

ESSENTIAL HYPERTENSIVE PATIENTS;

Comparison of anti-hypertensive effect of candesartan cilexetil and amlodipine

Dr. Shah Nawaz Jamali, Dr. Shahid Ahsan, Dr. Muhammad Jamil Laghari, Dr. Usman Ahmad.

ABSTRACT.....Objective: To compare blood pressure lowering effects of angiotensin II type I receptor blocker candesartan cilexetil in comparison with calcium channel blocker amlodipine in essential hypertensive patients. **Study design:** Randomized, open-labeled, prospective comparative study. **Place and duration:** The study was carried out in the department of pharmacology and therapeutics, Basic Medical Sciences Institute (BMSI), Jinnah Post Graduate Medical Centre (JPMC), Karachi from July 2007 to January 2008. **Subjects and methods:** In this study (80) newly diagnosed essential hypertensive patients were enrolled and divided into two groups (DR1) and (DR2) respectively. DR1 patients received candesartan 16mg once a day and DR2 patients received Amlodipine 10mg once a day for 3 months duration. **Results:** The mean systolic blood pressure of DRI was 162.23 on day 0 which decreased to 141.05 on day 90, versus DR2 which decreased from 160.12 on day 0 to 140 on day 90. The mean diastolic blood pressure decreased significantly for DR 1 group from 99.87 mmHg to 87 to 89. mmHg, versus DR2 which decreased from 98.5 to 86.25. All values of blood pressure have been taken in mmHg. The results of this study were observed statistically significant. **Conclusions:** Candesartan cilexetil is a newer and safer alternative for the treatment of essential hypertensive patients in comparison to conventional antihypertensive treatment.

Key words: Candesartan cilexetil, Amlodipine, Essential Hypertension, ARBs.

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INTRODUCTION

Hypertension affects from 20-30% of world population and is a major cardiovascular risk factor. The relation between cardiovascular risk and blood pressure is continuous, consistent across age groups, present in all ethnic groups, and independent of other risk factors¹. There is much uncertainty about the pathophysiology of hypertension². A small number of patients between 2 -5 % having an underlying renal or adrenal disease as the cause for their raised blood pressure³, in the remainder, however no clear single identifiable cause is found and their condition is labeled as "essential hypertension"⁴. Progress in understanding the pathogenesis of essential hypertension has been slow because essential hypertension is extremely complex at the molecular level⁵. Various population studies suggest that blood pressure is a continuous variable, with no absolute dividing line between normal and abnormal⁶.

Current international hypertension guidelines (JNC – IV) recommended weight control, reduce intake of sodium chloride salt, reduce alcohol consumption and

possibly increased dietary intake of potassium as nutritional approaches to prevent and treat hypertension⁷.

Hypertension can cause or is related to various cardiac manifestations, among them left ventricular hypertrophy, congestive heart failure, cardiac dysrhythmias and ischemic heart disease⁸.

The percentage of persons in whom hypertension is controlled is widely viewed as unsatisfactory and may in fact have decreased since 1990⁹. Little attention has been given to the clinical implications of blood pressure levels observed in persons with poorly controlled hypertension¹⁰. The benefits of drug intervention in hypertension is to reduce blood pressure are well established, especially in high-risk individuals¹¹. The ultimate public health goal of anti-hypertensive therapy is the reduction of cardiovascular and renal morbidity and mortality¹². Angiotensin II type I receptor antagonist are relatively a new class of antihypertensive agent¹³.

Candesartan cilexetil is a potent and selective angiotensin II type I receptor blocker, which binds tightly to and dissociates slowly from ATI receptor. It is administered orally as the pro-drug candesartan-cilexetil, which is rapidly and completely converted to active compound candesartan, during gastro-intestinal absorption¹⁴. The selective and competitive binding of candesartan onto the angiotensin II, a key mediator in the rennin-angiotensin system results in significant reductions in systolic and diastolic blood pressure with once daily dosage of 8-16 mg¹⁵. Among the different classes of drugs that are currently used in the treatment of hypertension calcium channel blockers (CCBs) play a special role because of their specific action on the constrictor tone of the vascular smooth muscle cells¹⁶.

Among dihydropyridines, amlodipine has been reported as an effective antihypertensive drug associated with regression of left ventricular hypertrophy and vascular hypertrophy, the anti-atherogenic and the remodeling effects¹⁷.

SUBJECTS AND METHODS

This study was conducted in the department of pharmacology and therapeutics, Basic Medical Sciences Institute (BMSI), in collaboration with the department of medicine, Jinnah Post-graduate Medical Centre, Karachi, from July 2007 to January 2008. Eighty patients with newly diagnosed essential hypertension were initially enrolled in this study after taking informed and written consent, selected from medical OPD of JPMC. Out of these seventy-four patients were associated throughout the study period. Out of remaining six patients four has not come for follow-up in amlodipine group two due to unknown reasons and two patients has complained of lethargy, dizziness, drowsiness and refused to continue the study while two patients were dropped in candesartan group, due to gastric upset and headache. Following patients were included in the study: patients of either sex with newly diagnosed essential hypertension,

patients aged between 20 – 70 years, patients having no history of using anti-hypertensive medications. The patients who were excluded from the study: patients having known history of allergy to angiotensin receptor blockers (ARBs) or CCBs, patients having a history of hepatic or renal impairment, pregnant or lactating women, and patients who were already taking anti-hypertensive treatment. The safety and tolerability were assessed by spontaneous reports of adverse events as observed and reported by the patients and has been shown in table IC.

STUDY DESIGN

The study period was consisted of 12 weeks (90 days) with weekly follow-up visits of patients; but the observations of the parameters were recorded on day 0, day45 and day 90 of the study period. The selected patients were divided into two groups. DR1 (Candesartan cilexetil) and DR2 (Amlodipine). Forty patients with newly diagnosed essential hypertension with the above mentioned criteria were provided Tab. Candesartan 16 mg once a day for 90 days in DR 1 group; while forty patients with newly diagnosed essential hypertension were provided Tab. Amlodipine 10 mg once daily for 90 days in DR2 group. Following parameters were observed during study period, systolic blood pressure (SBP), diastolic blood pressure (DBP) and safety profile of the patients.

RESULTS

The values are expressed in mean \pm SEM (standard error of mean). ANOVA was applied as a test of significance to observe the statistical significance of this comparative research project. A p-value of ≤ 0.05 was considered statistically significant. Out of 40 patients on day 0, 38 patients were treated with DR1 till day 90. Mean systolic B.P on day 0 was 162.23 ± 2.12 mmHg, which decreased to 148.68 ± 1.49 mmHg on day 45 and 141.05 ± 1.14 mmHg on day 90. This decrease in systolic B.P was observed statistically significant ($P < 0.001$), when compared between day 0 and day 90, as shown in Table-I A and

fig. 1A.

Out of 40 patients on DR2, 36 patients were treated till day 90th. The mean systolic B.P decreased from 160.12 ± 2.0 mmHg on day 0 to 147.08 ± 1.45 mmHg on day 45 and 140 ± 1.23 mmHg on day 90th of the treatment. This reduction was found statistically significant (p < 0.001), as shown in table-I A and figure 1A.

Both Candesartan cilexetil and Amlodipine decreased the mean diastolic B.P. In DR1 group mean diastolic B.P on day 0 was 99.87 ± 0.81 mmHg which decreases to 93.28 ± 0.71 mmHg on day 45 and 87.89 ± 0.67 mmHg on day 90th of the treatment. This decrease in diastolic B.P was found statistically significant with a P-value (P < 0.001) while in case of DR2 group mean diastolic B.P was decreased from 98.5 ± 0.61 mmHg on day 0 to 91.38 ± 0.67 mmHg on day 45 and 86.25 ± 0.60 mmHg on day 90th of the treatment. This decrease was also observed statistically significant as depicted in table-I B and figure 1B.

Groups	Day - 0	Day - 45	Day - 90	P-value
DR 1	162.23 ±2.12 (40)	148.68 ±1.49 (38)	141.05 ±1.14 (38)	<0.001
DR 2	160.12 ±2.0 (40)	147.08 ±1.45 (36)	140 ±1.23 (36)	<0.001

Table-I-A. Comparison of mean systolic B.P from Day 0 Day 90, of the treatment with DR 1, DR 2 in essential hypertensive patients

Values are expressed in mean ± SEM. ANOVA was applied as a test of significance. A p-value of ≤ 0.05 was considered statistically significant. DR1 (Candesartan cilexetil), DR 2 (Amlodipine). All observations are in mmHg.

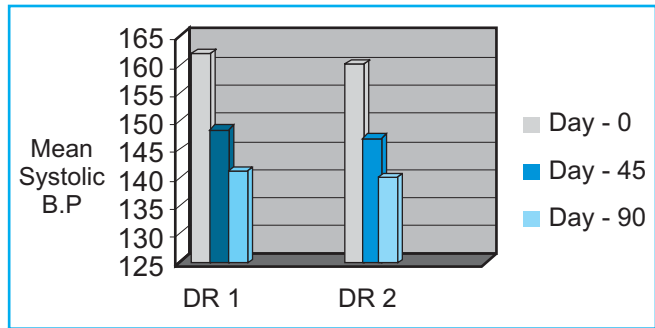


Figure 1-A. Changes in mean systolic B.P from Day 0 Day 90, of the treatment with DR 1, DR 2 in essential hypertensive patients

Groups	Day - 0	Day - 45	Day - 90	P-value
DR 1	99.87 ±0.85 (40)	93.28 ±0.71 (38)	87.89 ±0.67 (38)	<0.001
DR 2	98.5 ±0.61 (40)	91.38 ±0.67 (36)	86.25 ±0.60 (36)	<0.001

Table-I B. Comparison of mean diastolic B.P from Day 0 Day 90 of the treatment with DR 1 & DR 2 in essential hypertensive patients

Values are expressed in mean ± SEM. ANOVA was applied as a test of significance. A p-value of ≤ 0.05 was considered statistically significant. DR1 (Candesartan cilexetil), DR 2 (Amlodipine). All observations are in mmHg.

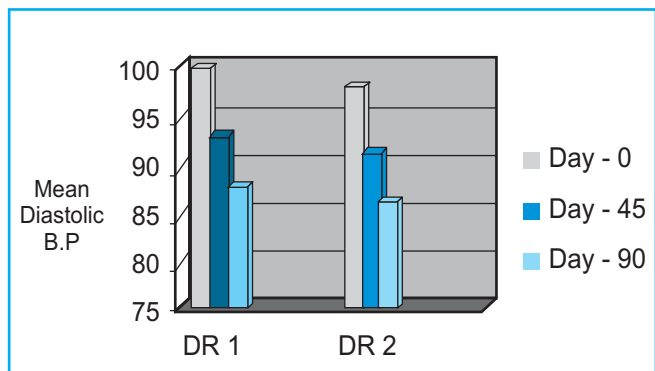


Figure 1-B. Changes in mean diastolic B.P from Day 0 Day 90 of the treatment with DR 1 & DR 2 in essential hypertensive patients

SIDE EFFECTS	ADESARTAN CILEXETIL	AMLODIPINE
Drowsiness	0	01 (2.6%)
Constipation	0	02 (5.26%)
Headache	01 (2.7%)	01 (2.6%)
Dizziness	0	02 (5.26%)
Abdominal pain	01 (2.7%)	0
Backache	01 (2.7%)	0
Edema	01 (2.7%)	0
Nausea / Vomiting	0	01 (2.6%)
Total Patients	04 (10.8%)	07 (18.4%)

Table-I C. Frequency of observed and reported side effects with DR1 & DR2 in essential hypertensive patients
Indicate the %age from total reactions

DISCUSSION

In this comparative research study the aim was to observe the efficacy and safety profile of essential hypertensive patients. This study demonstrates significant changes in blood pressure lowering effects with both Candesartan cilexetil and Amlodipine in essential hypertension. Present study revealed that candesartan cilexetil and amlodipine has significantly reduced the mean systolic and diastolic B.P in essential hypertensive patients. The results of both drug groups have shown statistically significant reduction with a P – value ($P < 0.001$). The literature search revealed that clinical trial was conducted by Cardiologia and his associates in 2005 and mentioned that angiotension receptor blockers like Candesartan cilexetil and losartan are effective in controlling blood pressure. In 2006, Asmar et al conducted a comparative multicentre research project to observe the efficacy of (ARBS) in long-term control of systolic blood pressure in essential hypertensive patients. Bonner G and his research fellows carried out a pilot research project to find out an angiotension receptor blocker with prolonged duration of action; his research observations were that Candesartan cilexetil is a long acting antihypertensive compound in comparison to

other angiotension receptor antagonists.

In 2004, a research study was conducted by Rashid et al at JPMC to compare blood pressure lowering effects between Atenolol and amlodipine in essential hypertensive patients. Similarly Hoshide et al in 2005 and Ishimtuu in japan conduted their research pilot studied to compare blood pressure lowering effects between calcium channel blockers and angiotension receptor antagonists to find out their efficacy and safety profile. The results of our DR1 group are in accordance with the research clinical trials of cardiologia et al (2005),¹⁸ Asmar et al (2006)¹⁹ but slightly differ from the results of Bonner G et al 2005²⁰. This difference may be due to the duration of their clinical trials. The result of our DR2 group also matches with the studies conducted by Rashid et al 2004²¹. Hoshide S et al 2005,²² and Ishimitsu T et al 2005²³. (Where explanation of these references) The tolerability of the two drugs was not quite similar and the incidence of side effects reported by the patients during the whole duration of study was more observed and reported in DR2 group in comparison to DR 1 group.

CONCLUSIONS

Candesartan Cilexetil is a newer alternative for the treatment of essential hypertension in comparison to conventional anti-hypertensive treatment.

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AUTHOR(S):

1. **DR. SHAH NAWAZ JAMALI**
Assistant Professor
Hamdard University Karachi.
2. **DR. SHAHID AHSAN**
3. **DR. MUHAMMAD JAMIL LAGHARI**
4. *Dr. Usman Ahmad*

Correspondence Address:

Dr. Shah Nawaz Jamali
Flat No. B-12, Gallant Summit,
Opposite Sindh Board of Technical Education, Block No. 11
Gulshan-e-Iqbal, Karachi.
sjamali74@gmail.com

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