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Research Article

CLINICAL EVALUATION OF ATORVASTATIN CO-ADMINISTERED WITH ACE INHIBITORS OR CALCIUM ANTAGONISTS IN DYSLIPIDEMIC PATIENTS

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ABSTRACT

A recent epidemiologic study revealed that 56.5% of patients with hypertension (HTN) also have concomitant dyslipidemia (DYS). Accordingly our aims in this study are to evaluate the blood pressure (BP), lipid parameters [i.e. Total Cholesterol (TC), Triglycerides (TGs), Low Density Lipoprotein Cholesterol (LDL-C), Very Low Density Lipoprotein Cholesterol (VLDL-C) and High Density Lipoprotein Cholesterol (HDL-C)] and the plasma concentration of Atorvastatin on Atorvastatin co-administration either with angiotensin converting enzyme inhibitors (ACEIs) or calcium antagonist (CCBs).Objective:The main objective of this study is to evaluate the effect of Atorvastatin co administered with ACEIs and CCBs, to assess the best combination to treat the concomitant hypertension and dyslipidemia, to determine the therapeutic drug concentration of Atorvastatin.Materials and Method:This interventional study is conducted on blood plasma sample before and after administration of drugs. Thirty patients (selected according to inclusion and exclusion criteria) are divided into three groups Atorvastatin with ACEIs (Group A), Atorvastatin (Group B), Atorvastatin with CCBs (Group C).Result: Most of the patients are found with the age group between 41-60 years. At the end of eight weeks, the mean values reduction of TC, TGs, LDL-C in all three groups are significant. In the Group A, we also find a significant reduction in VLDL-C after treatment. The blood pressure lowering in both the combination group is significant. But the Group C shows much more lowering than that of Group A. The bioavailability of Atorvastatin did not altered by concomitant administration of ACE inhibitors or Calcium antagonist.Conclusion: Based on the stages of hypertension combinations are best to treat the concomitant Hypertension and Dyslipidemia. The combination of CCBs with Atorvastatin resulted in a greater decrease in both diastolic and systolic blood pressure compared with the reduction achieved with ACE inhibitors,. But the plasma concentration of Atorvastatin is not influenced by ACEIs and/ or CCBs.

Keywords: Atorvastatin, ACE Inhibitors, Calcium Antagonist, Hypertension, Dyslipidemia

INTRODUCTION

A recent epidemiologic study revealed that 56.5% of patients with hypertension (HTN) also have concomitant dyslipidemia (DYS).[1] The recognition that hypertension and DYS coexist more than would be expected by chance and that their combination increases the risk of coronary heart disease has important implications for patient management.[2] The current level of simultaneous control of both HTN and DYS is poor, with comparatively few patients achieving recommended target levels for both conditions.[3]

Moreover, certain drugs used for antihypertensive therapy can further modify lipoprotein and glucose metabolism[4]. Several studies reported that some antihypertensive drugs have beneficial effects on the lipid status, whereas others adversely affect the lipid status.[5-9]. The superior antihypertensive efficacy of the Telmisartan/Hydrochlorothiazide combination observe may reflect the longer half-life of Telmisartan of 24h compared with 7–9h for valsartan.[10] In patients with mixed dyslipidemia, the combination of fenofibric acid + Atorvastatin/Ezetimibe significantly improve lipid and nonlipid parameters compared with Atorvastatin/ ezetimibe. [11] Accordingly our aims in this study are to evaluate the blood pressure (BP), lipid parameters [i.e. Total Cholesterol (TC), Triglycerides (TGs), Low Density Lipoprotein Cholesterol (LDL-C), Very Low Density Lipoprotein Cholesterol (VLDL-C) and High Density Lipoprotein Cholesterol (HDL-C)] and the plasma concentration of Atorvastatin on Atrovastatin co-administration either with Angiotensin converting enzyme inhibitors (ACEI) or calcium antagonist.

MATERIALS AND METHODS

Study design

This interventional, 8 weeks, randomized, open labeled parallel group study is conducted in cardiac department of multispecialty hospital in Trichy. The protocol is approved by Institutional Ethical Committee.

Patient selection

30 Patients are selected according to the exclusion and inclusion criteria mentioned below.

Inclusion Criteria

Both gender, Age of 19 – 80 yrs, Hypertensive Dyslipidemia patients, Non Hypertensive Dyslipidemia patients (for Atrovastatin group only), Diabetic & Non Diabetic, Coronary artery disease

Exclusion Criteria

Patients taking other statins, Hormone Replacement Therapy, hepatic disease, renal disease, respiratory insufficiency, severe infection, Pregnancy and Lactating females, patients allergic to Atorvastatin, ACE inhibitors and calcium antagonist are excluded from the study.

Method of Study

Demographic and other required information are collected from the selected patients. Fasting blood samples are collected for evaluation of lipid parameters and BP readings are also recorded (base value). The patients are randomized into three groups to receive either combination of Atorvastatin / ACE inhibitors (Enalapril, Ramipril) Group A or Atorvastatin 40 mg alone Group B or combination of Atorvastatin/ calcium antagonist (Amlodipine, Nifedipine) Group C. The participants are revealed at the eight week for follow-up evaluation. The baseline assessment includes lipid profile (i.e. TC, TGs, LDL-C, VLDL-C and HDL-C) and blood pressure .These assessments are also done at the end of eight week visit.

Sample collection for Atorvastatin analysis

5 ml blood sample are collected in heparinized tubes after two hrs of intake of the drug on the first day. Plasma is separated and then frozen immediately at -40 ^{0}C in ultra deep freezer until assayed. Plasma concentration of Atorvastatin is determined by high performance liquid chromatography.

Quantitative Analysis of Atrovastatin [10]

HPLC Instrument used - Shimadzu (LC-10AT), Kyoto, Japan. Mobile phase - The mobile phase consisted of Ammonium Acetate buffer (PH 7.5) –Acetonitrile (59:41, v/v).

Chromatographic condition - Column: 250mm × 4.6mm LD Luna Phenomenex, 5u C18 analytical column. A Guard-Pak precolumn module containing an ODS cartiage insert is placed serially just before the analytical column. Flow rate - 1ml/min at room temperature Detector - UV detector at 276nm

Sample preparation

To each 500ul of plasma sample, the internal standard (I.S) (500µl of 50µg/ml of Rosiglitazone) and 0.5ml of Acetonitrile are added to precipitate the proteins in the plasma. The content is vortexe for 1min and centrifuged at 6000 rpm for 10min. The supernatant is transferred to a clean similarly labeled tubes, and re –centrifuged for 3 min. The supernatant is filtered through a filtration assembly equipped with 0.2µ membrane filter, and 20ul of filtrate is injected to the column.

Standard preparation

A stock solution containing 1mg/ml of Atorvastatin is prepared in CAN - water (50:50). The calibration standards (0.01, 0.02, 0.05, and 0.1 0.2, 0.5, 1, 2, 5, and 10µg/ml) are prepared by spiking plain plasma with these drug solutions in such a way that the plasma: drug ratio would be 9:1. These are used for calibration.

STATISTICAL METHODS

The values for lipid profile (TC, TG, LDL-C, HDL-C & VLDL-C) and Blood Pressure between the treatments groups are statistically evaluated by Student't' test.

RESULTS

Out of 30 patients, 13 are females and 17 are males. Most of the patients are age groups of 41-50 years and 51-60 years. Patient

demographics and medical history of patients are given in Table 1.

At the end of eight weeks, the mean values reduction of TC, TGs, LDL-C in all three groups i.e Atorvastatin with ACE inhibitors (Group A), Atorvastatin (Group B) and Atorvastatin with Calcium antagonist (Group C) are significant. The mean values reduction of VLDL-C is significant in the Group A. But the mean values reduction of VLDL-C in other two groups is not significant. The mean value increases of HDL-C from the base mean value after 8 weeks of treatment in all the three groups are not significant. The effects of drugs on lipid profile at 8 weeks of treatment and plasma concentrations of Atorvastatin in three groups are given in Table 2.

The plasma concentration of Atorvastatin in Group A, Group B and Group C are 29.37±7.70, 28.32±4.40 & 29.95±10.95 respectively. Therefore the bioavailability of Atorvastatin doesn't altered by concomitant administration of ACE inhibitors or Calcium antagonist (Table 2).

Significant blood pressure reductions ($p < 0.001$) are achieved in both treatment groups. But highest decrease in both systolic blood pressure (SBP) & Diastolic blood pressure (DBP) is found with Calcium Antagonist/Atorvastatin combination (33.4 & 19 mmHg). The effects of drugs on Blood Pressure at 8 weeks treatments are given in Table 3.

Table 1: Demographics Characteristics at the Initial Visit of the selected Patients (n=30)

Patient Characteristics	Number (%)
Gender	
Male	13(43%)
femal	17(57%)
Age (Year)	
31-40	1(3%)
41-50	11(37%)
51-60	10(33%)
61-70	8(27%)
Social history	
Smoker	5(17%)
Alcoholic	4(13%)
Tobacco	2(7%)
Smoker & alcoholic	3(10%)
Postmenopausal	8(27%)
obese	8(27%)
Medical history	
HTN	12(40%)
DM & NON HTN	3(10%)
HTN & DM	9(30%)
NON HTN & NON DM	6(20%)
Family history OF CAD	30(50%)

Table 2: Effect on Lipid Profile on treatment with Atorvastatin/ACE-inhibitor), Atorvastatin alone, Atorvastatin/calcium antagonist and comparison of plasma concentration of Atorvastatin level after administration of these groups of drugs

Parameters (Unit)	Group A Mean ± SD(n=11)		Group B Mean ± SD(n=9)		Group C Mean ± SD(n=10)	
	Base	Review	Base	Review	Base	Review
TC (mg/dl)	202.1 ± 24.7	127.9 ± 19.4***	205.1 ± 16.0	153.7 ± 22.8**	208.7 ± 16.1	161.9 ± 28.0***
TG (mg/dl)	141.3 ± 38.4	95.3 ± 37.7**	124.4 ± 35.1	84.2 ± 22.0*	165.9 ± 57.9	124.1 ± 52.5
HDL-C (mg/dl)	37.2 ± 6.3	39.4 ± 5.5	37.9 ± 5.0	39.2 ± 5.6	43.8 ± 6.3	44.6 ± 9.6
LDL-C (mg/dl)	139.0± 22.8	76.2 ± 24.1***	144.7 ± 27.5	102.9 ± 27.9**	134.9 ±15.1	109.1 ± 14.6**
VLDL-C (mg/dl)	28.4 ± 9.4	20.0 ± 9.4*	22.6 ± 7.1	16.8 ± 4.2	33.3 ± 11.5	24.7 ± 10.4
Plasma concentration of Atorvastatin after 2 hr of drug administration in ng/ml		29.4 ± 7.7		28.3 ± 4.5		29.9 ± 11.0

Statistically significant difference is as expressed as P value * < 0.01, ** < 0.001, * < 0.0001, in comparison to Base value (by Student's t test); SD – Standard Deviation; Base – Initial Value (before treatment), Review – Value after 8 week treatment**
GroupA - Atrovastatin/ACE inhibitors, Group B – Atrovastatin, Group C -Atrovastatin/Calcium antagonist

Table 3: Effect on blood pressure on treatment with Atorvastatin/ACE-inhibitor (n=11), and Atorvastatin/calcium antagonist (n=10)

Parameters	GroupA		Group C	
	Base	Review	Base	Review
SBP	136.6 ± 9.5	121.2 ± 9.8**	162.4 ± 20.2	129.0 ± 13.7***
DBP	86.4 ± 9.2	74.5 ± 8.2*	99.0 ± 7.4	80.0 ± 8.2 ***

Statistically significant difference is as expressed as P value * < 0.01, ** < 0.001, * < 0.0001, in comparison to Base value (by Student's t test); SD – Standard Deviation; Base – Initial Value (before treatment), Review – Value after 8 week treatment GroupA - Atrovastatin/ACE inhibitors, Group C -Atrovastatin/Calcium antagonist SBP – systolic Blood Pressure, DBP – Diastolic Blood Pressure.**

DISCUSSION

In the present study, we have observed that Reduction level of lipid profiles with Group A is higher than that of other two Groups. These results are confirmation of the earlier work which concluded that ACE inhibitors may decrease the TC and TGs level[12], but calcium antagonists are metabolically neutral[8].

The combination of Calcium antagonist with Atorvastatin have resulted a significant greater decrease in both diastolic and systolic blood pressures compared with the reduction achieved with ACE inhibitors. ACE inhibitors have also showed significant reduction in blood pressure. This finding of our study similar to that another study in which calcium antagonist have significantly reduced the Blood Pressure than ACE inhibitors[13]. Determination Atorvastatin concentration by HPLC method shows the availability of this drug in plasma is not changed significantly when co-administered with ACE inhibitors or Calcium antagonist in dyslipidemic patients.

Concomitant HTN and DYS are very common and are associated with a high risk of CVD. So both combinations are best to treat concomitant Hypertension and Dyslipidemia depending on the stages of hypertension.

CONCLUSION

From this study, we conclude that Total cholesterol, Triglycerides, and LDL-C, are all significantly reduced while Atorvastatin co-administered with ACEIs or CCBs. But the plasma concentration of Atorvastatin is not influenced by ACEIs or CCBs; it is proved by HPLC method.

So the use of ACE inhibitors may reduce the cardiovascular risk by not only reducing blood pressure and also indirectly reducing Total cholesterol, Triglycerides and LDL-C. The combination of CCBs with Atorvastatin resulted in a significantly greater decrease in both diastolic and systolic blood pressure compared with the reduction achieved with ACE inhibitors.

Concomitant HTN and DYS are very common and are associated with a high risk of CVD. So both combinations are best to treat concomitant Hypertension and Dyslipidemia which is based on the stages of hypertension. We confirm the previous reports of beneficial effects of ACE inhibitors on Total cholesterol and Triglycerides.

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