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Antihypertensive Effect of Barnidipine 10 mg or Amlodipine 5 to 10 mg Once Daily in Treatment-Naive Patients with Essential Hypertension: A 24-Week, Randomized, Open-Label, Pilot Study

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ABSTRACT

BACKGROUND: Dihydropyridine calcium antagonists are largely employed for the treatment of hypertension, coronary heart disease, and heart failure.

OBJECTIVE: The aim of our study was to compare the antihypertensive effect of the dihydropyridine calcium antagonists barnidipine and amlodipine.

METHODS: This was a 24-week, randomized, open-label, pilot study. Consecutive treatment-naive patients with grade I or II essential hypertension (office sitting systolic blood pressure [BP] of 140–179 mm Hg and diastolic BP of 90–109 mm Hg) were enrolled. The primary end points were the effect of treatment with either barnidipine 10 mg or amlodipine 5 mg once daily on office and ambulatory BP, left ventricular mass index (LVMI), and markers of cardiac damage, serum procollagen type I C-terminal propeptide, and plasma amino-terminal pro–B-type natriuretic peptide concentrations. Patients were assessed at enrollment, and 12 and 24 weeks. During each visit, the prevalence of adverse events (AEs) was also monitored using spontaneous reporting, patient interview, and physical examination, the relationship to study drug being determined by the investigators. Compliance with treatment was assessed at each study visit by counting returned tablets.

RESULTS: Thirty eligible patients (20 men, 10 women; mean [SD] age, 47 [12] years) were included in the study; all patients completed the 24 weeks of study treatment. Twelve weeks after randomization, 6 patients in the amlodipine group had their dose doubled to 10 mg due to inadequate BP control. Mean BP reductions at study end were not significantly different between the barnidipine and amlodipine groups (office BP, –10.3/–9.4 vs –16.6/–9.1 mm Hg; ambulatory BP, 9.4/6.4 vs 8.1/5.1 mm Hg). Reductions in LVMI and markers of cardiac damage were not significantly different

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between the 2 groups. Significantly more patients in the amlodipine group reported drug-related AEs compared with those in the barnidipine group (9 [60%] vs 2 [13%]; $P < 0.05$).

CONCLUSION: In this small sample of treatment-naive hypertensive patients, the antihypertensive effect of barnidipine 10 mg once daily was not significantly different from that of amlodipine 5 to 10 mg once daily. (*Curr Ther Res Clin Exp.* 2008;69: 192–206) © 2008 Excerpta Medica Inc.

KEY WORDS: essential hypertension, ambulatory bloodpressure monitoring, barnidipine, amlodipine, left ventricular mass index, smoothness index.

INTRODUCTION

Due to their antihypertensive efficacy, dihydropyridine calcium antagonists are recommended by international guidelines as first-choice drugs for the treatment of hypertension, coronary heart disease, and heart failure.[1–3] However, treatment with many of these drugs is associated with adverse events (AEs),[4] which may reduce adherence to treatment and result in switching to other drug classes.[5]

Barnidipine is a long-acting dihydropyridine calcium antagonist[6,7] that has been evaluated in short- and long-term double-blind, randomized studies, and open-label studies of hypertensive patients of all ages.[8–11] In these studies, barnidipine was as effective in reducing blood pressure (BP) as monotherapy with other calcium antagonists (felodipine, amlodipine, and nitrendipine),[12–14] β-blockers (atenolol),[15] angiotensin-converting enzyme (ACE) inhibitors (enalapril),[15] and diuretics (hydrochlorothiazide).[16] Barnidipine was also reported to be effective and well tolerated in combination treatment with β-blockers or ACE inhibitors[10,11,15] and throughout an entire 24-hour period in studies using ambulatory BP monitoring.[17,18] The safety profile of barnidipine appears better than that observed with other calcium antagonists, being <3%.[7]

In the present study, we compared the antihypertensive effect of treatment with barnidipine or amlodipine administered once daily. This study is unique in that the study participants were treatment-naive patients with primary hypertension. In addition, we used ambulatory BP monitoring and measured left ventricular mass index (LVMI) and markers of cardiac fibrosis and function as our primary end points.

PATIENTS AND METHODS

This single-center, randomized, open-label, parallel-group, pilot study was conducted at the Centro Interuniversitario di Fisiologia Clinica e Ipertensione, IRCCS Policlinico, Università di Milano, Milano, Italy. Written informed consent was obtained from all patients prior to their inclusion in the study. The study was approved by the independent institutional review board of the study center.

STUDY POPULATION

The study included consecutive eligible adult (aged ≥18 years) outpatients of either sex with grade I or II essential hypertension (office sitting systolic BP [SBP] of 140–

179 mm Hg and/or office sitting diastolic BP [DBP] of 90–109 mm Hg).[3] All patients were naive to antihypertensive drug treatment and were enrolled between May 2005 and April 2006.

Patients were excluded if they met any of the following criteria: (1) malignant or secondary hypertension; (2) clinically significant heart disease (ie, cardiac valvular disease, major arrhythmias, heart failure, unstable angina, myocardial infarction) or cerebrovascular disease; (3) serious concomitant diseases (eg, renal insufficiency, malignancy, hepatic disorders, psychiatric disease, diabetes); (4) history of alcohol or drug abuse; (5) obesity (body mass index >30 kg/m^2); or (6) known hypersensitivity to dihydropyridine calcium antagonists. Pregnant or breastfeeding women or women of childbearing potential who were not practicing an effective method of birth control were also excluded.

STUDY DESIGN

Patients were administered barnidipine 10 mg or amlodipine 5 mg once daily in the morning for 24 weeks. The starting doses were those recommended by regulatory authorities and producers[6,7] and in guidelines[3]. After the initial 12 weeks of treatment, barnidipine or amlodipine doses were doubled in patients with inadequate control (office SBP ≥140 mm Hg or office DBP ≥90 mm Hg).

Randomization was accomplished through a computer-generated grid. The patient randomization numbers were allocated sequentially in the order in which the patients entered the study. The randomization code and treatment assigned were placed in a sealed envelope to be opened at the time of a patient's assignment to active treatment. Given the open-label design of the study, treatment identity was known to both the physician and the patient.

At the screening visit, medical history was recorded and a physical examination and 12-lead echocardiogram were performed. Physical examination was repeated after 12 and 24 weeks of treatment. Office BP was measured at study initiation and after 12 and 24 weeks of treatment. Twenty-four–hour ambulatory BP monitoring was performed at the initial and final visits. At study initiation and at the end of treatment, M-mode echocardiography was also performed and LVMI was computed. Blood samples were drawn at the initial and final visits to assess serum concentrations of procollagen type I C-terminal propeptide (PICP), a marker of collagen turnover used to quantify myocardial fibrosis, and plasma concentrations of amino-terminal pro–B-type natriuretic peptide (NT-proBNP), a biomarker of left ventricular dysfunction.

During each visit, the prevalence of AEs was also monitored using spontaneous reporting, patient interview, and physical examination. Compliance with treatment was assessed at each study visit by counting returned tablets.

BLOOD PRESSURE AND HEART RATE MEASUREMENT

Patients' BP was measured in the clinic using a standard sphygmomanometer 24 hours after drug administration. The mean of 3 measurements taken at 2-minute intervals after 5 minutes of rest in the sitting position was used as the office BP reference value. SBP and DBP values were taken at the first and fifth Korotkoff sounds,

respectively. Heart rate (HR) was measured by palpating the radial artery pulse. Two physicians measured both BP and HR, with the same physician always examining the same patient.

Ambulatory BP monitoring was performed noninvasively over 24 hours using an oscillometric validated device (Spacelabs 90207, Spacelabs Healthcare Inc. Issaquah, Washington). The device cuff was wrapped around the nondominant arm, and the patient was asked to keep his or her arm still during the automatic BP measurement. Each recording started in the morning, immediately after office BP assessment and administration of active treatment, when foreseen. The device was programmed to measure BP every 15 minutes during the day (7 AM–11 PM) and every 20 minutes during the night (11 PM–7 AM).

ECHOCARDIOGRAPHY

Echocardiography was performed (S.C.) with the patient in the supine left lateral decubitus position. Left ventricular internal diameters, left ventricular posterior wall thickness, and interventricular septum thickness were measured monodimensionally on the longitudinal parasternal view previously identified bidimensionally according to the recommendations of the American Society of Echocardiography.[19] Left ventricular volumes were calculated using the cube formula,[19] while left ventricular mass was calculated according to the Penn Convention[20] and indexed to body surface area by the formula of Dubois and Dubois.[21] The presence of left ventricular hypertrophy (LVH) was defined as an LVMI >110 g/m^2 in women and >131 g/m^2 in men.[22]

STATISTICAL ANALYSIS

Treatment effect was assessed by computing office sitting SBP and DBP changes (computed as final visit BP – baseline BP), which were considered the primary study end points. Secondary study end points were as follows: (1) changes in 24-hour, daytime (7 AM–11 PM), and nighttime (11 PM–7 AM) mean SBP and DBP and pulse pressure (computed as SBP – DBP); (2) 2-hour means of BP before and during treatment; (3) changes in SBP and DBP during the last 4 hours of the dosing interval; (4) determination of the smoothness index of SBP and DBP after 12 weeks of treatment; and (5) changes in office and ambulatory HR.

Before analyzing the 24-hour BP recordings, artifacts were removed according to previously described editing criteria.[23] Recordings were considered valid when ≤3 nonconsecutive hours were missing over the 24-hour monitoring period and when ≥1 BP measurement was available in the remaining hours.

The smoothness index was computed by dividing the mean of the 24 hourly BP changes after treatment by the corresponding SD.[24–26] This index is useful for quantifying whether treatment smoothly reduces BP throughout the 24-hour monitoring period. It has been found to be more reproducible and clinically relevant than other indices (eg, the trough-to-peak ratio).[25,26] According to recent publications, the higher the smoothness index, the smoother the BP control.[25,27]

Assessment of treatment effect at the final study visit compared with baseline was done by analysis of covariance using the baseline value as covariate and treatment as the

main effect. Baseline-adjusted mean changes and 95% CIs were computed. This analysis was applied to office and ambulatory BP, LVMI, PCIP, and NT-proBNP. Analysis of variance was used to assess differences in the smoothness index.

The occurrence of drug-related AEs was monitored during the study, and the percentage of patients with drug-related AEs in each group was compared using the Fisher exact test.

$P < 0.05$ was considered statistically significant. Data are shown as mean (SD), unless otherwise indicated. Because this was a pilot study, no sample size estimation was done.

RESULTS

DEMOGRAPHIC AND CLINICAL DATA

Thirty consecutive eligible patients (20 men, 10 women; mean [SD] age, 47 [12] years) were randomized to either barnidipine 10 mg (n = 15) or amlodipine 5 mg (n = 15) once daily. All patients had compliance >95%. No patients in the barnidipine group had their drug dose doubled; 6 patients in the amlodipine group had their drug dose doubled to 10 mg because their BP was inadequately controlled (office SBP ≥140 mm Hg or office DBP ≥90 mm Hg) after 12 weeks of treatment. There were no significant differences at baseline between the 2 groups in any demographic or clinical characteristics (**Table I**). Given the strict exclusion criteria used in the study, previous and concomitant diseases or treatments were rare (ie, <10% of patients) among study patients. All 30 patients completed the 24 weeks of study treatment.

Nineteen of the 30 patients (63%) (barnidipine group, 9; amlodipine group, 10) had valid ambulatory BP recordings. Reasons for exclusion from analysis were unavailability

Table I. Baseline demographic and clinical characteristics of study patients with essential hypertension randomly assigned to 1 of 2 treatment groups (N = 30).* Data are mean (SD) unless otherwise indicated.

Variable	Barnidipine (n = 15)	Amlodipine (n = 15)
Age, y	45 (9)	50 (15)
Sex, no. (%)		
Male	10 (67)	10 (67)
Female	5 (33)	5 (33)
LVMI, g/m^2	125 (31)	115 (25)
LVH, no. (%)	6 (40)	4 (27)
PICP, mg/L	60 (28)	47 (13)
NT-proBNP, pg/mL	64 (44)	41 (26)
Office SBP, mm Hg	145 (17)	147 (18)
Office DBP, mm Hg	98 (9)	96 (5)
Office HR, beats/min	72 (13)	78 (14)

LVMI = left ventricular mass index; LVH = left ventricular hypertrophy; PICP = procollagen type I C-terminal propeptide; NT-proBNP = amino-terminal pro–B-type natriuretic peptide; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.
*No significant between-group differences were found.

of 1 or both recordings (n = 7) or <21 hours of valid recordings (n = 4). Demographic and clinical characteristics of the patients with valid ambulatory BP recordings were similar to those of the total study population (**Table II**).

OFFICE BLOOD PRESSURE AND HEART RATE MEASUREMENTS

After 12 weeks of treatment, mean baseline-adjusted office SBP and DBP reductions were not significantly different in the barnidipine group (SBP: –15.4 mm Hg [95% CI, –21.0 to –9.9]; DBP: –12.1 mm Hg [95% CI, –16.0 to –8.2]) compared with the amlodipine group (SBP: –16.3 mm Hg [95% CI, –21.8 to –10.8]; DBP: –10.7 mm Hg [95% CI, –15.6 to –6.8]).

At the end of the 24 weeks of treatment, baseline-adjusted office SBP reductions (barnidipine: –10.3 mm Hg [95% CI, –17.3 to –3.4]; amlodipine: –16.6 mm Hg [95%

Table II. Demographic and clinical characteristics of patients with essential hypertension and valid ambulatory blood pressure monitoring during the study (n = 19).* Data are mean (SD) unless otherwise indicated.

Variable	Barnidipine (n = 9)	Amlodipine (n = 10)
Age, y	45 (7)	48 (12)
Sex, no. (%)		
Male	5 (56)	7 (70)
Female	4 (44)	3 (30)
LVMI, g/m^2	123 (25)	114 (22)
LVH, no. (%)	4 (44)	3 (30)
PICP, mg/L	61 (32)	45 (11)
NT-proBNP, pg/mL	78 (47)	34 (23)
Office SBP, mm Hg	144 (18)	145 (17)
Office DBP, mm Hg	99 (11)	96 (6)
Office HR, beats/min	66 (9)	77 (15)
24-Hour SBP, mm Hg	144 (11)	138 (9)
24-Hour DBP, mm Hg	89 (6)	84 (8)
24-Hour HR, beats/min	74 (7)	78 (7)
Daytime SBP, mm Hg	149 (10)	141 (9)
Daytime DBP, mm Hg	94 (6)	88 (8)
Daytime HR, beats/min	78 (8)	83 (9)
Nighttime SBP, mm Hg	130 (14)	130 (9)
Nighttime DBP, mm Hg	77 (8)	75 (10)
Nighttime HR, beats/min	65 (7)	68 (5)

LVMI = left ventricular mass index; LVH = left ventricular hypertrophy; PICP = procollagen type I C-terminal propeptide; NT-proBNP = amino-terminal pro–B-type natriuretic peptide; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.
*No significant between-group differences were found.

CI, –23.6 to –9.6]) and office DBP reductions (barnidipine: –9.4 mm Hg [95% CI, –13.5 to –5.4]; amlodipine: –9.1 mm Hg [95% CI, –13.2 to –5.1]) were not significantly different between the 2 treatment groups.

The mean change in office HR was not significantly different after 12 weeks (barnidipine: –1.7 beats/min [95% CI, –5.9 to 2.6]; amlodipine: –0.9 beats/min [95% CI, –3.3 to 5.2]) or 24 weeks (barnidipine: –1.5 beats/min [95% CI, –7.1 to 4.1]; amlodipine: –2.0 beats/min [95% CI, –7.7 to 3.6]) of treatment.

AMBULATORY BLOOD PRESSURE AND HEART RATE

In the 19 patients with valid ambulatory BP recordings, 24-hour, daytime, and nighttime SBP and DBP values were significantly (all, $P < 0.05$) reduced by treatment, with the exception of nighttime SBP in the amlodipine group (**Figure 1**). No statistically significant between-treatment differences were observed over the 24-hour period or during the daytime or the nighttime.

No significant between-group differences were found in 24-hour pulse pressure (barnidipine: –2.9 mm Hg [95% CI, –6.1 to 0.2]; amlodipine: –3.1 mm Hg [95% CI, –6.1 to –0.1]), daytime pulse pressure (–2.1 mm Hg [95% CI, –5.2 to 1.0] vs –3.4 mm Hg [95% CI, –6.3 to –0.5]), or nighttime pulse pressure (–4.1 mm Hg [95% CI, –7.9 to –0.3] vs –3.0 mm Hg [95% CI, –6.6 to 0.6]).

No significant between-group differences were found in reductions in BP during each 2-hour period of the 24-hour monitoring period, including the last 4 hours of the recording (barnidipine: SBP, –14.3 mm Hg [95% CI, –18.4 to –10.3] and DBP, –7.6 mm Hg [95% CI, –12.7 to –2.4]; amlodipine: –11.6 mm Hg [95% CI, –15.4 to –7.8] and –6.0 mm Hg [95% CI, –10.9 to –1.1]) (**Figure 2**).

Assessment of homogeneity of BP control using the smoothness index (**Figure 3**) showed no statistically significant difference between the barnidipine and amlodipine groups in either SBP or DBP.

Mean (95% CI) 24-hour (barnidipine: 1 bpm [–4 to 5]; amlodipine: –1 bpm [–6 to 3]), daytime (barnidipine: 1 bpm [–4 to 5]; amlodipine: –2 bpm [–6 to 3]), and nighttime HR values (barnidipine: 2 bpm [–3 to 6]; amlodipine: 0 bpm [–4 to 4]) did not change significantly in either treatment group.

MARKERS OF TARGET ORGAN DAMAGE

Figure 4 shows mean absolute values for LVMI at baseline and after 24 weeks of treatment, as well as corresponding baseline-adjusted changes. LVMI was significantly reduced ($P < 0.05$) by treatment with barnidipine but not with amlodipine, with no statistically significant difference between the 2 treatment groups. Three of the 6 patients (50%) with LVH at baseline in the barnidipine group experienced regression of this condition with treatment. In the amlodipine group, 1 of 4 patients (25%) with LVH experienced regression, but 2 patients who did not have LVH at baseline developed the condition by the final visit.

Serum concentrations of PICP and plasma concentrations of NT-proBNP were reduced, though not significantly, by barnidipine (–3.0 mg/L [95% CI, –9.8 to 3.9] and –7.2 pg/mL [95% CI, –15.2 to 0.9], respectively) but not by amlodipine

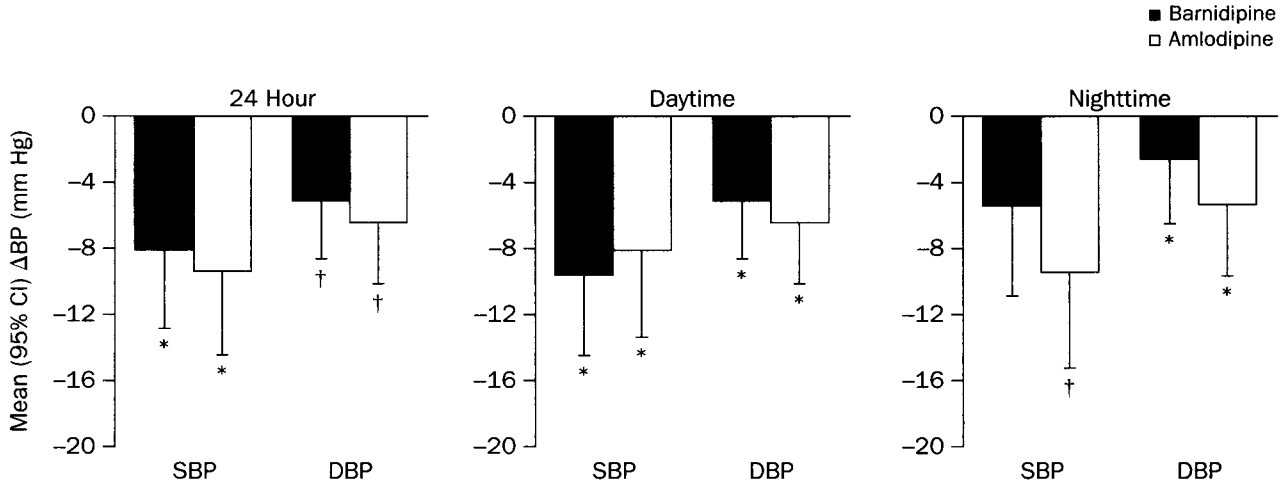

Figure 1. Twenty-four–hour, daytime, and nighttime baseline-adjusted changes (Δ) in systolic (SBP) and diastolic blood pressure (DBP) after 24 weeks in patients with essential hypertension randomized to treatment with barnidipine (n = 9) or amlodipine (n = 10). Data are shown as mean (95% CI). *$P < 0.01$ versus baseline; †$P < 0.05$ versus baseline.

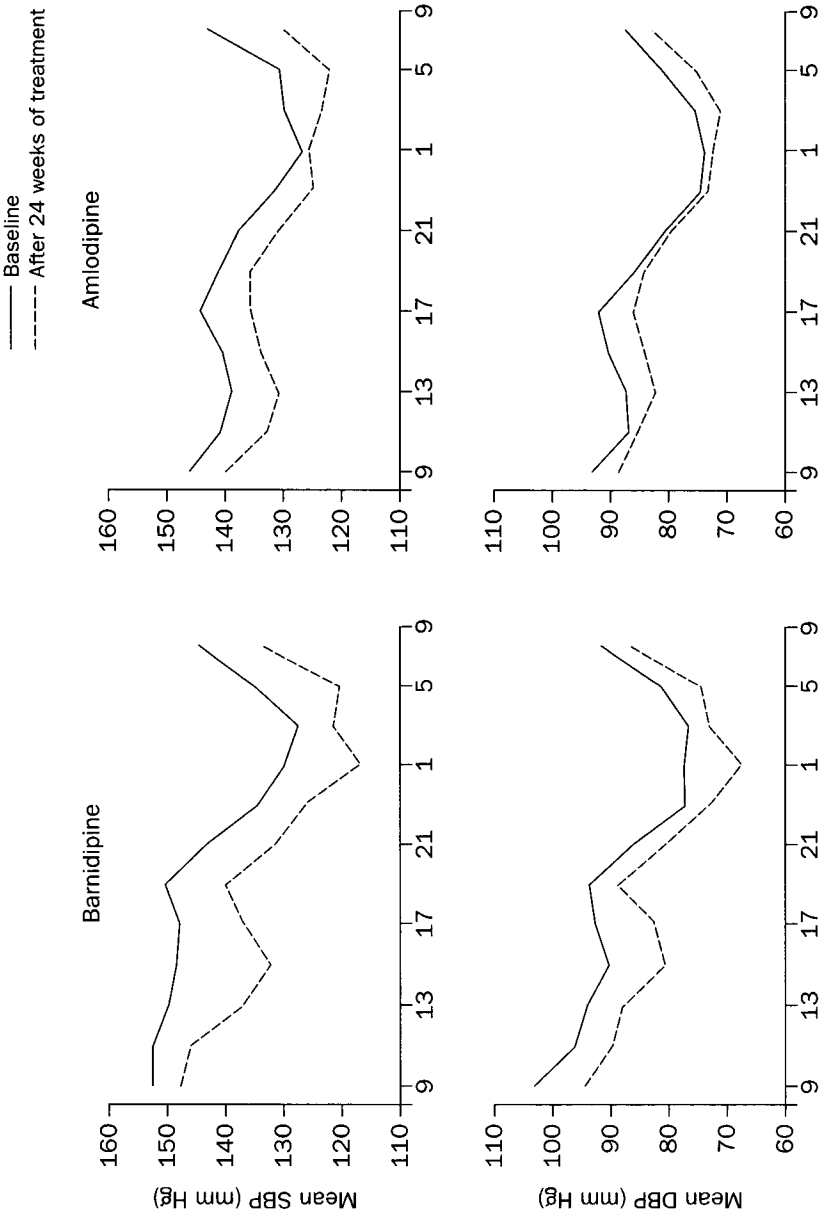

Figure 2. Mean 2-hour systolic (SBP) and diastolic blood pressure (DBP) values at baseline and after 24 weeks in patients with essential hypertension randomized to treatment with barnidipine (n = 9) or amlodipine (n = 10).

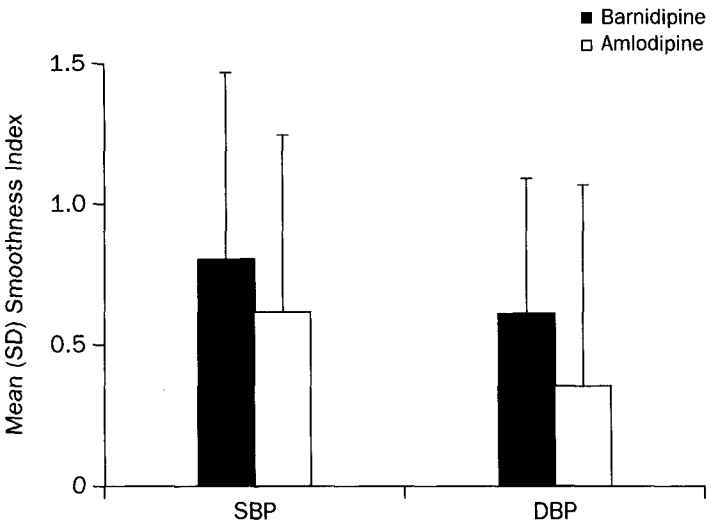

Figure 3. Mean (SD) smoothness index of systolic (SBP) and diastolic blood pressure (DBP) in patients with essential hypertension randomized to treatment with barnidipine (n = 9) or amlodipine (n = 10).

(0.6 mg/L [95% CI, −6.0 to 7.2] and 4.3 pg/mL [95% CI, −3.4 to 12.1]), although the difference between the 2 treatment groups was not statistically significant.

DRUG-RELATED ADVERSE EVENTS

A total of 11 patients (36.7%) reported drug-related AEs, with a significantly greater incidence in the amlodipine group compared with the barnidipine group (9 vs 2 patients; $P < 0.05$). A total of 13 AEs—10 in the amlodipine group and 3 in the barnidipine group—were recorded (**Table III**). No patient was withdrawn from the study due to AEs.

DISCUSSION

In this pilot study, barnidipine 10 mg was as effective as 5 to 10 mg of amlodipine in reducing office BP during 24 weeks of treatment in patients with grade I or II essential hypertension who were naive to hypertensive treatment. The incidence of drug-related AEs was significantly lower with barnidipine than amlodipine. Barnidipine has previously been reported to have a good tolerability profile.[7,28,29]

Both drugs were associated with comparable reductions in BP, not only office BP but also 24-hour ambulatory BP. Both barnidipine and amlodipine displayed a good smoothness index, with no statistically significant difference between treatments. These results support those of a previous open-label study in 40 Thai patients with essential hypertension in which 8 weeks of treatment with higher doses of barnidipine (10–15 mg) were associated with consistent 24-hour BP reduction and control, as quantified

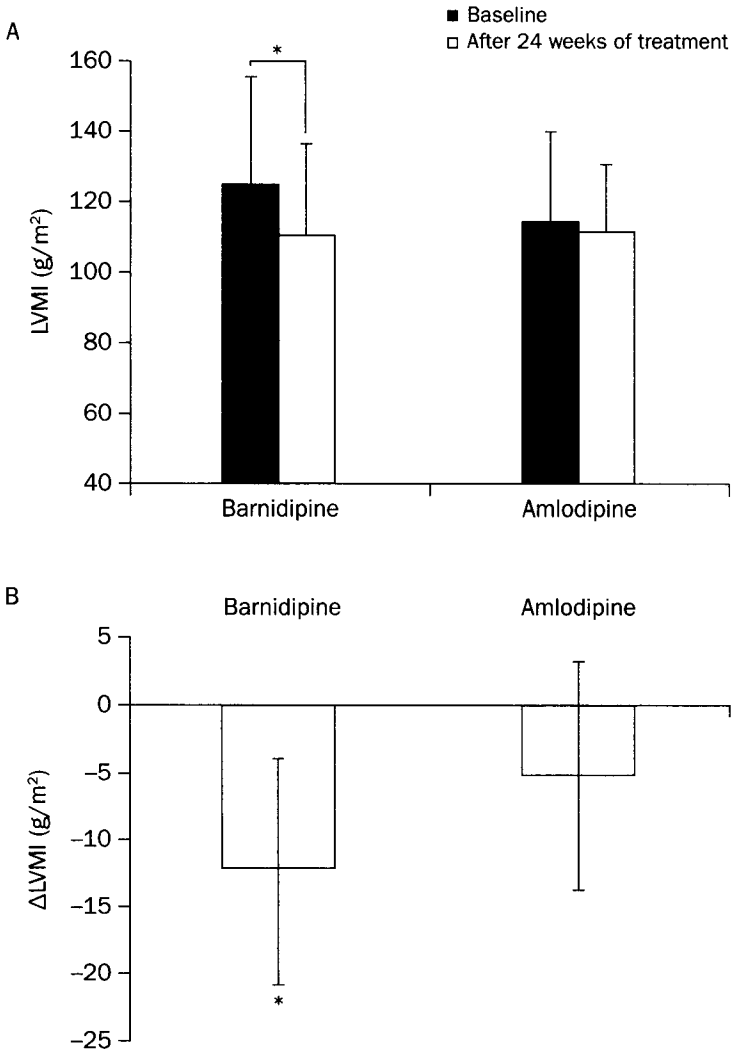

Figure 4. Mean (SD) left ventricular mass index (LVMI) at baseline and after 24 weeks (A) and corresponding baseline-adjusted mean (95% CI) changes (B) in patients with essential hypertension randomized to treatment with barnidipine or amlodipine. *$P < 0.05$ versus baseline.

by the smoothness index.[17] Our study also supports the findings of a review of 12-week studies of the antihypertensive effects of barnidipine and amlodipine.[14]

In the present study, barnidipine and amlodipine were associated with significantly reducing not only 24-hour SBP and DBP but also 24-hour pulse pressure, although the reduction in the latter was small. This is an important finding because even a limited reduction in pulse pressure may be clinically and prognostically beneficial for hyperten-

Table III. Prevalence of drug-related adverse events (AEs) in patients with essential hypertension randomly assigned to 1 of 2 treatment groups (N = 30).

AE	Barnidipine (n = 15)	Amlodipine (n = 15)
Ankle edema, no.	1	6
Headache, no.	1	2
Palpitations, no.	1	2
Total, no.	3	10
Total patients with AEs, no. (%)	2 (13)	9 (60)*

*$P < 0.05$ versus barnidipine.

sive patients.[30,31] Also, the fact that HR, a well known cardiovascular risk factor, did not increase with barnidipine administration may be regarded as a positive feature of this drug,[32] indirectly confirming the previous finding that barnidipine does not cause reflex neurohumoral activation.[33]

LVMI decreased significantly in the barnidipine group. Concentrations of PICP and NT-proBNP, which may be increased in hypertensive patients and are considered important markers of asymptomatic cardiac damage, also decreased in the barnidipine group, though not significantly.[34,35] A possible explanation for these favorable effects of barnidipine on cardiac organ damage might be due to the drug's lipophilic character, which allows it to concentrate in the tissues,[7] and to its antioxidant activity, which has potential cardiovascular-protective effects.[36,37]

Finally, our findings deserve some notes of caution. This was a single-center, open-label, pilot study with a limited sample size. Larger controlled, blinded studies are needed to demonstrate whether the antihypertensive effects of barnidipine are similar to those of amlodipine. Another limitation of our study was the analysis of ambulatory BP recordings, which was limited for technical reasons to 63% of the study patients; this occurred because many recordings were missing or qualitatively inadequate. Therefore, although it is known that when drug efficacy is tested using 24-hour BP monitoring fewer patients are needed due to the lack of a placebo effect[38,39] and to high reproducibility,[40] we cannot definitely conclude that barnidipine was similar to amlodipine in controlling 24-hour BP. However, this is the first study comparing barnidipine and amlodipine in newly diagnosed, treatment-naive hypertensive patients.

Another limitation of our study is that, in spite of similar office BP at baseline, patients treated with amlodipine had values of LVMI, PICP, NT-proBNP, and daytime BP numerically lower than those recorded in patients treated with amlodipine. This finding may be compatible with a larger prevalence of patients with a "white-coat effect" in the group of patients treated with amlodipine, this condition being also characterized by less pronounced signs of cardiac damage, as in our patients. Although this nonhomogeneity might have led to a better response in patients treated with amlodipine, no significant differences between treatments were observed after correction of on-treatment changes by baseline values.

CONCLUSIONS

In this randomized, open-label, pilot study in a small sample of treatment-naive hypertensive patients, the antihypertensive effect of barnidipine 10 mg once daily was not significantly different from that of amlodipine 5 to 10 mg once daily. The effects on LVMI and on concentrations of PICP and NT-proBNP, markers of cardiac damage, were not significantly different between the 2 drugs.

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