

Amlodipine 2.5 mg once daily in older hypertensives: a Brazilian multi-centre study

Décio Mion Jr^a, Katia C. Ortega^a, Marco A. M. Gomes^b, Osvaldo Kohlmann Jr^c, Wille Oigman^d and Fernando Nobre^e

Objectives The use of low-dose amlodipine has not yet been well established in the elderly. This study therefore aimed to evaluate the efficacy and tolerability of low-dose amlodipine in elderly patients with Joint National Committee VI stage I or II hypertension.

Patients and methods Sixty-five hypertensive individuals (aged 66.3 ± 5.3 years) received amlodipine 2.5 mg per day for 12 weeks before and after two periods of 4 weeks of placebo. At weeks 0, 12 and 16, patients were submitted to office, 24 h ambulatory blood pressure monitoring and home blood pressure measurement.

Results Office systolic and diastolic blood pressure showed decreases at weeks 8 (153 ± 17 , 90 ± 9 mmHg) and 12 (152 ± 16 , 90 ± 9 mmHg) compared with weeks 0 (164 ± 16 , 99 ± 6 mmHg) and 16 (162 ± 19 , 95 ± 9 mmHg). During ambulatory monitoring, a decrease was observed in the average 24 h systolic and diastolic pressure at week 12 (143 ± 13 , 86 ± 7 mmHg) compared with weeks 0 (155 ± 15 , 93 ± 6 mmHg) and 16 (152 ± 16 , 92 ± 8 mmHg). A daytime and night-time reduction in systolic and diastolic pressure was observed on home blood pressure monitoring at week 12 ($146 \pm 16/88 \pm 8$, $144 \pm 16/93 \pm 8$ mmHg) compared with weeks 0 ($159 \pm 17/94 \pm 8$, $161 \pm 19/93 \pm 8$ mmHg) and 16 ($153 \pm 16/93 \pm 8$, $154 \pm 17/92 \pm 8$ mmHg). Adverse reactions were infrequent.

Conclusions Amlodipine at a dose of 2.5 mg per day showed efficacy and good tolerability in elderly hypertensives. *Blood Press Monit* 9:83–89 © 2004 Lippincott Williams & Wilkins.

Blood Pressure Monitoring 2004, 9:83–89

Keywords: hypertension, elderly people, amlodipine, ambulatory blood pressure monitoring, home blood pressure measurement

^aUniversity of São Paulo General Hospital, ^bSchool of Medical Sciences of Alagoas, ^cFederal University of São Paulo, ^dUniversity of the State of Rio de Janeiro Pedro Ernesto Hospital and ^eClínicas Hospital, Medical School of Ribeirão Preto, University of São Paulo, Brazil.

Correspondence and requests for reprints to Professor Dr Décio Mion Jr, Instituto Central do Hospital das Clínicas, Avenida Dr Enéas de Carvalho Aguiar 255, 7^o andar, sala 7032, 05403-010 São Paulo, SP, Brazil.
E-mail: deciomion@uol.com.br

Received 20 September 2003 Revised 05 December 2003
Accepted 29 January 2004

Previous presentations, grants and conflicts of interest The authors received an institutional grant from Biosintética Farmaceutica which also provided the drugs and Omron devices used free of charge. Part of this study was presented as an oral presentation during the 10th Brazilian Hypertension Society Congress held in Campinas, São Paulo, Brazil, 2–4 August 2001. The authors declare no conflicts of interest regarding the data presented and discussed in this paper and the financing source that sponsored the study.

Introduction

Despite the benefits of hypertensive treatment for the elderly, this population is often treated inappropriately [1–3]. There is evidence that blood pressure control is even more beneficial for older than for younger individuals. Several studies have shown that the treatment of hypertension in patients between the ages of 60 and 69 has been responsible for a decrease of 30% in all cardiovascular complications, 26% of fatal coronary events and 33% of encephalic events. Nevertheless, many older patients are deprived of the benefits of antihypertensive treatment [4,5].

Amlodipine is considered to be a useful antihypertensive for treating elderly patients, with evidence that it is even more effective in this population than in individuals younger than 65 years of age [6,7]. In addition, amlodipine has been shown to be well tolerated by the elderly [8,9].

With the aim of reducing the incidence of adverse events, the use of low-dose antihypertensives has become a current trend. The purpose of the present study was to assess the efficacy and tolerability of amlodipine administered at a low dose (2.5 mg per day) to elderly patients with Joint National Committee (JNC) VI stage I or II hypertension [10].

Patients and methods

Ambulatory patients of both sexes and various races aged 60 years or over, with a body mass index of less than 30 kg/m², a diagnosis of essential hypertension and off all antihypertensive therapies for at least 4 weeks were included in the present study.

Hypertension was diagnosed when the average of the last two diastolic blood pressure readings out of a set of three measurements performed in the sitting position in the

office (office blood pressure measurement, OBPM) at visit 2 after a 4 week placebo phase ranged from 90 to 109 mmHg. Moreover, patients needed a mean diastolic blood pressure higher than 85 mmHg and a systolic blood pressure greater than 135 mmHg during the 24 h ambulatory blood pressure monitoring (ABPM) following the placebo phase to exclude patients with white-coat hypertension. Because the study aimed to analyse the efficacy of amlodipine 2.5 mg in patients with hypertension both in the office and during ABPM, the inclusion of white-coat hypertensives could make it difficult to interpret the results. The diagnosis of white-coat hypertension was established when office systolic blood pressure was ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg and the ABPM mean systolic and diastolic blood pressure were $< 135/85$ mmHg during the daytime.

Additional reasons for exclusion from the study were:

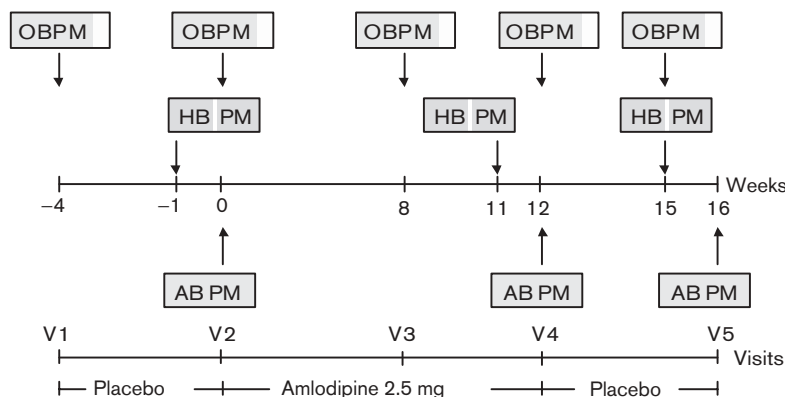
1. angina pectoris;
2. acute arrhythmia or atrioventricular block greater than first degree;
3. a history of secondary hypertension caused by hyperaldosteronism, pheochromocytoma, renal artery stenosis, aorta coarctation or Cushing's disease or syndrome;
4. hepatic dysfunction indicated by the medical history or clinically abnormal hepatic function tests (alkaline phosphatase, total bilirubin, glutamic-oxaloacetic transaminase);
5. renal failure indicated by elevated creatinine (> 1.4 mg/dl) and urea serum values;
6. orthostatic hypotension because of non-compensated autonomic dysfunction arising from a change in hydration or medication;
7. evidence of class III or IV cardiac failure according to the New York Heart Association criteria;
8. concomitant therapy with other antihypertensives;
9. malignant hypertension or a diastolic blood pressure of over 109 mmHg;
10. medical conditions that could interfere with the patients' participation until the end of the study, or adverse effects increasing the risk to the patients;
11. a previous history of hypersensitivity to calcium antagonists;
12. blood donation during the study;
13. a history of alcoholism, drug abuse or mental disturbance that could nullify the free informed consent or limit the patients' capacity to meet and understand the protocol rules;
14. participation in any other drug study in the month previous to entering this study or concomitantly with it.

Following a 4 week placebo phase (visits V1 and V2, weeks -4 to 0), patients were given a single 2.5 mg dose of amlodipine in the morning for 12 weeks (visits V2-V4, weeks 0-12). At the end of this period, patients entered another 4 week placebo phase (visits V4 and V5, weeks 12-16).

At each visit (V1-V5), a clinical evaluation was performed, including identifying adverse reactions and measuring body weight, heart rate and blood pressure by OBPM. Compliance with treatment was analysed by counting pills. During visits V2, V4 and V5 (corresponding to weeks 0, 12 and 16), blood pressure was also taken by ABPM and home blood pressure measurement (HBPM). As HBPM was performed for 7 consecutive days, the procedure started at weeks -1, 11 and 15 and ended at weeks 0, 12 and 16, respectively (Fig. 1).

When diastolic blood pressure at any visit was greater than 110 mmHg after amlodipine was started, the medication was suspended and the patient withdrawn from the study. Because the study was aimed at evaluating amlodipine in patients who complied with the prescribed medication regimen, as evidenced by a pill count of 80-100%, those who demonstrated a pill count lower than 80% at two consecutive visits were also withdrawn.

Fig. 1



OBPM was performed at all visits, the measurement being, whenever possible, taken by the same person. Measurements were taken after patients had been seated for 5 min and always on the arm that showed higher blood pressure readings. A properly calibrated mercury sphygmomanometer and a bladder with an appropriate size to wrap at least 80% of the arm circumference were used. Systolic and diastolic blood pressure levels were registered, being identified respectively at the moment the sound started and finished (Korotkoff's phases I and V). The average of the last two measurements out of a set of three was used as a representative blood pressure value at each visit. In case the difference between the last two readings was higher than 10 mmHg, additional measurements were obtained until the difference between the two last measurements was lower than 10 mmHg. Heart rate was measured immediately before blood pressure determination.

ABPM was performed by using SpaceLabs equipment model 90207 (SpaceLabs Medical, Redmond, WA, USA) [11]. Measurements were taken every 15 min from 0700 h until 2300 h and every 20 min from 2301 h to 0659 h. Records were considered suitable for the analysis when they showed at least 80 measurements in a 24 h period. Blood pressure was considered normal in ABPM when the systolic blood pressure was less than 135 mmHg and the diastolic blood pressure less than 85 mmHg for the total examination period.

HBPM was carried out using the OMRON IC-intensive control equipment (Omron Healthcare Inc, Vernon Hills, IL, USA) [12]. Three measurements were taken in the morning prior to taking amlodipine and another three measurements at night before dinner for 7 days. All measurements were taken with the patient seated. Blood pressure was considered normal during ABPM when the systolic pressure was below 135 mmHg and the diastolic pressure below 85 mmHg, considering all the measurements taken.

The size of the sample was calculated in 75 patients based on JNC VI hypertension stage I or II factor, admitting an alpha error of 5% and a beta error of 10% with a power of 90%. Each of the five research centres therefore included 50% of patients (seven or eight patients) showing a diastolic blood pressure of between 90 and 99 mmHg and 50% showing one between 100 and 109 mmHg.

Response classification for efficacy analysis at week 12 (visit 4) was undertaken as follows:

1. Office sitting diastolic blood pressure: a) category 1: diastolic blood pressure < 90 mmHg; b) category 2: diastolic blood pressure \geq 90 mmHg and a \geq 10 mmHg

decrease according to baseline; c) category 3: diastolic blood pressure 90 mmHg and a \geq 10 mmHg decrease according to baseline.

2. Office sitting systolic blood pressure: a) category 1: systolic blood pressure < 140 mmHg; b) category 2: systolic blood pressure \geq 140 mmHg and a \geq 10 mmHg decrease according to baseline; c) category 3: systolic blood pressure \geq 140 mmHg and a \geq 10 mmHg decrease according to baseline.

Statistical blood pressure analysis was performed by analysis of variance (ANOVA) followed by multiple comparisons (Newman-Keuls/Tukey HSD) with regard to JNC VI hypertension stage I or II factor. When variance homogeneity was not observed, ANOVA was replaced with Friedman or Mann-Whitney tests. Primary efficacy was evaluated by office blood pressure levels.

All patients freely signed an informed consent form. The study protocol was approved by the ethical research committees of all the institutions involved in the study.

Results

One hundred and fifty-nine patients were initially included in this study. Of these, 94 (59%) patients were withdrawn, including 48 because of white-coat hypertension. Other reasons for exclusion were:

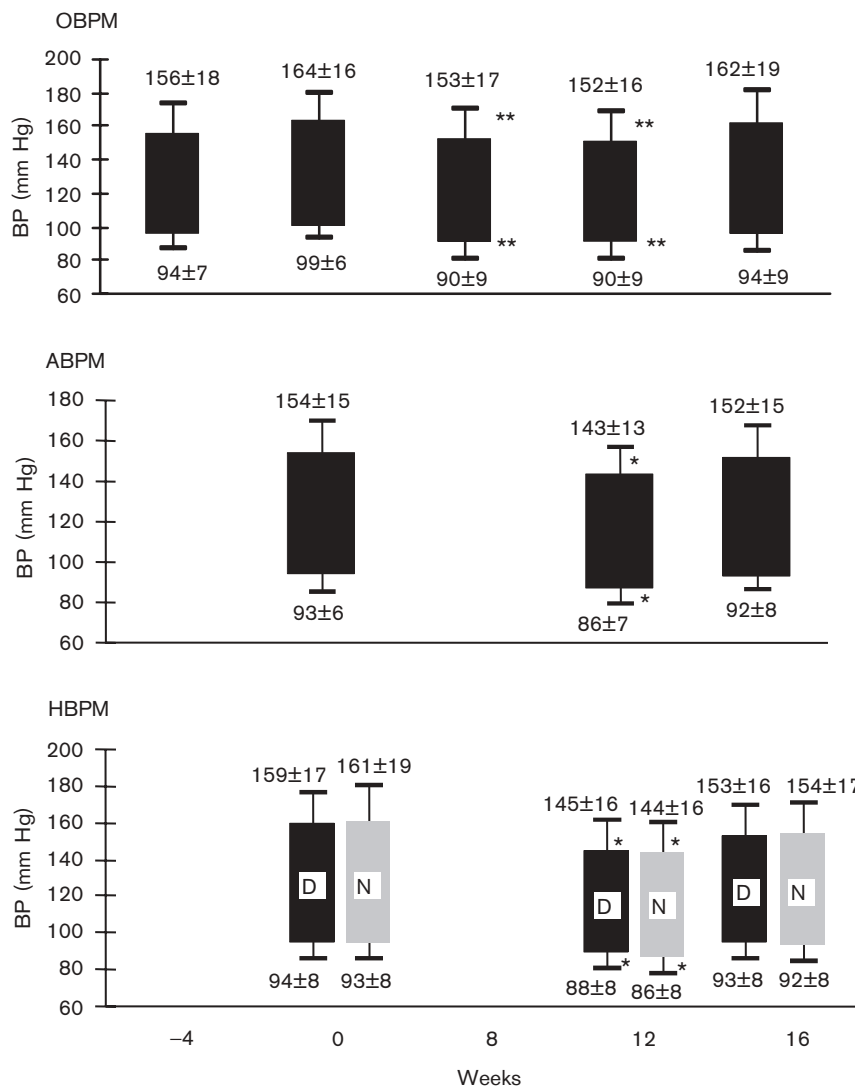
1. protocol violation – 19 patients;
2. discontinuance – 10 patients;
3. pill counts lower than 80% – 4 patients;
4. surgery that prevented the patients from continuing in the study – 2 patients;
5. an inability to apply HBPM correctly – 1 patient;
6. the presence of an adverse effect with placebo – 1 patient;
7. non-referred reason – 9 patients.

Therefore, of the initial 159 patients, 65 patients were included in the efficacy analysis because they completed all their visits; 49.3% of the 65 had JNC VI hypertension stage I, and 50.7% had JNC VI hypertension stage II. Eighty-nine patients were included in the tolerability analysis because they received at least one dose of amlodipine.

The patients' mean age was 66.3 ± 5.3 years (range 60–87 years). Forty-seven (72.3%) were female. Racially, the patients included 53.6% white, 14.5% black, 29.0% mulatto and 2.9% Asian individuals. The group's anthropometric evaluation showed a mean height of 157.7 ± 8.4 cm, a mean weight of 67.0 ± 11.3 kg and a mean body mass index of 27.0 ± 3.6 kg/m².

Blood pressure values obtained in the phases of the study by the three methods used are shown in Fig. 2. Office systolic and diastolic blood pressure measurements showed decreases ($P < 0.05$) at weeks 8 (153 ± 17 ,

Fig. 2



* $P < 0.05$ weeks 8 and 12 versus weeks 0 and 16

** $P < 0.05$ weeks 12 versus weeks 0 and 16

90 ± 9 mmHg) and 12 (152 ± 16, 90 ± 9 mmHg) compared with weeks 0 (164 ± 16, 99 ± 6 mmHg) and 16 (162 ± 19, 95 ± 9 mmHg), as shown in Table 1. In the ABPM evaluation, a decrease ($P < 0.05$) was observed in average 24 h systolic and diastolic blood pressure at week 12 (143 ± 13, 86 ± 7 mmHg) when compared with weeks 0 (155 ± 15, 93 ± 6 mmHg) and 16 (152 ± 16, 92 ± 8 mmHg). The systolic and diastolic night-time blood pressure fall showed no change. There was a significant decrease in mean systolic and diastolic blood pressure at week 12 compared with weeks 0 and 16 (Table 2). Similarly, a daytime and night-time systolic and diastolic blood pressure reduction ($P < 0.05$) on HBPM

was observed at week 12 (146 ± 16/88 ± 8, 144 ± 16/93 ± 8 mmHg) when compared with weeks 0 (159 ± 17/94 ± 8, 161 ± 19/93 ± 8 mmHg) and 16 (153 ± 16/93 ± 8, 154 ± 17/92 ± 8 mmHg) (Table 3). Heart rate, as evaluated by OBPM, ABPM and HBPM, and body weight did not change during the study.

Office pulse pressure measurements showed a decrease ($P < 0.05$) at week 12 (62 ± 13 bpm) when compared with weeks 0 (65 ± 15 bpm) and 16 (67 ± 16 bpm). In the ABPM evaluation, a decrease ($P < 0.05$) was observed in awake pulse pressure at week 12 (57 ± 11 bpm) in comparison with weeks 0 (61 ± 13 bpm) and 16

Table 1 Office systolic blood pressure, diastolic blood pressure and heart rate measurements (mean \pm SD)

	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Heart rate (bpm)
Week -4 (n=69)	156 \pm 18	94 \pm 8	75 \pm 9
Week 0 (n=69)	164 \pm 16	99 \pm 6	77 \pm 9
Week 8 (n=68)	153 \pm 17*	90 \pm 9*	77 \pm 10
Week 12 (n=65)	152 \pm 17*	90 \pm 9*	78 \pm 10
Week 16 (n=64)	162 \pm 19	95 \pm 9	78 \pm 10

* $P < 0.0001$ week 12 \neq week 0 and 16, week 8 \neq week 0 and 16.

Table 2 Systolic (SBP) and diastolic (DBP) ambulatory blood pressure measurements by daytime, night-time and 24 h (mean \pm SD)

	Daytime SBP/DBP (mmHg)	Night-time SBP/DBP (mmHg)	24 h SBP/DBP (mmHg)
Week 0 (n=69)	157 \pm 14/96 \pm 7	145 \pm 18/84 \pm 8	155 \pm 15/93 \pm 6
Week 12 (n=65)	145 \pm 13*/89 \pm 7*	136 \pm 14*/79 \pm 7*	143 \pm 13*/87 \pm 7*
Week 16 (n=59)	155 \pm 16/95 \pm 8**	143 \pm 17/83 \pm 9	152 \pm 16/92 \pm 8

* $P < 0.0001$ week 12 \neq week 0 and 16;

** $P < 0.0001$ week 0 \neq week 16.

Table 3 Systolic (SBP) and diastolic (DBP) home blood pressure measurements during 7 days, daytime and night-time (mean \pm SD)

	Daytime SBP/DBP (mmHg)	Night-time SBP/DBP (mmHg)
Week 0 (n=69)	159 \pm 17/94 \pm 8	161 \pm 19/93 \pm 8
Week 12 (n=65)	146 \pm 16*/88 \pm 8*	144 \pm 16*/86 \pm 8*
Week 16 (n=58)	153 \pm 16**/93 \pm 8**	154 \pm 17**/92 \pm 8**

* $P < 0.0001$ week 12 \neq week 0 and 16;

** $P < 0.00001$ week 0 \neq week 16.

(61 \pm 1 bpm). In the HBPM evaluation, a decrease ($P < 0.05$) was observed in pulse pressure at week 12 (57 \pm 13 bpm) compared with weeks 0 (63 \pm 14 bpm) and 16 (60 \pm 13 bpm).

The outcome analysis of the group of patients with JNC VI stage I hypertension did not show any difference when compared with the analysis of those with JNC VI stage II hypertension. According to patient classification, however, blood pressure was higher in patients with JNC VI stage II hypertension with OBPM. On ABPM, daytime systolic blood pressure in the group with stage II hypertension showed statistically significant higher levels when compared with night-time and 24 h systolic blood pressure, which were no different. Daytime, night-time and 24 h diastolic blood pressure were, however, statistically significantly higher in the group with JNC VI stage II hypertension than with JNC VI stage I hypertension. HBPM showed higher values of night-time diastolic and systolic blood pressure and daytime diastolic blood pressure higher in patients with JNC VI stage II

hypertension but no difference in daytime systolic blood pressure.

According to the response classification for efficacy analysis by OBPM at week 12 (visit 4), it was observed that:

1. Office sitting diastolic blood pressure: a) 28 (41%) patients had a diastolic blood pressure < 90 mmHg – category 1; b) 8 (12%) patients had a diastolic blood pressure ≥ 90 mmHg and a ≥ 10 mmHg decrease compared with baseline – category 2; c) 29 (42%) patients had a diastolic blood pressure ≥ 90 mmHg and a < 10 mmHg decrease compared with baseline – category 3.
2. Office sitting systolic blood pressure: a) 13 (20%) patients had a systolic blood pressure < 140 mmHg – category 1; b) 26 (40%) patients had a systolic blood pressure ≥ 140 mmHg and a ≥ 10 mmHg decrease compared with baseline – category 2; c) 11 (17%) patients had a systolic blood pressure ≥ 140 mmHg and a < 10 mmHg decrease when compared with baseline – category 3.

There was thus a 52% office blood pressure responsiveness (categories 1 and 2) when considering diastolic blood pressure and one of 60% for systolic blood pressure.

Concerning tolerability, 38 patients (43%) reported some adverse events. The most common were headache (17%), dizziness (10%), tiredness (7%), and oedema (5.6%). Exactly half of the adverse events stated were classified as being mild, 35% as moderate and only 3% as severe. In 12%, it was not stated how severe they were. Events considered to be severe were heartburn and epigastralgia, reported by only one patient.

Discussion

Amlodipine is a dihydropyridinic antihypertensive of the calcium channel antagonist group, whose half-life allows for the use of a daily single dose [13–15] in hypertension control while showing good tolerability [16]. The TOMHS study [17], carried out on patients with mild and moderate hypertension, showed that amlodipine was as efficient as other antihypertensives tested; it was, however, the only drug used during the 4 years of the study, whose patients demonstrated more than 80% treatment compliance.

Some studies [18–20] found that the antihypertensive effects of amlodipine and hydrochlorothiazide were comparable and showed a long-term effect. Other trials [21–23] have demonstrated an adequate 24 h control of blood pressure in patients with mild and moderate hypertension who received a single daily dose of either atenolol or amlodipine.

In the elderly, the efficacy of amlodipine has been shown by the ability of increasing doses of 2.5 mg intravenously administered [24] and 2.5, 5.0 and 10 mg administered orally to decrease both OBPM and ABPM readings [25]. Frick *et al.* [26] reported that amlodipine produced a dose-dependent decrease in blood pressure, with 2.5 mg as the minimum effective dose that was well tolerated; the mean age of patients studied was, however, 50.3 years. Other authors [27–29] have also suggested that low doses of amlodipine can control blood pressure, minimizing adverse effects reported as being dose dependent. Once again, no study tested the efficacy of a 2.5 mg dose exclusively in elderly patients. Pascual [29] analysed the role of amlodipine in the treatment of elderly people and concluded that this medication is appropriate for use in people over 75 years of age. Based on hypertension treatment guidelines, the author stated, however, that the initial dose should be at least 5.0 mg for this specific population.

The present study showed that it is possible to obtain 52% and 60% respectively of elderly patients responsive to treatment with low-dose amlodipine at 2.5 mg per day, when considering office diastolic and systolic blood pressure. In a study carried out by Prisant *et al.* [27], it was necessary to increase the dose of medication in 43% of non-elderly patients using amlodipine at 2.5 mg per day to control blood pressure, with a mean dose of 5.7 mg per day being used. In addition, in the study performed by Frick *et al.* [26], 89% of patients using amlodipine at 2.5 mg per day who were also non-elderly had to have this dose doubled for their blood pressure to be controlled.

The low incidence of adverse effects must be considered. Of particular interest is the low incidence of oedema, being observed in only 3.4% of the patients with JNC VI stage I hypertension and 2.2% of those with stage II hypertension. This undesirable effect was found in only 5.6% of the patients studied. Evaluations performed in other studies with calcium channel antagonists [30,31] showed higher percentages, possibly because of higher doses.

Previous trials have been performed to compare blood pressure evaluation by OBPM, ABPM and HBPM [32]. Such trials are justified when the differences found between blood pressures obtained by the three methods are analysed. Comparing values obtained by OBPM, ABPM and HBPM, significantly higher blood pressure values have usually been observed when OBPM is used instead of ABPM and HBPM. On the other hand, values found by ABPM and HBPM have not shown any significant differences. In the present study, blood pressure evaluation was performed by OBPM, ABPM and HBPM; however, the criterion used for evaluation of

efficacy was systolic and diastolic blood pressure obtained by OBPM.

In this study, it is suggested that amlodipine at a dose of 2.5 mg is efficacious in the elderly considering that 60% of patients are responsive and 20% achieve effective office systolic control (systolic blood pressure < 140 mmHg). Regarding office diastolic blood pressure, 52% of patients were responsive, whereas 41% had a diastolic blood pressure < 90 mmHg. The level of tolerability found was readily acceptable, with oedema present in only 5.6% of patients. An important practical finding of this study is that amlodipine at 2.5 mg per day can be suggested for the initial treatment of hypertension in the elderly.

Acknowledgements

The authors wish to thank Biosintética Farmaceutica, the sponsor of this study, for institutional help. Without their assistance, this study could not have been carried out.

References

- Duggan S, Ford GA, Eccles M. Doctors' attitudes towards the detection and treatment of hypertension in older people. *J Hum Hypertens* 1997; **11**: 271–276.
- Ford GA, Asghar MN. Management of hypertension in the elderly: attitudes of general practitioners and hospital physicians. *Br J Clin Pract* 1995; **39**:465–469.
- Kendall MJ. Hypertension in the elderly. *Basic Res Cardiol* 1998; **93**(suppl 2):43–46.
- Gueyffier F, Froment A, Gouton M. New meta-analysis of treatment of hypertension: improving the estimate of therapeutic benefit. *J Hum Hypertens* 1996; **10**:1–8.
- Lever AF, Ramsay LE. Treatment of hypertension in the elderly. *J Hypertens* 1995; **13**:571–579.
- Abernethy DR, Gutkowska J, Lambert MD. Amlodipine in elderly hypertensive patients: pharmacokinetics and pharmacodynamics. *J Cardiovasc Pharmacol* 1998; **12**(suppl 7):S67–S71.
- Kloner RA, Sowers JR, DiBona GF, Gaffney M, Wein M. For the Amlodipine Cardiovascular Community Trial Group. Sex- and age-related antihypertensive effects of amlodipine. *Am J Cardiol* 1996; **77**:713–722.
- Varrone JA. Study of the efficacy and safety of amlodipine for the treatment of hypertension in general practice. *Postgrad Med J* 1991; **67**(suppl 5):S28–S31.
- Cross BW, Kirby MG, Miller S, Shah S, Sheldon DM, Sweeney MT. A multicentric study of the safety and efficacy of amlodipine in mild to moderate hypertension. *Br J Clin Pract* 1993; **47**:237–240.
- Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1997; **157**:2413–2446.
- O'Brien E, Coats A, Owens P, Petrie J, Padfield PL, Littler WA, *et al.* Use and interpretation of ambulatory blood pressure monitoring: recommendations of the British Hypertension Society. *BMJ* 2000; **320**:1128–1134.
- Gomes MAM, Pierin A, Alavarce DC, Mion D Jr. Home blood pressure measurement with a automatic device (OMRON IC): acceptance and comparison office blood pressure measurement. *Am J Hypertens* 1999; **12**:165A.
- Broadhurst P, Heber ME, Brigden G, al-Khawaja I, Raftery EB. Intra-arterial monitoring of the antihypertensive effects of once-daily amlodipine. *J Hum Hypertens* 1992; **6**(suppl 1):S9–S12.
- Webster J, Robb OJ, Jeffers TA, Scott AK, Petrie JC. Once-daily amlodipine in the treatment of mild to moderate hypertension. *J Cardiovasc Pharmacol* 1988; **12**(suppl 7):S72–S75.
- Frick MH, McGibney D, Tyler HM. A dose-response study of amlodipine in mild to moderate hypertension. *J Intern Med* 1989; **225**:101–105.
- Onvik P, Herland OB, Thaulow E, Eide I, Midha R, Turner RR. Does antihypertensive treatment with amlodipine or enalapril affect quality of life? A multicenter study in general practice. *Tidsskr Nor Laegeforen* 1993; **113**:1337–1343.

- 17 Neaton JD, Grimm RH, Prineas RJ, Stamler J, Grandits GA, Elmer PJ, *et al.* Treatment of Mild Hypertension Study Research Group. Treatment of Mild Hypertension Study final results. *JAMA* 1993; **270**:713–724.
- 18 Burris JF, Ames RP, Applegate WB, Ram CV, Davidov ME, Mroczek WJ. Double-blind comparison of amlodipine and hydrochlorothiazide in patients with mild to moderate hypertension. *J Cardiovasc Pharmacol* 1988; **12(suppl 7)**:S98–S102.
- 19 Adolphe AB, Vlachakis ND, Rofman BA, Brescia D, Zellner SR. Long-term open evolution of amlodipine vs hydrochlorothiazide in patients with essential hypertension. *Int J Clin Pharmacol Res* 1993; **13**:203–210.
- 20 Rofman BA. Long-term open evaluation of amlodipine versus hydrochlorothiazide in patients with essential hypertension. *J Cardiovasc Pharmacol* 1988; **12(suppl 7)**:S94–S97.
- 21 Johnson BF, Frishman WH, Brobyn R, Brown RD, Reeves RL, Wombolt DG. A randomized, placebo-controlled, double-blind comparison of amlodipine and atenolol in patients with essential hypertension. *Am J Hypertens* 1992; **5**:727–732.
- 22 De Bruijn B, Cocco G, Tyler HM. Multicenter placebo-controlled comparison of amlodipine and atenolol in mild to moderate hypertension. *J Cardiovasc Pharmacol* 1988; **12(suppl 7)**:S107–S109.
- 23 Frishman WH, Brobyn R, Brown RD, Johnson BF, Reeves RL, Wombolt DG. Amlodipine versus atenolol in essential hypertension. *Am J Cardiol* 1994; **73**:50A–54A.
- 24 Abernethy DR, Gutkowska J, Lambert MD. Amlodipine in elderly hypertensive patients: pharmacokinetics and pharmacodynamics. *J Cardiovasc Pharmacol* 1988; **12(suppl 7)**:S67–S71.
- 25 Lacourciere Y, Poirier L, Lefebvre J, Archambault F, Cleroux J, Boileau G. Antihypertensive affects of amlodipine and hydrochlorothiazide in elderly patients with ambulatory hypertension. *Am J Hypertens* 1995; **8**: 1154–1159.
- 26 Frick MH, McGibney D, Tyler HM. Amlodipine: a double-blind evaluation of the dose–response relationship in mild to moderate hypertension. *J Cardiovasc Pharmacol* 1988; **12(suppl 7)**:S76–S78.
- 27 Prisant LM, Weir MR, Papademetriou V, Weber MA, Adebbile AI, Alemayechu D, *et al.* Low-dose drug combination therapy: an alternative first-line approach to hypertension treatment. *Am Heart J* 1995; **130**: 359–366.
- 28 Mehta JL, Lopez LM, Vlachakis ND, Gradman AH, Nash DT, O’Connell MT, *et al.* Double-blind evaluation of the dose–response relationship of amlodipine in essential hypertension. *Am Heart J* 1993; **125**: 1704–1710.
- 29 Pascual J. Hypertension control in the elderly with amlodipine. *Curr Med Res Opin* 2000; **16**:33–36.
- 30 Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T, *et al.* Morbidity and mortality in patients randomized to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: intervention as a goal in hypertension treatment (INSIGHT). *Lancet* 2000; **356**:366–372.
- 31 Webster J, Robb OJ, Jeffers TA, Scott AK, Petrie JC, Towler HM. Once daily amlodipine in the treatment of mild to moderate hypertension. *Br J Clin Pharmacol* 1987; **24**:713–719.
- 32 Gomes MA, Pierin AM, Segre CA, Mion D Jr. Home blood pressure measurement and ambulatory blood pressure measurement versus office blood pressure measurement. *Arq Bras Cardiol* 1998; **71**:581–585.