SPIRONOLOACTONE AS AN ADJUVANT TO THE TREATMENT OF CONGESTIVE CARDIAC FAILURE

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The co-administration of an aldosterone antagonist and a thiazide diuretic has been consistently effective in the treatment of cirrhotic oedema and ascites (Gantt and Dyniewicz, 1959; Ogden, Scherr, Spritz and Rubin, 1961; Shaldon, 1961). In renal oedema too, success has attended the use of spironolactone (Manning and Behle, 1961). In both of these conditions independent evidence implicates secondary hyperaldosteronism in the causation of the oedema. In the treatment of congestive heart failure, however, spironolactone has frequently disappointed and it has been suggested that it is less likely to be successful here because aldosterone probably plays an unimportant role in this condition (British Medical Journal, 1961).

Our own clinical impression regarding the efficacy of spironolactone as a diuretic seemed to accord with published reports such as those of Edmonds (1960), Farrelly, Howie and North (1960), and Stewart and Constable (1961): it seemed that the addition of spironolactone to thiazide or chlorothalidone therapy regularly resulted in a diminution of urinary potassium loss, and often increased sodium excretion to some extent, but only occasionally helped appreciably in the removal of oedema.

Exceptionally, however, we had seen striking responses to the addition of spironolactone, with rapid disappearance of oedema and ascites which had previously been accumulating steadily in spite of thiazide, chlorothalidone or mercurial therapy. The observation that some of these cases began to respond four, or even five days after starting spironolactone led us to believe that its 'latent period' might be much longer than the 24 to 48 hours usually quoted (Thomas and Bartter, 1961; Brit. med. f., 1961). It therefore appeared that spironolactone might not have been given a fair trial when used for less than a week at a time and we decided to review our results with this in mind.

Relatively few cases were found in which spironolactone had been given continuously for a week, after a similar control period during which they had gained weight on standard diuretic therapy; but comparison of their weight changes before and after the commencement of spironolactone caused us some surprise.

Material and methods

Two hundred and four episodes of congestive cardiac failure were treated in one ward of this hospital between October 1959 and September 1962. In 44 of these spironolactone had been given as part of the in-patient treatment. In only 14 instances, however, had it been given continuously for a week without other relevant changes in therapy and following a comparable control period. In two of these 14 weight loss occurred during the control period and in two others spironolactone had been given as the sole diuretic; these four were excluded from the present study.

There remained nine patients (representing 10 episodes of failure) with control periods of at least a week during which weight was gained on chlorothiazide (seven cases), mercurial injections (two cases) or chlorothalidone (one case), and who then received spironolactone as additional diuretic therapy without other changes in the régime. These 10 episodes of more or less resistant heart failure form the basis of this study.

All these patients were fully digitalized and were treated in bed on a low-salt diet, without fluid restriction, throughout the study period.

Those on thiazides were given potassium supplements, usually in the form of potassium chloride, 1 g. two or three times a day.

Eight suffered from chronic rheumatic heart disease (three male, five female) and one (male) from cor pulmonale. In addition to their peripheral oedema, three patients, representing four admissions, had obvious ascites; the serum albumin level was reduced to 3 g./100 ml. in two instances and 2.7 g./100 ml. in one.

The daily dosage of spironolactone was 400 mg. on seven occasions, 300 mg. on one occasion and 200 mg. in one other case. The readmitted patient received Aldactone 'A' (Searle), 100 mg. daily (equivalent to 400 mg. daily of the earlier spironolactone) during his second course of treatment.

Each patient was weighed daily on the same scales and records of urinary output and fluid intake were kept. Serum urea was estimated thrice weekly and serum electrolytes at least once a week. Complete urinary electrolyte data were obtained in only two cases.

Results

Fig. 1 shows the average daily weight gain in each case prior to the addition of spironolactone compared with the rate of weight change while on the aldosterone antagonist. It will be seen that in all but two cases, weight loss occurred while on spironolactone, and in the two exceptions the rate...
of weight gain became slower. Where weight loss occurred it was usually unspectacular, but in four instances rapid weight loss ensued and the concurrent loss of oedema fluid was in itself impressive. Two of the patients in whom the best responses were seen had gross ascites.

Figs. 2(a) and 2(b) show the mean daily urinary output plotted against mean daily fluid intake in eight instances during the control periods and spironolactone treatment periods respectively. Incomplete urinary collections precluded the charting of data for the remaining two cases. On each graph is reproduced the regression line relating urinary output to fluid intake in 25 patients without cardiac, renal or hepatic disease and without disturbances of fluid or electrolyte metabolism (Domenet, Evans and Brenner, 1961).

The addition of spironolactone to the diuretic regime resulted in increased urinary output in all cases and it will be seen that concomitantly their fluid intake increased to a much lesser extent.

**Urinary Electrolyte Changes**

Complete data are available for only two cases. In case (1) the basic diuretic therapy was hydroflumethiazide and in case (2), chlorothiazide. The addition of spironolactone increased the daily excretion of sodium and raised the Na:K ratio in both cases, as can be seen from Table 1.

**Serum Electrolytes and Urea**

Three cases showed abnormalities during the study period. In two of these the serum sodium concentration fell (from 137 to 126 mEq/l., and from 136 to 128 mEq/l., respectively) when spironolactone was added; in one the serum sodium rose from 130 to 138 mEq/l., while serum potassium rose from 4.6 to 5.5 mEq/l. Serum urea levels remained below 70 mg./l00 ml. throughout the study period in all cases.

**Illustrative Example**

Fig. 3 shows graphically the effect of adding spironolactone (Aldactone 'A' (Searle), 25 mg., q.d.s.) to a régime including bed-rest, digoxin, chlorothiazide and a low-sodium diet. The patient was a 53-year-old male suffering from congestive failure due to chronic rheumatic heart disease, and ascites was a prominent feature.

**Discussion**

In most patients with cirrhotic and nephrotic oedema the combined use of spironolactone and another diuretic is more effective than the use of either measure alone. This finding has been explained in terms of their action on the kidney (Pitts, 1959; Beyer and Baer, 1961). Spirono-
lactone is believed to block the activity of aldosterone in the distal tubule of the nephron (Gant and Dyniewicz, 1959; Mills, Thomas and Williamson, 1962), while thiazide derivatives, chlorthalidone and mercurial diuretics lessen re-absorption of sodium from the proximal tubule. However, it may be that the extrarenal effects of these drugs are of much greater importance than has hitherto been thought.

It has been widely held that, in congestive heart failure, the addition of spironolactone to chlorothiazide or other diuretic therapy, only rarely produces obvious clinical benefit, and it therefore seemed that secondary hyperaldosteronism might be relatively unimportant in this condition. Our experience appeared at first to accord with this view. Nevertheless there were occasional dramatic responses (as noted also by Heller, 1962) in terms of weight loss and clearing of edema, and it seemed that those cases in which ascites was a prominent feature might be the ones in which such favourable effects were most likely to occur. It was also noted that response to the addition of spironolactone sometimes occurred as late as the fourth or fifth day of its administration, a finding also reported by Perrin and Froment (1961) and Etienne-Martin, Klepping, Guerrin and Beaufils, (1962). Accordingly our records were searched in an attempt to re-appraise the efficacy of spironolactone when given for an adequate period and to see if the presence of cardiac ascites determined the likelihood of a favourable outcome.

To our surprise, the results of this search indicate that, in the group of patients studied, spironolactone always reduced the rate of weight gain (i.e. accumulation of edema) when added to thiazide or other diuretic therapy and with only two exceptions transformed weight gain into weight loss. Three of the patients had obvious ascites, including two of those who showed the most dramatic responses (one during each of two separate admissions). When spironolactone was added, mean daily urinary output was increased in all cases for whom data were available, and daily sodium excretion was also increased in the two cases in which it was studied. Urinary potassium loss was decreased in one case and increased in the other.

Thus it appears that, when given adequate time, spironolactone does assist in the treatment of congestive heart failure. Aldosterone may therefore play an important part in this condition. Our

**Table 1**

<table>
<thead>
<tr>
<th>Case</th>
<th>Etiology</th>
<th>Dietary Na (mEq/day)</th>
<th>Supplemental K (mEq/day)</th>
<th>Urinary excretion (mEq/day) Na</th>
<th>Urinary excretion (mEq/day) K</th>
<th>Urinary Ratio Na : K</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cor pulmonale</td>
<td>10</td>
<td>90</td>
<td>15</td>
<td>64</td>
<td>0.38 : 1</td>
</tr>
<tr>
<td>2</td>
<td>Rheumatic heart disease</td>
<td>30</td>
<td>26</td>
<td>4</td>
<td>20</td>
<td>0.13 : 1</td>
</tr>
</tbody>
</table>

**FIG. 3.—**The effect of adding spironolactone to chlorothiazide in treatment of severe congestive failure due to chronic rheumatic heart disease.
earlier impression that spironolactone was ineffective derived largely from experience of those cases—often very seriously ill and rapidly deteriorating—in which it had been given only for a day or two before some other change in treatment was made, or death supervened. Perhaps other observers' conclusions regarding the inefficacy of spironolactone were similarly based on study periods too short to allow for its long latent period.

It is unlikely that spironolactone’s extra help will be found necessary in the management of most cases of cardiac failure, for whom the older, well-tried, and cheaper diuretics are usually perfectly adequate. In the resistant case, and perhaps particularly where ascites is a feature, spironolactone should, however, be tried. We are not convinced that it promotes hyponatraemia or hyperkalaemia in such patients. It has been shown (Flear, 1960) that both are consequences of disease and its progression rather than complications of treatment given. Low serum levels of sodium are met in patients with long-standing heart-disease who have never been in failure, as well as in patients in congestive heart failure who have never received either diuretics or a diet low in sodium.

In our overall experience of spironolactone therapy for congestive heart failure, the only side-effects we have felt attributable to this drug are a rise in blood urea and mental confusion. These phenomena may occur spontaneously during the course of heart failure or may be provoked by the administration of any diuretic. When mental confusion has appeared during spironolactone therapy it has sometimes quickly cleared on stopping the drug.

Summary

During 10 courses of treatment administered to nine patients with congestive cardiac failure, spironolactone was added to thiazide, mercurial or chlorothalidone therapy after control periods during which oedema continued to accumulate. In all cases the spironolactone was given for at least a week, no change being made in the other diuretic therapy.

As judged by weight changes, the addition of spironolactone reduced the rate of oedema accumulation in two cases and caused frank loss of oedema fluid in the other eight. Urinary output was increased in the eight cases for whom data are available.

Response to spironolactone, in terms of weight loss and diuresis, was frequently delayed beyond the third day of treatment and if this 'latent period' applies generally in cases of heart failure it may explain the earlier erroneous clinical impression that spironolactone is largely ineffective in this condition.

Our thanks are due to Dr. O. Brenner for permission to study patients under his care and for much helpful criticism and advice.

REFERENCES


Spironolactone as an Adjuvant to the Treatment of Congestive Cardiac Failure
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Postgrad Med J 1964 40: 11-14
doi: 10.1136/pgmj.40.459.11

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