THE EFFECTS OF CAPTOPRIL ON PULMONARY AND SYSTEMIC ARTERIAL PRESSURES AND LIPOPROTEIN METABOLISM IN HIGH-ALTITUDE PULMONARY HYPERTENSION

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SUMMARY: The purpose of investigation was to assess the effect of captopril on both systemic and pulmonary arterial pressures (PAP) and lipoprotein metabolism in patients with high-altitude pulmonary hypertension (HAPH). Seventeen patients (mean age 44 ± 6.8 years) with HAPH and mild-moderate systemic arterial hypertension were included into the study. All the patients underwent right heart catheterization with measurements of systolic PAP (PAPs), mean PAP (PAPm), diastolic PAP (PAPd). After 4 weeks placebo phase patients with PAPs>25 mm Hg, PAPm>15 mm Hg and systemic diastolic blood pressure (DBP)> 100 mmHg received captopril (50-75 mg at 8 am) for a period of 12 weeks. Following both the placebo and at the 12-week treatment periods, at 8 am and after 12 hours fasting, blood samples were obtained for analysis of total cholesterol, triglycerides, apolipoprotein A1, apolipoprotein B. Patients with preexisting hypercholesterolemia (>250 mg/dl) and/or triglyceridemia (≥ 200 mm/dl) were excluded from the analysis. The statistical evaluation of the results were made using the Student's t tests. It was found that captopril significantly decreases pulmonary and systemic arterial hypertensions without any side effects on lipoprotein metabolism.

Key Words : Captopril, pulmonary hypertension, systemic hypertension, high altitude pulmonary hypertension.

INTRODUCTION

There presently seems to be considerable controversy concerning the underlying pathophysiologic mechanisms and the treatment of high altitude pulmonary hypertension (HAPH). Previous studies (9,15,22,24) have reported the salutary effects of different vasodilators such as hydralazine, phentolamine, isoproterenol, nifedipine in management of pulmonary hypertension. On the other hand long term use of these medications is limited by the development of undesirable effects as activation of sympathetic influences, increase of renin level or reduced number of favorable responders to the treatment among the patients (22,26). These considerations appear to be more important in cases of HAPH with concurrent systemic hypertension.

Among the main side effects of commonly used anti-hypertensive agents as diuretics and ß blockers are the disturbances of the lipid metabolism (1,7). In fact significant interest resulted initially from the known direct effects of them to lipid profile and secondly from epidemiologic findings (4,12).

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Angiotensin-converting enzyme (ACE) inhibitors on the other hand currently used in treatment of hypertension turned to be free of side effects (13,16,20,30). However the influence of ACE inhibitors on pulmonary and systemic hypertension and lipid metabolism in HAPH patients has presently not been clearly understood.

The aim of the present study was initially to determine the effects of long acting ACE inhibitor capoten on pulmonary and systemic pressures and secondly to evaluate its action on lipid metabolism during one month treatment of high-altitude pulmonary and systemic hypertension.

MATERIALS AND METHODS

Subjects used in this study were 17 outpatients (4 males) aged 40-58 years, with stable mild-to-moderate essential hypertension and high-altitude pulmonary hypertension. Exclusion criteria were severe or secondary systemic and pulmonary hypertension, myocardial infarction within the previous year, arrhythmias, angina pectoris, significantly abnormal clinical laboratory values, major organ failure, psychosis, current medication with other agents known to affect blood pressure, patients with preexisting hypercholesterinemia (>250mg/dl), and/or hypertriglyceridemia (≥200 mg/dl). Written informed consent was obtained from each subject. Patients on current anti-hypertensive therapy were gradually withdrawn from this treatment; new therapy were entered directly. Prior to admission, patients were instructed not to make any dietary changes during the course of the study.

Following a 4-week placebo phase, patients with PAPs>25 mm Hg, PAPm>15 mmHg and DBP>100 mm Hg received capoten (50-75 mg at 8 am.) for a period of 12 weeks. If need be to achieve a satisfactory blood pressure control, indapamide (2.5 mg at 8 am) was co-prescribed at eighth week. Monthly recordings of systemic blood pressure (systolic blood pressure-SBP; diastolic blood pressure DBP), PAP (PAPs, PAPm and PAPd) and heart rate (HR) were taken according to the American Heart Association recommendation and each patient was questioned about adverse drug reactions. Following both the placebo phase and at the end of the 12-week period, at 8 am after a 12-hour fast, blood was obtained for plasma lipid, blood glucose assays. Plasma samples were analyzed for triglycerides (27), total cholesterol (8), high density lipoprotein (HDL) (10,14) apolipoprotein A1 (23), apolipoprotein B (17), glucose and glycosylated hemoglobin (HbAlc) (29).

Observed values from the end of the placebo phase were compared with those from the end of the 12-week treatment phase using the Student's t tests. Level of statistical significance was taken as $p<0.05$.

Table 1: Changes in heart rate (HR), systemic and pulmonary blood pressures during capoten therapy (mean ± SD).

Variable	Baseline	Placebo	12 weeks
PAPs (mm Hg)	42 ± 5	40 ± 7	28 ± 3*
PAPm (mm Hg)	33 ± 4	31 ± 5	21 ± 3*
PAPd (mm Hg)	24 ± 2	23 ± 3	16 ± 2*
SBP (mm Hg)	158 ± 10	156 ± 9	140 ± 8*
DBP (mm Hg)	106 ± 6	104 ± 4	86 ± 3*
HR (beats/min.)	68 ± 5	66 ± 5	68 ± 5

* P < 0.001 differences are significant between baseline value and 12 weeks of treatment.

RESULTS

All 17 patients completed the study. During the placebo phase, there was no significant change in systemic (SBP, DBP), pulmonary (PAPs, PAPm and PAPd) blood pressures and HR. A significant decrease in both systemic and pulmonary arterial blood pressures ($p<0.001$) was observed following capoten administration. The largest decrease was noted during the first month of therapy, but a decrease was noted even on the last visit (Table 1). There was no significant variation in mean HR. Normalization of systemic blood pressure (i.e. DBP<90 mmHg) was reported in 13 patients on capoten monotherapy; and on 17 patients receiving capoten plus indapamide (co-therapy) when indicated.

Table 2: Concentrations of blood lipid profile during capoten therapy (mean±SD).

Variable	Placebo	12 weeks
Total Cholesterol (mg/dl)	234 ± 30	231 ± 28
High density lipoprotein (mg/dl)	45 ± 8	52 ± 5
Triglycerides (mg/dl)	143 ± 64	150 ± 76
Apolipoprotein A1 (mg/dl)	150 ± 31	147 ± 25
Apolipoprotein B (mg/dl)	143 ± 22	136 ± 35
Glucose (mg/dl)	105 ± 29	100 ± 37
Hemoglobin A1c (%)	5.5 ± 1	5.3 ± 1

There was no change with respect to blood lipid profile during the trial. Glucose metabolism was unchanged by capoten therapy (Table 2).

DISCUSSION

Influence of capoten on pulmonary and systemic blood pressures

Previous studies have reported hemodynamic effects of capoten on pulmonary circulation (3,19). Niarchos A.P. *et. al.* (19) have shown the significant decrease of both pulmonary and systemic vascular resistance after capoten treatment in patients with pulmonary hypertension secondary to collagen vascular disease. Some previous experimental findings also have indicated that ACE inhibitors diminish pulmonary pressure both in vivo and in vitro conditions (2). Our results confirmed preliminary reports (2,3,19,25) and extends them by showing benefits of capoten treatment in patients with HAPH and concurrent systemic hypertension. Pulmonary and systemic pressures decreased significantly after capoten use, however in the control series the same parameters remained constant throughout the treatment. There was no significant change in heart rates. Capoten monotherapy produced an anti-hypertensive effect in large group of patients (82,3%). It was well tolerated, with only two patients reporting side effects (1 diarrhea, 1 dry cough).

The mechanisms responsible for high pulmonary and systemic pressures in high-altitudes are still not clearly described. The possible explanation for salutary vasodilator action of capoten in HAPH and systemic hypertension is to be conditioned by influences on renin-angiotensin system. Several experimental and clinical studies have registered disturbances of neurohormonal regulation information of HAPH (18,28). Milledge G.S. *et. al.* (18) have obtained increased levels of plasma renin in high-altitudes. It was proposed that activity of plasma renin level is stimulated by hypoxia (28). It has been demonstrated that 45 minutes of hypoxia (12% of oxygen) induced elevation of plasma renin activity by 50% in subjects with high pulmonary arterial pressures (28). Although beneficial effects of capoten were shown in the studies of longer duration their underlying mechanisms are presently subject to further evaluation.

Effects of capoten on lipoprotein metabolism

We in these series of experiments did not observe any significant changes of total cholesterol and lipoprotein levels during one month treatment. These findings seem to support the results of the former reports (13,30). However some experimental studies suggest a possible reduction of atherosclerosis, produced by ACE inhibitors (5). Newer studies reveal that this reduction in cholesterol levels was not sufficiently documented. In an important study by Costa *et. al.* (6) patients with relatively high cholesterol values (mean value of 287 mg/dl) were reduced after six months of captopril therapy to a mean 247 mg/dl. On the other hand, in a group of patients with a lower initial cholesterol, namely 205 mg/dl, captopril therapy was associated with a minor and insignificant increase in the level (21). Furthermore in two other studies, captopril administration has been associated with an increase in 'beneficial' high-density lipoprotein concentration (6,11). In conclusion it is fair to say that ACE inhibitor therapy does not cause a significant increase circulating cholesterol and may, at least, sometimes, reduce it. Capoten is therefore found to be effective during one month management of high-altitude pulmonary hypertension with concurrent systemic hypertension without any adverse changes in lipid profile.

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