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Enalapril in heart failure

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1 Serum MK-422 and plasma angiotensin converting enzyme activity were measured during the introduction of enalapril therapy in eight patients with heart failure. In a second study of 16 patients, we recorded exercise tolerance, clinical status and haemodynamics before and after 12 weeks of placebo or enalapril treatment.

2 Increasing doses of enalapril gave step-wise increments in serum MK-422. Plasma converting enzyme activity remained low for at least 24 h after each dose of enalapril (5, 10 and 20 mg).

3 Compared to placebo patients (n = 8), those receiving enalapril (n = 8) tended to improve their exercise performance and clinical status, and showed a fall in right heart pressures after 12 weeks of treatment.

Keywords heart failure enalapril converting enzyme

Introduction

Converting enzyme inhibitors have advanced the treatment of severe cardiac failure. Enalapril has beneficial haemodynamic effects, at least in the short term (Fitzpatrick *et al.*, 1983). Although information is available from studies in normal volunteers and essential hypertensives, little is known of drug levels and plasma converting enzyme activity in patients with heart failure during the introduction of enalapril. We report this information in the present paper. We also present preliminary data on exercise performance, clinical status and haemodynamics during a 12-week double-blind, placebo-controlled study of enalapril in cardiac failure.

Methods

Two studies were carried out.

Short-term study

We administered enalapril to eight patients, aged 48–70 years, with heart failure [New York Heart Association (NYHA) functional class II–IV] under standardised conditions in hospital. Full details of the protocol have been described before (Fitzpatrick *et al.*, 1983). In brief a 2-day control period was followed by 3 days of enalapril therapy, 5, 10 and 20 mg given at 09.00 h on days 3, 4 and 5 respectively. Throughout the study and for 2 days beforehand, they received a diet of constant electrolyte content (sodium 91–116 mmol/day, potassium 54–67 mmol/day). The patients remained in bed, semi-supine. On the afternoon before day 1, a Swan-Ganz and a brachial or radial artery catheter were inserted for haemodynamic recordings and for hormone, enzyme and drug level measurements. Arterial blood was drawn for determination of angiotensin converting enzyme (ACE) activity (Lieberman, 1975) and MK-422 levels (by radioimmunoassay in the laboratory of Dr F. Fyhrquist, The Minerva Institute for Medical Research, Helsinki, Finland) before (08.30 h) and 4, 8 and 24 h after each dose of enalapril.

Vasodilators (prazosin or isosorbide dinitrate) had been taken by six subjects, but were with-

drawn at least 4 days before the study. Digoxin (0.125–0.25 mg/day) was continued throughout in unchanged dose. Maintenance doses of frusemide (40–500 mg/day) were also continued, and administered along with digoxin after 08.30 h haemodynamic and hormone recordings. For two patients however, frusemide was withdrawn 5 days before the study and reintroduced after its completion.

Long-term study

Sixteen patients aged 55–74 years with heart failure due to coronary artery disease or cardiomyopathy (NYHA functional class II–III) underwent a randomised, placebo-controlled, double-blind out-patient study of enalapril treatment (5 mg twice daily) for 12 weeks. Digoxin (0–0.25 mg/day) and frusemide (80–500 mg/day), were continued unchanged. Before randomisation, and again after 12 weeks of placebo or enalapril treatment, the patients undertook a symptom-limited treadmill exercise test (Patterson *et al.*, 1972). An assessment of change in clinical state, with particular reference to dyspnoea, fatigue and chest pain, was made at week 12, using a scoring system described by Feinstein & Wells (1975). Haemodynamic recordings were taken at the start of the study and after 12 weeks of placebo or enalapril therapy. For this purpose, a Swan-Ganz and arterial catheters were inserted at approximately 08.00 h. Baseline resting recordings (arterial pressure, right heart pressures and cardiac output by thermal dilution) were made with the patients supine at approximately 10.00 h, and again after 3 min of supine bicycle exercise at 75% of the previously determined maximal workload. The first dose of enalapril (5 mg) or placebo was given after completion of this initial exercise test, and repeat resting recordings were made 2 and 5 h later and again after a second bicycle exercise test at 5 h.

Statistical tests used were a *t*-test and the product moment correlation coefficient.

Results

Short-term study

The haemodynamic, hormone and electrolyte effects of enalapril have been reported elsewhere (Fitzpatrick *et al.*, 1983). Only one of the eight patients had abnormal liver function tests (elevated bilirubin, alkaline phosphatase and α-glutamyl-transpeptidase) prior to the initiation of enalapril therapy. There was considerable inter-patient variation in serum levels of MK-422 after enalapril administration. Overall, however, increasing doses of enalapril induced step-wise increments in serum MK-422 (Figure 1). The highest levels were generally seen 4 h after each dose, with a subsequent decline to near-baseline values at 24 h (Figure 1). The pattern in plasma ACE activity was opposite to that of serum MK-422. The lowest dose of enalapril, 5 mg, reduced ACE activity from a mean pre-treatment level of 16.4 U/ml to a nadir of 1.2 U/ml at 8 h, with a minor recovery to 3.2 U/ml by 24 h (Figure 1). Higher doses, 10 and 20 mg, resulted in barely detectable levels of plasma ACE activity at 4 and 8 h, and very low values by 24 h. For all results from the eight patients, there was a statistically significant though low-order inverse correlation between serum MK-422 levels and concurrent plasma ACE activity ($r = -0.347$, $P < 0.01$, $n = 78$).

Long-term study

Eight patients took enalapril 5 mg twice daily, and eight received a matching placebo during the

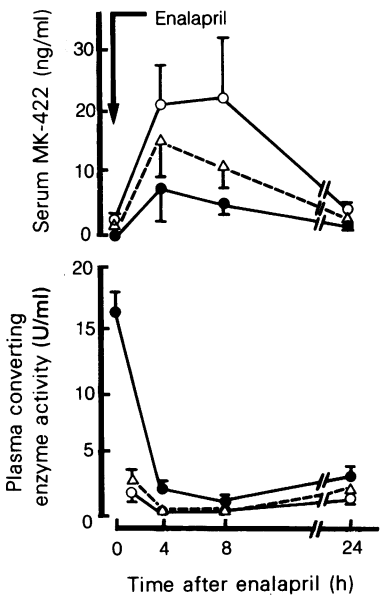

Figure 1 Serum MK-422 levels and plasma angiotensin converting enzyme (ACE) activity before and at intervals after administration of enalapril 5 mg (•), 10 mg (△) and 20 mg (○) in eight patients with heart failure. Serum MK-422 levels were significantly higher 24 h after 20 mg enalapril compared to 5 mg ($P < 0.025$), but other differences at any point in time were not significant. Plasma ACE activity was significantly lower 4 h after 10 and 20 mg enalapril compared to 5 mg ($P < 0.01$), and 24 h after 20 mg enalapril compared to 5 mg ($P < 0.05$).

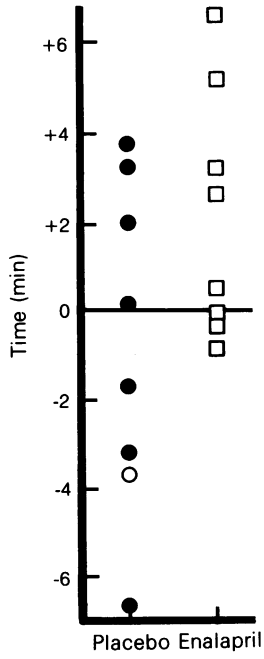

Figure 2 Change in treadmill exercise duration after 12 weeks of placebo (eight patients) or enalapril treatment (eight patients). One placebo patient had his second exercise test after 4 weeks (○). The difference between the groups failed to reach statistical significance ($P = 0.10$).

12-week trial. Exercise performance tended to improve in enalapril-treated patients, and variable changes occurred in those on placebo (Figure 2). The difference between the two groups however, was not statistically significant ($P = 0.10$). The clinical state improved in all patients receiving enalapril, the score range being between +2 and +9. Clinical improvement was also documented in five placebo subjects (+1 to +6), whereas one was unchanged (score zero) and two deteriorated (–9). The difference in score between enalapril and placebo patients failed to reach statistical significance ($P < 0.10$). Haemodynamic results from the first day of placebo or enalapril treatment and after 12 weeks are shown in Table 1. Right heart pressures were not altered by the first dose of enalapril in the baseline study, although recordings were taken only up to 5 h when maximum effects of the drug may not have developed (Fitzpatrick *et al.*, 1983). Arterial pressure was lower in enalapril-patients after the first dose, but differences between the groups were not statistically significant. Repeat recordings after 12 weeks showed lower right heart and arterial pressures in enalapril treated subjects, the differences being statistically significant on some occasions (Table 1). Cardiac output was not altered significantly by enalapril.

We did not encounter side-effects from enalapril in either the short-term or long-term study. In particular there was no symptomatic hypotension, skin complaints or taste disturbance. No patient developed proteinuria, or haematological or biochemical (SMAC-11) abnormality.

Table 1 Haemodynamic recordings

	Right atrial pressure (mm Hg)		*Mean pulmonary artery pressure (mm Hg)*		*Pulmonary artery wedge pressure (mm Hg)*		*Mean systemic arterial pressure (mm Hg)*	
	Placebo	*Enalapril*	*Placebo*	*Enalapril*	*Placebo*	*Enalapril*	*Placebo*	*Enalapril*
Baseline								
Resting	8 ± 1	9 ± 2	35 ± 0.7	32 ± 4	26 ± 2	21 ± 3	91 ± 6	92 ± 8
Exercise	15 ± 0.6	14 ± 3	51 ± 2	45 ± 5	36 ± 2	32 ± 4	110 ± 11	102 ± 8
→								
Resting	8 ± 1	10 ± 2	31 ± 2	29 ± 5	22 ± 2	20 ± 3	91 ± 6	80 ± 6
Resting	9 ± 1	9 ± 2	35 ± 3	33 ± 5	26 ± 3	21 ± 4	100 ± 7	88 ± 5
Exercise	15 ± 0.8	14 ± 3	53 ± 2	51 ± 6	36 ± 2	33 ± 4	114 ± 10	100 ± 5
3 months								
Resting	9 ± 1	6 ± 0.9	35 ± 4	23 ± 2*	22 ± 3	13 ± 2*	88 ± 4	89 ± 6
Exercise	16 ± 2	13 ± 4	49 ± 3	40 ± 4	30 ± 2	22 ± 3*	104 ± 6	99 ± 6
→								
Resting	9 ± 1	6 ± 1	30 ± 3	21 ± 2*	21 ± 3	12 ± 2*	81 ± 3	77 ± 4
Resting	9 ± 1	8 ± 2	34 ± 3	26 ± 3	25 ± 4	15 ± 3	91 ± 6	85 ± 5
Exercise	19 ± 1	14 ± 2	49 ± 6	42 ± 3	31 ± 4	23 ± 3	110 ± 6	98 ± 4

The arrow indicates timing of administration of placebo or enalapril 5 mg. * $P < 0.05$ placebo *vs* enalapril groups (*t*-test). Results are mean ± s.e. mean from eight patients who took placebo and eight who received enalapril.

Discussion

Activation of the renin-angiotensin system is evident during the evolution of heart failure in experimental animals (Watkins *et al.*, 1976; Riegger *et al.*, 1982) and in some patients with untreated cardiac failure (Brown *et al.*, 1970; Nicholls *et al.*, 1974). The majority of drugs used to treat this condition, including diuretics and most vasodilators, stimulate renin release further (Nicholls *et al.*, 1974, 1976; Markham *et al.*, 1983; Pouleur *et al.*, 1983). High circulating levels of angiotensin II are likely to place an added burden on the failing heart by means of a direct constrictor action on arterioles (and perhaps veins), and indirectly through stimulation of aldosterone secretion. Other possible adverse actions of angiotensin II include a direct toxic effect on the myocardium, stimulation of antidiuretic hormone release and thirst (leading to hyponatraemia), and activation of the sympathetic nervous system. The importance of these latter factors, however, is uncertain.

Confirmation that the renin-angiotensin system plays an important pathophysiological role in heart failure has come with the introduction of converting enzyme inhibitors. The picture with converting enzyme inhibitors is clearest in patients with severe grades of cardiac failure, where beneficial haemodynamic, electrolyte and clinical responses are often (though not always) seen in the short term. Experience with these agents in the long term and in those with mild heart failure, is limited.

In the present study we documented serum levels of MK-422, the active metabolite of enalapril, along with plasma converting enzyme activity during the introduction of enalapril to eight patients with heart failure. Serum MK-422 levels showed a wide range between patients taking the same dose of enalapril. Variability in the rate of absorption of enalapril from the gut, in rapidity of conversion to MK-422 (presumed to be by the liver), and in its volume of distribution, may be considerable in different patients with heart failure. These factors might also explain in part the relatively low peak (4 h) level of serum MK-422 compared to that reported after 10 mg enalapril in normal volunteers (Biollaz *et al.*, 1982). The levels of MK-422 8 and 24 h after 10 mg enalapril appear similar to those in normal subjects after the same dose (Biollaz *et al.*, 1982). Plasma ACE activity correlated inversely, though not intimately, with serum MK-422 levels. Recovery of plasma ACE activity was much slower than was the disappearance of MK-422. This sustained action of enalapril on plasma ACE activity has been noted in normal volunteers (Brunner *et al.*, 1981). That the changes in plasma ACE activity are physiologically meaningful is supported by our previous finding (in the same eight patients) that circulating angiotensin II levels remain below control-day values for 24 h after 5 mg enalapril, and the two larger doses (10 and 20 mg) resulted in further decreases in plasma angiotensin II (Fitzpatrick *et al.*, 1983).

In the long-term study we observed a trend toward improvements in exercise performance and clinical state, and a significant lowering of right heart pressures in those receiving enalapril. This is an on-going study. Our tentative conclusion is that enalapril, given as 5 mg twice daily, is often beneficial in patients with moderate degrees of heart failure, but further information is awaited.

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