Original Research Paper

Volume-8 | Issue-5 | May-2018 | PRINT ISSN No 2249-555X

Pharmacology

EFFECT OF CILNIDIPINE VERSUS LOSARTAN ON LIPID PROFILE IN PATIENTS OF HYPERTENSION WITH OR WITHOUT DIABETES

Mayuri K. Bhalerao — M.D. Pharmacology, Gajra Raja Medical college, Gwalior, M.P., India.

Saroj Kothari* — Professor and Head, department of Pharmacology, Gajra Raja Medical college, Gwalior, M.P., India. *Corresponding Author

ABSTRACT

Introduction: With the presence of the beneficial effects unlike other calcium channel blockers, status of cilnidipine over losartan on lipid profile (LP) of hypertensive patients with or without type 2 diabetes mellitus (DM) is yet to be established.

Aim: To investigate the comparison between cilnidipine and losartan with respect to changes in LP in hypertensive patients with or without DM.

Methods and materials: We conducted a longitudinal, prospective, open labelled, comparative clinical study. Of 161 enrolled hypertensives, 130 completed the study with follow up over a period of one year. Group I (n=34); and Group III (n = 32) patients with type 2 DM received cilnidipine 10-20mg orally OD. Group II (n =33); and Group IV (n = 31) patients with type 2 DM received losartan 50-100mg orally OD. HDL-C, LDL-C & TC; and TGs were assessed at the start and at the end of the study.

Statistical Analysis: Using the one-tailed paired Student's t-test.

Results: Post-treatment, both cilnidipine treated groups, showed significant increase in the HDL - C levels (group I from 46.55±8.21 to 48.91±9.02, p value = 0.000 and group III from 51.48±7.34 to 54.40±7.65, p value = 0.000) while losartan treated groups showed significant decrease in TC levels (group II from 205.83±37.67 to 204.99±37.67, p value = 0.035 and group IV 226.1±44.1 to 224.97±44.91, p value =0.030) at the end of 12 weeks of therapy. However, on inter-group comparison, there were no significant differences in HDL-C, LDL-C, TC and TGs between the cilnidipine and losartan groups.

Conclusion: The present study demonstrated that cilnidipine can be recommended as an alternative anti-hypertensive, may be more useful for patients of hypertension with or without diabetes mellitus from its effects on lipid metabolism.

KEYWORDS : Hypertensives, type 2 Diabetes mellitus, total cholesterol, HDL-Cholesterol, LDL-Cholesterol, triglycerides

INTRODUCTION

Hypertension is a major health problem in developed and developing countries[1,2] . It is an important risk factor for cardiovascular morbidity and mortality. Risk is further increased if high blood pressure is associated with DM and dyslipidemia.

Two of the major determinants of cardiovascular disease (CVD), hypertension and hyperlipidemia, commonly coexist. There is a high prevalence (5-25%) of low high density lipoprotein (HDL) cholesterol and a high triglyceride (TGL) levels in hypertensives as compared to normotensives.[3] Elevated total cholesterol (TC) levels augment the risk of CVD associated with hypertension. In fact, a large proportion of the cardiovascular risk in hypertensives can be attributed to dyslipidaemia.

The higher cardiovascular risk when these two conditions coexist warrants a strict emphasis on dietary and pharmacological therapy to successfully achieve BP control. Contrary to the goal, it is reported that only 32% of hypertensives manage to improve their LP, while this percentage falls to 11% for control of both BP and lipids.[4]

Patients with the common lipid triad (hypertriglyceridaemia, high LDL and low HDL) are at high risk for CVD. This risk is even greater when the lipid triad is accompanied by hypertension and diabetes. The Heart Protection Study (HPS),[5] which included 20,536 patients, reported a 24% relative reduction in the risk of major cardiovascular events after active lipid treatment and, a 25% reduction in the relative risk of stroke.

The antihypertensive drugs in use today were designed primarily to affect cellular and biochemical mechanisms contributing to increased BP, and not to address the disordered lipid metabolism that often accompanies hypertension. Angiotensin II receptor blockers (ARB) act through inhibition of AT1 receptors.[6] In experimental models, ARB improved the overproduction and accumulation of TGL in the liver, through mechanisms independent of their hypotensive action.[7] In another study the administration of losartan to children of essential hypertensive parents, with early metabolic abnormalities, was followed by significant reduction in TC and TGL.[8]

Calcium channel blockers (CCBs) are among the first line drugs for hypertension. Cilnidipine is novel and unique 1,4 dihydropyridine derivative with potent inhibitory action on L-type and N-type voltage dependent calcium channels unlike the other CCBs which have action only on L-type calcium channel.

Status of cilnidipine over losartan on LP of hypertensive patients with or without diabetes is yet to be established. Hence, the present work of clinicopharmacological comparison of cilnidipine versus losartan was planned.

Materials and Methods

After approval of protocol and study document from institutional ethical committee, we undertook randomized, prospective, open label, comparative clinical study of total 161 hypertensives with or without diabetes in G.R. Medical College, Gwalior. The study was conducted in the outpatient Cardiology clinic from July 2014 to June 2015. Patients were screened for selection criteria.

Selection of cases:

A) Inclusion Criteria:

1) Confirmed cases of hypertension having systolic (SBP) 140-180 mmHg and/or diastolic BP (DBP) 90-110 mmHg diagnosed by the physician.
2) Confirmed cases of hypertension with DM diagnosed by the physician.
3) The participant could be of either sex.
4) The participant must be 30 years and not more than 65 years old.

B) Exclusion Criteria: Patients of -

1) Thyrotoxicosis, acromegaly or hypothyroidism
2) Cushing's syndrome, pheochromocytoma, or scleroderma
3) hyperaldosteronism, or hyperparathyroidism
4) Pregnancy induced hypertension, eclampsia and pre-eclampsia or hypertension due to hormonal contraceptives (with ethinylestradiol)
5) Neurologic disorders, neurofibromatosis, or obstructive sleep apnoea
6) Cancers, all HIV or HBs Ag positive patients
7) Drugs viz. alcohol, nasal decongestants, NSAIDs, MAO Inhibitors, steroid use, nicotine use
8) Fever of unknown aetiology

9) Perioperative hypertension
10) Severe aortic stenosis, cardiogenic shock, heart failure and hypotension or recent history of unstable angina or myocardial infarction
11) Anti-tubercular therapy, or anti-psychotics

Over a period of 12 months, subjects of either sex fulfilling the selection criteria were enrolled if they provided written informed consent and were randomly allocated into 4 groups.

- Group I (n= 34) - 10-20mg of Cilnidipine
- Group II (n=33) - 50-100mg of losartan
- Group III (n= 32) with type 2 DM - 10-20mg of cilnidipine
- Group IV (n = 31) with type 2 DM - 50-100mg of losartan

Patients were instructed to take their medication in the morning after breakfast orally OD. The goal of BP was set at < 140/90 mmHg, for patients> 60 years <150/90 while for DM patients <130/80 [9] and attempts were made to keep the BP at this level.

For monitoring of LP, readings were first taken at the onset of study & then at the end of 12 weeks. The blood samples were collected from the antecubital vein between 8 a.m. and 10 a.m., with patient in sitting position, after 12 hours of fasting and avoiding alcohol.

After this, observations were analysed & appropriate statistical methods were applied to validate the results.

Statistical Analysis:
Values are expressed as the mean ± SD. Differences between pre-treatment and post-treatment values within the same group, and also differences between post-treatment values of cilnidipine and losartan groups were examined for statistical significance using one-tailed paired Student's t-test. P-value less than 0.05 denoted presence of statistically significant difference.

RESULTS

During the study, of total 161enrolled patients, 31 were dropped out. There were no significant differences in Baseline characteristics between the cilnidipine and losartan groups (Table 1).

Table 1:Baseline characteristics

Demographic Factors	Group I	Group II	Group III	Group IV
Age (years)	52.5+10.2	56.2+8.34	56.9+8.12	57+8.1
Male (%)	15(44)	16(48.48)	22 (68.75)	22 (71)
Female (%)	19(56)	17(51.52)	10 (31.25)	9(29)
LP parameters (mg/dl)				
HDL	46.55±8.21	45.6±7.64	51.48±7.34	51.02±7.58
LDL	140.49±23.36	141.43±20.6	149.83±21.61	150.22±37.19
TC	205.64±33.17	205.83±37.67	226.65±26.83	226.1±44.1
TG	133.89±51.56	133.96±44.59	174.18±67.21	173.85±67.25

There were significant differences ($p < 0.05$) in HDL – C in group I & group III while TC in group II & group IV parameters (Table 2).

Table 2:Changes in the LP parameters

LP parameters (mg/dl)	Group I (Pre-treatment values)	Group I (Post-treatment values)	P value	Group II (Pre-treatment values)	Group II (Post-treatment values)	P value
HDL	46.55±8.21	48.91±9.02	0.000	45.6±7.64	45.97±7.78	0.076
LDL	140.49±23.36	141.29±22.46	0.718	141.43±20.6	140.3±21.3	0.101
TC	205.64±33.17	203.85±36.84	0.514	205.83±37.67	204.99±37.67	0.035

On post-treatment comparison, there were no significant differences in HDL, LDL, TC & TG values between the cilnidipine and losartan groups (Table 3).

Table 3: Comparison of post – treatment LP parameters changes

LP parameters (mg/dl)	Group I (Post treatment Values)	Group II (Post-treatment values)	P Value	Group III (Post-treatment values)	Group IV (Post-treatment values)	P value
HDL	48.91±9.02	45.97±7.78	0.157	54.40±7.65	51.64±7.61	0.156
LDL	141.29±22.46	140.3±21.3	0.855	148.77±21.1	147.33±33.89	0.839
TC	203.85±36.84	204.99±37.67	0.901	225.98±26.51	224.97±44.91	0.913
TG	133.11±50.61	132.54±42.65	0.961	172.65±63.39	170.48±65.10	0.894

So, overall both cilnidipine groups, i.e. hypertension with or without diabetes showed significant increase in the HDL - C levels at the end of 12 weeks of treatment while there were no significant alterations in the TC, LDL – C or TG levels.

In present study, in losartan treated patients, both hypertension alone or diabetic hypertensives, there were no significant changes in HDL – C, LDL – C or TG levels but significant decrease in TC levels was observed at the end of 12 weeks of therapy.

While considering comparison of changes in LP, cilnidipine showed overall greater improvement in HDL – C than losartan but difference was not significant, both in patients of hypertension with or without diabetes. Though losartan showed significant changes in TC levels but on comparison with cilnidipine there was no significant difference.

Discussion

This is possibly the first randomized controlled study from India to compare effect on changes in LP of novel CCB, cilnidipine with standard drug treatment losartan.

Hypertension is not the only determinant of cardiovascular damage and the propensity of a subject to develop atherosclerotic vascular disease is markedly affected by the presence of traditional risk factors, such as age, gender, obesity, smoking, diabetes and dyslipidaemia. [10]

Epidemiological studies provide a large body of evidence for independent relationship between LP and cardiovascular risk. [11] Treating hypertension along with dietary and lifestyle modifications is the cornerstone of successful clinical management of these patients. [12]

There is no doubt that management of lipid disorders in hypertensives ameliorates their total cardiovascular risk. Clinical trials suggest that some antihypertensives may have beneficial effect on lipid metabolism, through various possible mechanisms. [13]

There have been several studies to find the effect of cilnidipine on LP of hypertensive patients and also comparing the effects of cilnidipine with other drugs like amlodipine, nislodipine. [14, 15, 16, 17] However, there have been no studies investigating the comparison of effect of cilnidipine and losartan on LP parameters.

In this study, once daily use of cilnidipine and losartan was equally efficacious in significantly decreasing and maintaining the BP level. Overall both cilnidipine groups, i.e. hypertension with or without

diabetes showed significant increase in the HDL - C levels. This finding is consistant with findings of study by Ahaneku JE et al. 2000, in which 16 adult hypertensives underwent serum lipids, lipoproteins and plasma fibrinolytic parameters evaluations. After 3 months of cilnidipine treatment, results showed cilnidipine had beneficial lipid and lipoprotein changes, including positive impact on HDL – C levels. [17] It seems therefore likely that N-type calcium channel inhibitory action is involved in improvement of LP with cilnidipine.

In losartan treated patients, there were no significant changes in HDL – C, LDL – C or TG levels but significant decrease in TC levels was observed. Although changes were small, this finding is consistent with possibility of an ARB- induced, angiotensin II-receptor-dependent amelioration of the LP in essential hypertensives. It is possible that lipid lowering property of ARB is due to numerous different mechanisms [18]. The whole spectrum of possible mechanisms through which ARB exert a beneficial effect on lipid metabolism remains unknown.

Concerning intergroup comparison, neither HDL – C, LDL-C, TC nor TG levels with cilnidipine differed significantly from those with losartan.

The study has its share of limitations. Patients < 30 years and >65 years were not included. Also, the small number of patients studied over a short period of time. Thus, more studies should be carried out and more light should be thrown on this aspect in future.

Conclusion

This is the first controlled, comparative clinical study to evaluate the effect of cilnidipine over LP of the patient, versus losartan. The present study demonstrated that cilnidipine in addition to its anti-hypertensive action showed overall more improvement in HDL –C levels but on comparison to losartan, the difference was not significant. Notwithstanding the limitations, we can conclude that our data suggest that cilnidipine can be recommended as an alternative anti-hypertensive, may be useful for patients with hypertension and diabetes mellitus from its effects on lipid metabolism. More light should be thrown on this aspect in future.

References:

1. Arun Chockalingam, Norman R Campbell, and J George Fodor, 1.Can J Cardiol. 2006 May; 22(7): 553–555.Worldwide epidemic of hypertension
2. P. M. Kearney, M. Whelton, K. Reynolds, P. Muntner, P. K. Whelton, and J. He, "Global burden of hypertension: analysis of worldwide data," The Lancet, vol. 365, no. 9455, pp. 217–223, 2005.
3. Kannel WB: Hypertension as a risk factor for cardiac events: epidemiologic results of long-term studies. J Cardiovasc Pharmacol 1993; 21: 27-37.
4. Fedder DO, Koro CE, L'Italien GJ: New National Cholesterol Education Program III Guidelines for Primary Prevention Lipid - Lowering Drug Therapy. Circulation 2002; 105: 152-156.
5. Heart Protection Study Collaborative Group: MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360: 7-22.
6. Meredith PA: Angiotensin II receptor antagonists alone and combined with hydrochlorothiazide: potential benefits beyond the antihypertensive effect. Am J Cardiovasc Drugs 2005; 5: 171-183.
7. Ran J, Hirano T, Adachi M: Angiotensin II type 1 receptor blocker ameliorates overproduction and accumulation of triglyceride in the liver of Zucker fatty rats. Am J Physiol Endocrinol Metab 2004; 2: 227-232.
8. Lerch M, Teuscher A, Beissner P: Effects of angiotensin II receptor blockade with losartan on insulin sensitivity, LP, and endothelin in normotensive offspring of hypertensive parents. J C Pharm 1998; 31: 576-580.
9. Derosa G, Ragonesi PD, Mugellini A, et al: Effects of telmisartan compared with eprosartan on blood pressure control, glucose metabolism and LP in hypertensive, type 2 diabetic patients: a randomized, double-blind, placebo-controlled 12-month study. Hypertens Res 2004; 27: 457-464.
10. Hanefeld M, Abletshauser C: Effect of angiotensin receptor antagonist valsartan on LP and glucose metabolism in patients with hypertension. J Int Med Res 2001; 29: 270- 279.
11. Seventh report of the Joint National Committee on prevention, detection, evaluation, treatment of high blood pressure. Hypertension. 2003; 42: 1206-1252.
12. Catena C, Novello M, Lapenna R, et al. New risk factors for atherosclerosis in hypertension: focus on the prothrombotic state and lipoprotein (a). JHypertens 2005; 23: 1617-1631.
13. Kwiterovich PO: The antiatherogenetic role of high-density lipoprotein cholesterol. Am J Cardiol 1998; 82: 13-2. Ahaneku JE
14. Sakata K, Urano T, Takada Y, Takada A. Influence of baseline values on lipids, lipoproteins and fibrinolytic parameters during treatment of hypertension with cilnidipine Pharmacological Research 2000; 41(1): 79–82.
15. Salve PS, Khanwelkar C effects of calcium channel blockers on different biochemical parameters in essential hypertensive patients, National Journal of Basic Medical Science. II (4): 353-356.
16. Masuda T, Ogura MN, Moriya T, Takahira N, Matsumoto T. et al. Beneficial effects of L- and N-type calcium channel blocker on glucose and lipid metabolism and renal function in patients with hypertension and type II diabetes mellitus. CardiovascTher. 2011; 29: 46–53.
17. Minami J, Ishimitsu T, Higashi T, Numabe A, Matsuoka H: Comparison between cilnidipine and nisoldipine with respect to effects on blood pressure and heart rate in hypertensive patients. Hypertens Res 1998; 21: 215−219.
18. Prisant LM: Preventing type II diabetes mellitus. J ClinPharmacol 2004; 44: 406-413.