Letter to the Editor

Primary aldosteronism (PA) is the most common form of secondary hypertension. The prevalence of PA is raised from 1% to 3% to 10% to 15% because of the introduction of the upright plasma aldosterone/plasma renin activity ratio (APR) as screening procedure. The pathogenesis of idiopathic PA (IPA), which accounts for 50% of the cases of PA, is still not clear, and several factors have been involved, such as hypersensitivity to angiotensin II or to other stimulating factors or aberrant receptors in the glomerulosa. IPA is usually treated with aldosterone receptor blockers, such as spironolactone, potassium canrenoate (KC), canrenone, or eplerenone, which have, respectively, a high (spironolactone), low (KC and canrenone), or quite absent (eplerenone) antiandrogen activity. The dose of these drugs can be progressively reduced to the lowest amount able to keep normal both blood pressure (BP) and serum potassium. In a previous study, we reevaluated 15 patients with IPA 1 month after withdrawal of therapy with KC after 3 to 24 years of treatment. One month after withdrawal, APR was increased only in 3 subjects and a significant inverse correlation between APR and the number of years of therapy with KC was evident. We concluded that long-term therapy with KC could normalize APR in many cases of IPA after a 1-month withdrawal of the drug. These data were consistent with possible regression of IPA after long-term therapy with KC or with a persistent inhibitory effect of KC on aldosterone synthesis after a 1-month withdrawal. We now report data on 3 additional subjects with IPA, who had not been taking KC for >5 years.

The patients (Table) had the diagnosis of IPA done, respectively, 25, 24, and 10 years earlier. We followed them after the diagnosis, and their BP and serum potassium were well controlled with KC for several years. The patients later decided to stop the follow-up at our center and were controlled by the family doctor. In all of the patients, KC (25 to 100 mg a day) had been withdrawn for >5 years, and BP was controlled, respectively, with a calcium antagonist (2 cases) and with an angiotensin-converting enzyme inhibitor in the third. After 1 month free of therapy, BP, APR, serum potassium, adrenal computed tomography scan, and ECG were reevaluated. Average calculated sodium intake was 3 g per day. Clinical, biochemical, and hormonal parameters at the moment of diagnosis and after a 1-month withdrawal of therapy are reported in the Table. Physical examination and ECG did not show any alteration in addition to a slight increase in BP, and the computed tomography scanner excluded the presence of an adrenal adenoma. The upright APR was normal in all 3 of the subjects.

Both after 1 month and several years of withdrawal from long-term therapy with KC, hyperresponsiveness of adrenal glomerulosa to angiotensin II became normal in almost all of the studied patients with IPA. The actual data show that the reason for the normalization of APR after a 1-month withdrawal of KC cannot be linked to the persistent effect of KC on the adrenal glomerulosa as hypothesized in the previous report.

Because in the previous study not all of the subjects normalized their plasma aldosterone, after long time with KC, we can speculate that IPA is not a homogeneous disease: in some cases the biochemical picture persists, whereas in others PA is reversed. It is known that PRA and aldosterone progressively decrease with age, and this could be another reason for the reversal of the biochemical picture, independent from the inverse correlation between length of treatment and APR found in our previous study. Furthermore, aging is associated with a reduced adrenal responsiveness to angiotensin II, contributing to lower gluconon steroid production of aldosterone and imbalance of sodium homeostasis. We hypothesize that prolonged treatment with KC can normalize the response of glomerulosa to angiotensin II and reverse the clinical picture in some cases of IPA. We did not find any evident cardiovascular alteration in our subjects, even after long-term withdrawal from the therapy, in agreement with a positive effect of aldosterone-receptor blockers to prevent further worsening of this aspect of the disease. Before the demonstration of cardiovascular effects of excess of aldosterone, PA was considered a benign form of hypertension. This was probably because of the praecox diagnosis and severe hypokalemia of the patients.

Clinical and Biochemical Data of the Patients

<table>
<thead>
<tr>
<th>Gender, Actual Age</th>
<th>Years of KC Therapy</th>
<th>Years Withdrawal From KC</th>
<th>APR Before</th>
<th>APR Now</th>
<th>Aldo After FF Test at Diagnosis, ng/dL Before</th>
<th>Aldo After FF Test at Diagnosis, ng/dL Now</th>
<th>s.K, mEq/L Before</th>
<th>s.K, mEq/L Now</th>
<th>BP at Diagnosis, mm Hg</th>
<th>BP Now, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>F, 57 y</td>
<td>6</td>
<td>6</td>
<td>58</td>
<td>8</td>
<td>31</td>
<td>4.2</td>
<td>4.5</td>
<td>160/100</td>
<td>135/90</td>
<td></td>
</tr>
<tr>
<td>M, 66 y</td>
<td>17</td>
<td>10</td>
<td>102</td>
<td>14</td>
<td>26</td>
<td>3.1</td>
<td>3.8</td>
<td>150/105</td>
<td>140/90</td>
<td></td>
</tr>
<tr>
<td>M, 67 y</td>
<td>19</td>
<td>9</td>
<td>67</td>
<td>5</td>
<td>69</td>
<td>3.3</td>
<td>3.9</td>
<td>180/105</td>
<td>135/90</td>
<td></td>
</tr>
</tbody>
</table>

F indicates female; M, male; KC, potassium canrenoate; APR, upright aldosterone (nanograms per deciliter); PRA (nanograms per milliliter per hour) ratio; Aldo, aldosterone; FF, fludrocortisone; s.K, serum potassium.

Fludrocortisone was 0.4 mg for 4 days.

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patients. Most of the patients who were not classified with PA using the new criteria would previously have been considered as affected by low renin hypertension, APR having not been calculated, and these subjects were at risk of cardiovascular complications.

The results of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study\(^4\) and the Randomized Aldactone Evaluation Study\(^5\) in fact show that aldosterone receptor blockers are effective in preventing cardiovascular complications, independent from the aldosterone value. Our data can strengthen this concept, showing that aldosterone receptor blockers also have a beneficial effect at the level of glomerulosa, restoring a normal reactivity to angiotensin II.

In conclusion, our data are consistent either with an exhaustion of the biochemical picture of PA in patients treated for the long term with KC, with reversal of PA to essential hypertension, or with an age-related reduction of renin and aldosterone with restoration of normal reactivity of glomerulosa to aldosterone.

**Disclosures**

None.

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**Decio Armanini**  
Cristina Fiore  
Donatella Pellati  

Departments of Medical and Surgical Sciences-Endocrinology  
University of Padua  
Padua, Italy

Spontaneous Resolution of Idiopathic Aldosteronism After Long-Term Treatment With Potassium Canrenoate
Decio Armanini, Cristina Fiore and Donatella Pellati

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