

# A Comparison of the Efficacy and Duration of Action of Candesartan Cilexetil and Losartan as Assessed by Clinic and Ambulatory Blood Pressure After a Missed Dose, in Truly Hypertensive Patients A Placebo-Controlled, Forced Titration Study

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The purpose of this double-blind, forced titration study was to compare the antihypertensive effect duration of candesartan cilexetil, which has a long-lasting binding to the human AT<sub>1</sub>-receptor, to that of losartan on ambulatory BP (ABP) not only during the 24-h dosing interval but also during the day of a missed dose intake. After a 4-week placebo lead-in period, 268 patients with sitting diastolic BP 95 to 110 mm Hg and mean awake ambulatory DBP  $\geq$ 85 mm Hg were randomized to receive either 8 mg of candesartan, 50 mg of losartan, or placebo for a 4-week period. Thereafter, the doses were doubled in all patients for an additional 4-week period. Ambulatory BP monitoring was performed for 36 h after dosing and clinic BP measured 48 h after dosing.

Candesartan cilexetil (16 mg) reduced ABP to a significantly greater extent than 100 mg of losartan, particularly for systolic ABP during daytime ( $P < .05$ ), nighttime ( $P < .05$ ), and 24-h ( $P < .01$ ) periods, systolic ( $P < .01$ ) and diastolic ( $P < .05$ ) ABP between 0 and 36 h, and both systolic ( $P < .001$ ) and diastolic ( $P < 0.001$ ) ABP during the day of a missed dose. Clinic BP at 48 h after dosing was significantly reduced exclusively with 16 mg of candesartan. The differences in BP reduction between 8 mg of candesartan and 50 mg of losartan were statistically significant for systolic ABP

during daytime ( $P < .01$ ), nighttime ( $P < .05$ ), 24-h ( $P < .01$ ), 0 to 36 h ( $P < .05$ ) and during the day of missed dose ( $P < .05$ ). Moreover, although losartan did not significantly reduce ambulatory BP in a dose-related manner, ambulatory systolic and diastolic BP reductions with 16 mg of candesartan were significantly greater ( $P < .01$  and  $< .001$ ) than those seen with 8 mg of candesartan during every period at the ABP supporting a dose-response relationship.

In conclusion, this forced titration study in ambulatory hypertensive patients demonstrates that candesartan cilexetil provides significant dose-dependent reduction in both clinic and ambulatory BP in doses ranging from 8 to 16 mg once daily. Furthermore, candesartan cilexetil is superior to losartan in reducing systolic ABP and in controlling both systolic and diastolic ABP on the day of a missed dose. The differences observed between both agents are most likely attributable to a tighter binding to, and a slower dissociation from, the receptor binding site with candesartan cilexetil. Am J Hypertens 1999;12:1181-1187  
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Angiotensin II (Ang II) receptor blockers, a new class of antihypertensive agents, inhibit the renin-angiotensin system by selectively blocking the AT<sub>1</sub> subtype of Ang II receptor.<sup>1</sup> Angiotensin II receptor blockers exert similar antihypertensive effects as angiotensin-converting enzyme (ACE) inhibitors.<sup>2,3</sup> However, the specificity of action of Ang II receptor blockers avoids the major ACE inhibitor-associated adverse reactions, cough and angioedema, which probably result from nonspecific interference with bradykinin metabolism.<sup>4</sup>

Losartan, the first of this new class of therapeutic agents, has produced significant reductions in blood pressure (BP) during clinical trials.<sup>2,5</sup> Candesartan cilexetil is a novel long-acting Ang II type I receptor antagonist that has been shown to exert an antihypertensive effect lasting 24 h.<sup>6</sup> Clinical studies have indicated that 8 or 16 mg once daily are suitable maintenance doses for the treatment of hypertension.<sup>7</sup> Moreover, it was recently demonstrated that candesartan cilexetil in the range of 2 to 32 mg once daily effectively reduces BP in a dose-related manner.<sup>8</sup> Candesartan cilexetil has been demonstrated to have a tight binding and slow dissociation rate from the AT<sub>1</sub> receptor,<sup>9</sup> whereas losartan appears to have a shorter lasting receptor binding.<sup>10</sup> Thus, there is reason to believe that candesartan cilexetil will offer a longer and more sustained antihypertensive effect than losartan, not only during the 24-h dosing interval but also during the first hours of a day of a missed dose intake.

The purpose of this study was to determine the differences in the antihypertensive effect duration between 8 to 16 mg of candesartan cilexetil taken once daily and 50 to 100 mg of losartan taken once daily in mild to moderate hypertensive patients. Because casual BP is a rather poor predictor of the daily BP profile,<sup>11</sup> mean ambulatory awake BP was used to establish the clinical diagnosis of hypertension. To our knowledge, this was the largest forced titration study to date comparing the antihypertensive efficacy of Ang II receptor blockers only in patients with hypertension documented by ambulatory BP.

## METHODS

**Patient Selection** Outpatients with mild to moderate essential hypertension who were aged 20 to 80 years were eligible for enrollment in this study. The subjects

were of either sex and any race. Outpatients who had received previous treatment for hypertension as well as those who were just diagnosed were eligible. Women were either surgically sterile, postmenopausal, or practicing an adequate method of contraception. Exclusion criteria included concomitant diseases that would present safety hazards, concomitant medications that directly or indirectly act on BP, and patients who worked during the night and slept during the day. The study was approved by the Investigational Review Board of each institution participating in the study and written informed consent was obtained from all patients before enrollment. The study was conducted in accordance with Declaration of Helsinki and the principles of Good Clinical Practice.

**Study Design** The study was of a multi-center (Canada and France), double-blind, double-dummy, placebo-controlled, three-arm parallel-group design with forced dose titration. The groups were unbalanced 3:3:1 with candesartan cilexetil: losartan: placebo, respectively. All previous antihypertensive agents were withdrawn after consent and before a 4-week single-blind placebo lead-in period. At the end of this phase, only patients with a mean sitting diastolic BP of 95 to 110 mm Hg, a mean sitting systolic BP of <200 mm Hg, and an awake (from drug intake to 10:00 PM) mean diastolic ambulatory BP of  $\geq 85$  mm Hg were randomized to the double-blind treatment with either 8 mg of candesartan cilexetil or 50 mg of losartan or placebo once daily. After 4 weeks, the daily dose was doubled in all patients for another 4 weeks. Patients with a clinic seated systolic BP >200 mm Hg or a diastolic BP >110 mm Hg (in two readings within 1 week) during the double-blind period were withdrawn from study. Candesartan cilexetil and matching placebo were manufactured by Astra Hassle AB Sweden. Losartan (50 mg) and matching placebo were obtained commercially. For blinding purposes, both the losartan and the placebo were encapsulated. In vitro dissolution tests as well as a bioequivalence study in healthy subjects insured that the characteristics of the losartan tablet was not altered by the encapsulation.<sup>12</sup> To preserve blinding of the treatment regimens, the double-dummy technique was used.

**Procedures** At all clinic visits, BP and heart rate measurements were taken using a fully automated device, which provided printouts of the results (OMRON HEM-705 CP). This device has been validated and found to be consistent with the requirements of the British Hypertension Society.<sup>13</sup> Clinic BP measurements were obtained at trough dose time, that is,  $24 \pm 2$  h after the previous dose. In addition, clinic BP assessments were performed in all Canadian centers at  $48 \pm 2$  h after dosing. At each occasion, sitting BP was

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measured three times, at least 1 min apart, after the patient was rested in a quiet room for at least 5 min. The mean of the three measurements were used in the data analyses. One measurement of BP and heart rate was also made after 2 min of standing.

Ambulatory BP monitoring (ABPM) using a portable Spacelab 90207 monitoring device, was performed during the 36 h after drug intake on regular working days at the end of the placebo run-in period (baseline) and after 4 (low dose) and 8 (high dose) weeks of double-blind therapy. The cuff was placed on the non-dominant arm and BP was registered automatically every 15 min from 6:00 AM to 10:00 PM and every 30 min from 10:00 PM to 6:00 AM. The accuracy of the monitors was validated by cross-checking, with a T-tube assembly to carefully obtained sphygmomanometer readings. The means of three of the clinic and ambulatory diastolic BPs were required to match within  $\pm 5$  mm Hg. The medication was then administered. On the day that the monitoring was completed, dubious readings were edited out for further analysis. The following quality control criteria were established as standards for acceptability for each ABPM report: 1) a minimum of 24 and 36 h, respectively, of data after dose; 2) a minimum of 75% of the readings had to be valid; 3) a minimum of one acceptable reading per hour during hours 23 and 24 after dose had to be available; and 4) a maximum of 2 consecutive h of missing data on only one occasion was permitted. When quality control criteria were not met, the ABPM was repeated between 1 and 7 days after the failed monitoring.

**Safety** The possibility of adverse events was investigated from the documentation of spontaneously reported complaints and also from direct nonleading questioning about side effects at the end of the placebo period and at each visit during the double-blind treatment phase.

**Statistical Analyses** All statistical analyses presented are based on the intent-to-treat data set (ie, all patients who took at least one dose of the double-blind study medication and for whom there was at least one measurement on an efficacy outcome). ABP measurements not meeting the quality criteria were set as missing. Analysis of covariance (ANCOVA) was applied to the assessments of changes based on adjustment for treatment factors. The linear model included treatment, center, and the interaction treatment by center as factors, and baseline values as a covariate. Centers having few patients were pooled to obtain a more balanced design. Both *P* values and 95% confidence intervals based on the estimated mean squares from the ANCOVA were used to estimate mean treatment differences. The differences in the proportion of responders (sitting diastolic BP at 24 h after dose  $\leq 90$

TABLE 1. PATIENT CHARACTERISTICS AT BASELINE

	Placebo (n = 37)	Candesartan Cilexetil (n = 116)	Losartan (n = 115)
Age (mean yr)	55	55	55
Gender (n)			
Male	21	72	72
Female	16	43	43
Race (n)			
White	36	112	109
Black	0	2	4
Oriental	1	1	2
BMI (kg/m <sup>2</sup> ) (male/female)	29/27	28/28	29/28
Mean clinic BP (mm Hg)			
Systolic baseline	163.3	162.1	160.6
Diastolic baseline	99.7	101.3	100.1
Mean awake ambulatory BP (mm Hg)			
Systolic baseline	154.6	155.1	153.0
Diastolic baseline	100.3	101.8	100.2

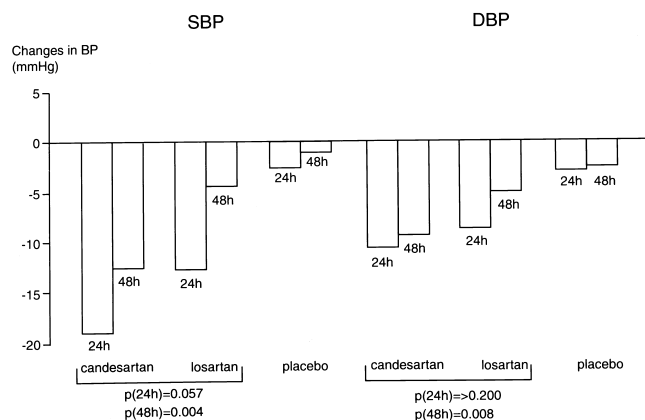
BP, blood pressure; BMI, body mass index.

mm Hg or a reduction of 10 mm Hg or more from baseline to the end of the study) were analyzed by using the Mantel-Haenszel  $\chi^2$  test stratified for center.

## RESULTS

**Patient Characteristics** A total of 363 outpatients from 11 centers in Canada and France were enrolled in the study. Hypertension was not documented by ABPM (mean awake diastolic ABP  $< 85$  mm Hg) in 46 patients (12.7%) who were considered to have white coat hypertension. Another 49 patients were not randomized due to other reasons. A total of 268 fully qualified patients were randomized to double-blind treatment (116 to candesartan cilexetil, 115 to losartan, and 37 to placebo). After randomization, patients who discontinued for any reason included: 10 from the candesartan group, 15 from the losartan group, and 5 from the placebo group. Thus, 238 patients completed the 8-week, double-blind period and met the quality criteria for 24-h ABPM, and of these 214 patients also met the quality criteria for 36-h ABPM. The treatment groups did not differ significantly in their baseline characteristics such as age, gender distribution, race, body mass index, clinic and ambulatory BP (Table 1).

**Effects on Clinic BP and Heart Rate** Changes in mean clinic sitting systolic and diastolic BP at 24 h (251 patients) and at 48 h (129 patients) after dose from baseline to the end of the study are illustrated in Figure 1. Compared with placebo treatment, both 16



**FIGURE 1.** Mean changes from baseline to week 8 in sitting systolic (SBP) and sitting diastolic (DBP) blood pressure at 24 and 48 h after dose in patients treated with candesartan cilexetil 16 mg, losartan 100 mg, or placebo.

mg of candesartan cilexetil and 100 mg of losartan once daily significantly ( $P < .001$ ) reduced systolic and diastolic BP 24 h after dose with a trend for a greater reduction ( $P = .057$ ) in systolic BP with candesartan cilexetil. Although the effect of losartan on systolic and diastolic BP at 48 h after dose was not significantly different from that of placebo, candesartan cilexetil was significantly ( $P < .01$ ) more effective than placebo in reducing both systolic and diastolic BP. Moreover, the differences in systolic ( $P = .004$ ) and diastolic BP ( $P = .008$ ) reductions between candesartan and losartan were statistically significant. The results after 4 weeks of treatment were nearly similar to those after 8 weeks. Although, the differences in BP reductions between 8 mg of candesartan and 50 mg of losartan were not statistically significant, the adjusted mean difference (95% CI) between the two treatments amounted to 3.9 mm Hg ( $-7.9, 0.2$ ) and 1.5 mm Hg ( $-4.0, 1.1$ ) for systolic and diastolic BP, respectively, 24 h after dose and to 3.2 mm Hg ( $-9.3, 2.9$ ) and 2.2 mm Hg ( $-5.5, 1.1$ ) for systolic and diastolic BP, respectively, 48 h after dose.

The adjusted mean changes when increasing the dose of 8 mg of candesartan cilexetil to 16 mg in clinic systolic ( $-5.5$  mm Hg [95% CI  $-8.4$  to  $-2.6$ ];  $P < .1$ ) and diastolic ( $-2.8$  mm Hg [95% CI  $-4.3$  to  $-1.3$ ];  $P < .01$ ) BP 24 h after dose and in systolic ( $-10.7$  mm Hg [95% CI  $-16.9$  to  $-4.4$ ];  $P < .01$ ) and diastolic ( $-4.9$  mm Hg [95% CI  $-8.7$  to  $-1.2$ ];  $P < .01$ ) BP 48 h after dose were all statistically significant. In contrast, the adjusted mean changes from increasing 50 mg of losartan 100 mg in clinic systolic ( $-2.9$  mm Hg [95% CI  $-5.9$  to  $0.1$ ];  $P = \text{NS}$ ) and diastolic ( $-2.2$  mm Hg [95% CI  $-3.8$  to  $-0.7$ ];  $P < .05$ ) BP 24 h after dose and in systolic ( $-5.5$  mm Hg [95% CI  $-12.1$  to  $1.1$ ];  $P = \text{NS}$ ) and diastolic ( $-2.6$  mm Hg [95% CI  $-6.5$  to  $1.4$ ];  $P =$

NS) BP 48 h after dose were much lower with statistical significance seen only for the 24-h after dose diastolic BP.

The results for standing BP were similar to those observed in the sitting position. Heart rate remained unchanged during the study in all treatment groups. The percentage of responders who were characterized as having a sitting diastolic BP  $\leq 90$  mm Hg or a decrease from baseline  $\geq 10$  mm Hg at the end of the double-blind therapy was 17% in the placebo group, 66% in the candesartan group, and 56% in the losartan group. The proportion of responders were significantly ( $P < .001$ ) higher for the candesartan cilexetil and losartan groups than for the placebo group.

**Effects on ABP** Mean reductions (95% CI) in ambulatory systolic and diastolic BP from baseline to 4 weeks of treatment with 8 mg of candesartan or 50 mg of losartan and to 8 weeks of treatment with 16 mg of candesartan or 100 mg of losartan for the different time intervals obtained during the 36-h monitoring period are given in Table 2. After 8 weeks of double-blind therapy, a minimal ( $-0.6$  to  $-2.2$  mm Hg) and statistically nonsignificant placebo response was observed, as expected with ABP measurements in truly hypertensive patients during all periods. The dose of 16 mg of candesartan cilexetil produced significantly greater reductions in systolic BP during daytime ( $P < .05$ ), nighttime ( $P < .05$ ), and 24-h ( $P < .01$ ) periods of the first 24 h monitored than did 100 mg of losartan. Moreover, 16 mg of candesartan cilexetil reduced both systolic and diastolic ambulatory BP to a significantly greater extent than 100 mg of losartan when measured 0 to 36 h after dose (Figure 2). In particular, the reduction in mean systolic and diastolic ambulatory BP during the day of a missed dose (6:00 AM to 6:00 PM) was significantly ( $P < .001$ ) better maintained with candesartan cilexetil than with losartan.

After 4 weeks of treatment, the differences in mean diastolic ABP reductions with 8 mg of candesartan cilexetil or 50 mg of losartan were not statistically different (Table 2 and Figure 2). However, the reductions (95% CI) in mean systolic ABP were significantly greater with 8 mg of candesartan cilexetil versus 50 mg of losartan during daytime ( $P < .01$ ), nighttime ( $P < .05$ ), 24-h ( $P < .01$ ), 0 to 36 h ( $P < .05$ ) periods and during the day of a missed dose ( $P < .05$ ).

The additional adjusted mean changes in ABP from low to high doses of candesartan cilexetil (8 or 16 mg) and of losartan (50 or 100 mg) are shown in Table 3. The differences in systolic and diastolic BP obtained when increasing 50 mg of losartan to 100 mg did not reach statistical significance. In contrast, BP reductions with 16 mg of candesartan cilexetil were significantly greater than those seen with 8 mg of candesartan

TABLE 2. MEAN CHANGES IN AMBULATORY BLOOD PRESSURE (mm Hg) FROM BASELINE VALUES FOR CANDESARTAN 8 AND 16 mg VERSUS LOSARTAN 50 AND 100 mg AT WEEKS 4 AND 8

Blood Pressure and Periods	Candesartan 8 mg (24 h, n = 109) (36 h, n = 97)	Losartan 50 mg (24 h, n = 106) (36 h, n = 95)	Candesartan 16 mg (24 h, n = 106) (36 h, n = 94)	Losartan 100 mg (24 h, n = 100) (36 h, n = 93)
<b>Systolic</b>				
Daytime	-12.3 (-14.3-10.3)***††	-8.4 (-10.4-6.4)***	-14.5 (-16.8-12.3)***†	-10.3 (-12.6-8.0)***
Nighttime	-10.7 (-12.8-8.6)***†	-6.9 (-9.0-4.8)***	-12.4 (-14.8-10.0)***†	-8.2 (-10.7-5.7)*
24 h	-11.6 (-13.4-9.8)***††	-7.7 (-9.5-6.0)***	-13.4 (-15.4-11.3)***††	-9.3 (-11.4-7.1)***
36 h	-10.8 (-12.5-9.1)***†	-7.1 (-8.8-5.5)***	-12.5 (-14.5-10.5)***††	-8.3 (-10.3-6.3)***
Daytime (Missed dose)	-9.6 (-11.5-7.7)***†	-6.3 (-8.2-4.4)**	-11.9 (-14.0-9.7)***†††	-6.1 (-8.2-4.0)**
<b>Diastolic</b>				
Daytime	-7.6 (-8.9-6.2)***	-6.0 (-7.3-4.6)***	-9.4 (-10.9-7.9)***	-7.7 (-9.3-6.2)***
Nighttime	-6.5 (-8.0-5.0)***	-4.8 (-6.3-3.4)**	-8.2 (-9.9-6.5)***	-5.8 (-7.5-4.1)*
24 h	-7.2 (-8.4-6.0)***	-5.6 (-6.7-4.4)***	-8.7 (-10.1-7.4)***	-6.9 (-8.3-5.5)***
36 h	-6.7 (-7.9-5.6)***	-5.2 (-6.3+1)**	-8.3 (-9.7-7.0)***†	-6.1 (-7.4-4.7)***
Daytime (Missed dose)	-6.0 (-7.4-4.7)***	-4.7 (-6.0-3.4)*	-8.0 (-9.5-6.5)***†††	-4.5 (-6.0-3.1)*

Values are mean (95% confidence intervals) \* P < .05, \*\* P < .01, \*\*\* P < .001 versus placebo; † P < .05, †† P < .01, ††† P < .001 versus losartan.

Datime was defined as 6:00 AM–10:00 PM, nighttime as 10:00 PM–6:00 AM and daytime (missed dose) as 6:00 AM–10:00 PM.

cilexetil during every period of the ABPM supporting a dose–response relationship.

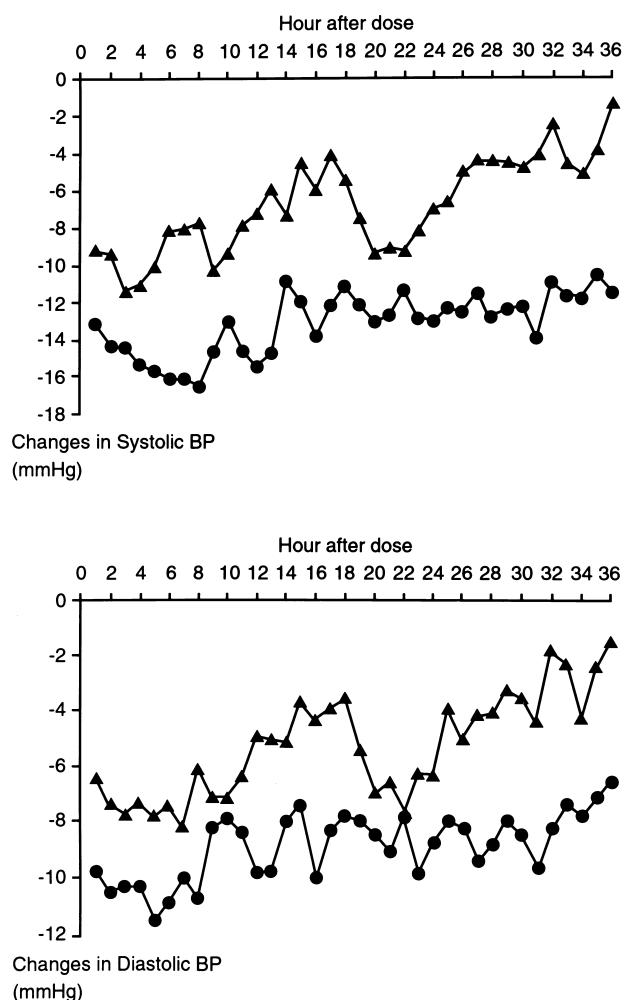
**Clinical and Laboratory Safety** There were no significant differences between the placebo-, candesartan cilexetil-, and losartan-treated groups in the frequency of adverse events. Adverse events were reported in 17 (46%) of the 37 patients receiving placebo, 49 (43%) of 115 receiving candesartan cilexetil, and 52 (45%) of 115 receiving losartan. The most common adverse event was headache with a crude rate of 12 to 16% in the different treatment groups. One patient in each treatment group discontinued because of adverse events; the patient in the placebo group withdrew because of pruritus, whereas the patient in the candesartan group withdrew because of fatigue and depression, and the patient in the losartan group, after an automobile accident. Two patients (one with septicemia and the other with inguinal hernia) of 115 in the candesartan cilexetil group and 2 patients (one with thrombophlebitis and pulmonary embolism, the other after a car accident) of 115 in the losartan group reported serious adverse events during double-blind treatment. Changes in routine laboratory variables, liver or kidney functions were negligible. None of the differences between candesartan cilexetil and losartan were significant. There were no clinically significant changes in electrocardiogram or physical examination results.

## DISCUSSION

This double-blind, placebo-controlled study in which patients were force titrated to either 16 mg of candesartan cilexetil or 100 mg of losartan, represents a

rigorous approach to the evaluation of new antihypertensive agents. Indeed, in contrast to the standard parallel-dose design, the present study allowed us to gather data at two dose levels in all patients studied. In this study, both 8 or 16 mg of candesartan cilexetil and 50 or 100 mg of losartan significantly decreased both systolic and diastolic clinic BP as compared to placebo 24 h after dosing, with no clearcut differences between the two treatments, although there was a trend in favor of candesartan cilexetil for systolic BP. However, 16 mg of candesartan cilexetil provided a significantly greater antihypertensive effect than 100 mg of losartan on systolic and diastolic BP 48 h after drug intake. In addition, there was evidence for dose-related antihypertensive effect on both systolic and diastolic clinic BP 24 and 48 h after dosing for candesartan when increasing the dose from 8 to 16 mg.

In recent years, ABPM has proved to be more reliable than the casual measurement of BP at the physician's office for evaluating and comparing the efficacy and duration of action of antihypertensive drugs.<sup>14,15</sup> In contrast to clinic BP results, the ABPM results of the present study showed that treatment with 16 mg of candesartan was associated with a greater reduction in diastolic BP during 22 to 24 h, 0 to 36 h, and on the day of missed dose than was treatment with 100 mg of losartan. More important, both 8 and 16 mg of candesartan cilexetil reduce systolic BP to a significantly greater extent than 50 and 100 mg of losartan during each period of the 36-h monitoring. These findings may be relevant in clinical practice as ABP has been shown to be an independent predictor of cardiovas-



**FIGURE 2.** Mean changes from baseline to weeks 4 and 8 in ambulatory blood pressure during 36 h after dose in patients treated with candesartan cilexetil 8 to 16 mg (●) or losartan 50 to 100 mg (▲).

cular risk.<sup>16</sup> Furthermore, the greater effect on systolic BP will result in a larger reduction of the pulse pressure, which has also been recently demonstrated to be an independent predictor of all cause, cardiovascular, and especially, coronary mortality.<sup>17</sup>

The duration of action of both candesartan cilexetil and losartan beyond 24 h was assessed in the present study by ABPM during the day of a missed dose and by clinic determinations of BP 48 h after dose intake. After 8 weeks in the study, almost twice as great a reduction in both systolic and diastolic ABP was seen with 16 mg of candesartan cilexetil as compared with 100 mg of losartan. Nearly similar findings were observed with 8 mg of candesartan cilexetil on ambulatory systolic BP. For practical reasons it was not possible to perform a full 48-h ABPM, but in a subset of patients ( $n = 129$ ), the clinic BP at 48 h after the

previous dose was measured. A significantly greater and dose-dependant reduction in both clinic systolic and diastolic BP was seen with 16 mg of candesartan cilexetil than with 100 mg of losartan. Our data showing a dose-response relationship in both clinic and ambulatory systolic and diastolic BP with candesartan cilexetil administered once daily are in contrast with previous reports showing no additional reduction in BP with losartan administered once daily at doses  $>50$  mg.<sup>2</sup> However, 50 mg of losartan twice daily showed a greater antihypertensive effect on ambulatory BP than 50 mg daily,<sup>5</sup> suggesting that twice-a-day administration of losartan may be needed in patients not adequately controlled with the once-a-day regimen.<sup>5</sup>

The apparent differences in antihypertensive efficacy and duration of action between candesartan cilexetil and losartan demonstrated in this study may be reflective of recent pharmacodynamic data. In vitro, the Ang II inhibitory effect during a drug wash-out period persisted much longer for candesartan cilexetil than for losartan and EXP 3174, the active metabolite of losartan.<sup>18</sup> These in vitro differences were confirmed with in vivo experiments. In healthy human volunteers, the in vivo Ang II receptor blocker effect of candesartan was approximately twofold greater than that of losartan and it persisted for longer.<sup>19</sup> These findings suggest that candesartan cilexetil has a higher affinity for and a slower off-rate from the site of action compared to losartan. The observed duration of action of candesartan during the present study suggest that this Ang II receptor blocker may provide added confidence of therapeutic coverage in

**TABLE 3. ADDITIONAL ADJUSTED MEAN CHANGES (mm Hg) IN AMBULATORY BLOOD PRESSURE (95% CI) FROM LOW TO HIGH DOSES OF CANDESARTAN (8–16 mg) AND LOSARTAN (50–100 mg)**

Blood Pressure and Periods	Candesartan Cilexetil	Losartan
Systolic		
Daytime	-2.6 (-4.3-0.9)*	-1.3 (-3.0+0.5) <sup>NS</sup>
Nighttime	-2.3 (-4.4-0.3)*	-1.2 (-3.3+0.8) <sup>NS</sup>
0-24 h	-2.2 (-3.6-0.7)*	-1.1 (-2.6+0.4) <sup>NS</sup>
0-36 h	-2.2 (-3.7+0.8)†	-1.0 (-2.4+0.5) <sup>NS</sup>
Daytime (missed dose)	-2.6 (-4.5-0.8)*	-0.1 (-1.8+2.0) <sup>NS</sup>
Diastolic		
Daytime	-2.1 (-3.3-0.9)*	-1.2 (-2.4, 0.0) <sup>NS</sup>
Nighttime	-2.1 (-3.5-0.7)*	-1.2 (-2.7+0.2) <sup>NS</sup>
0-24 h	-1.9 (-2.9-0.9)†	-1.0 (-2.0, 0.0) <sup>NS</sup>
0-36 h	-1.9 (-2.9-0.9)†	-0.9 (-1.0+0.2) <sup>NS</sup>
Daytime (missed dose)	-2.2 (-3.6-0.8)*	0.2 (-1.2+1.6) <sup>NS</sup>

\*  $P < .01$ ; †  $P < .001$  versus candesartan 8 mg. NS; not significant versus losartan 50 mg.

many patients who may not be 100% compliant with their once-daily medication regimen.

In conclusion, in patients with mild to moderate hypertension documented by ABPM, this forced titration study demonstrates that candesartan cilexetil provides significant dose-dependent reductions in both clinic and ambulatory BP in doses ranging from 8 to 16 mg once daily. Moreover, candesartan cilexetil is superior to losartan in reducing systolic ambulatory BP and in controlling systolic as well as diastolic ABP on the day of a missed dose. This may have important clinical applications.

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