A comparison of amlodipine with enalapril in the treatment of moderate/severe hypertension

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- 1 The safety and efficacy of amlodipine *vs* enalapril as monotherapy was evaluated in patients with moderate/severe hypertension (supine DBP 105–125 mm Hg, SBP 140–220 mm Hg).
- 2 After 2 weeks placebo treatment 31 patients were randomised by the technique of minimisation in an observer-blind study to receive once daily treatment with either amlodipine (15 patients) 5–10 mg, or enalapril (16 patients) 5–20 mg for 8 weeks. The study design concluded with 2 weeks placebo treatment. In addition to clinic measurements, home blood pressure monitoring (Copal UA-251) was performed during the study.
- 3 Clinic supine systolic blood pressure was reduced from 177 to 152 mm Hg (amlodipine) and 183 to 169 mm Hg (enalapril) (95% CI for the intergroup difference –22.1, 0.3, $P = 0.06$) after 8 weeks treatment.
- 4 Clinic supine diastolic blood pressure was reduced from 110 to 93 mm Hg (amlodipine) and 109–102 mm Hg (enalapril) (95% CI for the intergroup difference –17.7, –2.7, $P < 0.01$) after 8 weeks treatment.
- 5 Home blood pressure recordings confirmed these reductions in blood pressure. Although the reduction in blood pressure was greater for the amlodipine treated group, the differences between treatments were not statistically significant.
- 6 Both drugs were reasonably well tolerated. The adverse events occurring most frequently in the amlodipine group were headache (5), peripheral oedema (3), upper respiratory infection (3) and anxiety (2). The adverse events occurring most frequently in the enalapril treated patients were headache (6), dizziness (3) and upper respiratory infection (2).

Keywords amlodipine enalapril moderate/severe hypertension

Introduction

Since their introduction in the 1970s, calcium antagonists have assumed an important role in the treatment of ischaemic heart disease and hypertension. Calcium antagonists produce their effect by inhibiting the transmembrane influx of calcium ions upon which vascular smooth muscle depends for maintenance of tone; thereby resulting in vasodilatation (Opie, 1987).

Amlodipine is a recently developed dihydropyridine calcium antagonist that is structurally related to nifedipine, and has preferential activity on vascular smooth muscle compared with the myocardium (Burges *et al.*, 1987). Unlike its predecessors amlodipine has high bioavailability (60–65%), relatively slow absorption (6–12 h to achieve

peak plasma concentration) and a long elimination half-life (35–50 h). Consequently, 24 h blood pressure control can be achieved with once daily dosing and few vasodilator-related adverse effects (Burges *et al.*, 1989).

Novel antihypertensive drugs tend to be evaluated initially in mild hypertension. Such patients are more numerous, less likely to exhibit complications and biochemical abnormalities and are more appropriately subject to placebo controlled studies, at least in the short term. Patients with more severe hypertension do, however, continue to pose problems for clinicians in respect of their day to day management and there is a need for drugs that will minimise adverse effects and optimise

blood pressure control in this group of patients. In the present study the safety and efficacy of once daily amlodipine was compared with enalapril in patients with moderate/severe hypertension. As far as we know this is the first such study. Previous studies in this blood pressure range have studied amlodipine and captopril (Maclean *et al.*, 1988), or enalapril (Jensen *et al.*, 1989) in combination, and have shown significant reductions in systolic and diastolic blood pressure.

Methods

Approval for the study was obtained from the local ethics committee. Thirty-one patients (11 female and 20 male, aged 38–68 years) were recruited having given written informed consent.

Patient selection

Patients were recruited from the hypertension clinic database. They were either untreated or had had anti-hypertensive medication stopped at least 1 week (2 weeks in the case of diuretics) before entering the study. Patients were recruited if they had moderate/severe hypertension (DBP 105–125 mm Hg, SBP 140–220 mm Hg). They were excluded if there was a history of ischaemic heart disease, accelerated hypertension, serious systemic disease, asthma, adverse reaction to ACE inhibitors or calcium antagonists, or concomitant medication with drugs likely to affect blood pressure (e.g. steroids, NSAIDs). Women of child-bearing potential were also excluded.

Study design (Figure 1)

The study was designed as an observer-blind, randomised, parallel group study. The pharmacist dispensing and collecting the trial medication was unblinded, but the research nurse performing the blood pressure measurements was not aware of the patients' treatment—hence the term 'observer-blind'. Trial medication, in the form of single capsules, was taken once daily throughout the study. At each visit intercurrent illnesses, adverse events and concomitant medication were recorded.

Patients were recruited to a 2 week placebo run-in phase. At the initial visit medical history and clinical examination were performed. Routine haematology, biochemistry and urinalysis were undertaken and a 12 lead ECG recorded. Patients attended the research clinic at weekly intervals during the placebo run-in phase.

Patients proceeded to the main study if they satisfied the following criteria:

1. average supine and standing DBP 105–125 mm Hg
2. average supine and standing SBP 140–220 mm Hg
3. the difference between supine DBP at consecutive visits < 10 mm Hg

If the patient failed to meet the above criteria an extra visit was arranged 1 week later. Home blood pressure monitoring was performed at the end of the placebo run-in phase. Patients were randomised to active treatment with either amlodipine 5 mg or enalapril 5 mg using the

Figure 1 Outline of study, with summary of demographics.

technique of minimisation (Taves, 1974), whereby they were stratified by age, sex and supine diastolic blood pressure, thus allowing the two groups to be balanced. All medication was dispensed by the hospital pharmacy. Patients aged over 65 years in the enalapril group were given a single 2.5 mg starting dose. During the active treatment phase patients attended the clinic at fortnightly intervals. In the enalapril group, if after 2 weeks treatment supine blood pressure exceeded 140/90 mm Hg and an orthostatic change in systolic blood pressure was less than 25 mm Hg, the dose was increased to 10 mg daily. After 4 weeks treatment, using the same criteria the doses were titrated to a maximum of either enalapril 20 mg or amlodipine 10 mg. Following 8 weeks active treatment home blood pressure monitoring was repeated. Routine haematology, biochemistry and urinalysis were repeated at end of active treatment.

Patients proceeded to a 2 week placebo washout phase. Blood pressure was recorded at home on the penultimate day of the study and on the final day blood pressure was recorded at the clinic.

Methods of assessment

Throughout the study blood pressure was measured in duplicate with the Hawksley random zero sphygmomanometer. All measurements were performed 24 h postdose. Measurements were performed with the patient supine (5 min) and after standing (2 min), using Korotkoff phase 5 as the diastolic end point.

Home blood pressure monitoring was performed at the end of the placebo run-in phase, following 8 weeks active treatment, and after the 2 week placebo washout

phase. The device used was the Copal UA-251 semi-automatic sphygmomanometer (A&D Co. Ltd, Japan). Patients were instructed in the use of the device and were asked to perform single sitting measurements after 5 min rest. Recordings were made immediately predose and at hourly intervals for at least 12 h.

Withdrawals

One patient in the amlodipine group was withdrawn from the study due to severe ankle oedema, whilst a second patient was withdrawn due to severe headache, flushing and anxiety. In the enalapril group, one patient was withdrawn due to cold, numb hands and feet, whilst another patient discontinued because of severe palpitations. One patient in the enalapril group was withdrawn during active treatment due to lack of efficacy which was defined as a systolic blood pressure > 220 mm Hg or a diastolic blood pressure > 125 mm Hg on two consecutive visits.

Statistics

All clinic blood pressures and heart rates were measured in duplicate, and the mean of the replicates used in calculations throughout. The changes from baseline to final visit for each treatment group was analysed using the 1-sample *t*-test (SAS PROC MEANS). The principal analysis was in respect of the change in blood pressure and heart rate between the two treatment groups which was analysed using the 2-sample *t*-test (SAS PROC TTEST). A level of $P < 0.05$ was used for statistical significance. With 15 patients per group the study was designed to have a power of 80% to detect a difference of 10 mm Hg in systolic blood pressure.

Results

Fifteen patients (11 male, four female, age range 40–67 years) were randomised to receive amlodipine, and 16 (nine male, seven female, age range 38–68 years) to receive enalapril.

In the amlodipine group eight patients (53%) were maintained on a dose of 5 mg daily throughout the study, whilst seven patients (47%) required titration to 10 mg daily. In the enalapril group two patients (13%) were maintained on 5 mg daily, five patients (31%) received 10 mg and nine (56%) were titrated up to 20 mg daily.

Clinic blood pressure

For patients for whom clinic measurements were available at the end of the run in phase on placebo and at the end of active treatment ($n = 30$) supine blood pressure fell by 25/17 mm Hg (amlodipine) and 14/7 mm Hg (enalapril), whereas standing blood pressure fell by 24/17 and 17/8 mm Hg in the amlodipine and enalapril groups respectively (Table 1). This analysis includes four patients who withdrew because of side effects but who had been on active therapy for at least 3 weeks. The difference between the groups was statistically significant in favour of amlodipine in respect of supine diastolic pressure (95% CI for the difference $-17.7, -2.7$; $P < 0.01$), and of standing diastolic pressure (95% CI for the difference $-16.8, -0.7$; $P = 0.03$) and close to statistical significance in respect of supine systolic pressure.

One patient was excluded from the primary analysis because he had no data at the end of either the active treatment or placebo washout phases. Four other patients failed to complete the study (three due to side effects on active treatment and one because of lack of efficacy), whilst one further patient did not have data at the end of the trial within 18–30 h of the previous dose. Therefore 25 patients in the study had complete data at baseline and at the end of 8 weeks treatment. When these were analysed separately there was a statistically significant difference between the two groups for the changes in supine SBP ($P < 0.05$), supine DBP ($P < 0.01$) and for standing DBP ($P < 0.05$), but not for standing SBP.

For patients with complete measurements at each planned study visit ($n = 21$) the changes in supine systolic and diastolic blood pressure from baseline are shown in Figures 2 and 3 respectively. Ten patients did not have complete data and were therefore excluded from the figures for the following reasons: four patients were withdrawn from the study due to side effects, one

Table 1 Comparison of amlodipine with enalapril. Means, confidence intervals and significance values in respect of supine and standing blood pressures and heart rates. 95% CI and *P* values relate to the intergroup differences

Measurement	Treatment	n	Baseline mean	Final mean	Change from baseline (mean $\pm$ s.e. mean)	95% CI	P value
Supine SBP (mm Hg)	Amlodipine	15	177	153	-24.8 ± 3.4	$-22.1, 0.2$	0.06
	Enalapril	15	183	169	-13.9 ± 4.2		
Standing SBP (mm Hg)	Amlodipine	15	169	145	-24.1 ± 4.0	$-21.4, 7.4$	0.33
	Enalapril	15	176	159	-17.1 ± 5.8		
Supine DBP (mm Hg)	Amlodipine	15	110	93	-17.2 ± 2.3	$-17.7, -2.7$	< 0.01
	Enalapril	15	109	102	-7.0 ± 2.9		
Standing DBP (mm Hg)	Amlodipine	15	109	93	-16.7 ± 2.4	$-16.8, -0.7$	0.03
	Enalapril	15	112	104	-7.9 ± 3.1		
Supine HR (beats min ⁻¹)	Amlodipine	15	79	75	-3.7 ± 3.1	$-9.7, 6.3$	0.66
	Enalapril	15	76	74	-2.0 ± 2.4		
Standing HR (beats min ⁻¹)	Amlodipine	15	82	81	-0.4 ± 2.0	$-4.1, 8.1$	0.51
	Enalapril	15	80	78	-2.4 ± 2.3

Figure 2 Mean changes (95% CI) from baseline in supine systolic blood pressure recorded at clinic visits. Baseline (week 0) is the last weekly visit during the run-in phase on placebo. Week 10 represents the end of a 2 week washout period on placebo. Numbers relate to patients with complete data at each of the time points. ○ amlodipine $n = 11$; ● enalapril $n = 10$.

Figure 3 Mean changes (95% CI) from baseline in supine diastolic blood pressure recorded at clinic visits. Baseline (week 0) is the last weekly visit during the run-in phase on placebo. Week 10 represents the end of a 2 week washout period on placebo. Numbers relate to patients with complete data at each of the time points. ○ amlodipine $n = 11$; ● enalapril $n = 10$.

patient was withdrawn due to lack of efficacy, three patients had data outside the 18–30 h window after last dose at one of the time points, one patient had no data for week 4, and one patient completed the study early because he was going on holiday. We analysed our data (a) for all patients using their available data, (b) for 24 patients with complete data at weeks 0 and 8 and (c) for the 21 patients with complete data at each time point. The results show a virtually identical pattern. The blood pressure change was maximal after 8 weeks active treatment in the amlodipine group and after 6 weeks in the enalapril group and at both times were greater in the amlodipine group. After the placebo washout phase systolic blood pressure returned to baseline levels in both groups but supine diastolic blood pressures were still lower than at baseline.

Figure 4 Mean changes (95% CI) from baseline in heart rate on active treatment (weeks 0–8) and after washout (week 10). ○ amlodipine, ● enalapril.

Heart rate

The variation in heart rate is illustrated in Figure 4. Overall there was no significant change in heart rate in either treatment group during the study (Table 1).

Home blood pressure recording

The mean blood pressures during the monitoring period for patients in the amlodipine group were 179/105 mm Hg, 150/90 mm Hg and 161/99 mm Hg for the run-in, active treatment and washout phases respectively. The corresponding figures for the enalapril group were 181/105 mm Hg, 160/97 mm Hg and 174/102 mm Hg.

The results of home blood pressure measurement in 16 patients with technically satisfactory recordings both at baseline and at the end of 8 weeks amlodipine or enalapril treatment are shown in Figure 5. Overall, systolic and diastolic blood pressures are lower in the amlodipine group than in the enalapril group, reaching their nadir 7 h postdose which may represent a post-prandial fall in blood pressure. Patients were instructed to take their medication at 08.00 h.

For systolic blood pressure the mean area under the curve was 295 for amlodipine ($n = 7$) (95% CI 120–470) and 203 for enalapril ($n = 9$) (95% CI 128–278) treatment respectively. For diastolic blood pressure the mean area under the curve was 148 for amlodipine ($n = 7$) (95% CI 77–219) and 55 for enalapril ($n = 9$) (95% CI 9–101) treatment respectively. The reductions in areas under the curve (AUC) for both systolic and diastolic blood pressures from baseline to 8 weeks were statistically significant ($P < 0.05$) for both treatment groups. The difference between treatments for the reduction in AUC for diastolic blood pressure (consistently lower pressures on amlodipine) was significant ($P = 0.04$) but was not significant for systolic blood pressure ($P = 0.32$).

Adverse events

The adverse events encountered during the study are shown in Table 2. Overall the incidence of adverse effects was similar in the two groups, 86% of patients in

Figure 5 Mean sitting blood pressures a) systolic and b) diastolic self-recorded at home after 8 weeks of treatment with either amlodipine or enalapril. Blood pressures were measured at hourly intervals for 13 h after the morning dose of medication (target time 08.00 h). Data relate to patients with complete recordings (amlodipine $n = 7$; enalapril $n = 9$). ▲ enalapril placebo, ● enalapril active; △ amlodipine placebo, ○ amlodipine active.

each group either experiencing mild adverse effects, or no adverse effects at all.

Vasodilator related adverse effects occurred more frequently in the amlodipine group of patients. Three patients developed peripheral oedema. In two cases this was severe and necessitated the withdrawal of one patient

from the trial. Peripheral oedema was not reported in the enalapril group. Painful legs were reported in one patient in each group. Headache was reported by three patients. In one case the patient also had a coexisting cold, whilst in another a mild headache lasting one day was reported towards the end of the active treatment phase. One patient was withdrawn from the study due to severe headache and facial flushing 2 days after starting amlodipine 5 mg. Another patient also complained of severe facial flushing upon starting amlodipine but this was tolerated and resolved spontaneously after 3 days.

In the enalapril group, two patients experienced dizziness but this was not severe and they were able to continue in the study. Four patients complained of headache during the study, one patient had a severe headache upon starting enalapril, whilst two patients complained of headache 2–3 weeks after starting enalapril. The fourth patient developed a headache after 6 weeks enalapril treatment. One patient was withdrawn from the trial because they developed numb, white hands and feet within a fortnight of starting enalapril. A skin rash was noted in one patient 3 weeks after starting enalapril. The rash resolved after 3 days with continued treatment. One patient had palpitations upon starting enalapril which resulted in his admission to hospital. He was withdrawn from the study. Two patients had upper respiratory tract infections during the trial which were classified as concurrent illnesses.

Discussion

Hypertension remains an important risk factor for cardiovascular mortality and morbidity. The Veterans Administration Co-operative Study Group (1967) concluded that male patients with diastolic blood pressure > 115 mm Hg represent a very high risk group in whom anti-hypertensive treatment exerts a significant beneficial effect within 18 months. Since then the benefits of

Table 2 Summary of the severity of adverse events reported and patients withdrawn during the active treatment phases

Adverse events	Number of adverse events on amlodipine				Number of adverse events on enalapril			
	Mild	Moderate	Severe	Withdrawn	Mild	Moderate	Severe	Withdrawn
Headache	2	2	1	1	2	2	1	0
Respiratory infection	0	3	0	0	0	2	0	0
Lethargy	1	1	0	0	0	1	0	0
Nocturia	0	1	0	0	0	0	0	0
Oedema	1	0	2	1	0	0	0	0
Flushing	0	0	2	1	1	0	0	0
Indigestion	0	1	0	0	0	0	0	0
Chest pain	1	0	0	0	0	0	0	0
Anxiety	0	0	1	0	0	0	0	0
Palpitations	0	0	0	0	0	0	1	1
Epistaxis	0	0	0	0	1	0	0	0
Dizziness	0	0	0	0	0	2	0	0
Numb hands and feet	0	0	0	0	0	0	1	1
Conjunctivitis	0	0	0	0	1	0	0	0
Skin rash	0	0	0	0	1	0	0	0
Depression	0	0	0	0	1	0	0	0
Arthralgia	0	0	0	0	0	0	1	0

treating mild hypertension in both male and female patients have been established (Australian Therapeutic Trial Management Committee, 1980; MRC Working Party, 1985). There is ample evidence now that treated blood pressures are a better predictor of adverse cardiovascular outcome than untreated blood pressures (Bulpitt *et al.*, 1988) and that the risk of both stroke and cardiac events increases steeply when diastolic blood pressure on treatment exceeds 100 mm Hg (IPPPSH, 1985). There is a need to establish drug regimens in moderate to severe hypertension that are safe, effective and well tolerated.

Previous studies have shown that amlodipine is an effective antihypertensive agent in patients with mild to moderate hypertension when compared with placebo (Frick *et al.*, 1988; Heber *et al.*, 1989; Mroczek *et al.*, 1988; Webster *et al.*, 1987) and also when compared with atenolol (de Bruijn *et al.*, 1988; Frischman *et al.*, 1988), hydrochlorothiazide (Burris *et al.*, 1988; Rofman, 1988), verapamil (Lorimer *et al.*, 1988), nitrendipine (Englert, 1989) and captopril (Valasco *et al.*, 1989).

However, to date there have been no studies directly comparing amlodipine with other antihypertensive drugs in moderate/severe hypertension. In two studies of moderate/severe hypertension amlodipine was used in combination with either enalapril (Jensen *et al.*, 1990) or captopril (Maclean *et al.*, 1988). Jensen *et al.* (1990) randomised 38 patients with DBP > 95 mm Hg on enalapril to additional treatment with either amlodipine 10 mg or placebo for 4 weeks. The amlodipine group showed significantly greater reductions in supine blood pressures ($-19.4/-10.2$ mm Hg) than the placebo group. Maclean *et al.* (1988) showed that amlodipine produced additional reductions in blood pressure, 18/12 mm Hg (supine) and 20/12 mm Hg (standing), in patients who had failed to respond (DBP > 95 mm Hg) to low-dose captopril monotherapy. In our study amlodipine was shown to be more effective in reducing both systolic and diastolic blood pressures than enalapril. Neither drug had an effect on heart rate.

Comparative data is more readily available for enalapril with other calcium antagonists such as nitrendipine, verapamil, isradipine and diltiazem. Poncelet *et al.* (1991) compared the efficacy of enalapril with nitrendipine in patients with mild/moderate hypertension aged over 60 years. They found that clinic blood pressure was reduced by similar amounts in both groups (172/97 to 157/85 mm Hg on nitrendipine 20 mg vs 177/98 to 154/86 mm Hg on enalapril 20 mg). Vekaaik *et al.* (1991) compared nitrendipine (20–40 mg) with enalapril (20–40 mg) in 44 patients with mild/moderate hypertension. Mean clinic blood pressure fell from 172/107 mm Hg to 159/94 mm Hg on nitrendipine and 157/96 mm Hg on enalapril. Facial flushing was reported in 10 patients on nitrendipine and in three patients on enalapril, whilst three patients on enalapril complained of cough. The authors conclude that both nitrendipine and enalapril are equally effective antihypertensive agents, but that their use is limited by their specific side effects. In our study headache alone was reported by two patients, headache and flushing by one patient and flushing alone by another patient. No patients in our study had a cough attributable to enalapril treatment.

Fagher *et al.* (1991) concluded that both enalapril (20–

40 mg) and verapamil (240–480 mg) were equally effective as antihypertensive agents and were well tolerated. Eisner *et al.* (1991) compared the safety and efficacy of enalapril and isradipine in hypertensive patients. The reductions in blood pressure achieved were 12/9 mm Hg (isradipine) and 10/7 mm Hg (enalapril). Both drugs were similarly well tolerated.

Ferme *et al.* (1990) compared diltiazem (300 mg), enalapril (20 mg) and enalapril and diltiazem in combination. The reductions in supine blood pressure achieved with the three treatments were 22/20 mm Hg, 20/11 mm Hg and 23/19 mm Hg respectively. Although the reduction in diastolic blood pressure was significantly greater in the diltiazem group, the incidence of adverse events was higher. Weir *et al.* (1990) compared the efficacy of enalapril (up to 40 mg daily) and diltiazem (360 mg daily) in 159 patients. Both drugs were equally efficacious and reasonably well tolerated.

ACE inhibitors and calcium antagonists have also been compared with β -adrenoceptor blockers. Schrader *et al.* (1990) concluded that metoprolol was the most effective drug at reducing both systolic and diastolic blood pressure when compared with nitrendipine, mepindolol and enalapril, whilst Applegate *et al.* (1991) concluded that atenolol (50–100 mg), enalapril (5–20 mg) and diltiazem (120–360 mg) were equally effective at lowering diastolic blood pressure without significant differences in adverse effects in 240 older women with essential hypertension.

Just over half of the patients treated with amlodipine in our study achieved satisfactory blood pressure control (DBP < 90 mm Hg) on 5 mg daily. It is possible that a smaller dose may have been adequate for some of these patients. We continue to advocate the use of minimal effective doses of antihypertensives, particularly when initiating therapy, and the careful titration of dose against response.

Amlodipine has been shown by ambulatory monitoring to provide 24 h blood pressure control (Mroczek *et al.*, 1988). In our study home blood pressure monitoring performed up to 13 h postdose showed that blood pressure reduction was better maintained in the amlodipine than the enalapril group. Whereas it is not certain that this pattern of sustained blood pressure control is necessarily optimal for reducing risk, there is increasing evidence that home or ambulatory blood pressures are a better predictor of morbidity and mortality than 'office' blood pressures (Perloff *et al.*, 1991).

Overall, the frequency of adverse events was similar in the two groups, although the nature of these events varied reflecting the differing modes of action of amlodipine and enalapril (Table 2). Headache was reported with equal frequency in both groups, whereas peripheral oedema and flushing occurred in the amlodipine treated patients and dizziness was encountered in the enalapril group.

After the placebo washout phase, systolic blood pressure had returned to baseline levels in both groups, but there were still slight reductions in diastolic pressure averaging 4 mm Hg (supine) and 6 mm Hg (standing) on amlodipine, and 4 mm Hg (supine) and 5 mm Hg (standing) on enalapril, when compared with baseline values. This may have been due to patients not achieving baseline blood pressure upon entering the double-blind

phase, or the placebo washout phase being too short. However, a 2 week placebo run-in phase has been considered adequate in previous studies (Frick *et al.*, 1988; Varrone *et al.*, 1989; Webster *et al.*, 1987). A 4 week placebo washout period was used in a previous study of amlodipine (Webster *et al.*, 1987) and it was

demonstrated that most of the rise in blood pressure occurred in the first 2 weeks of this phase.

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