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"OBSERVATIONS ON THE EFFECTS OF NEWER ANTI-HYPERTENSIVE DRUGS CILNIDIPINE & BENIDIPINE ON TOTAL LIPID PROFILE & SERUM CREATININE IN HYPERTENSIVE PATIENTS"

Pharmacology

Dr. Sushil Kumar PG student, Final year, Dept of Pharmacology, Darbhanga Medical College

Dr. Swetabh Verma* Tutor, Pharmacology, Darbhanga Medical College.*Corresponding Author

Dr. Debarshi Jana Young Scientist (DST), Institute of Post-Graduate Medical Education and Research, A.J.C. Bose Road, Kolkata-700020

ABSTRACT

Aim of the present study is to observe the effects of newer anti-hypertensive drugs, cilnidipine and benidipine on the total lipid profile and serum creatinine level with an objective of providing guidelines for proper selection of the two above mentioned drugs in treatment of hypertension.
The study group was consist of 120 patients including both male and female of hypertension divided into three groups as follows :-
Control Group (Gr-I):- 40 hypertentive patients not taking cilnidipine and Benidipine as control group.
Test Group - 1 (Gr-II):- 40 hypertentive patients was be given cilnidipine as test group1.
Test Group - 2 (Gr-III):- 40 hypertentive patients was be given Benidipine as test group2.
We found that both SBP and DBP were significantly reduced inhypertentive patients taking cilnidipine and benidipine compared to control group hypertentive patients not taking cilnidipine and Benidipine during 24 weeks follow-up. Total cholesterol , triglyceride was significantly reduced in benidipine group compared to control and cilnidipine group during follow-up period. Our study showed that the difference of mean HDL was significantly higher but mean LDL was significantly lower in benidipine group compared to control and cilnidipine group during follow-up period. We can concluded that the metabolic interaction between beneficial lipid changes and Creatinine will be of value to better their understanding of the antiatherogenic effects of cilnidipine and benidipine treatment in hypertensive patients.

KEYWORDS

Anti-hypertensive Drugs, Cilnidipine, Benidipine , Lipid Profile

INTRODUCTION

Hypertension is ranked as the third most, important risk factor for attributable burden of disease in South Asia. Around the globe, about 1 billion patients are affected by hypertension and the burden is rising owing to escalating obesity and population aging and by 2025 it is projected that about 1.5 billion of patients will be affected worldwide [1].

Cardiovascular risk factors, including hypertension, tend to co-segregate more commonly than would be expected by chance. Approximately 40% of persons with essential hypertension also have dyslipidemia. Genetic studies have established a clear association between hypertension and dyslipidemia [2]. The term dyslipidemic hypertension (DH) was first used in 1988, in the context of familial dyslipidemia along with hypertension [3], which was proposed as a genetic syndrome found in approximately 12% of the patients with essential hypertension and 48% of the hypertensive sib ships [4]. Non-familial forms of DH are more common than the familial ones. Dyslipidemia, a strong predictor of cardiovascular disease (CVD) [5], causes endothelial damage [6-9], and the loss of physiological vasomotor activity that results from endothelial damage may become manifested as increased blood pressure (BP). Therefore, factors like dyslipidemia that cause endothelial dysfunction may lead to hypertension According to recent "Joint National Committee 8 guidelines", calcium channel blockers (CCBs) are one of the first-line recommended drugs for the treatment of hypertension [10]. Out of various subtypes of Ca2+ channels (i.e. L, N, T, P/Q, and R), clinically used common CCBs act on primarily L-type, T-type and N-type calcium channels. Structurally, CCBs are divided into the dihydropyridine type and the non-dihydropyridine type [11-13].

The renin-angiotensin-aldosterone system (RAAS) promotes atherogenesis. Angiotensin II, a major villain of the RAAS pathway, promotes atherogenesis through stimulation of the angiotensin type 1 receptor (At1), which increases lipid uptake in cells, vasoconstriction, and free radical production, to foster both hypertension and atherosclerosis [14].

Benidipine is an orally active drug for the treatment of hypertension and angina pectoris synthesized and developed by Kyowa Hakko Kogyo Co., Ltd. Benidipine, approved in Japan in November 1991, has become one of the three best selling CCBs and is highly useful as a potent, long-lasting antihypertensive and antianginal agent. Benidipine is the only DHP-derived CCB satisfying all of the following features: 1) developed in Japan, 2) used once daily, and 3) indicated for angina pectoris, hypertension, and renoparenchymal hypertension. This drug exhibits noteworthy pharmacological actions and fewer side effects.

Aims and Objectives :- Aim of the present study is to observe the effects of newer anti-hypertensive drugs, cilnidipine and benidipine on the total lipid profile and serum creatinine level with an objective of providing guidelines for proper selection of the two above mentioned drugs in treatment of hypertension.

MATERIAL AND METHODS

Cases of hypertensive patients were randomly selected from general medicine ward and OPD of DMCH Laheriasarai. The study group was consist of 120 patients including both male and female of hypertension divided into three groups as follows :-

Group (I) :- 40 hypertentive patients not taking cilnidipine and Benidipine as control group.

Group (ii) :- 40 hypertentive patients was be given cilnidipine as test group1.

Group (iii) :- 40 hypertentive patients was be given Benidipine as test group2.

Method :-

(A) Measurement of total lipid profile was be done by enzymatic method
(B) Measurement of blood pressure by Auscultatory and palpatory method with the help of mercury sphygmomanometer
(C) Serum creatinine estimation was be done by enzymatic method

Place of study :-

The study was done on indoor and outdoor patients of department of medicine, Darbhanga Medical College, Laheriasarai. Investigative procedure was be done at department of pharmacology, Darbhanga Medical College, Laheriasarai with all available facilities including well furnished laboratory, necessary equipments and Infrastructure.

Statistical Analysis:

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS (version 25.0; SPSS Inc., Chicago, IL, USA) and Graph Pad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved independent samples or

unpaired samplesUnpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. p-value ≤ 0.05 was considered for statistically significant.

RESULT AND ANALYSIS

In our study showed that control Group (Gr-I), 4(10.0%) patients were under ≤40 years old and in Test Group - 2 (Gr-III), 1(2.5%) patient was under ≤40 years old. In Control Group (Gr-I), 4(10.0%) patients were 41-50 years old, in Test Group - 1 (Gr-II), 6(15.0%) patients were 41-50years old and in Test Group - 2 (Gr-III), 10(25.0%) patients were 41-50years old.In Control Group (Gr-I), 13(32.5%) patients were 51-60 years old, in Test Group - 1 (Gr-II), 10(25.0%) patients were 51-60 years old and in Test Group - 2 (Gr-III), 9(22.5%) patients were 51-60 years old.

We found that control Group (Gr-I), 23(57.5%) patients were 61-70 years old, in Test Group - 1 (Gr-II), 20(50.0%) patients were 61-70 years old and in Test Group - 2 (Gr-III), 20(50.0%) patients were 61-70 years old. The association between Age vs three groups was not statistically significant (p=0.1681).21(52.5%) patients were female in Control Group (Gr-I), 18(45.0%) patients were female in Test Group - 1 (Gr-II) and 18(45.0%) patients were female in Test Group - 2 (Gr-III).19(47.5%) patients were male in Control Group (Gr-I), 22(55.0%) patients were male in Test Group - 1 (Gr-II) and 22(55.0%) patients were male in Test Group - 2 (Gr-III).

The difference of mean Age with three groups was not statistically significant (p=0.2528).

We showed that the difference of mean SBP Baseline with three groups was not statistically significant (p=0.2871).The difference of mean SBP at 6 weeks with three groups was statistically significant (p<0.0001). The difference of mean SBP at 24 weeks with three groups was statistically significant (p<0.0001).

It was found that the difference of mean DBP Baseline with three groups was not statistically significant (p=0.2226).The difference of mean DBP at 6 weeks with three groups was statistically significant (p<0.0001).The difference of mean DBP at 24 weeks with three groups was statistically significant (p<0.0001).

Our study showed that the difference of mean TC (mg/dl) Baseline with three groups was not statistically significant (p=0.0085). The difference of mean TC (mg/dl) at 6 weeks with three groups was not statistically significant (p=0.1594). The difference of mean TC (mg/dl) at 24 weeks with three groups was statistically significant (p=0.0069).

We found that the difference of mean TG (mg/dl) Baseline with three groups was statistically significant (p=0.0060). In our study showed that the difference of mean TG (mg/dl) at 6 weeks with three groups was statistically significant (p=0.0003). The difference of mean TG (mg/dl) at 24 weeks with three groups was statistically significant (p<0.0001).

We found that the difference of mean HDL (mg/dl) Baseline with three groups was statistically significant (p=0.0001). We found that difference of mean HDL (mg/dl) at 6 weeks with three groups was statistically significant (p<0.0001). The difference of mean HDL (mg/dl) at 24 weeks with three groups was statistically significant (p<0.0001).

Our study showed that the difference of mean LDL (mg/ dl) Baseline with three groups was statistically significant (p=0.0015). The difference of mean LDL (mg/ dl) at 6 weeks with three groups was statistically significant (p=0.0037). In our study showed that the difference of mean LDL (mg/ dl) at 24 weeks with three groups was statistically significant (p=0.0024).

The difference of mean Serum Creatinine Baseline at 6 weeks with three groups was statistically significant (p=0.0031). The difference of mean Serum Creatinine at 24 weeks with three groups was statistically significant (p<0.0001).

DISCUSSION

The study group was consist of 120 patients including both male and female of hypertension divided into three groups as follows :-

Control Group (Gr-I):- 40 hypertentive patients not taking cilnidipine and Benidipine as control group.

Test Group - 1 (Gr-II):- 40 hypertentive patients was be given cilnidipine as test group1.

Test Group - 2 (Gr-III):- 40 hypertentive patients was be given Benidipine as test group2.

Hoshide S et al [15] (2005) found that 24-h ambulatory BP monitoring before and after once-daily use of cilnidipine (n=55) and amlodipine (n=55) in 110 hypertensive patients. N-type calcium channel blockade by cilnidipine may not cause reflex tachycardia, and may be useful for hypertensive treatment. **Morimoto S et al [16] (2001)** found that systolic and DBP and HR were not significantly different between groups before antihypertensive treatment. Cilnidipine, but not nifedipine, significantly reduced white coat effects on SBP and HR. Furthermore, white coat effects on systolic BP and HR were significantly lower after treatment in the cilnidipine group compared with the nifedipine group.

Adake P et al [17] (2015) found that cilnidipine have shown efficacy in reducing blood pressure in hypertensive individuals. **Shetty R et al [18] (2013)** found that therapy with cilnidipine resulted in complete resolution of amlodipine-induced edema in all the cases without significant worsening of hypertension or tachycardia. Cilnidipine is an acceptable alternative antihypertensive for patients with amlodipine-induced edema.

Srivastava A et al [19] (2016) found that the serum lipid profile of recently diagnosed untreated hypertensive patient was deranged specially in a middle age group (the study group) as compared to healthy subjects. Based on the results obtained from the present study, it could be further envisaged that serum cholesterol; triglyceride levels are positively correlated with hypertensive patients whereas HDL-cholesterol has no significant changes with hypertension.

It was found that difference of mean SBP Baseline and DBP Baseline with three groups were not statistically significant. The difference of mean SBP at 6 weeks with three groups was statistically significant (p<0.0001). The difference of mean SBP at 24 weeks with three groups was statistically significant (p<0.0001).

The difference of mean DBP at 6 weeks with three groups was statistically significant (p<0.0001). The difference of mean DBP at 24 weeks with three groups was statistically significant (p<0.0001).

Kumar P et al [20] (2016) found that Cilnidipine was started at 10 mg/day, and then adjusted to 5 - 20 mg/day to achieve the target blood pressure. After 12 weeks of study, patients showed significant reduction in systolic blood pressure, diastolic blood pressure, mean BP, heart rate and serum triglyceride level from baseline values (P < 0.00).

Our study showed that the difference of mean TC (mg/dl) Baseline with three groups was not statistically significant (p=0.0085). The difference of mean TC (mg/dl) at 6 weeks with three groups was not statistically significant (p=0.1594). The difference of mean TC (mg/dl) at 24 weeks with three groups was statistically significant (p=0.0069). We found that the difference of mean TG (mg/dl) Baseline with three groups was statistically significant (p=0.0060). In our study showed that the difference of mean TG (mg/dl) at 6 weeks with three groups was statistically significant (p=0.0003). The difference of mean TG (mg/dl) at 24 weeks with three groups was statistically significant (p<0.0001).We found that the difference of mean HDL (mg/dl) Baseline with three groups was statistically significant (p=0.0001). We found that difference of mean HDL (mg/dl) at 6 weeks with three groups was statistically significant (p<0.0001). The difference of mean HDL (mg/dl) at 24 weeks with three groups was statistically significant (p<0.0001). Our study showed that the difference of mean LDL (mg/ dl) Baseline with three groups was statistically significant (p=0.0015). The difference of mean LDL (mg/ dl) at 6 weeks with three groups was statistically significant (p=0.0037). In our study showed that the difference of mean LDL (mg/ dl) at 24 weeks with three groups was statistically significant (p=0.0024).

Choudhury KN et al [21] (2014) found that the mean (± standard deviation) systolic blood pressure and diastolic blood pressure of the

participants were 137.94±9.58 and 94.42±8.81, respectively, which were higher in the hypertensive patients (P<0.001). The serum levels of TC, TG, and LDL were higher while HDL levels were lower in hypertensive subjects compared to normotensives, which was statistically significant (P<0.001). Hypertensive patients had 1.1 times higher TC and TG, 1.2 times higher LDL, and 1.1 times lower HDL than normotensives, which was statistically significant (P<0.05).

Sarkar D et al [22] (2007) found that most of the hypertensive patients (65%) were taking treatment irregularly. Serum total cholesterol, serum triglyceride and serum LDL cholesterol were greater in hypertensive than those of normotensive. The differences of mean of serum total cholesterol, serum LDL cholesterol in between two groups were statistically significant and in case of serum triglyceride it was statistically highly significant. Serum HDL cholesterol was less in hypertensive than those of normotensive. The differences of mean of serum HDL cholesterol in between two groups were statistically highly significant.

CONCLUSION:

It was found that both SBP and DBP were significantly reduced inhypertentive patients takingcilnidipine and benidipine compared to control group hypertentive patients not taking cilnidipine and Benidipine during 24 weeks follow-up.

Total cholesterol was significantly decreased in benidipine group compared to control and cilnidipine group at 24 weeks.

We also found that triglyceride was significantly reduced in benidipine group compared to control and cilnidipine group during follow-up period.

Our study showed that the difference of mean HDL was significantly higher but mean LDL was significantly lower in benidipine group compared to control and cilnidipine group during follow-up period. Mean Serum Creatinine was significantly lower in cilnidipine group compared to control and benidipine group during follow-up period.

Table1: Distribution of mean in all parameters: GROUP

		Number	Mean	SD	Minimum	Maximum	Median	p-value
Age (yrs)	Control Group (Gr-I)	40	59.7500	6.4281	47.0000	70.0000	62.0000	0.2528
	Test Group - 1 (Gr-II)	40	56.5500	10.3402	34.0000	70.0000	59.5000	
	Test Group - 2 (Gr-III)	40	57.5750	9.0579	35.0000	70.0000	59.5000	
SBP Baseline	Control Group (Gr-I)	40	156.3500	7.8953	142.0000	170.0000	156.0000	0.2871
	Test Group - 1 (Gr-II)	40	156.4000	8.0409	140.0000	178.0000	158.0000	
	Test Group - 2 (Gr-III)	40	158.9250	8.9023	140.0000	179.0000	158.0000	
SBP at 6 weeks	Control Group (Gr-I)	40	156.8000	6.7147	144.0000	174.0000	156.0000	<0.0001
	Test Group - 1 (Gr-II)	40	145.9000	7.8766	130.0000	160.0000	146.0000	
	Test Group - 2 (Gr-III)	40	147.7250	9.8215	130.0000	168.0000	146.0000	
SBP at 24 weeks	Control Group (Gr-I)	40	158.9500	5.7822	150.0000	176.0000	160.0000	<0.0001
	Test Group - 1 (Gr-II)	40	120.2000	3.0984	114.0000	128.0000	120.0000	
	Test Group - 2 (Gr-III)	40	121.1500	3.0344	114.0000	130.0000	122.0000	
DBP Baseline	Control Group (Gr-I)	40	89.5000	6.8050	76.0000	104.0000	90.0000	0.2226
	Test Group - 1 (Gr-II)	40	91.6000	5.9777	80.0000	98.0000	90.0000	
	Test Group - 2 (Gr-III)	40	91.8500	7.0221	74.0000	98.0000	95.0000	
DBP at 6 weeks	Control Group (Gr-I)	39	90.8718	4.9160	80.0000	100.0000	90.0000	<0.0001
	Test Group - 1 (Gr-II)	40	81.7000	3.8842	74.0000	88.0000	80.0000	
	Test Group - 2 (Gr-III)	40	80.7000	4.0141	74.0000	88.0000	80.0000	
DBP at 24 weeks	Control Group (Gr-I)	40	96.5000	4.7231	88.0000	106.0000	96.0000	<0.0001
	Test Group - 1 (Gr-II)	40	72.9000	1.1048	70.0000	74.0000	72.0000	
	Test Group - 2 (Gr-III)	40	72.7500	1.2558	70.0000	74.0000	72.0000	
TC (mg/dl) Baseline	Control Group (Gr-I)	40	218.5000	39.3342	171.0000	276.0000	244.0000	0.0085
	Test Group - 1 (Gr-II)	40	241.8425	34.0463	183.0000	280.0000	259.5000	
	Test Group - 2 (Gr-III)	40	219.6250	38.5205	176.0000	272.0000	210.0000	
TC (mg/dl) at 6 weeks	Control Group (Gr-I)	40	225.0250	40.2100	178.0000	281.0000	249.0000	0.1594
	Test Group - 1 (Gr-II)	40	230.3500	33.6723	162.0000	268.0000	246.0000	
	Test Group - 2 (Gr-III)	40	214.3250	39.1626	164.0000	270.0000	208.0000	
TC (mg/dl) at 24 weeks	Control Group (Gr-I)	40	228.6300	40.0079	180.0000	283.0000	252.5000	0.0069
	Test Group - 1 (Gr-II)	40	211.0000	34.1039	134.0000	251.0000	228.0000	
	Test Group - 2 (Gr-III)	40	201.7250	39.3179	141.0000	258.0000	194.0000	
TG (mg/dl) Baseline	Control Group (Gr-I)	40	173.9500	58.4904	94.0000	264.0000	164.0000	0.0060
	Test Group - 1 (Gr-II)	40	201.8250	57.8326	98.0000	272.0000	227.5000	
	Test Group - 2 (Gr-III)	40	158.5500	63.4495	95.0000	274.0000	125.0000	
TG (mg/dl) at 6 weeks	Control Group (Gr-I)	40	187.1750	61.8907	101.0000	272.0000	195.0000	0.0003
	Test Group - 1 (Gr-II)	40	181.4250	56.5408	72.0000	241.0000	210.0000	
	Test Group - 2 (Gr-III)	40	135.7000	61.4284	75.0000	264.0000	103.0000	
TG (mg/dl) at 24 weeks	Control Group (Gr-I)	40	190.2500	61.6245	105.0000	274.0000	198.0000	<0.0001
	Test Group - 1 (Gr-II)	40	149.4750	52.6707	58.0000	226.0000	178.0000	
	Test Group - 2 (Gr-III)	40	110.0000	57.0169	51.0000	242.0000	81.0000	
HDL (mg/dl) Baseline	Control Group (Gr-I)	40	34.1250	6.7337	18.0000	49.0000	33.0000	0.0001
	Test Group - 1 (Gr-II)	40	35.9750	6.0995	25.0000	52.0000	36.0000	
	Test Group - 2 (Gr-III)	40	40.5000	6.2224	30.0000	52.0000	40.5000	
HDL (mg/dl) at 6 weeks	Control Group (Gr-I)	40	35.4000	5.5645	22.0000	47.0000	34.0000	<0.0001
	Test Group - 1 (Gr-II)	40	39.4750	5.8834	29.0000	54.0000	39.5000	
	Test Group - 2 (Gr-III)	40	45.6250	7.1061	34.0000	58.0000	48.0000	
HDL (mg/dl) at 24 weeks	Control Group (Gr-I)	40	35.9500	5.4111	24.0000	47.0000	35.5000	<0.0001
	Test Group - 1 (Gr-II)	40	49.7250	7.4317	38.0000	68.0000	48.0000	
	Test Group - 2 (Gr-III)	40	58.5000	9.0185	38.0000	72.0000	58.0000	
LDL (mg/ dl) Baseline	Control Group (Gr-I)	40	133.8750	28.3840	72.0000	164.0000	145.5000	0.0015
	Test Group - 1 (Gr-II)	40	142.1825	26.4535	79.0000	179.0000	142.0000	
	Test Group - 2 (Gr-III)	40	118.7500	30.7752	75.0000	172.0000	103.5000	
LDL (mg/ dl) at 6 weeks	Control Group (Gr-I)	40	140.7750	29.0759	80.0000	176.0000	150.0000	0.0037
	Test Group - 1 (Gr-II)	40	134.9500	26.2698	74.0000	177.0000	138.5000	
	Test Group - 2 (Gr-III)	40	119.1750	31.7691	72.0000	174.0000	106.0000	

LDL (mg/ dl) at 24 weeks	Control Group (Gr-I)	40	142.8750	29.1945	82.0000	178.0000	152.0000	0.0024
	Test Group - 1 (Gr-II)	40	121.3750	26.9270	61.0000	171.0000	125.0000	
	Test Group - 2 (Gr-III)	40	120.7250	37.8208	64.0000	185.0000	112.0000	
Serum Creatinine Baseline	Control Group (Gr-I)	40	0.8553	0.2279	0.4600	1.4000	0.8000	0.1647
	Test Group - 1 (Gr-II)	40	0.9355	0.1743	0.6600	1.3000	0.9100	
	Test Group - 2 (Gr-III)	40	0.9238	0.2019	0.6500	1.5000	0.8900	
Serum Creatinine Baseline at 6 weeks	Control Group (Gr-I)	40	0.8473	0.1486	0.5400	1.1200	0.8400	0.0031
	Test Group - 1 (Gr-II)	40	0.7235	0.1492	0.4600	1.1000	0.7100	
	Test Group - 2 (Gr-III)	40	0.8045	0.1839	0.5000	1.2000	0.8000	
Serum Creatinine at 24 weeks	Control Group (Gr-I)	40	0.9458	0.2115	0.6400	1.7000	0.9150	<0.0001
	Test Group - 1 (Gr-II)	40	0.5368	0.1156	0.3300	0.8100	0.5200	
	Test Group - 2 (Gr-III)	40	0.6838	0.1566	0.4100	1.0000	0.6600	

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