Twenty-four year spironolactone therapy in an aged patient with aldosterone-producing adenoma

R Takeda, T Yamazaki, Y Ito, H Koshida, T Morise, I Miyamori, T Hashimoto and S Morimoto

The Second Department of Internal Medicine, Department of Laboratory Medicine, School of Medicine, Kanazawa University, Division of Endocrinology, Department of Internal Medicine, Kanazawa Medical University, Kanazawa, Japan


A case of primary aldosteronism treated with spironolactone therapy has been followed up for 24 years. This is probably the longest case of spironolactone therapy for primary aldosteronism that has ever been reported. Long-term treatment with spironolactone controlled the hypertension and prevented hypokalemic alkalosis in this patient, without any deleterious effects on steroid biosynthesis. Based on data obtained during dose reduction and subsequent withdrawal of spironolactone, it is suggested that the suppressed plasma renin activity associated with adenoma-induced aldosteronism develops prior to hypokalemia and hypertension.

Ryoyu Takeda. The Second Department of Internal Medicine, School of Medicine, Kanazawa University, Takaramachi 13-6, Kanazawa City, 920 Japan

It was reported recently by the research committee of Disorders of Adrenal Hormones in Japan that in 193 cases of localized aldosteronoma hypertension was cured by means of surgical removal of the aldosteronoma in 87.7% of cases (1). The remaining 12.3% showed no significant decrease in blood pressure and so the latter group still had to be treated with antihypertensive regimens. There are some patients with idiopathic hyperaldosteronism in which therapy is ineffective, and some patients who either refuse to consent to surgical therapy or are at risk as a result of severe cardiovascular and/or other complications such as old age. For these patients, spironolactone, a competitive antagonist of aldosterone, or trilostane (4x,5-epoxy-17β-hydroxy-3-oxo-5x-androstene-2-carbonitrile), a competitive inhibitor of the 3β-hydroxysteroid dehydrogenase, has been shown to be effective and safe even for long-term treatment.

We report the case study of a 75-year-old female in order to illustrate the long-term clinical effects of spironolactone on blood pressure and biochemical parameters. This patient has been followed-up for 24 consecutive years.

Patient and methods

Case Report and protocol

The patient is a 75-year-old female who visits our outpatient clinic regularly for hypertension and diabetes mellitus check-ups. The family history revealed that her mother suffered from diabetes mellitus.

At 50 years of age (in 1965), the patient was found to have blood pressure as high as 220 mmHg in systole when she visited her doctor because of general malaise. In May 1966 she was admitted to a local hospital because of her hypertension, proteinuria and electrocardiography (ECG) abnormalities. She had an episode of right thumb weakness associated with hypokalemia of 2.9 mmol·l⁻¹ during hospitalization. A year later (in May 1967) her doctor referred her to our hospital (first admission). Soon after admission the diagnosis of primary aldosteronism was made based on the characteristic laboratory data such as a marked hypokalemia, low plasma renin activity (PRA) and increased urinary excretion of aldosterone with normal levels of plasma cortisol and urinary 17-OHCS. Also, the pneumoretroperitoneum suggested enlarged contour of the right adrenal. Since then, spironolactone therapy has been carried out with an initial dosage of 300 mg daily, decreasing to 75 mg or occasionally to as little as 50 mg daily. Since discharge, the patient has been followed up in our outpatient clinic with this regimen. In March 1976, she was re-admitted to our hospital (second admission) because of syncope due to an attack of ventricular tachycardia precipitated by hypokalemia that had developed as a result of self-discontinuation of spironolactone therapy. Two years later she was treated for a urinary tract infection. The presence of aldosteronoma in the right adrenal was first confirmed by adrenal scintigraphy using [¹³¹I]19-cholesterol. Since the patient refused to consent to surgical therapy, spironolactone administration was continued. In May 1987, hyperglycemia over 11.0 mmol·l⁻¹ in the fasting blood
sugar became so manifest that the patient needed an oral hypoglycemic drug. In August 1988 she was admitted again (fourth admission) for evaluation of adrenal function under the long-term spironolactone therapy and for controlling hyperglycemia. This time it was confirmed that plasma aldosterone was markedly increased, though hypertension and hypokalemic alkalosis were normalized. Ultrasound and magnetic resonance imaging (MRI) of the abdomen showed a mass of 2.5 cm in diameter on the right adrenal. The cardiac silhouette on chest X-ray film (1990) increased to 65% in the cardiothoracic ratio, which was 55% at the first visit to our clinic in 1966. The ECG showed atrial flutter with high voltage in the leads of V5 and V6, and ST segment depression in the leads of I, II, aVf and V1-V6. Two years after the fourth admission, diabetes mellitus has been fairly well controlled with 5.0 mg a day of glibenclamide. Diabetic retinopathy or proteinuria have not been detected.

All blood samples were drawn through the indwelling catheter cannulated in the cubital vein and collected in tubes containing heparin. Immediately after centrifugation the separated plasma was frozen at -20°C until assayed.

PRA was measured using Skinner's method (2) until 1979, and subsequently using a previously described RIA kit (Diana-bot Co., Ltd., Tokyo, Japan) (3). The mean ± SD of normal controls by these methods was 1.2 ± 0.6 ng·l⁻¹·h⁻¹ and 1.4 ± 0.4 ng·l⁻¹·h⁻¹, respectively. The plasma cortisol, aldosterone, corticosterone and dehydroepiandrosterone (DHEAs) were determined using a conventional RIA kit. Blood sampling for evaluating the diurnal variance of these hormones was carried out at 24.00, 04.00, 08.00, 12.00, 16.00 and 20.00. The rapid ACTH stimulation test was performed with an intramuscular injection of 250 μg of synthetic ACTH and the responses of plasma cortisol and aldosterone at 30 min and 60 min after ACTH injection were determined. During a controlled period of spironolactone dosage reduction, serial measurements in blood pressure, serum potassium and PRA were made. Spironolactone was gradually reduced from 200 mg/day for one-and-a-half months to 50 mg/day for two months, to 25 mg for one-and-a-half months; it was finally withdrawn. Blood pressure, serum potassium levels and PRA at each period when the dosage of spironolactone was gradually reduced from 200 mg/day for one-and-a-half months to 50 mg/day for two months, then to 25 mg a day for one-and-a-half months before being withdrawn. The nature of the follow-up study was fully explained to the patient and informed consent was obtained.

Results

The patient showed a marked hypokalemia associated with suppressed PRA when not receiving spironolactone medication. Persistent hyperaldosteronemia with levels over 250 pmol·l⁻¹ was observed, irrespective of medication throughout all the periods of our observations. The presence of an adrenal tumor was confirmed repeatedly by means of [¹¹¹]I9 cholesterol or ultrasound and MRI (Figs. 1, 2). Also the normalization of hypertension, hypokalemia and suppressed PRA state with spironolactone therapy confirmed the diagnosis of primary aldosteronism.

After three years of spironolactone therapy in a dosage of 100 mg daily, it was found that a maintenance dosage of only 75 mg or 50 mg daily was required. At these doses, blood pressure and serum potassium levels responded well (Fig. 3). However, on one occasion, when the spironolactone dosage was reduced to 50 mg daily, a state of suppressed PRA was observed. When the dose was further reduced to 25 mg, hypokalemia was observed together with a tendency to elevation of blood pressure. Overt hypertension developed in the later phase of the placebo period (Fig. 4).

The diurnal profile of plasma cortisol was in parallel with that of plasma aldosterone, showing a peak at 00.40 and a nadir at 20.00. PRA showed an opposite

![Fig. 1](A) Magnetic resonance imaging of the right adrenal. (B) Computer tomography of the abdomen, showing the enlargement of the right adrenal.)
profile to the diurnal changes in plasma cortisol and aldosterone, peaking at noon. The basal level of plasma cortisol was 333.9 pmol·l⁻¹, which increased to 767.1 pmol·l⁻¹ at 30 min and to 560.2 pmol·l⁻¹ at 60 min in response to the rapid ACTH stimulation test carried out in 1988. The basal level of plasma aldosterone was 950.0 pmol·l⁻¹; this also increased linearly during the rapid ACTH test, reaching levels as high as three (2590.0 pmol·l⁻¹) and four times (3990.0 pmol·l⁻¹) compared with basal at 30 and 60 min respectively. The basal levels of plasma corticosterone and DHEAs were within normal ranges (92.5 pmol·l⁻¹ and 58.7 pmol·l⁻¹ respectively) (Table 1).

Discussion

It is generally accepted that the principal management of primary aldosteronism is surgical removal of the aldosterone-producing tumor unless other medical conditions exclude a safe perioperative course. However, the long-term medical management of poor surgical candidates and those who refuse surgical operation is less well defined. A few reports on the use of spironolactone (4), triolostane (5), triameterene and thiazide (6) have indicated that spironolactone is the most effective for therapy of primary aldosteronism.

The mechanism of action is thought to be based mainly on the competitive inhibition of aldosterone action at target organs. On the other hand, recent in vitro studies (7, 8) using rat, bovine or human adrenals have shown that spironolactone inhibits the enzymes involved in 11β,17α, 18- and 21 hydroxylation and 3β-hydroxysteroid dehydrogenase. These enzymes are essential for steroidogenesis. Also, it is well known that spironolactone can block testosterone biosynthesis and peripheral androgen action and so often causes gynecomastia in men. As observed in the present case and another report (9), spironolactone failed to decrease the plasma level of aldosterone and in fact tended to increase it. This is in contrast to the recent finding by Kater et al. (10), that urinary and plasma aldosterone failed to increase in aldosterone-producing adenomas, despite the normalization of plasma renin concentration and potassium. Plasma levels of cortisol and DHEAs were
within the normal ranges. The function of the pituitary-adrenal axis was shown to be intact, although the diurnal rhythm of plasma steroids shifted to slightly earlier in the morning. From these findings it is unlikely that long-term spironolactone therapy results in a state of glucocorticoid deficiency.

Fortunately, renal function, as shown in serum creatinine and glomerular filtration rate, in the present case was in the normal range for age-matched controls throughout the 24-year course of treatment (Fig. 1). There has never been a marked hyperkalemia despite spironolactone therapy.

It is interesting to note that a state of suppressed PRA developed prior to the re-occurrence of hypokalemia and hypertension in the course of dose reduction and subsequent withdrawal of spironolactone. This finding might explain the existence of normokalemic (11–13) or normotensive primary aldosteronism (14, 15), both of which have been encountered occasionally.

Diabetes mellitus, which developed insidiously three years ago, has been controlled easily with oral hypoglycemic drugs and a restriction of 1400 calories a day in the initial year. Responses of plasma immunoreactive insulin showed a delayed pattern with a peak value of 57.2 pmol·l⁻¹ at 3 h after 75 g of glucose ingestion, though the insulinogenic index at 30 min after glucose load dropped to 0.22. The incidence of diabetes mellitus and impaired glucose tolerance (IGT) in patients with primary aldosteronism has been reported to be 48% for patients over 60 years of age. Such a high prevalence of diabetes or IGT has been ascribed to the impaired insulin secretion due to chronic hypokalemia. However, in the

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**Table 1. Changes in serum sodium, potassium and plasma steroids during the long-term spironolactone therapy in the present case.**

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<tbody>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td>172/104</td>
<td>230/110</td>
<td>120/80</td>
<td>110/66</td>
<td>148/88</td>
</tr>
<tr>
<td>s-Na (mmol/l)</td>
<td>152</td>
<td>146</td>
<td>140</td>
<td>137</td>
<td>(137)</td>
<td>137</td>
</tr>
<tr>
<td>s-K (mmol/l)</td>
<td>2.1</td>
<td>1.9</td>
<td>4.3</td>
<td>4.6</td>
<td>(4.6)</td>
<td>4.9</td>
</tr>
<tr>
<td>PRA (nmol/ml/h)</td>
<td></td>
<td>1.2 ± 0.6</td>
<td>0.2</td>
<td>0.3 ~ 0.6</td>
<td>0.56</td>
<td>(0.66)</td>
</tr>
<tr>
<td>BIA</td>
<td></td>
<td>(N = 52)</td>
<td>(N = 10)</td>
<td>(N = 10)</td>
<td>(N = 10)</td>
<td>(N = 10)</td>
</tr>
<tr>
<td>RIA</td>
<td>1.4 ± 0.4</td>
<td>0.3 ~ 0.6</td>
<td>0.56</td>
<td>(0.66)</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>p-Aldosterone (pmol/l)</td>
<td></td>
<td>183.0 ± 78.0</td>
<td>250.0</td>
<td>669.0</td>
<td>(1156.0)</td>
<td>501.0</td>
</tr>
<tr>
<td>u-Aldosterone (nmol/24 h)</td>
<td></td>
<td>24.7 ± 7.8</td>
<td>49.5</td>
<td></td>
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<tr>
<td>p-Cortisol (pmol/l)</td>
<td>353.3 ± 96.6</td>
<td>356.0</td>
<td>333.9</td>
<td>(532.7)</td>
<td>284.3</td>
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<tr>
<td>Corticosterone (pmol/l)</td>
<td></td>
<td>141.6 ± 46.2</td>
<td></td>
<td>(92.5)</td>
<td></td>
<td></td>
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<tr>
<td>DHEAS (pmol/l)</td>
<td>2.0 ± 8.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(58.7)</td>
</tr>
<tr>
<td>u-17-OHCS (μmol/24 h)</td>
<td>22.9 ± 9.4</td>
<td>24.0</td>
<td>17.7</td>
<td>16.8</td>
<td>24.3</td>
<td>16.6</td>
</tr>
</tbody>
</table>

s: serum, p: plasma, u: urinary, u-17-OHCS: expressed as cortisol equivalent.

( ) ambulatory.
present study plasma potassium levels were maintained close to normal over almost the entire clinical course. There was a period of hypokalemia but this was ascribed to self-withdrawal of the drug for four months in 1976. In the light of these data it appears that hypokalemia does not play a role in the impairment of early insulin response.

Lastly, enlargement of the cardiac silhouette, which has been observed in the face of long-term control of high blood pressure and metabolic alkalosis, arouses a question as to the preventive effect of spironolactone on the cardiovascular complications associated with high blood pressure. However, account must be taken of the fact that in the present case there were obviously ST-T changes in the electrocardiogram, probably due to coronary heart disease. In addition, it is likely that diabetes mellitus, which has become worse in recent years, could cause deterioration of the myocardial lesions which have been known as diabetic cardiomyopathy, although the authors thus far have no direct evidence of this.

In conclusion, this rare case of primary aldosteronism, followed-up with spironolactone therapy for 24 years, is probably the longest case of spironolactone therapy for primary aldosteronism in the literature. The beneficial effects of spironolactone on hypertension and hypokalemic alkalosis were confirmed to be maintained without suppression of steroid biosynthesis even after long-term therapy for more than 20 years.

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References


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