NOTE

Effects of Various Doses of Captopril on Plasma Aldosterone Concentrations in Patients with Essential Hypertension

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Abstract

Various doses (5 mg, 12.5 mg and 25 mg) of angiotensin I converting enzyme inhibitor (SQ 14,225, captopril) were administered to 8 patients with essential hypertension on a three-crossover study design, and the time course of mean blood pressure (MBP), plasma renin activity (PRA), plasma angiotensin converting enzyme activity (ACE-A), plasma cortisol (PC) and plasma aldosterone (PA) were determined following administration of the drug. MBP fell in a dose dependent manner, and PRA showed a minor but significant increase in cases receiving 5 and 12.5 mg of the drug. A large and significant increase in PRA was observed following 25 mg of captopril. ACE-A was also reduced in a dose dependent manner. There was no difference between changes in PC at any of the three dose levels. The serum potassium concentration was determined before and 3 h after 25 mg of captopril treatment and no significant change was observed. In spite of the dose dependent and theoretical changes in the above parameters, lowered responses of PA to each dose of the drug were shown in reverse order against an increasing dose. That is to say, the grade of fall in PA following 25 mg of captopril was smaller than that following the other doses of the drug, and 5 mg induced a greater decrease in PA than 12.5 mg.

Based on these findings, the relatively high dose of captopril in the present study was apparently more effective in increasing some factors which suppressed reduction of PA by a fall in angiotensin II than a low dose of the drug.

The multiple actions of the angiotensin converting enzyme inhibitor, captopril (SQ 14,225), are due to inhibition of angiotensin II (A II) formation from angiotensin I (Gavras et al., 1978) and to potentiation of the biological action of bradykinin (Murthy et al., 1977). This duplicate action is attributable to the fact that angiotensin converting enzyme and kininase II are the same protein (Erdös and Yang, 1970). Theoretically therefore captopril should induce a hypotensive effect in patients whose hypertension depends mainly on factors other than the renin-angiotensin system. This is supported by the fact that captopril retained a significant hypotensive action in nephrectomized dogs (Vollmer et al., 1978). On the other hand, the possibility that extrarenal sources of renin (iso-renin) could be important in blood pressure regulation cannot be excluded (Ganten et al., 1976). Other data, however, have indicated a direct correlation between the degree of reduction in blood pressure after captopril administration and the pretreatment PRA value (Case et al., 1978). This suggests the possibility that captopril may have no effect in lowering blood pressure in low renin hypertension. Case et al.
(1977) reported that a nonapeptide inhibitor (SQ 20,881) was useful for reducing blood pressure in patients with normal and high renin hypertension but not in patients with low renin hypertension. Thus, the role of factors other than the renin-angiotensin system in the hypotensive mechanisms of captopril remains unclear. It is well known that a decrease in plasma aldosterone (PA) induced by captopril may follow the reduction in A II (Matthews et al., 1979). However, the place of PA reduction in the hypotensive mechanism of captopril should be secondary. The magnitude of the decrease in PA was significant but small compared to the fall in blood pressure noted in our previous study (Honda et al., 1981). On the other hand, exogenously administered kinin was found to induce a significant increase in PA in animal experiments (Eguchi et al., 1980). In addition, the role of changes in dopaminergic activity after captopril administration cannot be ruled out.

The present study was designed to examine which is more powerful in decreasing PA, a small dose or a relatively large dose of captopril, since the possibility exists that captopril-induced falls in PA are not necessarily in a dose-dependent order.

**Materials and Methods**

Eight patients with essential hypertension (EH) (7 males, 1 female) aged 33 to 58 years (41.3 ± 9.2, mean ± SD) were examined. The diagnosis of EH was established by excluding known causes of secondary hypertension. The patients were weaned off their medication for 2 weeks prior to admission. On admission to Nihon University Hospital, the patients were placed on a constant dietary regimen containing 7-8 g NaCl/day. A three-crossover study was designed in which 5, 12.5 and 25 mg doses of captopril were administered in three protocols, respectively, at 4-day intervals. The investigations were begun between 8 and 9 a.m. after overnight recumbency. Prior to administration of the drug, venous blood was drawn from the left antecubital vein. The subjects were given each dose of captopril and then venous blood was collected at 30, 60, 120 and 180 min after the treatment. The sampled blood was used to determine the angiotensin I converting enzyme activity (ACE-A), plasma renin activity (PRA), plasma cortisol (PC) and plasma aldosterone (PA). Serum potassium was determined before and 180 min after administration of 25 mg of captopril. Measurement of blood pressure was begun 20 min before the treatment at 10 min intervals, and continued until the last blood sampling, using an automatic sphygmomanometer (Nihon Koden Co., Tokyo). PRA was measured by radioimmunoassay employing the method of Haber et al. (1969). PA was determined by the radioimmunoassay developed by Nowaczynski et al. (1974). ACE-A was estimated by the spectrophotometric assay of Lieberman (1975). PC was measured using the kit of Le Commissariat à l'Energie Atomique, France. The results were expressed as mean standard error (SE). Statistical analysis was performed by Student's paired t-test, and P values of less than 0.05 were considered statistically significant.

**Results**

The responses of mean blood pressure (MBP) to each dose of captopril are expressed as percent changes in Fig. 1, A. There was no significant decrease throughout the period of observation when 5 mg of captopril was received. In the other cases receiving 12.5 and 25 mg, significant decreases occurred within 30 min, and maximum reductions were observed at 150 min in the case of 12.5 mg (−14.8%) and at 90 min in the case of 25 mg (−16.4%). Clear dose dependent decreases in MBP were shown within 90 min. However, similar changes in the two cases receiving 12.5 and 25 mg were observed from 120 min after treatment. The MBP in the cases receiving 12.5 and 25 mg of the drug revealed a slight upturn at 180 min.

The percent changes in ACE-A are shown in Fig. 1, B. Significant decreases began within 30 min in the case of both 5 and 25 mg, and within 60 min in the case of 12.5 mg. The levels of maximum decrease were −18.5% at 60 min in the case of 5 mg, and −28.7% at 120 min in the case of 25 mg. The reduced ACE-A in all cases revealed a slight upturn at 180 min after treatment.

Fig. 1, C shows the percent changes in PRA. Both 5 and 12.5 mg of the drug induced similar increases. The maximum levels were +179.7% at 60 min in the case of 5 mg, and 187.8% at
Fig. 1. Percent changes in mean blood pressure (MBP), plasma angiotensin I converting enzyme activity (ACE-A), plasma renin activity (PRA) and plasma aldosterone (PA) after administration of 5, 12.5 and 25 mg of captopril. Each point and vertical bar represent mean values + SE (n=8). The P values refer to a comparison with the values before administration of each dose of captopril.

120 min in the case of 12.5 mg. The largest increase in PRA was observed in the case receiving 25 mg, with a maximum level of +330.4% at 120 min.

As shown in Fig. 1, D, a significant decrease in PA began within 60 min and the minimum level was -22.5% at 120 min in the case of 25 mg. In the other two cases, a significant fall appeared from 30 min and the minimum levels were -36% at 120 min and -47.5% at 60 min in the case of 12.5 and 5 mg of captopril, respectively.

Slight and insignificant decreases in PC were observed in all cases, and there was no significant difference between the changes in PC in the three cases (Fig. 2). The serum potassium level was not altered by 25 mg of the drug within 3 h after treatment.

The absolute MBP, ACE-A, PRA, PA and PC values before each dose of drug administration are listed in Table 1.

Discussion

The renin-angiotension-aldosterone system is known to be important in the regulation of blood pressure. This concept is supported by many investigations where the trend of changes in PRA under a variety of physiological and pathological conditions appeared to influence the change in PA. There has been a good deal of evidence to indicate that PRA and PA
Table 1. Absolute values of the pretreatment levels of mean blood pressure (MBP), plasma renin activity (PRA), plasma angiotensin I converting enzyme activity (ACE-A), plasma aldosterone (PA) and plasma cortisol (PC) at each dose of captopril tested.

<table>
<thead>
<tr>
<th></th>
<th>before 5 mg</th>
<th>before 12.5 mg</th>
<th>before 25 mg</th>
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<tbody>
<tr>
<td>MBP (mmHg)</td>
<td>112.9 ± 3.6</td>
<td>115.7 ± 3.9</td>
<td>120.2 ± 9.2</td>
</tr>
<tr>
<td>PRA (ng/ml/h)</td>
<td>1.4 ± 0.4</td>
<td>1.9 ± 0.4</td>
<td>1.9 ± 0.3</td>
</tr>
<tr>
<td>ACE-A (U)</td>
<td>32.3 ± 1.8</td>
<td>30.9 ± 2.0</td>
<td>34.8 ± 4.2</td>
</tr>
<tr>
<td>PA (pg/ml)</td>
<td>97.4 ± 15.7</td>
<td>98.1 ± 18.5</td>
<td>91.0 ± 11.8</td>
</tr>
<tr>
<td>PC (µg/dl)</td>
<td>12.7 ± 2.1</td>
<td>10.5 ± 0.9</td>
<td>12.5 ± 1.6</td>
</tr>
</tbody>
</table>

change in parallel (Walker et al., 1976, Fraser et al., 1979). This relationship is due to the fact that A II plays the major role in the regulation of aldosterone secretion (Davis et al., 1961). Thus, the captopril-induced reduction in PA has been explained on the basis of decreased circulating A II resulting from inhibition of ACE-A. In our previous studies (Honda et al., 1981), 25 mg of captopril also caused a significant decrease in PA concomitant with a significant increase in PRA and decrease in blood pressure in patients with EH. However, we encountered some interesting and unexpected clinical examples where PA was not reduced by administration of 25 mg of the drug in spite of a fall in blood pressure and elevation of PRA. Similar exceptional cases were noted in a previous report by Bravo et al., (1979). They suggested that failure to inhibit aldosterone production sufficiently despite evidence of angiotensin blockade, might result from the presence of circulating A II at levels sufficient to maintain significant aldosterone production after administration of the drug. The possibility of increased ACTH or potassium retention was mentioned but dismissed because no significant changes in plasma cortisol and external potassium balance were observed.

Although a theoretical dose dependent reduction in PA was reported after intravenous infusion of SQ 20,881 in the study of Williams et al. (1978), a tendency for lower doses of captopril to be increasingly effective in reducing PA was observed in the present study. This demonstrates first that the captopril-changed PA does not have a direct relationship to the hypotensive mechanism of this drug. The inversely proportional changes in PA suggest several interesting hypotheses not only for elucidation of the hypotensive mechanism of captopril but also for investigation of the basic structure of hypertension. However, it is necessary first to clarify the mechanism underlying the present results.

The factors related to the regulation of PA include ACTH, the metabolic clearance rate of aldosterone (MCR), potassium balance and A II. The plasma ACTH was not determined in the present study but PC was essentially unchanged at each dose of captopril. An effect on the anterior pituitary cannot therefore be adduced to explain the complex changes in PA observed in the present study.

The possibility of changes in MCR requires careful consideration. The MCR of aldosterone was closely related with hepatic blood flow which was lower in an upright posture than a supine posture (Culbertson et al., 1951), and under A II infusion (Messerli et al., 1977). A captopril-induced increase in MCR was described by Honda et al. (1982). In this report, 25 mg of the drug was administered to patients with hypertension. The increase in MCR following captopril administration might be partially helpful in the reduction of PA. Since MCR is influenced by the plasma A II level, the value of MCR should be increased following captopril administration in a dose dependent manner. It is difficult therefore to explain the mechanism of the inconsistent-
looking changes in PA observed in the present study on the basis of MCR. The other factor which is known to play an important role in the regulation of aldosterone is the potassium balance (Bartter, 1956; Brunner et al., 1970). In our previous study, potassium loading significantly increased PA with a significant elevation of the serum potassium level (Ueda et al., 1982). However, there were no significant changes in the serum potassium level after the administration of 25 mg of captopril in the present study. The possibility of a potassium-induced change in PA can thus be excluded.

Another important factor which is changed after captopril administration is kinin. The role of captopril-increased kinin in the hypertensive action of the drug has been demonstrated in several reports (McCaa et al., 1978; Carretero et al., 1980). On the other hand, Eguchi et al. (1980) found that exogenously administered bradykinin enhanced PA in animal experiments. It is worthy of consideration therefore that captopril-enhanced kinin could influence the PA reduction which results from a decrease in A II. The correlation between the degree of increase in plasma kinin and that of captopril may be direct, so that the elevated kinin after administration of 25 mg of the drug could be stronger in inhibiting the PA reduction than that after 5 mg or 12.5 mg of the drug. A low dose of captopril might not have the ability to lower blood pressure and to elevate endogenous kinin. However, this dose should be sufficient for an A II-mediated fall in PA. On the other hand, 25 mg of captopril could lower blood pressure through a multiple action, due to a decrease in A II and an increase in kinin. Based on the above hypothesis explaining the mechanism underlying the present results, it is considered that excess kinin elevated by 25 mg of captopril could interrupt the reduction in PA. In addition, Hulthen and Hokfelt (1978) indicated that a higher dose of SQ 20,881 is required to inhibit kinin degradation than to inhibit angiotensin conversion. This was related to the report that purified converting enzyme from human lung has a specific activity for bradykinin which is 14 times higher than that for angiotensin I (Nishimura et al., 1977). Thus, 5 mg of captopril might act only in the conversion of angiotensin I, and 25 mg of the drug could exert a multiple action inhibiting both the conversion of angiotensin I and the degradation of kinin. However, although the present study supports the interaction of kinin and aldosterone, it does not prove it.

Another way to explain the present results is the role of a dopaminergic mechanism in controlling aldosterone secretion. Edwards et al. (1975) suggested the dopaminergic inhibition of aldosterone production, and this proposition has been supported by several investigators (McKenna et al., 1979, Carey et al., 1979, Noth et al., 1980). If changes in dopamine mediated a curious alteration in PA in the present study, it should be considered that captopril might suppress the dopaminergic activity in a dose dependent manner. In this theory, 25 mg of captopril might be a dose adequate to decrease the dopaminergic suppression of PA while 5 mg of the drug might be insufficient to do so. However, the role of dopamine under captopril administration is not clear, and the above mentioned possibility is too slight to discuss now.

We looked at possible explanations for a novel effect of captopril on PA, and because these were all constituted from indirect evidence, further studies on this problem will be required.

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