Haemodynamic and hormonal responses to oral enalapril in salt depleted normotensive man

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A combination of dietary sodium restriction (40 mmol day^{-1}) and frusemide pre-treatment has been used to activate the renin angiotensin system (RAS) in order to characterise the haemodynamic and hormonal responses to enalapril in young normotensives. Enalapril significantly reduced supine blood pressure with a mean maximum fall of 19 ± 7.6 , compared with $6.5 \pm 6.8 \text{ mm Hg}$ with placebo. Similar but greater responses were seen in erect blood pressure. Mean maximal plasma ACE inhibition ($78 \pm 5.7\%$) was associated with a significant increase in PRA from $5.2 \pm 2.1 \text{ ngAI ml}^{-1} \text{ h}^{-1}$ to a peak of $29.1 \pm 6 \text{ ngAI ml}^{-1} \text{ h}^{-1}$. This simple well tolerated regimen produced consistent RAS activation and gave readily measurable falls in blood pressure following enalapril. This model may be used to undertake detailed assessments of ACE inhibition, renin inhibition and angiotensin receptor blockade.

Keywords enalapril blood pressure activated renin angiotensin systems model system

Introduction

Angiotensin converting enzyme (ACE) inhibitors are effective in the treatment of hypertension and heart failure (Braunwald, 1991; Williams, 1988). The relationships between drug concentrations and drug effects have not been clearly defined and controlled comparative studies of different ACE inhibitor drugs have received little attention although there is recent evidence to suggest that there may be important differential effect and time-effect profiles for different drugs (MacFadyen *et al.*, 1991a).

Because of the need for stabilisation and drug free washout intervals, for example, controlled crossover studies in patients are difficult. The principal aim of this study was to define a simple *in vivo* salt-deplete model in man suitable for assessing blockade of the renin-angiotensin system (RAS) and for identifying differential drug effects.

Methods

Eight healthy normotensive male volunteers (25.6 ± 4.6 years, $70.5 \pm 6.1 \text{ kg}$) gave written consent for their participation in the study, which was approved by the local Ethics Review Committee.

Activation of the RAS was provoked by a short programme of salt depletion (days 1–4) based on a diet containing $40 \text{ mmol sodium day}^{-1}$ (supplied by the

Dietetics Department) and pre-treatment with frusemide 40 mg twice daily at 08.00 h and 12.00 h (days 1–3).

According to a randomised, double-blind, crossover design subjects received either enalapril 5 mg or matched placebo on day 4 after an overnight fast. Study days were 14 days apart.

On each study day, after bladder voiding and baseline measurements, drugs were administered with 200 ml of fluid. Thereafter, at frequent intervals blood pressure and heart rate were recorded (Datascope Accutorr 3A, Paramus, New Jersey) and blood samples were obtained for serum drug concentration (Tocco *et al.*, 1982), electrolytes, plasma ACE and renin activity (Derckx *et al.*, 1979).

Blood pressure and heart rate were compared using repeated measures analysis of variance with Bonferroni correction for within treatment comparisons. Electrolyte data were compared using Friedman one way analysis of variance.

Results

Effects of salt depletion

The salt depletion regimen was well tolerated and no spontaneous symptoms were reported. Urinary volume was significantly increased on the pre-study day (d3) in

Figure 1 Baseline corrected changes (mean $\pm$ 1 s.d.) in a) supine and b) erect blood pressures and heart rate following oral placebo (○) or enalapril (●).

comparison with the screening day (1907 ± 982 vs 1279 ± 106 ml) with significant falls in urinary sodium excretion (98 ± 29 vs 189 ± 69 mmol 24 h $^{-1}$). There were significant falls in serum sodium (139.7 ± 1.1 vs 142.5 ± 1.0 mmol l $^{-1}$) and serum potassium (3.8 ± 0.2 vs 4.2 ± 0.3 mmol l $^{-1}$). There was a small rise in urinary potassium excretion but urea and creatinine excretion were unchanged. Supine plasma renin activity was significantly elevated at 5.6 ± 0.9 ngAI ml $^{-1}$ h $^{-1}$.

Supine blood pressure was reduced from $124/69 \pm 8/7$ (on screening) to $115/69 \pm 8/7$ and $108/65 \pm 9/6$ mm Hg before enalapril or placebo respectively.

Enalapril vs placebo

Because supine blood pressure was slightly higher on the enalapril study day responses were individually corrected to the pretreatment (baseline) values on each study day. Baseline corrected changes in blood pressure are illustrated in Figure 1. Enalapril caused a mean maximal fall in supine systolic blood pressure of 18.9 ± 7.6 mm Hg at about 5 h post dose, compared with 6.5 ± 6.8 mm Hg following placebo. Similarly, enalapril caused a significantly greater fall in erect systolic blood pressure of 24.2 ± 9.8 compared with 13.4 ± 5.7 mm Hg following placebo. Heart rate was not significantly altered by either therapy.

The peak plasma enalapril concentration of 50 ± 20.8 ng ml $^{-1}$ was observed at 1.25 ± 0.25 h but the maximum concentrations of enalaprilat were not attained until 4–6 h post dose. Near maximal plasma ACE inhibition was observed after about 2 h and maximum inhibition of $78 \pm 5.7\%$ occurred at 5.2 ± 1.2 h. Following enalapril plasma renin activity peaked at 29.1 ± 6 ngAI ml $^{-1}$ h $^{-1}$ (Figure 2).

Urine volumes were significantly lower during the two study days (P, 1148 ± 319 ml; E, 1003 ± 284 ml)

Figure 2 Plasma renin activity (mean $\pm$ 1 s.d.) following enalapril (●) or placebo (○).

with a greater sodium loss following enalapril (25 ± 7 mmol 24 h^{-1}) compared with placebo (11 ± 6 mmol 24 h^{-1}). Potassium excretion was not significantly altered but tended to be lower following enalapril (59 ± 15 mmol) compared with placebo (71 ± 11).

Discussion

Although dietary salt restriction has been widely used to activate the RAS, a very low sodium diet (< 10 mmol Na^+ per day) has usually been employed (Hollenberg *et al.*, 1981). In general, such low salt diets are unpalatable for unselected volunteers, difficult to control and liable to non-compliance. This study employed moderate sodium restriction (40 mmol) combined with diuretic pretreatment, which has also been used previously but with variable success (Edmonds & Wilson, 1960; Levine *et al.*, 1976). To avoid any acute haemodynamic effects (Johnston *et al.*, 1984) frusemide was not administered on day 4 but a persistent degree of hyperreninaemia was confirmed (Tuck *et al.*, 1982). To prevent fluid depletion a high fluid intake was encouraged during the pre-study period and the fluid intake on the study day was controlled (1.2 l). The absence of changes in urinary urea and creatinine supports the absence of overt fluid depletion and that urinary collections were reasonably complete. In keeping with the moderate activation of the RAS during the study day there was a degree of antinatriuresis.

Although it is not universally accepted, ACE inhibitors do cause a small fall in blood pressure in salt replete volunteers (Kiowski *et al.*, 1992). In this present study, there were considerable reductions in blood pressure despite a low dose of enalapril. The role of RAS activation in the blood pressure response to ACEI has practical importance in relation to clinical concerns about the 'first dose hypotension' which occasionally is symptomatic and rarely is associated with hypoperfusion damage. The origin and significance of this acute blood pressure fall is unclear (MacFadyen *et al.*, 1991b) but many factors may play a role. With this model of RAS activation it will be possible to undertake controlled studies to investigate the contributions of a particular drug, dosage and the level of activation of the RAS. Since the baseline levels of circulating renin in our study are easily comparable with those seen in renovascular hypertension (Hodsman *et al.*, 1983) or heart failure (Anand *et al.*, 1989) studies with this model avoid the variable disease and patient factors involved in the clinical response.

This study has described a simple and well tolerated model based on moderate dietary sodium restriction and an accompanying short period of diuretic therapy. Double-blind studies can readily be performed by supplementing the standard 40 mmol sodium diet with coated salt tablets or placebo. Such a model is suitable for initial dose ranging and dose-response studies with a variety of agents which act via the RAS and for studies of the role of RAS activation and neurohumoral changes in the individual response.

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(Received 29 April 1992,
accepted 12 October 1992)