A COMPARISON BETWEEN FLUVASTATIN AND LOVASTATIN EFFECTS IN IRANIAN PATIENTS WITH HYPERCHOLESTEROLEMIA

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Abstract - The aim of this study was to determine the effect of lovastatin and fluvastatin compared with placebo in patients with high levels of total cholesterol and low density lipoprotein cholesterol (LDL - C) on plasma lipid profile. In a prospective single blind clinical trial with convenient sampling 120 hypercholesterolemic men and women with total cholesterol > 220 mg/dl, LDL - C ≥ 160 mg/dl, triglyceride ≤ 350 mg/dl were selected and we divided them in 3 groups randomly. First group took lovastatin 20 mg daily, second group took fluvastatin 40 mg daily and third group took a placebo, all for 12 weeks. Compared with placebo, drug therapy of hypercholesterolemia with either lovastatin or fluvastatin decreases total cholesterol and LDL - C significantly but has no effect on high density lipoprotein and triglyceride. Decrease of total cholesterol and LDL - C in both drugs are the same after first 6 weeks but lovastatin was more effective after second 6 weeks. Mild increase in alanine aminotransferase (ALT) and white blood cells (WBC) in the fluvastatin group appeared after 6 and 12 weeks that their means weren't more than 21 for ALT and 7000 for WBC.
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Key words: Fluvastatin, lovastatin, hypercholesterolemia

INTRODUCTION

Hyperlipidemia is a major risk factor for atherosclerosis and coronary artery disease. It has been known for well over a decade that reduction of low density lipoprotein cholesterol (LDL-C) decreases the likelihood of cardiovascular morbidity and mortality and possibly mortality from all causes. More recently, clinical trials have demonstrated that lowering serum lipid levels may relate progression or induce progression of angiographically documented atherosclerosis, which, in turn, lowers the risk of cardiovascular events (1). Hyperlipidemia warrants such intervention, primarily to cut the risk of cardiovascular disease and minimize coronary morbidity and mortality. Other issues, such as reducing the possibility of pancreatitis or promoting the regression of xanthoma, while of vital significance to the individual, are of little consequence to society as a whole (2). The levels of LDL-C are now well recognized to be causally related to the development of coronary heart disease. The recent availability of 3-hydroxy-3- methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors offers an effective means of reducing the levels of serum LDL-C in patients with hypercholesterolemia. HMG-CoA reductase inhibitors primarily reduce LDL-C by increasing the catabolism of LDL via increasing the number of available LDL-C receptors. LDL is hetero- genous, and at least seven subspecies have been identified with density gradient ultracentrifugation and gradient gel electrophoresis. The various subclasses of LDL-C have different compositions, with associated differences in the characteristics of metabolism(3). By reducing hepatic cholesterol concentrations HMG-CoA reductase inhibitors promote clearance of LDL-C and very low density lipoprotein cholesterol (VLDL-C) remnants by reduction of hepatic cholesterol concentrarions and up-regulating LDL-C receptor synthesis. As a result of these actions, the agents markedly reduce LDL-C levels and often provide modest decreases in serum triglycerides (TG), as well. Moreover, these agents are well tolerated and relatively free of adverse reactions (1). The HMG - CoA reductase inhibitors include lovastatin, simvastatin and pravastatin, as well as the newest agent of this class, fluvastatin. Fluvastatin is the first entirely synthetic HMG-CoA reductase inhibitor and is characterized by its bio- pharmaceutical profile: the agent has a high rate of absorption, is administered in active form, has no active circulatory metabolites (unlike the other available HMG-CoA reductase inhibitors); and has a biologic half-life of 30 minutes. These factors may result in a low incidence of systemic (i.e. extrahepatic) adverse events (1).

Unlike-generation inhibitors, fluvastatin is not derived from compactin, a fungal metabolite (4). The HMG-CoA reductase inhibitors have been the most effective agents for reduction of plasma LDL-C levels. These drugs are appropriate therapy for hypercholesterolemia only when elevated LDL-C levels contribute to the hypercholesterolemia (5). All of the HMG-CoA reductase inhibitors demonstrate a plateauing dose-response curve (5). Thus, the greatest cholesterol reduction per milligram of dose occurs with low doses. At the maximum prescribed doses lovastatin generates the greatest reduction of LDL-C (40%) (5). In addition to their major effects on LDL-C levels, the HMG-CoA reductase inhibitors cause relatively small reductions in fasting plasma TG levels and small increase in HDL-C levels. They appear to have no effect on lipoprotein (a) (5). As fluvastatin 40 mg and lovastatin 20 mg have been the same effective agents for reduction of plasma LDL-C levels, we selected them for therapy.

MATERIALS AND METHODS

In a prospective single blind clinical trial with covenient sampling, we selected 120 hyper-cholesterolemic men and women, (total cholesterol ≥ 220 mg/dl, LDL-C ≥ 160 mg/dl, TG < 350 mg/di), aged 28 to 37 years, divided in 3 groups randomly. First group took lovastatin 20 mg/day, second group took fluvastatin 40 mg/day and third group took a placebo; all for 12 weeks. Before beginning treatment, all subjects experienced dietary therapy for 6 months and were on the same diet during the treatment. At the first study and after 6 and 12 weeks, we checked total cholesterol, TG, LDL-C, LDL / HDL ratio, aspartate aminotrasferase (AST), alanine amino transferase (ALT), hemoglobin and WBC. Clinical adverse experiences were also monitored during the study.

Patient charactristics at randomization

	Fluvastatin	Lovastatin	Placebo
men/women	17/23	9/31	12/28
mean age(Yrs)	55/9	55/8	54/5

Statistical Analyses

A repeated measures analysis of variance was performed and for showing the changes in each factor we analyzed Eis; and defined E_1, E_2, E_3.

E_1 = mean quantity at first-mean quantity after 6 weeks. E_2 = Mean quantity at first-mean quantity after 12 weeks.

E_3 = Mean quantity after 6 weeks-mean quantity after 12 weeks and for comparing with E(s), the Tukey proceduce with significance level 0.05 was utilized for this purpose.

RESULTS

One hundred and twenty patients entered the study and it was completed with 117 patients. One patient taking fluvastatin for 6 weeks was excluded from the study because of severe rise in ALT and AST serum levels and the other 2 patients were excluded because they developed GI syptoms. The effects of lovastatin, fluvastatin and placebo on plasma lipid analyses at the first study and week 6 and 12 after treatment periods are summarized in Table 1. The Effects of long-term fluvastatin, lovastatin and placebo treatment on biochemical have summarized in Table 2.

Fluvastatin and lovastatin decreased total cholesterol, LDL-C, LDL-C/HDL-C ratio and differences were statistically significant in both drug groups. Compared with the fluvastatin group, the lovastatin group had a 22 percent decrease in total cholesterol, a 28.5 percent decrease in LDL-C, and a 31.4 percent decrease in LDL-C/HDL-C ratio. The fluvastatin group had a decrease of 18.7%, 26% and 27.8% in the respective lipid levels. The placebo group had a 2.2% decrease in total cholesterol, a 2.5% decrease in LDL-C and 1.8% increase in LDL-C/HDL-C ratio; that none of these figures were statistically significant. In comparison with placebo, lovastatin and fluvastatin both increased HDL-C, 4.8% during 12 weeks. None of these differences were statistically significant. The group receiving fluvastatin had a 12.8% decrease in TG, and this difference was of borderline statistical significance (P=0.068). But in the placebo group an increase of 4.8% and in lovastatin

Table 1. Lipid levels at baseline and after 6 and 12 weeks treatment with fluvastatin and lovastatin and placebo

		Mean at baseline	Mean in week 6	% Change during First 6 weeks	Mean in week 12 Second 6 weeks	% change during during 12 weeks	% Total chang	P.Value
Placebo								
	T-Cholesterol(mg/dl)	267.1 ± 28.64	259.93 ±30.25	-2.7	261.10 ±30.68	0.5	-2.2	0.056
	TG (mg/dl)	203.30 ± 75.81	204.65 ±69.01	0.6	213 ± 110.80	4.1	4.8	0.677
	LDL-C (mg/dl)	183.70 ±23.36	177.30 ±33.06	-3.5	179.18 ±30.82	1.1	-2.5	0.327
	HDL-C(mg/dl)	49.45 ± 12.21	48.08 ± 11.55	-2.8	46.98 ± 10.79	-2.3	-5	0.203
	LDL-C/HDL-C ratio	3.91 ± 1.15	3.93 ± 1.19	0.5	3.98 ± 1.01	1.3	1.8	0.888
Fluvastatin								
	T-choloesterol (mg/dl)	275.49 ±68.36	229.95 ±60.91	-16.5	223.86 ±48.57	-2.6	-18.7	0.000
	TG (mg/dl)	223.28 ± 113.23	204.90 ± 114.70	-8.2	194.78 ±90.87	-4.9	-12.8	0.068
	LDL-C (mg/dl)	197.97 ± 47.85	149.74 ± 59.73	-24	146.44 ±46.61	-2.2	-26	0.000
	HDL-C (mg/dl)	43.72 ± 13.10	42.49 ± 8.16	-2.8	44.42 ± 10.37	4.5	1.6	0.569
	LDL-C/HDL-C ratio	4.77 ± 1.67	3.65 ± 1.61	-23.5	3.44 ± 1.18	-5.8	-27.9	0.000
Lovastatin								
	T-cholesterol (mg/dl)	279.85 ± 35.19	232.12 ± 48.21	-17.1	217.88 ± 41.35	-6.1	-22.1	0.000
	TG(mg/dl)	221.45 ± 106.02	225.93 ± 119.35	2	214.40 ± 97.21	-5.1	-3.2	0.662
	LDL-C(mg/dl)	191.90 ± 29.80	150.55 ± 45.17	-21.5	137.30 ± 43.56	-8.8	-28.5	0.000
	HDL-C (mg/dl)	45.65 ± 9.75	46.65 ± 9.67	2.2	47.85 ± 10.49	2.6	4.8	0.155
	LDL-C/HDL-/C ratio	4.36 ± 0.99	3.41 ± 1.32	-21.8	2.99 ± 1.12	-12.3	-31.4	0.000

Table 2. Effects of long - term fluvastatin. lovastatin and placebo treatment on biochemical

	Mean at baseline	Mean in week 6	% Change during first 6 weeks	Mean in week 12	% change during second 6 weeks	% change durind 12 weeks	P-Value
Placebo							
Aspartate aminotransferase (AST)IU/L	16.55 ± 8.96	16.88 ± 9	2	17.0 ± 8.93	0.7	2.7	0.519
Alanine aminotransferase (ALT) IU/L	13.4 ± 6.54	13.62 ± 6.48	1.6	14.2 ± 6.63	4.3	6	0.222
Hemoglobin(g/dl)	14.09 ± 1.58	13.78 ± 1.44	-2.2	13.85 ± 1.33	0.5	-1.7	0.027
White blood cells (WBC)$\times 10^3$	6.94 ± 1.66	7.01 ± 1.49	1	7.08 ± 1.49	1	2	0.532
Fluvastatin							
Aspartate aminotransferase (AST)IU/L	18.64 ± 10.65	19.92 ± 16.90	6.9	18.92 ± 15.05	-5	1.5	0.390
Alanine aminotrasferase (AST)IU/L	16.26 ± 11.56	20.41 ± 23.89	25.5	17.5 ± 13.07	-14.3	7.6	0.075
Hemoglobin (g/dl)	13.69 ± 1.26	13.62 ± 1.24	-0.5	13.76 ± 1.40	1	0.5	0.696
White blood cells (WBC)$\times 10^3$	6.36 ± 1.49	6.52 ± 1.32	2.5	7.02 ± 1.39	7.7	10.4	0.002
Lovastatin							
Aspartate aminotransferase (AST)IU/L	17.70 ± 9.24	16.78 ± 7.41	-5.2	15.62 ± 6.71	-7	-11.8	0.132
Alanine aminotransferase (ALT) IUL	16.22 ± 10.72	14.60 ± 7.50	-10.6	13.85 ± 6.88	-5.1	-14.6	0.101
Hemoglobin (g/dl)	13.18 ± 1.34	13.94 ± 1.23	0.4	13.89 ± 1.20	-0.4	0.08	0.856
White Blood Cells (WBC)$\times 10^3$	6.98 ± 1.77	6.76 ± 1.86	-3.2	6.87 ± 1.75	1.6	-1.6	0.303

group a decrease of 3.5%, were found and these differences were not statistically significant. Three patients receiving fluvastatin had clinical adverse reactions which resulted in discontinuation of therapy. Because of elevated ALT and AST in one patient, which was considered serious and this patient was excluded from the second 6 weeks of trial. Two patients didn't tolerate fluvastatin because of epigastric pain and were exempted. One patient in the lovastatin group had constipation.

AST and ALT in the lovastatin group were decreased 11.8% and 14.6% compared with fluvastatin that increased 2% and 7.6% and 6%, respectively. In the placebo group hemoglobin was decreased 1.7% and white blood cells in the fluvastatin group increased 10.4% which was not more than 71000 / mm^3.

DISCUSSION

Hyperlipidemia is a major risk factor of atherosclerosis and coronary disease. It has been known for well over a decade that reduction of LDL-C decreases the likelihood of cardiovascular morbidity and mortality (1). Inhibitors of HMG-CoA reductase are the most effective class to reduce LDL-C levels, and have become widely used. It is likely that the magnitude of risk reduction produced by lipid-lowering therapy is proportional to the degree of cholesterol lowering achieved, which is an important consideration when selecting an agent and determining the dosage to use. The result of several multicenter comparative trials have clearly established that the 4 members of this class are not all equipotent on a miligram basis in terms of their effect on lowering LDL cholesterol. They have shown that the hypolipidemic effect of 5mg simvastatin approximately equals that of 15 mg pravastatin, 15 mg lovastatin and 40 mg fluvastatin all of which are given once daily(6). The results of this study indicate that in comparison with placebo, drug therapy of hypercholesterolemia with either lovastatin or fluvastatin lowered total cholesterol, LDL-C, LDL-C/HDL-C ratio significantly but had no effect on HDL-C and TG. Reduction of total cholesterol and LDL-C by both drugs were the same after 6 weeks but lovastatin had more marked reduction after second 6 weeks. Lovastatin was tolerated better than fluvastatin and its adverse effects were less than fluvastatin. Mild increase in ALT and WBC in fluvastatin group appeared after 6 and 12 weeks that weren't more than 21 units for ALT and 7100 for WBC.

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