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A placebo-controlled comparison of the efficacy and tolerability of candesartan cilexetil, 8 mg, and losartan, 50 mg, as monotherapy in patients with essential hypertension, using 36-h ambulatory blood pressure monitoring

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SUMMARY

This double-blind, randomised, controlled study compared the efficacy of candesartan cilexetil 8 mg ($n = 87$) and losartan 50 mg ($n = 89$), once daily for 6 weeks, relative to placebo ($n = 80$) in patients with mild-to-moderate essential hypertension (diastolic blood pressure (DBP): 95–115 mmHg). Ambulatory BP measurements were done every 15 min over 36 h.

At the end of the 6-week treatment, the mean change in DBP between the baseline and the 0–24-h period after the last dose of study medication was greater in patients receiving candesartan cilexetil 8 mg (-7.3 mmHg $\pm$ 6.9 mmHg) compared with losartan 50 mg (-5.1 mmHg $\pm$ 4.9 mmHg) ($p < 0.05$) or placebo (0.3 mmHg $\pm$ 6.5 mmHg) ($p < 0.001$). The mean change in systolic BP (SBP) during this time was greater in patients receiving candesartan cilexetil 8 mg (-10.8 mmHg $\pm$ 11.3 mmHg), or losartan 50 mg (-8.8 mmHg $\pm$ 8.9 mmHg) than placebo (1.2 mmHg $\pm$ 9.9 mmHg) ($p < 0.001$). Candesartan cilexetil 8 mg was associated with a greater reduction in DBP and SBP, relative to placebo, when compared with losartan 50 mg, during both daytime and night-time, and between 12 and 24 h after dosing ($p < 0.001$). Both active treatments were well tolerated.

In patients with mild-to-moderate essential hypertension, candesartan cilexetil 8 mg therefore had greater, more consistent antihypertensive efficacy throughout the day and the night, and long-lasting efficacy after the last dose, compared with losartan 50 mg. This greater efficacy is maintained with an excellent tolerability associated with members of the angiotensin Il type 1-receptor blocker class.

Keywords: Hypertension; ambulatory blood pressure measurement; antihypertensive drug treatment; candesartan cilexetil

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INTRODUCTION

Hypertension is the major treatable cause of cardiovascular mortality in the industrialised world (1), and recent national and international guidelines emphasise the benefits of reducing blood pressure (BP) (2–4). Indeed, even small BP reductions, when achieved at a population level, can result in major reduction in cardiovascular risk (5). Thus, even small differences in efficacy between different antihypertensive drugs could lead to substantial differences in population outcome.

Five classes of antihypertensive agents are now recommended for the first-line treatment of hypertension; the newest addition to this list is the angiotensin Il type 1 (AT_1)-receptor blocker class (2). AT1-receptor blockers represent a class of effective and well-tolerated orally active antihypertensive drugs. All these drugs have the common properties of blocking the AT_1 receptor thereby relaxing vascular smooth muscle, increasing salt excretion, decreasing cellular hypertrophy and inducing antihypertensive effects without modifying heart rate and cardiac output (6). These agents effectively control hypertension when given once daily and cause no significant adverse effects or laboratory abnormalities (7,8). Thus, fewer adverse events were reported for AT_1-receptor blocker therapy compared with other antihypertensive medication such as beta-blockers and angiotensin-converting enzyme (ACE) inhibitors. In addition, the effectiveness of AT_1-receptor blocker therapy in reducing clinical events such as stroke or end-stage renal disease in hypertension and associated conditions has been shown in a number of large trials (9–11). AT_1-receptor blockers are therefore differentiated from each other on the basis of the magnitude and duration of their antihypertensive effects.

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Losartan was the first available AT_1-receptor blocker, and many others have since become available. Of these, candesartan cilexetil shows particularly tight and long-lasting binding to the AT_1-receptor. Indeed, in a review published in 1999, candesartan cilexetil had the highest AT_1-receptor-binding affinity of those compounds tested, which were ranked in the following order (highest affinity = 1): candesartan cilexetil (1), saprisartan (1), zolasartan (3), irbesartan (5), valsartan (10), telmisartan (10), EXP-3174 (the active metabolite of losartan) (10), tasosartan (20), losartan (50), eprosartan (100) (12).

The most reliable way of determining whether members of the AT_1-receptor blocker class are similarly distinguished from each other at a clinical level is by performing a direct, head-to-head comparison. The present paper compares directly the antihypertensive efficacy and tolerability of two AT_1-receptor blockers, candesartan cilexetil 8 mg (13–16), and losartan 50 mg (17–20), in adult patients with mild-to-moderate essential hypertension, using clinic measurements and 36-h ambulatory BP monitoring (ABPM). At the time of the start of this trial, these were the maximum approved doses of candesartan cilexetil and losartan in France, although guidelines in other countries at that time recommended a maximum candesartan cilexetil dose of 16 mg and a maximum losartan dose of 100 mg per day. ABPM was used, because such measurements correlate more closely with target-organ damage and are more reliable in predicting clinical outcomes, compared with clinic BP measurements (21). ABPM also avoid the problem of so-called 'white-coat' or 'office' hypertension – the tendency for BP to increase above its everyday level as a result of the often subconscious physiological stress induced in patients by their visits to a clinic (22). ABPM also enables BP to be assessed throughout the dosing interval, so that diurnal fluctuations can be observed and permit reliable information to be obtained on clinical efficacy at night and during the latter part of the dosing interval (23). Finally, ABPM allows to provide multiple BP measurements and to increase the power of the study.

MATERIALS AND METHODS

Patient Characteristics at Baseline

We enrolled a total of 433 patients from 126 general practitioner centres and 28 cardiology centres. They were then screened for inclusion in the study. Subjects were men or women, aged 18–75 years, with mild-to-moderate essential hypertension [diastolic BP (DBP) of 95–115 mmHg after a 2- or 4-week placebo run-in period].

The main exclusion criteria were severe hypertension, secondary hypertension, heart failure (NYHA class III or IV), myocardial infarction within the previous 6 months, heart valve abnormalities, angina pectoris, arrhythmia, history of stroke, severe renal impairment (creatinine clearance <30 ml/min, Cockcroft method), severe hepatic impairment (aspartate aminotransferase or alanine aminotransferase greater than twice the upper normal limit, gammaglutamyl transpeptidase greater than three times the upper normal limit) and serum potassium >5.0 mmol/l. Patients were also excluded, if contraindicated for renin-angiotensin system interventions or if hypersensitive to any component of the study medications. This study complies with the Declaration of Helsinki and was approved by an independent ethics committee (Grenoble, France). Written informed consent was obtained from all patients prior to their inclusion in the study.

Treatment

All patients recruited to the study entered an initial placebo run-in period. The run-in lasted 14 days for patients who had not previously received antihypertensive treatment and 28 days for patients who had received previous therapy. Previous antihypertensive medications were discontinued during this 28-day placebo phase. Other treatments prohibited during the study included antiarrhythmic and antiangina agents, drugs with vasodilator or systemic vasoconstrictor activity, immunosuppressant and cytotoxic drugs, lithium, antithyroid medication, long-term corticosteroid and no steroid anti-inflammatory drugs.

Patients completing the placebo run-in were randomised in equal numbers to receive double-blind treatment with candesartan cilexetil 8 mg, losartan 50 mg or placebo, once daily for 6 weeks.

BP and Heart Rate Measurement

Clinic BP was assessed in triplicate using a mercury sphygmomanometer after the patients had rested in a lying position for 10 min, and the mean of each set of three values determined. Heart rate was also measured in triplicate while patients were lying, and the mean value determined. Ambulatory DBP and SBP were measured for 36 h in each patient before the first dose, and 0–36 h after the last dose of study medication. Ambulatory BP values were determined and recorded automatically at 15-minute intervals by a brachial pressure monitor (Spacelabs^{TM} Model 90207, Spacelabs Medical, Redmond, WA, USA), worn on the nondominant arm that was kept intentionally still during monitoring cycles while the patient was awake. ABPM data were analysed centrally on the return of the monitor to the clinic.

Primary Endpoint

The primary efficacy variable was the change in mean ambulatory DBP from the baseline to the 0–24-h period after the last dose of study medication.

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Secondary Endpoints

Secondary variables were:

1 Changes in ambulatory SBP from the baseline to the 0–24-h period after the last dose of study medication,
2 Changes in ambulatory DBP and SBP from the baseline to the 0–36-h period after the last dose of study medication,
3 Changes in DBP and SBP during the daytime (7 am to 10 pm) and night-time(10 pm to 7 am),
4 Changes in DBP and SBP between 12 and 24 h after dosing,
5 Changes in heart rate between the baseline and the end of the 6-week study period,
6 Tolerability of study medication.

Statistical Analyses

Data were divided into two populations. The safety population comprised all patients randomised to double-blind treatment. The intention-to-treat (ITT) efficacy population comprised all patients who had received at least one dose of study medication and who had provided at least one complete recording of ambulatory DBP made over a 24-h period after dosing.

Baseline characteristics for both the ITT and the safety population were summarised, with comparisons of baseline variables between treatment groups made using two-sided *t*-tests (for quantitative variables) or χ^2 tests (for qualitative variables). Normal data distribution and homogeneity of variance were confirmed by comparing actual normal probability plots and scatter plots of residuals with their predicted values.

Efficacy comparisons between treatment groups were made using ANOVA followed by *t*-tests. In addition, any effects of treatment-by-baseline and treatment-by-centre interactions were assessed by analysis of covariance, with interaction terms disregarded if not significant.

Statistical significance for all efficacy comparisons was set at the 5% level.

Between-group comparisons of adverse event incidences were made on a nonstatistical basis.

Sample Size

The calculation of sample size for the ABPM analysis was based on the results of a previous study (24), and these results suggest that the standard deviation of the mean for change in ambulatory DBP between the 12th and the 24th hour (the main criterion adopted in this study) is close to 10 mmHg. Furthermore, the minimum improvement of clinical value was taken as 5 mmHg. Assuming a dropout rate of approximately 10% and a number of 'white coat' patients of 20%, the required number of evaluable patients per treatment group was 69 (two-sided *t*-test) to allow statistically meaningful conclusions to be reached, a p-value <0.05 was considered statistically significant. Allowing for withdrawals or failure to provide data, we therefore set an overall enrolment target of 270 patients.

RESULTS

Patient Availability

Of the 433 screened individuals, 123 patients did not progress beyond the placebo run-in, for reasons including failure to comply with inclusion criteria, loss to follow-up and withdrawal of consent. A total of 310 patients, completed the placebo run-in, were randomised and received at least one dose of study medication (safety population). Fifty-four of these 310 patients were excluded from the efficacy (ITT) population, because they did not provide at least one complete set of 24-h ambulatory DBP measurements. The efficacy (ITT) population therefore comprised 256 patients.

Baseline Characteristics of Patients

The efficacy (ITT) population consisted of 153 men (59.8%) and 103 women (40.2%). Middle-aged patients (aged 45–65 years) formed the greatest proportion (64.8%) of this population, in which the mean age was 54.2 years. Patients aged >65 years represented 16% of the ITT population. Baseline patient characteristics are summarised in Table 1. There were no significant differences between treatment groups for any of these baseline variables.

Primary Efficacy Variable

Changes in DBP (baseline to 0–24-h period after dosing). The mean change in DBP between the baseline and the 0–24-h period after the last dose of study medication was significantly greater in patients receiving candesartan cilexetil 8 mg (-7.3 mmHg $\pm$ 6.9 mmHg) than in patients receiving losartan 50 mg (-5.1 mmHg $\pm$ 4.9 mmHg, $p < 0.05$), or placebo (0.3 mmHg $\pm$ 6.5 mmHg, $p < 0.001$) (Figure 1).

Secondary Efficacy Variables

Changes in SBP (baseline to 0–24-h period after dosing). The mean change in SBP between the baseline and the 0–24-h period after the last dose of study medication was significantly greater ($p < 0.001$) in patients receiving candesartan cilexetil 8 mg (-10.8 mmHg $\pm$ 11.3 mmHg), or losartan 50 mg (-8.8 mmHg $\pm$ 8.9 mmHg), compared with those receiving placebo ($+1.2$ mmHg $\pm$ 9.9 mmHg) (Figure 1). There was no difference of the mean change in SBP between candesartan cilexetil and losartan groups.

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Table 1 Baseline characteristics of patients (intention-to-treat population, mean ± SD)

	Candesartan cilexetil 8 mg (n = 87)	*Losartan 50 mg (n = 89)*	*Placebo (n = 80)*	*Total (n = 256)*
Sex				
Male	53 (60.9%)	49 (55.1%)	51 (63.8%)	153 (59.8%)
Female	34 (39.1%)	40 (44.9%)	29 (36.2%)	103 (40.2%)
Age range (years)				
<45	20 (23.0%)	18 (20.2%)	11 (13.8%)	49 (19.1%)
45–54	29 (33.4%)	29 (32.6%)	21 (26.3%)	79 (30.9%)
55–59	12 (13.8%)	15 (16.9%)	16 (20.0%)	43 (16.8%)
60–65	17 (19.5%)	8 (9.0%)	19 (23.7%)	44 (17.2%)
>65	9 (10.3%)	19 (21.3%)	13 (16.2%)	41 (16.0%)
Age (years)	54 ± 11	54 ± 11	56 ± 11	54 ± 11
Family history of hypertension	59 (57%)	52 (50%)	54 (54%)	165 (54%)
Current antihypertensive therapy	31 (35.6%)	28 (31.5%)	33 (41.3%)	92 (35.9%)
Clinic SBP (mmHg)	160 ± 14	161 ± 15	162 ± 16	161 ± 15
Clinic DBP (mmHg)	101 ± 6	101 ± 6	100 ± 5	101 ± 5
Resting HR (bpm)	75 ± 11	75 ± 9	72 ± 10	74 ± 10
24-h SBP (mmHg)	140 ± 14	140 ± 16	139 ± 11	139 ± 14
24-h DBP (mmHg)	91 ± 10	89 ± 9	88 ± 8	89 ± 9

DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

Changes in DBP and SBP (baseline to 0–36-h period after dosing). The mean changes in DBP and SBP between the baseline and the 0–36-h period after the last dose of study medication were −7.1 mmHg ± 6.8 and −10.3 mmHg ± 11.2 mmHg, respectively, with candesartan cilexetil 8 mg (Figure 1). This was compared with mean changes in DBP and SBP in patients receiving losartan 50 mg, of −4.7 mmHg ± 4.6 and −8.2 mmHg ± 8.8 mmHg, respectively, and of +0.2 mmHg ± 6.2 and +1.1 mmHg ± 9.2 mmHg, respectively, in patients receiving placebo. Patients receiving either active treatment had a lower BP ($p < 0.001$) than those receiving placebo. There was no difference of the mean change in SBP between candesartan cilexetil and losartan groups. Patients treated by candesartan cilexetil had a higher decrease of DBP over the 0–36-h period than those treated by losartan ($p < 0.01$).

Daytime and night-time changes in DBP and SBP. Candesartan cilexetil 8 mg was associated with mean changes in DBP (Figure 2) and SBP of −7.0 mmHg ± 7.3 and −10.0 mmHg ± 11.6 mmHg, respectively, during daytime, and of −7.0 mmHg ± 7.6 mmHg and

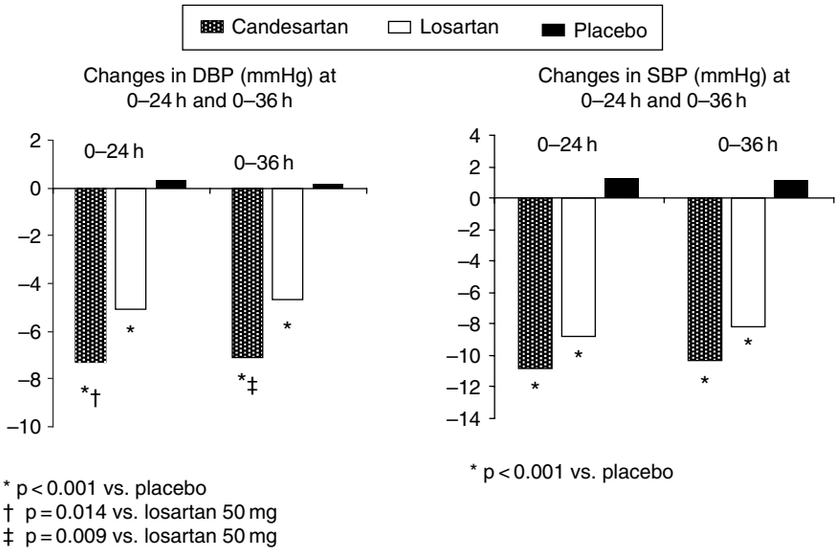

Figure 1 Mean changes from baseline in 0–24-h and 0–36-h diastolic blood pressure (DBP) and systolic blood pressure (SBP) in patients with mild-to-moderate hypertension, after 6 weeks of once-daily treatment with candesartan cilexetil 8 mg, losartan 50 mg or placebo. Data are means

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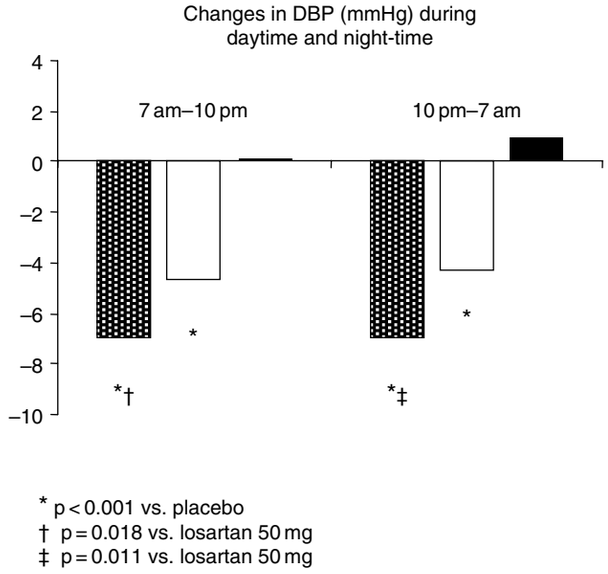

Figure 2 Mean changes from baseline in daytime (7 am to 10 pm) and night-time (10 pm to 7 am) diastolic blood pressure (DBP), in patients with mild-to-moderate hypertension receiving once-daily candesartan cilexetil 8 mg, losartan 50 mg or placebo. Data are means

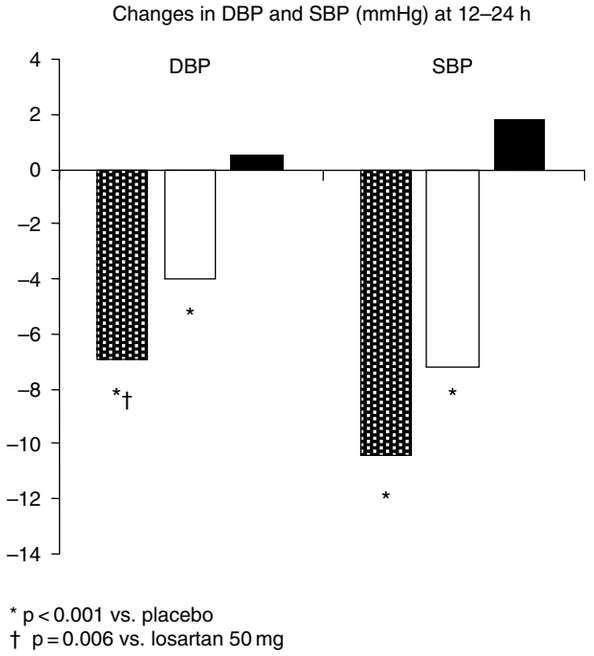

Figure 3 Mean changes in diastolic blood pressure (DBP) and systolic blood pressure (SBP) between 12 and 24 h after receiving candesartan cilexetil 8 mg, losartan 50 mg or placebo, in patients with mild-to-moderate hypertension. Data are means

-10.5 mmHg $\pm$ 12.6 mmHg, respectively, during night-time. These changes were higher for the DBP with candesartan cilexetil 8 mg than those observed in patients receiving losartan 50 mg. Indeed, with losartan, mean changes in DBP and SBP were of -4.7 mmHg $\pm$ 4.8 mmHg ($p < 0.05$) and -7.9 mmHg $\pm$ 9.5 mmHg (ns), respectively, during daytime, and of -4.3 mmHg $\pm$ 5.9 mmHg ($p < 0.05$) and -8.1 mmHg $\pm$ 10.8 mmHg (ns), respectively, during night-time. Mean changes in DBP and SBP in the placebo group were lower ($p < 0.001$) than those in the both treated groups: $+0.1$ mmHg $\pm$ 6.5 mmHg and $+0.6$ mmHg $\pm$ 9.6 mmHg, respectively, during daytime, and of $+1.0$ mmHg $\pm$ 7.3 mmHg and $+2.3$ mmHg $\pm$ 10.1 mmHg, respectively, during night-time.

Changes in DBP and SBP (12–24 h after dose). The mean changes in DBP and SBP between 12 and 24 h after dosing were -6.9 mmHg $\pm$ 7.8 mmHg and -10.4 mmHg $\pm$ 13.0 mmHg, respectively, in patients receiving candesartan cilexetil 8 mg (Figure 3). Losartan 50 mg was associated with a smaller decrease in DBP than candesartan cilexetil (-4.0 mmHg $\pm$ 5.7 mmHg, $p < 0.01$) and trended towards a smaller decrease in SBP (-7.2 mmHg $\pm$ 10.4 mmHg, $p = 0.057$), between the same two time points. These reductions were higher than changes in DBP and SBP of $+0.5$ mmHg $\pm$ 7.0 mmHg and $+1.8$ mmHg $\pm$ 10.1 mmHg, respectively, in patients receiving placebo ($p < 0.001$ for all comparisons between active treatments and placebo).

Changes in heart rate. The mean changes in heart rate from baseline to the end of the 6-week treatment period were similar in all three treatment groups (candesartan cilexetil: $+0.8$ bpm $\pm$ 5.5 bpm, losartan: $+1.9$ bpm $\pm$ 6.8 bpm, placebo: $+1.1$ bpm $\pm$ 6.4 bpm).

Tolerability. The tolerability of both active drugs in this comparative study was excellent, with no clinically significant difference in the type or incidence of adverse events compared with those reported by patients receiving placebo.

'Treatment-by-Baseline BP' and 'Treatment-by-Centre' Interactions

Covariance analysis revealed no significant 'treatment-by-baseline BP' or 'treatment-by-centre' interactions.

Compliance with Therapy

Compliance with therapy, assessed at the end of the 6-week treatment period, was similar in all three treatment groups. Ninety-seven percent of patients in the candesartan cilexetil group, 100% of those in the Iosartan group and 96% of those in the placebo group were considered highly compliant with therapy ($\geq$80% of treatment taken).

DISCUSSION

The AT_1-receptor blockers are now accepted as an important advance in hypertension therapy. All members of this drug class combine an excellent tolerability with efficacy that is at

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least as great as that of ACE inhibitors and other first-line antihypertensive drugs (25–29). However, it is important to establish if any one AT_1-receptor blocker offers efficacy benefits over any other. This is a particularly useful distinction to make, as even small differences in efficacy could have a major impact on population outcome. Moreover, recent guidelines have established that efficacy means more than just a short-term effect measured in the clinic a few hours after dosing. The ideal antihypertensive agent shows maintained efficacy throughout, and potentially beyond, the dosing interval, as many patients often forget to take their medication at the proper time.

The results of our study clearly show that treatment with candesartan cilexetil 8 mg, once daily for 6 weeks, is associated with significantly greater reductions in DBP, measured 0–24 and 0–36 h after dosing, when compared with losartan 50 mg once daily, given over the same period. This greater efficacy of candesartan cilexetil, relative to that of losartan, is consistent with the results of other direct comparisons of these two agents. The results of a number of head-to-head clinical comparisons have confirmed the superior efficacy of candesartan celexetil compared with losartan in terms of reduction in BP and maintenance of antihypertensive efficacy between doses, when compared at once daily maximum doses (30–34). A study performed in mild-to-moderate hypertensive patients has found, using ABPM, that candesartan reduced both SBP and DBP to a significantly greater extent than losartan when measured at 24 or 36 h postdose (35). As previously mentioned, there are some pharmacodynamic and pharmacokinetic differences between these AT_1-receptor blockers, which may reflect in their clinical efficacy, especially at the end of the dosing interval. It is possible that these differences may be due to molecular differences and to variations in the degree and duration of receptor blockade (36,37). In a randomised, double-blind, parallel-group study, candesartan cilexetil was shown to display the highest pharmacological potency (i.e. antagonistic activity per mg substance) of the AT_1-receptor blockers studied (losartan, irbesartan, valsartan and telmisartan) (38). Candesartan cilexetil showed a clear dose–response relationship for efficacy in the range 4–16 mg (39,40), whereas there appears to be little increase in efficacy when the dose of losartan is increased from 50 to 100 mg.

In addition, ambulatory monitoring allowed us to show that, although the antihypertensive effects of both candesartan cilexetil 8 mg and losartan 50 mg persisted for more than 24 h, the efficacy of candesartan cilexetil remained much greater than that of losartan for at least 36 h after dosing. This is consistent with the findings of other investigators (13,33,35,41). Indeed, significant antihypertensive effects of candesartan cilexetil have been detected 48 h after dosing, when the effects of losartan have virtually disappeared (35). Receptor-binding studies have shown that candesartan has the highest affinity for the AT_1 receptor and that it dissociates from the receptor more slowly than other antagonists in the class. The prolonged binding of candesartan to the receptor is reflected in a longer duration of antihypertensive action, compared with losartan (42). This suggests that in patients who might miss one 24-h dose, effective BP control is more likely to be maintained in those receiving candesartan cilexetil than in those given losartan. This observation has important practical implications, because a clinically useful antihypertensive therapy should be capable of maintaining BP reductions, even if a dose is delayed for several hours or missed altogether through patient oversight or other circumstances.

We also found that reductions in DBP in patients receiving candesartan cilexetil 8 mg were larger than the reductions associated with losartan 50 mg, regardless of whether measurements were made during the daytime (7 am to 10 pm) or during the night-time (10 pm to 7 am). The greater efficacy of candesartan cilexetil 8 mg, relative to that of losartan 50 mg, was not therefore affected by diurnal fluctuations in BP and was maintained throughout a full 24-h period. These findings are consistent with those of other reports (35). All reductions in BP, whether in patients receiving candesartan cilexetil or losartan, were also achieved without a significant change in resting heart rate.

The reductions in SBP in patients receiving candesartan cilexetil 8 mg or losartan 50 mg are also clinically important in the context of the increased recognition of the significance of elevated SBP in cardiovascular disease (43,44).

As in other clinical trials, the tolerability of candesartan cilexetil 8 mg and losartan 50 mg in this comparative study was excellent, with no clinically significant difference in the type or incidence of adverse events compared with those reported by patients receiving placebo. This was reflected in high compliance with AT_1-receptor blocker therapy over the full 6-week treatment period.

In conclusion, in patients with mild-to-moderate hypertension, candesartan cilexetil 8 mg had greater, more consistent antihypertensive efficacy, throughout both the day and the night, compared with that of losartan 50 mg. The persistence of this greater antihypertensive effect beyond the 24-h dosing interval might provide greater BP control in patients receiving candesartan cilexetil 8 mg, compared with those given losartan 50 mg, if a dose is delayed or missed. Furthermore, the superior antihypertensive effect of candesartan cilexetil 8 mg, compared with losartan 50 mg, is maintained without any compromise of the excellent tolerability that is a general characteristic of the AT_1-receptor blocker class.

REFERENCES

1 Swales JD. Current clinical practice in hypertension: the EISBERG (Evaluation and Interventions for Systolic Blood Pressure Elevation – Regional and Global) project. *Am Heart J* 1999; **138**: S232–7.

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Journal compilation © 2006 Blackwell Publishing Ltd

2 European society of hypertension – European society of cardiology guidelines. 2003 European society of hypertension – European society of cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; **21**: 1011–53.
3 Chobanian AV, Bakris GL, Black HR et al., Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, National High Blood Pressure Education Program Coordinating Committee. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. The JNC 7 Report. *JAMA* 2003; **289**: 2560–72.
4 Prise en charge des patients atteints d'hypertension artérielle essentielle. Actualization 2005: Haute Autorité de la Santé.
5 MacMahon S, Rodgers A. The effects of antihypertensive treatment on vascular disease: reappraisal of the evidence in 1994. *J Vasc Med Biol* 1994; **4**: 265–71.
6 Hernandez-Hernandez R, Sosa-Canache B, Velasco M, Armas-Hernandez MJ, Armas-Padilla MC, Cammarata R. *J Hum Hypertens* 2002; **16** (Suppl. 1): S93–9.
7 Dina R, Jafari M. Angiotensin II-receptor antagonists: an overview. *Am J Health Syst Pharm* 2000; **57**: 1231–41.
8 Moore MA. Improving the managed care of hypertension with angiotensin antagonists. *Am J Med Sci* 2002; **323**: 25–33.
9 Muller-Nordhorn J, Willich SN. Angiotensin II antagonists in the treatment of hypertension – effective and efficient? *Herz* 2003; **28**: 733–7.
10 Moore MA. Drugs that interrupt the renin-angiotensin system should be among the preferred initial drugs to treat hypertension. *J Clin Hypertens* 2003; **5**: 137–44.
11 Sleight P, Yusuf S. New evidence on the importance of the renin-angiotensin system in the treatment of higher-risk patients with hypertension. *J Hypertens* 2003; **21**: 1599–608.
12 Timmermans PB. Pharmacological properties of angiotensin II receptor antagonists. *Can J Cardiol* 1999; **15** (Suppl. F): 26F–28F.
13 Stoukides CA, McVoy HJ, Kaul AF. Candesartan cilexetil: an angiotensin II receptor blocker. *Ann Pharmacother* 1999; **33**: 1287–98.
14 Easthope SE, Jarvis B. Candesartan cilexetil: an update of its use in essential hypertension. *Drugs* 2002; **62**: 1253–87.
15 Gleiter CH, Morike KE. Clinical pharmacokinetics of candesartan. *Clin Pharmacokinet* 2002; **41**: 7–17.
16 Ostergren J. Candesartan for the treatment of hypertension and heart failure. *Expert Opin Pharmacother* 2004; **5**: 1589–97.
17 McIntyre M, Caffe SE, Michalak RA, Reid JL. Losartan, an orally active angiotensin (AT1) receptor antagonist: a review of its efficacy and safety in essential hypertension. *Pharmacol Ther* 1997; **74**: 181–94.
18 Lindenfeld J, Borer J, Armstrong PW. Losartan potassium (Cozaar). *Circulation* 2002; **105**: e9100.
19 Podzolkov VI, Bulatov VA, Son EA, Os I. Central and peripheral haemodynamic effects of losartan and combination with hydrochlorothiazide in mild to moderate essential hypertension. *Blood Press* 2003; **12**: 239–45.
20 Messerli FH. Effects of losartan in hypertension without vascular disease. *Ann Intern Med* 2004; **140**: 169–77.
21 Verdecchia P, Clement D, Faggard R, Palatini P, Parati G. Blood pressure monitoring. Task force III. Target-organ damage, morbidity and mortality. *Blood Press Monit* 1999; **4**: 303–17.
22 Lantelme P, Milon H, Gharib C, Gayet C, Fortrat JO. White coat effect and reactivity to stress: cardiovascular and autonomic nervous system responses. *Hypertension* 1998; **31**: 1021–9.
23 Smolensky MH, Portaluppi F. Ambulatory blood pressure monitoring. Application to clinical medicine and antihypertension medication trials. *Ann N Y Acad Sci* 1996; **783**: 278–94.
24 Andersson OK, Neldal S. The antihypertensive effect and tolerability of candesartan cilexetil, a new generation angiotensin II antagonist, in comparison with losartan. *Blood Press* 1998; **7**: 53–9.
25 Arakawa K, Ogihara T, Iimura O et al. Evaluation of clinical usefulness of TCV-116 (candesartan cilexetil) in patients with essential hypertension. A double-blind, parallel group comparison study using enalapril maleate as control drug. *J Clin Ther Med* 1996; **12**: 2613–21.
26 Franke H, Hermann WM, Magin SG. Comparison of the efficacy and safety of candesartan cilexetil 4, 8 and 12 mg with placebo and enalapril 10 mg in patients with mild to moderate essential hypertension. *Am J Hypertens* 1997; **10**: 90A.
27 Franke H. Antihypertensive effects of candesartan cilexetil, enalapril and placebo. *J Hum Hypertens* 1997; **11** (Suppl. 2): S61–2.
28 Himmelmann A, Keinänen-Kiukaanniemi S, Webster A, Redon J, Asmar R, Hedner T. Ambulatory assessment of once-daily candesartan cilexetil versus enalapril in patients with hypertension. *J Renin Angiotensin Aldosterone Syst* 2000; **1**: 101.
29 Zanchetti A, Omboni S, Di Biagio C. Comparison of the antihypertensive efficacy of candesartan cilexetil versus placebo or enalapril in patients with mild to moderate essential hypertension. *Am J Hypertens* 1997; **10**: 90A.
30 Gradman AH, Lewin A, Bowling BT et al. Comparative effects of candesartan cilexetil and losartan in patients with systemic hypertension. Candesartan Versus Losartan Efficacy Comparison (CANDLE) Study Group. *Heart Dis* 1999; **1**: 52–7.
31 Bakris G, Gradman A, Reif M et al., CLAIM Study Investigators. Antihypertensive efficacy of candesartan in comparison to losartan: the CLAIM study. *J Clin Hypertens* 2001; **3**: 16–21.
32 Hansson L. The relationship between dose and antihypertensive effect for different AT1-receptor blockers. *Blood Press* 2001; **10** (Suppl. 3): 33–9.
33 Meredith PA. Clinical comparative trials of angiotensin II type 1 (AT1)-receptor blockers. *Blood Press* 2001; **10** (Suppl. 3): 11–7.
34 Vidt DG, White WB, Ridley E et al., CLAIM Study Investigators. A forced titration study of antihypertensive efficacy of candesartan cilexetil in comparison to losartan: CLAIM study II. *J Hum Hypertens* 2001; **15**: 475–80.
35 Lacourcière Y, Asmar R. 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. Candesartan/lLosartan Study Investigators. *Am J Hypertens* 1999; **12**: 1181–7.
36 Burnier M, Maillard M. The comparative pharmacology of angiotensin II receptor antagonists. *Blood Press* 2001; **10** (Suppl. 1): 6–11.

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37 Ferrario C, Abdelhamed AI, Moore M. AII antagonists in hypertension, heart failure, and diabetic nephropathy: focus on losartan. *Curr Med Res Opin* 2004; **20**: 279–93.
38 Belz GG, Breithaupt-Grogler K, Butzer R, Fuchs W, Hausdorf C, Mang C. The pharmacological potency of varions AT(1) antagonists assessed by Schild regression technique in man. *J Renin Angiotensin Aldosterone Syst* 2000; **1**: 336–41.
39 Elmfeldt D, George M, Hübner R, Olofsson B. Candesartan cilexetil, a new generation angiotensin II antagonist, provides dose dependent antihypertensive effect. *J Hum Hypertens* 1997; **11** (Suppl. 2): S49–53.
40 Elmfeldt D, Olofsson B, Meredith P. The relationships between dose and antihypertensive effect of four AT1-receptor blockers. Differences in potency and efficacy. *Blood Press* 2002; **11**: 293–301.
41 Mancia G, Dell'Oro R, Turri C, Grassi G. Comparison of angiotensin II receptor blockers: impact of missed doses of candesartan cilexetil and losartan in systemic hypertension. *Am J Cardiol* 1999; **84**: 28S–34S.
42 Gradman AH. AT(1)-receptor blockers: differences that matter. *J Hum Hypertens* 2002; **16** (Suppl. 3): S9–16.
43 Ogden LG, He J, Lydick E, Whelton PK. Long-term absolute benefit of lowering blood pressure in hypertensive patients according to the JNC VI risk stratification. *Hypertension* 2000; **35**: 539–43.
44 Takagi S, Saitoh S, Nakano M et al. Relationship between blood pressure level and mortality rate: an 18-year study conducted in two rural communities in Japan. *J Hypertens* 2000; **18**: 139–44.

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