Plasma enalapril levels and hormonal effects after short- and long-term administration in essential hypertension

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- 1 Enalapril lowers blood pressure both acutely and during long-term therapy in patients with essential hypertension.
- 2 After a single 10 mg dose of enalapril a close relationship between plasma enalaprilic acid (MK-422) levels, angiotensin converting enzyme (ACE) inhibition and the acute hypotensive and hormonal effects was demonstrated.
- 3 During long-term administration of enalapril, a similar relationship between the plasma enalaprilic acid level, ACE inhibition and the hypotensive effect was shown, although the dose-response curve for plasma enalaprilic acid to ACE inhibition was displaced to the right compared to the acute dose-response curve.
- 4 Several weeks' administration of enalapril was needed to reach stable plateau levels of plasma enalaprilic acid and ACE inhibition.
- 5 During long-term treatment with enalapril in essential hypertension, there was sustained inhibition of ACE and the associated hormonal changes.

Keywords enalapril plasma enalaprilic acid hormonal effect essential hypertension

Introduction

Until recently, effective treatment for hypertension has involved either interrupting the sympathetic nervous system by adrenergic-blocking drugs, decreasing total peripheral resistance with vasodilators or reducing extracellular volume by diuretics. The introduction of orally effective angiotensin converting enzyme (ACE) inhibitors (Ondetti *et al.*, 1977; Ondetti & Cushman, 1982) has opened up a new approach to the treatment of hypertension. By modifying endogenous vasoactive hormonal systems, in particular the renin-angiotensin system, peripheral vascular resistance is decreased and thus the fundamental haemodynamic fault in hypertension is corrected. This is a theoretical advantage for ACE inhibitors, but increasing experience with the use of ACE inhibitors is revealing several practical advantages for ACE inhibitors over conventional antihypertensive drugs. ACE inhibitors have already been shown

to be effective long-term therapy for hypertension (Case *et al.*, 1978; Brunner *et al.*, 1980; Heel *et al.*, 1980; Johnston *et al.*, 1982). They lower blood pressure without a resultant tachycardia. The acute hypotensive response is due to blocking the formation of angiotensin II and thus lowering peripheral resistance, usually with a small rise in cardiac output and organ blood flow (Vidt *et al.*, 1982). This paper will describe some of the specific indications and advantages of ACE inhibitors in the treatment of hypertension.

Enalapril (MK-421, Merck Sharp & Dohme) is a second generation ACE inhibitor (Patchett *et al.*, 1980). It is a non-sulphydryl substituted dipeptide, a competitive inhibitor of ACE which is more potent and longer acting than the first ACE inhibitor captopril (Biollaz *et al.*, 1981; Gavras *et al.*, 1981). The drug can easily be measured, allowing detailed studies on its

pharmacokinetics and pharmacodynamics (Jackson *et al.*, 1982; Millar *et al.*, 1982; Ulm *et al.*, 1982).

Studies on the conversion of enalapril (MK-421) to enalaprilic acid (MK-422) *in vitro* and *in vivo* in man

Enalapril (MK-421) is a prodrug, being the esterified form of the bioactive parent diacid enalaprilic acid (MK-422). Enalaprilic acid however is poorly absorbed, whereas the esterified MK-421 is nearly completely absorbed from the gastrointestinal tract. The conversion of enalapril in humans is thought to occur in the liver (Tocco *et al.*, 1982) giving rise to the possibility that conversion may be slow and/or incomplete in patients with hepatic dysfunction. After administration of a single oral dose of enalapril to man, plasma MK-421 levels reach a peak in 1 h and then decline. Plasma MK-422 reaches a peak at 4–6 h and then falls (Figure 1). Presumably the delay in appearance is due to the time taken for hepatic conversion.

We have directly confirmed the conversion of enalapril by human liver *in vitro*. Human liver

specimens obtained from fresh autopsy material were homogenised in buffer, centrifuged and the supernatant incubated at 37°C with a fixed concentration of MK-421. Timed samples over 3 h were taken and the concentration of MK-422 formed measured by radio-immunoassay (Johnston *et al.*, 1983). Eight hepatic specimens were obtained from normal livers and four from cirrhotic livers. The rate of conversion of MK-421 to MK-422 by cirrhotic liver was significantly slower than by normal liver homogenates when expressed per wet weight, per mg protein or related to hepatic enzyme activity (Figure 2).

In a preliminary study, a patient with congestive heart failure and hepatic congestion and another patient with alcoholic cirrhosis showed delayed appearance of MK-422 in their plasma after a single oral dose of MK-421. Further suggestive evidence that conversion may be delayed or lessened in hepatic dysfunction was the finding that following a single oral dose of 10 mg enalapril to nine patients with congestive cardiac failure, the plasma level of MK-422 measured 4 h later was 20.4 ± 3.6 ng/ml, which was less than half the level found in 18 hypertensive patients given the same enalapril dose, 44.3 ± 6.8 ng/ml ($P < 0.001$; Table 1). However, after treatment for two to four weeks, the plasma MK-422 levels were comparable in patients with essential hypertension and in those with congestive heart failure. After equilibration, equivalent plasma MK-422 levels were achieved for the same dose of enalapril in these two groups of patients.

Figure 1 (a) Plasma enalapril (MK-421) and (b) plasma enalaprilic acid (MK-422) in 12 essential hypertensives plotted against time after a single oral dose of enalapril 10 mg.

Figure 2 Enalaprilic acid (MK-422) concentration after incubation of enalapril (MK-421) with homogenate of normal human liver (●; $n = 8$) compared to liver obtained from patients with cirrhosis (■; $n = 4$).

Table 1 Plasma enalaprilic acid (MK-422) after a single dose of enalapril 10 mg and after administration of enalapril 10 mg twice daily for 4 weeks in patients with essential hypertension or congestive cardiac failure

	Enalaprilic acid (MK-422) (ng/ml)	
	Acute	Chronic
Hypertensives	44.3 ± 6.3 (18)	34.8 ± 3.6 (17)
Congestive cardiac failure	20.4 ± 3.6 (9)	51.2 ± 4.8 (10)

The number of patients in each study is in brackets.

Acute haemodynamic and hormonal effects of enalapril in patients with essential hypertension

The haemodynamic and hormonal effects of a single dose of 10 mg enalapril were studied in 12 patients with essential hypertension. All studies were conducted in the metabolic unit and approved by the Prince Henry's Hospital Advisory and Ethics Committee. All subjects gave written consent. The patients were studied resting in bed for the first 8 h. Blood samples for the determination of plasma drug levels, plasma ACE, angiotensin I and II, aldosterone, renin and bradykinin were drawn 0, 1, 2, 4, 8, 24, 32 and 48 h after enalapril. Blood pressure and heart rate were measured by an automatic recording device (Dynamap) at frequent intervals in the lying, sitting and standing position.

There was a significant fall in mean arterial blood pressure without a change in heart rate in all positions (Jackson *et al.*, 1982). The decrease in blood pressure commenced within 1 h, was maximal between 5–8 h and lasted for 24 h. This slower onset of action, but more prolonged hypotensive effect of enalapril contrasts with the more acute and shorter effect of captopril 50 mg in hypertension (Figure 3). A similar time course for inhibition of ACE, decreases in plasma angiotensin II and aldosterone, with reciprocal increases in blood angiotensin I and plasma renin was found (Figure 4). There was no change in blood bradykinin. This time sequence of events paralleled the appearance and clearance of MK-422 in the plasma and there was a close correlation between the serum MK-422 level, ACE inhibition, the blood pressure response and hormonal changes (Johnston *et al.*, 1983). The acute hypotensive effect of enalapril in this situation then appears to be a direct result of ACE inhibition and the consequent fall in plasma angiotensin II (Johnston *et al.*, 1984b).

Figure 3 Fall in blood pressure in 12 patients with essential hypertension who received enalapril 10 mg (---) compared with fall in pressure found in 17 hypertensive patients given captopril 50 mg (—). Note the more rapid onset with captopril but the longer duration of action of enalapril.

Chronic haemodynamic and hormonal effects of enalapril in patients with essential hypertension

To establish whether these hormonal changes persisted and to investigate further the pharmacokinetics of enalapril, nine patients with essential hypertension were entered into a dose-ranging study. Enalapril was commenced at 5 mg twice daily. The patients were seen fortnightly and if their diastolic blood pressure had not fallen to 90 mm Hg or below, the dose of enalapril was increased to 10 and then 20 mg twice daily. Two patients required only 10 mg/day, two 20 mg/day and the remaining five 40 mg/day to achieve their target blood pressure.

Blood pressure, heart rate and body weight were recorded at each visit and blood samples taken 3–4 h after their last dose of enalapril.

Figure 4 Changes in: (a) plasma aldosterone ($\blacktriangle$) and angiotensin II ($\bullet$); (b) blood angiotensin I ($\bullet$) and plasma renin ($\blacktriangle$), and (c) blood bradykinin ($\bullet$), after administration of 10 mg enalapril to 12 patients with essential hypertension. ANG = angiotensin.

Serum MK-422 increased in proportion to the 5, 10 and 20 mg doses.

The serum MK-422 concentration, ACE inhibition of ACE and only a 6 mmHg drop in the three dose levels are shown in Table 2. Enalapril 10 mg daily produced only 10% inhibition of ACE and only a 6 mm Hg drop in arterial pressure. These results suggest that to achieve a greater than 50% inhibition of ACE in man the dose of enalapril must exceed 10 mg twice daily. However, unlike the report of Biollaz *et al.* (1982) our study demonstrated proportional falls in blood pressure for all degrees of ACE inhibition (Johnston *et al.*, 1983). It has been shown with captopril (Laragh *et al.*, 1980) that it takes some weeks to achieve maximal reduction in blood pressure in hypertensive patients and this has also been noted with enalapril (Brunner *et al.*, 1983). In the five patients who were titrated up to the maximum

Figure 5 Plasma angiotensin converting enzyme (ACE) activity plotted (a) as a percentage of the initial level and (b) plasma enalaprilic acid (MK-422) over a period of 52 weeks in five patients with essential hypertension who were treated with increasing doses of enalapril. P = placebo.

dose of 40 mg/day, MK-422 levels and ACE inhibition often took more than 4 weeks to reach a plateau level (Figure 5) and individual responses were very variable. In each individual there was always a significant and close correlation between drug level and degree of ACE inhibition ($r = 0.78$, $P < 0.001$, $n = 12$).

As in the acute study, there was a close relationship between serum MK-422 and ACE inhibition and also between these two variables and the fall in blood pressure after 16 weeks (Johnston *et al.*, 1983). At 16 weeks hormonal

Table 2 Relationship between daily enalapril dose, serum MK-422, plasma angiotensin converting enzyme (ACE) activity and fall in blood pressure (Δ MAP)

Daily dose (mg)	Serum MK-422 (ng/ml)	Plasma ACE (% initial)	Δ MAP (mm Hg)
10	21.8 $\pm$ 3.0	90 $\pm$ 7	6 $\pm$ 3
20	34.8 $\pm$ 4.9	70 $\pm$ 6	12 $\pm$ 2
40	68.0 $\pm$ 7.0	41 $\pm$ 3	17 $\pm$ 2

Figure 6 (a) Blood pressure, (b) angiotensin converting enzyme (ACE) activity expressed as a percentage of the initial concentration, plasma renin and (c) plasma angiotensin II and urinary aldosterone levels in nine patients treated for up to 52 weeks with enalapril.

changes were also similar to those in the acute study (Figure 6), but after 52 weeks' therapy, although there was still evidence of ACE inhibition and plasma renin remained high, plasma angiotensin II and plasma aldosterone had tended to return to their pretreatment levels. Similar findings have been reported after chronic captopril therapy (Johnston *et al.*, 1979; Staessen *et al.*, 1981; Biollaz *et al.*, 1982; Clauser *et al.*, 1983). The rise in renin is thought to be due both to the decrease in blood pressure and the removal of angiotensin inhibition on renal renin release. However, the disproportionately high renin levels compared to the plasma angiotensin II concentration seen after chronic ACE inhibition suggests that renin also may be stimulated by uncompensated negative sodium balance (Jover & Mimran, 1984; Jackson & Johnston, unpublished observations).

These studies show that enalapril is effective in the long term in lowering blood pressure and maintaining prolonged ACE inhibition with elevated plasma renin, though angiotensin and aldosterone concentrations tend to return to pretreatment levels. In the case of aldosterone this may be due to stimulation by other factors such as uncompensated sodium depletion or changes in potassium metabolism (McCaa *et al.*, 1978; Clauser *et al.*, 1983).

Advantages and drug interactions of ACE inhibitors in the treatment of hypertension

The particular haemodynamic and hormonal effects of ACE inhibitors convey some unique

advantages for this class of compound over conventional antihypertensive therapy as well as some specific and important drug interactions. As ACE inhibitors do not have any central or autonomic nervous system effects (Reid *et al.*, 1983), patients generally feel well and alert. They retain normal postural reflexes with no postural hypotension and the cardiovascular response to exercise is maintained (Millar *et al.*, 1982). The reason for the lack of reflex tachycardia is not known but may represent some indirect interference with the baroreflex or sympathetic nervous system with withdrawal of angiotensin's central effect on parasympathetic vagal tone. There is also no interference with sexual activity.

Another major advantage of ACE inhibitors is their synergism with low sodium diets (Figure 7; Millar *et al.*, 1981) or diuretics. They potentiate the hypotensive effect of diuretics but because they block the formation of angiotensin II they also prevent the secondary hyperaldosteronism and resultant hypokalaemia which is produced by diuretics (Johnston *et al.*, 1979, 1984a). Similarly they may prevent the fluid retention associated with peripheral vasodilators. Conversely in patients with limited renal potassium excretion or in patients who are receiving potassium sparing diuretics, there is danger of hyperkalaemia. Renal blood flow and glomerular filtration rate are usually well maintained and may even improve with ACE inhibitors (Hollenberg, 1982).

Figure 7 Blood pressure responses to 10 mg enalapril in nine patients with essential hypertension studied on a 100 mmol Na diet (●) or on a 40 mmol Na diet (▲). There was no difference in the degree of ACE inhibition (b) produced by this dose of enalapril between the two sodium diets, but a greater hypotensive effect on the lower sodium diet was noted.

Finally, because of the long half-life of the active metabolite, enalaprilic acid, the risk of rapid hypertensive rebound is extremely high.

B. Jackson is a Research Fellow of the National Health and Medical Research Council of Australia. The experimental studies reported in this paper were supported by the NHMRC of Australia, the National Heart Foundation of Australia and a grant from Merck Sharp & Dohme.

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