

Antihypertensive Efficacy of Amlodipine and Losartan after Two ‘Missed’ Doses in Patients with Mild to Moderate Essential Hypertension

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We compared the effects of amlodipine (5 – 10 mg, *n* = 94) and losartan (50 – 100 mg, *n* = 94) on the lowering of blood pressure (BP) at steady state and after two missed doses, as well as on tolerability. This was a randomized, double-blind study of 12 weeks of active treatment followed by 2 days of placebo treatment. Twenty-four-hour ambulatory blood pressure monitoring and office BP measurements were performed at baseline, week 12 and after the 2-day drug holiday. After 12 weeks, amlodipine

was significantly more effective than losartan in reducing both 24-h systolic blood pressure (SBP) (–18.0 versus –10.8 mmHg) and diastolic blood pressure (DBP) (–10.6 versus –8.0 mmHg). While mean SBP and DBP for both treatments increased comparably during the drug holiday, BP values remained significantly lower than baseline for both treatments. The superior BP-lowering effect of amlodipine compared with losartan was maintained during the drug holiday.

KEY WORDS: AMLODIPINE; LOSARTAN; ANTIHYPERTENSIVE DRUGS; HYPERTENSION; AMBULATORY BLOOD PRESSURE MONITORING; DRUG HOLIDAY; THERAPEUTIC COVERAGE

Introduction

Hypertension is a major risk factor for cardiovascular disease, the course of which can be modified with therapy. Although effective antihypertensive drugs are widely available, high blood pressure (BP) remains

poorly treated. In Latin America, it is estimated that 53% of the cardiovascular disease burden is attributable to suboptimal BP control.¹

Even when antihypertensive treatment is initiated, < 50% of the patients reach

recommended BP goals^{2,3} primarily as a result of insufficient up-titration/combination of drugs and poor compliance.^{4,5} On the basis of a review of compliance rates observed in multiple studies in which electronic monitoring was used, the mean compliance rate observed for 17 hypertension studies was 73% (range, 39 – 93%).⁶

Regular antihypertensive treatment is necessary to reduce the risk of target organ damage associated with increased morbidity and mortality. Even among patients with mild hypertension, long-term compliance with antihypertensive therapy lowered BP and provided clinical benefit.⁷ In addition, damage to target organs is more closely correlated to BP measured by 24-h ambulatory BP monitoring (ABPM) than to measurements made in the doctor's office.^{8–11} Long-term damage seems to be related to BP variability within the 24 h.^{9,12,13} Therefore, therapeutic coverage over a 24-h period is necessary to diminish the potential for damage to target organs.

Ideally, antihypertensive treatment should not only provide stable therapeutic coverage between doses, but should also provide a prolonged therapeutic effect in the event that one or more doses are missed. Amlodipine besylate, a dihydropyridine calcium-channel blocker with a half-life of 35 – 50 h,¹⁴ has demonstrated therapeutic coverage for up to 3 days after the last dose in a non-comparative study¹⁵ and a favourable safety profile.¹⁶

Losartan, the first drug belonging to the angiotensin II receptor inhibitor class, is a prodrug that is converted in the liver to an active metabolite with a half-life of 6 – 9 h. Losartan has a duration of activity of at least 24 h after a 50 mg dose and it has a good safety profile.¹⁷ The efficacy of losartan after occasional missed doses has only been evaluated in one study.¹⁸

The primary purpose of this study was to compare the effects on BP control of missing two consecutive doses of amlodipine and losartan after the drugs were taken daily for 12 weeks in patients aged ≥ 18 years with mild-to-moderate essential hypertension. Additionally, this study compared the efficacy and tolerability of the two drugs in this study population.

Patients and methods

STUDY DESIGN

This was a randomized, double-blind, double-dummy, parallel group, flexible-dose escalation study designed to compare the efficacy and tolerability of amlodipine and losartan following two consecutive missed doses after 12 weeks of treatment (steady state). Seventeen investigators in six countries in Central and South America undertook the study. The trial was conducted according to the principles in the Declaration of Helsinki and was approved prior to study start by the appropriate ethics review committees and health authorities. All patients gave their written informed consent to participate in the study.

PATIENTS

Male and female patients aged 18 – 79 years who had mild to moderate essential hypertension and who had not taken antihypertensive medications for at least 4 weeks prior to randomization were eligible for enrolment. Mild to moderate hypertension was defined as: (i) an average of two diastolic blood pressure (DBP) readings > 95 mmHg but not > 115 mmHg in the sitting position, documented on two separate occasions at least 1 week apart (provided the difference was not > 10 mmHg); and (ii) a baseline mean daytime ambulatory DBP measurement > 90 mmHg.

Exclusion criteria were as follows: angina pectoris; myocardial infarction; stroke; transitory ischaemic attack; balloon dilatation of the coronary arteries or coronary bypass operation within the previous 3 months; clinical heart failure (New York Heart Association classes II – IV); serious arrhythmia; history of secondary hypertension; hepatic dysfunction (liver function test values exceeding two times the upper limit of normal); renal impairment (serum creatinine > 150 $\mu\text{mol/l}$); symptomatic orthostatic hypotension; malignant hypertension or systolic blood pressure (SBP) > 200 mmHg and/or DBP > 115 mmHg; or a history of alcohol or drug abuse or psychological or other emotional problems. Also excluded from participation were female patients who were pregnant, breast-feeding, or of child-bearing age who were not using appropriate contraception; patients taking concomitant medications that could alter BP; medical conditions that would interfere with the ability to complete the study; and known hypersensitivity to calcium channel blockers of the same class or to angiotensin II receptor inhibitors.

TREATMENT REGIMEN

After a 4-week, single-blind, placebo, washout period, patients were randomly assigned to receive 5 mg amlodipine or 50 mg losartan orally once daily for the first 6 weeks of treatment. If sitting DBP was > 90 mmHg after 6 weeks, the dose was doubled to 10 mg amlodipine or 100 mg losartan once daily. After the 12-week treatment period, patients received identical placebo capsules for 2 days in order to simulate two missed doses of antihypertensive medication (i.e. a drug holiday). Patients were instructed to take their study medication daily at breakfast, except in the morning of a study visit

when medication was taken after all clinical evaluations had been completed.

PROCEDURES

Each patient underwent 24-h ABPM at the end of the 4-week placebo period, at the end of the 12-week treatment period and during the 2-day drug holiday (48-h ABPM). During ABPM, BP was measured every 15 min from 06.00 to 22.00 h and every 30 min from 22.00 to 06.00 h. The ABPM measurements were started in the morning between 08.00 and 10.00 h, before study medication was taken, and the next dose was not taken until after the ABPM had been completed. Efficacy parameters assessed were daytime BP (06.00 – 22.00 h), night-time BP (00.00 – 06.00 h), mean 24-h BP and BP load (percentage of ABPM measurements above 140/90 mmHg during the day and above 120/80 mmHg at night). Differences between baseline and steady state (week 12) and between baseline and the second 24-h interval of the 2-day drug holiday were compared by treatment group. The ABPM was repeated if < 80% of the measurements were available or if ≥ 2 h of consecutive measurements were missing.

Sitting BP measurements were taken at each study visit (i.e. at the end of weeks –4, –1, 0, 6, 12 and week 12 + 2 days [end of the 2-day drug holiday]). BP was measured in the same arm by the same clinical personnel using a conventional sphygmomanometer and the appropriate cuff size. The measurements were performed after 5 min of rest with the patient in the sitting position. DBP readings were recorded with the disappearance of Korotkoff Phase V sounds. Each BP determination consisted of two consecutive measurements, 2 min apart. The average of the two measurements was used for statistical analysis.

SAFETY AND TOLERABILITY

All adverse events volunteered by the patient or observed by the investigator regardless of suspected causality were recorded during the study and for 30 days after the patient completed or discontinued participation in the study.

STATISTICAL ANALYSIS

The primary efficacy end-point was the comparison between the treatment groups of the mean changes in ABPM values (SBP and DBP) for the last 9 h of monitoring between the end of treatment (week 12) and the end of the drug holiday (week 12 + 2 days). The last 9-h ABPM was the mean of all ABPM measurements taken from 23.00 to 08.00 h. Efficacy analyses were based on patients who took at least one dose of study medication (intention-to-treat population) and had at least one efficacy evaluation performed during or after treatment.

Pairwise comparisons of treatment differences in the mean changes in the last 9-h ABPM were evaluated using analysis of variance (ANOVA) and a generalized linear model (SAS Institute, Cary, NC, USA). Other treatment comparisons (baseline versus steady state and baseline versus end of the 2-day drug holiday), other ABPM variables and sitting BP employed the same ANOVA model as in the primary response analysis.

The proportion of BP readings above 140/90 mmHg during waking hours and above 120/80 mmHg during sleep (described as the BP load) was calculated and differences between the treatments were also assessed by ANOVA. Analysis of efficacy response variables excluded patients with missing data. All statistical tests of significance were performed as two-sided tests. P -values ≤ 0.05 were considered statistically significant.

Results

PATIENT CHARACTERISTICS

A total of 194 patients were randomized. Amlodipine was received by 97 patients, three of whom withdrew from the study before the final visit as a result of therapeutic failure (one patient) and protocol violations (two patients). Losartan was also received by 97 patients and three of them discontinued as a result of loss to follow-up (one patient), protocol violation (one patient) and adverse reaction (one patient [unrelated to treatment]).

Mean patient age and duration of hypertension were slightly greater in the losartan group (Table 1). Most patients were < 65 years of age (84% in the amlodipine group and 76% in the losartan group). There were no significant differences between treatment groups in age range, gender, race, weight, height, body mass index, or the proportion of patients who had concomitant diseases or took concomitant medications during the study (Table 1).

The median duration of treatment was 85 days for both treatment groups. Daily doses of amlodipine and losartan were doubled at the week-6 visit to 10 mg and 100 mg, respectively, for 54 of 97 patients (55.6%) receiving amlodipine and for 73 of 97 patients (75.3%) receiving losartan. The mean daily dose of amlodipine was 7.8 mg and the mean daily dose of losartan was 87.7 mg.

ABPM AND OFFICE BP MONITORING DATA

After 12 weeks of treatment (steady state), mean reductions in SBP were significantly greater ($P < 0.001$) for patients who received amlodipine than for those who received losartan, based on ABPM (last 9 and 24 h) and office visit (sitting) measurements (Tables 2, 3 and 4, respectively). For example, the mean \pm SD last 9-h SBP at steady state was

TABLE 1:
Baseline patient characteristics by treatment group: amlodipine (5 – 10 mg daily) and losartan (50 – 100 mg daily)

Characteristic	Amlodipine	Losartan
Number of patients	97	97
Age (years)	51.8 ± 10.7	55.4 ± 10.3
Age range (years)	26 – 75	33 – 72
Age group (n, %)		
18 – 44 years	26 (27)	16 (16)
45 – 64 years	55 (57)	58 (60)
≥ 65 years	16 (16)	23 (24)
Gender (male/female)	41/56	45/52
Race (white/black/other)	38/16/43	40/12/45
Weight (kg)	72.3 ± 13.8	72.7 ± 13.9
Height (cm)	161.6 ± 9.7	162.6 ± 10.9
Body mass index (kg/m ²)	27.6 ± 4.3	27.4 ± 4.0
Duration of hypertension (years)	7.2 ± 7.9	10.1 ± 9.1
Concomitant disease present at study entry (n, %)	45 (46.4)	47 (48.5)
Concomitant medication taken during study (n, %)	41 (42.3)	41 (42.3)

Values are mean ± SD unless otherwise specified.

123.6 ± 13.7 mmHg for amlodipine and 133.0 ± 19.1 mmHg for losartan ($P = 0.0001$). Mean reductions in DBP were also significantly greater ($P < 0.05$) for patients who received amlodipine compared with losartan, based on ABPM (24 h) and office visit (sitting) measurements only. For example, the mean ± SD 24-h DBP at steady state was 84.5 ± 8.2 mmHg for amlodipine and 88.3 ± 9.5 mmHg for losartan.

Based on the last 9 h, 24 h and office visit measurements (Tables 2, 3 and 4, respectively), increases in mean ± SD SBP were observed during the 2-day drug holiday that were comparable between the treatment groups; they ranged from 4.5 ± 11.1 to 5.9 ± 11.6 mmHg for amlodipine and from 4.3 ± 10.0 to 6.0 ± 13.3 mmHg for losartan. However, after the 2-day drug holiday, the mean SBP values were significantly lower for both treatments when compared with baseline values ($P < 0.001$), with reductions in the amlodipine group (mean ± SD

changes from $-13.3 ± 16.0$ mmHg to $-15.4 ± 14.7$ mmHg) still significantly ($P < 0.01$) greater than those in the losartan group (mean ± SD changes from $-5.8 ± 15.2$ mmHg to $-7.8 ± 16.1$ mmHg).

Based on the last 9 h, 24 h and office visit measurements (Tables 2, 3 and 4, respectively), mean ± SD increases in DBP were also observed during the 2-day drug holiday and were comparable between treatment groups. The increases ranged from 1.8 ± 8.4 to 3.3 ± 7.3 mmHg for amlodipine and 2.4 ± 5.7 to 2.8 ± 7.1 mmHg for losartan. However, after the 2-day drug holiday, the mean DBP values, like the SBP values, were still significantly lower for both treatments compared with their baseline values ($P = 0.0001$), with reductions in the amlodipine group (mean ± SD changes from $-8.4 ± 11.8$ mmHg to $-11.0 ± 8.6$ mmHg) significantly greater than those in the losartan group (mean ± SD changes from $-5.1 ± 9.3$ mmHg to $-6.5 ± 10.1$ mmHg) ($P < 0.05$).

Antihypertensive efficacy of amlodipine and losartan

TABLE 2:
Mean ambulatory blood pressure results for the last 9 h of monitoring by treatment group: amlodipine (5 – 10 mg daily) and losartan (50 – 100 mg daily)

Characteristic	Amlodipine		Losartan		P-value ^a
	No. of patients	Mean ± SD	No. of patients	Mean ± SD	
SBP (mmHg) ^b					
Baseline	93	141.7 ± 17.3	92	143.1 ± 18.2	
Steady state	93	123.6 ± 13.7	92	133.0 ± 19.1	
Change		-18.0 ± 13.9		-10.1 ± 13.7	0.0001
Baseline	91	141.3 ± 17.2	90	143.2 ± 18.4	
2-day drug holiday	91	128.0 ± 14.9	90	137.4 ± 18.4	
Change		-13.3 ± 16.0		-5.8 ± 15.2	0.001
Steady state	91	122.9 ± 13.2	91	132.8 ± 19.3	
2-day drug holiday	91	127.8 ± 14.9	91	137.2 ± 18.4	
Change		4.9 ± 12.5		4.4 ± 10.1	NS
DBP (mmHg) ^b					
Baseline	93	89.5 ± 9.9	92	90.4 ± 8.8	
Steady state	93	79.2 ± 8.7	92	82.7 ± 10.2	
Change		-10.3 ± 10.0		-7.7 ± 8.7	NS
Baseline	91	89.3 ± 10.0	90	90.4 ± 8.9	
2-day drug holiday	91	80.9 ± 9.9	90	85.3 ± 10.6	
Change		-8.4 ± 11.8		-5.1 ± 9.3	<0.05
Steady state	91	78.8 ± 8.5	91	82.4 ± 10.3	
2-day drug holiday	91	80.8 ± 9.9	91	85.2 ± 10.6	
Change		2.1 ± 10.4		2.8 ± 7.1	NS

SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, not significant.

^aBetween-treatment comparison (ANOVA model with fixed treatment and centre effects).

^bBaseline ambulatory blood pressure monitoring (ABPM) was conducted at the end of the 4-week placebo run-in period. Steady-state ABPM was conducted at the end of the 12-week treatment period. Drug holiday ABPM was conducted after 2 days of placebo medication that simulated missed doses of antihypertensive therapy.

TABLE 3:
Summary of the mean ambulatory blood pressure results for the last 24 h of monitoring by treatment group: amlodipine (5 – 10 mg daily) and losartan (50 – 100 mg daily)

Characteristic	Amlodipine		Losartan		P-value ^a
	No. of patients	Mean ± SD	No. of patients	Mean ± SD	
SBP (mmHg) ^b					
Baseline	94	147.8 ± 14.2	92	149.5 ± 14.9	
Steady state	94	129.9 ± 11.4	92	138.7 ± 17.3	
Change		-18.0 ± 11.4		-10.8 ± 12.2	0.0001
Baseline	91	147.5 ± 14.2	90	149.6 ± 15.0	
2-day drug holiday	91	133.9 ± 13.9	90	143.3 ± 15.7	
Change		-13.6 ± 13.5		-6.3 ± 13.2	< 0.001
Steady state	92	129.3 ± 10.9	91	138.9 ± 17.4	
2-day drug holiday	92	133.8 ± 13.8	91	143.2 ± 15.7	
Change		4.5 ± 11.1		4.3 ± 10.0	NS

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TABLE 3 (continued):
Summary of the mean ambulatory blood pressure results for the last 24 h of monitoring by treatment group: amlodipine (5 – 10 mg daily) and losartan (50 – 100 mg daily)

Characteristic	Amlodipine		Losartan		P-value ^a
	No. of patients	Mean ± SD	No. of patients	Mean ± SD	
DBP (mmHg) ^b					
Baseline	94	95.2 ± 8.1	92	96.3 ± 7.2	
Steady state	94	84.5 ± 8.2	92	88.3 ± 9.5	
Change		-10.6 ± 8.0		-8.0 ± 8.4	< 0.05
Baseline	91	95.0 ± 8.1	90	96.3 ± 7.3	
2-day drug holiday	91	86.1 ± 9.0	90	90.8 ± 9.8	
Change		-9.0 ± 9.5		-5.5 ± 8.6	< 0.05
Steady state	92	84.3 ± 8.0	91	88.4 ± 9.4	
2-day drug holiday	92	86.1 ± 9.0	91	90.8 ± 9.8	
Change		1.8 ± 8.4		2.4 ± 5.7	NS

SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, not significant.

^aBetween-treatment comparison (ANOVA model with fixed treatment and centre effects).

^bBaseline ambulatory blood pressure monitoring (ABPM) was conducted at the end of the 4-week placebo run-in period. Steady-state ABPM was conducted at the end of the 12-week treatment period. Drug holiday ABPM was conducted after 2 days of placebo medication that simulated missed doses of antihypertensive therapy.

TABLE 4:
Summary of the mean office visit sitting blood pressure results by treatment group: amlodipine (5 – 10 mg daily) and losartan (50 – 100 mg daily)

Characteristic	Amlodipine		Losartan		P-value ^a
	No. of patients	Mean ± SD	No. of patients	Mean ± SD	
SBP (mmHg) ^b					
Baseline	94	156.5 ± 13.2	94	158.9 ± 14.4	
Steady state	94	134.9 ± 12.4	94	145.2 ± 17.2	
Change		-21.6 ± 12.6		-13.7 ± 16.4	<0.001
Baseline	93	156.3 ± 13.1	93	158.9 ± 14.4	
2-day drug holiday	93	140.9 ± 16.9	93	151.1 ± 18.2	
Change		-15.4 ± 14.7		-7.8 ± 16.1	<0.001
Steady state	94	135.1 ± 12.7	93	145.1 ± 17.3	
2-day drug holiday	94	140.9 ± 16.8	93	151.1 ± 18.2	
Change		5.9 ± 11.6		6.0 ± 13.3	NS
DBP (mmHg) ^b					
Baseline	94	102.2 ± 6.1	94	102.5 ± 6.0	
Steady state	94	87.9 ± 8.8	94	93.5 ± 9.3	
Change		-14.3 ± 7.7		-9.0 ± 8.8	0.0001
Baseline	93	102.1 ± 6.0	93	102.5 ± 6.0	
2-day drug holiday	93	91.1 ± 10.6	93	96.1 ± 11.3	
Change		-11.0 ± 8.6		-6.5 ± 10.1	0.001
Steady state	94	87.8 ± 8.7	93	93.5 ± 9.3	
2-day drug holiday	94	91.1 ± 10.5	93	96.1 ± 11.3	
Change		3.3 ± 7.3		2.6 ± 7.7	NS

SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, not significant.

^aBetween-treatment comparison (ANOVA model with fixed treatment and centre effects).

^bBaseline ambulatory blood pressure monitoring (ABPM) was conducted at the end of the 4-week placebo run-in period. Steady-state ABPM was conducted at the end of the 12-week treatment period. Drug holiday ABPM was conducted after 2 days of placebo medication that simulated missed doses of antihypertensive therapy.

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DAYTIME AND NIGHT-TIME ABPM

Daytime (06.00 – 22.00 h) and night-time (00.00 – 06.00 h) ABPM results were in accordance with the last 9 h and 24 h ABPM and office BP results (Table 5).

BP LOAD

At baseline, SBP/DBP measurements were above 140/90 mmHg in the daytime and above 120/80 mmHg at night for similar percentages of patients in both treatment

TABLE 5: Summary of the mean daytime and night-time ambulatory blood pressure results from baseline to steady state and to the 2-day drug holiday by treatment group: amlodipine (5 – 10 mg daily) and losartan (50 – 100 mg daily)

Characteristic	Amlodipine		Losartan		P-value ^a
	No. of patients	Mean ± SD	No. of patients	Mean ± SD	
SBP (mmHg) ^b					
Daytime (06.00 – 22.00 h)					
Baseline	94	150.4 ± 13.7	92	152.3 ± 14.5	
Steady state	92	132.2 ± 11.1	92	141.7 ± 17.1	
Change		-18.1 ± 11.5		-10.6 ± 12.3	0.0001
2-day drug holiday					
Baseline	91	150.0 ± 13.8	90	152.5 ± 14.6	
2-day drug holiday	91	136.3 ± 14.1	90	146.2 ± 15.4	
Change		-13.8 ± 13.5		-6.3 ± 13.9	<0.001
Night-time (00.00 – 06.00 h)					
Baseline	93	137.7 ± 18.7	92	139.3 ± 19.3	
Steady state	93	120.0 ± 15.2	92	128.0 ± 19.5	
Change		-17.7 ± 14.5		-11.3 ± 14.1	<0.01
2-day drug holiday					
Baseline	90	137.4 ± 18.6	90	139.3 ± 19.5	
2-day drug holiday	90	123.2 ± 16.0	90	132.7 ± 19.6	
Change		-14.2 ± 16.3		-6.7 ± 14.9	<0.01
DBP (mmHg) ^b					
Daytime (06.00 – 22.00 h)					
Baseline	94	97.7 ± 8.2	92	99.1 ± 7.4	
Steady state	94	86.8 ± 8.4	92	91.1 ± 9.8	
Change		-11.1 ± 7.9		-7.8 ± 8.8	<0.05
2-day drug holiday					
Baseline	91	97.5 ± 8.2	90	99.2 ± 7.5	
2-day drug holiday	91	88.3 ± 9.3	90	93.5 ± 10.2	
Change		-9.3 ± 9.5		-5.7 ± 9.4	<0.05
Night-time (00.00 – 06.00 h)					
Baseline	93	85.9 ± 11.0	92	87.1 ± 9.7	
Steady state	93	75.7 ± 9.5	92	78.3 ± 11.4	
Change		-10.2 ± 10.6		-8.8 ± 9.1	NS
2-day drug holiday					
Baseline	90	85.9 ± 11.0	90	87.0 ± 9.8	
2-day drug holiday	90	77.1 ± 10.3	90	81.1 ± 11.9	
Change		-8.7 ± 11.8		-5.9 ± 9.2	NS

SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, not significant.

^aBetween-treatment comparison (ANOVA model with fixed treatment and centre effects).

^bBaseline ambulatory blood pressure monitoring (ABPM) was conducted at the end of the 4-week placebo run-in period. Steady-state ABPM was conducted at the end of the 12-week treatment period. Drug holiday ABPM was conducted after 2 days of placebo medication that simulated missed doses of antihypertensive therapy.

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groups. At steady state and even after the 2-day drug holiday, however, a greater decrease in BP load was observed among patients who received amlodipine (Table 6).

SAFETY AND TOLERABILITY

Adverse events were experienced by 40 of 97 patients (41.2%) who received amlodipine and 32 of 97 patients (33.0%) who received losartan. They were generally mild and none of them resulted in discontinuation. The two most frequently reported adverse events were oedema (10 patients [10.3%] in the amlodipine group and four patients [4.1%] in the losartan group) and headache (eight patients [8.2%] in the amlodipine group and

seven patients [7.2%] in the losartan group). Adverse events considered to be related to treatment were reported for 14 patients (14.4%) in the amlodipine group and eight patients (8.2%) in the losartan group. One serious adverse event (thrombocytopenia) was observed in a patient in the losartan group, but was not related to treatment.

Discussion

The purpose of this study was to compare the effects on BP of missing two consecutive (daily) doses of amlodipine and losartan after a 12-week (steady-state) period and to compare the efficacy and tolerability of these treatments in a cohort of patients aged ≥ 18

TABLE 6: Summary of the mean daytime and night-time blood pressure load at baseline, steady state and the 2-day drug holiday by treatment group: amlodipine (5 – 10 mg daily) and losartan (50 – 100 mg daily)

Blood pressure load ^a	Amlodipine		Losartan		P-value ^a
	No. of patients	Mean ± SD	No. of patients	Mean ± SD	
SBP (mmHg) ^b					
Daytime (06.00 – 22.00 h)					
Baseline	96	70% ± 27%	96	74% ± 24%	NS
Steady state	95	29% ± 26%	93	50% ± 31%	0.0001
2-day drug holiday	92	38% ± 29%	88	60% ± 30%	0.0001
Night-time (00.00 – 06.00 h)					
Baseline	96	79% ± 27%	96	81% ± 29%	NS
Steady state	94	43% ± 34%	93	61% ± 36%	<0.001
2-day drug holiday	91	51% ± 36%	91	67% ± 35%	<0.01
DBP (mmHg) ^b					
Daytime (06.00 – 22.00 h)					
Baseline	96	72% ± 20%	96	76% ± 18%	NS
Steady state	95	37% ± 27%	89	52% ± 27%	<0.001
2-day drug holiday	92	42% ± 27%	91	57% ± 28%	<0.001
Night-time (00.00 – 06.00 h)					
Baseline	96	63% ± 32%	96	68% ± 30%	NS
Steady state	94	32% ± 30%	93	41% ± 33%	0.05
2-day drug holiday	91	38% ± 30%	91	47% ± 36%	<0.05

SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, not significant.

^aBetween-treatment comparison (ANOVA model with fixed treatment and centre effects).

^bBaseline ambulatory blood pressure monitoring (ABPM) was conducted at the end of the 4-week placebo run-in period. Steady-state ABPM was conducted at the end of the 12-week treatment period. Drug holiday ABPM was conducted after 2 days of placebo medication that simulated missed doses of antihypertensive therapy.

years with mild to moderate essential hypertension.

The decrease in treatment efficacy during the last 9 h was similar for the two drugs after two missed doses (SBP/DBP $4.9 \pm 12.5/2.1 \pm 10.4$ mmHg in the amlodipine group and $4.4 \pm 10.1/2.8 \pm 7.1$ mmHg in the losartan group). The results were consistent using the other BP variables.

Although most of the patients in the present study were of age < 65 years, age is not considered to have played a major role in the study outcome since a study in patients > 65 years has shown similar results.¹⁸ Despite more frequent up-titration in the losartan group (75.3% versus 55.5%), amlodipine was significantly more effective in reducing SBP and DBP (by most measures) than losartan. These efficacy results are comparable with results observed after 12 weeks of treatment with either amlodipine or losartan in previous studies.^{19,20} Both of these studies suggested that amlodipine monotherapy was as potent as losartan plus hydrochlorothiazide.

In the present study the 24-h BP-lowering effect was still statistically significant for both drugs after two missed doses but a greater reduction from baseline was maintained for amlodipine (SBP/DBP $13.6 \pm 13.5/9.0 \pm 9.5$ mmHg) than losartan ($6.3 \pm 13.2/5.5 \pm 8.6$ mmHg) ($P < 0.001/P < 0.05$).

Approximately half of daytime BP measurements were over 140/90 mmHg in the losartan group compared with about one-third in the amlodipine group. Night-time measurements showed that approximately 60% of SBP measurements in the losartan group were above 120 mmHg

compared with 40% in the amlodipine group. Night-time measurements of DBP > 80 mmHg were 40% and 30% for losartan and amlodipine, respectively. The duration of action of amlodipine in this study is consistent with those in previous studies in which it was compared with enalapril, felodipine, nifedipine GITS, diltiazem and losartan in the elderly population.^{18,21–25}

Treatment with either amlodipine or losartan was well tolerated; no patient in either treatment group withdrew from the study as a result of treatment-related adverse events and only one serious adverse event (unrelated to treatment) was observed. Adverse events (all-cause and treatment-related) were experienced by a higher percentage of patients who received amlodipine (41% and 14%, respectively) than of those who received losartan (33% and 8%, respectively). The two most frequently occurring all-cause adverse events in either treatment group were oedema and headache.

In conclusion, this study shows that the rate of BP increase was similar for amlodipine and losartan after the 2-day drug holiday. Although SBP and DBP values remained significantly lower than baseline in both groups after the drug holiday, patients should be encouraged to adhere strictly to their treatment regimen.

Acknowledgement

This research was supported by Pfizer, Inc.

Conflicts of interest

No conflicts of interest were declared in relation to this article.

- Received for publication 7 March 2006 • Accepted subject to revision 5 May 2006
- Revised accepted 25 June 2007

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