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Original Research Article

COMPARATIVE STUDY OF ANTI-HYPERTENSIVE ACTION OF AZILSARTAN WITH OLMESARTAN AND CANDESARTAN IN MILD TO MODERATE HYPERTENSION

Kali Charan Rajak[1], Awadhesh Kumar Jha[2], Shambhu Kumar[3]

[1]Tutor, Department of Pharmacology, Government Medical College Bettiah, India.
[2]Associate Professor, Department of Pharmacology, Government Medical College Bettiah, India
[3]Assistance Professor, Department of Pharmacology, Government Medical College Bettiah, India

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Corresponding Author:
Dr. Awadhesh Kumar Jha,
Email: jha66awadhesh@gmail.com

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Abstract

Background: Hypertension has been identified as the leading risk factor for mortality worldwide. It may lead to damage of heart, kidney, brain, vasculature and the other organs results in premature morbidity and death. The objective of the study was to compare efficacy and tolerability of once daily treatment of the new angiotensin type1 receptor blocker (ARB) Azilsartan with Olmesartan and Candesartan. **Materials and Methods:** The study was a prospective, randomized open label comparison. Total 400 patients were recruited for the study. Patients were divided into four groups. Group A comprising of 100 patients received azilsartan (40mg), Group B comprising of 100 patients received azilsartan (80mg), Group C comprising of 102 patients received olmesartan (40mg) and Group D comprising of 98 patients received candesartan (12mg). Blood pressure was monitored at base line, after 2 weeks, 4 weeks and 8 weeks of treatment. **Results:** All drugs reduced both systolic blood pressure (SBP) and Diastolic blood pressure (DSP) significantly, but the reduction in SBP and DSP with azilsartan (80mg) was significantly greater than other drugs. The difference in BP reduction between azilsartan (40mg) and olmesartan (40mg) were not significant but both azilsartan (40mg) and olmesartan (40mg) were significantly more effective than candesartan (12mg). **Conclusion:** The study indicates that azilsartan (80mg) is more effective in the control of hypertension than olmesartan and candesartan with similar safety profile.

INTRODUCTION

Hypertension is a common disorder in adults around the globe and among the most common attributable causes of mortality.[1] The goal of antihypertensive therapy is to maintain blood pressure of <140/90mmHg for most people.[2] The angiotensin receptor blockers (ARBs) have been in clinical use since 1995 and known to be effective antihypertensive agent with excellent tolerability profiles. Azilsartan medoximil, a new generation ARB for the treatment of essential hypertension. Azilsartan was discovered through the efforts of scientists from Takeda, a Japanese pharmaceutical company by modifying the tetrazole ring present in candesartan. The chemical structure of azilsartan is very similar to the structure of candesartan and differs only by replacement of candesartan.[3] member tetrazole ring with the oxa-oxadiazole ring of azilsartan. This modification makes azilsartan less acidic and more lipophilic than candesartan. Azilsartan was recently approved and has been shown to provide a more potent and sustained antihypertensive effects than other ARBs. Azilsartan medoximil, olmesartan medoximil and candesartan cilexetil are prodrugs and require activation in liver in their active forms azilsartan, olmesartan and candesartan respectively.[4,5] Molecular interaction of azilsartan with the AT(1) receptor and its strong inverse agonist activity towards the production of inositol phosphate(IP) could explain its strong BP lowering activity.

MATERIALS AND METHODS

Study Design

We undertook randomized, open label comparative study of hypertensive patients in Government Medical College and Hospital, Bettiah between May 2019 to Feb 2020. Total four hundred patients were recruited for this study. Patients were randomly divided into four groups. Group A comprising of 100 patients received azilsartan (40mg), Group B comprising of 100 patients received azilsartan

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(80mg), Group C comprising of 102 patients received olmesartan (40mg), Group D comprising of 98 patients received candesartan (12mg) respectively.

Inclusion Criteria

- Male and female of age between 25yrs to 55yrs.
- Systolic B.P between 130-169mm Hg and diastolic BP between 90-109mmHg

Exclusion Criteria

- Pregnant and lactating women
- Patients already on other antihypertensive drugs
- Patients with other condition like severe hypertension, diabetic, hepatic failure, renal failure, heart failure, acute severe asthma
- Secondary hypertension
- Chronic use of corticosteroids, NSAIDs and sex hormones like oral contraceptive pills.

A physical examination, 12 lead electrocardiography and laboratory test were performed. Sitting cuff blood pressure was measured with mercury sphygmomanometer. Patients were seated for minimum of 5 minutes before the first measurement. Three recordings were taken, each separated by a minimum period of one minute. The pulse rate was measured once at the time of second blood pressure reading. Patients who met the entry criteria for the study during screening were assigned to receive a once daily dose of one of the following ARBs; 40mg or 80mg azilsartan, 40mg olmesartan, 12mg candesartan group wise. Patients in the treatment phase of the study were required to visit the clinic prior to taking their daily dose 0f medication at 2, 4 and 8 week after commencing treatment. At each visit sitting cuff blood pressure was measured in triplicate, heart rate was also measured, compliance was assessed by pill count and patients were queried for adverse events.

Statistical Analysis

Values are expressed as the mean±SD. The difference of the baseline characteristics and change in BP between groups was compared using an unpaired t test. The differences between values before and after antihypertensive medication within the same group were tested using a paired t-test. P value <0.05 considered statistically significant.

RESULTS

Table 1 summarizes the baseline characteristics of the patients enrolled for this study. There were no significant differences in background factors between these groups. The difference in blood pressure reduction after treatment with azilsartan, olmesartan and candesartan were apparent within 2 weeks. The difference in both DBP and SBP response between azilsartan (80mg) and the comparison drugs were significant for all comparisons at both 2 and 4 weeks. The difference in BP response with azilsartan (40mg) was comparable with olmesartan (40mg). Compare to candesartan (12mg), the change in BP were significant with both

Azilsartan (40mg) and olmesartan (40mg). [Table 2]

Table 1: Base line demographic characteristics of hypertensive patients enrolled for study

Azilsartan (40mg)	Azilsartan (80mg)	Olmesartan (40mg)	Candesartan (12mg)	
Group-A	Group-B	Group-C	Group-D	
No of patients	100	100	102	98
Age	52±9.5	51±8.40	52±8.2	51±8.44
Gender	Male- 67.4	Male- 66.3	Male- 67.7	Male- 68.2
Female- 33.6	Female- 37.7	Female- 34.3	Female- 38.8	
BMI(Kg/m²)	25±2.4	24±2.9	25±2	24±3
Baseline blood pressure	DBP	102±3.6	102±2.7	102±2.5	102±3.4
SBP	157±12.5	158±11.6	157±1	156±12.8	

Table 2: Change in Diastolic blood pressure (ΔDBP) and Systolic blood pressure (ΔSBP) after 2 and 4 week of treatment.

Azilsartan (40mg)	Azilsartan (80mg)	Olmesartan (40mg)	Candesartan (12mg)		
2 weeks	Δ DBP	-10.8	-12.7	-10.6	-9
Δ SBP	-13.7	-15.8	-13.4	-9.4	
4 weeks	Δ DBP	-11.3	-14.3	-11.4	-9.7
Δ SBP	-13.8	-16.2	-13.6	-10.4	

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Table 3: Adverse events during the treatment period.

	Atzilsartan (40mg)	Azilsartan (80mg)	Olmesartan (40mg)	Candesartan (12mg)	
Serious AEs, N (%)	0	0	0	0	
Common AEs, N (%)	Headache	10(9.5)	8(7.5)	10(9.8)	9(9.1)
Dyslipidemia	9(5.7)	5(3.7)	2(1.9)	2(2.04)	
Dizziness	8(5.7)	7(7.5)	5(5.8)	3(4.08)	
Diarrhoea	7(1.9)	0	1(0.98)	0	
Coughing	1	2(1.8)	2(1.9)	1(1.02)	
Arthralgia	4(1.9)	2(1.8)	3(3.9)	6(6.12)	
N=100	N=100	N=102	N=98		

DISCUSSION

Although several previous head to head comparisons of ARBs in which clinical blood pressure was used as the primary efficacy variable have been published.[6-7] Azilsartan, an angiotensin type 1 (AT1) receptor blocker (ARB) was recently approved by regulatory clinical market. The development of AT1 receptor blockers (ARBs) can be traced back to the pioneer work of scientist at Takeda pharmaceutical who described a series of benzylimidazole compounds that inhibited the ability of angiotensin to stimulate the vascular contraction and increase blood pressure (BP).[8-9] More than 15 years after the clinical introduction of Losartan, the FDA approved Takeda's azilsartan medoximil as the 8th ARB for the treatment of hypertension.20 Azilsartan was discovered by modifying the tetrazole ring present in candesartan.[10,11] Chemical structure of azilsartan is very similar to the structure of candesartan and differ only by replacement of candesartan 5 member tetrazole ring with the 5 member oxa-oxadiazole ring of azilsartan. Unlike candesartan which must be orally administered as a prodrugs candesartan cilexetil to ensure adequate bioavailability, azilsartan has been shown to be effective in reducing

BP when orally administered as either the ester prodrugs, azilsartan medoximil or as the primary compound.[3-5] During gastrointestinal absorption , azilsartan medoxidil is rapidly hydrolyzed to azilsartan, the bioactive molecule that selectively and competitively blocks angiotensin induced activation of AT1 receptor in an insurmountable fashion.[6,7] Azilsartan in clinically approved doses as azilsartan medoximil has been shown to lower 24-hour BP in hypertensive patients significantly more than the maximum approved dose of olmesartan medoximil, the later being considered by some to be one of the most potent ARBs for lowering BP.[8-10] Given the close structural relationship between azilsartan and candesartan, head to head studies comparing the BP effects of these two drugs are of particular interest. Azilsartan 40-80mg per day lowered systolic and diastolic BP significantly more than candesartan cilexetil (12mg).[11] The result regarding the binding affinity of azilsartan and candesartan demonstrated that these ARBs interact with the same sites in the AT1 receptor [(Tyr (113), Lys (199), and Gln (257)] The hydrogen bonding between the ox diazole of azilsartan- Gln (257) is stronger than that between the tetrazole of candesartan-Gln (257).[9,10] An examination of the inhibition of inositol phosphate (IP) production by ARBs using constitutively active mutant receptors indicated that inverse agonist had a stronger activation with Gln (257) than candesartan. There was no difference among treatment groups in the incidence of clinical and laboratory adverse events. As a class, ARBs are noted for having a side effects profile similar to that of placebo.[11] A placebo group was not included in the current study, but the total adverse events rare, is similar to that reported for the placebo group in several placebo controlled trials carried out in hypertensive patients.

CONCLUSION

This study has shown that azilsartan (80mg) lowered BP to a significantly greater extent than olmesartan (40mg) and candesartan (12mg). Azilsartan (40mg) was non-inferior to olmesartan (40mg). Both azilsartan (40mg) and olmesartan (40mg) are significantly more effective than candesartan (12mg). Azilsartan had a similar safety and tolerability profile to olmesartan and candesartan.

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