. } 5 days per week
5	60	M	Alcoholic	2 yr.	Chlorothiazide 2 g. Aldactone 1,200 mg. } 7 days per week
6	53	M	Cryptogenic	1 yr.	Chlorothiazide 2 g. Aldactone 1,200 mg. } 5 days per week
7	18	F	Cryptogenic	3 mth.	Chlorothiazide 2 g. Aldactone 1,200 mg. } 7 days per week
8	20	F	Cryptogenic	2 yr.	Chlorothiazide 2 g. Aldactone 1,200 mg. } 7 days per week

TABLE II

PLASMA SPIRONOLACTONE METABOLITE LEVEL AND 24-HOUR URINE VOLUME, SPIRONOLACTONE METABOLITE CONTENT, SODIUM AND POTASSIUM EXCRETION DURING A CONTROL PERIOD AND THREE-DAY COURSES OF ALDACTONE AND ALDACTONE A

Case No.	Spironolactone Dosage		Plasma Spironolactone Metabolite (µg./100 ml.)	24-Hour Urine			
	Aldactone (mg./day)	Aldactone A (mg./day)		Volume (ml.)	Spironolactone Metabolite ¹ (mg.)	Na (mEq.)	K (mEq.)
1	Control	—	0	1,000	0	0.6	70
	400	—	21.5	2,300	2.6	72	157
	—	100	18.5	1,820	2.5	81	139
2	Control	—	0	600	0	0.8	77
	—	100	11.0	1,770	12.6	72	128
	400	—	10.3	1,770	14.3	81	117
3	Control	—	0	1,000	0	1.0	42
	800	—	89.0	1,750	2.5	25	127
	—	200	89.0	1,800	3.2	36	116
4	Control	—	0	1,800	0	0.7	70
	—	200	80.5	2,510	5.1	100	169
	800	—	48.0	2,410	4.7	85	165
5	Control	—	0	600	0	0.6	70
	1,200	—	21.5	1,950	7.0	10	117
	—	300	27	2,000	7.4	15	118
6	Control	—	0	800	0	0.9	70
	—	300	46	2,330	16.5	62	120
	1,200	—	36.5	2,200	18.5	61	155
7	Control	—	0	500	0	0.8	55
	1,200	—	71	1,830	15.5	108	160
	—	300	76.5	1,850	18.0	115	158
8	Control	—	0	900	0	0.9	42
	—	300	108	1,770	14.1	219	172
	1,200	—	74.5	1,750	8.3	203	157

¹Plasma for spironolactone metabolite levels was obtained four hours after the daily dose of Aldactone or Aldactone A given orally. The results are the mean of three daily plasma levels during the control period and courses of Aldactone and Aldactone A.

and Aldactone A were given as one daily dose and chlorothiazide was given as 1 g. b.d. at 6 a.m. and 12 noon.

RESULTS

The results are all expressed as the mean value of three consecutive daily readings during control and treatment periods. The urinary sodium excretion for 24 hours averaged 1 mEq. or less in the control period for all patients (Table II, Fig. 1). No spironolactone metabolite was detectable in plasma or urine during the control period.

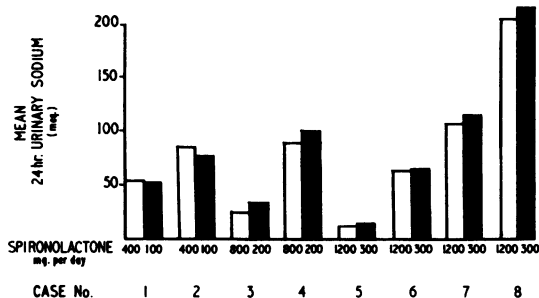


FIG. 1. The mean urinary sodium excretion during two three-day courses of spironolactone. The drug was given as Aldactone (unshaded bars) at maintenance diuretic doses (Table I) compared with one quarter of the dose given as Aldactone A (black bars). All patients received chlorothiazide, 2 g. daily, with each course of spironolactone.

All patients experienced a sodium diuresis when given Aldactone and chlorothiazide. Twenty-four-hour urinary sodium excretion varied from 10 to 203 mEq. There was no correlation between the quantity of sodium excreted and the dose of Aldactone, as the largest and the smallest sodium diuresis occurred in patients receiving 1,200 mg. Aldactone daily. There was no significant difference in the sodium excretion values for the three-day periods on Aldactone A at one quarter the dose of Aldactone whether the former preparation was given before or after the Aldactone course. All patients lost the weight which had accumulated in the period off diuretics and weight loss was unaffected by the type of Aldactone preparation.

Four-hour plasma spironolactone metabolite levels ranged from 10.3 to 74.5 μ g. per 100 ml. with Aldactone A. Twenty-four-hour urinary excretion of spironolactone metabolite ranged from 2.5 to 18.5 mg. for aldactone and 2.5 to 18.0 mg. for Aldactone A. The plasma levels of spironolactone

metabolite tended to increase with the dose of Aldactone or Aldactone A but the urinary excretion of the drug bore little relation to the administered dose. Both plasma and urinary levels were, however, comparable for the same patient when Aldactone and Aldactone A were each given for three-day periods (Fig. 2).

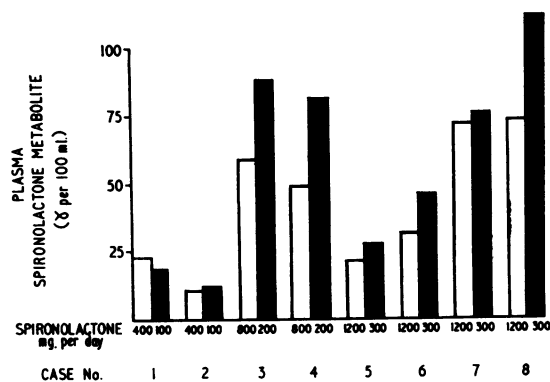


FIG. 2. The mean four-hour plasma spironolactone metabolite level during two three-day courses of spironolactone. The drug was given as Aldactone (unshaded bars) at maintenance diuretic doses (Table I) compared with one quarter of the dose given as Aldactone A (black bars). Both preparations were given as one daily dose at 6 a.m. All patients received chlorothiazide, 2 g. daily, with each course of spironolactone.

DISCUSSION

Aldactone A given in one quarter of the dosage of Aldactone has proved strictly comparable in regard to plasma levels of the drug, urinary excretion, and sodium diuretic effects. These results suggest that preservation of the small particle size of chemical spironolactone enhances the absorption of the drug at least fourfold. The results confirm the observation that a reduced dosage of the small particle preparation gave equivalent plasma levels to conventional Aldactone in normal subjects (Gantt *et al.*, 1962). The dose of spironolactone may now be reduced to one quarter, if Aldactone A is used and this should reduce the cost of spironolactone therapy considerably.

The reason why preservation of the small particle size of spironolactone enhances its absorption fourfold is not clear but presumably small particles are absorbed more rapidly and the disintegration time of the Aldactone A tablet is considerably shorter than that of the old Aldactone tablet (Gantt *et al.*, 1962). The addition of Tween 80, previously reported to enhance the absorption of spironolactone (Gantt, Gochman, and Dymiewicz, 1961), has now

been retracted (Gantt, *et al.*, 1962) as it appears that whilst encapsulating spironolactone with Tween 80 the small particle size was preserved and this was responsible for the improved absorption rather than the addition of the detergent itself.

The four-hour plasma level of spironolactone metabolite represents the peak concentration following oral administration of the drug (Gantt, Gochman, and Dyniewicz, 1961). The higher plasma values found in patients requiring larger doses of spironolactone (whichever preparation was used) suggests that poor absorption of the drug was not the principal cause of the need for the higher dosages. The possibility that such patients require larger doses of spironolactone to inhibit higher effective rates of aldosterone production seems more likely.

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REFERENCES

- Cloudus, B. F., Higgins, J. A., Rosevear, J. W., and Summerskill, W. H. J. (1960). Treatment of 'refractory' ascites with a new aldosterone antagonist in patients with cirrhosis. *Proc. Mayo Clin.*, 35, 97-105.
- Gantt, C. L., Gochman, N., and Dyniewicz, J. M. (1961). Effect of a detergent on gastrointestinal absorption of a steroid. *Lancet*, 1, 486-487.
- , Gochman, N., and Dyniewicz, J. M. (1962). Gastrointestinal absorption of spironolactone. *Ibid.*, 1, 1130-1131.
- Gochman, N., and Gantt, C. L. (1962). A fluorimetric method for the determination of a major spironolactone (Aldactone) metabolite in human plasma. *J. Pharmacol.*, 135, 312-316.
- Hadgraft, J. W. (1960). Preparations for water and electrolyte balance. *Pharm. J.*, 184, 277-279.
- Morrison, R. S., and Chalmers, T. C. (1960). Combined diuretic and steroid therapy in cirrhosis with ascites. *Ann. N.Y. Acad. Sci.*, 88, 907-914.
- Shaldon, S. (1961). The clinical application of aldosterone antagonists in the treatment of oedema. *Proc. roy. Soc. Med.*, 54, 259-261.
- , McLaren, J. R., and Sherlock, S. (1960). Resistant ascites treated by combined diuretic therapy (spironolactone, mannitol and chlorothiazide). *Lancet*, 1, 609-613.
- , and Sherlock, S. (1962). Aszitesbehandlung bei Patienten mit Leberzirrhose. *Med. Klin.*, 57, 1317-1320.