EFFECT OF CAPTOPRIL ON THE SYSTEMIC AND RENAL RESPONSES TO ACUTE ISOTONIC VOLUME EXPANSION IN NORMAL MAN

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Summary
Systemic, humoral and renal responses to isotonic volume expansion (VE, 1800ml in 3 hours) were assessed in normal subjects before and during captopril administration (CEI). Captopril, which otherwise induced a decrease in pre-saline mean arterial pressure (MAP) unmasked the volume-dependence of MAP since during captopril administration MAP increased linearly during volume expansion (+18.7 ± 3.8% at the end of VE). In addition, captopril prevented the fall in plasma aldosterone produced by VE but did not modify the natriuretic response to saline.

These results demonstrate that circulating angiotensin II is not an important determinant of the natriuretic response to volume expansion in normal man. However, a role for intrarenal renin cannot be excluded.

Introduction
Acute expansion of the extracellular compartment by saline infusion has been shown to suppress the secretion of renin and aldosterone [1]. In addition, in normal subjects, it has been shown that the magnitude of the increase in urinary sodium excretion produced by volume expansion is inversely correlated with baseline renin level in some [2] but not all [3] studies. In order to study the influence of the baseline renin level as well as that of the saline-induced change in circulating angiotensin, the systemic and renal responses to acute intravenous saline administration were assessed before and during inhibition of angiotensin I converting enzyme by captopril.

Subjects and methods

Subjects and protocol

Studies were carried out in seven normotensive subjects (six males and one female) aged 23 to 47 years. The subjects had no family history of hypertension, since such
a characteristic may alter the renal response to acute sodium loading [4]. Informed consent was obtained from all subjects.

After an overnight bed rest, venous catheters were placed in both forearms and the subjects were asked to empty their bladder at 8.00am. At 9.00am a control one-hour urine collection was obtained and blood samples were drawn. An infusion of isotonic sodium chloride was then given at a rate of 10ml/min during a three hour period; blood samples were drawn hourly and all urine was collected during the saline infusion (volume expansion period, VE). Blood pressure was determined every two minutes with an Arteriosonde R. After completion of saline infusion (noon), the subjects were permitted to move about and received a diet containing approximately 100mmol Na+ and 60mmol K+. Post-saline urine collections were obtained at 8pm and 8am the next morning and blood was drawn at 8am whilst subjects were still recumbent.

The procedure was repeated after a four to seven day period of oral administration of the converting enzyme inhibitor (CEI) captopril (SQ 14,225, Squibb and Sons, Princeton, NJ, USA) at a dose of 100mg tid.

Laboratory methods

In all urine samples, the concentration of Na, K, creatinine were determined. In blood samples, haematocrit, Na, K and creatinine were measured. Plasma renin activity (PRA) was measured by radioimmunoassay using the CEA-Sorin kit and plasma aldosterone concentration (PA) was estimated by radioimmunoassay [5].

Results

Effect of CEI on pre-saline parameters

During the 24 hour period prior to saline infusion, urinary sodium and potassium excretions were $119 \pm 15$ and $45 \pm 5$ respectively before captopril and $146 \pm 19$ ($p < 0.05$) and $53 \pm 3$ mmol/day during captopril; however, no change in body weight occurred. Captopril administration was associated with a slight increase in serum K+ from $4 \pm 0.1$ to $4.2 \pm 0.08$ mmol/L ($p < 0.10$) whilst serum Na+ and haematocrit were unchanged. Pre-saline mean values of other variables are shown in Table I.

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 $8.8 \pm 2.6\%$ by the end of VE. The response of MAP to VE after CEI was progressive and volume-dependent ($5.5 \pm 1.6$, $12.3 \pm 3$ and $18.7 \pm 3.8\%$ at the end of the 1st, 2nd and 3rd hour of infusion). The mean value of MAP achieved at the end of VE was similar before and during captopril. Heart rate was unresponsive to VE in both studies (Table I).
TABLE I. Effect of captopril on systemic, hormonal and renal responses to saline infusion

<table>
<thead>
<tr>
<th></th>
<th>Before 8am – 9am</th>
<th>During saline 9am – Noon</th>
<th>Post-saline 8pm – 8am</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control CEI</td>
<td>Control CEI</td>
<td>Control CEI</td>
</tr>
<tr>
<td>Urinary volume (ml)</td>
<td>184 ± 55 219 ± 73</td>
<td>334 ± 64 381 ± 71</td>
<td>779 ± 91 1004 ± 221</td>
</tr>
<tr>
<td>Urinary sodium (mmol)</td>
<td>9.5 ± 2 8.5 ± 1.7</td>
<td>32.1 ± 6 29 ± 6</td>
<td>87 ± 8 105 ± 20</td>
</tr>
<tr>
<td>Urinary potassium (mmol)</td>
<td>4.4 ± 0.9 4.8 ± 1</td>
<td>15 ± 2.2 15 ± 3.3</td>
<td>22 ± 4 28 ± 4</td>
</tr>
<tr>
<td>GFR (ml.min⁻¹)</td>
<td>119 ± 13 123 ± 14</td>
<td>99 ± 11 100 ± 12</td>
<td>123 ± 10 111 ± 10</td>
</tr>
<tr>
<td>Fractional excretion (%)</td>
<td></td>
<td></td>
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<tr>
<td>Sodium</td>
<td>0.99± 0.18 0.89± 0.23</td>
<td>1.32± 0.26 1.26± 0.31</td>
<td>1.14± 0.16 1.20± 0.12</td>
</tr>
<tr>
<td>Potassium</td>
<td>15.2 ± 2.2 13.5 ± 2.5</td>
<td>20.5 ± 2.4 19 ± 3.7</td>
<td>9.3 ± 1.8 10.5 ± 1.3</td>
</tr>
<tr>
<td>MAP mmHg</td>
<td>80 ± 2 71 ± 2*</td>
<td>87 ± 1.9 84 ± 4</td>
<td>9.3 ± 0.7 9.9 ± 1.6</td>
</tr>
<tr>
<td>Heart rate b.min⁻¹</td>
<td>62 ± 3 62 ± 4</td>
<td>61 ± 4 60 ± 3</td>
<td></td>
</tr>
<tr>
<td>PRA pmol.ml⁻¹ h⁻¹</td>
<td>0.96± 0.20 17.2 ± 4*</td>
<td>0.46± 0.09 5.6 ± 2.4*</td>
<td></td>
</tr>
<tr>
<td>PA pmol.l⁻¹</td>
<td>271 ± 19 205 ± 14*</td>
<td>190 ± 22 176 ± 23</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.05 compared to control
Effect of CEI on the humoral response to volume expansion

As shown in Table I, CEI prevented the response of aldosterone to VE. The fall in haematocrit expressed as per cent of the pre-saline value 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 I, 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 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 [6] 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 captopril. This suggests that, during acute VE, changes in angiotensin II and aldosterone are not important in the renal response to VE. However, since an inverse correlation between pre-infusion plasma renin activity and the level of fractional excretion of sodium achieved during VE was found in normal subjects [2] and in patients with hypertension [3], it may be 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 of the natriuretic response to VE after CEI might have resulted from volume depletion prior to VE (this is unlikely since body weight and haematocrit were unchanged by CEI) or from the fact that after CEI the presaline renal perfusion pressure was lower than control. It has been shown in rats that reduction of renal artery pressure by clamping before VE prevents the natriuretic response to this manoeuvre [7].

References

4 Wiggins RC, Basar I, Slater JDH. Clinical Science 1978; 54: 639

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Open Discussion

WARREN (Southampton) Couldn’t one interpret the fact that blood pressure rose and that there was no natriuresis in the presence of captopril as evidence that at the large doses of captopril that you used there was no interference from the potentially increased circulating bradykinin? I think that the levels of captopril you were using were those that some people say are associated with increased bradykinin levels.

MIMRAN In fact, up to now there is no definite agreement on the role of bradykinin in the renal or systemic effect of captopril. I should say that in a study that we have performed, we did not often see any effect of trasyrol, the inhibitor of kallikrein, on the hypotensive effect of captopril in normal subjects; this suggests that there might be no role for kinin in the effect of captopril and that the effect of captopril is totally related to inhibition of angiotensin II generation. However, we have no definite answer on the kinin issue.

JAHN (Strasbourg) Non-volume dependent hypertension in chronic renal failure is transformed by bilateral nephrectomy or by haemofiltration into a volume-dependent hypertension. Is there an analogy with your study?

MIMRAN I think it is totally different; it is impossible to compare results obtained by pharmacological inhibition of the renin-angiotensin system with nephrectomy.

PARSONS (Chairman) One of the interesting features of angiotensin excess is thirst. We often see very thirsty dialysis patients with not terribly high osmolarity or serum sodiums. I know these were acute experiments, but did you see any difference in water intake or thirstiness in these patients who were heavily blocked (I don’t think we shall see anybody as well-blocked again!)?

MIMRAN We did not monitor the water intake in our subjects; however, the urinary output on captopril was not significantly different from that observed before captopril.

DI GIULIO (Paris) I am not sure that the oral administration of captopril causes intracerebral inhibition of angiotensin II synthesis. Local synthesis of angiotensin is not inhibited because I am not aware that captopril can cross the cerebral barrier and thirst related to angiotensin II will not be decreased by captopril administration as shown by clinical experience.

MIMRAN Some groups have studied the cerebral passage of captopril in animals and I think they found there was no transfer of the drug.