Section: General Medicine

Research

STUDY ON THE ANTIHYPERTENSIVE EFFECTS OF AZILSARTAN AND CANDESARTAN IN MILD TO MODERATE HYPERTENSION

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Abstract

Background: Hypertension (HTN), also known as high blood pressure (HBP), is a long-term medical condition in which the blood pressure in the arteries is persistently elevated. High blood pressure typically does not cause symptoms. Long-term high blood pressure, however, is a major risk factor for coronary artery disease, stroke, heart failure, atrial fibrillation, peripheral arterial disease, vision loss, chronic kidney disease, and dementia. Objectives- the primary objective of the present study is to compare the antihypertensive efficacy of the following antihypertensive treatments in patients with mild to moderate hypertension. **Materials and Methods:** This study was conducted in the Pharmacology Department of MGM Medical College & Hospital and was planned as a prospective, single-blind, randomised controlled trial with two matched treatment groups. In a systematic manner, 100 individuals with low to moderate essential hypertension who visited the OPD in General Medicine were recruited during the period January 2021 to September 2022. Group A received AZILSARTAN MEDOXOMIL 40mg (1 or 2 tablets once daily) and Group B received CANDESARTAN CILEXETIL 8 mg (1 or 2 tablets once daily) depending on the blood pressure. **Result:** On calculating we found both the arms were comparable in terms of baseline sitting DBP and SBP (p value = 0.578 and 0.689 respectively). The mean ABPM level was significantly reduced in azilsartangroup compared to candesartan group after 8 weeks of treatment. Discontinuations due to adverse events and serious adverse events were infrequent in both groups (only 2% in both the groups). The most common TEAEs occurring was nasopharyngitis (18.8% in the azilsartan group vs. 16.2% in the candesartan group), upper respiratory tract inflammation (10% vs. 8%, respectively), and pharyngitis (8% vs. 6%, respectively).**Conclusion:**And hence, azilsartan given once daily has the potential to provide higher rates of hypertension control over a 24-h period (including the night and early morning hours) and might be expected to provide greater protection against cardiovascular events in patients with essential hypertension, although this remains to be proven in prospectively designed clinical studies. Azilsartan, a relatively novel angiotensin receptor blocker, has been shown to reduce blood pressure in a safe and effective manner. Its effectiveness is on par with that of candesartan, and its adverse effects are milder, making it suitable for usage in all patients.

INTRODUCTION

Hypertension, commonly known as high blood pressure (HBP), is a chronic medical disorder characterised by consistently high blood pressure within the arteries. High blood pressure typically has no symptoms.[1] However, high blood pressure that has been untreated for an extended period of time greatly increases the likelihood of developing cardiovascular disease, stroke, heart failure, atrial fibrillation, peripheral artery disease, vision loss, chronic kidney disease, and dementia.[2]

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In India, hypertension is the leading cause of morbidity and mortality due to its impact on overall health.[3] Due to ischemic heart disease and stroke, it is a major cause of death in India, accounting for an estimated 1.6 million fatalities annually. The leading cause of death in the United States is hypertension, accounting for 24% of deaths from coronary heart disease and 57% of deaths from stroke. Recent estimates place the prevalence of hypertension at 29.8% in the general population and 33.8% in urban areas, making it one of the most frequent non-communicable disorders.[4-7]

Changes in the ocular fundus detectable with ophthalmoscopy may be an indicator of hypertension on a physical examination. Hypertensive retinopathy is classified from I (mild) to IV (severe), with grades I and II potentially being difficult to identify.[8] Recent recommendations for the management of hypertension in adults have been issued by the Eighth Joint National Committee (JNC 8), based on evidence-based thresholds, targets, and drugs.[9]

The hypertension medication azilsartan acts as an angiotensin II receptor antagonist.[10] By inhibiting angiotensin II at the AT1 receptor, a hormone that constricts blood vessels and increases water retention in the kidneys, azilsartanmedoxomil reduces blood pressure.[11] Candesartan is an angiotensin receptor blocker that is typically prescribed to patients with hypertension or heart failure. Candesartan, like other angiotensin II receptor antagonists, is prescribed for treating high blood pressure. When taken with a diuretic like chlortalidone, candesartan produces an additional hypertensive impact. The thiazide diuretic hydrochlorothiazide is included in the combo formulation.[12]

MATERIALS AND METHODS

After receiving clearance and approval from the Institutional Ethics Committee at MGM Medical College & LSK Hospital Kishanganj, Bihar, the present study was done with patients' written informed consent. This study was an apost-registration (Phase IV), prospective, single-blind, randomised, controlled investigation done by the Department of Medicine. The duration of the investigation was two years. One hundred patients with mild to moderate essential hypertension who presented to the OPD Medicine were recruited sequentially. Male subjects aged 25 to 65 years with mild to moderate essential hypertension and systolic blood pressures between 130 and 169 mm Hg and diastolic blood pressures between 90 and 109 mm Hg, as well as postmenopausal female subjects with a comparable blood pressure range, were enrolled as study subjects. Patients were randomised into two groups at random using computer-generated numbers. Depending on blood pressure, Group A received AZILSARTAN MEDOXOMIL 40mg (1 or 2 tablets once day) while Group B received CANDESARTAN CILEXETIL8 mg (1 or 2 tablets once daily).

The following categories of demographic data were collected: age, gender, and anthropometric factors. Patients were measured for weight and height while wearing light clothing. The formula for calculating body mass index was weight (kg) divided by the cube of height (m).

During both the 4-week placebo run-in period and the 16-week treatment period, patients' blood pressure and pulse rate were measured and they underwent physical examinations at clinic visits every two weeks. The investigator monitored supine blood pressure at least three times at 1- or 2-minute intervals at trough (243 h post-dose) using a digital or manual BP monitor, and the mean of two stable consecutive supine BP measures was used for analysis. At baseline (week 0) and week 8, blood pressure was monitored at 30-minute intervals for 26 h using an oscillometric monitor, beginning at 1000 hours (1 h). Patients administered the study medication 1 h after the beginning of morning measurements and after the conclusion of measurements the following day. During the period of ABPM, patients were directed not to take a bath, nap in the afternoon, engage in physical activity, or consume alcoholic or caffeinated foods/drinks. The primary quality criteria for an acceptable ABPM recording comprised the following: (1) a minimum of 80% of the predicted BP readings throughout a 24-hour period; (2) no more than 2 nonconsecutive hours with 1valid BP reading; and (3) the absence of behaviours that significantly alter BP (afternoon nap,drinking and so on).

Concerning adverse occurrences, all patients were asked non-leading questions at each appointment. Additionally, a 12-lead resting electrocardiogram was conducted at baseline and week 16. The patients underwent clinical laboratory testing (haematology, serum chemistry, urinalysis) at weeks 0 (baseline), 2, 4, and 8 after fasting for at least 10 hours. The occurrence of adverse events, clinical laboratory tests, vital signs, body weight, and resting 12-lead electrocardiogram data were used to evaluate the drug's safety.

Analytical Statistics

The data were examined for accuracy and completeness before being coded and entered into version 23.0 of (Statistical Package for the Social Sciences) for analysis. The data are provided in frequency tables, cross tables, and graphs. The presentation of categorical data is based on frequency and percentages. Normally distributed continuous data are given as the mean and standard deviation. Using an unpaired t test, the difference in baseline parameters and BP change across groups was evaluated. Using a paired t-test, the difference between values before and after antihypertensive medication was evaluated within the same group. A p value less than or equal to 0.05 was considered statistically significant.

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RESULTS

Age distribution of both the medicine group is resented in Table 1. In both the groups 56-65 years groupwas the commonest age group constituting 38% of Azilsartanmedoxomil and 34% of Candesartan cilexetil group. The mean age was 50.48 and 50.22 years for Azilsartanmedoxomil and Candesartan cilexetil group respectively with statistically significant difference (p value =0.899).

[Table 2] presents the sex distribution of the study subjects. In both the arms majority of the patients were male (58% of Azilsartanmedoxomil and 64% of Candesartan cilexetil group) and above analysisboth the groupswere comparable in terms of gender.

Comparison of anthropometric parameter between two groups shows no significant differenceregarding height, weight and BMI. Data is presented in [Table3].

The mean duration of hypertension in Azilsartanmedoxomil and Candesartan cilexetil group was 7.44 years and 6.52 years and on calculating we found no significant difference as regards to duration of hypertension. Data is manifested in [Table 4].

[Table 5] shows the comparison of baseline sitting DBP and SBP.Oncalculating we found both the arms were comparable in terms of baseline sitting DBP and SBP (p value = 0.578 and 0.689 respectively).

Reductions from baseline to week 8 in mean ABPM were generally greater in the azilsartan group than in thecandesartan group. The mean reductions from baseline to week 8 inthe 24-h, daytime and night-time mean DBP and SBP during ABPMwere all significantly greater in the azilsartan group than in the candesartan group. Data is presented in [Table 6].

The study drugs were equally well tolerated and there were noclear differences in the incidences of treatment-emergent adverseevents (TEAEs) between the two treatment groups. TEAEs were reported by 58% of patients who received azilsartan and 52% who received candesartan. Data is tabulated in [Table7].

The vastmajority of TEAEs were either mild or moderate in intensity in thetwo groups (28 of 50 in the azilsartan group; 25 of 50 in thecandesartan group).[Table 8] presents the data.

Discontinuations due to adverse events and serious adverse events were infrequent in both groups (only 2% in both the groups). Data is shown in [Table 9].

The most common TEAEs occurring was nasopharyngitis (18.8% in the azilsartangroup vs. 16.2% in the candesartan group), upper respiratory tract inflammation (10% vs. 8%, respectively), and pharyngitis (8% vs.6%, respectively). Data is tabulated in [Table 10].

Table 1: Age Distribution (years)

Age Group (years)	Group A (Azilsartanmedoxomil) (n=50)		Group B (Candesartancilexetil) (n=50)		p value
	Frequency	Percentage	Frequency	Percentage	0.899
25-35 years	5	10.0	4	8.0	
36-45 years	11	22.0	13	26.0	
46-55 years	15	30.0	16	32.0	
56-65 years	19	38.0	17	34.0	
Total	50	100.0	50	100.0	
Mean Age:	50.48±10.73		50.22±9.80		

Table 2: Sex Distribution

Sex	Group A (Azilsartanmedoxomil) (n=50)		Group B (Candesartancilexetil) (n=50)		p value
	Frequency	Percentage	Frequency	Percentage	0.538
Male	29	58.0	32	64.0	
Female	21	42.0	18	36.0	
Total	50	100.0	50	100.0	
Male: Female	1.38:1		1.78:1		

Table 3: Comparison of mean Anthropometric Variables

Anthropometric Variables	Group A (Azilsartanmedoxomil) (n=50)		Group B (Candesartancilexetil) (n=50)		p value
	Mean	±SD	Mean	±SD	
Height (cms)	161.9	±9.54	164.64	±10.17	0.167
Weight (kgs)	64.24	±7.09	65.62	±5.36	0.274
BMI (kg/m^2)	24.45	±2.74	24.27	±2.35	0.725

Table 4: Duration of Hypertension

Duration (years)	Group A (Azilsartanmedoxomil) (n=50)		Group B (Candesartancilexetil) (n=50)		p value
	Frequency	Percentage	Frequency	Percentage	0.174
<5 years	14	28.0	19	38.0	
5-10 years	26	52.0	23	46.0	
>10 years	10	20.0	8	16.0	
Total	50	100.0	50	100.0	
Mean Duration	7.44±3.41		6.52±3.32		

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Table 5: Comparison of Baseline sitting BP (mmHg)

Baseline Sitting BP (mmHg)	Group A (Azilsartanmedoxomil) (n=50)		Group B (Candesartancilexetil) (n=50)		p value
	Mean	±SD	Mean	±SD	
DBP (mmHg)	101.92	±4.75	101.38	±4.93	0.578
SBP (mmHg)	154.4	±7.59	153.8	±7.38	0.689

Table 6: Comparison of Changes in ABPM values from baseline to week 8

ABPM Values (mmHg)	Group A (Azilsartanmedoxomil) (n=50)		Group B (Candesartancilexetil) (n=50)		p value
	Mean	±SD	Mean	±SD	
24-hr mean DBP (mmHg)	10.34	±(-0.55)	4.9	±0.23	<0.0001
Day time mean DBP (mmHg)	14.82	±(-0.25)	6.6	±0.89	<0.0001
Night time mean DBP DBP (mmHg)	5.54	±(-0.12)	2.32	±(-0.86)	<0.0001
24-hr mean SBP (mmHg)	15.3	±1.08	9.1	±(-0.16)	<0.0001
Day time mean SBP (mmHg)	13.1	±2.15	7.4	±0.47	<0.0001
Night time mean SBP DBP (mmHg)	15.8	±0.64	10.9	±0.5	<0.0001

Table 7: Treatment-emergent Adverse Events (TEAE)

Adverse Events	Group A (Azilsartanmedoxomil) (n=50)		Group B (Candesartancilexetil) (n=50)		p value
	Frequency	Percentage	Frequency	Percentage	0.546
Patients experiencing at least 1 TEAE	29	58.0	26	52.0	
No TEAE	21	42.0	24	48.0	
Total	50	100.0	50	100.0	

Table 8: Type of Adverse Events

Type of Adverse Events	Group A (Azilsartanmedoxomil) (n=50)		Group B (Candesartancilexetil) (n=50)		p value
	Frequency	Percentage	Frequency	Percentage	
Mild Events	25	50.0	22	44.0	
Moderate Events	3	6.0	3	6.0	0.986
Severe Events	1	2.0	1	2.0	

Table 9: Incidence of different TEAEs

TEAEs	Group A (Azilsartanmedoxomil) (n=50)		Group B (Candesartancilexetil) (n=50)		p value
	Frequency	Percentage	Frequency	Percentage	0.914
Treatment-related TEAEs	4	8.0	2	4.0	
TEAEs leading to drug discontinuation	1	2.0	1	2.0	
Serious TEAEs	0	0.0	0	0.0	

Table 10: Most Common TEAEs

TEAEs	Group A (Azilsartanmedoxomil) (n=50)		Group B (Candesartancilexetil) (n=50)	
	Frequency	Percentage	Frequency	Percentage
Nasopharyngitis	10	20.0	8	16.0
Upper respiratory tract inflammation	5	10.0	4	8.0
Pharyngitis	4	8.0	3	6.0
Gastroenteritis	2	4.0	2	4.0
Blood creatine phosphokinase increased	2	4.0	1	2.0
Seasonal allergy	1	2.0	1	2.0
Back pain	1	2.0	0	0.0

DISCUSSION

Hypertension is a prevalent condition among adults worldwide and one of the most prevalent causes of death. Hypertension is a leading risk factor for cardiovascular disease, and precise blood pressure (BP) control is essential for preventing cardiovascular disease.[13]

The average BP level over 24 hours, nocturnal and early morning BP levels are more closely connected with organ damage and cardiovascular events than office BP.[14]

In actual reality, however, it is not uncommon for antihypertensive medications to fail to provide an adequate antihypertensive impact that lasts for 24 hours.[15]

In the J-MORE (Jichi Morning Hypertension Research) study, 60.7% of treated hypertensives with well-controlled clinic BP had masked morning hypertension (systolic BP (SBP) X135mmHg; diastolic BP (DBP) X85mmHg), and only 16.4% of

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patients had well-controlled clinic and morning BP levels.[16]

These findings may be attributable to the limited BP-lowering efficacy and duration of action of some antihypertensives, underscoring the necessity of once-daily therapies that reduce BP for a complete 24 hours when delivered once.

Antihypertensive therapy aims to maintain blood pressure 140/90 mm Hg in the majority of patients.[17] Azilsartanmedoximil, a new generation ARB for the treatment of essential hypertension, was discovered by Japanese pharmaceutical company Takeda scientists by altering the tetrazole ring present in candesartan. The only difference between the chemical structures of azilsartan and candesartan is the substitution of candesartan's five-member tetrazole ring with azilsartan'soxa-oxadiazole ring. This change renders azilsartan more lipophilic and less acidic than candesartan. Azilsartan was newly licenced, and it has been demonstrated that its antihypertensive effects are stronger and more persistent than those of other ARBs.

In vitro research revealed that azilsartan has greater affinity for and slower dissociation from AT1 receptors than other ARBs (olmesartan, telmisartan, valsartan and irbesartan).[18]

The purpose of the current study was to assess the efficacy and safety of azilsartan 40–80 mg once daily vs candesartan cilexetil 8-16 mg once daily in individuals with mild to moderate essential hypertension.

Azilsartan (40–80mg once daily) achieved a substantially higher reduction from baseline of sitting trough SBP and sitting trough DBP than candesartan (8–16mg once daily) in individuals with mild to moderate essential hypertension at all time points from weeks 2 to 8 across the treatment duration. In addition, the proportions of clinical responders and well-controlled patients at week 8 were considerably greater in the azilsartan group compared to the candesartan group. When the time-courses of BP changes with two ARBs were evaluated by ABPM at 14 weeks, it was found that azilsartan provided a significantly greater reduction from baseline in mean SBP and DBP than candesartan during the 24-h time period, as well as in the daytime during waking, at night during sleep, and in the early morning (SBP), indicating a more sustained duration of action.

In this trial, the prolonged duration of antihypertensive activity of azilsartan was not at the expense of tolerance, since both ARBs were similarly well tolerated. The majority of TEAEs were low in severity, and nasopharyngitis, upper respiratory tract inflammation, and pharyngitis were the most frequently reported adverse events with both medicines. Azilsartan had a slightly higher rate of treatment-related adverse effects than candesartan. Importantly, these occurrences posed no clinical concern, as they did not result in syncope or gout, as they were often of mild severity and recovered without intervention. Overall, treatment-related adverse events were uncommon in both groups. There was no discernible trend of time- or dose-dependence in the incidence of TEAEs with either medication, and there were no clinically significant laboratory test results, vital signs, body weight, or 12-lead electrocardiogram abnormalities.

In preclinical and clinical trials, a novel angiotensin receptor blocker, azilsartan, was demonstrated to provide cardiovascular advantages by decreasing blood pressure. These advantages are a result of its high affinity for and sluggish dissociation from AT1R. In clinical trials, antihypertensive medication has been related with reductions in (1) stroke incidence by an average of 35-40%, (2) myocardial infarction (MI) by an average of 20-25%, and (3) heart failure (HF) by an average of over 50%.[19]

Azilsartan in clinically approved doses as azilsartanmedoxomil has been shown to reduce 24-hour blood pressure in hypertensive patients significantly more than the maximum clinically approved dose of olmesartanmedoxomil, which is considered by some to be one of the most potent ARBs for lowering blood pressure.[20]

CONCLUSION

And hence, azilsartan given once daily has the potential to provide higher rates of hypertension control over a 24-h period (including the night and early morning hours) and might be expected to provide greater protection against cardiovascular events in patients with essential hypertension, although this remains to be proven in prospectively designed clinical studies. Azilsartan, a relatively novel angiotensin receptor blocker, has been shown to reduce blood pressure in a safe and effective manner. Its effectiveness is on par with that of candesartan, and its adverse effects are milder, making it suitable for usage in all patients.

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