CONTROL OF ESSENTIAL HYPERTENSION WITH CAPTOPRIL, AN ANGIOTENSIN CONVERTING ENZYME INHIBITOR

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1 Captopril, an orally active angiotensin converting enzyme inhibitor, was compared with hydrochlorothiazide (HCT) in the treatment of mild and moderate essential hypertension.

2 Twenty outpatients received no antihypertensive therapy for 2 weeks, after which they were given placebo for 8 weeks. Since their diastolic blood pressure remained above 100 mm Hg, they were then randomized to receive either captopril (twelve patients) or HCT (eight patients) for a 4-week titration period. If the supine diastolic blood pressure (SDBP) was normalized, (≤ 90 mm Hg) by the end of the titration period, the established regimen was continued for an 8-week maintenance period; if not, the alternate drug was added in increasing doses for up to 4 weeks and the combined therapy was maintained for the remaining 4 weeks.

3 After the first 4 weeks of therapy, both groups showed a statistically significant decrease in both systolic and diastolic blood pressure. Normalization of SDBP occurred in 75% of patients treated with captopril alone, and the addition of HCT produced normalization in the remainder. HCT alone resulted in normalization of SDBP in 50% of patients and the blood pressure of the remaining patients was normalized after the addition of captopril.

4 Captopril given orally, either alone or in conjunction with HCT, is an effective agent for the control of mild and moderate essential hypertension.

5 In our series the main side effects encountered were vertigo and dizziness, transient eosinophilia, a rise of BUN and or/a rise of SGPT or SGOT.

Introduction

Elevated arterial pressure is associated with a significantly greater risk of cardiovascular morbidity and mortality (Paul 1971; Miall & Chinn, 1974; Millar-Craig, Bishop & Raftery, 1978). Effective control of hypertension is now accepted as a means of reducing such complications (Veterans Administration Cooperative Study Group, 1967, 1970; Berglund, Sannerstedt, Anderson, Wedel, Wilhelmsen, Hansson, Sivertsson & Wikstrand, 1978). Unfortunately, the various major classes of antihypertensive drugs have unwanted symptomatic or biochemical side effects and furthermore not every patient responds to therapy (Atkinson & Robertson, 1979).

The renin-angiotensin system has been implicated as one of the aetiological factors of hypertension (Laragh, Baer, Brunner, Buhler, Sealey & Vaughan, 1972). Inhibition of the angiotensin converting enzyme

(ACE), which is responsible for the conversion of angiotensin I to angiotensin II, a powerful vasoconstrictor, can significantly reduce elevated blood pressure (Wallace, Keim, Weber, Sealey & Laragh, 1977).

Captopril (SQ 14, 225) is a potent orally active specific inhibitor of ACE. (Cushman, Cheung, Sabo & Ondetti, 1977) which has been reported to lower the blood pressure in patients with severe essential (Case, Atlas, Laragh, Sealey, Sullivan & McKinstry, 1978), as well as renovascular (Gavras, Brunner, Turini, Kershaw, Tift, Cuttelod, Gavras, Vukovich & McKinstry, 1978; Case *et al.*, 1978) hypertension.

The purpose of this study was to assess the efficacy and safety of captopril in comparison with hydrochlorothiazide in the treatment of mild to moderate essential hypertension.

Methods

Twenty patients from the hypertension outpatient clinic of Ain Shams University Hospital, Cairo, were included in this study. Sixteen were females and four were males, with a mean age of 52.3 years (range 45 to 63 years). All patients had mild to moderate hypertension graded as stage 1 or 2 according to the WHO classification. Supine diastolic blood pressure (SDBP) was the main criterion for inclusion in the study and for judging responses to therapy. Mild and moderate hypertension were defined as SDBP of 100 to 110 mm Hg and 111 to 120 mm Hg, respectively. An SDBP of ≤ 90 mm Hg was considered to be the therapeutic objective and was termed normalization. Blood pressure was measured at approximately the same time of day on every visit to avoid circadian variations (Millar-Craig *et al.*, 1978), with supine readings taken after 10 min of recumbent rest and standing readings after 2 min in an erect position. Blood pressure was measured by the same person throughout the study; this person was unaware of the patient's medication.

None of our patients had a history of drug or other significant allergy, gastrointestinal disease which could affect drug absorption, or serious renal impairment. They received no anti-hypertensive medication for 2 weeks before entering the study to better judge the severity of their hypertension. (Prior to these 2 weeks, all but one patient had been receiving reserpine.) The study then was subdivided into three periods:

Period A (8 weeks)

Placebo tablets were given three times a day. At the end of the first 4 weeks, which were considered to be an appropriate washout period, baseline blood pressure readings were obtained. The second 4 weeks were designed to identify and eliminate from further study those patients whose SDBP fell below 100 mm Hg on placebo therapy.

Period B (4 weeks)

Patients were randomly assigned to treatment groups according to a 3:2 ratio of captopril and hydrochlorothiazide (HCT) populations. Captopril was given three times daily starting with a total daily dose of 75 mg, which was increased weekly to a maximum of 450 mg if SDBP remained above 90 mm Hg. HCT was given twice a day for 2 weeks in a dose of 50 mg/daily, which was increased to 100 mg for another 2 weeks if needed. Patients' salt intake was not modified.

Period C (8 weeks)

Patients whose SDBP decreased to normal in period

B were maintained on the same therapy during this period. Patients whose blood pressure was not fully controlled had the alternate drug added to their antihypertensive dosage regimen, with the dose being titrated in the same fashion as in period B. The dose of the combination which most adequately controlled the blood pressure was then continued for the remaining portion of the 8 weeks.

Each patient underwent a battery of laboratory investigations every 4 weeks. These included a haemogram, (haemoglobin, haematocrit, total and differential leucocytic count and platelet count) blood chemistries (total serum protein, albumin, cholesterol, BUN, uric acid, bilirubin, alkaline phosphatase, LDH, SGPT, SGOT, glucose, creatinine, calcium, phosphorus, sodium, potassium, chloride and CO_2) and urinalysis. Haemograms were also performed at fortnightly intervals.

Results

None of our patients responded on placebo during period A. Twenty patients were thus given active treatment.

Of the twelve patients randomized to the captopril treatment group, ten were females and two were males, with an average age of 51.9 years (range 45 to 63 years). The eight patients who received HCT included six females and two males, with an average age of 52.8 years (range 45 to 62 years).

Comparison of blood pressure responses achieved at the end of washout (middle of placebo period) and at the end of placebo treatment periods revealed that none of the patients had an observable placebo response; in fact, the average blood pressure of the twenty patients increased from 180.1/109 to 184/111 mm Hg.

Table 1 shows the drug dosage used for maintenance of full response.

Table 2 compares mean blood pressures of captopril- and HCT-treated groups at the end of placebo period A with those at the end of dose titration period B. The twelve patients who received captopril showed significant decreases in both supine systolic (SSBP) and supine diastolic blood pressures, with a mean percent decrease of 20.56 ± 5.5 in SSBP ($P < 0.001$) and 17.38 ± 5.4 in SDBP ($P < 0.01$). The eight patients who received HCT also showed a statistically significant decrease in both SSBP and SDBP, with a mean percent decrease of 13.86 ± 13.5 ($P < 0.05$) and 14.4 ± 7.5 ($P < 0.01$), respectively. There were no statistically significant differences between the mean percent decreases in the two groups.

Nine of the twelve patients who received captopril had their blood pressure normalized at the end of period B. They were maintained on the same dose of

Table 1 Drug dosage used for maintenance of full response

<i>Drug group</i>	<i>Total daily dose (mg)</i>	<i>Number of patients</i>	<i>Drug group</i>	<i>Total daily dose (mg)</i>	<i>Number of patients</i>
Captopril (CP)	75 150 300 450	1 3 4 1	Hydrochloro-thiazide (HCT)	50 100	1 3
CP + HCT	450 CP + 50 HCT	3	HCT + CP	100 HCT 75 CP 100 HCT + 150 CP	2 2
Total number of patients		12	Total number of patients		8

Table 2 Mean $\pm$ s.e. mean supine blood pressures at end of placebo (A8) and dose titration (B4) periods

<i>Drug</i>	<i>Number of patients</i>	<i>Supine blood pressure (mm Hg)</i>		<i>Mean % decrease</i>		<i>P</i>
			<i>Week A8</i>	<i>Week B4</i>		
CP	12	Systolic	186.0 $\pm$ 10.6	147.5 $\pm$ 9.5	20.56 $\pm$ 5.46	<0.001
		Diastolic	111.0 $\pm$ 4.0	91.7 $\pm$ 6.3	17.38 $\pm$ 5.43	<0.01
HCT	8	Systolic	181.4 $\pm$ 8.1	156.3 $\pm$ 26.3	13.86 $\pm$ 13.495	<0.05
		Diastolic	110.0 $\pm$ 5.0		14.4 $\pm$ 7.46	<0.01

*Differences between treatment groups not statistically significant.

captopril throughout the eight weeks of period C and the blood pressure of all of them remained under control. The remaining three patients had HCT (50 mg/day) added to their therapy, and their SDBP dropped from a mean of 100 ± 8.7 mm Hg at the end of period B to 81.75 ± 5 mm Hg at the end of period C. Four of eight patients were normalized on HCT alone (one on 50 mg/day and three on 100 mg/day). Two of the four remaining patients needed the addition of 75 mg/day of captopril and two required 150 mg/day to achieve normalization of their blood pressure.

Figure 1 illustrates serial average blood pressure responses for all patients throughout the study. Table 3 shows the blood pressure responses during the titration and the second drug and maintenance periods. The greatest percent decrease of SDBP occurred in the captopril-treated patients who had HCT added to their regimen, as shown in Figure 2.

One patient receiving 100 mg HCT daily experienced a sharp though asymptomatic drop of blood

pressure for three hours after the first 25 mg dose of captopril was added to his regimen.

Side effects consisted of three complaints of vertigo or dizziness in the captopril-treated group and one report of dizziness and one of fatigue in the HCT-treated group. Eosinophilia with absolute counts ranging from 325 to 876 mm³ occurred in four patients in the initial weeks of starting captopril and in one patient in HCT. The counts dropped to normal with continuation of therapy.

The post-treatment mean values of the biochemical parameters for all patients on captopril did not show any statistically significant change from the pre-treatment values. However, elevation of BUN, just exceeding the upper limit of our laboratory normal range, occurred in two patients, one on captopril alone and the other on combined therapy. Also, four patients on combined therapy showed an elevation of SGPT that ranged between 10–25% above the upper normal limits, and one of them also showed a similar rise in SGOT.

Table 3 Serial BP responses (mean $\pm$ s.e. mean) for all four groups of medication throughout the study period. For time of stages see **Figure 1**.

Stage		Captopril alone	CP + HCT	HCT alone	HCT + CP
C1	SBP	143.67 $\pm$ 15.40	158.33 $\pm$ 10.41	134.25 $\pm$ 18.19	143.75 $\pm$ 11.09
	DBP	86.90 $\pm$ 5.29	99.33 $\pm$ 7.51	85.25 $\pm$ 7.09	91.50 $\pm$ 7.23
C2	SBP	135.67 $\pm$ 7.33	132.67 $\pm$ 7.51	130.00 $\pm$ 0.00	138.00 $\pm$ 16.41
	DBP	85.11 $\pm$ 6.13	84.33 $\pm$ 8.14	83.00 $\pm$ 3.56	86.25 $\pm$ 9.46
C3	SBP	136.67 $\pm$ 9.39	129.67 $\pm$ 21.46	134.25 $\pm$ 7.80	140.00 $\pm$ 7.48
	DBP	85.22 $\pm$ 4.24	84.33 $\pm$ 8.14	85.25 $\pm$ 0.96	90.25 $\pm$ 2.06
C4	SBP	136.00 $\pm$ 7.76	116.67 $\pm$ 10.07	131.75 $\pm$ 4.03	133.75 $\pm$ 7.68
	DBP	83.22 $\pm$ 3.87	78.67 $\pm$ 7.57	82.50 $\pm$ 5.57	87.75 $\pm$ 2.63
C6	SBP	131.89 $\pm$ 6.55	126.00 $\pm$ 5.59	128.00 $\pm$ 12.75	129.75 $\pm$ 8.88
	DBP	79.44 $\pm$ 4.98	82.67 $\pm$ 2.52	82.00 $\pm$ 7.83	86.25 $\pm$ 3.50
C8	SBP	139.56 $\pm$ 9.82	128.33 $\pm$ 22.55	133.25 $\pm$ 9.00	131.75 $\pm$ 6.95
	DBP	83.33 $\pm$ 3.24	81.67 $\pm$ 6.51	84.75 $\pm$ 4.99	85.25 $\pm$ 2.22

Discussion

Angiotensin II, the highly potent vasoconstrictor agent, is an octapeptide produced by cleavage of a two aminoacid fragment from the carboxyl-end of the decapeptide angiotensin I. The enzyme responsible for this conversion, peptidyl dipeptide hydrolase or angiotensin converting enzyme, is also partially responsible for the inactivation of the most potent naturally occurring vasodepressor agent, bradykinin (Erdos, 1975). Thus, the inhibition of this enzyme not only might be expected to block the production of angiotensin II but also might prevent the degradation of bradykinin, both of which may be important in the control of elevated blood pressure (Williams & Hollenberg, 1977).

Decreasing the blood level of angiotensin II has been shown to produce a decrease in blood pressure (Brunner & Gavras, 1976). Captopril, an orally active angiotensin converting enzyme inhibitor, competitively inhibits the conversion of angiotensin I to angiotensin II and simultaneously blocks the inactivation of bradykinin. These actions suggest its potential usefulness as an agent for the control of hypertension.

Under the conditions of the present study, captopril alone in doses of 75 to 450 mg/day controlled the majority of patients with mild or moderate

essential hypertension. Similar results were reported by Gavras *et al.* (1978) in patients with renal and essential hypertension and Brunner, Gavras, Tunrini, Waeber & Wauters (1978) in renal hypertensives. The addition of hydrochlorothiazide to captopril resulted in full control of the blood pressure of the remaining patients; similarly, captopril produced a good therapeutic effect when added to diuretic therapy in patients whose blood pressure could not be adequately controlled by hydrochlorothiazide alone. However, volume- and/or salt-depleted patients receiving the first dose of captopril should be observed closely for occasional marked decrease in blood pressure (Case *et al.*, 1977). In this series only one of the four patients who had captopril added to a hydrochlorothiazide regimen showed a marked though asymptomatic drop of blood pressure, probably because all patients were allowed a normal salt intake.

The vast majority of hypertensive patients encountered in clinical practice have only mildly or moderately increased blood pressure and are free of symptoms. Since therapy for such patients is usually life-long, any drugs utilized must incur only minimal side effects if they are to be a positive addition to the antihypertensive armamentarium.

In the present study, side effects with captopril were limited to vertigo or dizziness in three patients,

Figure 1 Serial blood pressure responses throughout study period. ○ captopril alone ($n = 9$), ● captopril + hydrochlorothiazide ($n = 3$), △ hydrochlorothiazide alone ($n = 4$), ▲ hydrochlorothiazide + captopril ($n = 4$).

Figure 2 Percent decreases in mean supine blood pressure (A8 - C8) ■ systolic BP, □ diastolic BP, ▨ % decrease before addition of second drug.

they are explainable in view of the reduction in the blood pressure. Pulse rate increased from a mean of 66.8 ± 5.9 to 75.4 ± 8.1 beats/min. A small but significant increase in pulse rate, which correlated well with the decrease in blood pressure, was also reported by Gavras *et al.* (1978), who attributed it to baro-receptor-mediated sympathetic stimulation in response to the lower blood pressure. Other investigators (Case *et al.*, 1978) have reported that rashes, sometimes accompanied by fever, may occur after captopril administration. In our investigation we did not encounter such a reaction during the study proper, but a maculopapular rash without fever

appeared in one of the patients who continued long-term therapy with 450 mg of captopril per day. The rash occurred 5 months after the initiation of captopril therapy and persisted for 10 days. It responded well to antihistaminics and dose reduction of captopril to 300 mg/day. The transient eosinophilia encountered in four patients on captopril is difficult to explain but together with the reported fever and skin rashes may suggest hypersensitivity reactions. In one patient on captopril alone and another on combined therapy BUN was elevated. Although this can be due to the lowering of blood pressure affecting the kidney perfusion, it may also be an early sign of drug toxicity and these patients are now closely followed up in the long term therapy for any signs of renal affection. Farrow & Wilkinson (1979) reported reversible renal failure during treatment with captopril. Recent reports of proteinuria associated sometimes with membranous glomerulopathy or nephrotic syndrome (Prins, Hoorntje, Weering & Donker, 1979) as well as reports of possible association with agranulocytosis in severely ill, renally impaired patients (van Brummelen, Willemze, Tan & Thompson, 1980; Amann, Buhler, Conen, Brunner, Ritz & Speck, 1980) require further investigations with captopril in critically sick patients specially those with systemic lupus erythematosus and/or impaired renal function. Liver function tests have also to be closely followed up in the patients under treatment with captopril alone or in combination with other drugs because we encountered a rise of SGPT or SGOT in some of our patients.

In this limited study, captopril given orally, either alone or in conjunction with hydrochlorothiazide, was effective in controlling the blood pressure in mild to moderate essential hypertension.

In view of the side effects recorded in the present study and those previously reported in the literature, further study for the efficacy and safety of captopril in a long term study is mandatory.

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