CAPTOPRIL IN SEVERE AND REFRACTORY HYPERTENSION

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The acute and long-term effects of captopril were investigated in 29 patients with hypertension. Of these, 23 had essential hypertension, five had hypertension secondary to chronic renal failure and one had coarctation of the aorta. Seventeen patients had refractory hypertension. The acute administration of captopril (25 mg) significantly decreased blood pressure in all patients. This antihypertensive effect correlated significantly when compared to basal plasma renin activity, in the upright position. During long-term treatment (10 ± 2 months), 93 per cent of the patients also required a diuretic and 48 per cent needed a beta-blocker as a third drug. Side effects were observed in two patients. Captopril alone or in association with a `diuretic or a beta-blocking drug was effective in 76.5 per cent of the patients with refractory hypertension.

Despite the several classes of antihypertensive drugs available today, the treatment of severe and refractory hypertension is still a difficult matter [1,2]. Very often the treatment in infects can dramatically change the patient's quality of life.

Converting enzyme inhibition has been a new approach to the treatment of hypertension. The efficacy of captopril, and orally active converting enzyme inhibitor, has been demonstrated in different types of human hypertension [3,4] and in different animal models of experimental

hypertension [5]. The fact, that the secondary effects of captopril due to its own hypotensive action are minimal, makes it an interesting drug in the treatment of hypertension. Although its efficacy has been demonstrated in severe, and in refractory hypertension, adequate control of blood pressure (BP) is not always achieved by captopril alone, and other drugs need to be added [6,7].

The purpose of the present study was to investigate the acute and long-term hypotensive effect of captopril alone and associated to a diuretic or a beta-blocker and to correlate the acute effects with the long-term effects. An attempt was also made to correlate these effects to the action of captopril on the renin-angiotensin-aldosterone system.

PATIENTS AND METHODS

Twenty-nine patients (18 males and 11 females) between 23 and 70 years of age (mean 46 ± 10 years) had been hospitalized for hypertension. Twenty-three patients had essential hypertension, five had hypertension secondary to chronic renal failure and one patient had coarctation of the aorta. Eighteen patients were in stage II of the WHO classification and 11 patients in stage III. All patients but one had previous antihypertensive treatment with a double or triple association (11 received a beta-blocker or methyldopa plus a diuretic, and 17 had a beta-blocker plus a diuretic plus a vasodilator). Seventeen patients, resistant to standard triple therapy, were considered as having refractory hypertension [1].

All the antihypertensive treatment was stopped for at least one week before beginning the study and all patients were given a diet with 120 mM of sodium per day.

Plasma renin activity (PRA) and plasma aldosterone level (ALDO) were measured by radioimmunoassay [8-9] in peripheral venous blood, collected from the patients after 60 minutes supinely and after 60 minutes in active orthostatic position. Patients then received 25 mg of captopril (CAP) orally and blood pressure was measured by mercury sphygnomanometer every 10 minutes during the first hour, every 20 minutes during the second hour, and every 30 minutes until the 4th hour. Phase V was used as measure of diastolic pressure. A second dosage of PRA and ALDO took place 180 minutes after the administration of captopril.

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Following this acute study patients were treated by CAP 25 mg t.i.d. This dose was increased at two-week intervals to 25 mg t.i.d. After the f our week titration period, furosemide (40 mg once daily or increased later to 40 mg b.i.d., if necessary) was added if supine diastolic pressure (SDBP) was greater than 95 mmHg. Propranolol was added if control of blood pressure (BP) under previous regimen was not achieved. In a few patients (n=3) with refractory hypertension, higher doses of captopril (less than 300 mg/day) were used.

Statistical evaluation used Student's t test and regression lines by the least square method. Results are expressed as mean ± SD.

RESULTS

Acute response to captopril - The acute effects of captopril on supine systolic (SSBP) and diastolic (SDBP) blood pressure, heart rate (HR), plasma renin activity (PRA) and plasma aldosterone, are illustrated in figure 1. The decrease in SSBP and SDBP was statistically significant from the 10th minute throughout to the 240th minute. The major hypotensive effect was achieved at 86 ± 39 minutes. SSBP dropped from 193.1 ± 29.1 mmHg to 161 ± 26.4 mmHg (P < 0.001) and SDBP from 117.3 ± 14.5 to 98 ± 34 mmHg. There was a modest but significant decrease in HR from 73 ± 12 to 68 ± 11 (P < 0.001) at the peak.

PRA increased from 4.03 ± 6.7 ng/ml/h to 10.87 ± 17.7 ng/ml/h (P < 0.01) on the third hour after the administration of captopril. ALDO decreased from 13.37 ± 12.5 ng,/100ml to 9.46 ± 9.5 ng/100 ml (P < 0.001).

No significant correlation was found between the acute BP response and the supine PRA (r = 0. 37, P < 0.1), nor between this acute effect on BP and the increase of PRA under CAP (r = 0.14, P > 0. 1). There was no correlation between the acute fall in BP and control ALDO. On the other hand, there was a significant relationship between control upright PRA and the decrease in SOBP (r = 0,43, P < 0.05).

Long-term effects of captopril - After the acute response, most of the patients had an increase in BP during the following two weeks and by the end of the second week, most of them had a significant increase in their SDBP (P < 0.001). Three subgroups were considered according to their acute response (fig. 2): a 1st group, those patients whose SDBP decreased less than ten per cent; a 2nd group, in whom decrease in pressure was between 10 and 20 per cent; and a 3rd group, whose SDBP decreased more than 20 per cent. In the 1st group, only one patient (25%) had an increase in SDBP by the end of the 2nd week; in the 2nd group, eight patients (42qo) had an increase in SDBP; and in the 3rd group, four patients (66.6%) had an increase in SDBP.

When the dose of captopril was increased from 75 mg per day to 150 mg per day, there was a small but non significant decrease in SDBF (P < 0.2) (fig. 3).

During long-term treatment (10 ± 2.8 months, range 6 to 15 months), 93.1 per cent of the patients required a diuretic (furosemide) and 48 per cent of these, needed a beta-blocker (propranolol) as a third drug. The effect of the diuretic on the SDBP in addition to that achieved by the converting-enzyme inhibitor was 13.5 ± 5.4% (P < 0.001), whereas the beta-blocker induced an additional decrease of 19.3 ± 5.5% (P < 0.001) to the previous levels.

Captopril alone or in association with diuretics and/or beta-blockers achieved the control of hypertension in 74% of patients.

In the group of patients with refractory hypertension, CAP (75 mg) alone controlled BP in one case, CAP (150 ± 82 mg) plus furosemide (80 ± 43 mg) was successful in five case and CAP (177.2 ± 57.8 mg) plus furosemide (94.5 35.2 mg) and propranolol (145.4 ± 19.2 mg) were used in 11 access land was successful in seven. Considering the overall number of patients with refractory hypertension, 76.5% of these had controlled BP.

Long-term response to CAP could not be predicted from the acute BP response (r = 0.27; P > 0.1).

Serum creatinine levels did not change significantly under CAP (199 ± 256 μmol/1 vs. 223 ± 344 μmol/1, P < 0. 6) even when the group of patients with impaired renal function was considered separately (358.4 ± 334.5 μmol/ 1 vs. 418.6 ± 469 μmol/1, P < 0-6). The group of patients with normal renal function had no increase in creatinine levels (86.7 ± 13.2 Amol/1 vs. 84.9 ± 14.1 μ/mol/1).

Serum potassium levels increased significantly (4.0 ± 0.5 mmol/1 vs. 4.5 ± 0.6 mmol/1. P < 0. 005). This increase was still significant when the patients with renal impairment were eliminated from the group. There was a slight, but non significant decrease in potassium levels after the addition of furosemide (4.5 ± 0.6 mmol/1 vs. 4.3 ± 0.5 mmol/1 P < 0.10). After the association of propranolol, a small but non significant increase in this level was observed (4.3 ± 0.3 mmol/1, P < 0.20).

Side-effects - Captopril was well-tolerated in al. most all the patients. Severe hypotension after the first dose was not observed. Disorders of taste developed in two patients (6.8%) and the medication was discontinued in one of them. There was no change in total or fractional white blood cell count.

Four patients had significant proteinuria before entering the study, which did not increase under treatment with CAP. On the contrary, it decreased slightly during long-term treatment. The patients without previous proteinuria did not develop this anomaly during the study.

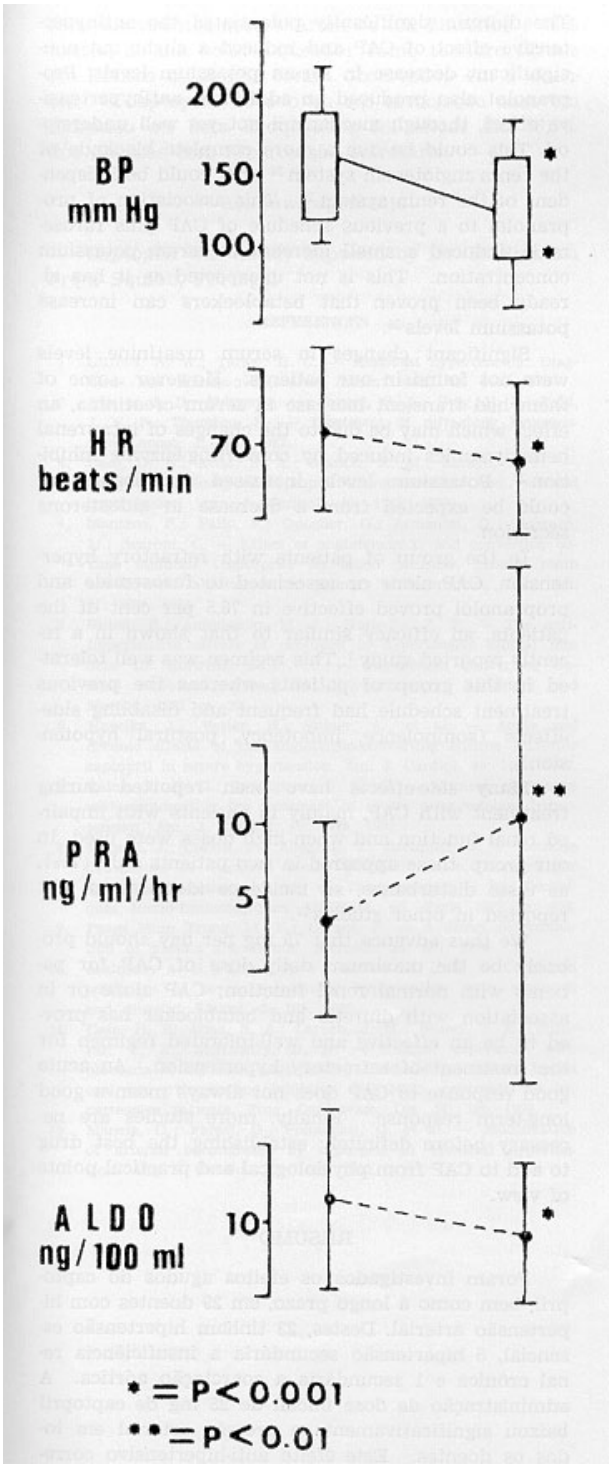

Fig. 1 - Changes in blood pressure (BP), heart (HR), plasma renin activity (PRA) and plasma aldosterone (ALDO) following a single oral single dose of captopril (25 mg). Data are shown as mean ± SD.

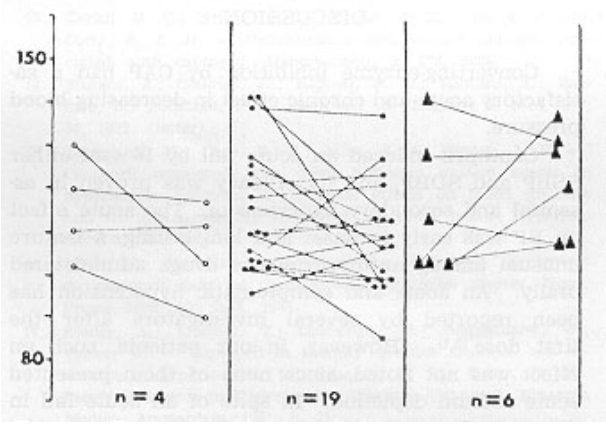

Fig. 2 - Blood pressure and after two weeks treatment with captopril. Open circles indicate patients having a less than ten per cent decrease in diastolic blood pressure; full circles indicate patients having a ten to twenty per cent fall; triangles indicate patients having a more than twenty per cent fall.

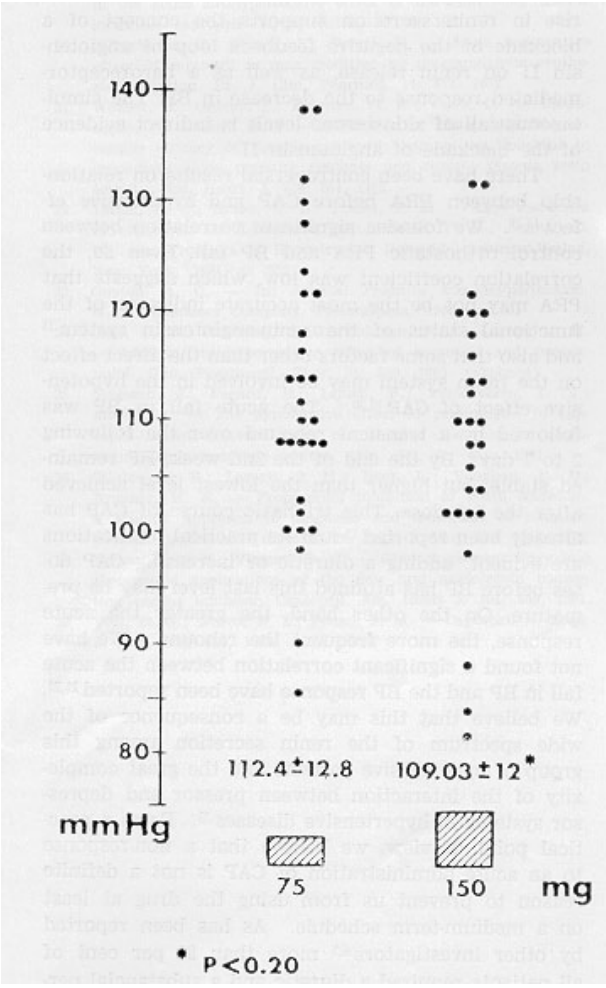

Fig. 3 - Changes in diastolic blood pressure induced by increasing the daily dose of captopril from 75 to 150 mg

DISCUSSION

Converting-enzyme inhibition by CAP had a satisfactory acute and chronic effect in decreasing blood pressure.

Captopril induced an acute fall by 16% of either SSBP and SDBP, and its efficacy was proven in essential and secondary hypertension. The acute effect on BP was early in onset and long-lasting, a feature unusual among antihypertensive drugs administered orally. An acute and symptomatic hypotension has been reported by several investigators after the first dose [10,11]. However, in our patients, such an effect was not noted, since none of them presented acute sodium depletion. In spite of an acute fall in BP, HR did not increase. Actually, there was a significant decrease of HR at the peak. The mechanisms involved in this hemodynamic feature of CAP are not completely understood. Pontentiation of baroreceptors [12], venous dilation 13 and increase of parasympathetic activity have been suggested [14]. The reactive rise in renin secretion supports the concept of a blockade of the negative feedback loop of angiotensin II on renin release, as well as a baroreceptormediated response to the decrease in BP. The simultaneous fall of aldosterone levels is indirect evidence of the blockade of angiotensin II.

There have been controversial results on relationship between PRA before CAP and hypotensive effect [15-17]. We found a significant correlation between control orthostatic PRA and EP fall. Even so, the correlation coefficient was low, which suggests that PRA may not be the most accurate indicator of the functional status of the renin-angiotensin system land also that some factors other than the direct effect on the renin system may be involved in the hypotensive effect of CAP [19,20]. The acute fall in BP was followed by a transient rebound over the following 2 to 7 days. By the end of the 2nd week, BP remained stable, but higher than the lowest level achieved after the 1st dose. This triphasic course of CAP has already been reported 15 and its practical implications are evident: adding a diuretic or increasing CAP doses before BP has attained this last level may be premature. On the other hand, the greater the acute response, the more frequent the rebound. We have not found a significant correlation between the acute fall in BP and the BP response have been reported [21,22]. We believe that this may be a consequence of the wide spectrum of the renin secretion among this group of hypertensive patients and the great complexity of the interaction between pressor and depressor systems in hypertensive diseases [23]. From a practical point of view, we believe that a non-response to an acute administration of CAP is not a definite reason to prevent us from using the drug at least on a medium-term schedule. As has been reported by other investigators [6,7] more than 90 per cent of all patients required a diuretic and a substantial percentage of them needed a beta-blocker as a third drug.

The diuretic significantly potentiated the antihypertensive effect of CAP and induced a slight but non-significant decrease in serum potassium levels. Propranolol also produced an additional antihypertensive effect, through mechanism not yet well understood. This could be due a more complete blockade of the renin angiotensin system [24] or it could be independent of the renin system [25]. This association of propranolol to a previous schedule of CAP plus furosemide induced a small increase in serum potassium concentration. This is not unexpected as it has already been proven that beta-blockers can increase potassium levels [26].

Significant changes in serum creatinine levels were not found in our patients. However, some of them had transient increase in serum creatinina, an effect which may be due to the changes of intra-renal hemodynamics induced by converting-enzyme inhibition [27]. Potassium levels increased significantly as could be expected from a decrease in aldosterone secretion.

In the group of patients with refractory hypertension, CAP alone or associated to furosemide and propranolol proved effective in 76.5 per cent of the patients, an efficacy similar to that shown in a recently reported study [2]. This regimen was well tolerated in this group of patients whereas the previous treatment schedule had frequent and disabling side effects (somnolence, impotency, postural hypotension).

Many side-effects have been reported during treatment with CAP, mainly in patients with impaired renal function and when high doses were used. In our group, these appeared in two patients only (7%), as taste disturbance, an incidence identical to that reported in other studies [28].

We thus advance that 75 mg per day should probably be the maximum daily dose of CAP for patients with normal renal function; CAP alone or in association with diuretic and beta-blocker has proved to be an effective and well-tolerated regimen for the treatment of refractory hypertension. An acute good response to CAP does not always mean a good long-term response. Finally, more studies are necessary before definitely establishing the best drug to add to CAP from physiological and practical points of view.

RESUMO

Foram investigados os efeitos agudos do captopril, bem como a longo prazo, em 29 doentes com hipertensão arterial. Desses, 23 tinham hipertensão essencial, 5 hipertensão secundária a insuficiência, renal crônica e 1 secundária à coarctação aórtica. A administração de dose inicial de25 mg de captopril. baixou significativamente a pressão arterial em todos os doentes. Esse efeito anti-hipertensivo correlacionou-se significativamente com atividade da renina plasmática basal, medida em ortostatismo. Durante o tratamento a longo prazo (10 ± 2 meses),

93% dos doentes necessitaram de um diurético e 48% desses, de um betabloqueador como terceiro fármaco. Efeitos colaterais foram observados em 2 doentes. O captopril, isolado ou em associação com um diurético ou beta-bloqueador foi eficaz em 76,5% dos doentes com hipertensão refratária.

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