The acute haemodynamic effects of intravenous enalaprilic acid (MK422) in patients with left ventricular dysfunction

R. S. HORNUNG & W. S. HILLIS

Department of Materia Medica, University of Glasgow, Stobhill General Hospital, Balornock Road, Glasgow G21 3UW

- 1 Intravenous enalaprilic acid (2.5 mg) was given to 11 patients with stable cardiac failure (NYHA functional class II–IV).
- 2 Reductions in mean right atrial, pulmonary artery and pulmonary capillary wedge pressure of 25%, 18% and 30% respectively ($P < 0.01$), were observed. Cardiac output rose by 13% (NS) and mean blood pressure fell by 20% ($P < 0.01$) with a decrease in systemic vascular resistance of 24% ($P < 0.01$). Heart rate was unaltered.
- 3 The haemodynamic effects correlated with control plasma renin activity ($r = 0.78$, $P < 0.01$).
- 4 Marked hypotension occurred in several subjects but no other side-effects were noted.
- 5 The rapid onset of action and mixed venous and arteriolar dilating activity of intravenous enalaprilic acid may be an advantage in some clinical situations where parenteral vasodilating therapy is required.

Keywords enalaprilic acid haemodynamics cardiac failure

Introduction

Vasodilatory drugs now have an established role in the treatment of patients with cardiac failure. Drugs with varying modes of action have been assessed in this context including those with predominantly arteriolar, venous or combined vasodilatory properties. The angiotensin converting enzyme (ACE) inhibitors captopril and enalapril maleate (MK421) have venous and arteriolar dilating activity and have been shown to provide haemodynamic and symptomatic improvement following both acute and chronic treatment taken by the oral route (Levine *et al.*, 1980; Sharpe *et al.*, 1984). Enalaprilic acid (MK422) is the active diacid produced *in vivo* by hydrolysis of enalapril maleate (Abram *et al.*, 1984). It is inactive when administered orally and has therefore been developed as an intravenous formulation, with a potential role as a parenteral vasodilator with a rapid onset of action. The aim of this open pilot study was to assess the acute haemodynamic effects of intravenous enalaprilic acid in patients with cardiac decompensation and raised left ventricular filling pressure.

Methods

Eleven patients, eight males and three females with a mean age 59.3 years (range 45–65 years) entered this study. All presented with stable cardiac failure due to ischaemic heart disease or congestive cardiomyopathy and were graded in New York Heart Association Functional Class II to IV. Their clinical details are shown in Table 1. The patients were maintained on their usual diuretic therapy with or without digoxin, the dosage remaining unaltered for at least 4 weeks prior to entry. Haemodynamic confirmation of ventricular dysfunction was defined as a left ventricular filling pressure > 14 mm Hg measured at rest, with the patients having taken their usual morning dose of diuretic 2–3 h earlier. Patients were excluded who had a recent myocardial infarction (within 3 months prior to the study), unstable angina pectoris, arterial hypotension (systolic blood pressure < 100 mm Hg) or bradycardia (resting heart rate < 48 beats min^{-1}). Other exclusion criteria included obstructive valvular disease, hypertrophic obstructive cardiomyopathy, recent cerebrovascular accident

Table 1 Clinical details of the patients

Patient	Age (years)	Sex	Aetiology of cardiac failure	NYHA functional class	Usual daily treatment
1 JP	64	M	IHD	III	Digoxin, frusemide 80 mg
2 PN	60	M	IHD	III	Digoxin, frusemide 80 mg
3 JMCF	45	F	IHD	IV	Digoxin, frusemide 120 mg
4 JB	50	M	IHD	III	Bumetanide 5 mg
5 AM	54	M	IHD	II	Frusemide 80 mg
6 EMCD	69	F	Cardiomyopathy	III	Digoxin, frusemide 80 mg
7 RW	66	M	Cardiomyopathy	III	Digoxin, frusemide 40 mg
8 PG	68	M	Cardiomyopathy	II	Frusemide 80 mg
9 MMCI	62	F	IHD	IV	Digoxin, frusemide 160 mg
10 JK	47	M	Cardiomyopathy	II	Bumetanide 5 mg
11 DW	67	M	IHD	III	Digoxin, frusemide 160 mg

(Mean dose of frusemide, 110 mg daily)

IHD—Ischaemic heart disease

or confirmed evidence of significant renal or hepatic impairment. No patients were entered who were receiving concurrent therapy with peripherally active anti-hypertensive or other vasodilator therapy.

Patients were admitted to hospital for right heart catheterisation, performed in the fasting state between 10.00 and 11.00 h. The maintenance morning dose of diuretic therapy was given at 08.00 h. A Swan-Ganz triple lumen flow directed thermodilution catheter was introduced via a peripheral vein under fluoroscopic control using an X-ray image intensifier and positioned in the pulmonary artery. This enabled serial recordings of right atrial (RA) pulmonary artery (PA) and pulmonary capillary wedge (PCW) pressures. Cardiac output (CO) was measured by the thermodilution technique using a cardiac output computer (WTI model MC401, Advanced Electronic Equipment, B. V. Holland). Continuous electrocardiographic and heart rate (HR) recording was performed and systemic blood pressure (BP) was measured using a standard arm cuff sphygmomanometer. Baseline values were recorded for 30 min to establish steady state conditions following which a single fixed dose of 2.5 mg of enalaprilic acid was administered intravenously to each patient. Serial pressure recordings were made thereafter each minute for 5 min and then every 5 min for a total of 60 min post-dosing. Cardiac output was measured in triplicate during the base-line control period then 5 min following drug administration and thereafter every 10 min for 1 h. From the above parameters, systemic vascular resistance (SVR) was calculated using the formula

$$\text{SVR} = \frac{\text{Mean BP} - \text{Mean RA}}{\text{CO}} \times 80 \text{ dyn}^{-1} \text{cm}^{-5}$$

Blood samples were taken for measurement of plasma renin activity (PRA) before drug administration. Statistical comparison of the results before and after drug administration was made using Student's paired *t*-test, and included Bonferroni's correction method.

Results

The haemodynamic results for the group are shown in Figures 1a and b. A rapid onset of action was observed with changes being evident during the first 5 min and maximum effects occurring 10–15 min following drug administration. These effects were sustained during the 1 h of observation. There was a significant reduction in the right heart pressures. Results are expressed in mean values $\pm$ s.d. The maximum fall in RA pressure was from 8 ± 4 to 6 ± 4 mm Hg (25%), $P < 0.01$. The pulmonary artery pressure fell from 33 ± 8 to 27 ± 10 mm Hg (18%, $P < 0.01$), and pulmonary capillary wedge pressure from 20 ± 4 to 14 ± 6 mm Hg (30%, $P < 0.01$). The cardiac output increased from 3.4 ± 1 to 3.8 ± 1.2 l min⁻¹ (13%) NS. Systemic blood pressure was reduced from 90 ± 15 to 75 ± 16 mm Hg (20%, $P < 0.01$) and there was an associated fall in the systemic vascular resistance from $2,100 \pm 400$ to $1,600 \pm 300$ dyn s⁻¹ cm⁻⁵ (24%), $P < 0.01$. A significant correlation ($r = 0.78$, $P < 0.01$) was found between the initial PRA value and the percentage fall in systemic vascular resistance (Figure 2). The significant reduction in left ventricular filling pressure (measured as pulmonary capillary wedge pressure) and systemic vascular resistance indicated the combined venous and arteriolar dilating activity following enalaprilic acid.

Figure 1 (a) Acute haemodynamic effects of intravenous enalaprilic acid on right atrial, pulmonary artery and pulmonary capillary wedge pressure (mean values $\pm$ s.d.) and (b) acute haemodynamic effects of intravenous enalaprilic acid on heart rate, systemic blood pressure, cardiac output and systemic vascular resistance (mean values $\pm$ s.d.). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Figure 2 Relationship of initial plasma renin activity to the percentage reduction in systemic vascular resistance (SVR). ($r = 0.78$, $P < 0.01$).

Significant hypotension occurred in three subjects with systolic blood pressure falling to 65–70 mm Hg. These three patients had a relatively severe degree of heart failure (NYHA class III or IV) and their baseline systolic blood

pressures were between 104 and 110 mm Hg. Two were receiving frusemide 80 mg daily and the other frusemide 120 mg daily. Their initial plasma renin activity values were all high i.e. 10–15 ng ml⁻¹ h⁻¹. Serial recordings thereafter showed that pre-drug blood pressure levels were restored approximately 24 h after drug administration. Heart rate did not alter significantly during the period of hypotension in these patients and they did not develop any other features of circulatory shock. They maintained their urinary output, and had no other complications. No other side-effects were encountered or reported by the other patients in this study.

Discussion

In this study intravenous enalaprilic acid, (MK422), has been evaluated for the first time in patients with left ventricular dysfunction and raised left ventricular filling pressures. The acute effects observed confirm the rapid onset of

action and haemodynamic changes consistent with combined arterial and venodilating properties. A relatively small increase in cardiac output was seen with the dosage used (2.5 mg). It may have been that the patients had only limited capability of increasing stroke volume because of relatively poor left ventricular function.

The choice of drugs with both venous and arteriolar dilating action in parenteral formulations is limited. Intravenous nitrates and hydralazine may be used in combination but each drug may require separate dose titration. Sodium nitroprusside has a similar action, however it is light degradable and the duration of infusion is limited by accumulation of cyanide. Therefore there is a continued need for new safe compounds. Drugs which may be given parenterally and have mixed vasodilating effects can be useful in monitoring the acute effects of reduction in preload and afterload in patients with cardiac failure. This may help assess the clinical response when the introduction of longterm vasodilator therapy is being considered. In addition parenteral vasodilator therapy may be indicated in emergency situations where rapid control of cardiac failure or hypertension is required in patients who are unable to take their drugs orally. The intravenous formulation of enalaprilic acid which has been shown in this study to have mixed venous and arteriolar dilating activity may therefore be an advantage in the treatment of some patients with cardiac failure compared with the other parenteral vasodilators.

The degree of hypotension observed in some of our patients however, indicates the need for caution even when using small doses of this drug for the treatment of cardiac failure. Such patients

have usually already received treatment with diuretics which increase plasma renin activity and therefore 'prime' the renin angiotensin system to the action of ACE inhibitors. It is now well recognised that the ACE inhibitors taken orally for the first time may cause a marked drop in blood pressure in hypertensive patients, especially those already on diuretics (Hodsman *et al.*, 1983). Profound hypotension has also been documented in patients with cardiac failure when started on captopril (Kramer *et al.*, 1982) and enalapril (Cleland *et al.*, 1985). Such 'first dose' responses are thus of continuing concern as a cause of unpredictable morbidity following the use of ACE inhibitors. In contrast a study of the haemodynamic effects of intravenous enalaprilic acid in subjects with coronary artery disease and normal left ventricular filling pressures, who were not receiving diuretic therapy, showed only small non significant falls in blood pressure (Hillis *et al.*, 1984). The heart rate was shown to be unaffected by enalaprilic acid in this study. The lack of reflex tachycardia following the administration of ACE inhibitors has not been fully explained, although several mechanisms have been proposed. These include active stimulation of central parasympathetic inhibitory pathways (Cody *et al.*, 1981; Ibsen *et al.*, 1983), the removal of angiotensin II potentiation of post-junctional sympathetic activity (Lee *et al.*, 1980) and altered baroreflex sensitivity (Marker *et al.*, 1980).

Overall we conclude that the mixed vasodilator activity and rapid onset of action of intravenous enalaprilic acid may give the drug a potential role particularly in the treatment of severe cardiac failure and it therefore appears to warrant further study.

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