Effect of angiotensin converting enzyme inhibitors on erythropoietin concentrations in healthy volunteers

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The possibility that the ACE inhibitors, enalapril and captopril, may decrease plasma EPO concentrations was studied in a single-blind, cross-over study in 10 healthy volunteers. Plasma EPO concentrations, haemoglobin concentration, red blood cell count, plasma creatinine concentration and mean arterial pressure were measured at baseline and after 28 days treatment with both ACE inhibitors. A significant fall in mean plasma EPO concentration occurred with both ACE inhibitors and returned to baseline after stopping the drugs. It is likely that ACE inhibitors decrease EPO formation, by inhibition of angiotensin-II production. This effect could be important in patients with renal failure, renal transplantation or other chronic conditions with an associated anaemia. Haematological parameters should be monitored in such patients when they are treated with an ACE inhibitor.

Keywords erythropoietin renin-angiotensin system
angiotensin converting enzyme inhibitors

Introduction

Erythropoietin (EPO) is predominantly produced and released by the kidney and is regulated primarily by the local tissue concentration of oxygen (Nathan, 1977). EPO release is also affected by additional factors such as androgens, prostaglandins of the E series, thyroid hormone and β -adrenoceptor agonists (Johnston, 1987). In addition, the renin-angiotensin system has been reported as having an effect on EPO formation (Gould *et al.*, 1973; Nakao *et al.*, 1967).

Angiotensin-converting enzyme (ACE) inhibitors are strong inhibitors of angiotensin-II production. Experiments in renin-injected rats, given a single oral dose of captopril, have shown a pronounced fall in EPO concentrations. This effect of captopril could be prevented by simultaneous infusion of angiotensin-II given in subpressor doses (Gould *et al.*, 1980).

A deterioration in the degree of anaemia has been reported in patients on regular haemodialysis treatment who have been treated with captopril for hypertension (Hirakata *et al.*, 1984, 1986), while other workers (Griffing & Melby, 1982) have observed a small fall in the mean haematocrit of normal and hypertensive volunteers given enalapril alone or with hydrochlorothiazide. Sizeland *et al.* (1990) have shown in a study of stable renal transplant recipients, that treatment of hypertension with an ACE

inhibitor was associated with a significant fall in the mean haemoglobin concentration over a 6-month period and postulated that this was due to a direct effect on EPO synthesis or release.

The aim of this study was to investigate the potential role of ACE inhibition in affecting EPO concentrations in healthy volunteers. Captopril was compared with enalapril in order to document whether or not the changes in EPO concentrations were due to an individual agent or to a class effect.

Methods

Ethics

All subjects gave written informed consent. The study was approved by the Otago Area Health Board Ethics Committee.

Subjects

Ten healthy volunteers (eight males) with a mean age of 26.7 (range 19–48) years were enrolled in the study. All were non-smokers.

Protocol

Captopril in a dose of 6.25 mg twice daily was compared with enalapril 5 mg once daily in a randomised, single-blind, cross-over study. The following investigations were undertaken following a 12 h overnight fast: blood pressure, height and weight measurements and blood samples drawn for EPO concentration, haemoglobin concentration and red blood cell count.

Blood samples for EPO measurements (EDTA anti-coagulant) were kept at 4° C and separated as soon as possible. The plasma was then stored at -20° C until analysed. Plasma EPO concentrations were measured by radioimmunoassay (EPO-Trac, Incstar Corp., Stillwater, Mn). The method had a lower limit of detection of 4.4 mu ml⁻¹ and the coefficient of variation of control plasma was 7.6%. Haematological parameters were measured using a Technicon H6010 automatic cell counter. Plasma creatinine concentrations were analysed in an Hitachi 737 autoanalyser. The blood pressure was the mean of three readings taken over 15 min in the supine position, using a mercury sphygmomanometer.

Statistics

The data were analysed as a cross-over trial using 'SPSS-X Release 3.1' statistical package.

Results

Statistical analysis of the data did not demonstrate any significant first or second order carry-over effects and showed that the 28-day washout period was adequate. The order of drug administration did not influence the results. Therefore the results were expressed for each drug over a 28-day period as well as for the combined effects of both drugs.

The study data are summarised in Table 1. There was a significant fall in the mean plasma EPO concentrations

Table 1 Mean (s.e. mean) plasma EPO and clinical data

	Day 0	Day 28	P
EPO (mu ml ⁻¹)			
Captopril	11.4 (1.2)	9.0 (1.4)	< 0.05
Enalapril	11.8 (0.9)	9.6 (0.8)	< 0.05
Haemoglobin (g l ⁻¹)			
Captopril	140.8 (4.6)	138.1 (6.0)	NS
Enalapril	142.6 (5.2)	140.4 (4.8)	NS
Red blood cell count (10 ¹² l ⁻¹)			
Captopril	4.98 (0.14)	4.84 (0.16)	NS
Enalapril	4.99 (0.12)	4.91 (0.14)	NS
Plasma creatinine (μmol l ⁻¹)			
Captopril	84 (3)	85 (1)	NS
Enalapril	91 (2)	88 (2)	NS
Mean arterial pressure (mmHg)			
Captopril	87.7 (9.8)	85.6 (8.6)	NS
Enalapril	85.4 (3.9)	81.4 (5.2)	NS

NS – not significant.

Figure 1 Mean (s.e. mean) plasma EPO concentrations during each phase of the study, pooling the data for captopril and enalapril ($n = 10$, * $P < 0.05$).

at the completion of 28 days treatment with either captopril or enalapril. In 9 of the 10 subjects the EPO concentrations fell with both drugs. In the remaining subject the plasma EPO concentration remained unchanged with both drugs. The mean EPO concentrations had returned to baseline at the end of the 28-day washout period between drugs and within 14 days of the completion of the study (Figure 1).

The mean haemoglobin concentrations and red blood cell count demonstrated an insignificant downward trend over the 28-day study period. The mean arterial blood pressure and plasma creatinine concentrations did not change significantly during the 28-day treatment period (Table 1). No subject reported any side effects.

Discussion

This study demonstrated that the administration of both low-dose captopril and enalapril to healthy volunteers over a period of 28 days was associated with a significant fall in plasma EPO concentrations. This fall in EPO was accompanied by a downward trend in haemoglobin concentration and red blood cell count. The EPO concentrations returned to baseline following cessation of drug treatment.

These findings support a number of observations that have shown that hypertensive patients treated with an ACE inhibitor may have a reduction in their haemoglobin concentration. This has been reported in healthy volunteers and hypertensive individuals (Griffing & Melby, 1982), and patients with chronic renal failure (Dreyling *et al.*, 1990; Fiklocki & Keusch, 1990; Kamper & Nielsen, 1990), on regular haemodialysis treatment (Hirakata *et al.*, 1984, 1986), or on continuous ambulatory peritoneal dialysis (Arteaga *et al.*, 1990; Miranda *et al.*, 1990) and those with a stable renal transplant (Sizeland *et al.*, 1990). Fyhrquist *et al.* (1989) have shown that enalapril normalised the elevated serum erythropoietin concentrations in patients with congestive heart failure.

It seems most likely that the ACE inhibitors decrease EPO production by reducing angiotensin-II concentrations, which can directly regulate erythropoiesis. It is possible that the ACE inhibitors may improve renal blood flow which in turn could result in a fall in EPO

production. However, this is unlikely to be the case in healthy volunteers. Similarly, it is unlikely that the small fall in systemic blood pressure that accompanies the use of an ACE inhibitor would result in a redistribution of extracellular fluid with an increase in plasma volume and resultant haemodilution.

The fall in haemoglobin concentration associated with the use of an ACE inhibitor is almost certainly of no significance in most clinical situations. It could be important, however, in patients with renal failure, renal transplantation or other chronic disorders associated with anaemia.

This effect of the ACE inhibitors has been useful

therapeutically for the management of the erythrocytosis that may accompany a successful renal transplant. We have several patients who have required regular venesection to control their haematocrit, but this has become unnecessary with the introduction of an ACE inhibitor.

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