Effects of simvastatin on lipid profile, atherogenic index and serum transaminases in hyperlipidemic patients

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Abstract

Background and objectives: Hyperlipidemia is characterized by increased concentrations of lipids including triglycerides, total cholesterol, low density lipoproteins, very low density lipoproteins in the blood and some times decreased high density lipoproteins .
Many drugs have been used for treatment of this disorder. The present study was designed to estimate the effects of simvastatin on lipid profile, atherogenic index, transaminases, creatinine, uric acid and alkaline phosphatase.
Methods: This study covered 70 subjects, they were divided into two groups, the first group included 45 hyperlipidaemic patients which were treated with 20mg simvastatin and second group included 25 normal subjects. After 12 hours fasting, serum lipid profile, transaminases; alkaline phosphatase, uric acid and creatinine were measured for the patients in 3 intervals before treatment, after 8 weeks and 16 weeks of treatment, and one time for normal subjects.
Results: : After therapy, simvastatin showed a significant reduction in serum (TC, TG, LDL, VLDL and atherogenic index) and also, significant rise in HDL noticed, by performing a comparison between the group before treatment, and groups after treatment.Serum ALT, AST and ALP were significantly increased but were still within normal levels.Insignificant effect was observed from serum creatinine, uric acid and also body mass index by performing a comparison between group before treatment and groups after treatment.
Conclusions: Simvastatin was effective in controlling lipid profile and atherogenic index, with no significant abnormality in liver functions.

Key words: Hyperlipidaemia , simvastatin, lipid profile , atherogenic index

Introduction

Hyperlipidemia is a lipid abnormality with genetic or familial origins (primary hyperlipidemia). Hyperlipidemia could also be caused by endocrine, hepatic or renal diseases (secondary hyperlipidemia). Primary hyperlipidemia includes familial or polygenic hypercholesterolemia, familial combined hyperlipidemia, familial hypertriglyceridemia, and dysbetalipoproteinemia[1].
3-Hydoxy-3-methyl-glutaryl-Coenzyme A (HMG-CoA) reductase inhibitors presently provide the most potent drug treatment for hypercholesterolemia[2], statins are the drugs of first choice for patients with high or more than optimal LDL-C levels [3]. HMG-I CoA reductase inhibitors are the drug of choice for LDL-C reduction and are by far the most widely used class of lipid-lowering drugs [4]; these compounds are structural analogs of HMG-CoA. Lovastatin, atorvastatin, fluvastatin, pravastatin, simvastatin, and rosuvastatin belong to this class. They are most effective in reducing LDL-C [5]. Statins are reversible competitive inhibitor of HMG-CoA reductase which is the rate limiting enzyme of cholesterol biosynthesis. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate, a rate limiting step in the formation of

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endogenous cholesterol. The inhibition of HMG-CoA reductase leads to the decrease in the intracellular stores of cholesterol and these results in the up regulation of the number of low density lipoprotein receptors on the cell membrane, thus increasing the clearance of LDL-C from plasma [6].

Simvastatin compete to block HMG-CoA reductase , simvastatin is a lactone that hydrolyzed to the active drug, 30% to 50% of simvastatin is absorbed after oral administration [7].

Methods

The present work was carried out in outpatient department of Rizgary Teaching Hospital in Erbil city, for a period of 6 months. It has covered 45 non treated hyperlipidemic patients receiving simvastatin, 20mg daily at bed time (25 males, 20 females), and their ages ranged between 31-65 years (mean±SD, 42.2±9.44), and 25 control normolipidemic subjects , their ages ranged between 24-42 years (33.1±6.17) and included (13 males and 12 females).Any patient with other diseases or on other medications that might affect the study were excluded. Before treatment, 8 ml of venous blood was drawn from each fasting (12 hours) patient of newly diagnosed as hyperlipidemic and as same as for the control group. The serum was separated and utilized for determination of total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), uric acid and serum creatinine (SCr)**.** The same procedure was carried out for patients after 8 and 16 weeks of treatment. All these tests estimated by enzymatic colorimetric methods.

Statistical analysis:

The statistical evaluation of the results, mean and standard deviation (SD) was calculated. The variables difference was compared to each other with student t-test. Values less than 0.05 ($p<0.05$) is regarded to be significant [8] .

Results

In (Table 1) the effect of simvastatin on lipid profile, serum alanine aminotransferase, serum aspartate aminotransferase, serum uric acid, serum creatinine, serum alkaline phosphatase, atherogenic index and body mass index are shown before, after 8 weeks and 16 weeks. A significant reduction was observed for total serum cholesterol, triglycerides, low density lipoproteins, very low density lipoproteins and atherogenic index and a significant increase was observed for high density lipoproteins by performing a comparison between group before treatment, group after 8 weeks treatment and group after 16 weeks treatment. Serum alanine aminotransferase, and aspartate aminotransferase had increased insignificantly after 8 weeks of treatment, but had significantly increased after 16 weeks of treatment yet within normal ranges. Serum alkaline phosphatase had both increased after 8 and 16 weeks of treatment nevertheless within normal ranges. An insignificant effect was observed for serum ,creatinine, uric acid and body mass index (weight in kg / height in m^2) in both 8 and 16 weeks of treatment..

The percentage of change of lipid profile and atherogenic index for treatment of hyperlipidemia by simvastatin was markedly noted after 16 weeks of treatment in comparison to 8 weeks treatment shown in (Table 2).

Table 1: Effects of Simvastatin on TC, TG, LDL, HDL, VLDL, ALT, AST, SCr ,U.A, ALP , atherogenic index and BMI

Parameters	Control (n=25)	Before Treatment (n=45)	After 8weeks (n=45)	After 16weeks (n=45)
TC mmol/L	4.034±0.756[a]	6.186±0.978[b]	5.134±0.645[c]	4.310±0.455[d]
TG mmol/L	1.790±0.220[a]	2.799±0.503[b]	2.507±0.422[c]	2.229±0.455[d]
HDL-C mmol/L	1.238±0.148[a]	0.890±0.136[b]	0.983±0.132[c]	1.097±0.107[a]
LDL-C mmol/L	2.419±0.793[a]	3.957±0.879[b]	3.006±0.613[c]	2.185±0.414[d]
VLDL-C mmol/L	0.359±0.043[a]	0.558±0.100[b]	0.498±0.084[c]	0.442±0.067[d]
ALT (IU)/L	10.16±1.863[a]	15.333±4.106[b]	15.733±2.766[b]	22.777±4.636[c]
AST (IU)/L	10.16±2.656[a]	15.6±5.297[b]	15.488±3.671[b]	22.555±5.181[c]
S.Cr µmol/L	61.541±21.265[a]	77.792±7.678[b]	75.434±7.201[b]	76.416±6.294[b]
UA µmol/L	254±0.058[a]	344±0.083[b]	364±0.081[b]	386±0.082[b]
ALP (IU)/L	68.337±13.699[a]	65.795±20.886[a]	80.466±21.460[a]	97.98±18.821[b]
Atherogenic Index (TC/HDL)	3.318±0.815[a]	7.072±1.405[b]	5.299±0.932[c]	3.953±0.494[d]
BMI	25.650±1.507[a]	28.728±1.787[b]	27.958±1.967[b]	27.055±1.762[c]

*Data represented by mean ± SD.
*Values with non-identical superscript (a, b, c, d) are representing significant difference at level P< 0.05.

Table 2: Percentage of changes of serum TC, TG, HDL, LDL, VLDL and Atherogenic index

Parameters	After 8 weeks treatment % change by	After 16 weeks treatment % change by
TC	17.00918% (↓)	30.32994% (↓)
TG	10.44197% (↓)	20.35211% (↓)
HDL-C	10.512% (↑)	23.3006% (↑)
LDL-C	24.04173% (↓)	44.77982% (↓)
VLDL-C	10.74837% (↓)	20.74121% (↓)
Atherogenic index TC/ HDL	25.06431% (↓)	44.10125% (↓)

Discussion

According to the lipid hypothesis, abnormally high cholesterol levels (hypercholesterolemia), or, more correctly, higher concentrations of LDL and lower concentrations of functional HDL are strongly associated with cardiovascular disease because these promote atheroma development in arteries (atherosclerosis) [9]. This disease process leads to myocardial infarction (heart attack), stroke and peripheral vascular disease. The major effect of statins is in reducing LDL cholesterol concentrations, primarily mediated by inhibition of the rate-limiting step in cholesterol biosynthesis resulting in an increase in LDL receptors in the liver[10], also can reduce triglycerides and increase HDL-C [11].

In (Table1&2) it is clearly shown that serum, total cholesterol, and LDL-C were significantly reduced in hyperlipidemic patients treated with simvastatin after 8 and 16 weeks of treatment. These results are in agreement with other studies conducted earlier[12,13], where they concluded that simvastatin 20 mg/day will significantly reduce serum total cholesterol by 25 % and 22.8% respectively after several weeks of therapy. Further, for LDL-C, results clearly show a decrease in serum LDL-C by 44.7% this is in conformity with other findings documented by other authers [14,15], where they found a decrease in serum LDL-C by 29.7% and 33.6% by using simvastatin for several weeks. The mechanism responsible for the triglyceride-lowering effect of statins is poorly defined. In theory it could be related to decreased VLDL production (presumably secondary to decreased availability of hepatic free cholesterol for particle assembly), increased clearance of VLDL through the LDL receptor (or other lipoprotein receptors), increased delipidation of VLDL particles via lipoprotein lipase (LPL), or a combination of the above mechanisms. This reduction appears to be due to increased TG clearance rather than decreased production[16].The tables indicate clearly that both triglyceride and VLDL were significantly reduced after 8 and 16 weeks of treatment. These results are in agreement with the results reported by Peter et al [17] and Branchi et al [18], they had found that simvastatin 20mg daily reduce significantly serum triglyceride. The finding concerning VLDL-C, is similar to that reported by Fernando et al[19] who found that serum VLDL-C is reduced by 16% after several weeks of treatment by simvastatin. HDL-C, has notably increased by 10.5% after 8 weeks and by 23.3% after 16 weeks of treatment (Table 2). These results coincide with the results reported earlier [20,21], where they noted that treatment by simvastatin 20mg for several weeks increase the serum HDL-C by 18% and 8.1%. Concerning the atherogenic index (TC / HDL-C) ,it was significantly reduced as shown in the tables, which agrees with the findings by Abdul-Basit et al [20], who showed a decrease by 26.4% after treatment with simvastatin 20 mg.

Review of the literature demonstrated controversial effects of simvastatin on hepatic function. Some studies reported an elevations of liver parameters during simvastatin therapy [22], whereas others studies showed that simvastatin has no effect on liver parameters [23,24] . After 16 weeks of treatment, serum ALT, AST, and ALP had markedly increased however, within normal ranges. Such findings were relevant with the findings conducted by Jyh-Gang et al [25], who proved that serum ALT, AST and ALP had significantly increased yet within normal ranges after several weeks of therapy by simvastatin 20 mg. The findings indicates that simvastatin 20 mg did not change significantly serum creatinine and uric acid after the 2 intervals of therapy as in (Table 1). Such findings were similar to other findings reported earlier [26,27], using simvastatin 20mg as therapy.

Conclusion

Simvastatin was effective in controlling lipid profile and atherogenic index with no significant abnormality in liver functions.

References

1-Farnier M, Davignon J. Current and future treatment of hyperlipidemia: the role of statins. Am J Cardiol 1998;82(4B):3J-10J.

2.Jochen K, Jean-Paul T, Bozidar V. Textbook of clinical pharmacology.1st ed. New York : McGraw-Hill; 2000:700-14.

3.National Cholesterol Education Program (NCEP). Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults executive summary of the third report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA2004; 285: 2486–97

4.Kasper D,Braunwald E,Hauser S,Longo D,Fauci A. Harrison's principles of internal medicine;16th ed. New York: McGraw-Hill professional; 2004: 2293-8.

5.Katzung B.G. Textbook of basic and clinical pharmacology.10thed. Online edition electronic book. 2007.

6.Blum C. Comparison of properties of four inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. Am J Cardiol 1994; 73 Suppl D: 3-11.

7. Mycek J, Harvey A, Champe C, Fisher D. Lippincott's illustrated reviews: Pharmacology 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2000: 207-15.

8.Daniel W.W. Biostatistics: A foundation for analysis in the health science.3rd ed, New York: John Wiley and Sons;1983;134: 206–24.

9.Ballantyne CM: Low-density lipoproteins and risk for coronary artery disease. Am J Cardiol 1998;82:3Q-12Q.

10.Bilheimer D, Grundy S, Brown M, Goldstein J. Mevinolin and colestipol stimulate receptor-mediated clearance of low-density lipoprotein from plasma in familial hypercholesterolemia heterozygotes. Proc Natl Acad Sci 1983;80: 4124–8 .

11.Schaefer E, McNamara JR, Tayler T,Daly J, Gleason J. Comparisons of effects of statins (atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin) on fasting and postprandial lipoproteins in patients with coronary heart disease versus control subjects. Am J Cardiol 2004;93:31-9.

12.Wierzbicki A, Lumb P, Semra Y, Chik G, Christ E . Atorvastatin compared with simvastatin-based therapies in the management of severe familial hyperlipidaemias. Q J Med 1999;92: 387-94.

13.Santosh S, Pawan K . Effect of simvastatin and atorvastatin on coenzyme Q10. The Internet Journal of Cardiology 2007; 4 (1).

14.Antti J, Jukka M, Risto H, Arja V, Merja R . Effects of diet and simvastatin on serum lipids, insulin, and antioxidants in hypercholesterolemic men. JAMA 2002; 287: 598-605.

15.Osamu N, Masatoshi M, Motoshige M, Takahiro N, Iwao N . Effect of simvastatin on the lipid profile of hemodialysis patients. Kidney Int 1999;56: 219–21.

16.William L, John M, Bruce W, William S. The effect of high dose simvastatin on triglyceride rich lipoprotein metabolism in patients with type 2 diabetes mellitus. J Lipid Res 2006;47: 193-200.

17.Peter J, Stephanie K, Irene L, Donald H. Comparative dose efficacy study of atorvastatin versus simvastatin, paravastatin, lovastatin and fluvastatin in patients with hypercholesterolemia(The curves study).Am J Cardiol 1998;81:582-7 .

18.Branchi A, Fiorenza A, Torri A, Muzio F, Rovellini A. Effects of atorvastatin 10mg and simvastatin 20mg on serum triglyceride levels in patients with hypercholesterolemia. Curr Therap Res 2001;8: 405-15.

19.Fernando C, Ana C, Juan F, Jose P, Garcia O. Comparison of the hypolipidemic effect of gimfibrozil versus simvavtatin in patients with type III hyperlipoproteinemia. Medscape Am J 1999; 138 (1):156-62.

20.Abdul-Basit A, Humaira R, Zafar H, Rubina H,Yakoob A. The effect of simvastatin on diabetic dyslipidemia. Journal of Baqai Medical University. 2001; 2 :6-8.

21.Emel A, Banu N, Canan O, Sema G and Sezer C. The Effect of simvastatin treatment on plasma ubiquinone, blood ATP concentrations, total antioxidant capacity and muscle related markers. Turk J Med Sci 2002;32:323-8.

22.Kubota T, Fujisaki K, Itoh Y, Yano T, Sendo T. Apoptotic injury in cultured human hepatocytes induced by HMG-CoA reductase inhibitors. Biochem. Pharmacol.2004; 67:2175-86.

23.Scott R, Lintott C, Wilson M. Simvastatin and side effects. N Z Med 1991; 104:493-5.

24.Darioli R, Bovet P, Brunner HR, Bercher L. Evaluation of tolerance, efficacy and safety of 3-year simvastatin use in the treatment of primary hypercholesterolaemia. Schweiz. Med. Wochenschr 1990; 120:85-91.

25.Zena A., Isam M .Comparative effects of lovastatin and simvastatin on liver function tests in hyperlipidemic patients. The Medical Journal of Basrah University 2007;25(1):20-4.

26.Jyh-Gang L, Mei-Mei H, Wey-Wen J and Jung-Kuei P. Efficacy and safety of 20 mg/day simvastatin in patients with renal impairment and combined hyperlipidemia. FJJM 2005; 3(1):51-5

27.Haralampos J, Anna I, Sofia G, Vasilios G, Eleni T. Effects of statin treatment on uric acid homeostasis in patients with primary hyperlipidemia. Medscape Am Heart J 2004; 148(4):635-40.