Section: Pharmacology

Original Research Article

COMPARATIVE STUDY OF ANTI-HYPERTENSIVE ACTION OF LOSARTAN AND CANDESARTAN IN MILD TO MODERATE HYPERTENSION

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Abstract

Background: The present study is one of two identically designed, concurrently conducted, forced-titration studies that provide a direct comparison of the blood pressure lowering effects of these two ARBs at once-daily maximum doses. **Materials and Methods:** In this 8- week, double- blind, randomized, parallel- group, forced- titration study was conducted in OPD of, Patna Medical College and hospital, Patna, Bihar. double- blind, randomized, parallel- group, forced- titration study, and candesartan were compared to Losartan in 564 hypertensive patients. The study population consisted of men and women without childbearing potential between 18 and 80 years of age with moderate hypertension (a mean sitting diastolic BP [DBP] of 95–114 mm Hg). **Result:** A total of 564 patients were randomized to either candesartan (n=292) or Losartan (n=272). Five hundred seventeen patients (95%) completed the entire 8- week, double- blind treatment period: 95% for candesartan and 93% for Losartan. The mean treatment compliance during the placebo run- in phase was 96.5%. **Conclusion:** This study confirms that candesartan cilexetil is a more effective antihypertensive agent than Losartan when compared at once-daily maximum doses. Both drugs are well tolerated.

INTRODUCTION

Angiotensin II receptor blockers (ARBs) inhibit the renin-angiotensin system by selectively blocking the AT1 subtype of angiotensin II receptor. Various studies have demonstrated their effectiveness in lowering blood pressure with an excellent tolerability and safety profile.[1] Further large-scale studies are being conducted to determine whether the use of this class of drugs will result in end-organ protection, as well as beneficial effects on morbidity and mortality.[2] Different ARBs vary in their binding characteristics to the AT1 subtype of angiotensin II receptor. Preclinical studies have demonstrated that candesartan is a highly selective, insurmountable ARB.[3] It has an in vitro affinity for the AT1 receptor 80 times greater than that of Losartan and 10 times greater than that of EXP-3174, the active metabolite of losartan.[4] However, it remains uncertain whether these differences in pharmacologic properties result in greater blood pressure (BP) lowering efficacy for candesartan, compared to that of other ARBs. Clinically, candesartan is administered as candesartan cilexetil, an inactive prodrugs that is hydrolyzed to candesartan during absorption from the gastrointestinal tract. Three previous studies have demonstrated greater antihypertensive efficacy of candesartan when compared to Losartan. However, these studies either evaluated the starting doses of both drugs or used a response titration design for comparison at once-daily maximum doses.[5–7] The present study is one of two identically designed, concurrently conducted, forced-titration studies that provide a direct comparison of the blood pressure lowering effects of these two ARBs at once-daily maximum doses.

MATERIALS AND METHODS

In this 8- week, double- blind, randomized, parallel- group, forced- titration study was conducted in OPD of, Patna Medical college and hospital, Patna, Bihar. Candesartan was compared to Losartan in 564 hypertensive patients from 60 sites throughout the Bihar. The study population consisted of men and women without childbearing potential between 18 and 80 years of age with moderate hypertension (a mean sitting diastolic BP [DBP] of 95–114 mm Hg). Major exclusion criteria included systolic BP (SBP of ≥180 mm Hg or DBP of ≥115 mm Hg, known hypersensitivity to ARBs, secondary hypertension, severely impaired liver function, significant renal impairment, hemodynamically significant valvular heart disease, angina pectoris requiring more than short- acting nitrates, and a recent history of myocardial infarction, coronary

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revascularization procedures, stroke, or transient ischemic attack. Current use of an antihypertensive agent was cause for exclusion, unless it could be discontinued safely by the first week of the placebo run- in period. The study protocol was approved by the Institutional Committee and all patients provided written informed consent.

For each patient, visits were scheduled at the same time in the morning. Patients were instructed to refrain from taking the study medication on the morning of clinic visits until after BP was measured. All BP determinations were performed in the sitting position with a mercury sphygmomanometer under standardized conditions. Blood pressure was measured three times at 2- minute intervals and the mean value computed. The differences in the DBP readings were required to be no more than 5 mm Hg, with additional readings performed if necessary until such consistency was obtained. To be eligible for the study, patients' DBP had to be in the range of 95–114 mm Hg measured on two visits during the single-blind, 4- or 5- week placebo run- in period.

Once eligibility was confirmed, patients were randomized in a 1:1 ratio to candesartan 16 mg once daily, or Losartan 50 mg once daily. After 2 weeks of randomized treatment, all patients were required to double their dose of candesartan (16 to 32 mg once daily), or Losartan (50 to 100 mg once daily) for an additional 6 weeks. Patients were evaluated at weeks 1, 2, 4, and 8 during the 8- week double- blind period. Patients were also seen at follow up visits, 48 hours following their last dose of study medication and 2 weeks after they had discontinued therapy with the study medication. Post- study treatment for hypertension was not instituted until after the 48-hour assessment was completed. Trough sitting BP (24±3 hours after dose) and heart rate were recorded at each visit. In addition, peak BP (6±2.5 hours after dose) was measured at week 3 or 4 of the placebo run- in period, and also at week 8 of the double-blind period.

Compliance with the protocol- defined treatment regimen was assessed by tablet and capsule counts derived from the drug accountability case report form. The actual number of tablets and capsules used (number of tablets and capsules dispensed minus number of tablets and capsules returned) was divided by the expected number of tablets and capsules used, then multiplied by 100 to obtain a compliance percentage. This compliance percentage was calculated for all randomized patients by treatment group for the placebo run- in phase and for the randomized treatment period.

Statistical analyses were performed with an intent-to- treat approach, with the last observation carried forward (i.e., last available BP on treatment carried forward to week 8 for patients who withdrew). An analysis of covariance was employed for the primary efficacy parameter to ascertain whether candesartan cilexetil 16 mg titrated to 32 mg was different from Losartan 50 mg titrated to 100 mg with respect to reducing trough DBP over an 8- week treatment period. In order to accomplish this comparison, the generalized linear models procedure in SAS® was utilized, with the change from baseline to double-blind week 8 in trough sitting DBP as the response variable; treatment, center, and treatment by center were fixed effects in the model and the baseline trough sitting DBP was the covariate. The appropriateness of employing an analysis of covariance was assessed by examining the linear model using the same response variable and including treatment, baseline value, and treatment by baseline interaction value as fixed effects in the model. This interaction term was assessed at the 0.10 level of significance to determine the parallelism of slopes between the treatment groups assumed in the covariate analysis. In all cases, the analysis was repeated with exclusion of the covariate.

The investigations of other secondary efficacy variables were identical to the aforementioned analyses. The secondary efficacy end points included the change from baseline to week 8 in trough SBP, the changes in peak SBP and DBP, and changes in trough SBP and DBP, 48 hours after the last dose of the study medication. In addition, the proportion of responders (either a sitting trough DBP at week 8 of <90 mm Hg or a decrease from baseline of ≥10 mm Hg) and controlled patients (a sitting trough DBP at week 8 of <90 mm Hg) at week 8 were analyzed across treatment groups by means of Fisher's exact test. All data analyses are presented using the least-squares means. A p value of <0.05 was taken as statistically significant. All changes in BP are expressed as means with 95% confidence intervals (CI). Adverse events and laboratory data were compared descriptively between the two treatment groups. Laboratory data were evaluated according to predefined limits of change and mean change from baseline.

RESULTS

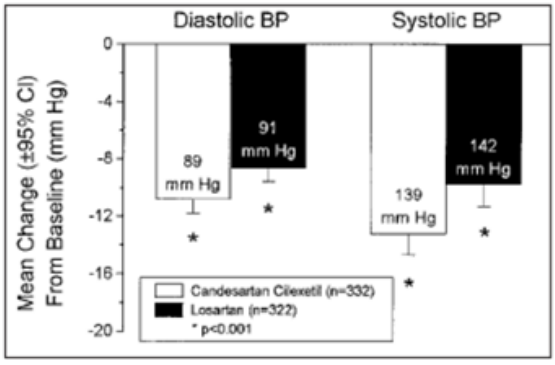

Figure 1: Effects of candesartan cilexetil and Losartan on trough blood pressure (BP). Labels within bars are the trough sitting BP readings (24±3 hours after dosing) at week 8. CI=confidence interval.

A total of 564 patients were randomized to either candesartan (n=292) or Losartan (n=272). Five hundred seventeen patients (95%) completed the entire 8- week, double- blind treatment period: 95%

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for candesartan and 93% for Losartan. The mean treatment compliance during the placebo run- in phase was 96.5%. During the double- blind portion of the study, compliance was similar between the two treatment groups, with the mean compliance for candesartan cilexetil at 103.2% and for Losartan at 102.1%. The study population was 49.1% female and 13.7% black, with a mean age of 51.4 years and a mean baseline BP of 151/90 mm Hg. About 7% of patients had diabetes mellitus. Patient characteristics at baseline were similar in the two treatment groups.

As shown in [Figure 1], candesartan lowered mean sitting trough SBP/DBP by 12.3/11.9 mm Hg, compared to a mean reduction of 8.9/7.8 mm Hg by Losartan at week 8 ($p<0.001$ for both DBP and SBP). Peak mean sitting SBP/DBP was reduced by 12.5/16.1 mm Hg with candesartan treatment, and by 16.2/11.1 mm Hg with Losartan treatment [Figure 2] $p<0.05$ for both DBP and SBP). At 48 hours after dosing, candesartan continued to produce reductions in mean SBP/DBP of 12.1/11.2 mm Hg, while Losartan provided mean reductions of 3.5/5.0 mm Hg ; $p<0.0001$ for both DBP and SBP). The trough-to-peak ratio was 0.96 for the candesartan group, and 0.77 for the Losartan group. The proportion of patients who responded to treatment was significantly higher ($p=0.033$) in the candesartan group (64.2%) than in the Losartan group (56.0%). Proportionately, more candesartan patients than Losartan patients attained control of DBP after treatment (57.0% compared to 49.6%; $p=0.023$) Overall, the incidence and intensity of adverse events were similar in the two treatment groups. A total of 260 of 564 (45.0%) patients reported a treatment-emergent adverse event—44.6% in the candesartan cilexetil group and 47.5% in the Losartan group. Most adverse events were mild to moderate in intensity and resolved despite continued treatment, including dose escalation. The most common adverse events for the candesartan group were respiratory infection (10.0%), dizziness (6.1%), headache (5.5%), and sinusitis (6.5%), whereas those for the Losartan group were respiratory infection (10.9%), headache (4.3%), pharyngitis (2.7%), and back pain (2.4%).

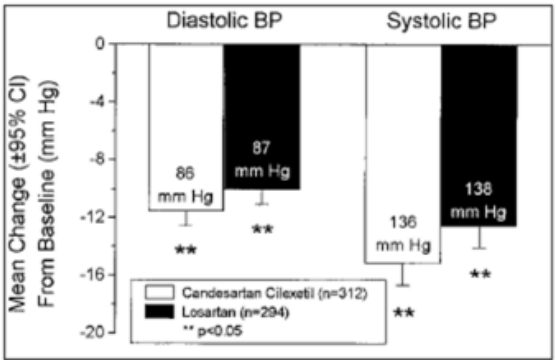

Figure 2: Effects of candesartan cilexetil and Losartan on peak blood pressure (BP). Labels within bars are the peak sitting BP readings (6±2.5 hours after dose) at week 8. CI=confidence interval.

Group and one was in the Losartan group. All events were considered by the investigators unlikely to be related to study medication. There were no deaths during this trial. Minor changes from baseline in laboratory values were observed in isolated. Patients. There were no clinically meaningful changes in mean laboratory values in either treatment group and no laboratory evidence of deterioration in renal, hepatic, or metabolic function.

DISCUSSION

This study demonstrates that candesartan had greater efficacy in lowering arterial pressure when compared to Losartan. Moreover, the duration of effect and response/control rates was significantly better with candesartan than Losartan. Side effect profiles were similar between the two groups. Data from this study, taken together with three other randomized, double-blind studies comparing candesartan and Losartan, demonstrate superior antihypertensive efficacy of candesartan over Losartan. Anderson and Neldam,[5] evaluated candesartan 8 and 16 mg vs. losartan 50 mg and found that candesartan 16 mg once daily (n=84) reduced trough DBP more effectively than losartan 50 mg once daily (n=83), by 3.7 mm Hg ($p<0.05$). Also, in the Candesartan versus Losartan Efficacy Comparison Study (CANDLE),6 candesartan 16 mg, dosetitrated if necessary to 32 mg once daily (n=160), reduced trough DBP more effectively than Losartan 50 mg, dose-titrated if necessary to 100 mg, once daily (n=169), by 2.1 mm Hg ($p<0.05$). Lastly, Lacourciere and Asmar,[7] compared the effects of candesartan 8 mg force-titrated to 16 mg (n=116) and losartan 50 mg force-titrated to 100 mg (n=115) once daily, as assessed by clinic and ambulatory blood pressure. They found that candesartan 16 mg reduced ambulatory BP to a significantly greater extent than 100 mg of losartan, particularly systolic ambulatory BP during the daytime ($p<0.05$), nighttime ($p<0.05$), and 24- hour period ($p<0.01$). In addition, candesartan lowered both SBP and DBP after a missed dose to a greater extent than losartan (11.9/8.0 mm Hg and 6.1/4.5 mm Hg, respectively; $p<0.05$). The net difference of candesartan cilexetil (CC) in lowering trough BP by 3.5/2.2 mm Hg more than losartan may appear too small to be of clinical significance, as it is common in clinical practice to encounter spontaneous BP variation of this magnitude in an individual patient. But in this study, precautions were taken to minimize spontaneous fluctuation of BP or recruitment of patients with labile BP. Blood pressure was measured under the same standardized conditions at each visit, and differences in serial DBP readings during each visit were required to be <5 mm Hg. The fact that CC consistently lowered trough, peak, and 48 hours post-dose BP compared to losartan indicated true differences between the two drugs. It is interesting to note that the SBP/DBP differences between

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candesartan cilexetil and losartan widened at 48 hours post-dose, i.e., 5.9 /4.3 mm Hg, respectively. Thus, candesartan c produces an extended therapeutic antihypertensive effect that may confer additional protection to a patient with occasional missed doses. Furthermore, the CC group, compared with the losartan group, had statistically significantly higher rates of responders (64.2% and 56.0%, respectively) and controlled patients (58.0% and 49.6%, respectively). The BP differences, although moderate, might result in clinically important benefits. Epidemiologic data show that cardiovascular risk increases with every mm Hg of BP above 110/70 mm Hg.[8,9] In the cohort of men screened for the Multiple Risk Factor Intervention Trial (MRFIT),[9] SBP increases of 20 mm Hg and 40 mm Hg increased the 11.6-year risk of coronary heart disease deaths by 156% and 244%, respectively. Every SBP increment resulted in a 6%–8% increase in risk. Blood pressure reductions, even minor, assume clinical importance in high-risk patients. About 8% of the study population had diabetes mellitus. It should be noted that the Hypertension Optimal Treatment (HOT) Study demonstrated that a mean decrease of 4.1 mm Hg in DBP was associated with a 51% reduction in major cardiovascular events in patients with diabetes mellitus.[10] Finally, only a moderate advantage over Losartan in the treatment of hypertension could be expected from candesartan as monotherapy, despite the superior binding characteristics of this agent to angiotensin II. This pathway maybe only one, rather than the sole, effector in the pathogenesis of hypertension. In general, hypertension is a multifactorial disease and a single antihypertensive agent targeting one mechanism provides long-term BP control for only approximately 50% of hypertensive patients.[11] However, in situations in which the renin-angiotensin system is activated, candesartan cilexetil may exert a greater antihypertensive effect. This occurs when candesartan cilexetil is used with a diuretic, such as hydrochlorothiazide. Ohman et al,[12] reported that candesartan cilexetil plus hydrochlorothiazide (16 and 12.5 mg, respectively) reduced DBP/SBP by 19.4/10.4 mm Hg (n=151), whereas losartan plus hydrochlorothiazide (50 and 12.5 mg, respectively) reduced DBP/SBP by 13.7/7.8 mm Hg (n=148). The difference of 5.7/2.6 mm Hg in SBP/DBP reduction was statistically significant ($p<0.05$). These findings suggest that ARBs with different binding characteristics may exert different degrees of antihypertensive efficacy, both as monotherapy and in combination with other agents.

CONCLUSION

The results of this randomized, double-blind, parallel-group, forced-titration study in a diverse population of hypertensive patients indicates that 32 mg of candesartan, given once daily, lowers the peak, trough, and 48-hour post-dose BP more effectively than 100 mg of losartan given in the same time course.

There is no difference in their safety/tolerability profile. This study confirms that candesartan cilexetil is a more effective antihypertensive agent than losartan when compared at once-daily maximum doses. Both drugs are well tolerated.

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