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International Journal of Current Research
Vol. 8, Issue, 06, pp.33349-33353, June, 2016

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

EVALUATION OF EFFICACY AND SAFETY OF ORAL OLMESARTAN AND CHLORTHALIDONE FIXED DOSE COMBINATION IN THE MANAGEMENT OF HYPERTENSION IN INDIAN PATIENTS

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ARTICLE INFO

Article History:
Received 14th March, 2016
Received in revised form
28th April, 2016
Accepted 15th May, 2016
Published online 30th June, 2016

Key words:

Olmesartan, Chlorthalidone,
Hypertension, JNC VIII,
Fixed dose combination.

ABSTRACT

Introduction: Despite many therapeutic options available only one-third of hypertensive patients achieve target Blood pressure (BP). Different clinical studies have reported that reducing the blood pressure can substantially decrease cardiovascular risk and all cause mortality.
Aim: The present study was undertaken to evaluate the efficacy and safety of, fixed dose combination of Olmesartan 40 mg + Chlorthalidone 12.5mg, in the management of hypertension uncontrolled with Olmesartan monotherapy.
Materials and Method: 105 patients were enrolled in this postmarketing surveillance (PMS) study. Patients were prescribed to take fixed dose combination for 60 days.
Result: There was a significant decrease ($p<0.0001$) in systolic blood pressure (SBP) & diastolic blood pressure (DBP) from the baseline to 15th, 30th and 60th days of the treatment. At the end of the study period of 60 days 93.4% & 91.6 % patients of age group >60 years and <60 years achieved the Joint National Committee (JNC VIII) recommended goal respectively. (<150/90 for elder patients aged above 60 year and 140/90 for those aged less than 60 years).
Conclusion: Thus fixed dose combination therapy of Olmesartan & Chlorthalidone has been shown to be excellent in efficacy and tolerability & gives another option for the optimal management of hypertension.

Citation: Dr. G. Chitti Pantulu, Dr. Avinash Shende, Dr. Prathmesh Mule and Dr. A. A. Faruqui. 2016. "Evaluation of efficacy and safety of oral olmesartan and chlorthalidone fixed dose combination in the management of hypertension in Indian Patients", International Journal of Current Research, 8, (06), 33349-33353.

INTRODUCTION

Hypertension is a very common and serious condition which can lead to many health related problems and cardiovascular disease (CVD). It is the most important cause of morbidity and mortality. It is estimated that 18% of adult men and 13% of adult women have high blood pressure. It is associated with at least 7.6 million deaths per year worldwide (13.5% of all deaths), making it the leading risk factor for CVD (Lawes *et al*., 2008 and Benjamin *et al*., 2013). Data of hypertensive patients have shown that increase in systolic blood pressure leads to increase in cardiovascular disease in any age group. The World Health Organization (WHO) has estimated that high blood pressure causes one in every eight deaths, making hypertension the third leading killer in the world. Globally, there are one billion hypertensives and four million people die annually as a direct result of hypertension (Lewington *et al*., 2002). An achievement of recommended goal of target blood pressure (BP) [< 150/90 mmHg in elderly >60 years hypertensive, < 140/90 mm Hg in hypertensives with diabetes mellitus (DM)], CKD (Chronic kidney disease) is difficult in majority of patients with hypertension (American Diabetes Association, 2010 and Ong *et al*., 2007). Clinical studies have shown that for every 20mmHg increase in systolic BP, or for every 10mmHg increase in diastolic BP, doubles the risk of CVD. It has been observed in meta-analysis studies that for every 20mmHg reduction in systolic BP there is 40–45% reduction in cardiovascular disease (Staessen *et al*., 2001). Hypertension acts synergistically with diabetes and dyslipidemia; can coexist frequently in increasing the risk of both macrovascular and microvascular complications.[5] Hence, BP control has been found to be difficult to achieve with monotherapy (Lewis *et al*., 2001). National Health and Nutrition Examination Survey (NHANES III) has shown that

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64% of patients with hypertension also have dyslipidemia and conversely, approximately 47% of patients with dyslipidemia have hypertension. Hypertension and hypercholesterolemia are the two leading risk factors for heart disease; these two together cause an increase in coronary heart disease related events (Devabhaktuni *et al*., 2009). Various studies have shown that tight control of BP is required to produce the maximum reduction in clinical cardiovascular end points (Lewington *et al*., 2002 and Hansson *et al*., 1998). In India, the situation is more alerting as hypertension contributes for nearly 10% of all deaths. Prevalence of hypertension in India is reported to vary from 4-15% in urban and 2-8% in rural population (Sandozi *et al*., 2010). The European Society of Hypertension and Cardiology, states that the primary goal of treatment is to achieve the maximum reduction in long-term total risk of cardiovascular morbidity and mortality (Mancia *et al*., 2007). Recent epidemiological studies indicate that the approach of using monotherapy for the control of hypertension is not successful in most patients and especially in those with some co morbidities (eg. DM, heart failure), (Oparil *et al*., 1998 and Larochelle *et al*., 1997). The achievement of BP goal typically require 2 or more medications in single-pill fixed-dose combination (FDC) products because more than 50% will require more than one drug for appropriate control of their BP (Norris, 2007). Combination of drugs make them available in a convenient dosing form, lowers the dose and can be given in once daily schedule thus improving patient compliance. Combination of drugs, leads to an additive or synergistic antihypertensive effect at lower doses of individual components and at the same time the drugs in combination counteract the side effects of each other. This helps more patients to achieve normal BP and even can be effective in hard-to treat populations. Early normalization of BP may greatly motivate the patients to adhere to lifelong treatment.[16] Monotherapy achieves only a limited number of patients target goal of BP. Since hypertension is multifactorial disease, most patients require two or more antihypertensive agents with different mechanisms of action for the optimal management (Sanjay Kalra *et al*., 2010 and Mancia *et al*., 2009). This approach is also recommended by the Joint National Committee (JNC VIII) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. This study was conducted to find out the efficacy and tolerability of fixed dose combination of Olmesartan and Chlorthalidone in the management of hypertension uncontrolled with Olmesartan therapy.

MATERIALS AND METHODS

This study was a post marketing, non-randomized, open and non-comparative, multi centric study. The fixed dose combination of Olmesartan 40 mg and Chlorthalidone 12.5 mg was administered to hypertensive patients once daily for 2 months (60 days). Informed consent was taken from the patients and the post marketing surveillance was in accordance with the principles in declaration of Helsinki and Good Clinical Practice (GCP).

Inclusion Criteria

Both male and female hypertensive patients aged >24 years old with seated cuff ≥160 mmHg and DBP≥100 mmHg and who were willing to give informed consent were included.

Exclusion Criteria

Patients with any condition which in the opinion of the treating physician makes the patient unsuitable for inclusion like; known or suspected secondary hypertension, history of asthma or angina, female patient who is pregnant or plans to conceive and patients with known hypersensitivity to any of the ingredient of the fixed dose combination were excluded from the study.

Patient Distribution

Out of 105 patients 62 were female and 43 were male patients in the age range of 24-86 years old (Table 1).

Efficacy and Safety Evaluations

To evaluate the Efficacy following parameters were observed.

Primary outcome Measures

Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were included in primary outcome, which were evaluated at 15th, 30th and 60th day of treatment.

Secondary Outcome Measures

Global assessment of efficacy and safety were included in this outcome & patients achieving the goal set by JNC VIII that is <150/90 for elder patients aged above 60 year and 140/90 for those aged less than 60 years with or without diabetes. Global assessment regarding safety was evaluated by recording any adverse event or any complaint during the therapy during every visit. Safety outcomes include mainly symptoms related to hypotension like blurred vision, confusion, dizziness, nausea, vomiting, weakness or any other untoward effects. Patients were interviewed and asked about the type of adverse events throughout the study.

Statistical analysis

Data analysis on patient demographics and various outcome measures were performed using graph pad prism 6. Comparison between the baseline values with the value on the 15th, 30th and 60th day of treatment were made, as well as comparison in between these days were made by applying one way analysis of variance & the Turkeys multiple comparison test. Value of $P<0.05$ were considered as significant.

RESULTS

SBP and DBP were recorded. In addition, overall efficacy and tolerability was assessed at the end of the study period. The baseline characteristics of patients are summarized in the Table 1. Systolic Blood Pressure (SBP) The SBP was measured at base line and then subsequently at 15th, 30th and 60th days of treatment. The baseline SBP (Mean±SD) was 164.8±14.48 mmHg. The mean SBP at 15th, 30th and 60th days of treatment were 155.2±12.1 mmHg, 147.4±9.75 mmHg and 138.6±7.29 mmHg respectively. There was statistically significant ($p<0.0001$) decrease in SBP from the baseline to the 15th, 30th and 60th day of treatment (Table 2, Fig. 1). SBP decreased by -9.60±2.38 mmHg, -17.40±4.73 mmHg and -26.20±7.19 mmHg from the baseline to 15th, 30th and 60th day of treatment respectively (Table 3).

Table 1. Baseline characteristics of all patients

Male/Female (n)	43/62
Age (yrs) range	24-86
Number of patients > 60 years	33
Number of patients < 60 years	72
SBP (Mean±SD)mm Hg	164.80±14.48
DBP (Mean±SD)mm Hg	96.72±7.28

Table 2. Effect of drug therapy on BP

	Baseline	Day 15***	Day 30***#	Day 60***#
Mean±SD mmHg (SBP)	164.8±14.48	155.2±12.1	147.4±9.75	138.6±7.29
Mean±SD mmHg (DBP)	96.72±7.28	89.31±5.66	85.96±5.03	82.054±4.97

*** p<0.0001 vs. baseline, # p<0.0001 vs. Day 15

Table 3. Change in SBP and DBP from the baseline (Mean±SD mmHg)

BP	Day 15	Day 30	Day 60
ΔSBP	-9.60±2.38	-17.40±4.73	-26.20±7.19
ΔDBP	-7.41±1.62	-10.76±2.25	-14.67±2.31

Table 4. Percentage of patients (>60 years and <60 years) achieving the target BP respectively <150/90 mmHg and <140/90 mmHg

	Day 15	Day 30	Day 60
% of patients (n) >60 years	(12/33) 36.3%	(24/33) 72.7%	(31/33) 93.4%
% of patients (n) <60 years	(10/72) 13.8%	(35/72) 48.6%	(66/72) 91.6%

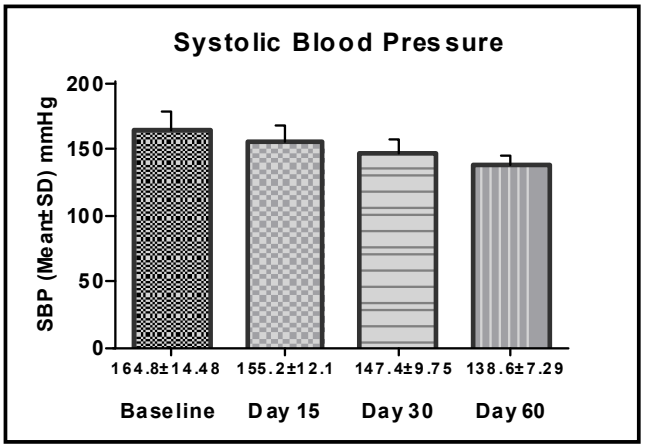

Fig. 1. Change in Systolic Blood Pressure from baseline to day 60

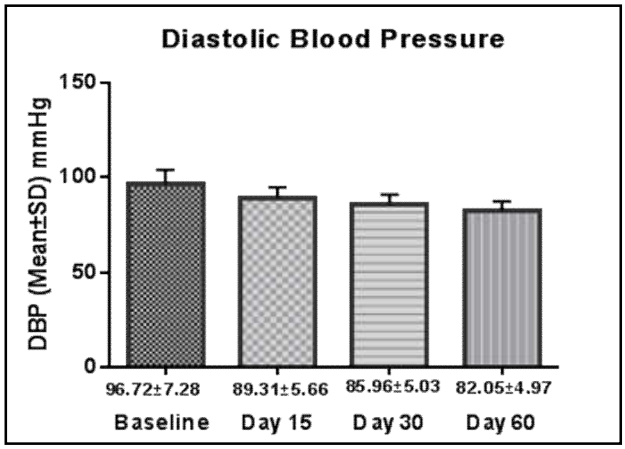

Fig. 2. Change in Distolic Blood Pressure from baseline to day 60

Diastolic Blood Pressure (DBP)

The DBP was measured at base line and then subsequently at 15th, 30th and 60th days of treatment. The baseline DBP (Mean±SD) was 96.72±7.28 mmHg. The mean DBP at 15th, 30th and 60th days of treatment were 89.31±5.66 mmHg, 85.96±5.03 mmHg and 82.054±4.97 mmHg respectively. There was a statistically significant (p<0.0001) decrease in DBP from the baseline to the 15th, 30th and 60th day of treatment (Table 2, Fig. 2). DBP decreased by -7.41±1.62 mmHg, -10.76±2.25 mmHg and -14.67±2.31 mmHg from the baseline to 15th, 30th and 60th day of treatment respectively. (Table 3).

Achievement of JNC VIII goal

As per JNC VIII recommended target goal for patients >60 years old is 150/90 mmHg and 140/90 mmHg for patients of age <60 years. During and after the treatment following are the percentage of patients achieving the target BP goal (Table 4).

Global Assessment of Safety

Treatment was well tolerated and 13 out of 105 patients (12.3 %) complained about the side effects like general weakness, headache and dizziness.

DISCUSSION

The goal for the optimal management of Hypertension is the effective control of BP with minimum complications and adverse effects that improves the patient quality life. Most guidelines in optimal management of hypertension, recommends combination therapy to achieve the target goal

BP. European guidelines and many other guidelines suggest the need of fixed dose combination therapy for the treatment of hypertension (Mancia *et al*., 2009 and Chobanian *et al*., 2003). Treatment adherence is an important issue for a chronic disease such as hypertension, with improvements in adherence expected to result in better long-term clinical outcomes, including reduced CV and renal morbidity/mortality and, consequently, containment of health care costs (Paramore *et al*., 2001). The prevalence of hypertension is increasing from last one decade hence appropriate antihypertensive drug therapy is important (Gupta *et al*., 2004). European guidelines and many other guidelines suggest the need of fixed dose combination therapy for the treatment of hypertension (Mancia *et al*., 2009 and Law *et al*., 2009). Clinical studies have shown that using fixed dose combinations in a single pill helps in improving the control of hypertension and are efficient to achieve target goal of BP with no safety issues (Alleman *et al*., 2008 and Pool *et al*., 2007). A study conducted by Bramhabhatt *et al* using the same drug combination for 2 months (60 days) in the management of hypertension reported that at the end of the study period 95.4% & 90.9% patients of age group >60 years and <60 years achieved the JNC VIII recommended goal respectively (Mancia *et al*., 2007). Result of the present study is comparable wherein 93.4% & 91.6% of the patients of age group >60 and <60 years respectively achieved the JNC VIII goal. Side effects were mild in nature and did not require discontinuation of therapy. Overall no safety concern for treatment was identified.

Conclusion

Fixed dose combination therapy of Olmesartan with Chlorthalidone is an effective, safe and convenient treatment approach in controlling the blood pressure and achieving the desired blood pressure goal according to JNC VIII in Indian patients.

Acknowledgments

Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to Mr. Jatinkumar D. Dedakia (M.Pharm-Pharmacology) for doing the statistical analysis.

Competing Interests

All authors had access to the data and vouch for the veracity and completeness of the data and the data analysis.

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