Acute haemodynamic and hormonal effects of captopril are diminished by indomethacin

H. WITZGALL, F. HIRSCH, B. SCHERER AND P. C. WEBER
Medizinische Klinik Innenstadt der Universität München, München, F.R.G.

(Received 2 April 1981; accepted 23 December 1981)

Summary

1. The acute haemodynamic and hormonal effects of 100 mg of captopril (SQ 14.225) orally were tested in twelve healthy men in the sodium replete state before and after indomethacin pretreatment.

2. Without indomethacin, mean arterial blood pressure was reduced at 30 and 60 min after captopril ($P < 0.02$). Heart rate did not change during the whole experiment. Although plasma renin activity (PRA) increased ($P < 0.002$), plasma and urinary aldosterone and plasma 18-hydroxycorticosterone (18-OH-B) decreased after captopril ($P < 0.02$). Prostaglandin (PG) $E_2$, sodium and potassium excretion rates remained constant after captopril.

3. Under indomethacin pretreatment, the fall in mean arterial blood pressure was less than without indomethacin at 30 and 60 min after captopril ($P < 0.05$). Heart rate was constantly lower than without indomethacin during the whole experiment ($P < 0.05$). Indomethacin pretreatment decreased basal PG $E_2$ excretion ($P < 0.02$) and baseline PRA as well as the increase in PRA after captopril ($P < 0.05$). Control mineralocorticoid levels were significantly lower than without indomethacin. In indomethacin-pretreated subjects, aldosterone did not further decrease after captopril, and 18-OH-B fell only slightly.

4. Without indomethacin pretreatment a significant, positive correlation was found between PRA values before captopril and the maximum decrease of mean arterial blood pressure after captopril. Under indomethacin pretreatment this correlation was no longer demonstrable. The results suggest that prostaglandins may contribute to the haemodynamic and hormonal actions of captopril.

Key words: aldosterone, blood pressure, captopril, 18-hydroxycorticosterone, indomethacin, prostaglandins.

Introduction

An orally active inhibitor of angiotensin-converting enzyme, captopril (SQ 14.225), has recently been developed [1]. Angiotensin-converting enzyme, a peptidylpeptide hydrolase (EC 3.4.15.1), removes a dipeptide from the decapeptide angiotensin I (ANG I) to produce the potent vasoactive octapeptide angiotensin II (ANG II). Angiotensin-converting enzyme is identical with kininase II, which inactivates the vasodepressor nonapeptide bradykinin.

The importance of the drug as a therapeutic tool for the management of essential hypertension [2], severe treatment-resistant hypertension [3] and heart failure [4] has now been widely accepted. Inhibition of ANG II formation is probably the major mechanism by which captopril reduces blood pressure [5]. However, since captopril lowers blood pressure also in states not associated with high ANG II levels [6] and in anephric animals and man [7, 8], other mechanisms may be involved [9, 10]. Like ANG II, bradykinin stimulates membrane phospholipase $A_2$ in various tissues and thereby the production of vasoactive compounds of the prostaglandin (PG) cascade [11]. Recently published data suggest the participation of PGs in the
The aim of the present study was to evaluate further the significance of the PG system in the haemodynamic and hormonal effects of captopril in man. In normotensive sodium-replete subjects we could demonstrate that the acute blood pressure lowering and renin stimulating effects of captopril were significantly reduced after effective inhibition of PG formation by indomethacin.

Methods

Protocol

Twelve healthy male volunteers aged 26 to 42 years (mean 33 ± 2 SEM) were investigated under active orthostasis and ad lib diet from 08.00 to 12.00 hours. All subjects were fully informed of the experimental nature and the potential risks of the new drug, and written informed consent was obtained. Blood pressure (random zero sphygmomanometer) and heart rate were recorded twice in the sitting position (2 min rest) at 60 min, 30 min and immediately before and 30, 60 and 90 min after the oral ingestion of 100 mg of captopril. Excretion of aldosterone, PGE₂, sodium and potassium was measured in the urine samples collected for 90 min before and for 90 min after captopril. Urinary sodium excretion was determined in the 24 h period preceding the study. Venous blood was drawn for the determination of plasma renin activity (PRA), ANG I concentration, plasma aldosterone and 18-hydroxycorticosterone (18-OH-B) 60 min and immediately before, and at 30 and 90 min after captopril. The same protocol was performed again 14 days later under PG blockade with 200 mg of indomethacin (50 mg, respectively, at 01.00, 06.00, 08.00 and at 09.30 hours together with captopril).

Analytical methods

Sodium and potassium were determined by standard methods. PRA and ANG I were measured by radioimmunoassay (RIA) [14]. Plasma aldosterone and 18-OH-B were determined by RIA with preceding paper chromatography as described elsewhere [15]. Urinary aldosterone 18-glucuronide excretion was measured by RIA without preceding chromatography [16], and PGE₂ excretion by RIA after silicic acid column chromatography [17].

Statistical analysis

Values are means ± SEM. The evaluation of the difference between values was performed by variance analysis. When a significant F-value was obtained, single comparisons were made by t-test analyses. Linear regression analyses were performed with data demonstrated in Fig. 2.

Results

Response to captopril without indomethacin pretreatment

Heart rate before captopril application was 74 ± 2, 76 ± 2, and 75 ± 2 min⁻¹ and remained constant after captopril. Mean arterial blood pressure fell continuously from a control value of about 96 mmHg to a minimum of about 88 mmHg 60 min after captopril and then started to increase again (Fig. 1).

Fig. 1. Behaviour of mean arterial blood pressure (BP), heart rate (HR), plasma renin activity (PRA), plasma aldosterone (Aldo) and 18-hydroxycorticosterone (18-OH-B), 60 min and immediately before and 30 and 90 min after captopril. Determinations were performed both without (●) and under (O) indomethacin pretreatment. Significance of differences: (1) P < 0.02 and (2) P < 0.05 vs without indomethacin; (a) P < 0.005, (b) P < 0.02 and (c) P < 0.05 vs respective control level.
PRA increased continuously from a basal value of 2.6 ± 0.4 before to 9.7 ± 2.0 ng of ANG I·ml⁻¹·h⁻¹ at 90 min after captopril. Plasma ANG I concentration paralleled PRA: basal 80 ± 9 pg/ml and 300 ± 75 90 min after captopril. A significant, positive correlation was obtained by plotting log of PRA level before captopril vs the maximum decrease of mean arterial blood pressure after captopril (r = 0.72; n = 12; P < 0.01) (Fig. 2). Plasma aldosterone fell from basal 192 ± 12 to 143 ± 11 pg/ml 90 min after captopril (Fig. 1). Corresponding to plasma values, urinary aldosterone excretion fell from basal 12.7 ± 1.6 to 8.2 ± 1.0 ng/min. PGE₂ excretion rates remained constant (217 ± 19 and 224 ± 23 pg/min) (Table 1). Sodium excretion in the preceding 24 h was 194 ± 23 mmol. Sodium and potassium excretion during the experiment did not change significantly after captopril (Table 1).

Response to captopril under indomethacin pretreatment

Indomethacin reduced urinary PGE₂ excretion (to 72 ± 11 pg/min, P < 0.005). No further change of PGE₂ excretion was observed after captopril (80 ± 11 pg/min) (Table 1). Heart rate was significantly (P < 0.05) and constantly lower than without indomethacin pretreatment. Baseline blood pressure on indomethacin was unchanged compared with the control, but fell significantly less after captopril than without indomethacin pretreatment (P < 0.05) (Fig. 1). Under indomethacin, basal PRA (1.2 ± 0.2) as well as the increase of PRA after captopril (to a maximum of 3.0 ± 0.5 ng of ANG I·ml⁻¹·h⁻¹) were significantly reduced (P < 0.05). Baseline ANG I was 60 ± 9 and increased only to 160 ± 39 pg/ml 90 min after captopril (n.s. and P < 0.05 vs without indomethacin). No correlation between baseline log PRA before captopril and the maximum decrease of blood pressure after captopril could be demonstrated under indomethacin pretreatment (r = −0.40, n = 12; P > 0.05) (Fig. 2).

Control plasma aldosterone (140 ± 12 pg/ml) was decreased under indomethacin (P < 0.01) and remained unchanged after captopril (Fig. 1). Similarly to plasma values, baseline aldosterone excretion (6.4 ± 0.6) was significantly reduced by indomethacin (P < 0.002) and no further decrease occurred after captopril (7.4 ± 1.7 ng/min). The preceding 24 h urinary sodium excretion was comparable with that for the 24 h period without indomethacin (188 ± 21 mmol). Also, sodium and potassium excretion rates at 90 min before and 90 min after captopril remained unchanged, and were similar with and without indomethacin pretreatment (Table 1).

![Fig. 2. Correlation between log plasma renin activity (PRA) before captopril and the maximum decrease of mean arterial blood pressure (BP) after captopril.](image)

**Table 1. Sodium, potassium, aldosterone and PGE₂ excretion before and after captopril both without and with pretreatment with indomethacin.**

Sodium, potassium, aldosterone and PGE₂ excretion 90 min before (control) and 90 min after captopril both without and with pretreatment with indomethacin (200 mg). *P < 0.02 vs respective control level. **P < 0.002 vs without indomethacin.

<table>
<thead>
<tr>
<th></th>
<th>Without indomethacin</th>
<th></th>
<th>With indomethacin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control 90 min After captopril 90 min</td>
<td>After captopril 90 min</td>
<td>Control 90 min After captopril 90 min</td>
<td></td>
</tr>
<tr>
<td>Sodium (μmol/min)</td>
<td>208 ± 25</td>
<td>204 ± 32</td>
<td>204 ± 25</td>
<td>192 ± 38</td>
</tr>
<tr>
<td>Potassium (μmol/min)</td>
<td>106 ± 13</td>
<td>95 ± 12</td>
<td>104 ± 10</td>
<td>103 ± 10</td>
</tr>
<tr>
<td>Aldosterone (ng/min)</td>
<td>12.7 ± 1.6</td>
<td>8.2 ± 1.0*</td>
<td>6.4 ± 0.6**</td>
<td>7.4 ± 1.7</td>
</tr>
<tr>
<td>PGE₂ (pg/min)</td>
<td>217 ± 19</td>
<td>244 ± 23</td>
<td>72 ± 11**</td>
<td>80 ± 11**</td>
</tr>
</tbody>
</table>
Discussion

Captopril reduced blood pressure significantly less in normotensive sodium-replete subjects after pretreatment with indomethacin. Baseline blood pressure under indomethacin was not different, but heart rate was significantly lower both before and after captopril.

Indomethacin, in the dose given, was an effective inhibitor of PG biosynthesis, as demonstrated by the decrease of urinary PGE₂ excretion by about 70%. Inhibition of PG formation reduces the vasodilating capacity of the vasculature, and therefore induces an increase in peripheral vascular resistance [18]. A compensatory reduction of heart rate may have prevented both an increase of basal blood pressure under indomethacin and a more marked difference in the blood pressure lowering effect of captopril. Alternatively, indomethacin may have reduced heart rate and increased vascular resistance by decreasing vasodilating β-adrenoceptors, which mode of action has previously been suggested [19].

In two recent studies, rapid and short-lasting elevations of either immunoreactive PGE₂ [13] or of 13,14-dihydro-15-oxo-PGE₂ [20] in plasma have been reported after captopril, whereas in one of those studies, plasma 6-oxo-PGF₁α, the stable hydrolysis product of prostacyclin, remained unchanged after captopril [20]. In another study, however, the possible contribution of an increase of prostacyclin to the effects of captopril was discussed [21]. Thus the specific action of captopril on the PG system is unknown. Failure of urinary PGE₂ excretion to increase after captopril has also been observed in a previous study [22] and may be due to the fact that changes in urinary PG excretion do not necessarily reflect transient changes of vascular PG biosynthesis.

Renin release is controlled by intrarenal PG production [23, 24], and stimulated PG formation may contribute to the increase of PRA after captopril [12, 21]. Therefore the significant reduction by indomethacin of both baseline PRA before and stimulated PRA after captopril is most likely to be due to the effective inhibition of PG formation (Fig. 1). Furthermore, the significant positive relationship between pre-captopril PRA and the captopril-induced fall in blood pressure observed in subjects not pretreated with indomethacin was abolished under indomethacin pretreatment (Fig. 2). The disappearance of the positive correlation between pre-captopril PRA and post-captopril fall in blood pressure after indomethacin pretreatment suggests that indomethacin interferes with mechanism(s), probably prostaglandin synthesis, involved in the blood pressure lowering and renin stimulating effects of captopril.

Captopril induced a sustained fall in plasma aldosterone, aldosterone excretion and plasma 18-OH-B without indomethacin pretreatment. The effective decrease of ANG II formation by captopril is most probably the reason for the fall of the mineralocorticoid levels. Our results support the hypothesis that ANG II is a dominant stimulator even for 18-OH-B secretion [25]. Under indomethacin, basal aldosterone and 18-OH-B production was significantly reduced. This could be the result of both the inhibition of PG-mediated baseline renin secretion and hence reduced ANG II production, and the consequence of decreased adrenal PG formation, since these are possibly involved in the secretion of these mineralocorticoids [26]. The absence of a further decrease of aldosterone and the smaller reduction of 18-OH-B levels after captopril could then be due to their already diminished basal release as a result of indomethacin pretreatment.

Acknowledgments

This work was supported by Deutsche Forschungsgemeinschaft. The authors are grateful to B. Bauriedel, R. Herbst and B. Krischer for excellent technical assistance and to S. Havenstein for her secretarial assistance. The investigational drug was generously supplied by Dr R. K. Liedtke, Squibb, von Heyden, Regensburg, Federal Republic of Germany.

References


Indomethacin reduces captopril effects


