Effect of converting enzyme inhibition on the systemic and renal responses to acute isotonic volume expansion in normal man

A. MIMRAN and J. RIBSTEIN

Department of Medicine, Centre Hospitalier Universitaire, Montpellier, France

Summary

1. Systemic, humoral and renal responses to isotonic volume expansion (1800 ml in 3 h) were assessed in normal subjects before and during captopril administration.

2. Captopril, which otherwise induced a decrease in pre-saline mean arterial pressure (MAP), unmasked the volume-dependence of MAP, which increased linearly during volume expansion (+ 18.7 ± 3.8% at the end of volume expansion).

3. Captopril prevented the fall in plasma aldosterone produced by volume expansion but did not modify the natriuretic response to saline.

4. These results suggest that intrarenal rather than circulating angiotensin II may be one of the determinants of the natriuretic response to volume expansion in normal man.

Key words: angiotensin, captopril, converting enzyme, angiotensin II, volume expansion.

Abbreviations: CEI, converting enzyme inhibitor; MAP, mean arterial pressure; PRA, plasma renin activity; VE, volume expansion.

Introduction

The exact influence of basal levels as well as the degree of suppression of the activity of the renin–angiotensin–aldosterone system in the systemic and renal responses to acute expansion of the extracellular compartment by saline infusion is unclear. In normal subjects, it has been shown that the renal response to volume expansion is inversely correlated with baseline renin levels [1] and positively correlated with age in some [1] but not all studies [2] conducted in a large number of subjects. In the present study, volume expansion was carried out before and during suppression of endogenous angiotensin II generation by the converting enzyme inhibitor captopril in normal subjects.

Subjects and methods

Subjects and protocol

Studies were carried out in seven normotensive subjects (six males and one female) aged 23–47 years. The subjects had no family history of hypertension since such a characteristic may alter the renal response to acute sodium loading [3]. Informed consent was obtained from all subjects.

After overnight bed rest of the subjects venous catheters were placed in both forearms and the subjects emptied their bladders at 08.00 hours. At 09.00 hours a control 1 h urine collection was obtained and blood samples were drawn. An infusion of sodium chloride solution (150 mmol/l :saline) was then given at a rate of 10 ml/min during a 3 h period; blood samples were drawn hourly and all urine was collected during the saline infusion (volume expansion period, VE). Blood pressure was determined every 2 min with an Arteriosonde R. After completion of saline infusion (noon), the subjects were permitted to move about and received a diet containing approximately 100 mmol of Na⁺ and 60 mmol of K⁺ per 24 h. Post-saline urine collections were obtained at 20.00 hours and 08.00 hours the next morning and blood was drawn at 08.00 hours whilst subjects were still recumbent.

The procedure was repeated after a 4–7 day
period of oral administration of the converting enzyme inhibitor (CEI), captopril (SQ 14 225, Squibb and Sons, Princeton, NJ, U.S.A.) at a dose of 100 mg thrice daily.

**Laboratory methods**

In all urine samples, the concentrations of Na⁺, K⁺ and creatinine were determined. In blood samples, packed cell volume and plasma Na⁺, K⁺ and creatinine were measured. Plasma renin activity (PRA) was measured by radioimmunoassay of angiotensin I generated at pH 5.5 with the CEA-Sorin Kit and plasma aldosterone concentration was estimated by the radioimmunoassay technique reported by Vetter et al. [4].

Results were expressed as means ± SEM.

**Results**

**Effect of CEI on pre-saline measurements**

During the 24 h period before saline infusion, urinary sodium and potassium excretions were 119 ± 15 and 45 ± 5 (SEM) mmol/day respectively before CEI and 146 ± 19 (P < 0.05) and 53 ± 3 mmol/day during CEI; however, no change in body weight occurred. Captopril administration was associated with a slight increase in serum K⁺ from 4 ± 0.1 to 4.2 ± 0.08 mmol/l (P < 0.05), whereas serum Na⁺ and packed cell volume were unchanged. Pre-saline mean values of other variables are shown in Table 1.

**Effect of CEI on the systemic response to volume expansion**

During the control study, volume expansion (VE) was associated with a slight rise in mean arterial pressure (MAP), which was significant 150 min after the start of the infusion and reached 8.8 ± 2.6 SEM % by the end of VE. The response of MAP to VE after CEI was progressive and volume-dependent (5.5 ± 1.6, 12.3 ± 3 and 18.7 ± 3.8% at the end of hours 1, 2 and 3 of infusion). The mean value of MAP achieved at the end of VE was similar before and during CEI. Heart rate was unresponsive to VE in both studies (Table 1).

**Effect of CEI on the humoral response to volume expansion**

As shown in Table 1, CEI prevented the response of aldosterone to VE. The fall in packed cell volume induced by VE was similar before (-5.4 ± 1.6%) and after (-6.6 ± 1.3%) CEI.

**Effect of CEI on the renal response to volume expansion**

As shown in Table 1, the amount of sodium excreted before, during and after saline infusion was not affected by CEI.

**Discussion**

In the present investigation, inhibition of converting enzyme was associated with no modification

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**Table 1. Effect of captopril on systemic, hormonal and renal responses to saline infusion**

Mean results ± SEM are shown. *P < 0.05, compared with control. GFR, Glomerular filtration rate.

<table>
<thead>
<tr>
<th></th>
<th>Before saline (08.00–09.00 hours)</th>
<th>During saline (09.00–12.00 hours)</th>
<th>Post-saline (12.00–20.00 hours)</th>
<th>(20.00–08.00 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>CEI</td>
<td>Control</td>
<td>CEI</td>
</tr>
<tr>
<td>Urinary volume (ml)</td>
<td>184 ± 55</td>
<td>219 ± 73</td>
<td>334 ± 64</td>
<td>381 ± 71</td>
</tr>
<tr>
<td>Urinary sodium (mmol/24 h)</td>
<td>9.5 ± 2</td>
<td>8.5 ± 1.7</td>
<td>32.1 ± 6</td>
<td>29.3 ± 6</td>
</tr>
<tr>
<td>Urinary potassium (mmol/24 h)</td>
<td>4.4 ± 0.9</td>
<td>4.8 ± 1</td>
<td>15 ± 2.2</td>
<td>15 ± 3.3</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>119 ± 13</td>
<td>123 ± 14</td>
<td>99 ± 11</td>
<td>100 ± 12</td>
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<tr>
<td>Fractional excretion (%)</td>
<td>0.99 ± 0.18</td>
<td>0.89 ± 0.23</td>
<td>1.32 ± 0.26</td>
<td>1.26 ± 0.31</td>
</tr>
<tr>
<td>Sodium</td>
<td>15.2 ± 2.2</td>
<td>13.5 ± 2.5</td>
<td>20.5 ± 2.4</td>
<td>19 ± 3.7</td>
</tr>
<tr>
<td>Potassium</td>
<td>80 ± 2</td>
<td>71 ± 2*</td>
<td>87 ± 1.9</td>
<td>84 ± 4</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>62 ± 3</td>
<td>62 ± 4</td>
<td>61 ± 4</td>
<td>60 ± 3</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>0.96 ± 0.20</td>
<td>17.2 ± 4*</td>
<td>0.46 ± 0.09</td>
<td>5.6 ± 2.4*</td>
</tr>
<tr>
<td>PRA (pmol h⁻¹ ml⁻²)</td>
<td>271 ± 19</td>
<td>205 ± 14*</td>
<td>190 ± 22</td>
<td>176 ± 23</td>
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<tr>
<td>Plasma aldosterone (pmol/l)</td>
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</table>
of the renal response to acute isotonic volume expansion; however, CEI unmasked the volume-dependence of arterial pressure. The linear increase in arterial pressure associated with VE after CEI and thus in subjects with a non-functional renin–angiotensin system suggests that suppression of this system is an important means of preventing an increase in arterial pressure when the extracellular compartment is expanded. Recently, Hall et al. [5] made a similar observation during chronic changes in sodium intake in dogs.

The sodium excretory capacity of the kidney in response to VE was not modified when changes in angiotensin II and aldosterone induced by VE were prevented by CEI. This suggests that, during acute VE, aldosterone is a negligible determinant of the renal response. However, since an inverse correlation between pre-infusion PRA and the level of fractional excretion of sodium achieved during VE was found in normal subjects [1], it could be emphasized that intrarenal rather than circulating angiotensin II generation is the main determinant of the renal response to VE. In addition, the lack of expected increase in the natriuretic response to VE after CEI might have resulted from volume depletion before VE, although this is unlikely since body weight and packed cell volume were unchanged by CEI. Alternatively, after CEI the presaline renal perfusion pressure might have been lower than control, since it has been shown in rats that reduction of renal artery pressure by clamping before VE prevents the natriuretic response to this manoeuvre [6].

References