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EFFICACY OF ONCE-DAILY AMLODIPINE IN THE CONTROL OF 24-HOUR BLOOD PRESSURE USING AMBULATORY BLOOD PRESSURE MONITORING

SAMEER HURAIB, AKRAM ASKAR, HASAN ABU-AISHA, JAMAL AL-WAKEEL, AHMAD MITWALLI, AND SULIMAN AL-MAJED

Department of Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia

ABSTRACT

To evaluate the efficacy, tolerance, and acceptance of once-daily amlodipine in the control of 24-hour blood pressure (BP), we conducted an open-label, uncontrolled trial in 20 patients (17 men and 3 women) with mild-to-moderate hypertension and without evidence of secondary hypertension except as a result of nephropathy. A 2-week washout placebo period was followed by a 12-week period of active treatment. The starting dose of amlodipine was 5 mg once daily; this was increased to 10 mg once daily if BP was not controlled within 6 weeks of starting treatment. Clinic and ambulatory BP measurements were obtained before starting active treatment (week 0) and then at 6 and 12 weeks after the start of treatment. The mean age (±SD) was 49.2 ± 13.7 years. Mean clinic systolic BP fell from 162.4 ± 15.4 mm Hg at week 0 to 136.8 ± 8.7 mm Hg at week 12. Clinic diastolic BP fell from 102.8 ± 5.1 mm Hg at week 0 to 81.3 ± 6.1 mm Hg at week 12. Ambulatory systolic BP fell from 147.8 ± 8.8 mm Hg at week 0 to 136.0 ± 10.6 mm Hg at week 12. Ambulatory diastolic BP fell from 90.4 ± 4.5 mm Hg at week 0 to 81.0 ± 5.0 mm Hg at week 12. There was a significant reduction in systolic BP between week 0 and week 6 (P = 0.0001), as well as between week 0 and week 12 (P = 0.0008). Similarly, significant reductions were obtained in diastolic BP between week 0 and week 6 (P = 0.0002), as well as between week 0 and week 12 (P = 0.001). The drug amlodipine was well tolerated and well accepted by patients. The results indicate that monotherapy with amlodipine 5 mg once daily is effective in controlling BP over a 24-hour period.

INTRODUCTION

The benefits of ambulatory blood pressure (BP) monitoring in the assessment of the efficacy of drug treatment are well established.[1] The new generation of ambulatory recorders enables 24-hour ambulatory measurements to be obtained; these not only demonstrate the circadian rhythm of BP but also provide further evidence of the duration of the drug effect.

Amlodipine* is a calcium antagonist that has been indicated to be an

* Trademark: Amlor (Pfizer, Jeddah, Saudi Arabia).

Address correspondence to: Dr. Sameer O. Ben Huraib, Department of Medicine (38), College of Medicine, KSU, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

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effective once-daily antihypertensive agent.[2] It achieves significant reduction in BP values in both the supine and standing positions without causing tachycardia. After oral administration at therapeutic doses, amlodipine is completely absorbed. Its bioavailability is 60% to 80%, and its peak plasma level is slow, occurring 6 to 12 hours after administration.[3] The distribution volume is 20 L/kg. Its elimination half-life is 35 to 50 hours, allowing once-daily dosing. Steady-state plasma concentrations are reached after 7 to 8 days of administration.[3] The mechanism of its antihypertensive action is linked to the direct relaxing effect on vascular smooth muscle.

The purpose of this open-label, uncontrolled study was to evaluate the efficacy of once-daily amlodipine in the control of 24-hour BP, as well as its tolerance, and acceptance, when administered to ambulatory patients with mild-to-moderate hypertension.

PATIENTS AND METHODS

The 20 consecutive patients (17 men, 3 women) selected for this study were ambulatory patients over 18 years old who presented with arterial hypertension, defined as a diastolic BP >95 mm Hg and <115 mm Hg in more than one reading during different visits at the hypertension clinic of King Khalid University Hospital. These patients either were not receiving treatment or were receiving treatment that was poorly tolerated or insufficient to control BP (diastolic BP >95 mm Hg). Patients who continued to have abnormal diastolic BP values after 2 weeks of placebo treatment were included. Informed consent was obtained from all patients.

Patients with secondary hypertension were excluded, except those with hypertension due to nephropathy. Patients with malignant hypertension, diastolic BP >130 mm Hg, eye fundal examination showing phase III or IV hypertension changes, and renal insufficiency were also excluded if their diastolic BP became <95 mm Hg after the 2-week placebo phase. Women who were pregnant and patients with severe hepatic insufficiency or severe chronic illness were excluded, as were patients undergoing hemodialysis.

The duration of this noncomparative study was 14 weeks. The study began with a 2-week preinclusion placebo washout phase, followed by 12 weeks of treatment with amlodipine.

Patients were seen and examined at the hypertensive clinic at the preinclusion visit (week −2), at the inclusion visit (week 0), and at weeks 6 and 12. The starting dosage of amlodipine was 5 mg once daily, increased to 10 mg if BP was not well controlled after 6 weeks of treatment. Amlodipine was given either as monotherapy or in addition to the patient's current antihypertensive medications if the patient's BP remained >95 mm Hg after the 2-week placebo period. Compliance was checked by counting remaining tablets at each visit.

Clinic BP and heart rate were measured after 5 minutes in the supine position and after 2 minutes in the standing position. BP was measured with a standard mercury sphygmomanometer in the same (dominant) arm throughout the study; phase V diastolic BP was measured and recorded to the nearest 2 mm Hg. These measurements were made by the same clinician throughout the entire study period. Ambulatory BP was measured using the "Quiet Track" ambulatory BP monitoring system (Welch Allyn Tycos, Arden, North Carolina) before starting active treatment and then at 6 and 12 weeks after beginning treatment. Heart rate was also measured at weeks 0, 6, and 12.

Efficacy was judged to be excellent if treatment resulted in normalization of BP (diastolic BP <90 mm Hg and systolic BP <140 mm Hg); good if diastolic BP <90 mm Hg but systolic BP >140 mm Hg; fair if patients showed some response, but diastolic and systolic BP were not normalized; and poor if patients showed no response to treatment. Tolerance was rated excellent if no side effects were reported, good if minor side effects were reported, fair if moderate side effects were reported but treatment continued, and poor if treatment was withdrawn. Acceptance was evaluated globally by both patients and the investigator.

Statistical Analysis

The STATPAC gold statistical analysis package (David S. Walonick, Minnesota) was used to analyze the data. One-way analysis of variance was used to compare results at weeks 0, 6, and 12. Values are given as mean ± SD. Student's *t* test was used to determine difference in the means. A $P < 0.05$ was considered to be significant.

RESULTS

Of the 20 patients included in the study, two dropped out, one woman because of pregnancy and one man because of uncooperation (ie, did not like to come for frequent visits because of living outside the city). The mean age was 49.2 ± 13.7 years (range, 18 to 76 years). Mean body weight was 78.9 ± 11.5 kg (range, 56 to 102 kg), and mean height was 168.4 ± 10.5 cm (range, 137 to 180 cm). The mean duration of hypertension was 6.1 ± 3.6 years (range, 2 to 16 years). Two patients required an increase in dosage to 10 mg once daily to have good control. The etiology of hypertension was essential in 44.4% of patients and renal in the balance of the patients (Table I).

Clinic supine BP measurements are shown in Figure 1. The mean systolic BP at the beginning was 162.4 ± 15.4 mm Hg; at 6 weeks, 140.3 ± 9.8 mm Hg; and at 12 weeks, 136.8 ± 8.7 mm Hg. The mean diastolic BP

Table I. Etiology of hypertension (N = 18).

Causes	No. of Patients (%)
Essential	8 (44.4)
Diabetic nephropathy	5 (27.8)
Focal segmental glomerulosclerosis	3 (16.7)
Obstructive nephropathy	1 (5.6)
Hypoplastic kidney	1 (5.6)

at the beginning was 102.8 ± 5.1 mm Hg; at 6 weeks, 86 ± 9.2 mm Hg; and at 12 weeks, 81.3 ± 6.1. BP reductions were significant ($P = 0.0004$ for systolic BP and 0.0003 for diastolic BP between weeks 0 and 6; $P = 0.0002$ for both systolic and diastolic BP between weeks 0 and 12).

For visual reading, mean hourly BP was recorded. Mean systolic BP and diastolic BP were plotted at week 0 (start of ambulatory amlodipine treatment), after 6 weeks, and after 12 weeks (end of study). Table II shows the mean ambulatory BP measurements for all systolic and diastolic BP reading over 24 hours at weeks 0, 6, and 12. There was a statistically significant difference in the hourly mean systolic BP ($P = 0.008$) and the hourly mean diastolic BP ($P = 0.001$) between the recording at week 0 and that at week 12 (Figure 2). Mean heart rate was 81 ± 6 beats/min before starting treatment and 84 ± 5.5 beats/min and 83 ± 6.3 beats/min at weeks 6 and 12, respectively (NS).

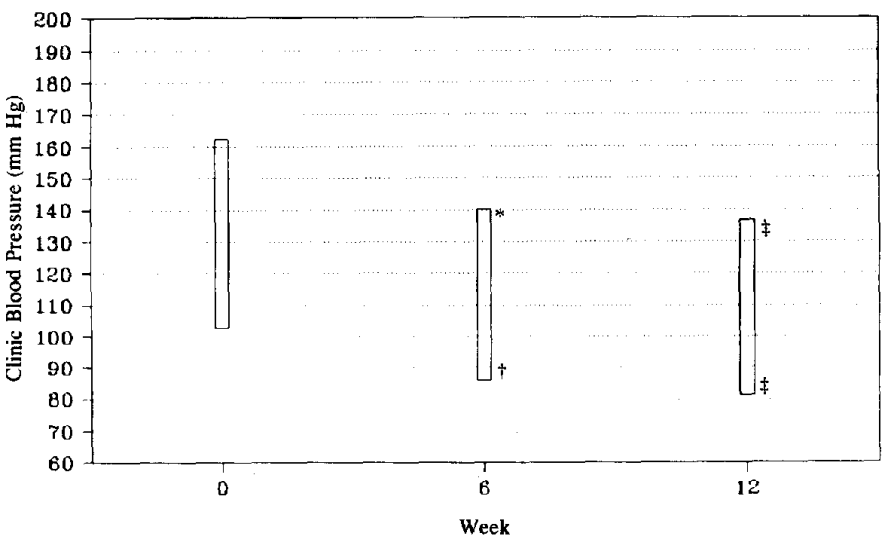

Figure 1. Clinic supine blood pressure measurements before and after treatment with amlodipine. * $P = 0.0004$; † $P = 0.0003$; ‡ $P = 0.0002$, versus week 0.

Table II. Ambulatory blood pressure (BP) measurements (mean ± SD) at weeks 0, 6, and 12.

	Week 0	Week 6	Week 12
Systolic BP	147.8 ± 8.8	132.7 ± 6.6*	136.0 ± 10.6†
Diastolic BP	90.4 ± 4.5	80.0 ± 4.1‡	81.0 ± 5.0§

* $P = 0.0001$ versus week 0.
† $P = 0.008$ versus week 0.
‡ $P = 0.0002$ versus week 0.
§ $P = 0.001$ versus week 0.

DISCUSSION

BP varies spontaneously throughout the day, being the highest on waking in the morning and lowest during sleep. It also varies with physical and mental activity.[4] Ambulatory BP measurement is more precise than clinic BP measurement in that it provides multiple readings and thus is more reliable and helps to identify the patients most likely to benefit from the introduction of antihypertensive therapy.[4] Conventional clinic BP measurement is influenced by many factors that make the technique unsuitable for research in drug efficacy.[1] Clinic BP measurement cannot provide assessment of duration of effect or of the effect of antihypertensive drugs on BP during sleep. Calcium antagonists have been increasingly promoted as first-line antihypertensive agents,[5,6] and the development of substances with a long duration of action appears to be a major advance. Amlodipine

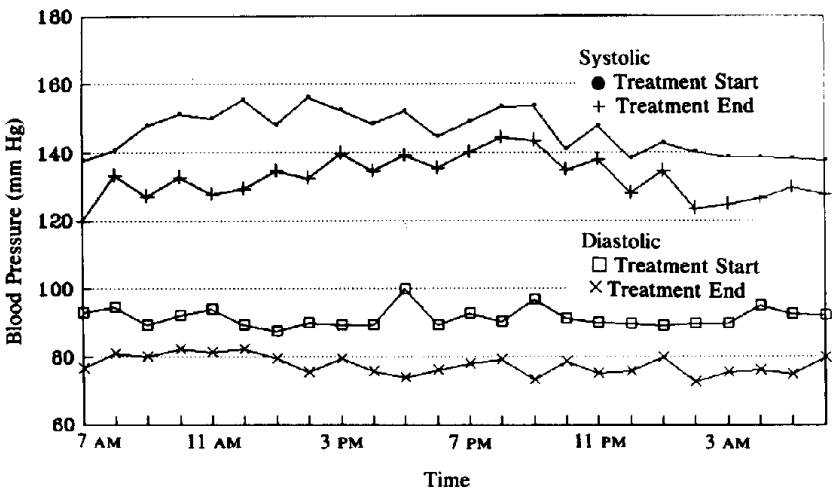

Figure 2. The hourly means for systolic and diastolic blood pressures from baseline to the end of treatment with amlodipine. There was a statistically significant difference in hourly mean systolic BP ($P = 0.008$) and hourly mean diastolic BP ($P = 0.001$) between week 0 and week 12.

Table III. Efficacy, tolerance, and acceptance of amlodipine by patients (N = 18).

	No. of Patients			
	Excellent	Good	Fair	Poor
Efficacy	14	3	1	0
Tolerance	15	1	2	0
Acceptance	15	1	1	1

Excellent = no side effects to poor = treatment was withdrawn.

has advantages over existing calcium antagonists because of its smooth onset of action and once-daily dosing with no reflex tachycardia.[7]

The study showed that a once-daily dose of amlodipine effectively lowers daytime and nighttime BP. Its efficacy in normalizing diastolic BP was 94%, with excellent or good tolerance and compliance in the majority of patients. Other studies[3,7] have reported the efficacy of amlodipine to be 91% to 95%. In comparison studies, amlodipine 5 to 10 mg once daily, was equivalent to multiple doses of other calcium antagonists.[7] Other comparison studies have demonstrated that amlodipine is as effective as captopril,[8] enalapril,[9] and atenolol[10] when given as once-daily monotherapy. However, Lacourciere et al[8] showed that amlodipine produced a greater reduction in diastolic BP than captopril.

The results of 24-hour ambulatory BP monitoring confirm that amlodipine has a significant antihypertensive effect throughout the dosing interval and a uniform effect throughout the circadian cycle[8,11–13]; there was no significant difference in BP reduction between the daytime and nighttime periods. Our findings are in accordance with those of previous studies[8,12] for amlodipine.

Side effects are important factors in the clinical use of drugs. Amlodipine in this study was well tolerated, and there were no major adverse effects. This is in contrast with most of the previous studies,[10,12,13] which reported ankle edema and headache as the most common side effects of amlodipine treatment, although these were seldom severe enough to warrant discontinuation of therapy. This absence of side effects could be because of the small number of patients studied and the short duration of the study. The absence of reflex tachycardia during amlodipine therapy had been proved by almost all studies, including this one, and could be explained by the gradual vasodilatation produced by amlodipine.

CONCLUSION

Once-daily amlodipine was effective in reducing BP in patients with mild-to-moderate hypertension and effectively reduced ambulatory BP over the

entire 24-hour period. However, this was an uncontrolled study, and controlled trials are needed to confirm these findings.

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