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The Influencing Aspects of Atorvastatin on C-Reactive Protein and Lipid Profile in Patients with Stroke

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Abstract: The present study was designed to determine the effects of atorvastatin on C-Reactive Protein (CRP) and lipid profile in patients with stroke, since their anti-inflammatory properties have been investigated recently. Ninety five patients with or without stroke were recruited for the study, of which 60 belongs to control (untreated) and 35 were test group (treated) and received daily with 10 mg day^{-1} of atorvastatin. The patients were followed for over a period of 3 months. For entire study population, CRP along with lipid profile, Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvic Transaminase (SGPT) were measured 1st day and at the end of 3rd month of the treatment. Treatment with atorvastatin decreases both inflammatory activity and atherogenic lipoproteins. The results of this study will provide important information on how to maximize the therapeutic benefits of atorvastatin in a broader range of patients at risk for cerebrovascular morbidity and mortality.

Key words: Vascular disease, inflammation, hyperlipemic, CRP, statin

INTRODUCTION

Statins [3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors] therapy is well established as an effective mean for reducing risk of Coronary Heart Disease (CHD) (Sacks *et al*., 1996; Downs *et al*., 1998; The Kyushu Lipid Intervention Study Group, 2000; Heart Protection Study Collaborative Group, 2002). The unexpected finding of a reduced incidence of stroke in the 2 first major statin trials conducted in patients with known CHD (Scandinavian Simvastatin Survival Study (4S) Group, 1994; Sacks *et al*., 1996) has aroused considerable interest and expectations for stroke prevention in the general population and in patients with earlier stroke.

Statin therapy lowers the risk of cardiovascular events by reducing plasma Total Cholesterol (TC) and Low-Density Lipoprotein (LDL) cholesterol levels. Epidemiological studies suggest that hyperlipidemia is not a major risk factor for stroke, yet statins decrease the risk of stroke in patients with vascular disease or at high risk of vascular disease (Engstrom *et al*., 2002; Bowman *et al*., 2003; Heart Protection Study Collaborative Group, 2002; Sever *et al*., 2003; Byington *et al*., 2001; Cheung *et al*., 2004). Moreover, the benefit of statins appears to be independent of baseline cholesterol; persons with normal cholesterol experience a similar degree of risk reduction as patients

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with elevated cholesterol (Heart Protection Study Collaborative Group, 2002). However, the statin therapy results in a greater clinical benefit when levels of the inflammatory biomarker C-Reactive Protein (CRP) is elevated and that statins lower CRP levels in a manner largely independent of LDL cholesterol levels. These findings, along with basic laboratory evidence, have led to the hypothesis that, in addition to being potent lipid-lowering agents, statins may also have anti-inflammatory properties that are important for prognosis and treatment in stroke patients.

MATERIALS AND METHODS

Patients

The study population consisted of 35 patients (test group) with a mean age of 64.5±7.2 years, admitted to the RMC Hospital, Brain and Nerve Centre, Trichy. The control group included 60 patients with mean age of 57.6±6.3 years, who entered the one day hospitalized health check program, were included in this study. The present study included taking of a full medical history, physical examinations and blood chemistry. All patients gave written informed consent before the study. This study was carried out from April 2005-September 2007.

Biochemical Parameters and Assay

Samples for the analysis of CRP, lipid profile, Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvic Transaminase (SGPT) were obtained in the fasting state. The venous blood samples were drawn into pyrogen-free blood collection tubes without additive. The serum was collected after centrifugation at 3500 rpm for 3 min and then stored at -70°C until analyzed. CRP was measured by using immunoturbidometry method. Estimation of TC, serum triglycerides (TG) and High Density Lipoprotein (HDL) cholesterol, SGOT and SGPT were performed by using commercial kits by colorimetrically. The value of LDL cholesterol and Very Low-Density Lipoprotein (VLDL) cholesterol, were calculated using Friedwald's equation.

Statistical Analysis

Statistical analysis was performed with SPSS 12 statistical software package. Data were recorded on a pre-designed proforma and managed on spreadsheet. All the entries were checked for any error. Descriptive statistics for quantitative variables were computed by mean and standard deviation. Means in the two groups were compared by Student's t-test. In this study, $p<0.05$ has been considered as statistically significant.

RESULTS

Baseline characteristic of the patients were shown in the Table 1 (age, sex, alcohol consumption, smoking history, diabetes, hypertension and treatment). The present study demonstrates that considerable variability in CRP, TC, TG, HDL cholesterol and LDL cholesterol are observed between control and test groups. There was no significant increase in CRP level was observed in control group. Moreover, mean levels of CRP decreased significantly ($p<0.001$) in test group after administration of atorvastatin. There were no significant increases in the TC, TG and LDL cholesterol and a significant increase ($p<0.001$) in the mean levels of HDL cholesterol was noted in control group. However, as shown in Table 2 dose of 10 mg day^{-1} atorvastatin induced significant reductions in TC ($p<0.001$) and LDL cholesterol ($p<0.001$) and not in TG levels at the end of the 3rd month compared with data obtained from test group. There was a significant increase in the mean HDL cholesterol ($p<0.01$) level from baseline to data available from 3rd month of atorvastatin therapy in test group. The present study also measured serum hepatic enzymes including, SGOT and SGPT in all patients from each group at

Table 1: Baseline clinical characteristics

Variables	Control (n = 60)	Test group (n = 35)
Age (years)	57.6±6.3	64.5±7.2
Sex (male/female)	40/20	24/11
Systemic hypertension (%)	7 (12)	19 (54)
Diabetes mellitus (%)	14 (23)	21 (60)
Smoking consumption (%)	18 (30)	9 (26)
Alcohol consumption (%)	6 (10)	4 (11)
Oral hypoglycemic (%)	14 (23)	18 (51)
Insulin (%)	Nil (0)	3 (9)
Antihypertensive (%)	7 (12)	19 (54)
Atorvastatin (%)	Nil (0)	35 (100)
Other lipid lowering drugs (%)	2 (3)	Nil (0)

Table 2: Changes in mean CRP and lipid profile levels in patients with stroke after 3 months of atorvastatin therapy

Parameters	Control (untreated)		Test group (treated)	
	1st day	3rd month	1st day	3rd month
C-reactive protein	0.5±0.30	0.6±0.30	1.9±0.50	1.1±0.30
Total cholesterol	157.2±21.8	161.5±24.3	190.6±28.6	164.0±27.6
Triglycerides	130.9±57.7	137.9±57.3	156.2±67.6	150.4±56.9
HDL cholesterol	39.1±6.00	45.8±9.30	38.3±5.90	42.2±9.00
LDL cholesterol	92.1±22.8	88.7±21.0	119.2±25.8	93.0±22.4
VLDL cholesterol	26.0±11.5	27.5±11.4	35.4±17.2	28.4±9.90
SGOT	26.0±6.40	24.7±4.80	26.0±7.70	29.4±13.3
SGPT	26.9±5.40	25.9±4.70	28.0±6.50	30.1±13.8

Data are expressed as Mean±SD

1st day and the end of 3rd month. There were no significant difference in the control group and a minor elevation of SGOT and SGPT were observed in some patients in test group following atorvastatin therapy and these elevations are not clinically significant.

DISCUSSION

Statins were found in several large-scale studies to substantially reduce cardiovascular morbidity (by approximately 30%) and mortality in mildly hyperlipemic or even normolipemic cohorts (Velasco, 1999). Importantly, the risk of stroke was also significantly decreased by statins in several studies (Plehn *et al*., 1999). It is now commonly believed that the beneficial effects of statins are not mediated solely by lipid lowering, but effects on systemic inflammatory parameters have also been observed in clinical studies (Ridker *et al*., 1998a).

The present study suggests that atorvastatin primarily reduces the lipid fraction most available, rather than targeting only one lipid fraction. The Heart Protection Study (HPS) trial, in which LDL cholesterol reduction was the main explanation for stroke risk and coronary event reduction in the group receiving statin (Heart Protection Study Collaborative Group, 2002).

CRP, a marker of systemic inflammation, has been shown to be an independent risk factor for vascular events, including stroke (Ridker *et al*., 2002; Rost *et al*., 2001). Statins may provide protection against vascular events through anti-inflammatory effects that are reflected by reductions in CRP. In the Cholesterol and Recurrent Events (CARE) study, reduction of CRP levels was noted after administration of pravastatin over a 5 year follow-up period (Ridker *et al*., 1998b). In the Pravastatin Inflammation/CRP Evaluation (PRINCE) after trial (Albert *et al*., 2001), the effect of pravastatin on reduction of CRP levels was observed at the end of 24 weeks of therapy. The CRP levels were significantly reduced even as early as 12 weeks. The CRP concentration was reduced by cerivastatin

among 785 patients with primary hypercholesterolemia after 8 weeks of administration of cerivastatin (Ridker *et al*., 2001) and lovastatin reduced CRP concentration during a 1 year follow-up period, independent of its effect on lipids (Ridker *et al*., 2001).

Patients treated with atorvastatin achieved a median LDL cholesterol level of 62 mg dL^{-1} compared with 95 mg dL^{-1} on standard therapy. There was also a significant 16% reduction in the primary endpoint of death, myocardial infarction, unstable angina requiring hospitalization, coronary revascularization, or stroke on intensive therapy. However, study participants who attained a CRP level of less than 2 mg dL^{-1}, regardless of which statin they were assigned, appeared to have a comparable risk reduction to patients who achieved LDL cholesterol levels less than 70 mg dL^{-1} (Ridker *et al*., 2005). The benefit obtained from lower CRP held regardless of the achieved LDL cholesterol level. In a similar study, the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, patients aged 30 to 75 years with coronary artery luminal narrowing of 20 to 50% and moderate hypercholesterolemia (LDL cholesterol of 125-210 mg dL^{-1}) were randomly assigned to 40 mg day^{-1} of pravastatin or intensive therapy with 80 mg day^{-1} of atorvastatin (Nissen *et al*., 2004). After 18 months of treatment, coronary artery disease was reassessed using intravascular ultrasound. Compared with baseline, patients on atorvastatin had a 46.3% reduction in LDL and a 36.4% decrease in CRP levels compared with 25.2 and 5.2%, respectively, among patients taking pravastatin.

CONCLUSION

The results suggest that the vascular protection provided by statins is in lower inflammation in conjunction with independent of cholesterol reduction. This may provide an added protective effect, as has been seen with cerebrovascular events. Future trials exclusively designed to address the effects of strategies aimed at reducing inflammation and lipid levels on the risk of cerebrovascular event will be helpful to guide treatment and management decisions for such patients.

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