The hypotensive effect of propranolol in captopril-treated patients does not involve the plasma renin–angiotensin–aldosterone system

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Summary

1. With a double-blind cross-over protocol, 20 hypertensive captopril-treated patients were studied by adding in a variable sequence a placebo and propranolol (80 mg three times a day) to their captopril regimen (200 mg three times a day), during periods each lasting 1 month. During captopril-placebo treatment their diastolic blood pressure remained elevated between 90 and 114 mmHg.

2. The additional administration of propranolol produced a significant hypotensive effect, but no alterations of the plasma angiotensin II and aldosterone concentrations and of the urinary aldosterone excretion occurred. The present data indicate that in captopril-treated patients the hypotensive effect of propranolol is achieved independently of changes in the plasma angiotensin II and aldosterone concentration.

3. The additional administration of propranolol also produced an increase in the serum potassium levels in the absence of any change in the plasma aldosterone concentration or in the urinary aldosterone excretion.

Key words: aldosterone, angiotensin II, captopril, propranolol, renin.

Abbreviations: ANG, angiotensin; PRA, plasma renin activity.

Introduction

Several investigators [1–3] have related the blood pressure-lowering effect of β-adrenoceptor-blocking drugs to their ability to inhibit renin secretion and hence angiotensin II-mediated arteriolar vasoconstriction and the adrenal aldosterone secretion.

The hypothesis that propranolol may also lower blood pressure via mechanisms not involving the angiotensin–aldosterone system was investigated in hypertensive patients being treated with captopril, the orally active inhibitor of the angiotension I-converting enzyme. These patients provide a situation in which the angiotensin–aldosterone system is already inhibited [4]. The hypotensive effectiveness of propranolol was therefore evaluated in this situation and related to the changes occurring in the angiotensin–aldosterone system.

Methods

Twenty hypertensive patients (eight males and 12 females) gave informed consent and were included in the study. Their age averaged $48 \pm 1.8$ years (mean \pm SEM) and their body weight $75 \pm 2.9$ kg. The aetiology of their blood pressure elevation was established by appropriate laboratory tests, including plasma renin activity and plasma aldosterone concentration, an intravenous pyelogram, renal artery arteriography and selective catheterization of the renal veins, if indicated. The criteria of the World Health Organisation were applied to evaluate the severity of their disease: three patients belonged to stage 1, 15 patients had progressed to stage 2 and two patients to stage 3.

The trial had a randomized double-blind cross-over design with each treatment period lasting 1 month. All patients were on chronic treatment with captopril, 200 mg three times daily, which was continued throughout the study. During the first month a placebo was added to the captopril regimen. During this captopril-placebo
period diastolic blood pressure had to remain between 90 and 114 mmHg. Thereafter 10 patients received, in addition to captopril, 1 month of active treatment with propranolol, 80 mg three times daily; 10 other patients received a matching placebo. Finally, during the last month of the trial the alternative treatment was combined with captopril.

The nature of the different treatment periods was not known to the examining physician. Patients were instructed to take the first dose of their medication upon arising, usually around 08.00 hours, the afternoon dose around 15.00 hours and the evening dose around 22.00 hours. Each dose consisted of two tablets of 100 mg of captopril and one tablet of the study medication. The placebo and active study medication were identical in appearance and the number of tablets and times of dosing were the same in each treatment period. Tablets left in the bottles were counted to check the patient's compliance with the regimen. Patients observed a moderate sodium restriction.

Patients were examined at the outpatient clinic in the early afternoon at the end of each 1 month interval. Blood pressure was measured 5 times consecutively in the recumbent position, and two times standing, always by the same physician using a standard mercury sphygmomanometer. Diastolic blood pressure was recorded at the point of disappearance of sounds (Korotkoff, phase 5). Body weight, supine and recumbent pulse rate were determined on each visit. Blood was withdrawn from an antecubital vein between 8 and 10 h after the last drug intake (morning dose at 08.00 hours), and after the patient had been seated for 15 min. Blood tests included haemoglobin, total and differential leucocyte count, serum electrolytes, serum urea and creatinine concentration, plasma renin activity (PRA) and plasma angiotensin I (ANG I), angiotensin II (ANG II) and aldosterone concentrations. Twenty-four hour urine samples were analysed for electrolytes, creatinine and aldosterone. A radioimmunoassay was used for the measurement of PRA [5], ANG I [6], ANG II [7], plasma aldosterone [8] and urinary aldosterone [9].

The means of the last two recumbent blood pressure readings and of the two standing readings were used for statistical analysis. Results for PRA, ANG I, ANG II and plasma and urinary aldosterone were logarithmically transformed to improve their distribution, and the geometric means, together with the 95% confidence limits, are therefore reported. Statistical methods included Student's t-test for paired data and linear regression analysis. Results from both placebo periods were pooled since statistically similar values were obtained for all variables during these periods.

Results

As shown in Table 1, when placebo was replaced by propranolol a significant decrease of blood pressure was observed. Also, supine and recumbent pulse rate decreased, but body weight did not change significantly.

Adding propranolol to the converting enzyme inhibitor produced a significant decrease of PRA and ANG I, and ANG II and plasma and urinary aldosterone remained unchanged (Table 1).

Linear regression analysis did not show a significant relationship between the hypotensive effect produced by propranolol during converting enzyme inhibition and the concomitantly occurring changes in the renin–angiotensin–aldosterone system. The propranolol-induced decrease of supine pulse rate, however, was related to the decrease of PRA (r = 0.45, P < 0.05) and to the reduction of diastolic blood pressure (r = 0.60, P < 0.01).

Discussion

It has been suggested that propranolol's hypotensive effect is mediated mainly via suppression of the renin–angiotensin–aldosterone system [1, 2]. In the present study this hypothesis was tested in patients in whom the angiotensin–aldosterone system was already inhibited by chronic captopril therapy at high doses. In them propranolol produced an additional and significant hypotensive effect. Furthermore, when propranolol was combined with captopril, a significant decrease of PRA and ANG I was observed. Since at the same time the angiotensin I-converting enzyme was inhibited, ANG II and plasma and urinary aldosterone, on average, remained unchanged. Moreover, regression analysis confirmed that the hypotensive effect produced by propranolol during converting enzyme inhibition was not related to changes of ANG II and plasma.
Propranolol and captopril in hypertension

TABLE 1. Results obtained during the two treatment periods
N.S., Not significant.

<table>
<thead>
<tr>
<th></th>
<th>Captopril + placebo</th>
<th>Captopril + propranolol</th>
<th>P (value between two periods)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standing systolic</td>
<td>170 ± 6.2</td>
<td>158 ± 7.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Standing diastolic</td>
<td>116 ± 3.3</td>
<td>107 ± 3.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Supine systolic</td>
<td>172 ± 6.5</td>
<td>165 ± 6.9</td>
<td>N.S.</td>
</tr>
<tr>
<td>Supine diastolic</td>
<td>112 ± 3.3</td>
<td>103 ± 2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standing</td>
<td>87 ± 2.5</td>
<td>69 ± 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Supine</td>
<td>79 ± 2.5</td>
<td>65 ± 1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>74 ± 2.7</td>
<td>75 ± 2.8</td>
<td>N.S.</td>
</tr>
<tr>
<td>Serum concn. (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>140.3 ± 0.52</td>
<td>141.1 ± 0.60</td>
<td>N.S.</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.2 ± 0.07</td>
<td>4.4 ± 0.09</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Urea</td>
<td>5.7 ± 0.32</td>
<td>6.3 ± 0.40</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Creatinine</td>
<td>91.3 ± 3.36</td>
<td>98.4 ± 5.92</td>
<td>N.S.</td>
</tr>
<tr>
<td>Urinary sodium excretion (mmol/24 h)</td>
<td>121 ± 14.4</td>
<td>126 ± 15.1</td>
<td>N.S.</td>
</tr>
<tr>
<td>Urinary potassium excretion (mmol/24 h)</td>
<td>67 ± 6.1</td>
<td>68 ± 8.4</td>
<td>N.S.</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>100 ± 5.2</td>
<td>92 ± 8.1</td>
<td>N.S.</td>
</tr>
<tr>
<td>Plasma renin activity (mmol h^{-1} l^{-1})</td>
<td>3.2 (1.6–6.1)</td>
<td>0.8 (0.2–2.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma ANG I concn. (pmol/l)*</td>
<td>154 (88–271)</td>
<td>102 (50–205)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Plasma ANG II concn. (pmol/l)*</td>
<td>7.9 (5.9–10.7)</td>
<td>7.9 (5.9–10.6)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Plasma aldosterone concn. (pmol/l)*</td>
<td>350 (297–411)</td>
<td>341 (277–419)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Urinary aldosterone excretion (nmol/24 h)*</td>
<td>16–1 (11–22.5)</td>
<td>12.8 (9.4–17.2)</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

* Geometric means and 95% confidence limits (see the Methods section); for the items without asterisks the arithmetic means ± SEM are presented.

or urinary aldosterone. The present study proves that in patients whose angiotensin–aldosterone system is already inhibited, propranolol does have a blood pressure-lowering effect and that this hypotensive action is not dependent upon further suppression of the plasma angiotensin–aldosterone system, nor upon the urinary aldosterone excretion. In view of these findings we wonder to what extent the hypotensive effect produced by β-adrenoceptor-blocking drugs in patients without additional therapy is mediated by inhibition of the renin–angiotensin–aldosterone system, as suggested by Bühler et al. [1, 2].

In previously untreated subjects β-adrenoceptor blockade produces a blood pressure-lowering effect, which is correlated with the decrease of the heart rate [10]. Also, in the present study a correlation was found between the propranolol-induced decrease of supine pulse rate and diastolic blood pressure. The pulse rate-lowering effect of propranolol was also significantly correlated with the decrease of PRA. These findings suggest that the effects of propranolol on blood pressure and plasma renin may both be mediated by an effect on β-adrenoceptors. They could also explain why in previous studies [1–3] a correlation was obtained between the hypotensive effect of a β-adrenoceptor-blocking agent and the decrease of PRA, although these changes may not be causally related, as suggested by the present data.

When in the present study propranolol was added to the captopril regimen, the serum urea concentration rose significantly, and the serum creatinine tended to increase, but no changes of the creatinine clearance occurred. Our findings on the influence of propranolol on renal function, in captopril-treated patients, do not seem to be different from what was reported previously in patients with normal angiotensin I-converting enzyme activity [11–14].

The serum potassium concentration increased significantly when propranolol was combined with captopril therapy. This is similar to other studies showing that propranolol [1, 2, 15] and other [13, 16–18] β-adrenoceptor drugs may increase serum potassium. Several mechanisms underlying the increase of serum potassium during β-adrenoceptor blockade have been proposed, including: inhibition of the aldosterone secretion [1, 2], reduction of the renal blood flow leading to changes in renal function [11, 19] and an altered catecholamine-dependent intracellular potassium uptake [20, 21]. In the present study the propranolol-induced increase in serum potassium occurred in the absence of any decrease in plasma or urinary aldosterone or in creatinine clearance and was not related to
changes in serum creatinine and urea, nor to changes in plasma ANG II and plasma or urinary aldosterone. This does not support the idea that alterations of renal function and of aldosterone’s action on the renal tubule explain the increase in serum potassium produced by propranolol in captopril-treated patients.

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References