Influence of spironolactone on endogenous steroid metabolism in man

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Summary

1. Mild secondary hyperaldosteronism was induced in ten healthy young males by a low sodium diet for 14 days. After 7 days on the diet, five subjects each were treated with spironolactone (group S) or triamterene (group T) daily.

2. The daily negative sodium balance was identical during the first 3 days of medication with both drugs but sodium loss was more severe during the following days in group S. Consequently, the plasma renin activity was higher during the last days of spironolactone compared with triamterene medication.

3. Changes in plasma electrolytes were similar in both groups.

4. No influence of either drug on the synthesis chain leading to cortisol was observed.

5. Plasma concentrations of deoxycorticosterone and corticosterone, however, increased considerably in group S, whereas triamterene did not influence these steroids.

6. Whereas triamterene induced a prompt increase of plasma aldosterone, an increase was delayed for the first 3 days of treatment with spironolactone. Later, plasma aldosterone concentrations rose rapidly in group S and were no longer different from those in group T.

7. Results are interpreted as being due to an initial inhibition of aldosterone synthesis by spironolactone, which is finally compensated, at least in part, by increased activation of the renin-angiotensin system.

Key words: aldosterone synthesis, cortisol synthesis, electrolyte changes, renin-angiotensin system, spironolactone, triamterene.

Introduction

Spirolactones are well known to be competitive antagonists of aldosterone at various receptor sites. In addition, evidence has been provided of their inhibitory action on aldosterone synthesis both in animals and in man (Erbler, 1972, 1973, 1974a, b). But neither administration of a single high dose of spironolactone (Erbler, 1974a) nor treatment of normal subjects without hyperaldosteronism (Erbler, 1974b) is representative of therapeutic conditions. Therefore we examined the influence of chronically administered spironolactone on plasma levels of several adrenal steroids in the state of mild secondary hyperaldosteronism. Control conditions were achieved by administration of triamterene in order to attain similar changes in electrolyte metabolism.

Methods

Ten healthy young (aged 23–34 years) males, who had given written consent for investigation, received a diet containing 75 mmol of sodium daily for 14 days. Athletic activities as well as night work were forbidden during the experimental period. After 7 days on the diet, five subjects each were treated with 100 mg (0.240 mmol) of spironolactone three times daily (Aldactone; Boehringer/Mannheim) or 100 mg (0.395 mmol) of triamterene (Jatropur; Röhm Pharma) twice daily respectively for a further 7 days. Before breakfast, each morning at 08.00 hours, venous blood was drawn for the determination of steroids, plasma renin activity, angiotensin II and
Erratum


Line 7 of the left-hand column of Table 1 should read ‘11-Deoxycorticosterone (pmol/l)’.

<p>| TABLE 1. Daily sodium balance, plasma renin activities and plasma concentrations of endogenous steroids in five healthy young males given 100 mg of spironolactone (S) three times daily and 100 mg of triamterene (T) twice daily |
|---|---|---|---|---|---|---|---|---|---|---|---|</p>
<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺ balance (mmol/24 h)</td>
<td>±6 8</td>
<td>±7 4</td>
<td>±9 6</td>
<td>±2 6</td>
<td>±10 4</td>
<td>±8 2</td>
<td>±5 0</td>
<td>±8 0</td>
</tr>
<tr>
<td>PRA (nmol h⁻¹ l⁻¹)</td>
<td>±0 6 2</td>
<td>±1 0 9</td>
<td>±1 0 1</td>
<td>±0 8 6</td>
<td>±0 6 2</td>
<td>±0 3 9</td>
<td>±4 2 9</td>
<td>±1 4 0</td>
</tr>
<tr>
<td>Progesterone (nmol/l)</td>
<td>±0 1 8</td>
<td>±0 1 7</td>
<td>±0 3 3</td>
<td>±0 2 4</td>
<td>±0 3 1</td>
<td>±0 3 3</td>
<td>±0 2 9</td>
<td>±0 3 2</td>
</tr>
<tr>
<td>17-Hydroxyprogesterone (nmol/l)</td>
<td>±0 3 7</td>
<td>±0 4 2</td>
<td>±0 0 0</td>
<td>±0 5 5</td>
<td>±0 5 5</td>
<td>±0 3 3</td>
<td>±0 6 4</td>
<td>±0 5 8</td>
</tr>
<tr>
<td>11-Deoxy cortisol (nmol/l)</td>
<td>±0 2 1</td>
<td>±0 2 3</td>
<td>±0 3 2</td>
<td>±0 5 5</td>
<td>±0 3 9</td>
<td>±0 5 0</td>
<td>±0 4 3</td>
<td>±0 4 5</td>
</tr>
<tr>
<td>Cortisol (nmol/l)</td>
<td>3 4 0</td>
<td>4 1 9</td>
<td>4 8 2</td>
<td>4 1 1</td>
<td>4 6 3</td>
<td>3 8 9</td>
<td>5 2 9</td>
<td>4 8 0</td>
</tr>
<tr>
<td>11-Deoxycorticosterone (nmol/l)</td>
<td>2 7 2</td>
<td>2 6 3</td>
<td>5 5 9</td>
<td>2 3 3</td>
<td>6 4 4</td>
<td>3 9 6</td>
<td>6 7 7</td>
<td>2 5 7</td>
</tr>
<tr>
<td>Corticosterone (% S)</td>
<td>±3 3 2</td>
<td>±3 0 2</td>
<td>±7 5 6</td>
<td>±8 4 8</td>
<td>±1 5 1</td>
<td>±2 0 5</td>
<td>±9 0 7</td>
<td>±5 7 5</td>
</tr>
<tr>
<td>Aldosterone (nmol/l)</td>
<td>±3 4 0</td>
<td>±3 5 9</td>
<td>±0 4 5</td>
<td>±0 7 3</td>
<td>±0 6 1</td>
<td>±1 0 9</td>
<td>±0 9 4</td>
<td>±1 4 6</td>
</tr>
</tbody>
</table>

(1) Because of large inter-individual variations in the absolute amounts of corticosteroids concentration, values for each subject under medication were referred to their own basic values and were expressed as percentages.
plasma sodium and potassium. Urine was collected at daily intervals.

Sodium and potassium in plasma and urine were determined by flame photometry. PRA \(^{(1)}\) and plasma angiotensin II were assayed according to Oelkers, Schöneshöfer & Blümel (1974) and Düsterdieck & McElwee (1971) respectively. Plasma levels of progesterone, 17-hydroxyprogesterone, deoxycortisol, cortisol, deoxycorticosterone, corticosterone and aldosterone were simultaneously determined by a radioimmunological procedure developed in our laboratory by M. Schöneshöfer & S. Spörl. Briefly, this method involves three steps: (1) separation by liquid–liquid partition into four fractions, (2) purification of the individual steroids by paper chromatography, and (3) the quantification by radioimmunoassay. This effects the complete separation of the steroids from spironolactone and all its metabolites (Abshagen & Rennekamp, 1975). The coefficients of variation for replicate interassay determination ranged from 12.7% for cortisol to 22.9% for deoxycorticosterone. All results are given as mean values of a group, deviations as \( \text{SEM} \times (n = 5) \). Analysis of statistical significance was carried out with Student's \( t \)-test for unpaired experiments.

Results

Administration of the 75 mmol/day sodium diet was followed by a considerable urinary sodium loss during the first days of the control period. After 3–5 days on this regimen, sodium excretion approached sodium intake, and a new balance was attained in all individuals. Administration of both spironolactone and triamterene then initiated a prompt increase in sodium excretion. The increase in sodium excretion was similar in both groups during the first 3 days of medication. During the last 4 days on spironolactone, however, sodium loss was significantly greater than in the triamterene group (Table 1). Plasma sodium concentrations fell from 145 mmol/l (\( \text{SEM} \times 1:33 \)) to 139 mmol/l (\( \text{SEM} \times 1:56 \)) at the end of spironolactone medication, whereas no change occurred in the triamterene group (143.9 mmol/l, \( \text{SEM} \times 1:0 \), to 145 mmol/l, \( \text{SEM} \times 1:0 \)). Plasma potassium increased slightly under the influence of both drugs (by 0.37 mmol/l, mean value, with spironolactone; by 0.36 mmol/l with triamterene).

In accordance with the kinetics of sodium excretion, PRA rose to a similar extent during the first 2 days of treatment in both groups. Thereafter, PRA rose more rapidly in the spironolactone group and was more than twice as high as in the triamterene group at the end of the study. Changes in plasma angiotensin II concentrations resembled those of PRA in both groups.

Neither spironolactone nor triamterene caused changes in the plasma levels of progesterone, 17-hydroxyprogesterone and deoxycortisol. A slight elevation in plasma cortisol by approximately 30% was observed in the spironolactone group. Marked alterations occurred in the synthesis chain leading to aldosterone during treatment with spironolactone, but not with triamterene. Plasma deoxycorticosterone rose finally to 305% (\( \text{SEM} \times 27 \)) and corticosterone to 263% (\( \text{SEM} \times 46 \)) of control in the spironolactone group. Triamterene caused a rapid increase of plasma aldosterone, whereas the plasma concentrations of aldosterone fell slightly on the first day of spironolactone administration and increased at a markedly slower rate during the next 2 days. Thus, during the first 3 days of medication, plasma aldosterone was significantly lower in the spironolactone group than in the triamterene group. Later on, plasma aldosterone concentrations increased rapidly in the spironolactone group and were no longer significantly different from that of the triamterene group.

Discussion

The metabolic disposition of spironolactone involves hydroxylation reactions which most likely take place in the C-11 and C-18 positions, as has been evidenced by mass spectroscopy (Erbler, 1973; Sadée, Finn, Schmiedek & Baethmann, 1975). Results presented in this paper are consistent with the hypothesis of a competitive inhibition of 11β- and 18-hydroxylases in the zona glomerulosa by metabolites of spironolactone. Consequently, the precursors of these hydroxylation steps, deoxycorticosterone and corticosterone, accumulated and the plasma concentrations of the successor aldosterone could not be raised to the same extent as in the triamterene group during the first 3 days of spironolactone medication. During the last 4 days of the study, however, plasma aldosterone increased rapidly in the spironolactone group, whereas deoxycorticosterone and corticosterone levels remained elevated. The greater sodium loss during the last 4 days of treatment with spironolactone, compared with triamterene—possibly a

\(^{(1)}\) Abbreviation: PRA, plasma renin activity.
consequence of their different molecular mechanism of action at tubular receptor sites—may have initiated compensatory mechanisms. In this respect, the larger increase of PRA and plasma angiotensin II in the spironolactone group may be of importance.

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References


