Br. J. clin. Pharmac. (1984), **18**, 215S–229S

An overview of the clinical pharmacology of enalapril

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1 Enalapril maleate is a prodrug which when administered orally is hydrolysed to release the active converting enzyme inhibitor enalaprilat. Enalapril maleate is 60% absorbed and 40% bioavailable as enalaprilat. Both compounds undergo renal excretion without further metabolism. The functional half-life for accumulation of enalaprilat is 11 h, and this is increased in the presence of a reduction in renal function.

2 Inhibition of converting enzyme inhibition is associated with reductions in plasma angiotensin II and plasma aldosterone, and with increases in plasma renin activity and plasma angiotensin I. Acute and chronic effects have been reviewed. When given with hydrochlorothiazide, enalapril attenuates the secondary aldosteronism and ameliorates the hypokalaemia from diuretics.

3 Both acutely and chronically in patients with essential hypertension, enalapril reduced blood pressure with a rather flat dose-response curve. No evidence of a triphasic response such as seen with captopril has been demonstrated with enalapril, and blood pressure returns smoothly to pretreatment levels when the drug is abruptly discontinued. Once- or twice-daily dosing gives similar results. The antihypertensive effects of enalapril are potentiated by hydrochlorothiazide.

4 Haemodynamically, blood pressure reduction is associated with a reduced peripheral vascular resistance and an increase in cardiac output and stroke volume with little change in heart rate.

5 Renal vascular resistance decreases, and renal blood flow may increase without an increase in glomerular filtration in patients with normal renal function. In patients with essential hypertension and glomerular filtration rates below 80 ml/min/m^2, both renal blood flow and glomerular filtration rates may increase.

Keywords enalapril clinical pharmacology disposition haemodynamics renal function review

Introduction

Enalapril maleate resulted from a targeted research programme using molecular modelling to discover potent, long-lasting inhibitors of angiotensin converting enzyme (ACE) which would be useful in the treatment of hypertension and congestive heart failure. Only molecules lacking the mercapto group were studied in the hope of improving on the tolerance of captopril due to the similarity in the side-effect profile between captopril and penicillamine. Enalapril is a prodrug developed as the ethyl ester of the active converting enzyme inhibitor enalaprilat (Figure 1). This approach was taken in order to improve oral absorption. The chemical synthesis of enalapril was first published by Patchett *et al.* (1980), and its pharmacological properties were described by Gross *et al.* (1981) and Sweet *et al.* (1981a, b). Initial

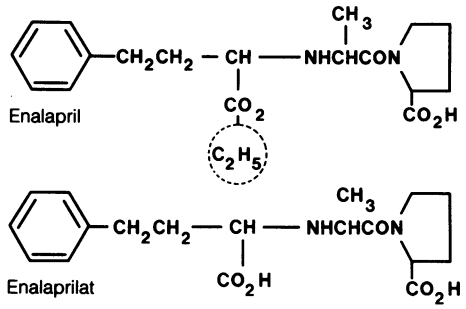

Figure 1 Chemical structures of enalapril (MK-421), and enalaprilat (MK-422). Enalaprilat is the active converting enzyme inhibitor.

clinical pharmacological results were presented by Gomez *et al.* (1983a), and world-wide clinical experience was reviewed by Smith (1983) and Davies *et al.* (in press).

Disposition

When enalapril maleate was given orally to healthy volunteers, peak concentrations of the prodrug appeared in the systemic circulation at approximately 1 h after dosing. Hydrolysis takes place, probably in the liver, with a gradual release of the active converting enzyme inhibitor enalaprilat. Peak concentrations of enalaprilat appeared between 3½ and 4½ h in normal volunteers and in patients with hypertension (Biollaz *et al.*, 1982b) (Figure 2). There was no further metabolism of enalaprilat in man or in other species, with the exception of the rhesus monkey (Tocco *et al.*, 1982; E. Ulm, unpublished data). Both enalapril and enalaprilat appeared in the urine. Various studies (Ulm *et al.*, 1982; Ulm, 1983; Irvin *et al.*, 1984) reported that about 60% of oral enalapril was absorbed whereas only about 3% of enalaprilat was absorbed when given orally (Ulm, 1983). Conversion of enalapril to enalaprilat was about 60% efficient, and bioavailability of enalapril (expressed as enalaprilat) averaged about 40% using intravenous enalaprilat as a reference standard (Ulm, 1983; Irvin *et al.*, 1984). Renal clearance was 158 ± 47 ml/min (Ulm *et al.*, 1982).

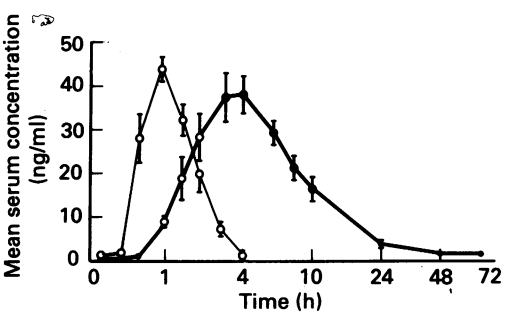

Figure 2 Mean serum concentrations of enalapril maleate (○) and enalaprilat (●) following 10 mg enalapril maleate given to 12 normal volunteers.

Serum concentration *vs* time profiles of enalaprilat following 5, 10, 20 and 40 mg doses of enalapril maleate showed that peak plasma concentrations were proportional to dose. The plasma profile was polyphasic with a prolonged terminal phase where drug concentrations were independent of dose (Irvin *et al.*, 1984). A. E. Till (unpublished data) demonstrated that if the area under the curve of the terminal phase was subtracted from the total area under the plasma time curve, the corrected area was linear with respect to dose. With repeat daily dosing in normal volunteers, steady state concentrations were reached by the third day, and only a small accumulation factor was identified (Till *et al.*, 1983). Johnston *et al.* (1983, 1984a, b) and DeLeeuw *et al.* (1983) have correlated serum enalaprilat levels, inhibition of converting enzyme, and blood pressure reduction. Ferguson *et al.* (1983) reported that serum concentrations of enalapril were similar when the drug was administered during fasting or after a standard breakfast. By contrast, food has been shown to depress the absorption of captopril by about 50% (Kripalani *et al.*, 1980).

Saris *et al.* (1984) demonstrated that serum concentrations of enalapril and enalaprilat were increased and urinary excretion was decreased in patients with renal failure (Figure 3). Peak serum concentrations occurred later in these patients than in patients with normal renal function. The drug was removed by haemodialysis. Antihypertensive effects tended to be greater and more prolonged at these higher serum concentrations. Accordingly, dosage in patients with renal failure should be reduced and possibly given less frequently than in individuals with normal renal function. Current clinical experience has not demonstrated an increase in incidence or change in type of side-effect profile of enalapril in patients with renal failure.

E. Ulm (unpublished data) studied the binding of enalaprilat in human plasma both by equilibrium dialysis and by ultrafiltration. Two binding sites were demonstrated: a low-affinity high-capacity site and a high-affinity low-capacity binding site which may be associated with the prolonged terminal phase of the plasma profile, and probably represents drug bound to circula-

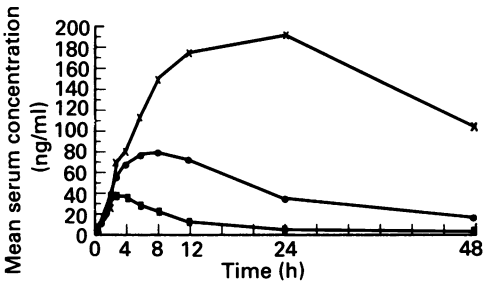

Figure 3 Mean serum concentrations of enalaprilat measured in nine normal volunteers (■ = mean creatinine clearance 123 ml/min), eight patients with moderate renal insufficiency (● = mean creatinine clearance 32 ml/min) and nine patients with marked renal insufficiency (x = mean creatinine clearance < 3 ml/min).

ting converting enzyme. Overall, not more than 50% of enalaprilat is bound to plasma proteins.

Biochemical effects

Effects on converting enzyme activity

Initial studies in man by Brunner *et al.* (1981) confirmed the long duration of inhibition by converting enzyme activity (Figure 4) predicted from animal studies. Following a single 10 mg dose, converting enzyme inhibition was almost complete for at least 10 h, was markedly depressed at 24 h, and still had not returned to baseline by 72 h (Brunner *et al.*, 1981). Converting enzyme inhibition has been confirmed by other investigators (Gavras *et al.*, 1981; Ferguson *et al.*, 1982), and Johnston has correlated converting enzyme inhibition to both plasma levels of enalaprilat and to antihypertensive effects of enalapril (Jackson *et al.*, 1982; Johnston *et al.*, 1983). DeLeeuw *et al.* (1983) showed a dose-response relationship between plasma levels of enalaprilat and ACE inhibition. *In vitro*, the enzyme inhibitor complex for enalapril is stable, whereas with captopril this is not the case (Brunner *et al.*, 1981).

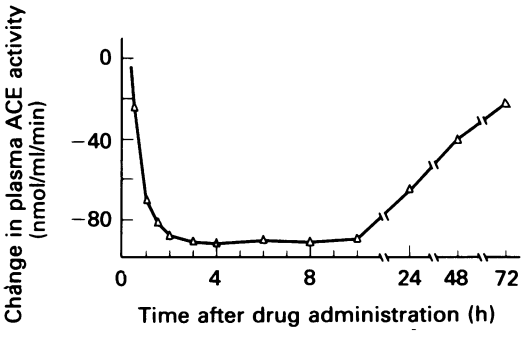

Figure 4 Changes in plasma ACE activity in 12 normal volunteers following 10 mg enalapril maleate.

Effect on plasma renin activity, active renin concentration and angiotensin II

As predicted, plasma renin activity and active renin concentration increased and plasma angiotensin II levels decreased following enalapril (Biollaz *et al.*, 1981; Brunner *et al.*, 1981; Gavras *et al.*, 1981; MacGregor *et al.*, 1981; Johnston *et al.*, 1984a). Increases in plasma renin activity were greater in the upright than in the supine position (Griffing *et al.*, 1982a; Cody *et al.*, 1983b). Restricted sodium diet potentiated both the increase in plasma renin and the decrease in plasma angiotensin II levels (Jackson *et al.*, 1982; Shoback *et al.*, 1983a) (Table 1). On a high-sodium diet, only the increase in plasma renin activity was statistically significant from baseline.

Table 1 Effects of enalapril maleate 20 mg in normal volunteers on deplete sodium diet (10 mEq) and replete sodium diet (200 mEq) per 24 h with measurements of diastolic blood pressure (DBP), plasma renin activity (PRA), plasma angiotensin II (AII), plasma aldosterone (PA), renal plasma flow (PAH), and glomerular filtration

	10 mEq/day		*200 mEq/day*	
	Pre	*Post*	*Pre*	*Post*
Number of subjects	11		9	
DBP (mm Hg)	71	61*	72	67
PRA (ng/ml/h)	4.6	26*	0.6	7.9*
AII (pg/ml)	46	21*	21	17
PA (ng/100 ml)	30	10*	4	3
PAH clearance (ml/min/1.73 m^2)	589	740*	614	671
Inulin clearance (ml/min/1.73 m^2)	92	90	100	102

* $P < 0.01$ from pretreatment values.

The time course for the reduction of plasma angiotensin II levels was somewhat shorter than that for converting enzyme inhibition (DiCarlo *et al.*, 1983). MacGregor *et al.* (1981) reported that angiotensin II levels had returned to control by 24 h after dosing in normal volunteers on their usual sodium intake. The effects of a 20 mg dose were somewhat greater and lasted longer than those of a 5 mg dose.

Hodsman *et al.* (1982) also reported that plasma angiotensin II levels in renovascular hypertension patients had returned to pretreatment values 24 h after low doses, while converting enzyme was still inhibited, but the effect on angiotensin II lasted at least 24 h with larger doses. Shoback and colleagues demonstrated that following a 10 mg dose of enalapril in volunteers on a restricted sodium diet, angiotensin II levels were still reduced at 24 h (Shoback *et al.*, 1983a, b). Using angiotensin I challenges administered at various times after enalapril administration, Given *et al.* (in press) demonstrated that reduction in blood pressure and angiotensin II levels and increases in plasma renin activity were present for at least 22 h (Figure 5). When plasma angiotensin II levels were depressed, angiotensin I levels were increased. The increase in active renin observed during chronic administration was higher than that noted after the first dose. However, angiotensin I did not increase in proportion, which probably reflected a fall in renin substrate with prolonged converting enzyme inhibition (Hodsman *et al.*, 1984).

Hodsman *et al.* (1983a, b) measured the effects of enalapril in patients with renovascular hypertension and related the effects of converting enzyme inhibition, reduction of angiotensin II and aldosterone, and increases in angiotensin I levels and active renin to the reductions in blood pressure (Figure 6). Six hours after the initial dose, blood pressure was reduced, converting enzyme was inhibited, and plasma angiotensin II levels were reduced. These effects were also observed on the sixth treatment day and after three months of dosing. Interestingly, the increases in active renin and in angiotensin I levels were greater six days and three months after dosing than after the first dose, although ACE and plasma angiotensin II reductions were similar acutely and chronically. The time course of effects of a dose given during chronic therapy were studied by measurements taken just before and for several hours after dosing. Small further reductions of plasma ACE activity and angiotensin II were demonstrated with concomitant increases in active renin and angiotensin I, whereas blood pressure was well-controlled throughout.

Biollaz *et al.* (1982a) and Brunner *et al.* (1983) studied the effects on blood pressure and hormonal parameters during 6 months therapy in a small group of patients with essential hypertension. While blood pressure and plasma ACE were reduced initially and the effect maintained long-term, the early reduction in plasma angiotensin II levels were not maintained. Plasma angiotensin II returned towards or above control by 4–5 months after initiation of therapy (Figure 7). Plasma renin activity during this period continued to increase and appeared to plateau at about 4 months. These patients continued on chronic therapy and were readmitted for study of the responses to the next day's dose. Parameters were measured before the dose and for 6 h thereafter. The expected effects on ACE, angiotensin II and

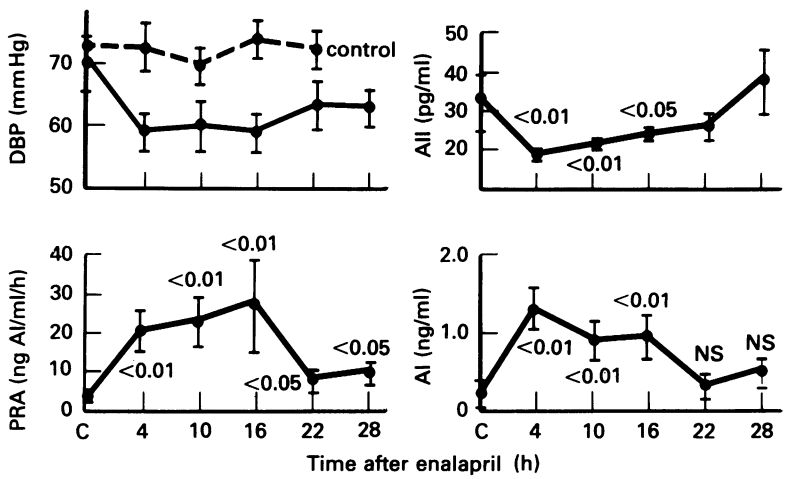

Figure 5 Effects of enalapril maleate 10 mg in seven sodium depleted normal volunteers challenged with 10 ng/kg^{1}/min^{-1} infusions of angiotensin I administered at various time intervals (see abscissa) on diastolic blood pressure (DBP), plasma renin activity (PRA), plasma angiotensin II (AII) and plasma angiotensin I (AI).

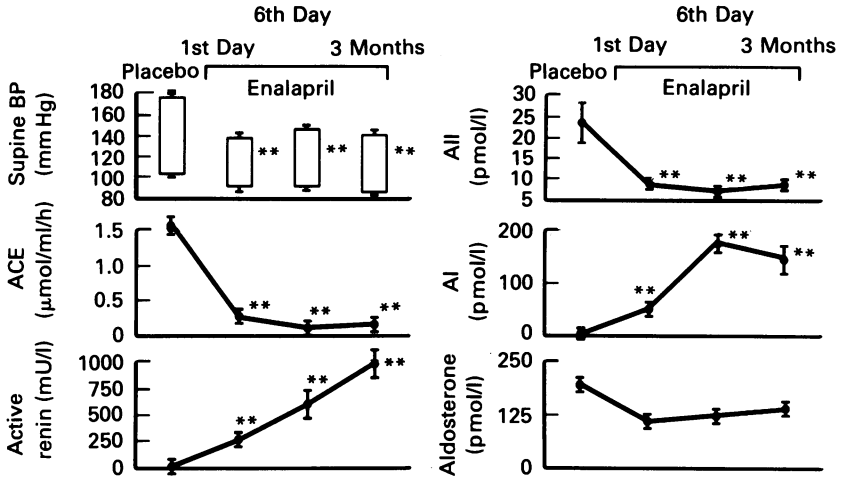

Figure 6 Effects of enalapril maleate once-daily in 10 patients with unilateral renal artery stenosis with measurements taken before treatment (placebo) and 6 h following the first day dose (1st day), 6th day, and 3 months. Supine blood pressure (Supine BP), angiotensin converting enzyme (ACE), active renin, plasma angiotensin II (AII), plasma angiotensin I (AI) and plasma aldosterone (mean ± s.e. mean; $^{**}P < 0.01$).

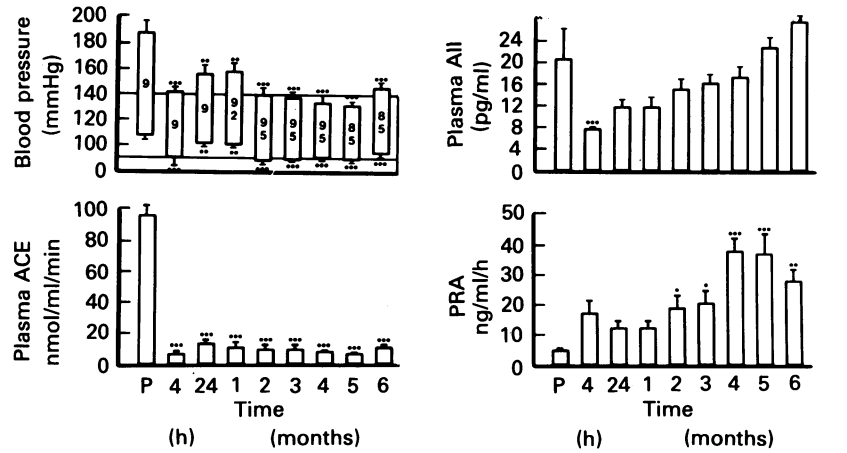

Figure 7 Effects of enalapril maleate in nine patients with essential or renovascular hypertension treated over 6 months. Blood pressure, plasma angiotensin II (plasma AII), plasma angiotensin converting enzyme (ACE), and plasma renin activity (PRA) measured before therapy (placebo), 4 and 24 h following the first dose, and before daily dosing at 1–6 months treatment. Values expressed as mean ± s.e. mean. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

plasma aldosterone were confirmed. Blood pressure continued to be well-controlled throughout the period. Because of the high levels of plasma angiotensin I measured during long-term ACE inhibition (Brunner *et al.*, 1983), concern has been expressed about cross-reactivity of angiotensin I and angiotensin II in the laboratory assay as a possible explanation for higher than expected plasma angiotensin II values. This has been excluded by both Brunner *et al.* (1983) and Hodsman *et al.* (1983b).

Effect on plasma aldosterone

Early studies confirmed the expected reduction in plasma aldosterone following enalapril (Biollaz *et al.*, 1981; Brunner *et al.*, 1981; Gavras *et al.*, 1981; MacGregor *et al.*, 1981; Ferguson *et al.*, 1982; Johnston *et al.*, 1984a). The effect was more obvious in volunteers on a sodium-restricted diet (Shoback *et al.*, 1983a) (Table 1). Additionally, the reduction in plasma aldosterone following enalapril was much greater

when measured during ambulation than during rest in the supine position (Griffing *et al.*, 1982a; Cody *et al.*, 1983b; Griffing & Melby, 1983). Furthermore, enalapril reduced the secondary aldosteronism seen in volunteers treated with hydrochlorothiazide alone (Figure 8), in spite of the enhanced effect on plasma renin activities (Griffing & Melby, 1982; Griffing *et al.*, 1983). The reduction in plasma aldosterone was associated with reductions in aldosterone secretion rate and was particularly marked in volunteers receiving concomitant hydrochlorothiazide (Griffing *et al.*, 1982a, b). Acutely and chronically enalapril alone produced small but statistically significant increases in serum potassium and associated decreases in urinary potassium excretion. Given with hydrochlorothiazide, enalapril attenuated kaliuresis and maintained plasma potassium in the normal range (Griffing & Melby, 1982; Griffing *et al.*, 1983; Gomez *et al.*, in press). This net effect depends on the dose of enalapril and hydrochlorothiazide administered. Enalapril also attenuates the hydrochlorothiazide-induced hyperglycaemia, hyperuricaemia, and hypercholesterolaemia (Gomez *et al.*, 1984).

Cody *et al.* (1983b) reported on the effects of captopril and enalapril in patients with essential or renovascular hypertension treated chronically in common protocols. While this was not a crossover study, some of the patients were common to both protocols. Usual and high doses of the two inhibitors were studied. While both inhibitors reduced plasma aldosterone, particularly while ambulatory, the effect was greater with enalapril (Figure 9). The percentage of patients having postural increases in plasma aldosterone greater than 50% of baseline was somewhat smaller with higher doses of the inhibitors, and the percentage of patients controlled appeared to be greater for enalapril than captopril.

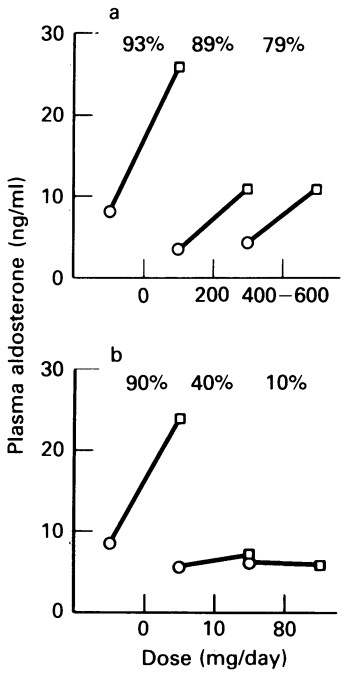

Figure 9 Effect on plasma aldosterone in patients with essential or renovascular hypertension treated with (a) captopril (28 patients) or (b) enalapril (10 patients). Plasma aldosterone was measured supine (○) and after 4 h ambulation (□). Percentage figures reflect the portion of patients having postural increments exceeding 50%.

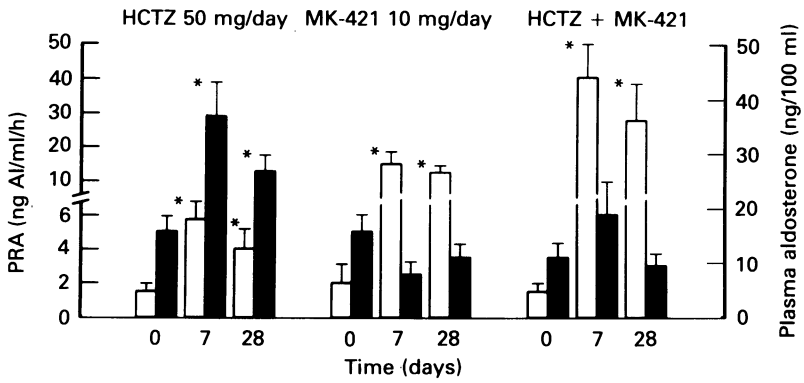

Figure 8 Effect of hydrochlorothiazide (HCTZ), enalapril maleate (MK-421) and concomitant administration of hydrochlorothiazide and enalapril maleate on plasma renin activity (PRA; □) and plasma aldosterone (■) in three groups of six normal volunteers measured on days 0, 7 and 28. $*P <$ 0.05 compared to control.

Effects on catecholamines, bradykinin and prostaglandins

Catecholamines While plasma catecholamines have been evaluated by a number of investigators (Fitz *et al.*, 1982; Ibsen *et al.*, 1983; Reid *et al.*, 1983; Shoback *et al.*, 1983b; Johnston *et al.*, 1984a; Nadeau *et al.*, 1984) because of the interest in the potential interactions of the renin angiotensin and the sympathetic nervous systems, enalapril produced little change in either plasma noradrenaline or andrenaline. During a study involving tilting, Ibsen *et al.* (1983) demonstrated increases in plasma noradrenaline in normal volunteers which were larger on enalapril than on placebo. DeLeeuw *et al.* (1983) and Johnston *et al.* (1984a) reported a small increase in plasma noradrenaline with 1.25 mg enalapril, a dose which did not affect blood pressure in hypertensive patients studied during metabolic balance conditions. A 5 mg dose decreased both plasma noradrenaline and blood pressure. Morioka reported that the expected increases in exercise-induced plasma noradrenaline was reduced in patients with hypertension but there was no effect on resting values (Morioka *et al.*, 1983). In patients with congestive heart failure, reductions in plasma noradrenaline have been reported in patients demonstrating beneficial haemodynamic and clinical responses (DiCarlo *et al.*, 1983; Fitzpatrick *et al.*, 1983; Turini *et al.*, 1983).

Bradykinin Several investigators (Jackson *et al.*, 1982; Odya *et al.*, 1983; Shoback *et al.*, 1983b) have reported that plasma bradykinin or urinary kinins, and urinary kallikrein (Fitz *et al.*, 1982) were not increased by enalapril in normal volunteers or in patients with hypertension. Interpretation of these findings is usually limited because of methodological problems.

Prostaglandins Captopril has been demonstrated to increase prostaglandins, possibly through stimulation of bradykinin, and the hypotensive effects are antagonised by indomethacin, particularly in low-renin hypertensive patients (Abe *et al.*, 1980; Salvetti *et al.*, 1980; Moore *et al.*, 1981). Several investigators (Fitz *et al.*, 1982; Oparil *et al.*, 1983; Shoback *et al.*, 1983b) have measured the effect of enalapril on various prostaglandin parameters (Table 2) in either plasma or urine and, with one exception, have failed to demonstrate increases in either normal volunteers or patients with hypertension. Shoback *et al.* (1983b) compared captopril and enalapril in normal subjects on low- and high-sodium diets. This was not a crossover study; experimental conditions were carefully standardised. Both converting enzyme inhibitors reduced diastolic blood pressure, plasma angiotensin II and increased plasma renin activity in normal volunteers on a low-sodium diet. Increases in PGE_2 metabolite were demonstrated only with captopril and not with enalapril (Table 3). Vlasses *et al.* (1984) demonstrated that captopril and enalapril reduced blood pressure to a similar extent and that adding the two converting enzyme inhibitors together, did not cause a further reduction in blood pressure. This suggested that the two agents shared common antihypertensive mechanisms and may question the relevance of changes in prostaglandins reported for captopril. Oparil *et al.* (1983) failed to demonstrate an attenuation of enalapril's antihypertensive effect when either sulindac or indomethacin was co-administered in a group of patients with low-renin essential hypertension.

Antihypertensive effects of enalapril

Initial studies in normal volunteers, given infusions of angiotensin I to produce an increase in blood pressure, were studied as a model to demonstrate the potential antihypertensive effects of enalapril maleate (Biollaz *et al.*, 1981). They confirmed that doses of 2.5, 10 and 20 mg attenuated the increase in blood pressure, but a dose of 1.25 mg showed little activity. Doses of 10 and 20 mg showed similar potency, suggesting that the top of the dose-response curve was being approached. Given *et al.* (in press) studied the time course of response

Table 2 Effects of enalapril on prostaglandins

PGE_2	Fitz *et al.* (1982)	No change
PGE_2M	Shoback *et al.* (1983a,b)	Slight increase
PGE_2M	Fitz *et al.* (1982)	No change
$PGF_{1\alpha}$	Fitz *et al.* (1982)	No change
$PGF_{1\alpha}$	Vlasses *et al.* (1984)	No change
$PGF_{1\alpha}$ (Urine)	Oparil *et al.* (1983)	Increase
$D6KPGF_{1\alpha}$	Nadeau *et al.* (1984)	No change
TXB_2	Vlasses *et al.* (1984)	No change

Table 3 Captopril *vs* enalapril in normal subjects on low- and high-sodium diets

	Low-sodium diet		*High-sodium diet*	
	Captopril	*Enalapril*	*Captopril*	*Enalapril*
Decreased BP	−13	−15	−11	−14
PRA	+14	+21	+3.5	+6.9
AII	−13	−17	N/C	N/C
BK	+1	N/C	N/C	N/C
PGE_2M	+60	N/C	+32	N/C

BP = blood pressure; PRA = plasma renin activity; AII = angiotensin II; BK = bradykinin; PGE_2M = PGE_2 metabolite; N/C = no change.

following 10 mg enalapril in normal volunteers (Figure 10). Angiotensin pressor responses were inhibited by 4 h, and the effect of enalapril was maintained to at least 28 h. Kono *et al.* (1982) also confirmed a 24-h duration of effect following 20 mg using angiotensin I infusion. Angiotensin II and angiotensin I levels showed the expected pattern of response, and changes were statistically significant to at least 28 h. In volunteers maintained on either a low- or high-salt diet, the onset and duration of effect was dose-related. In volunteers given a low-sodium diet, blood pressure was reduced by 2.5 mg, whereas in volunteers on a high-sodium diet, changes were not seen until a dose of 5 mg was given. Following doses of 10 and 20 mg, the effects lasted longer than with doses of 5 mg. The antihypertensive effects were more substantial in volunteers on the low-sodium diet. Hodsman *et al.* (1984) also reported that 10 mg once-daily reduced blood pressure for 24 h after the first and eighth doses in a 1-week metabolic balance protocol using a diet containing 150 mEq/24 h sodium.

During initial dose-finding studies in hypertensive patients, Gavras *et al.* (1981), Gomez *et al.* (1981) and Ferguson *et al.* (1982) demonstrated effects with doses of 2.5 and 5 mg which lasted a shorter time than the effects seen with 10 and 20 mg (Figure 11). Once these patients' blood pressures were controlled, they continued treatment on an outpatient basis. In some circumstances (Ferguson *et al.*, 1982), blood pressure reductions were less well-maintained, but the patients' salt intake was also less well-controlled. Under metabolic balance conditions Nadeau *et al.* (1984) studied the time course of response in patients with severe hypertension receiving 20 mg twice-daily. As shown in Figure 12, antihypertensive effects were seen with the first dose, reached full effects by about 3 days, and were maintained over the next 12 days. No triphasic response was seen or has been reported for captopril (Case *et al.*, 1980). The onset of antihypertensive activity was gradual, and peak effects were seen at about 4 h, consistent with the time course for

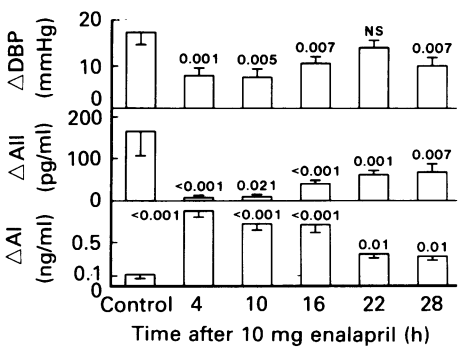

Figure 10 Duration of action of enalapril maleate 10 mg in seven normal volunteers assessed by angiotensin I challenges with measurements of the change from baseline in diastolic blood pressure (DBP), angiotensin II (AII), and plasma angiotensin I (AI). Data expressed as mean ± s.e. mean.

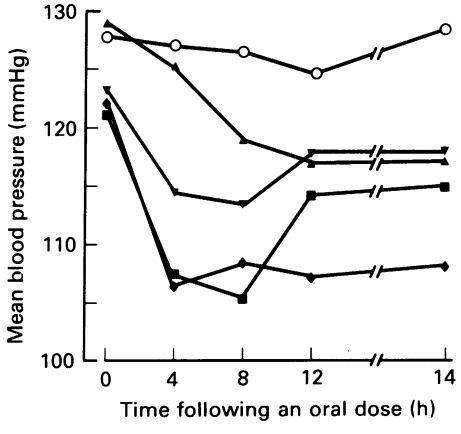

Figure 11 Effect of placebo (○), and single doses of enalapril maleate 2.5 (▼; day 1), 5 (▲; day 3), 10 (■; day 5) and 20 mg (◆; day 7) on mean blood pressure in six patients with essential hypertension (n = 6).

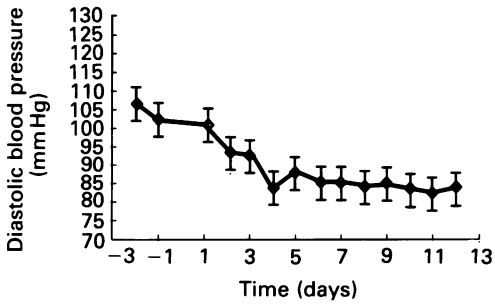

Figure 12 Effect of enalapril maleate 20 mg twice-daily on 12 h mean supine diastolic blood pressure in eight patients with essential hypertension (mean ± s.e. mean).

converting enzyme inhibition and the reduction of angiotensin II levels. The onset of activity of enalapril and captopril were directly compared in a large multicentre study (to be published) in which patients with moderate to severe blood pressure maintained on hydrochlorothiazide were then randomised to receive enalapril or captopril long-term. Figure 13 shows the blood pressure responses measured over the first 4 h and confirmed a more gradual onset of antihypertensive activity with enalapril compared to captopril.

In patients with hypertension, the addition of hydrochlorothiazide to enalapril produces significant additional reduction of blood pressure, and occasionally symptomatic hypotension occurred in volume contracted patients. Enalapril attenuated the hypokalaemia secondary to diuretic therapy (Vlasses *et al.*, 1984; Gomez *et al.*, in press).

When enalapril treatment was discontinued in patients whose hypertension had been controlled for some months by enalapril, blood pressure returned to control values in a gradual fashion with no evidence of overshoot (Guthrie *et al.*, 1982). Plasma renin activity returned to baseline in an approximately parallel fashion. Adverse effects were not seen from abrupt cessation of enalapril therapy.

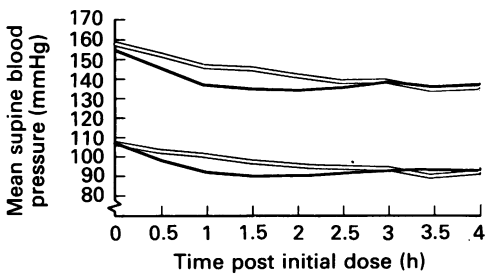

Figure 13 Effect of enalapril (79 patients) and captopril (82 patients) on mean supine systolic and diastolic blood pressure given to patients with moderate to severe hypertension maintained on hydrochlorothiazide 50 mg daily.

Dose-response studies

Based upon open dose-ranging studies, dose-response studies were undertaken in order to both identify the minimally effective dose and explore the clinically useful part of the dose-response curve. In a parallel design multicentre dose-response study (to be published), placebo was compared to daily doses of 5, 20, 40 and 80 mg given in two divided doses. While there was some variability between groups, for example at week 2, all doses reduced blood pressure compared to placebo and overall a shallow dose-response curve was seen (Figure 14). While the time of measuring blood pressure following dosing was standardised within clinics, some clinics measured blood pressure just before the daily dose, and others measured blood pressure 4–8 h after dosing. This did not change the interpretation of the results, although it changed the magnitude of blood pressure reduction. In a second study (Wilhelmsson *et al.*, 1983) using a partially balanced crossover design with an extension period in order to permit study of a wide range of doses, a shallow dose-response curve was again seen. In this case the extent of antihypertensive response was smaller since measurements were made just before the next dose. Based upon these data, and confirmatory information from large multicentre dose titration studies, the dosage recommendation is 10–40 mg given in a single dose or in two divided doses. It is recognised that a small number of patients may respond at lower doses and that some additional effects may be seen with doses higher than 40 mg/day. Across the recommended dose range side-effect incidence was small and not related to dose.

Dose frequency

Because of the long duration of effect of enalapril, administration schedules of once- and twice-daily were considered feasible. In patients with mild to moderate hypertension, Bergstrand *et al.* (1982) and Gomez *et al.* (1983b) compared the effects of once- and twice-daily regimens over four-week treatment periods (Table 4). The effects of the two regimens were virtually identical. The time course of response following once- or twice-daily dosing was compared (Figure 15) with hourly measurements being

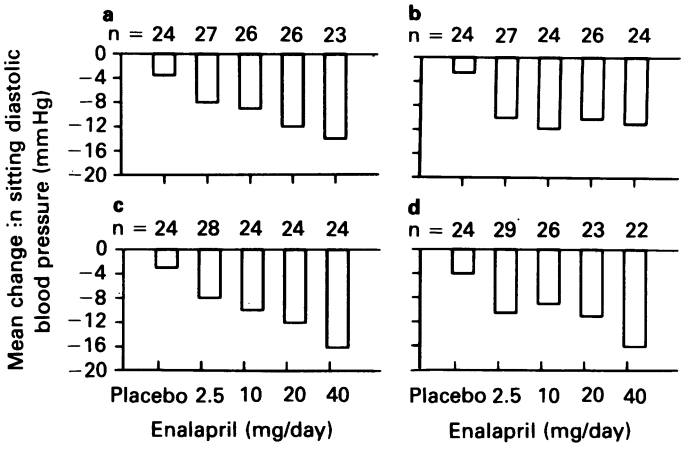

Figure 14 Mean changes in sitting diastolic blood pressure following various doses of enalapril maleate given twice-daily assessed at weeks 1 to 4 in 24 outpatients with essential hypertension. (a) Week 1, (b) week 2, (c) week 3, (d) week 4.

taken during the daytime on the day before, the initial day, and the 28th day of treatment (to be published). Again, the time course of response was similar, and antihypertensive effects were well-maintained. Finally, in a multicentre parallel design study in patients with mild hypertension (entrance criteria diastolic blood pressure 90–104 mmHg), once- or twice-daily enalapril therapy was compared to placebo (to be published). Doses of 10 mg once-daily or 5 mg twice-daily were administered for the first four weeks, and then the doses doubled and quadrupled over the succeeding four-week periods to a maximum of 40 mg daily. Once- or twice-daily therapy gave similar results. Reports from individual investigators confirm these pooled observations (Chrysant *et al.*, 1983; Morioka *et al.*, 1983; Wilkins *et al.*, 1983). Accordingly, enalapril can usually be given once- or twice-daily with similar efficacy.

Effects on cardiac function

Normal volunteers

Ibsen *et al.* (1983) studied the haemodynamic effects of enalapril in normal volunteers and demonstrated a reduction in blood pressure through a fall in total peripheral resistance and an increase in arterial compliance. Cardiac output was increased principally due to a higher stroke volume, because heart rate was unchanged. During head-up tilting, blood pressure fell due to a decrease in cardiac performance, while reflex increases in arterial and venous tone were largely unimpaired. Baroreceptor sensitivity tested by phenylephrine infusion was enhanced by enalapril. Millar *et al.* (1982a, b), Reid *et al.* (1983) and Ajayi *et al.* (in press) confirmed these findings and also reported that enalapril did not change the heart

Table 4 The antihypertensive effect of enalapril (20 mg/day) administered either as 20 mg four times daily or 10 mg twice-daily

Regimen	n	*Week 0*	*Week 4*	*Change**
Mean supine blood pressure: (systolic/diastolic, mm Hg)				
Four times daily	53	162/104	146/92	−17/−11
Twice daily	53	161/102	145/92	−16/−11
Mean erect blood pressure: (systolic/diastolic, mm Hg)				
Four times daily	53	162/106	142/94	−20/−12
Twice daily	53	159/105	139/93	−20/−12

* All within-treatment changes were significant, $P < 0.001$.

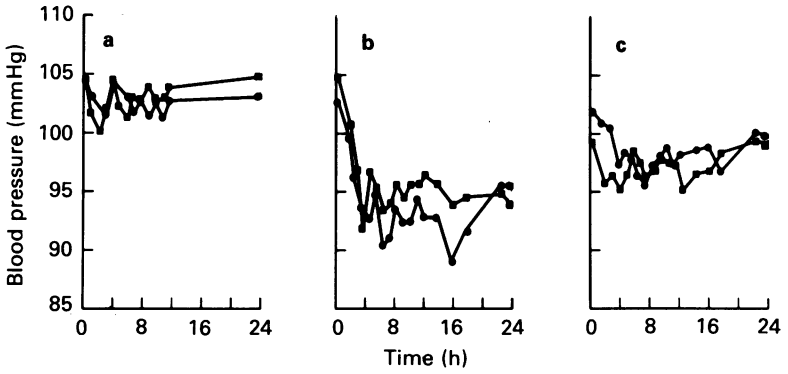

Figure 15 Mean standing diastolic blood pressure (a) before, (b) on the first day of therapy and (c) after 28 days therapy of enalapril maleate given either 40 mg once-daily (●) or 20 mg twice-daily (■) to 27 patients with essential hypertension. Note: not all patients present data at all times.

rate or blood pressure responses after Valsalva manoeuvre or after the cold pressor test. Others (Nadeau *et al.*, 1983; Dunn *et al.*, 1984) have also shown that enalapril has no effect on baroreceptor responses. Ajayi *et al.* (in press) reported that the lack of increase in heart rate following reductions of blood pressure with enalapril was associated with enhanced vagal stimulation. Those reflex responses resulting from facial immersion in water were attenuated by converting enzyme inhibitors.

Hypertensive patients

Blood pressure reduction was associated with a decrease in peripheral resistance and an increase in cardiac output and stroke volume without a change in heart rate (Fouad *et al.*, 1983, in press; Morioka *et al.*, 1983; Dunn *et al.*, 1984; Nakashima *et al.*, 1984). Results from the study by Dunn *et al.* (1984) in patients with hypertension are shown in Figure 16. Kallay *et al.* (1983) noted that the haemodynamic patterns varied with age and reported that the hypotensive effect of enalapril in the young were associated with decreases in cardiac output, while in older patients the decrease in blood pressure was more associated with reductions in peripheral vascular resistance. When the younger patients were tested in the upright position, a decrease in cardiac output was associated with a reduction in venous return. Simon *et al.* (1984) confirmed the decrease in peripheral vascular resistance and forearm vascular resistance, but reported that forearm venous tone was unaffected by enalapril. Both Nakashima *et al.* (1984) and Dunn *et al.* (1984) measured effects of enalapril on left ventricular

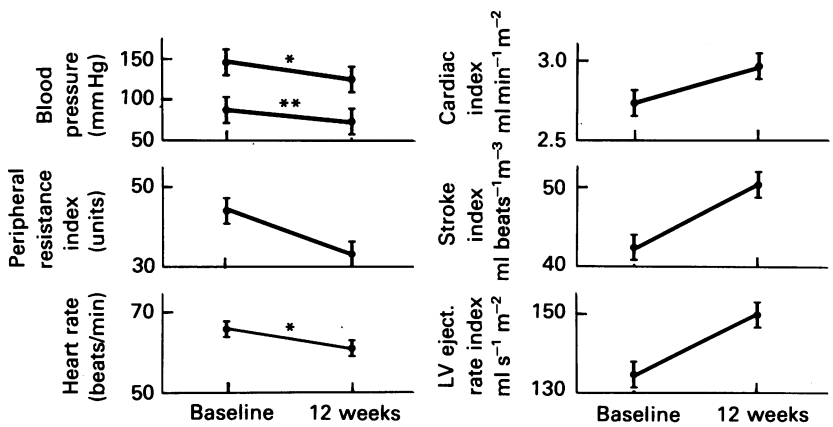

Figure 16 Haemodynamic effects of enalapril maleate in eight patients with essential hypertension with measurements at baseline and after 12 weeks treatment. LV eject = left ventricular ejection.
* $P < 0.05$, ** $P < 0.01$.

mass index and other related indices. Enalapril reduced left ventricular hypertrophy, particularly in patients with abnormalities before therapy.

Congestive heart failure

Several investigators (Cody *et al.*, 1983a, b; DiCarlo *et al.*, 1983; Dunkman *et al.*, 1983; Fitzpatrick *et al.*, 1983; Turini *et al.*, 1983; Levine *et al.*, 1984) have noted haemodynamic changes and clinical improvement in patients with congestive heart failure of New York Heart Association Class IIb to IV on maintenance digitalis and diuretics. A reduction in peripheral resistance and mean blood pressure was observed. This was associated with a reduction in filling pressure measured as pulmonary capillary wedge pressure or pulmonary artery pressure and usually accompanied by an increase in cardiac output and stroke volume. Heart rate either did not change or decreased slightly. The effects were seen with initial doses and maintained over at least three months of treatment.

Effects on renal function

In normal volunteers (Shoback *et al.*, 1983a) and in patients with hypertension (Bauer & Jones, 1983; Navis *et al.*, 1983; Reams *et al.*, 1983; Simon *et al.*, 1983; Dunn *et al.*, 1984; Johnston *et al.*, 1984a) with normal renal function, enalapril often caused an increase in renal blood flow and usually decreased renovascular resistance, but did not change glomerular filtration as measured either by creatinine clearance or inulin clearance. The effect on renal blood flow in normal volunteers was statistically significant only in those maintained on a restricted sodium intake and not in those on a high-sodium diet (Shoback *et al.*, 1983a). Simon *et al.* (1983) reported that renal blood flow increased in younger patients with milder hypertension and did not change in older patients with more severe blood pressure although the pretreatment renin levels were similar in the two groups. Bauer (in press) measured inulin clearance and PAH clearance in patients with essential hypertension treated either with enalapril or enalapril/hydrochlorothiazide and reported the findings after eight weeks' and one year's therapy. In those patients with glomerular filtration rates of 80 ml/min/1.73 m^2 or greater, enalapril produced a statistically significant decrease in renal vascular resistance associated with reduction in mean blood pressure, it tended to increase renal blood flow which was non-significant, and it did not change inulin clearance. In patients with glomerular filtrations less than 80 ml/min/1.73 m^2, both renal blood flow and inulin clearance, which were reduced at baseline, were increased significantly, often into the normal range.

The authors gratefully acknowledge the researchers whose results have been quoted and the other members of the Enalapril Project Team in Merck who contributed to the programme. We are especially indebted to Mrs Marjory White, who typed and coordinated the final manuscript.

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