Indian J Physiol Pharmacol 2009; 53 (1): 73–82

STUDY OF PLASMA LEVEL OF ATORVASTATIN AND ITS EFFECT ON LIPID PROFILE

HEEMA R. VALERA* AND BARNA GANGULY**

*Department of Clinical Pharmacy,
Institute of Science and Technology for
Advanced Studies and Research,
Vallabh Vidyanagar (Gujarat)

and

**Department of Pharmacology,
Pramukh Swami Medical College,
Karamsad (Gujarat)

(Received on December 20, 2008)

Abstract : Atorvastatin, being one of the most commonly used antihyperlipidemic agents, is prescribed frequently by physicians all over the world but only a few data is available stating its effect in different ethnic population, more so from this part of India. The present study was designed focusing mainly on local population and was planned to determine plasma level of atorvastatin 10 mg and its effect on lipid profile in newly diagnosed hyperlipidemic patients attending Medical OPD of Shri Krishna Hospital, Karamsad (Gujarat).

Study-I was carried out in 6 healthy volunteers to determine t_{max} after single dose of atorvastatin 10 mg under fasting conditions, on the basis of which Study-II was conducted in 15 patients, collecting blood samples at a particular time (i.e t_{max} of Study-I) after administration of atorvastatin 10 mg/day on day 1 as well as on the last day after 8 weeks of treatment. The plasma concentrations were determined by RP-HPLC system. Atorvastatin 10 mg/day for 8 weeks with a plasma level range (7.45, 12.08) ng/mL significantly ($P<0.05$) reduced all the parameters of lipid profile from the study population. The mean decrease in HDL-C triggers a question on the effect of atorvastatin on HDL-C, which requires further study on a larger population of our country.

Key words : atorvastatin, hyperlipidemia, HDL-C, lipid profile, plasma level

INTRODUCTION

Hyperlipidemia- a well-known risk factor for cardiovascular disease, especially atherosclerotic coronary artery disease (CAD) is one of the major causes of premature death globally (1) and it is expected to be the most important cause of mortality in

*Corresponding Author : Heema R. Valera, 6/A, Keshav Apartments, Near Memnagar Lake, Memnagar, Ahmedabad – 380 052; Tel. No.: +91-79-27437358; E-mail: hima_rv@yahoo.co.in

India by the year 2015 (2). South Asians and particularly Asian Indians have been found to have the highest mortality rate due to CAD amongst all ethnic groups so far studied (3). Hyperlipidemia and medications used to lower cholesterol have received generous exposure from last decade and hence, as a result, public is aware that high cholesterol is a risk factor for cardiovascular disease (4). Patients in whom treatment with lifestyle modifications fails should be started on lipid-lowering agents. Patients with multiple risk factors and very high cholesterol levels may need early intervention with drug therapy because diet therapy may not reduce LDL cholesterol to the goal range (4). 3-Hydroxy 3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) are widely used in the prevention of cardiovascular events and are generally well tolerated. These agents are the most potent LDL-lowering drugs available and generally are preferred in patients with elevated LDL. Statins reduce LDL by 20 to 60%, decrease triglycerides by 10 to 40%, and increase HDL by 5 to 15% (4). Currently available products include lovastatin, pravastatin, simvastatin, fluvastatin and atorvastatin (5) which reduce the risk of CHD and total mortality, with a 30% risk reduction (6). Atorvastatin, being one of the most commonly used antihyperlipidemic agents, is prescribed very often by physicians world wide. But there are less available data on atorvastatin's effect on various profiles and parameters of different ethnic population more so from this part of world. The study was designed to focus mainly on the local population of Kramsad-Gujarat with a dietary habit of high calorie content more specifically high oil content on the daily basis, which is different to some extent from that of the other parts of the country. The present study was planned to determine plasma level of Atorvastatin 10 mg in newly diagnosed patients of hyperlipidemia attending Medicine OPD of Shri Krishna Hospital, Karamsad. The patients were instructed not to change their dietary habit throughout the treatment period.

METHODS

The study was conducted at Shri Krishna Hospital, Karamsad (Gujarat, India) and the analytical analysis was carried out at Sophisticated Instrumentation Centre for Applied Research and Testing (SICART, Vallabh Vidyanagar, Gujarat, India). The study protocol was approved by HREC (Institutional Human Research Ethics Committee of Shri Krishna Hospital, Karamsad) and the statistical analysis was carried out using SPSS software.

Participants

The entire study was conducted in two subparts, Study-I and Study-II with total 21 participants [6 healthy, adult male volunteers for Study-I and 15 newly diagnosed cases of hyperlipidemia (of either sex) for Study-II].

No formal sample size calculation was performed for Study-I carried out on healthy volunteers, as it was planned to characterize only the absorption profile more specifically tmax of atorvastatin 10 mg after single oral administration, hence considering it as a pilot study, only 6 healthy male volunteers with the homogenous demographic profile were enrolled.

For Study-II in patients, the sample size was calculated on the basis of following formula :

Sample size $n = 4pq/d^2$

Where, p = expected prevalence, q = 100-p, d = degree of precision.

Based on the experience of last few years, the expected prevalence (p) was considered to be 50% in a year. Hence, considering p = 50%, q = 100-50 = 50% and d = ± 10%, from the above formula, about 100 newly diagnosed patients were expected to receive the treatment with atorvastatin yearly.

This was the expected prevalence of one year in such a tertiary care rural hospital here, and as the present study was planned to be completed within 4 months with the patient recruitment period of 2 months only. Hence, approximately 16 newly diagnosed cases of hyperlipidemia were expected in the duration of two months. However, we could enroll 15 patients to take part in the Study-II.

All the participants were enrolled based on the inclusion and exclusion criteria. Patients with impaired renal or hepatic functions; diabetes mellitus type I or uncontrolled diabetes mellitus type II; hypothyroidism; with the history of MI, CAD, sever or unstable angina pectoris, severe cardiac arrhythmia or clinically manifested heart failure were excluded. Also alcoholics and patients taking other lipid lowering agents, antioxidant vitamins, immunosuppressive drugs, drugs known to be associated with myopathy in association with HMG Co-A reductase inhibitors and other drugs known to modulate lipid parameters like corticosteroids and isotretinoin were excluded. Pregnant and breast feeding women were also excluded to take part in the study. Patients were asked not to change their eating habits during the course of the study.

All the participants (i.e. healthy volunteers recruited for Study-I and newly diagnosed cases of hyperlipidemia recruited for Study-II) were treated with atorvastatin tablets 10 mg of the same batch of same manufacturer, to avoid formulation factor that sometimes interferes with the study result.

The study was started only after study protocol approval and permission from institutional human research ethics committee (HREC).

Study-I : On healthy volunteers

Six volunteers were screened for their healthy status one week prior to study and a written informed consent for participation in the study was obtained from each healthy volunteer after explaining them the study aspects. They were hospitalized at medicine IPD of Shri Krishna Hospital, Karamsad, one night prior to the day of dosing, being reevaluated by the physician at the time of admission for their vital signs (pulse rate, blood pressure and temperature). When admitted, the volunteers received written information explaining the events to be carried out during the study period, with the scheduled time for the drug administration, meals, blood sampling and subsequent discharge. The volunteers fasted overnight for at least 10 hours prior to dosing and

lunch was provided 4 hours post-dose. A single oral dose of Atorvastatin tablets 10 mg was administered to each volunteer with approximately 240 ml of water. They were informed to remain in sitting position for first 3 hours after dosing and also advised to avoid severe physical exertion throughout the confinement period.

Atorvastatin is rapidly absorbed after oral administration with peak plasma concentrations within 1-2 hours (24), hence, to characterize only the absorption profile of atorvastatin, the blood samples were collected 30 minutes prior to drug administration (pre-dose) and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0 and 6.0 hours post-dose administration.

Study-II: On newly diagnosed patients of hyperlipidemia

On Visit 1 (Day 0): A detailed history of the O.P.D. patients was taken with special reference to history of drug intake and allergy. The baseline investigations including lipid profile, ECG and recording of vital signs were carried out on O.P.D. basis.

Baseline reports of all the investigations were collected and the newly diagnosed hyperlipidemic patients were prescribed with Atorvastatin tablets 10 mg/day by physician. Also, the patients were explained the study aspect and asked for their willingness to participate. Written informed consent for participation was obtained from each patient willing to take part in the study. On day 1 (i.e. the first day of drug administration); the patients were asked to report to the O.P.D. after an over night fast of at least 10 hours and the first dose of drug was administered. The blood samples from each patient were withdrawn at tmax obtained from Study-I after administration of drug for determination of plasma drug concentration.

On visit 2 (8 weeks after visit 1): Detailed history of patients, drug intake and event of any adverse drug reaction were reported. All the patients were instructed to visit the O.P.D after an over night fast of at least 10 hours and the last dose of drug was administered to each patient and blood samples were collected at tmax obtained from Study-I. All the investigations including estimation of lipid profile, recording of vital signs and ECG were carried out after 8 weeks of treatment with atorvastatin tablets 10 mg.

Out of 15 patients, 1 patient was dropped out because of his failure to come for routine follow-up visit.

Blood sample collection, plasma separation and its handling prior to analysis

Blood samples from all the participants were collected in BD Vacutainer (Lithium Heparin 68 USP units) and immediately centrifuged at 4000 rpm for 10 minutes under cooling conditions to separate supernatant plasma. Separated plasma samples were collected with the help of micropipette in RIA vials previously labeled and then stored at −40°C until analyzed.

Analysis of Atorvastatin

Plasma sample analysis was performed by a validated high performance liquid chromatography (HPLC) with UV- detection.

The HPLC conditions were optimized to obtain an adequate separation of the eluted compound by the use of C-18 prontosil column, mobile phase containing methanol : acetonitrile : water (45 : 45 : 10 v/v/v) and 1.0 ml/min flow rate. Ibuprofen was applied as an internal standard, neutralizing the error inherent in sample injection; eliminating random errors. The optimum wavelength for detection was 240 nm at which much better detector response for drug was obtained.

Clinical laboratory measurement of parameters of lipid profile

Triglyceride reagent (GPO-ADPS), cholesterol reagent (CHOD-PAP) and HDL-cholesterol reagents (by immunoinhibition) are intended for *in-vitro* quantitative determination of triglyceride, cholesterol and HDL-C determination respectively in human serum.

Statistical Analysis

Data handling and statistical analysis were carried out using Microsoft Excel and SPSS software.

Student's t-test for paired variables was used to compare the differences between lipid parameters at baseline and after 8 weeks treatment period.

Linear regressions were used to determine the relationship between parameters of lipid profile (i.e. % change from baseline) and plasma concentration of Atorvastatin 10 mg after 8 weeks of treatment.

RESULTS

Study I: On healthy volunteers

Plasma level of atorvastatin in healthy volunteers :

After single dose administration of Atorvastatin 10 mg tablet to 6 healthy male volunteers, the peak plasma level (C_{max}, mean ± SD) of 14.04 ± 2.26 ng/ml was achieved at the peak time (tmax, median) of 1.5 hours. AUC_{0-6} (mean ± SD) was found to be 45.38 ± 9.30 ng.hr/ml calculated using trapezoidal formula.

Study II: On newly diagnosed patients of hyperlipidemia

Evaluation of plasma concentration of Atorvastatin 10 mg in hyperlipidemic patients :

As per the results obtained from Study-I on healthy volunteers, the blood samples from hyperlipidemic patients were collected at 1.5 hour after administration of one tablet of atorvastatin 10 mg on day 1 as well as on last day i.e. after 8 weeks of treatment; to determine plasma concentrations as shown in Table I.

Evaluation of lipid profile in hyperlipidemic patients :

Lipid profile including Total serum cholesterol (TC), Triglycerides, HDL-C, LDL-C, VLDL-C, TC/HDL-C and LDL-C/HDL-C were evaluated before starting the treatment and after 8 weeks of treatment. Table II and Fig. 1 show the value of parameters of lipid

TABLE I: The plasma concentration of Atorvastatin 10 mg in hyperlipidemic patients after first dose (on day 1) and after 8 weeks of treatment; at 1.5 hour following drug intake.

Patient number	*Concentration, ng/ml (at 1.5 hours after administration of first dose, on day 1)*	*Concentration, ng/ml (after 8 weeks, at 1.5 hours after administration of dose)*
1	8.42	11.26
2	0.33	8.5
3	3.14	10.19
4	1.68	7.45
5	5.13	9.66
6	2.25	10.43
7	8.85	10.83
8	0.98	9.03
9	4.93	10.19
10	4.39	12.08
11	2.09	8.59
12	3.25	9.14
13	8.36	12.05
14	6.06	11.72
Mean±SD	4.28±2.82	10.05±1.46

Note: Patient No. 15 was dropped out from the study, as he was not able to arrive for routine follow-up.

TABLE II: Effect of Atorvastatin 10 mg on LIPID PROFILE (mean±SEM).

Lipid profile	*Before treatment (mg/dl) (i.e. baseline)*	*After 8 weeks treatment (mg/dl)*	*% Reduction from baseline after 8 weeks of treatment*
Total cholesterol	223.09±8.92	142.67±7.07	35.95±2.17
Serum triglyceride	178.43±29.88	103.87±12.97	35.98±4.76
HDL-C	50.82±2.44	45.92±2.19	8.90±3.01
LDL-C	136.41±6.38	77.39±6.36	42.97±4.23
VLDL-C	35.69±5.98	20.80±2.59	35.82±4.83
TC/HDL-C	4.49±0.25	3.22±0.23	28.66±3.29
LDL-C/HDL-C	2.73±0.16	1.79±0.18	36.21±5.32

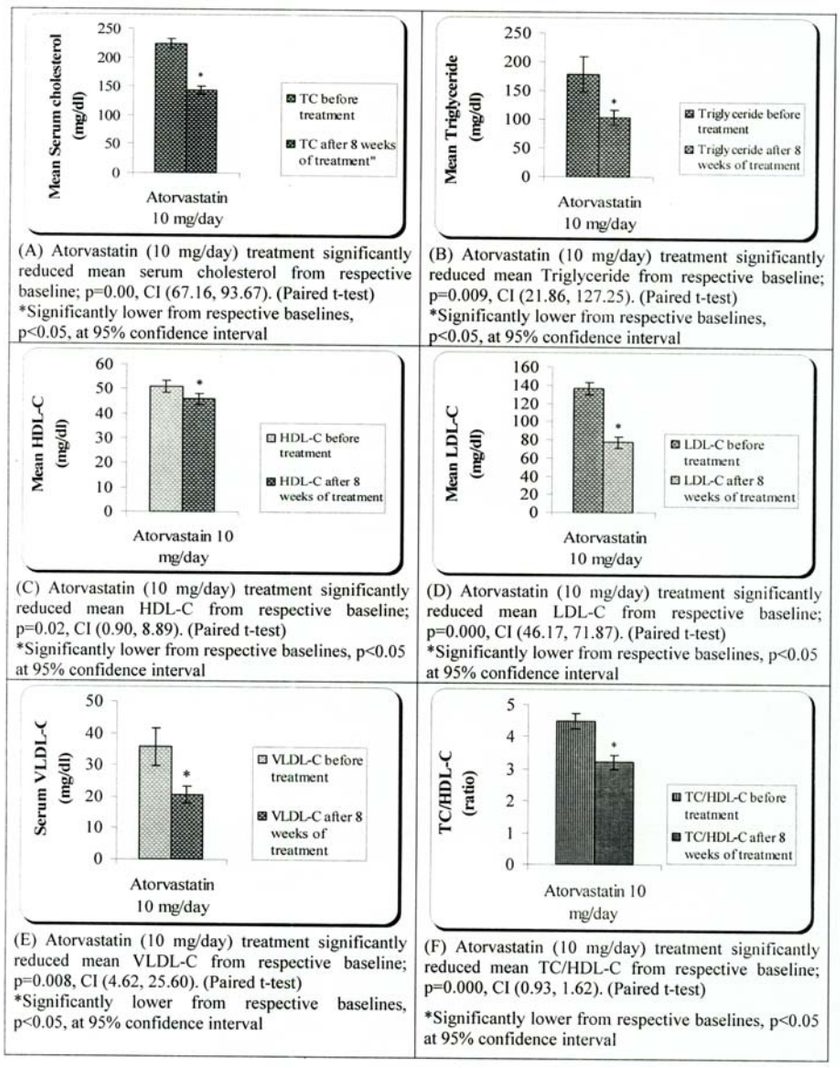
profile before treatment (i.e. baseline), after treatment and % reduction from baseline after treatment. Fig. 2 shows relationship between parameters of lipid profile (i.e. % change or decrease from baseline) and plasma concentration of Atorvastatin 10 mg after 8 weeks of treatment.

DISCUSSION

Present study involves the data of 6 healthy male volunteers and total 14 patients (5 male and 9 female newly diagnosed cases of hyperlipidemia).

In this study, all the participants were treated with Atorvastatin Tablets 10 mg/day; of the same brand and from the same batch to avoid formulation factor that sometimes interferes with the results.

The time (tmax) required to achieve maximum plasma concentration (C_{max}) of Atorvastatin 10 mg was considered as 1.5 hours as obtained form the results of Study-I on healthy volunteers and on the basis of which, blood samples were collected from 14 hyperlipidemic patients to determine plasma concentrations of atorvastatin at 1.5 hour after first intake of Atorvastatin Tablets 10 mg as well as after 8 weeks treatment period. As shown in Table I, plasma concentration (mean ± SD) for patients on day 1 at 1.5 hours after first intake of Atorvastatin Tablets 10 mg was 4.28 ± 2.82 ng/ml (range: 0.33, 8.52) and after 8 weeks, it was found to be 10.05 ± 1.46 ng/ml (range: 7.45, 12.08). A high degree of inter-subject variability observed in Cmax in this study is noteworthy, which may be due to age, gender, food intake, presence of concomitant disease and drug therapy, level of CYP3A4 expression and activity and all the factors which influence the body's handling of atorvastatin (7). An important characteristic of CYP3A4 is the large inter-individual variability in activity (about 5-fold), which reflects genetic polymorphism combined with modulation by environmental factors (8). Intake of known strong inhibitors or inducers of CYP3A4 did not occur in this study.



(A) Atorvastatin (10 mg/day) treatment significantly reduced mean serum cholesterol from respective baseline; p=0.00, CI (67.16, 93.67). (Paired t-test)
*Significantly lower from respective baselines, p<0.05, at 95% confidence interval

(B) Atorvastatin (10 mg/day) treatment significantly reduced mean Triglyceride from respective baseline; p=0.009, CI (21.86, 127.25). (Paired t-test)
*Significantly lower from respective baselines, p<0.05, at 95% confidence interval

(C) Atorvastatin (10 mg/day) treatment significantly reduced mean HDL-C from respective baseline; p=0.02, CI (0.90, 8.89). (Paired t-test)
*Significantly lower from respective baselines, p<0.05 at 95% confidence interval

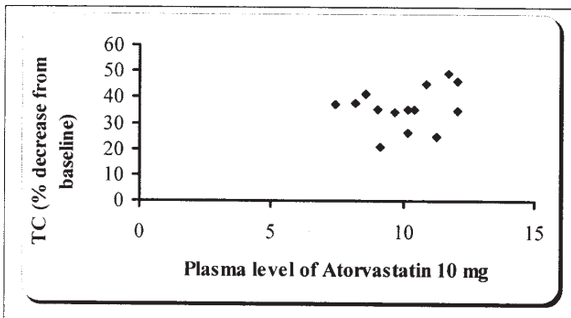
(D) Atorvastatin (10 mg/day) treatment significantly reduced mean LDL-C from respective baseline; p=0.000, CI (46.17, 71.87). (Paired t-test)
*Significantly lower from respective baselines, p<0.05 at 95% confidence interval

(E) Atorvastatin (10 mg/day) treatment significantly reduced mean VLDL-C from respective baseline; p=0.008, CI (4.62, 25.60). (Paired t-test)
*Significantly lower from respective baselines, p<0.05, at 95% confidence interval

(F) Atorvastatin (10 mg/day) treatment significantly reduced mean TC/HDL-C from respective baseline; p=0.000, CI (0.93, 1.62). (Paired t-test)
*Significantly lower from respective baselines, p<0.05 at 95% confidence interval

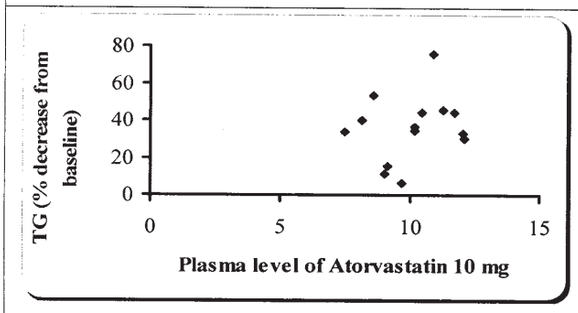
(G) Atorvastatin (10 mg/day) treatment significantly reduced mean LDL-C/HDL-C from respective baseline; p=0.000, CI (0.48, 1.17). (Paired t-test)
*Significantly lower from respective baselines, p<0.05 at 95% confidence interval

Fig. 1: Mean value of parameters of lipid profile before treatment (i.e. baseline) and after treatment with Atorvastatin 10 mg for 8 weeks.



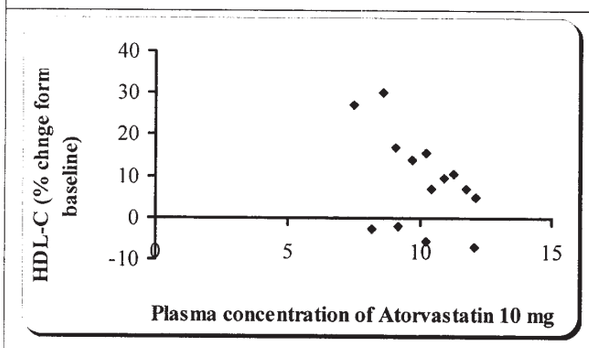
(A) Relationship between TC (% decrease from baseline) and plasma concentration of Atorvastatin 10 mg after 8 weeks of treatment

Scatter plot shows random pattern, with correlation coefficient r = 0.21



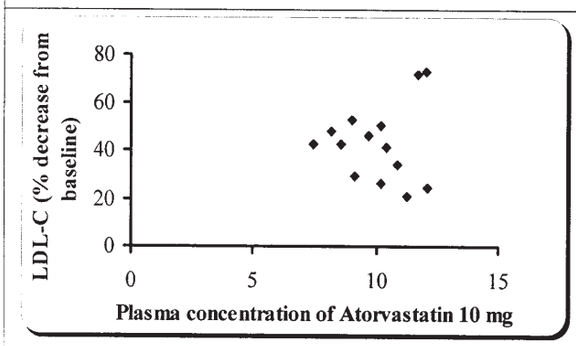
(B) Relationship between TG (% decrease from baseline) and plasma concentration of Atorvastatin 10 mg after 8 weeks of treatment

Scatter plot shows random pattern with correlation coefficient r = 0.21



(C) Relationship between HDL-C (% change from baseline) and plasma concentration of Atorvastatin 10 mg after 8 weeks of treatment

Scatter plot shows random pattern with correlation coefficient r = -0.46



(D) Relationship between LDL-C (% decrease from baseline) and plasma concentration of Atorvastatin 10 mg after 8 weeks of treatment

Scatter plot shows random pattern with correlation coefficient r = 0.089

Fig. 2: Relationship between parameters of lipid profile (i.e. % change from baseline) and plasma concentration of Atorvastatin 10 mg after 8 weeks of treatment.

It is evident that there was no adverse event by any of the participant during the course of the study. Patients' vital signs (B.P. and Pulse rate) were recorded during each visit and ECGs were performed before and after treatment and no significant abnormality was found throughout the treatment period.

As shown in Table II and Fig. 1 (A) to (G), 8 weeks' treatment with Atorvastatin Tablets 10 mg/day significantly ($P<0.05$) reduced the mean values of all the parameters of lipid profile i.e. serum cholesterol, serum triglycerides, HDL-C, LDL-C, VLDL-C, TC/HDL-C ratio and LDL-C/HDL-C ratio from the respective baselines.

In the present study, the changes in all the parameters of lipid profile were as per the previous studies (9, 10, 11, 12) except a significant reduction ($P<0.05$) in HDL-C level after 8 weeks of treatment with Atorvastatin 10 mg. However, 4 patients out of 14 patients in this study, showed a slight increase in HDL-C level which was non-significant ($P>0.05$). More recently, the importance of drug therapy on HDL-C metabolism has been recognized (14). Numerous studies have identified HDL cholesterol and its major protein component, apolipoprotein A-I (apoA-I), as having a direct protective role against the development of CAD (14, 15). There has been tremendous interest in the effect of HMG-CoA reductase inhibitors on HDL-C metabolism, with reports that the various agents in this class appear to have quantitatively different effects on HDL-C levels (11, 16, 17). Atorvastatin, in contrast to some other statins, appears to lose its HDL-raising effect at higher doses (11, 16, 21). For example, in clinical studies comparing high therapeutic doses of atorvastatin (20 and 40 mg) and simvastatin (40 and 80 mg) in hypercholesterolemic subjects, atorvastatin produced a smaller increase in HDL cholesterol and apoA-I than simvastatin at corresponding drug doses (16, 17). It was also found in previous studies that atorvastatin also demonstrated a significantly attenuated increase in HDL cholesterol compared with the new HMG-CoA reductase inhibitor rosuvastatin at low doses (3% HDL apoA-I elevation with 10 mg atorvastatin versus 7% HDL apoA-I elevation with 10 and 5 mg rosuvastatin) (22). It is revealed that HDL cholesterol reduction after high-dose atorvastatin is an early and transient event in HFH patients which magnitude depends on the presence of a residual LDL-R activity ((23). In the present study, it has been observed that even a smaller dose i.e. 10 mg atorvastafin daily for 8 weeks significantly reduced HDL-C from baseline in the patients from Karamsad-Gujarat. Although after the treatment period, all the other parameters were well within the target normal range in the majority of patients, the significant decrease in HDL-C level pointing towards further dose reduction to 5 mg atorvastatin on daily basis, in this population.

In present study, as per the published data (13) we could not conclude any correlation between plasma atorvastatin concentration and subsequent mean reduction in all the parameters of lipid profile [Fig 2 (A) to (D)]. Moreover, a significant reduction ($P<0.05$) in HDL-C level a triggers a question on beneficial effect of atorvastatin on HDL-C. To explain this, a detailed study on a larger population of our country is necessary.

REFERENCES

1. Enas EA, Mehta JL. Malignant Coronary Artery Disease in young Asian Indians. Thoughts on Pathogenesis, prevention and therapy. *N Engl J Med* 1995; 333: 1301–1307.
2. Heller R. For INCLEN Multicentre Collaborative Group. Risk factors for cardiovascular disease in the developing world. A multicentre collaborative study in the International Clinical Epidemiology Network (INCLEN). *J Clin Epidemiol* 1992; 45: 841–847.
3. Enas EA, Yusuf S, Mehta JL. Prevalence of Coronary Artery Disease in Asian Indians – Editorial. *Am J Cardiol* 1992; 70: 945–949.
4. Herfindal ET, Gourley DR. Textbook of Therapeutics. Drug and Disease management, Seventh edition: 407–427.
5. Dipro TJ, Talbert RL, Yee GC, Natzke GR, Wells BG, Posey LM, Pharmacotherapy – A pathophysiologic Approach, Sixth edition, Mc Graw Hill, Medical Publishing Division: 429–452.
6. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 334: 1383–1389.
7. Tall AR. Plasma high-density lipoprotein. Metabolism and relationship to atherogenesis. *J Clin Invest* 1990; 86: 379–384.
8. Shek A, Ferrill MJ. Statin-fibrate combination therapy. *Ann Pharmacother* 2001; 35: 908–917.
9. Whitfield LR, Stern RH, Sedman AJ, Abel R, Gibson DM. Effect of food on the pharmacodynamics and pharmacokinetics of atorvastatin, an inhibitor of HMG-CoA reductase. *Eur J Drug Metab Pharmacokinet* 2000; 25(2): 97–101.
10. Course JR, Kastelein J, Isaacsohn J, et al. A large, 36 week study of the HDL-C raising effects and safety of Simvastatin versus atorvastatin. *Atherosclerosis* 2000; 151: 8–9.
11. Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin and fluvastatin in patients with hypercholesterolemia (the CURVES study). *Am J Cardiol* 1998; 81: 582–587.
12. Pedersen TR, Tobert JA. Benefits and risks of HMG-CoA reductase inhibitors in the prevention of coronary heart disease. *A Reappraisal Drug Saf* 1996; 14: 11–24.
13. Stern RH, Yang BB, Hounslow NJ, et al., Pharmacokinetics and pharmacodynamic relationships of atorvastatin, an HMG-CoA reductase inhibitor. *J Clin Pharmacol* 2000; 40: 616–623.
14. von Eckardstein A, Assmann G. Prevention of coronary heart disease by raising high-density lipoprotein cholesterol? *Curr Opin Lipidol* 2001; 11: 627–637.
15. Roeters van Lennep JE, Westerveld HT, Roeters van Lennep HWO, et al. Apolipoprotein concentrations during treatment and recurrent coronary artery disease events. *Arterioscler Thromb Vasc Biol* 2000; 20: 2408–2413.
16. Crouse JR III, Frohlich J, Ose L, et al. Effects of high doses of simvastatin and atorvastatin on high-density lipoprotein cholesterol and apolipoprotein A-I. *Am J Cardiol* 1999; 83: 1476–1477.
17. Kastelein JJP, Isaacsohn JL, Ose L, et al. Comparison of effects of simvastatin versus atorvastatin on high-density lipoprotein cholesterol and apolipoprotein A-I levels. *Am J Cardiol* 2000; 86: 221–223.
18. Illingworth DR, Grouse JR III, Hunninghake DB, et al. A comparison of simvastatin and atorvastatin up to maximal recommended doses in a large multicenter randomized clinical trial. *Curr Med Res Opin* 2001; 17: 43–50.
19. Ma P, Hegele RA, Yale JF, et al. CAVEAT: a randomized, double-blind, parallel group evaluation of cerivastatin 0.4 mg and 0.8 mg compared to atorvastatin 10 mg and 20 mg once daily in patients with combined (type IIb) dyslipidemia. *Br J Cardiol* 2000; 7: 780–786.
20. Wierzbicki AS, Lumb PJ, Semra Y, et al. Atorvastatin compared with simvastatin-based therapies in the management of severe familial hyperlipidemias. *QJM* 1999; 92: 387–394.
21. Wierzbicki AS, Lumb PJ, Chik G, et al. High-density lipoprotein cholesterol and triglyceride response with simvastatin versus atorvastatin in familial hypercholesterolemia. *Am J Cardiol* 2000; 86: 547–549, A9.
22. Davidson M, Ma P, Stein EA, et al. {Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with type Ha or lib hypercholesterolemia. *Am J Cardiol* 2002; 89: 268–275.
23. Sposito A.C, Gonbert S, Bruckert E, et al. Magnitude of HDL Cholesterol Variation After High-Dose Atorvastatin Is Genetically Determined at the LDL Receptor Locus in Patients With Homozygous Familial Hypercholesterolemia. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2003; 23: 2078.
24. Lipitor® (atorvastatin calcium): Prescribing Information; http://www.pfizer.com/files/products/uspi_lipitor.pdf