Shukla et al., Biochem Pharmacol (Los Angel) 2018, 7:4
DOI: 10.4172/2167-0501.1000256

Biochemistry & Pharmacology: Open Access

Research Article Open Access

Efficacy and Safety of Atorvastatin in Dyslipidemic Patients at Tertiary Care Hospital

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Abstract

Aims: The objective of the study was to assess the safety, effectiveness and Adherence of morning *versus* evening atorvastatin administration in dyslipidemic Patients.

Settings and design: A comparative study conducted at KLE's Dr. Prabhakar Kore Charitable Hospital & Medical Research Centre; Department of Medicine; Belagavi, Karnataka, India.

Methods and material: Patients who were prescribed atorvastatin 40 mg p.o. daily by their physician were interviewed by clinical pharmacist for study enrolment. Patients were excluded if they had any history diseases or medication known to effect serum lipid levels, blood samples were collected after overnight fasting period and serum lipid levels were measured at 4th and 8th week.

Statistical analysis used: Paired t-test; SPSS version 20.0

Results: 85 male patients (83.3%) and 17 (16.6%) female patients with a mean ± S.D. age of 56.72 ± 10.09 years were enrolled into the study. All patients were receiving atorvastatin in the evening, after four week the same patients were changed to morning dose. No significant change in lipid values measured were found between morning and evening administration after 8 weeks. There were no difference in the incidence of clinical adverse reactions among the morning and evening regimen.

Conclusions: Atorvastatin 40 mg was found to be safe and effective regardless of the time of drug administration i.e. morning *versus* evening without much change in the levels of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. On the contrary, significant adherence levels increased with morning administration than evening which may contribute to increase in compliance.

Keywords: Atorvastatin; Dyslipidaemia; Adherence

Introduction

Cardiovascular diseases (CVD) are one of the most prevalent diseases in healthy men and women and globally a major cause of death and disability [1]. Recently World Health Organization has declared that by 2020, 60% of cardiovascular cases will be of Indian origin because India has a disproportionately higher burden of coronary artery diseases than most developing countries [2,3]. Increasing exposer to risk factors for coronary artery diseases, such as diabetes, dyslipidaemia, hypertension and smoking are due to the rapid increase in socio-economic growth in developing countries [4]. The risk of Coronary artery diseases in Indians is 3-4 times higher than Americans, 6 times higher than Chinese and 20 times higher than Japanese [5]. Moderate lifelong reduction in LDL-C level (<70 mg/dl) as seen in people with hypobetalipoproteinaemia is associated with substantial reductions in risk of CVD and MACE, even in the presence of highly prevalent non-lipid risk factors (smoking, hypertension, etc.) [6,7]. It has been reported that 2% reduction in coronary events can be achieved by 1% decrease in serum cholesterol levels [8]. There are multiple statins available in the Indian market. Among different types of statins, atorvastatin is now considered one of the most effective statins, not only for its effects on LDL level as well as the ability to meet recommended treatment guidelines for this parameter, but also for its impact on other lipid profiles such as the level of triglyceride (TG) and also the capacity to modify lipoprotein composition in a non-atherogenic manner [9]. There are recommendations that statins to be dosed at bedtime to provide the greatest medication concentration when endogenous cholesterol production is the highest [10]. Alternatively, the longer half-lives of rosuvastatin, atorvastatin, pitavastatin, and pravastatin allow these agents to maintain a therapeutic drug concentration over a 24 hour period and allow alternate administration times. Even if properly counseled to take statins with a shorter half-life at bedtime, some patients do not comply which may result in decreased efficacy. Agents with longer half-lives allow for greater flexibility in administration time, which may improve compliance and ultimately result in greater LDLC reduction and ability to achieve cholesterol goals [11]. Therefore, this study is conducted to assess the safety, efficacy and adherence in morning and evening of atorvastatin in patients with dyslipidaemia.

Subjects and Methods

Study design

The comparative, open-label, observational study was conducted at KLE's Dr. Prabhakar Kore Hospital, Belagavi, Karnataka, India. This study was carried out from October 2015 to March 2016. The protocol was approved by institutional ethics committee. Informed consent was obtained from the patients prior to the study.

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Received: May 19, 2018; **Accepted:** October 09, 2018; **Published** October 16, 2018

Citation: Shukla S, Ganachari MS, Appajigol J, Salimath G, Gaur S, et al. (2018) Efficacy and Safety of Atorvastatin in Dyslipidemic Patients at Tertiary Care Hospital. Biochem Pharmacol (Los Angel) 7: 256. doi: 10.4172/2167-0501.1000256

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Patient selection

102 patients with dyslipidemia each taking atorvastatin 40 mg tablets in the evening were selected for the study after clinical and baseline investigations.

Inclusion criteria: Patients aged 30 years old and above having low density lipoprotein cholesterol (LDL-C) higher than 100 mg/dl, triglycerides (TG) more than 150 mg/dl, total cholesterol (TC) more than 200 mg/dl or High density lipoprotein cholesterol (HDL-C) less than 40 mg/dl were included in the study.

Exclusion criteria: Patients had diseases or conditions known to affect serum lipoprotein levels (e.g. Primary hypothyroidism; nephrotic syndrome; type 1 or uncontrolled type 2 diabetes mellitus; hepatic dysfunction; serum Creatine phosphokinase levels>3 times the upper limit of normal; uncontrolled hypertension); Patients allergic to HMG-CoA reductase inhibitors; patients on medications known to effect lipid levels were excluded from the study.

Study visit and treatment schedule

Patients meeting all inclusion but no exclusion criteria were enroll in the study. Initial readings of lipid levels like LDL, TC, TG and HDL were taken as baseline. All patients were counseled and encouraged throughout the study to follow the hypolipidemic diet (Step II diet described in the NCEP ATP II guidelines). The patient information leaflet was provided to the patients being counseled and date of their next follow-up was noted. First values for the lipids were taken at the end of 4th week when patients were on evening dose of atorvastatin 40 mg and the same patients were changed to morning dose of atorvastatin 40 mg, the second values for the lipids were taken at the end of 8th week. Adherence level were checked by counting the pills and patients were also checked for adverse drug event. Procedure of study visit and treatment schedule is summarized in Figure 1.

Statistics

All the values were expressed in mean ± SD. The baseline, first lipid values (After 4th week) and second lipid values of atorvastatin were compared by Paired t-test. P<0.05 was considered as significant (Figure 2).

Results

The data collected was evaluated for demography and treatment pattern. During the study period, 102 dyslipidemic patients were enrolled. Out of 102 patients, 02 patients lost the follow up and 02 patients withdrawal from the study due to adverse reaction.

Common diagnosis

The patients enrolled into the study were having the following diagnosis: 43 (42.15%) patients were diagnosed with hypertension; 26 (25.49%) patients were diagnosed with diabetes mellitus; 70 (68.6%) Patients were diagnosed as coronary artery disease; 92 (90.19%) patients were diagnosed with ischemic heart disease; 84 (82.3%) were having Myocardial infarction and 6 (5.88%) were diagnosed as Unstable angina.

The demographic characteristics of the study participants are shown in Table 1.

Effect of atorvastatin on serum lipids

Changes in serum lipid levels (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) are summarized in Table 2.

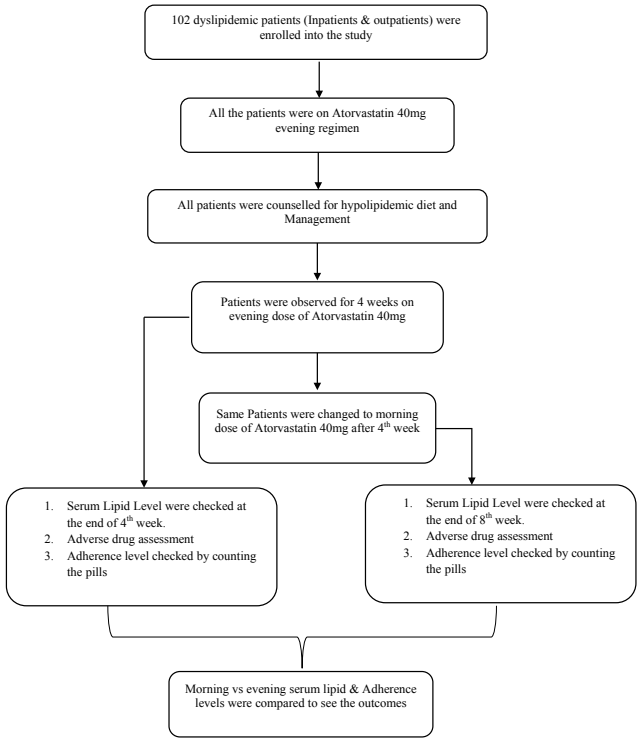

Figure 1: Study procedure for atorvastatin in patients with dyslipidemia.

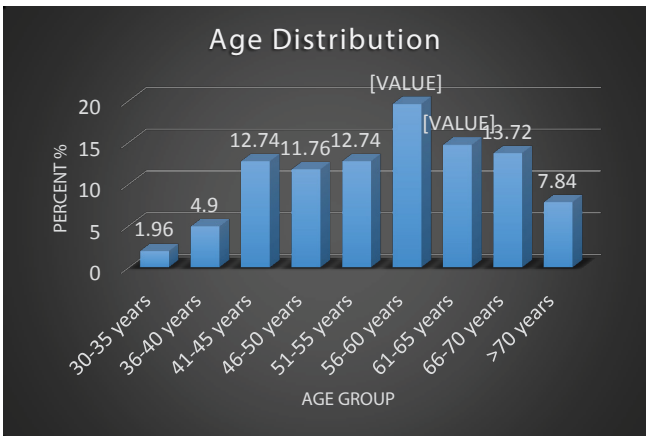

Figure 2: Age distribution (n=102).

Characteristic	No. (%) of Patients
Male	85 (83.33)
Female	17 (16.66)
Hypertension	43 (42.15)
Diabetes Mellitus	26 (25.49)
Coronary Artery Disease	70 (68.6)
Ischemic Heart Disease	92 (90.19)
Myocardial Infarction	84 (82.3)
Unstable Angina	6 (5.88)
Smoking	12 (11.76)
Alcoholic	07 (6.86)

Table 1: Characteristic of the patients receiving atorvastatin 40 mg (N=102)

Variable (mg/dl)	Baseline (SD)	Evening intake (SD)	% Change	Evening intake (SD)	Morning intake (SD)	% Change
Total Cholesterol	197.62 (24.75)	182.7 (18.30)	-7.54	182.7 (18.30)	167.98 (18.49)	-8.05
LDL- Cholesterol	135.24 (20.83)	117.48 (18.30)	-13.12	117.48 (18.30)	99.36 (17.13)	-15.42
HDL- Cholesterol	34.20 (7.7)	36.93 (5.5)	7.98	36.93 (5.5)	39.44 (7.08)	6.79
Triglycerides	144.58 (49.07)	139.69 (34.3)	-4.89	139.69 (34.3)	135.84 (28.01)	-2.75

Table 2: Mean ± S.D. Baseline and percentage Change of lipoprotein parameters after morning versus evening atorvastatin administration (N=98). (Comparison of the percent changes between morning *vs.* evening regimen P>0.05 (P_0.656))

Evening		Morning	
Characteristic	No. of Patients	Characteristic	No. of Patients
Muscle pain	1	Common cold	1
Fever	1	Gastritis	1
Back pain	1*	Muscle pain	1*
Gastritis	1	weakness	1

Table 3: Adverse experiences to atorvastatin therapy. (*Symptoms in the same patient)

Dosage Regimen	Pill	Frequency	Percentage (%)
Evening	0	54	55.1
	1	22	22.4
	2	18	18.36
	3	4	4.08
	Total	98	100
Morning	0	70	71.4
	1	24	25.26
	2	4	4.08
	3	0	0
	Total	98	100

Table 4: Number of tablets skipped.

Total cholesterol level: No significant decrease in total cholesterol were seen after morning *versus* evening administration of atorvastatin. The values for the mean percent decrease in TC level on fourth and 8th week were 8.05% and 7.54% respectively.

Low density lipoprotein cholesterol level: No significant changes in serum LDL cholesterol level were detected in the morning and evening administration of atorvastatin 40 mg. The values for the mean percent decrease in LDL level on fourth and 8th week were 15.42% and 13.12% respectively.

High density lipoprotein cholesterol: The pattern of change in serum HDL cholesterol levels is as follows, no statistically significant changes were found after morning and evening administration of atorvastatin.

Triglycerides: No significant changes in serum TG levels were found after morning and evening administration of atorvastatin. The values for the mean percent decrease in TG level after morning and evening administration were 2.75% and 4.89% respectively.

Adverse Reaction

Various symptoms were recorded, and those for which a cause-effect relation with the administered drug could not be ruled out were handled as adverse reactions. Adverse experiences are shown in Table 3. The numbers of cases of adverse reactions and the incidence of adverse reactions in morning and evening administrations were as follows: four cases (3.92%) in the evening administration group and four cases (4.04%) in the morning administration group. Drug administration had to be discontinued in two patients, one patient in evening administration group and one patient in morning administration group. The one patient in the evening administration group was a 68-year-old man who experienced unexplained Muscle pain and a 56-year-old women who experienced Back pain with Muscle pain. These adverse reactions did not require any special treatment, and they all disappeared after drug administration was discontinued.

Assessment of adherence level

Table 4 summarizes the number of tablet skipped by patients during morning and evening administration. In evening, 44 (44.89%) of the patients had missed at least one dose while in morning, 28 (28.57%) had missed at least one dose. Out of those who missed their does in the evening, 22 (22.4%) had skipped only one pill; 18 (18.3%) 2 pills; 4 (4.08%) 3 pills. In morning, 24 (25.2%) missed 1 pill; 4 (4.08%) 2 pills.

Discussion

The present study was performed to determine the most effective time of administration of atorvastatin to maximize its efficacy and to determine the safety of atorvastatin in patients with dyslipidemia.

The lipid lowering effect of atorvastatin can be noted between week 2 & 4 and it's reaches to maximum therapeutic effect between week 4 and 6. The mean elimination half- life of atorvastatin is 14 hours and the active metabolites of atorvastatin is having half-life of 20-30 hours [12]. Due to the longer half-lives of atorvastatin and their active metabolites, it appears that atorvastatin maintain a therapeutic drug concentration over a 24- hours period and allow alternate administration times without altering its lipid- lowering ability.

Plakogiannis et al., conducted a study to evaluate the effects of morning *versus* evening administration of atorvastatin in hyperlipidemic patients and found that the morning *versus* evening atorvastatin administration were equally effective in reducing total cholesterol, LDL cholesterol, and triglyceride levels and increasing the level of HDL cholesterol when compared with the baseline values. From baseline to 4th week percent change in lipoprotein level were as follows in morning *versus* evening group, respectively: Total cholesterol, -34.7% *versus* -34.6%; LDL cholesterol, -47.4% *versus* -46.6%; HDL cholesterol, 7.3% *versus* 7.6%; and triglycerides, -29.5% *versus* -28.1%. No statistically significant differences in lipid values were found between morning and evening administration group after 4 weeks [13].

Plakogiannis et al. study has several limitations. First the study lacked a randomized, double-blind design. Second, all patients enrolled in the study were male patients which may not allow the results to be extrapolated to the female population [13].

Cilla et al., conducted a non-blinded, randomized, 2 way crossover study to evaluate the effects of atorvastatin administration times and found similar changes in the lipoprotein profile regardless of morning or evening administration. Sixteen normolipidemic subjects with mean baseline LDL cholesterol value of 116 mg/dL and a mean age of 33.6 years were randomized to receive atorvastatin 40 mg at morning or evening time once daily for 15 days. All patients taking atorvastatin demonstrated statistically significant reduction in total cholesterol,

LDL cholesterol, and triglycerides levels when compared with baseline cholesterol values. Percent change in lipoprotein values from baseline to day 15 in morning *versus* evening groups as follows, respectively: total cholesterol, -33.1% *versus* -34.3%; LDL cholesterol, -47.2% *versus* -48.2%; HDL cholesterol 1.3% *versus* 2.3%; and triglycerides, -22.8% *versus* -26.4%. Despite small change in lipoprotein values favouring evening administration, no statistical and clinical significance were achieved. The data from the study are difficult to interpret and derive a conclusion for several reasons. First, the study was nonblinded and had small sample size (n=16). Second, method used for data analysis was not mentioned. Third, the study participants had normal lipid values, because of that these findings may not be reproducible in the dyslipidemic population. Fourth, since the half-life of HDL cholesterol is 5 days, 15 days may not be an adequate time of therapy to determine a rise in HDL cholesterol levels. To find out the true change in HDL cholesterol values, atorvastatin should have continued for an additional 10 days. Fifth, the P values were not provided for any of the compared lipid values [14].

In this study of dyslipidemic adults, morning *versus* evening administration of atorvastatin were equally effective in reducing total cholesterol, LDL cholesterol and triglycerides levels and increasing the level of HDL cholesterol when compared with baseline values, following mean percent changes in lipoprotein values from baseline to week 8 (study completion) in morning *versus* evening administration, respectively: LDL cholesterol, -15.42% *versus* -13.12%; total cholesterol, -8.05% *versus* -7.54%; HDL cholesterol, 6.79% *versus* 7.98%; and triglycerides, -2.75% *versus* -4.89%. No statistically significant differences in lipid values were found between morning and evening administration after 8 weeks.

The evaluation of the safety profile of atorvastatin showed adverse drug reaction rates of 3.92% in the evening and 4.04% in the morning administration. The incidence of atorvastatin in this study were not higher than other studies (3.6-12%) or of lovastatin study (10-14%).19 These adverse reactions did not require any special treatment, and they all disappeared after drug administration was discontinued. There were no adverse reactions that were considered to represent a clinical problem of particular importance, so it can be concluded that atorvastatin is a generally well tolerated drug regardless of time.

Data comparing the effects of morning *versus* evening administration of Rosuvastatin, lovastatin and pravastatin didn't showed any significant difference in the lipoprotein levels. However, evening administration of simvastatin produced a significant grater reduction in both LDL cholesterol (28.5% *versus* 19.3% in simvastatin 5 mg evening and morning groups, respectively) and total cholesterol levels (21% *versus* 14% in the simvastatin 5 mg evening and morning groups, respectively) [13].

The mean percent difference in adherence level between morning patients were found to be more than evening patients. Because 44.89% of the patients had missed their dose in the evening while 28.57% had missed in morning.

Conclusion

In consideration of the findings discussed, Out of 102 dyslipidemic patients, only 2 patient's atorvastatin dose was titrated to the lower dose which clearly emphasizes on the safety of 40 mg of Atorvastatin. The incidence of clinical adverse reactions were 7, 2 were moderate and 5 were mild according to WHO severity scale, which also indicates the safety of atorvastatin 40 mg. Changes in the levels of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were similar among dyslipidemic patients receiving atorvastatin 40 mg daily, regardless of time of day the drug was administered. Mean adherence level of atorvastatin in the morning was found to be 98.92% whereas in the morning mean adherence level was 97.85%. Significant adherence levels increased with morning administration than evening which may contribute to the increase in the compliance rate towards statin-therapy.

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