RELATIONSHIP BETWEEN BLOOD PRESSURE AND BLOOD LEVELS OF ANGIOTENSIN I CONVERTING ENZYME INHIBITOR (SQ 14,225)

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The time courses of mean blood pressure (MBP), plasma renin activity (PRA), plasma aldosterone (PA), serum prostaglandin E (PGE), serum angiotensin I converting enzyme (ACE), and blood levels of angiotensin I converting enzyme inhibitor (SQ 14,225) (captopril) were studied in 6 patients with essential hypertension (5 men and 1 woman, aged 44 ± 5.6 (mean ± S.E.) years) before and 30, 60, 120 and 180 min after administration of 25 mg captopril.

MBP and ACE began to fall within 30 min and reached a significant minimum between 60 and 180 min after captopril administration. PRA was significantly increased 60 min after captopril administration and continued for 180 min. On the other hand, PA had begun to fall significantly 180 min after captopril administration. The blood levels of captopril were significantly increased 30 min after captopril administration, with a peak at 120 min. The levels at 180 min were half the peak. The levels of PGE were not significantly changed within 180 min after captopril administration.

These results suggest a discrepancy between the changes in MBP and the blood levels of captopril. The blood pressure lowering effect may be due to inhibition of angiotensin II (Ang. II) during the short-acting effect, and due to decrease of PA, metabolites of captopril, increase of kinin in the blood, inhibition of the slow pressor effect of Ang. II, increases of other depressor hormones such as prostacyclin and other depressor mechanisms during the long-acting effect.

CAPTOPRIL (SQ 14,225) is a potent and specific angiotensin I converting enzyme inhibitor1−5. It has been clinically tried in the treatment of various types of hypertension6−9 i.e., essential hypertension, renovascular hypertension, and hypertension associated with renal insufficiency. So far, it has been suggested that the principal actions in the blood pressure lowering effect of captopril might be due to blockade of the formation of angiotensin II (Ang. II), and to potentiation of the depressor effect of bradykinin10−13. However, we have as yet very little information as to the relationship between the blood pressure lowering effect of captopril and its concentration in the blood, since a highly sensitive method for the determination of captopril in biological fluids has not been available.

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In this study, we investigated the discrepancy between the blood levels of captopril and its blood pressure lowering effect using our newly developed method for the determination of captopril in the blood.\textsuperscript{14}

**MATERIALS AND METHODS**

**Patients**

Six patients (5 men and 1 woman) with essential hypertension aged 25 to 63 years (mean: 44 ± 5.6 (S.E.)) were used as subjects. They had complete clinical examinations (including renal angiography) and known causes of secondary hypertension were excluded. Their basic clinical and laboratory data are presented in Table I. The serum levels of sodium and potassium, and glomerular filtration rates (GFR) were within normal limits in all patients. Antihypertensive therapy had been withheld for at least 3 weeks prior to this study. All subjects were on a diet containing 5–8g NaCl, daily.

**Test procedures**

Immediately after the control sample had been drawn at 9:00 a.m. after 2 hours recumbency, captopril was administered in a single oral dose of 25 mg and 4 other blood samples were obtained at 30, 60, 120 and 180 min later. These blood samples were determined for their plasma renin activity (PRA), serum prostaglandin E (PGE), plasma aldosterone (PA), serum angiotensin I converting enzyme (ACE), serum electrolytes and captopril.

The subjects were kept recumbent throughout the study. Blood pressure and pulse rate were measured automatically every 5 min for 30 min before the captopril administration and for 180 min thereafter. Mean blood pressure (MBP) was calculated as the diastolic pressure plus one-third of the pulse pressure.

PRA was determined using a CEI-IRE-SORIN kit. PA was determined by a radioimmunoassay technique as described previously.\textsuperscript{15} Serum PGE was measured with a kit from Clinical Assay Inc. Serum levels of ACE were estimated by the spectrophotometric assay of Lieberman.\textsuperscript{16} The measurements of ACE were done within 3–4 days after blood sampling, in order to avoid the effect of storage on ACE activity in blood samples.\textsuperscript{17} Blood captopril concentrations were determined by our newly developed method.\textsuperscript{14} Serum electrolytes were measured by flame photometry.

Statistical comparisons were made by Student's $t$ test for paired data.

**RESULTS**

The changes in MBP, PRA, PA, ACE, PGE, and blood captopril concentrations before and after captopril administration are summarized in Table II. MBP began to fall within 30 min and reached a significant minimum between 60 and 180 min. On the other hand, PRA was significantly increased 60 min after captopril administration ($p < 0.05$) and a peak was reached at 120 min. The mean level of PRA was still high.
180 min after captopril administration ($p < 0.05$).

PA began to fall significantly at 180 min after captopril administration ($p < 0.05$). The mean level at 180 min was 69.3% of the mean baseline level.

The mean level of ACE was significantly decreased 60 min after captopril administration ($p < 0.02$). The mean level 180 min after captopril administration was still significantly low.

The levels of PGE were not significantly changed within 180 min after captopril administration.

The blood levels of captopril were significantly increased after captopril administration ($p < 0.05$), with a peak at 120 min. However, the levels 180 min after captopril administration had decreased to half the peak at 120 min.

The mean levels of serum sodium, potassium, and chloride before captopril administration were $140.3 \pm 1.4$, $4.3 \pm 0.4$ and $104.3 \pm 3.7$, and those after were $140.8 \pm 1.3$, $4.1 \pm 0.5$ and $103 \pm 3.7$ (mean $\pm$ S.D.) mEq/L, respectively. There was no significant difference between the levels before and after captopril administration.

**DISCUSSION**

Several mechanisms have so far been reported for the depressor effect of captopril. In general, it is thought that this depressor effect may be due mainly to inhibition of Ang II and to potentiation of bradykinin. However, no report has yet discussed the relationships between blood levels of captopril, several hormones and blood pressure.

In the present study, investigations were made of changes in blood pressure, several hormones and blood levels of captopril. We found that the peak in blood levels of captopril occurred 120 min after the administration of captopril, and at 180 min the meal level was half the peak. However, the levels of MBP and ACE at 180 min were still significantly decreased, being as low as the levels 120 min after captopril administration.

On the other hand, the levels of PRA 180 min after captopril administration were slightly lower than those at 120 min but were still significantly high compared to the baseline levels. The levels of PA began to fall significantly 180 min after captopril administration.

Based on these results, it was apparent that discrepancies existed among the changes in MBP,
PRA, PA, ACE and blood levels of captopril after its administration. It is considered difficult therefore to explain the decreased MBP 180 min after captopril administration by the blood levels of captopril. Furthermore, it is worthy of note that there were remarkable discrepancies between the time courses of PA, PRA, ACE and blood captopril levels.

From the present study, it is speculated that changes in MBP, PRA and ACE followed changes in blood captopril first and that changes in PA followed afterwards. In any case, it is considered that the blood pressure lowering effect of captopril may be due to inhibition of Ang II during the short-acting effect, and to other factors as well as the decreased levels of PA during the long-acting effect.

It has been reported in general that the blood pressure lowering effect of captopril continues for about 6 hours. However, we cannot explain such a decreased blood pressure for 6 hours simply from blood levels of captopril, because the captopril levels at 6 hours after captopril administration will be more decreased compared to those at 3 hours.

Several authors have suggested other mechanisms, i.e., kinin and prostaglandins, for the blood pressure lowering effect of captopril apart from the inhibition of Ang II. However, we cannot regard PGE as a factor in the blood pressure lowering effect of captopril, since in the present study, the levels of PGE did not change within 180 min after captopril administration. Similar findings have been reported following kininase inhibition by captopril in dog and in human. However, we cannot exclude the possible role of prostaglandins as a depressor factor after more than 180 min.

We therefore propose several mechanisms which may be involved in the blood pressure lowering effect of captopril during the long-acting effect. The first is related to the pharmacological action of captopril. In general, it is thought that a time difference exists between the pharmacological action and levels of a pharmacological agent in the blood. It is speculated therefore that the blood pressure lowering effect of captopril may be partially due to metabolites, if captopril is changed to several metabolites. The second mechanism would involve changes in the kallikrein-kinin system as previously reported. However, detailed comments cannot be given on this since we did not measure the kinin in the blood. The third mechanism concerns the disappearance of Ang II in the blood. Bean et al reported that Ang II has a slow pressor effect. It is speculated therefore that the slow pressor effect of Ang II may disappear slowly with captopril. Finally, it is worthy to note the recent report of Dusting et al. They reported that angiotensin I stimulated the release of prostacyclin from rat mesenteric arterial wall. Thus, we are able to speculate that the accumulated angiotensin I following captopril administration may stimulate the release of vascular prostacyclin, and the released prostacyclin may decrease blood pressure.

From the present study, it is suggested that there is a discrepancy between the changes in MBP and the levels of captopril in the blood and that the blood pressure lowering effect may be due to inhibition of Ang II during the short-acting effect, and to decrease of PA, metabolites of captopril, increase of kinin in the blood, inhibition of the slow pressor effect of Ang II, and increases of other depressor hormones such as prostacyclin during the long-acting effect. Further studies will be required to clarify the mechanism of action of captopril.

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