SPIRONOLACTONE AND AMILORIDE IN THE TREATMENT OF LOW RENIN HYPERALDOSTERONISM AND RELATED SYNDROMES


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SUMMARY

1. Prolonged treatment with spironolactone in low-renin hyperaldosteronism invariably corrects plasma electrolyte abnormalities and usually lowers blood pressure.

2. Total exchangeable sodium, total body water, extracellular fluid and plasma volumes are reduced; total exchangeable and total body potassium, plasma renin and angiotensin II concentrations are increased.

3. Spironolactone is similarly effective in patients with apparently isolated deoxycorticosterone (DOC) excess; also in suspected mineralocorticoid excess not associated with elevation of aldosterone or DOC.

4. Studies of amiloride reveal similar effectiveness to spironolactone in low-renin hyperaldosteronism and in suspected mineralocorticoid excess.

Key words: spironolactone, amiloride, hypertension, sodium, potassium, renin, angiotensin, aldosterone, deoxycorticosterone.

The value of prolonged treatment with the aldosterone antagonist spironolactone in patients with hypertension, aldosterone excess and low plasma renin has been shown in several studies (Brown, Davies, Lever, Peart & Robertson, 1965; Spark & Melby, 1968; Crane & Harris, 1970; Brown, Ferriss, Fraser, Lever & Robertson, 1971b; Brown, Davies, Ferriss, Fraser, Haywood, Lever & Robertson, 1972a). Blood pressure is usually lowered, the potassium deficiency corrected, and the elevated total exchangeable sodium reduced. Plasma electrolyte abnormalities are consequently also corrected and the depressed plasma renin and angiotensin II concentrations restored to normal or even occasionally high values.

In a detailed study of a single patient with low renin hyperaldosteronism, prolonged treatment with amiloride, a potassium-conserving diuretic which acts independently of aldosterone, led to similar correction of hypertension and biochemical abnormalities (Kremer, Brown, Davies, Fraser, Lever & Robertson, 1973).

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In the present paper, our experience of the use of prolonged spironolactone therapy in patients with low renin hyperaldosteronism and related syndromes of mineralocorticoid excess is reviewed. We also present data on the use of amiloride in a smaller series of similar patients.

PATIENTS AND METHODS

Initial diagnostic data were obtained in the metabolic ward while the patients consumed a diet of known and constant sodium and potassium content, fixed at a value within the ranges Na 120–150, K 40–89 mEq daily (in some of the early studies in the spironolactone-treated group a normal ward diet was taken; Brown et al., 1972a). No dietary restrictions were imposed when the patients left hospital. No patient had received diuretics, potassium supplements, oral contraceptives, carbenoxolone or liquorice for at least 4 weeks before any of the investigations reported here. No hypotensive agents other than spironolactone or amiloride were used in any of the present studies.

Peripheral venous blood samples for estimation of electrolytes, renin, angiotensin II and steroids were taken between 08.30 and 10.00 hours after overnight recumbency and fasting. Various biochemical measurements and estimations of total exchangeable sodium (Na\(_E\)), total exchangeable potassium (K\(_E\)) and total body potassium (K\(_T\)) were performed as detailed elsewhere (Brown et al., 1972a; Brown, Ferris, Fraser, Lever, Love, Robertson & Wilson, 1972b; Davies & Robertson, 1973).

Spironolactone (‘Aldactone-A’; Searle), 50–400 mg daily, was given by mouth, dosage short of the maximum being used if blood pressure control was satisfactory or if side-effects were limiting.

In other instances amiloride (‘Midamor’; Merck, Sharp & Dohme) was introduced after an initial period of out-patient observation without therapy, initially in a dose of 10 mg daily, increasing each week by 10 mg daily to a maximum of 40 mg daily.

In eight patients, separate courses of amiloride and spironolactone were given. After at least 4 weeks on the final full dose of either drug, patients were re-admitted and again assessed under controlled dietary circumstances as before.

The blood pressure readings reported are restricted to those obtained under out-patient conditions with the patient seated. In the study of amiloride, the sphygmomanometer devised by Rose, Holland & Crowley (1964) was employed so as to minimize observer bias.

The following diagnostic groups emerged from the initial diagnostic procedures (Table 1).

*Hyperaldosteronism with low renin*

Seventy-two patients had hypertension, abnormally high plasma aldosterone (>18 ng/100 ml) on at least one occasion and concurrent plasma renin concentration either subnormal (fifty-five cases) or in the lower part of the normal range. In thirty-eight cases the adrenals were explored; twenty-three had a unilateral adrenocortical adenoma; fifteen bilateral adrenocortical nodular hyperplasia.

*Apparently isolated deoxycorticosterone (DOC) excess*

Five patients with hypertension had intermittently or persistently subnormal plasma renin concentration and intermittently subnormal plasma potassium. In these, however, plasma aldosterone was repeatedly within the normal range. All had persistently elevated plasma
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deoxycorticosterone levels. The adrenals were examined subsequently in one of these patients, histology revealing bilateral nodular hyperplasia.

Suspected mineralocorticoid excess

Eight hypertensive patients resembled the previous two groups regarding hypokalaemia and low renin levels, but in these plasma aldosterone and DOC levels were found to be normal.

RESULTS

Spironolactone

The results are given in Table 1.

Low renin hyperaldosteronism (see also Brown et al., 1972a). Spironolactone produced a highly significant reduction in both systolic and diastolic pressure, being equally effective in patients with, as in those without, adrenocortical adenomata. Occasional unresponsive patients

| Table 1. Changes induced by treatment with spironolactone and amiloride |
|------------------|------------------|------------------|------------|------------------|
|                  | Systolic (mmHg) | Diastolic (mmHg) | Plasma     |                 |
|                  | B               | D               | P          |                  |
| Spironolactone   |                 |                 |            |                  |
| Aldo. excess; Low renin (n = 67) | 201 (2.9) | 149 (3.3) | <0.001 | 122 (1.5) | 97 (1.8) | <0.001 | 142.3 (0.36) | 138.3 (0.36) | <0.001 | 3.1 (0.09) | 4.5 (0.05) | <0.001 |
| DOC excess (n = 5) | 193 (13.2) | 137 (6.4) | <0.001 | 123 (6.8) | 95 (4.2) | <0.001 | 142.0 (0.35) | 138.7 (2.07) | <0.001 | 3.4 (0.05) | 4.3 (0.10) | <0.001 |
| Suspect mineralocorticoid excess (n = 8) | 191 (12.3) | 142 (6.2) | <0.002 | 117 (5.7) | 95 (3.1) | <0.005 | 142.2 (0.84) | 137.5 (0.44) | <0.001 | 3.5 (0.21) | 4.6 (0.26) | <0.001 |
| Amiloride         |                 |                 |            |                  |
| Aldo. excess; Low renin (n = 5) | 185 (5.7) | 160 (7.8) | <0.002 | 113 (2.6) | 97 (3.3) | <0.002 | 142.9 (2.69) | 139.6 (2.35) | <0.001 | 2.9 (0.15) | 4.5 (0.07) | <0.001 |
| Suspect mineralocorticoid excess (n = 5) | 173 (4.1) | 154 (2.4) | <0.001 | 109 (4.4) | 92 (1.9) | <0.001 | 140.9 (0.40) | 139.3 (0.36) | <0.001 | 3.6 (0.14) | 4.6 (0.09) | <0.001 |

Table 1 (contd)

| Plasma |
|------------------|------------------|------------------|------------|------------------|
| Urea (mg/100 ml) | Renin (units/l) | Angiotensin II (pg/ml) | NaRE (mEq) | K (mEq) |
| B | D | P | B | D | P | B | D | P | B | D | P |
| 35.2 | 49.8 | <0.001 | 4.8 | 19.4 | <0.001 | 5.3 | 43.2 | <0.05 | 2967 | 2494 | <0.001 |
| (1.6) | (2.8) | | (0.3) | (2.6) | | (0.6) | (7.7) | | (110) | (99) | |
| 31.6 | 40.7 | <0.01 | 4.5 | 21.8 | <0.001 | — | — | — | 26 | 286 | <0.05 |
| (1.5) | (2.7) | | (0.3) | (10.8) | | | | | (219) | (342) | |
| 33.3 | 52.2 | <0.001 | — | — | — | 5.9 | 10.6 | <0.001 | 2956 | 2675 | <0.01 |
| (1.3) | (2.6) | | | | | (0.6) | (1.3) | | (169) | (131) | |
| 34.2 | 45.4 | <0.001 | 7.6 | 33.8 | <0.001 | — | — | — | 2795 | 2977 | <0.05 |
| (1.2) | (1.6) | | (0.8) | (4.2) | | | | | (213) | (225) | |

Means (± SEM). B = before treatment; D = during treatment. Comparisons by t-test. Only changes with P < 0.05 shown.
were seen in both groups; pre-treatment blood urea levels were in these significantly higher than in the responsive patients. The hypotensive effect of spironolactone usually predicted accurately the subsequent response to adrenal surgery. Plasma electrolyte abnormalities were corrected in all cases; significant increases in $K_E$ and $K_T$ and significant reductions in $Na_E$, total body water, extracellular fluid and plasma values were seen. Plasma urea rose during treatment and body weight fell slightly. Marked increases in plasma renin and angiotensin II, and less consistent increases in plasma aldosterone, occurred.

Apparently isolated DOC excess (see also Brown et al., 1972b). A clear fall in blood pressure occurred in each of the patients treated with spironolactone. Plasma electrolyte abnormalities were corrected in all, whereas plasma urea and renin concentrations increased significantly.

Suspected mineralocorticoid excess. Plasma electrolyte abnormalities were corrected in all eight patients in this group, and in six of the eight there was also a good hypotensive response, diastolic pressure falling to 95 mmHg or less (Beevers, Brown, Ferris, Fraser, Lever & Robertson, 1973).

Side effects. The side effects induced by spironolactone included gynaecomastia, epigastric discomfort, Raynaud's phenomenon, menstrual irregularities, lassitude, cutaneous pigmentation, excessive sweating and impotence (Brown et al., 1971b). Hyperkalaemia was a danger in patients with renal impairment. Only in two cases were side effects sufficiently severe to lead to withdrawal of the drug.

Amiloride

Low renin hyperaldosteronism. Five patients have so far been studied, including the one previously reported in detail (Kremer et al., 1973). Hypokalaemia was corrected in all, and three also showed a distinct fall in $Na_E$, with a rise in $K_E$ and $K_T$. Plasma renin concentration rose to a mean value in the middle of the normal range. Three of the five had significant individual reductions in systolic and diastolic pressures.

One woman had previously responded well to spironolactone (300 mg daily); subsequent treatment with amiloride (40 mg daily) maintained a mean blood pressure of 137/91 mmHg. A single adrenocortical adenoma was later removed from this patient who currently has normal blood pressure and plasma electrolyte values without further treatment.

Another (male) patient showed no hypotensive response to 40 mg of amiloride daily, despite the expected correction of $Na_E$, $K_E$, $K_T$ and plasma electrolytes. Spironolactone (400 mg daily) was similarly without effect on the arterial pressure. A total left and subtotal right adrenalectomy was performed for bilateral micronodular hyperplasia. Post-operative measurements of plasma electrolytes and aldosterone have been normal, but the blood pressure remains unchanged.

Suspected mineralocorticoid excess. Significant lowering of systolic and diastolic pressure was also observed in this group. Plasma electrolyte abnormalities were corrected whereas urea and renin concentrations rose significantly.

The pooled data on $Na_E$, $K_E$ and $K_T$ for all ten patients treated with amiloride are given in Table 1. In addition, mean plasma bicarbonate fell, whereas plasma chloride, angiotensin II and aldosterone rose, but with the small number of patients studied, these changes were not statistically significant in the group as a whole.

Side effects. No side effects have so far been noted in patients receiving amiloride.
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DISCUSSION

These studies have shown that prolonged therapy with large doses of spironolactone, a steroidal lactone, is effective in correcting the electrolyte abnormalities of patients with either adrenocortical aldosterone-secreting adenomata, or bilateral adrenocortical hyperplasia. Blood pressure is also usually lowered, the pre-operative hypotensive response predicting the subsequent effect of adrenal surgery. Spironolactone is therefore used routinely as a pre-operative measure and may also be employed long-term in patients unsuitable or unwilling to undergo surgery.

Spironolactone is similarly effective in patients with DOC excess, and in those in whom both plasma aldosterone and DOC are normal, but where low plasma renin and potassium concentrations suggest excess of an unidentified mineralocorticoid.

The results in more limited studies of amiloride, a diuretic which acts independently of aldosterone, indicate that this agent can also be effective in such patients and may be useful as alternative therapy, particularly when side effects of spironolactone are troublesome. The results further suggest that mineralocorticoid excess causes hypertension via changes in electrolyte (and particularly sodium) balance and/or distribution (see Brown, Düsterdieck, Fraser, Lever, Robertson, Tree & Weir, 1971a; Brown, Fraser, Lever & Robertson, 1971c; Davies, Beevers, Brown, Fraser, Ferriss, Lever, Medina, Morton & Robertson, 1973).

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