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Once daily amlodipine in the treatment of mild to moderate hypertension

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1 The antihypertensive efficacy of once-daily amlodipine was studied in a group of 30 patients with mild to moderate hypertension in a double-blind, placebo controlled parallel group study. The dose range of amlodipine was 2.5–10 mg daily titrated at 2 weekly intervals for a total treatment period of 8 weeks.

2 Amlodipine produced a significant reduction in blood pressure compared with placebo, the mean difference between baseline and 8 weeks (corrected for placebo effect) being 16/12 mm Hg supine, 14/4 mm Hg standing.

3 Blood pressure returned to baseline values during a terminal 4 week washout period on placebo.

4 There were no significant effects on heart rate.

5 Two patients experienced slight ankle oedema while receiving amlodipine 10 mg daily but the active drug was otherwise well tolerated.

6 Plasma concentration of amlodipine, sampled 24 h after the preceding dose, increased as the dose titration sequence was followed, averaging 2.5 ng ml^{-1} on 2.5 mg, 4.9 ng ml^{-1} on 5 mg and 10.5 ng ml^{-1} on 10 mg.

Keywords amlodipine hypertension once-daily dose-titration

Introduction

Calcium antagonists are widely used in the treatment of hypertension. Drugs of this type are associated with troublesome adverse reactions including vasodilator effects, such as headache, dizziness, facial flushing, palpitations, ankle/leg oedema, and adverse effects on atrioventricular conduction, myocardial contractility, and the gastrointestinal tract. Such adverse effects are a significant problem in 20–50% of patients (McInnes, 1986; Sorkin *et al.*, 1985). The presently available calcium antagonists also suffer from limitations in their pharmacokinetic features. Interindividual variation in absorption and metabolism is very wide (Sorkin *et al.*, 1985; Dow & Graham, 1986) and administration in divided daily doses is usually necessary.

Amlodipine is a novel dihydropyridine calcium antagonist that has been developed with a view to overcoming some of the disadvantages of currently available calcium antagonists. Animal studies have shown it to have a similar potency to nifedipine (Burges *et al.*, 1985). Pharmacokinetic studies in man have shown that amlodipine undergoes slow absorption after oral dosing (average time to peak concentration 8 h) but has high bioavailability (64%), high volume of distribution (mean 20 l kg^{-1}) and average elimination half-life of 45 h (Faulkner *et al.*, 1986). These properties result in a gradual onset and long duration of antihypertensive effect. The gradual onset of effect may minimize 'peak dose' vasodilator adverse effects while the long duration may facilitate once daily dosing.

Early clinical studies have indicated that amlodipine is effective in angina (Jackson *et al.*,

1985). At doses up to 15 mg daily amlodipine shows little effect on blood pressure in normal volunteers but an antihypertensive effect has been observed in preliminary studies in hypertensive patients (Tyler, personal communication).

We have recently investigated the efficacy of once daily amlodipine in patients with mild to moderate hypertension. The primary aim of this double-blind placebo-controlled parallel group study was to compare with placebo the antihypertensive effect of once daily amlodipine administered in incremental dosage across the range 2.5–10 mg daily.

Methods

Patients

Patients with mild to moderate uncomplicated hypertension whose untreated supine diastolic blood pressure was in the range 95–114 mm Hg inclusive (phase V diastolic), were invited to participate. In order for patients to be included in the double-blind treatment phase, the following criteria required to be fulfilled. The average supine diastolic blood pressure calculated from combined duplicate measurements taken after 1 week and 2 weeks of the placebo run-in period must be in the range 95–114 mm Hg inclusive. In addition, the average diastolic blood pressure calculated from duplicate measurements recorded after 1 week on placebo should differ from the average value after 2 weeks on placebo by 10 mm Hg or less.

Exclusion criteria were women of child bearing potential, concomitant therapy with other antihypertensive drugs (any previous treatment was stopped 6 weeks prior to double-blind treatment), concomitant therapy with non-steroidal anti-inflammatory drugs, oral hypoglycaemic drugs, anticoagulants, or other compounds strongly bound to plasma proteins, malignant or accelerated hypertension, major haematological, renal, hepatic, endocrine, cardiac or cerebrovascular disease, clinically important abnormalities of pre-study screening data or history of drug allergy.

Suitable patients satisfying the blood pressure criteria for diagnosis and reproducibility underwent a full medical examination including detailed ophthalmoscopy, 12-lead electrocardiography and a range of biochemical and haematological investigations.

Drug administration

Amlodipine was supplied as 2.5 mg and 5 mg capsules, with matching placebo. Patients allocated to amlodipine therapy received 2.5 mg once daily for 2 weeks, 5 mg once daily for 2 weeks and 10 mg (i.e. two capsules) once daily for 4 weeks. Patients allocated to placebo received the equivalent numbers of placebo capsules. The titration sequence was followed provided that no clinically important adverse effects occurred, that no changes in laboratory tests suggesting drug toxicity appeared and that the supine systolic blood pressure had not fallen below 130 mm Hg or the diastolic blood pressure below 85 mm Hg.

Provision was made that dosage could be maintained or reduced, at the investigator's discretion, in the event of excessive lowering of blood pressure or adverse effects from therapy. Therapy could be discontinued if serious adverse reactions occurred. Patients were to be removed from the study and treated appropriately if the supine diastolic blood pressure rose to more than 120 mm Hg.

Drugs were administered once daily immediately on rising except on the day preceding the study visit when patients were instructed to take their capsules at 24 h before their allotted study visit time.

Measurements

Patients attended an outpatient research clinic at weekly intervals during the run-in period on placebo and thereafter at 2 weekly intervals during the 8 week randomized phase and subsequent 4 week withdrawal phase. At each visit patients were allocated a fixed appointment time.

Blood pressure was measured in duplicate after 5 min rest in the supine position and after 2 min standing. Measurements were made using a Hawksley random zero sphygmomanometer and using phase V as the diastolic end point.

Heart rate was measured from the radial pulse. Body weight was also recorded. A blood sample was drawn at the end of weeks –2, 0, 2, 4, 6, 8 (relative to start of double-blind therapy) for haematology and biochemistry screening. An aliquot of plasma was separated and stored at –20°C for subsequent measurement of plasma amlodipine concentrations at the end of weeks 0, 2, 4, 6 and 8. A 12-lead electrocardiogram was also performed at the above times.

A full ophthalmological examination was undertaken before the study and again at the end of double-blind therapy. This included an assessment of visual acuity, slit lamp examination, assessment of intraocular pressure and fundoscopy. Calcium channel antagonists may

rarely cause conjunctival suffusion (non-specific vasodilator effect) and one case report linked nifedipine with transient retinal ischaemia (Pitlik *et al.*, 1983). No adverse ophthalmic effects have been observed with amlodipine, but a detailed examination was included as a safety measure.

Plasma amlodipine concentrations were measured by a gas chromatographic method provided by Pfizer Central Research (Huntingdon Research Centre).

Volunteered side effects were recorded at each visit.

Data analysis

Results were analysed using a one-way analysis of variance, with treatment as the grouping factor. Data relating to blood pressure were tested using one-sided tests, testing the null hypothesis of 'no difference between treatment means' against the alternative of a larger fall on amlodipine relative to placebo. The primary analysis for judging efficacy was the comparison of end of single-blind run-in on placebo – 'baseline' (week 0) – to 'end of double-blind period' (week 8) for blood pressures and heart rate. This was supplemented by a comparison of the changes in blood pressure and heart rate between 'end of double-blind period' (week 8) and 'end of terminal washout period' (week 12). These analyses excluded the blood pressure and heart rate data from five patients (one amlodipine, four placebo) because the time since the last dose of study medication at the 8 week visit was outwith the predetermined 'window' of 18–30 h.

An additional 'end point' comparison of amlodipine *vs* placebo after double-blind therapy was undertaken in all patients. This incorporated the last blood pressure and heart rate data recorded during double-blind therapy in all 30 patients, irrespective of protocol violations (intention to treat approach).

The study was approved by the Grampian Health Board/University of Aberdeen Joint Ethics Committee. All patients gave informed written consent.

Results

Forty-five patients entered the run-in phase. Fifteen of these were not randomized for a variety of reasons (blood pressure too low – 8, blood pressure too high – 2, problems with laboratory investigation – 5). Thirty patients completed the double-blind randomized phase (fifteen on amlodipine, fifteen on placebo). The age range of the patients was 31–60 years (amlodipine) and 42–64 years (placebo). All patients were Caucasian. One patient subsequently failed to complete the placebo withdrawal phase.

Three patients took their study medication by error on the morning of the 8 week visit only (approximately 6 h prior to blood pressure measurement). Two patients took their medication within 8 h of their clinic appointment on several occasions. All these patients were excluded from the primary efficacy analysis.

Amlodipine was titrated to the maximal dose of 10 mg daily in 13 patients and to 5 mg daily in two patients. The mean terminal dosage of amlodipine was 9.3 mg daily. Fourteen patients on placebo titrated up to the maximal number of capsules (two daily); one received one capsule daily throughout.

Blood pressure

In the primary analysis the changes from baseline after 8 weeks double-blind therapy, and the comparison of differences between amlodipine and placebo are shown in Table 1. On amlodipine, both supine and standing systolic blood pressures showed similar significant reductions of about 15 mm Hg more than on placebo. In the amlodipine group the supine diastolic pressure was significantly lowered at 8 weeks by about 11 mm Hg more than on placebo. Only the standing diastolic blood pressure showed a clinically less important reduction on amlodipine of about 4 mm Hg.

The 'end points–all patients' analysis confirmed the efficacy of amlodipine. In this analysis the mean reduction in blood pressure, corrected for placebo effect, was 14/11 mm Hg (supine), 14/6 mm Hg (standing), both statistically significant.

The effects of withdrawing active therapy during the terminal 4 week 'washout' period at the end of 8 weeks double-blind allocations are summarized in Table 2. In the amlodipine group blood pressures rose to levels similar to those observed at baseline. The only rise in blood pressure that was not statistically significant was that of standing diastolic. There was no evidence of overshoot of blood pressure during the withdrawal period and most of the rise in blood pressure occurred within the first 2 weeks (Figure 1). In the placebo group the changes in blood pressure were minimal and not statistically significant.

The incremental dosage in the study was designed as a safety measure rather than as a

Table 1 Mean blood pressures and heart rates at baseline and after 8 weeks double-blind therapy with amlodipine or placebo: the mean changes between baseline and 8 weeks are also shown, together with the mean difference between treatment groups (with 95% confidence intervals and corresponding *P* values)

Variable	*Treatment group*	n	*Baseline mean*	*8-week mean*	*Mean change (8-week – Baseline)* ± s.e. mean	*Mean difference (95% CI) in changes between treatment groups* (Amlodipine-placebo)	*Significance of pairwise comparisons* P
Supine systolic (mm Hg)	Amlodipine	14	158.4	139.4	−19.0 ± 4.4	−16.2 (−29.6, −2.8)	0.010
	Placebo	11	166.4	163.5	−2.9 ± 4.7		
Supine diastolic (mm Hg)	Amlodipine	14	104.7	89.5	−15.2 ± 1.6	−11.7 (−17.1, −6.2)	<0.001
	Placebo	11	104.6	101.1	−3.5 ± 2.1		
Supine heart rate (beats min^{-1})	Amlodipine	14	71.3	72.1	0.9 ± 2.1	−5.0 (−12.0, 2.0)	0.156
	Placebo	11	68.5	74.4	5.8 ± 2.8		
Standing systolic (mm Hg)	Amlodipine	14	157.6	140.4	−17.2 ± 2.6	−14.3 (−25.9, −2.7)	0.009
	placebo	11	163.1	160.1	−3.0 ± 5.4		
Standing diastolic (mm Hg)	Amlodipine	14	107.6	100.8	−6.9 ± 1.9	−4.4 (−9.8, 1.10)	0.057
	Placebo	11	107.5	105.0	−2.5 ± 1.8		
Standing heart rate (beats min^{-1})	Amlodipine	14	79.4	80.9	1.4 ± 2.7	1.3 (−8.5, 11.0)	0.793
	Placebo	11	80.7	80.9	0.2 ± 4.1		

Table 2 Mean blood pressure and heart rates at 8 weeks and after 4 weeks withdrawal from either amlodipine or placebo therapy: the mean changes from 8 weeks to end of withdrawal phase are shown, together with the mean difference between treatment groups (with 95% confidence intervals and corresponding *P* values)

Variable	*Treatment group*	n	*End of D–B mean*	*End of washout mean*	*Mean change (Washout-end DB)* ± s.e. mean	*Mean difference (95% CI) in changes between treatment groups* (Amlodipine-placebo)	*Significance of pairwise comparisons* P
Supine systolic (mm Hg)	Amlodipine	14	139.4	156.9	17.5 ± 2.6	15.1 (5.8, 24.3)	0.002
	Placebo	11	163.5	166.0	2.5 ± 3.8		
Supine diastolic (mm Hg)	Amlodipine	14	89.5	102.0	12.5 ± 1.6	11.6 (6.4, 16.7)	<0.001
	Placebo	11	101.1	102.0	0.9 ± 1.9		
Supine heart rate (beats min^{-1})	Amlodipine	14	72.1	74.1	2.0 ± 2.9	1.8 (−8.3, 12.0)	0.715
	Placebo	11	74.4	74.5	0.2 ± 4.2		
Standing systolic (mm Hg)	Amlodipine	14	140.4	153.9	13.5 ± 4.2	13.0 (0.6, 25.4)	0.021
	placebo	11	160.1	160.6	0.5 ± 4.2		
Standing diastolic (mm Hg)	Amlodipine	14	100.8	107.8	7.1 ± 3.3	2.4 (−6.2, 11.1)	0.283
	Placebo	11	105.0	109.6	4.6 ± 2.1		
Standing heart rate (beats min^{-1})	Amlodipine	14	80.9	79.9	−1.0 ± 2.3	−4.6 (−15.6, 6.3)	0.390
	Placebo	11	80.9	84.5	3.6 ± 5.2		

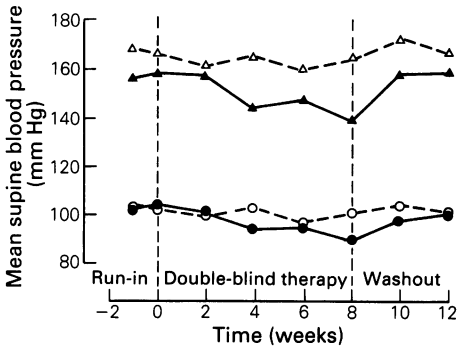

Figure 1 Mean supine blood pressure at baseline, during double-blind therapy and during washout on placebo: ---- systolic, placebo; ○ systolic, amlodipine; ---- diastolic, placebo; ○ diastolic, amlodipine.

formal experiment to examine the dose-response profile of amlodipine as an antihypertensive. We were thus unable entirely to separate the influence of time from the influence of treatment in respect of the incremental phase. Nevertheless our data are consistent with a progressive effect over the dose range evaluated.

Heart rate

Heart rate changes are summarised in Tables 1 and 2. No clinically important changes in heart rate were recorded in either treatment group, in either position, either during double blind therapy or during the terminal washout phase.

Plasma concentration

The mean plasma concentrations of amlodipine are shown in Table 3. These show that the plasma concentrations increased as the amlodipine dose was increased. The individual results also provided an indication of compliance with drug ingestion. All patients in this group had measurable amounts of amlodipine in plasma. In two patients the plasma concentrations at weeks 6 and 8 were below the levels expected from a daily dose of 10 mg amlodipine, but we are unable to say whether this was a result of pharmacokinetic variations or of incorrect dosing.

Other observations

No significant changes in body weight were observed throughout the study in either group. No consistent changes in the electrocardiogram were observed during double-blind therapy. Two patients in the amlodipine group and one patient in the placebo group showed moderate rises in creatinine phosphokinase (CPK) during double-blind therapy. In the two amlodipine patients the rise in CPK to double the baseline value paralleled the increase in amlodipine dosage. In the one patient in which the test was repeated during the terminal withdrawal phase the result had reverted to normal. No other abnormalitites of haematological or biochemical investigations were noted during the course of the study. Initial detailed ophthalmological assessment detected two patients with previously unrecognised retinal holes that were treated with laser photocoagulation. No further abnormalities developed by the time of the follow-up examination.

Adverse events

Seven patients in each group experienced adverse effects possibly related to study medication (Table 4). Eight adverse symptoms were reported in the patients on amlodipine and

Table 3 Mean plasma concentrations of amlodipine (ng ml^{-1}): blood samples were drawn 24 h after the preceding dose of amlodipine at 2 week intervals

	Week number				
	0	2	4	6	8
Dose of amlodipine	0	2.5 mg	5 mg	10 mg	10 mg
n	13	15	15	13	12
Mean (s.e. mean)	0	2.54 (0.35)	4.93 (0.33)	10.47 (0.94)	10.75 (0.99)
Mean time after preceding dose (h) (s.e. mean)	23.7 (5.5)	25.6 (2.1)	24.0 (6.7)	24.9 (5.5)	24.4 (4.4)

Table 4 Adverse effects volunteered by patients: All treatment-related events occurring during double-blind study are listed, irrespective of severity

(a) *Incidence of treatment-related side effects during double-blind therapy*

	Amlodipine	*Placebo*
Number of patients: Evaluable	15	15
With treatment-related adverse effects	7	7
Withdrawn with side effects	0	0

(b) *Occurrences of treatment-related side effects during double-blind therapy*

Side effects	Amlodipine	Placebo
Dependent oedema	2	0
Headache	2	3
Fatigue	2	2
Flushing	1	2
Conjunctivitis	1	0
Dizziness	0	2
Palpitations	0	1
Other	0	12
Total	8	22

twenty-two in the patients on placebo. Two patients on amlodipine had mild ankle oedema confirmed by examination. None of the patients required to discontinue double-blind medication because of adverse effects.

Discussion

The study shows that amlodipine is an effective and well tolerated antihypertensive drug when given in once daily dosage to hypertensive patients. There was no evidence of postural hypotension or reflex tachycardia. Our conclusions are based on the comparison of blood pressure at baseline compared with those at the end of 8 weeks treatment. Dose titration over the double-blind treatment period appeared to be associated with a stepwise increment in antihypertensive effect.

To our knowledge this is the first demonstration of a dihypropyridine calcium antagonist with once-daily efficacy in hypertension. Currently available drugs in this class suffer the disadvantage of a requirement for two-, three- or four-times daily dosing. It is likely that a once daily dosage regimen, such as we have shown for amlodipine, may improve the acceptability of calcium antagonists in the treatment of hypertension.

We measured the blood pressure only at one time point (24 h post-dose) at each visit. We are thus unable to comment on the diurnal variation in blood pressure in our patients. If a 24 h action is confirmed by ambulatory blood pressure studies currently in progress, then it would be a further advantage of amlodipine over other dihydropyridines.

Finally, our data indicate that starting with a low dose and titrating slowly upwards, even in drugs with a relatively 'flat' dose-response, results in a low incidence of adverse effects. Our previous experience with other antihypertensive drugs has led us to advocate this low dose approach on previous occasions (Jeffers *et al.*, 1977; Webster *et al.*, 1987) and we believe that such a policy should also apply to the introduction of calcium antagonists.

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