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CLINICOPHARMACOLOGICAL COMPARISON OF EFFICACY AND SAFETY OF AZILSARTAN VERSUS ENALAPRIL AMONG PATIENTS OF HYPERTENSION WITH DIABETES.

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ABSTRACT **Background:** Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are well established drugs for the treatment of hypertension with or without renal disease Azilasartan is a new angiotensin receptor blocker used in the treatment of hypertension. Present study is planned to compare the antihypertensive efficacy and safety of azilsartan with enalapril in patients of hypertension with diabetes.

Material and Method: This is a longitudinal, prospective , randomized , comparative study between Azilsartan and Enalapril. The study was conducted in department of pharmacology and out patient cardiology of J.A. group of hospital, Gajra Raja Medical College Gwalior, M.P. Total 90 patients diagnosed as hypertension with diabetes were enrolled and divided into two groups (45 in each group) during February 2018 to March 2019. Group I received azilsartan 40-80 mg once daily and group II received enalapril 5-10 mg once daily for 12 weeks. Baseline systolic blood pressure and diastolic blood pressure were recorded in the start and at the 4th, 8th, 12th weeks after therapy. Fasting and post prandial blood sugar were recorded in the start and after 12 weeks of therapy. All the patients were screened for any adverse drug reaction on every visit.

At the end of 12 week significant ($P<0.05$) reduction in systolic blood pressure and diastolic blood pressure was seen in both the groups. SBP decreased by -22.76 mmHg in azilsartan treated group and -20.59 mmHg in enalapril treated group as compared to baseline blood pressure.

On comparing the two groups reduction fall in DBP with azilasartan -11.46 mmHg was significant ($P<0.05$) as compared to -10.19 mmHg with enalapril at the end of 12 weeks.

Blood sugar control in azilsartan group was found better as compared to enalapril group.

Conclusion: Azilsartan and enalapril are proved to be effective in patients of hypertension with diabetes. However azilasartan has shown significantly better efficacy in lowering DBP as compared to enalapril.

KEYWORDS : Azilsartan, Enalapril ,Hypertension, diabetes, blood pressure

INTRODUCTION:

Hypertension occurs more commonly in diabetes than in non-diabetics. About 20 to 60% of patients with diabetes , depending on obesity , ethnicity , and age develop hypertension[1]. Most patients with both disorders have a markedly worsened risk for premature microvascular and macrovascular complications. Patients with hypertension are at two to three times higher risk of developing diabetes than patients with normal blood pressure[2,3]. The simultaneous presence of hypertension and diabetes is devastating to the cardiovascular system. In patients with diabetes blood pressure events and can slow down the progression of renal disease[3,4].

Many effective drugs are available to treat hypertension. Knowledge of their antihypertensive mechanism and site of action allows accurate prediction of efficacy and toxicity. Several studies indicate that about forty percent of patients with hypertension do not have adequate blood pressure control[5]. Hence, there is need for search of newer antihypertensive drugs.

Angiotensin converting enzyme inhibitors are well established drugs to treat hypertension with diabetes but development of cough and angioedema with their prolong use is a limitation[6]. Angiotensin receptor blockers act by blocking action of angiotensin II on AT1 receptors are equally efficacious and devoid of cough and angioedema[7]. Azilsartan medoxomil (AZL-M) is a newer angiotensin receptor blocker and is promising drug to control blood pressure. It is a prodrug and is converted into active metabolite in the GIT[7].

Till now, there is no study available regarding its effectiveness in hypertension with diabetes. Therefore, present work is undertaken to compare the clinicopharmacological action and safety of azilsartan versus enalapril in patients of hypertension with diabetes.

MATERIAL AND METHODS:

The study was conducted in department of pharmacology and out patients department of cardiology in Gajra raja medical college, Gwalior, M.P. during academic session February 2018 to March 2019 after the approval institutional ethical committee.

This was prospective, comparative, parallel , open ,randomized , clinical trial. A total of 90 patients were enrolled in the study as per the selection criteria. Patients with already diagnosed hypertension with diabetes of either sex within the age group of 35-65 years with blood pressure of >140/90 mmHg were included in the study . The upper limit of blood pressure in both groups was 180/110 mmHg . Patients belonging to hypertension were selected as per JNC VIII report.

The following categories of patients were included and excluded from the study:

Inclusion Criteria

1) Confirmed Cases of hypertension with Diabetes Mellitus [having Systolic blood pressure (SBP) 140-180 mm of Hg, Diastolic blood pressure (DBP) 90-110 mm of Hg] diagnosed by the physician.
2) The participant could be of either sex.
3) The participant must be 35 years and not more than 65 years old.

Exclusion Criteria-

1) Undiagnosed cases
2) Patients suffered from CVS, CNS, endocrine disease, pulmonary disease. cancer
3) Pregnancy
4) Fever of unknown etiology
5) Unable to provide informed consent
6) All HIV or HBsAg positive patients
7) Patients of allergic reaction (drug under study)

Demographic data:

Demographic characteristic were recorded in the case report form (Table 1)

Recording of blood pressure:

The patients were examined by the consultant physician for diagnosis.

Systolic and diastolic blood pressure was measured in right arm, sitting posture by auscultatory method using standard mercury sphygmomanometer. The pressure at which the sounds were first heard was taken as the systolic pressure and the pressure at which the sounds disappeared was taken as the diastolic pressure[8]. Diagnosed cases of hypertension with diabetes were randomly allocated in two group having 45 patients in each groups using random number table . Group A (receive tablet Azilsartan 40-80mg) and Group B (receive tablet Enalapril 5-10mg) once daily for 12 weeks. All patients were instructed to take the tablet orally with glass of water in the morning.

The patients were advised to report for follow-up every 4,8,12weeks. On each visit, blood pressure was recorded.

Measurements of blood sugar:
Fasting blood sugar (FBS) and postprandial blood sugar (PPBS) level were measured at the start of therapy and after 12 weeks.

Recording of adverse effects:
Patients were observed at every visit for cough, ankle oedema, nasopharyngitis, headache or any other adverse effects after start of treatment.

Statistical Analysis:
All the data analysis was performed by using SPSS (version 20) software. Quantitative variables were expressed as the mean and standard deviation. P-value of < 0.05 is considered as significant.

RESULT-

Patients demographics:
A total of 90 patients were already diagnosed hypertension with type 2 diabetes of either sex the age group of 35-65 years. These patients had blood pressure between >140/90with upper limit of blood pressure 180/110 mmHg. Total 7 out of 90 patients were dropped out from study, thus 41 patients in group I and 42 patients in group II completed the study. There were no remarkable differences between the treatment groups for baseline demographic characteristic (Table 1). The mean age of patients was 52 years in both treatment groups; males accounted for 60% of azilsartan group and 54% of enalapril group. The baseline mean sitting blood pressure were 155.4/94.35 mmHg. All patients were married and 86% were literate.

Effect on blood pressure level in two group:
The mean change in SBP after 12 weeks with azilsartan was -22.76±3.03 mmHg and with enalapril was -20.76±3.4 mmHg.these effects were statistically significant ($p<0.0001$) as comparing the effects on systolic blood pressure of two drugs azilsartan showed better efficacy but was not significant ($p>0.05$) as compared to enalapril.

The mean change in DBP after 12 weeks with azilsartan was -11.46±1.1mmHg and with enalapril was -10.19±0.7 mmHg.these effect were statistically significant ($p<0.001$). on intergroup comparison, azilsartan showed significant ($p<0.05$) decrease in diastolic blood pressure as compared to enalapril treated group.

Comparison of blood glucose level in two groups:
patients of both groups were treated with either metformin or glimepiride or combination as per instruction of treating physician. The mean change in FBS and PPBS after 12 weeks with azilsartan group was -26.88±14.44 mg/dl and with enalapril group was -22.62±13.89 mg/dl. These effect were statistically significant ($p<0.001$) as compared to baseline value. On comparison the azilsartan showed better sugar control than enalapril treated patients but was not significant ($p>0.05$). the results showed that sugar control was better in azilsartan group.

Safety and tolerability
Both the drugs in our study were well tolerated and were found to be safe. Only two adverse reaction reported were headache and nasopharnyngitis out of 41 (4.8%) patients treated with azilsartan, Ankle oedema and cough were reported in three patients out of 42 patients (7.14%) treated with enalapril .

DISCUSSION:

ARBs are considered as one of the best available therapeutic option for the treatment of hypertension. They act by preventing the binding of angiotensin II on AT1 receptor[9]. Azilsartan is a newer ARB found superior to other sartans such as valsartan, olmesartan, and candesartan in lowering blood pressure[7]. In present study, azilsartan at the dose of 40-80 mg once daily for 12 weeks decreased blood pressure by 22.76 mmHg. An earlier double blind study revealed decreased in blood pressure with azilsartan by 14.3 mm Hg after 6 weeks of treatment and was better than valsartan 10 mmHg and Olmesartan 11.7 mmHg . Our study shows similar results in patients of hypertension with diabetes. In present study azilsartan showed better reduction in SBP than enalapril but was not significant. When compared the effect on DBP , azilsartan was found to be superior to angiotensin converting enzyme inhibitors enalapril. Our study is in accordance with a double blind study where azilsartan showed significant fall in DBP as compared to ramipril[10]. Effect of azilsartan on DBP might be due to reduction of vascular inflammation, proliferation and endothelial dysfunction [11,12,13,14]. Present study revealed that azilsartan treated patients showed better control of fasting and post prandial blood sugar as compared to enalapril treated patients[14].This might be due to increased sensitivity to insulin by azilsartan as reported earlier in an animal study suggesting a possible role of azilsartan in the treatment of DM[14]. In another animal study azilsartan has shown vascular protection in diabetes induced vascular dysfunction[15,16].

Azilsartan was found safe drug in this study as only headache and nasopharyngitis were reported in two patients (4.8%) whereas enalapril caused cough and ankle oedema in three patients (7.1%) .Thus, azilsartan found safe and better tolerated drug[10].

CONCLUSION:

The results of present study revealed that azilsartan a new angiotensin receptor blocker has shown superior BP lowering effects when compared with enalapril and is well tolerated in patients of Hypertension with DM. Thus, the present study demonstrated that Azilsartan can be used safely and effectively as an anti-hypertensive for the management of hypertensive patients with or without diabetes. However, the study has its share of limitation. The small number of patients studied over a short period of time. Thus, a firm conclusion cannot be drawn. Extensive studies for longer duration and large number of patients are needed to establish azilsartan as new therapeutic strategy for the treatment of hypertension with metabolic disorder with other antihypertensive drugs .

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