ANTIHYPERTENSIVE EFFECT OF SPIRONOLACTONE IN ESSENTIAL, RENAL AND MINERALOCORTICOID HYPERTENSION

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SUMMARY

1. The hypotensive effect of spironolactone has been studied in twenty-four patients with various forms of hypertension.
2. In essential hypertension a greater fall of blood pressure was achieved in patients with renin activity hypo-responsive to postural change than in those in whom renin responded normally to posture.
3. A poor hypotensive response was observed in patients with renal or renal arterial disease and secondary aldosteronism.
4. The variable hypotensive response seen in patients with primary aldosteronism predicted the response to adrenal surgery.
5. Blood pressure was not lowered by spironolactone in one case of 17-hydroxylation deficiency or in one case of malignant ovarian arrhenoblastoma producing aldosterone.

Key words: hypertension, spironolactone, plasma renin activity, aldosterone, primary aldosteronism, 17-hydroxylase.

Spironolactone has been reported to have only a modest effect in lowering the blood pressure in essential hypertension (Wolf, Mendlowitz, Roboz, Styan, Kornfeld & Weigl, 1966; Johnston & Grieble, 1967; Winer, Lubbe & Colton, 1968). During the last few years the finding of an unexpected high incidence of suppressed renin activity in essential hypertension (Jose, Crout & Kaplan, 1970; Williams, Rose, Dluhy, McCaughn, Jagger, Hickler & Lauler, 1970; Crane, Harris & Johns, 1972) supported speculations on the role of mineralocorticoids on the pathogenesis of this form of hypertension. It has been shown (Crane & Harris, 1970; Spark & Melby, 1958) that these patients respond to high doses of spironolactone with normalization of blood pressure. Further, aminogluthethimide, an adrenocortical inhibitor, has also been found to have an antihypertensive effect in a similar group of patients (Woods, Liddle, Mikelakis & Brill, 1969).

Forms of hypertension certainly due to a mineralocorticoid excess include primary aldosteronism. Correspondence: Dr F. Mantero, Istituto di Semeiotica Medica della Universita di Padova, Italy.
steronism (adenoma and bilateral hyperplasia), 17α- and 11β-hydroxylase deficiency syndromes, selected cases of Cushing's syndrome, and very rare malignant tumours producing mineralocorticoids. Spironolactone is usually effective in such cases in correcting the metabolic abnormalities, although good control of the high blood pressure is not always achieved (Bartter, 1966; Spark & Melby, 1958). Hypertension with secondary aldosteronism does not usually respond to spironolactone (Laidlaw, Yendt, Bird & Gornall, 1964).

We present here the results of our experience in the treatment with spironolactone of various groups of hypertensive patients.

PATIENTS AND METHODS

The patients comprised twelve cases of essential hypertension, four cases of hypertension with renal disease, seven cases of primary aldosteronism, one case of malignant ovarian arrhenoblastoma, and one case of 17α-hydroxylase deficiency syndrome.

Plasma renin activity was measured either by bioassay by the method of Boucher, Veyrat, de Champlain & Genest (1964) (normal mean and range: 9.0±7.6 ng l⁻¹ min⁻¹), or by radioimmunoassay of generated angiotensin I (by the method of Stockigt, Collins & Biglieri, 1971), modified (normal range: 0.57±0.23 ng ml⁻¹ h⁻¹). Aldosterone excretion was determined by isotope derivative dilution assay (Kliman & Peterson, 1960) (normal range: 4–15 μg/24 h).

RESULTS

Essential hypertension

Twelve patients, considered by the usual criteria to have essential hypertension, showed two distinct patterns of plasma renin activity in response to the upright posture. Six patients had a normally elevated plasma renin activity after 3 h standing, with a mean and range of 1.78±0.17 ng ml⁻¹ h⁻¹, whereas in the other six patients the plasma renin activity remained at recumbent levels, averaging 0.64±0.12 ng ml⁻¹ h⁻¹. The two groups did not differ in regard to aldosterone excretion, which was normal in both, with means respectively of 7.0±1 and 9.0±2 μg/24 h. Serum sodium (respectively 145±3 and 142±6 mEq/l) and serum potassium (3.9±0.5 and 3.9±0.4 mEq/l) were also not significantly different in the two groups. However, both systolic and diastolic blood pressures were higher in the normal renin group, averaging 200±13/121±7 compared with 180±15/107±7 mmHg in the low-renin group; only the diastolic pressure was significantly different (P<0.05).

In all twelve patients, treatment with 400 mg of spironolactone/day (Aldactone, Lepetit) was started during hospitalization, and continued at home until the end of the fourth week. In all the patients with hyporesponsive plasma renin activity normal blood pressure was achieved during treatment. In two cases 1 week was sufficient to reduce the blood pressure to normal levels. The mean overall blood pressure after 4 weeks of high dose treatment was 132±5/86±6 mmHg. There was a mean weight loss of 3.1±2 kg. Reduction of the dose to 100 mg/day was followed by a prompt rise of the blood pressure in all but one case.

In the patients with normal renin responsiveness, spironolactone in high dose produced a variable fall of the blood pressure, but in no case was normal pressure reached. The mean blood pressure after treatment was 170±9/104±6. Weight loss was minimal in this group, ranging from 0 to 2.2 kg in all but one patient who lost 6 kg. The mean weight loss was 2.1±2 kg.
Both groups showed a non-significant decrease of serum sodium, but a significant increase of serum potassium to 5.3±0.4 and 4.9±0.6 mEq/l, respectively. Marked hyperkalaemia occurred in one patient of each group.

**Hypertension with renal disease**

Spironolactone has also been given to four hypertensive patients who presented parenchymal or vascular renal disease.

Patient Z.L. (male 34 years) had a positive urine culture and a small left kidney; hypertension was very severe (215/140 mmHg). Renal function was not grossly impaired and blood urea was normal. Plasma renin activity was slightly elevated (2.73 ng ml⁻¹ h⁻¹) and urinary aldosterone normal (9.98 μg/24 h). Spironolactone (400 mg/day) produced a slow but progressive fall in blood pressure, which was 140/100 mmHg after 4 weeks, together with weight loss (4 kg). Severe hyperkalaemia occurred. Reduction of the dose to 200 mg was followed by a prompt rise of the blood pressure to pretreatment values.

Patient C.M. (female, 46 years) had fibromuscular right renal artery stenosis; blood pressure was 190/100 mmHg. Both peripheral and bilateral renal vein plasma renin activities were low (respectively 0.53; 0.77; 0.79 ng ml⁻¹ h⁻¹) and aldosterone excretion was normal (9.43 μg/24 h). Spironolactone (400 mg/day) was very effective and the patient became normotensive after 1 week on medication. A dose of 200 mg/day was then sufficient to maintain an acceptable level of blood pressure. The results of the renal vein renin assays and the effectiveness of spironolactone in our view contraindicated operation.

Patient G.P. (female, 40 years) had fibromuscular dysplasia of the left renal artery. Peripheral plasma renin activity (3.75 ng ml⁻¹ h⁻¹) and urinary aldosterone (20.55 μg/24 h) were increased; serum potassium was low. Spironolactone (400 mg/day for 3 weeks) corrected the hypokalaemia but did not affect the blood pressure; further, the hypertension persisted also after the surgical correction of the stenosis, with a good renal revascularization. No hypotensive effect was obtained by a further trial with spironolactone.

Patient B.P. (female, 46 years) had bilateral arteriosclerotic renal artery stenosis; peripheral plasma renin activity was elevated (2.97 ng ml⁻¹ h⁻¹) and aldosterone normal (10.51 μg/24 h). During 3 weeks' treatment with spironolactone (400 mg/day) only minimal changes in her blood pressure were seen.

**Primary aldosteronism**

We have also studied seven patients with primary aldosteronism. Three had a right adrenal adenoma, two had a left adrenal adenoma and one had two adenomas in the left adrenal gland. In two cases the contralateral gland was hyperplastic. The seventh case probably has 'idiopathic aldosteronism.'

The short-term spironolactone test (6 days) was in every case very effective in the normalization of the serum potassium, from a mean of 2.5±0.4 to 3.8±0.1 mEq/l, but not sufficient to induce an effect on blood pressure. Long-term treatment was accomplished in four cases.

In patient S.R. (male, 30 years), the adenoma was localized by selective adrenal venography; blood pressure was 220/130 mmHg, serum potassium 2.7 mEq/l, plasma renin activity (standing) was 0.24 ng ml⁻¹ h⁻¹, and urinary aldosterone 48.58 μg/24 h. With spironolactone (400 mg/day) we obtained normotension in 8 days. To exclude the possibility that venography could have been responsible for the fall of the blood pressure (as in the case described by
spironolactone was stopped for a few days, when the blood pressure rose promptly, becoming normal again after treatment was restored. A noteworthy finding was the normal value of aldosterone excretion after 4 weeks of treatment (11.20 μg/24 h). Within 2 days after the left adrenalectomy blood pressure fell to 135/85 mmHg and has remained normal.

In another patient (L.L., female, 44 years), who had a blood pressure of 215/125 mmHg, undetectable plasma renin activity, and elevated urinary aldosterone (33-76 μg/24 h), the success of treatment with spironolactone (400 mg/day for 18 days) in reducing the blood pressure to normal levels was followed by the normalization of the pressure after left adrenalectomy; two adenomas were found.

In the patient C.E. (female, 46 years), who had a blood pressure of 215/140 mmHg, plasma renin activity (14 ng l⁻¹ min⁻¹) was not suppressed, and aldosterone excretion was 20.37 μg/24 h. Spironolactone (500–800 mg/day) and aminoglutethimide (500–1000 mg/day) for 10 days each, had only mild antihypertensive effect, whereas serum potassium rose promptly. After removal of the right adrenal gland, containing an adenoma, serum potassium became normal, as did aldosterone excretion (5.6 μg/24 h). However, the blood pressure remained elevated (165/110 mmHg) after 1 year of follow up, and was not affected by a further trial with spironolactone.

Patient Z.R. (female, 36 years) had a blood pressure of 160/110 mmHg, undetectable plasma renin, and aldosterone excretion of 71.3 μg/24 h; normotension was obtained after 15 days of treatment with first 200 mg (7 days) and then 400 mg of spironolactone. After removal of one adrenal, which was grossly normal, hypokalaemia and hypertension persisted, but urinary aldosterone fell to a value of 28.2 μg/24 h. The patient is maintained normokalaemic with 200 mg of spironolactone/day, although the blood pressure is now slightly elevated, after 1 year of treatment. The patient refuses right adrenal exploration.

Other cases

Finally, we present here two rare examples of mineralocorticoid hypertension, where spironolactone has been administered for diagnostic or therapeutic purposes.

The case of 17α-hydroxylase deficiency syndrome was a genetic male, characterized by pseudohermaphroditism, severe hypertension (200/140 mmHg), hypokalaemic alkalosis, very low cortisol levels (0.4 μg/100 ml of plasma), low 17-hydroxylated steroids, including sexual hormones, high plasma corticosterone (26.8 μg/100 ml) and high tetrahydrodeoxycorticosterone (780 μg/24 h). Plasma renin activity was suppressed, and urinary aldosterone very low. On normal sodium intake, 15 days of treatment with spironolactone (600 mg/day) had no effect on blood pressure, whereas serum potassium rose slightly. When salt intake was restricted, spironolactone administration induced only minimal change in blood pressure after 1 week. On the contrary, dexamethasone administration (2 mg/day) for 10 days was followed by prompt sodium diuresis and potassium retention, normalization of blood pressure and kalaemia, together with suppression of deoxycorticosterone and corticosterone secretion.

We also had the opportunity to study an unusual case of malignant ovarian arrhenoblastoma producing aldosterone. The patient (female, 31 years) had severe hypertension (220/140 mmHg), hypokalaemic alkalosis, optic fundi of grade IV, but no impairment of renal function. Aortography showed two left renal arteries without stenosis. She was in poor general condition, and a pelvic mass was palpable. Plasma renin activity was undetectable and aldosterone excretion...
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extremely elevated (151.4 µg/24 h). Other hormonal tests were negative. The patient died 3 months after admission. Necropsy showed a massive golden-yellow ovarian neoplasm, histologically undifferentiated arrhenoblastoma. Adrenal glands were normal. Aldosterone was found in the tumour tissue at a concentration of 0.05 pg/g wet weight.

During the first month of hospitalization, high doses of spironolactone (400–600 mg/day), alone or in association with other antihypertensive drugs had no effect on lowering the blood pressure, although hypokalaemia was corrected.

DISCUSSION

From the data we have presented some assumptions can be made. In a certain number of patients with essential hypertension, the high blood pressure can be completely reversed by treatment with high doses of spironolactone: these patients are characterized by a hyporesponsiveness of plasma renin activity, although aldosterone excretion is normal.

To explain this finding, it has been suggested that other unknown mineralocorticoids could be involved in the pathogenesis of hypertension. Melby, Dale & Wilson (1971) found elevated levels of 18-hydroxy-deoxycorticosterone in three of twelve patients with low-renin essential hypertension. Another suggestion is that normal production of aldosterone in patients with sustained hypertension may represent inappropriately high levels in relation to their hypertension. The routine utilization of spironolactone in such patients is limited because of the high doses required, the side effects (fatigue, nausea, menstrual disturbances, and hyperkalaemia) and the high cost.

The antihypertensive effect obtained in the normal renin group seems purely diuretic.

In renal hypertension, when secondary aldosteronism is present, spironolactone eventually corrects the hypokalaemia, but has usually no effect on the blood pressure.

The effect of spironolactone pre-operatively in patients with primary aldosteronism indicates the post-operative behaviour of the blood pressure. A noteworthy finding is the normalization of aldosteronuria occurring after long-term treatment with spironolactone in the case S.R.; this is in contrast with what is usually described in hyperaldosteronaeic patients, but is confirmed by some similar findings obtained by E. G. Biglieri (personal communication). A direct inhibitory effect of the drug on the glomerulosa could be postulated.

Finally, in cases with chronic mineralocorticoid excess, e.g. the 17α-hydroxylase deficiency syndrome we have described, only very high doses of spironolactone, for long periods of time, can eventually be effective in the controlling of the hypertension. Adrenocorticotropic hormone blockade is a more rapid and effective method of lowering blood pressure. In the case with the malignant ovarian arrhenoblastoma, we were very impressed by the resistance of hypertension to treatment.

REFERENCES


F. Mantero, D. Armanini and S. Urbani


