A comparison of amlodipine with enalapril in the treatment of isolated systolic hypertension

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- 1 The safety and efficacy of amlodipine and enalapril were compared in patients with isolated systolic hypertension (supine DBP < 95 mm Hg and supine SBP 160–200 mm Hg).
- 2 After 2 weeks treatment with placebo 31 patients were randomised by the technique of minimisation in an observer-blind study to receive once daily treatment with either amlodipine (16 patients) or enalapril (15 patients) 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 Mean supine systolic blood pressure was reduced from 185 to 164 mm Hg (amlodipine) and 183 to 159 mm Hg (enalapril) (95% CI for the difference between the drugs –10.5, 15.3) after 8 weeks treatment.
- 4 Mean supine diastolic blood pressure was reduced from 86 to 80 mm Hg (amlodipine) and 88 to 80 mm Hg (enalapril) (95% CI for the difference between the drugs –4.9, 7.6) after 8 weeks treatment.
- 5 Home blood pressure recordings confirmed these reductions in blood pressure, although there was no significant difference between treatments for the reductions in blood pressure.
- 6 Both drugs were reasonably well tolerated. The adverse events occurring most frequently in the amlodipine group were headache (2), peripheral oedema (5) and palpitations (2). The adverse events occurring most frequently in the enalapril group were headache (2), peripheral oedema (2), palpitations (2) and dizziness (3).

Keywords amlodipine enalapril isolated systolic hypertension

Introduction

Isolated systolic hypertension (ISH) is known to be an important risk factor for cardiovascular morbidity, particularly for stroke (Curb *et al.*, 1985; Kannel *et al.*, 1981; O'Malley *et al.*, 1988). The risks associated with ISH are well documented but the benefits of treating this pattern of elevated blood pressure have until recently not been fully established. The recent publication of the results of the SHEP study (SHEP Cooperative Research Group, 1991) provides the first clear evidence that treatment may reduce the risk of morbid events.

There has also been interest in the possible mechanisms contributing to ISH. It is generally agreed that a common feature, especially in older patients, is reduced compliance in large arteries (Simon *et al.*, 1979), leading to a loss of the normal Windkessel effect and a

steeper than normal rise in systolic blood pressure. Baroreflex responsiveness is also reduced (Rowlands *et al.*, 1983) and this exaggerates the response of systolic pressure to pressor stimuli. This pattern of hypertension occurs with increasing frequency in elderly patients (Curb *et al.*, 1985; Wilking *et al.*, 1988). Such patients may respond rather differently to antihypertensive drugs than patients with 'essential' hypertension, in whom the primary haemodynamic abnormality is an increase in peripheral resistance mediated by arteriolar tone.

Systolic pressure in elderly patients with isolated systolic hypertension can be specifically lowered, at least in theory, by actively increasing arterial compliance, by reducing forward pulse wave velocity during ventricular ejection and by altering the timing

during systole of the reflected pressure waves (Simon *et al.*, 1985; Safar, 1989). Vasoactive drugs that reduce smooth muscle tone in the large arteries actively increase arterial compliance. This effect has been demonstrated for calcium antagonists (Kohn *et al.*, 1987; Levenson *et al.*, 1983; Safar *et al.*, 1983) and angiotensin converting enzyme (ACE) inhibitors (Levy *et al.*, 1988; Safar *et al.*, 1986; Simon *et al.*, 1985).

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 which is structurally related to nifedipine, and which has preferential activity on vascular smooth muscle compared with the myocardium (Burgess *et al.*, 1987). Unlike its predecessors, amlodipine has high bioavailability (60–65%), a 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 side-effects (Burgess *et al.*, 1989). Previous studies have shown amlodipine to be an effective antihypertensive agent in patients with mild to moderate hypertension when compared with placebo (Webster *et al.*, 1987) and also when compared with atenolol, hydrochlorothiazide and verapamil (Julius, 1988).

The present study was designed to evaluate the safety and efficacy of once daily amlodipine in patients with isolated systolic hypertension. As a comparator we chose the angiotensin converting enzyme (ACE) inhibitor enalapril. This too can be used in a once daily dosing regimen (Webster *et al.*, 1986) and our previous experience had suggested that it might be particularly effective in controlling systolic pressure. This effect of ACE inhibitors has been confirmed by others (Enalapril in Hypertension Study Group (UK) 1984). As both drugs are now emerging as potential first-line therapies for hypertension we decided that a direct comparison in ISH would be appropriate.

Methods

Patient selection

Patients were recruited from the hypertension clinic database on the basis of a known systolic blood pressure exceeding 160 mm Hg and a diastolic blood pressure less than 95 mm Hg. They were either untreated or had had their antihypertensive medication stopped at least 1 week (2 weeks in the case of diuretics) before entering the study. Patients satisfying the initial screening procedure (that also included routine biochemistry, haematology and electrocardiography) underwent a 2 week 'run-in' phase on placebo. Blood pressure was measured in duplicate at weekly intervals.

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

1. average supine SBP 160–220 mm Hg
2. average standing SBP 140–220 mm Hg
3. difference in supine SBP at present and previous visit ≤ 25 mm Hg
4. average supine DBP < 95 mm Hg
5. difference in supine DBP at present and previous visit ≤ 10 mm Hg.

If the patient failed to meet the above criteria an extra visit was arranged 1 week later.

Patients 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 inter-current illnesses, adverse events and concomitant medication were recorded.

Patients were randomised to active treatment with either amlodipine or enalapril using the technique of

Figure 1 Outline of study design. Patients over the age of 65 years in the enalapril group received a starting dose of 2.5 mg.

minimisation (Taves, 1974), whereby they were stratified by age, sex and supine systolic blood pressure, thus allowing the two groups to be balanced. All medication was dispensed by the hospital pharmacy. During the active treatment phase patients attended the research clinic at fortnightly intervals.

The initial dose of both drugs was 5 mg except that subjects in the enalapril group aged over 65 years were given a single 2.5 mg starting dose. In the enalapril group, if after 2 weeks treatment supine BP exceeded 140/80 mm Hg and an orthostatic change of less than 25 mm Hg was observed, 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. At the end of 8 weeks active treatment routine haematology, biochemistry and urinalysis were repeated and patients proceeded to a 2 week placebo washout phase.

Methods of assessment

Throughout the study clinic blood pressure was measured in duplicate using the Hawksley random zero sphygmomanometer. Measurements were performed 24 h postdose and at the same time of day for each patient. Measurements were performed with the patient supine (5 min) and after standing (2 min).

Home blood pressure monitoring was performed at the end of the placebo run-in phase, during the eighth week of active treatment, and during the second week of the placebo washout phase using a 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.

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 were analysed using the 1-sample *t*-test (SAS PROC MEANS). The changes in blood pressure and heart rate between the two treatment groups were analysed using the 2-sample *t*-test (SAS PROC TTEST). A level of $P < 0.05$ was used for statistical significance. With fifteen patients per group the study was designed to have a power of 80% to detect a difference of 10 mm Hg in clinic systolic blood pressure.

For patients in whom technically satisfactory home blood pressure recordings were available, mean heart rate and blood pressure were plotted against hours post dose for each phase and each treatment group. Measurements were used if they were recorded within 30 min of the 'target' hour. Amlodipine and enalapril were compared by analysing differences in blood pressure between the end of 'run-in' and end of active treatment at all time points using 2-sided *t*-tests. In addition the two treatments were compared by analysing the area under the blood pressure curves over the period 0–12 h post dose using a two sided *t*-test.

All patients gave informed written consent to the

study. The study was approved by the Joint Ethics Committee of the University of Aberdeen and Grampian Health Board.

Results

Sixteen patients (four male, 12 female, aged range 48–73 years) were randomised to receive amlodipine, and fifteen (three male, 12 female, age range 45–76 years) to receive enalapril. One patient was withdrawn from the trial due to vasodilator-related side effects after 13 days treatment with amlodipine. No patients were withdrawn in the enalapril group.

In the amlodipine group twelve patients (75%) were maintained on a dose of 5 mg daily throughout the study, whilst four patients (25%) required titration to 10 mg daily. In the enalapril group three patients (20%) were maintained on 5 mg daily, six patients (40%) received 10 mg and a further six (40%) were titrated to 20 mg daily.

Clinic blood pressure

The mean blood pressures in both groups at the end of the 'run-in' period were similar: amlodipine group 185/86 mm Hg supine, 170/86 mm Hg standing; enalapril group 183/88 mm Hg supine, 172/88 mm Hg standing.

At the end of 8 weeks treatment supine systolic blood pressure had fallen by 21 and 24 mm Hg (95% CI for the intergroup difference –10.5, 15.3), and supine diastolic blood pressure had fallen by 6 and 8 mm Hg (95% CI for the intergroup difference –4.9, 7.6) in the amlodipine and enalapril groups respectively. Standing systolic blood pressure had fallen by 20 and 26 mm Hg (95% CI for the intergroup difference –6.3, 20.7), and standing diastolic blood pressure had fallen by 9 and 9 mm Hg (95% CI for the intergroup difference –6.9, 7.7) in the amlodipine and enalapril groups respectively (Table 1). Although the reduction in blood pressure was significant in both groups ($P < 0.01$) there was no significant difference between treatments.

The change in supine systolic blood pressure from baseline is shown in Figure 2. The magnitude of the change in blood pressure, the time course of the response to active treatment and the offset of effect during the washout phase is similar in both the amlodipine and enalapril groups. Following the 2 week placebo washout phase blood pressure did not return completely to baseline levels.

The change in supine diastolic blood pressure from baseline is illustrated in Figure 3. Again the magnitude and pattern of blood pressure changes are similar in both groups. Following the placebo washout phase diastolic blood pressure returned to baseline levels in both groups.

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).

Table 1 Mean (and 95% CI) blood pressure and heart rate data for amlodipine and enalapril treatment groups. All the reductions in blood pressure from baseline are statistically significant. The 95% confidence intervals and *P* values in the table refer to the differences between the groups in respect of the changes in blood pressure from baseline

	Treatment	n	Baseline mean	Final mean	Change from baseline	95% CI	P value
Supine SBP (mm Hg)	Amlodipine	16	185	164	-21.0 ± 4.5	-10.5, 15.3	0.70
	Enalapril	15	183	159	-23.4 ± 4.4	-6.3, 20.7	
Standing SBP (mm Hg)	Amlodipine	16	170	150	-19.5 ± 4.2	-4.9, 7.6	0.28
	Enalapril	15	172	146	-26.7 ± 5.1	-6.8, 7.7	
Supine DBP (mm Hg)	Amlodipine	16	86	80	-6.6 ± 2.2	-5.5, 9.5	0.66
	Enalapril	15	88	80	-8.0 ± 2.1	-5.7, 6.9	
Standing DBP (mm Hg)	Amlodipine	16	86	77	-9.3 ± 2.7	-3.0 $\pm$ 2.0	0.90
	Enalapril	15	88	79	-9.8 ± 2.2		
Supine HR (beats min ⁻¹)	Amlodipine	16	78	74	-4.0 ± 2.4		0.59
	Enalapril	15	73	67	-6.0 ± 2.8		
Standing HR (beats min ⁻¹)	Amlodipine	16	82	79	-3.3 ± 2.3		0.84
	Enalapril	15	77	73	-3.0 ± 2.0

Figure 2 Mean (95% CI) changes 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. Data relate to patients with complete results at each of the time points (○, amlodipine *n* = 14; ●, enalapril *n* = 14).

Figure 4 Mean changes from baseline in supine heart rate recorded at clinic visits. ○, amlodipine; ●, enalapril.

Figure 3 Mean (95% CI) changes from baseline in supine diastolic blood pressure recorded at clinic visits. ○ amlodipine; ● enalapril.

Home blood pressure recording

The mean blood pressures during the monitoring period for patients in the amlodipine group were 179/84 mm Hg, 155/74 mm Hg and 167/76 mm Hg for the run-in, active treatment and washout phases respectively. The corresponding figures for the enalapril group were 178/82 mm Hg, 160/75 mm Hg and 169/82 mm Hg.

Figure 5 demonstrates the variation in home blood pressure recorded at the end of 8 weeks of amlodipine or enalapril treatment. There was a tendency for blood pressure in the enalapril group to rise from baseline 8–12 h post dose, but there was no significant difference between treatments.

For systolic blood pressure the mean area under the curve was 248 for amlodipine (*n* = 12) (95% CI 142–354) and 179 for enalapril (*n* = 11) (95% CI 79–278) treatment respectively. The fall in systolic blood pressure from baseline was significant at *P* = 0.001 and *P* = 0.005 for amlodipine and enalapril respectively, but there was no significant difference in blood pressure reduction between treatments (*P* = 0.37).

For diastolic blood pressure the mean area under the

Figure 5 Hourly means of home blood pressures a) systolic and b) diastolic recorded during the eighth week of active treatment. Pressures are presented at hourly intervals after the ingestion of study medication for patients with complete recordings (amlodipine $n = 12$ systolic, 11 diastolic; enalapril $n = 11$ systolic, 10 diastolic). Δ amlodipine placebo, $\circ$ amlodipine active; $\blacktriangle$ enalapril placebo, $\bullet$ enalapril active.

curve was 98 for amlodipine ($n = 11$) (95% CI 65–132) and 69 for enalapril ($n = 10$) (95% CI 22–116) treatment respectively. The fall in diastolic blood pressure from baseline was significant at $P = 0.000$ and $P = 0.019$ for amlodipine and enalapril respectively, but there was no significant reduction in blood pressure between treatments ($P = 0.32$).

Table 2 Adverse events by treatment group, designated as treatment-related and as either moderate or severe by the study observer

Adverse event	Amlodipine	Enalapril
Feeling cold	0	1
Headache	2	2
Lethargy	1	1
Weakness	0	1
Oedema	5	2
Dyspepsia	0	1
Nausea	1	1
Palpitations	2	2
Chest pain	1	0
Itchy eyes	0	1
Dizziness	1	3
Paraesthesiae	1	0
Anorexia	1	0
Flatulence	0	1
Insomnia	1	0
Flushing	0	1
Phlebitis	1	0

Adverse events

In the amlodipine group 86% of patients were classified as having 'no side effects' or 'side effects not significantly interfering with patient's functioning', whilst in the enalapril group the corresponding proportion was 87%.

The more troublesome adverse events encountered during the study are shown in Table 2. Vasodilator-related symptoms (hot, swollen legs) occurred more frequently in the amlodipine treated patients. This adverse event resulted in the withdrawal of one patient from the study after 13 days of amlodipine treatment.

Overall, the incidence of adverse events was similar in the two groups.

Discussion

This study has shown that both amlodipine and enalapril produce satisfactory reductions in blood pressure over a period of 8 weeks in patients with ISH. Both drugs were equally effective in reducing systolic blood pressure without excessively reducing diastolic blood pressure and were relatively well tolerated and reduced blood pressure without adverse postural effects. Neither drug had a significant effect on heart rate.

In the absence of a parallel control group it is difficult to ascertain the exact contribution of the individual drugs to the observed reduction in blood pressure. However, the inclusion of a placebo washout phase strengthens our design in this respect and confirms a substantial drug effect. During the active treatment phase blood pressure declined gradually from baseline. We believe that this largely reflects a dose response to our careful upwards titration of dosage but recognise that there may be a smaller contribution from regression to the mean with time. In our study the 5 mg dose of amlodipine proved highly effective and it is possible that a lower initial dose might be adequate in a useful proportion of patients. There is a need for caution when prescribing drugs with long elimination half-lives to elderly patients, because of the possibility of accumulation and excessive pharmacological effects.

The technique of minimisation used in this study resulted in the two treatment groups being well balanced for age, sex and baseline systolic blood pressure. Had we used simple randomization we have determined that the two groups would have been significantly imbalanced for baseline systolic blood pressure (Cornish *et al.*, 1991). We suggest that this technique merits wider use to achieve balance in trials of this size.

Two minor differences in efficacy between the two drugs were noted in this study. Enalapril had a marginally greater effect than amlodipine on clinic standing systolic blood pressure (difference from baseline at 8 weeks 26.7 mm Hg vs 19.5 mm Hg). This difference was not statistically significant but this may be attributable to the power limitations of the study. The study was designed with 80% power to detect a clinic difference of 10 mm Hg between treatments. Nevertheless a real mean difference of 7 mm Hg could be of some

clinical importance. A second difference appeared in the home blood pressure recordings, with a tendency for the blood pressure in the enalapril group to rise in the second half of the observation period, whereas the blood pressure control in the amlodipine group was slightly more uniform. Again these differences were not statistically significant though they may be of some clinical importance. The long term implications of such small differences in blood pressure control are far from clear and are beyond the remit of this study.

The adverse events encountered with the dihydropyridines, such as amlodipine, are related to their pharmacodynamic activity. Excessive vasodilatation causes flushing, headache, dizziness and reflex tachycardia. Peripheral oedema may be due in part to pre-capillary arteriolar dilatation but also to an effect upon lymphatic channels (McHale & Allen, 1983; Olszewski & Engeset, 1979). In the placebo-controlled trials of amlodipine (Osterloh, 1989) the most frequently occurring adverse event was oedema (9.8%) which accounted for most of the differences between the two groups. However, most occurrences of oedema were of mild or moderate severity and less than 1% of patients stopped treatment as a consequence.

Few studies have been conducted comparing tolerance to amlodipine with tolerance to other calcium antagonists, making any definitive conclusions difficult. However, in a study *vs* verapamil (Osterloh, 1989) oedema was observed more commonly in patients receiving amlodipine whereas constipation was more common in verapamil-treated patients. When compared with diltiazem, amlodipine was found to be equally well tolerated (Osterloh, 1989). In a study comparing amlodipine with nitrendipine the total number of adverse events was higher in the nitrendipine group, and statistically significant increases in heart rate were seen after 2 and 4 weeks of treatment (Englert, 1989).

In our study, of the sixteen patients randomised to amlodipine treatment, five patients experienced peripheral oedema. In four patients this symptom was tolerated, but in one patient oedema developed after 5 days treatment which was so severe that shoes could not be worn and the patient had to be withdrawn from the study. Our findings are in keeping with those found in the above studies.

Although studies have been conducted comparing the efficacy of enalapril with other ACE inhibitors, few studies have compared tolerance to enalapril with other

ACE inhibitors. In a comparison of enalapril with ramipril, Mroczek (1991) found a similar antihypertensive effect and side effect profile between the two drugs. Johnston *et al.* (1991) compared enalapril with lisinopril. After 12 weeks treatment both drugs had a similar adverse event profile but lisinopril (10–40 mg) produced a greater reduction in sitting blood pressure than enalapril (5–20 mg) of 25/12 mm Hg and 17/12 mm Hg respectively.

Dry cough is an adverse event often associated with ACE inhibitors. Yeo *et al.* (1991) found an excess of persistent dry cough of 16% in patients taking enalapril for an average of 27 months. They concluded that the cough was not related to age, duration of treatment or chronic respiratory disease. Cough was not reported as an adverse event in our study.

In our study fifteen patients were randomised to enalapril treatment. Three of these patients experienced dizziness, compared with one in the amlodipine group. However this symptom did not necessitate withdrawal from the trial. No patients experienced first dose hypotension but this may have been due to the fact that all patients were advised to take their first 5 mg (2.5 mg for patients aged over 65 years) dose before retiring to bed.

The encouraging feature of both drugs is that they produced a substantial reduction in systolic blood pressure without precipitating orthostatic symptoms and without an excessive reduction in diastolic blood pressure. In the longer term it would be hoped that this pattern of blood pressure reduction would diminish the risk of adverse cardiovascular events such as stroke without compromising either cerebral or coronary blood flow.

Factors other than minor differences in blood pressure reduction may determine the choice of treatment in ISH, particularly as these patients are often elderly. Amlodipine is thus likely to be preferred if there is co-existing angina or renal impairment, whereas enalapril may be advantageous if there is co-existing heart failure. Our data suggest that both amlodipine and enalapril are worthy of longer term evaluation in this form of hypertension.

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