Enalapril Maleate versus Captopril
A Comparison of the Hormonal and Antihypertensive Effects

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Summary

24 hypertensive patients were randomised into 2 groups to compare the antihypertensive effects of enalapril and captopril over a 10-week period. In the hydrochlorothiazide run-in period, blood pressure was reduced from 171 ± 4/109 ± 1mm Hg to 160 ± 4/103 ± 1mm Hg (p < 0.05). Angiotensin-converting enzyme (ACE) inhibition decreased blood pressure to 132 ± 3/87 ± 2mm Hg. Captopril decreased diastolic blood pressure significantly more after 3 hours than enalapril (-24 versus -17mm Hg, p < 0.05). After 10 weeks of therapy, this antihypertensive response was maintained at 134 ± 3/83 ± 1mm Hg. There was no difference between the captopril and enalapril treated groups. Acute and chronic responses of plasma renin activity, plasma aldosterone and ACE were determined. There was an acute positive correlation between the rise in plasma renin activity and the fall in blood pressures with captopril but not with enalapril. With chronic treatment there was no difference in the ability of either of the 2 drugs to reduce blood pressure, inhibit ACE, reduce aldosterone or stimulate plasma renin activity.

In 1973 it was shown that teprotide, a parenteral angiotensin-converting enzyme (ACE) inhibitor, was effective in lowering blood pressure (Gavras et al., 1974). Since then, 2 oral ACE inhibitors have been developed – enalapril maleate and captopril. Both these drugs have been found to be effective in reducing blood pressure in several animal species (Bengis et al., 1978; Harris et al., 1978; Muirhead et al., 1978; Murthy et al., 1977, 1978; Vollmer and Boccagno, 1977) as well as in man (Bravo and Tarazi, 1979; Brunner et al., 1979; Case et al., 1978; Gavras et al., 1978; Johns et al., 1980). Captopril has been associated with several side effects such as rash, taste disturbance, leucopenia and proteinuria. These side effects are thought to be due to the presence of the sulphhydryl group in the compound. Many efforts have been made to develop an orally effective ACE inhibitor without the sulphhydryl group. Enalapril maleate is such a drug, and is the major focus of this report.

The study was carried out on 24 patients who were randomised and assigned to receive either enalapril or captopril. The antihypertensive effects of both drugs were compared, together with their ability to increase plasma renin activity, to decrease plasma aldosterone and to decrease ACE.
1. Methods

1.1 Patients

24 patients with essential hypertension were randomised to receive either enalapril or captopril therapy. There were 18 men and 6 women, aged 35-62 years. Average duration of hypertension was 10.6 years (1.2-25 years) and mean arterial pressure was 114-145 mmHg.

1.2 Experimental Design

All patients signed a consent form approved by the Institutional Review Board prior to entry into the study. All antihypertensive medications were withdrawn, and sympathetic drugs were appropriately tapered over 3 weeks prior to randomisation and treatment. Patients continued on their customary diet unless the sodium content was judged to be unusually high. A 24-hour urine collection was obtained to measure sodium and potassium excretion rates. Blood samples were obtained in the upright position to determine plasma renin activity, plasma aldosterone concentration and ACE activity. The samples were stored at -20°C until assayed, except for ACE which was stored under liquid nitrogen.

The subjects were then started on 50 mg/day hydrochlorothiazide. After 4 weeks, 24-hour urine and 3-hour upright plasma samples were collected for measurement of sodium and potassium excretion rates. Blood samples were obtained in the upright position to determine plasma renin activity, plasma aldosterone concentration and ACE activity. Double-blind randomisation was then carried out. A single dose of captopril (25 mg) or enalapril (5 mg) was then given, and blood samples for plasma renin activity, plasma aldosterone concentration and ACE activity were obtained after 3 hours in the upright position. Patients were treated for 10 weeks on hydrochlorothiazide (50 mg) plus either captopril or enalapril. The maximum dose of captopril was 100 mg thrice-daily and for enalapril 20 mg twice-daily. After 10 weeks of ACE inhibition, blood pressure, sodium and potassium excretions, plasma renin activity, plasma aldosterone concentration and ACE activity were re-evaluated.

Plasma renin activity was determined by measuring angiotensin I generated at 37°C and pH 5.7 according to the method of Sealey et al. (1972). Plasma aldosterone concentration was measured using the radioimmunoassay of Kubasik et al. (1979). ACE activity was determined by the radioassay of Rohatgi and Ryan (1980). Urine sodium and potassium were determined by flame photometry.

2. Statistical Analysis

Student's paired and unpaired t-test, or a one-way analysis of variance was used, and a p value of less than 0.05 was considered statistically significant. Data are expressed as the mean ± 1 standard error of the mean.

3. Results

3.1 Blood Pressure

13 patients were randomised to receive captopril and 11 to receive enalapril therapy.

There was a significant (p < 0.05) decrease in diastolic blood pressure in both groups 4 weeks after hydrochlorothiazide therapy. Three hours after acute administration of the ACE inhibitors, there was a significantly greater decrease in diastolic blood pressure with captopril when compared with enalapril (-24 versus -17 mmHg, p < 0.05). After 10 weeks of ACE inhibition, the decrease in diastolic blood pressure was the same with the 2 drugs (-26 and -25 mmHg, respectively).

Plasma renin activity increased from a control level of 3.0 ± 0.8 to 10.1 ± 3.0 ng angiotensin I/ml/hour (p < 0.05) after 4 weeks of hydrochlorothiazide therapy. After 3 hours of captopril and enalapril therapy, plasma renin activity increased to 33 ± 3.8 (p < 0.05) and 37 ± 3.9 ng angiotensin I/ml/hour (p < 0.05), respectively. There was a further increase in plasma renin activity after 10 weeks of ACE inhibition - 53 ± 11 ng angiotensin I/ml/hour for captopril and 72 ± 15 ng angiotensin I/ml/hour for enalapril. The increase from their 3-hour level was significant for both drugs (p < 0.05).

ACE activity was normal (96 ± 4 units) and