Clinical and biochemical comparative study between alternate and every day clofibrate – lovastatin combination therapy on mixed hyperlipidaemia

Al – Mousilly M. Maiada*
Al – Kunany A. Bahir

Received 17/2/2004 ; accepted 10/7/2004

الخلاصة

يعتبر مرض ارتفاع الدهون من النوع المختلط من أكثر أمراض ارتفاع الدهون شيوعاً حيث يعاني مرضاه من ارتفاع مستوى الكولسترول والكليسيرول ثلاثي الأحماض , يصاحبه ازدياد في احتمالية الإصابة بتصلب الشرايين وأمراض القلب التاجية المزمنة . إن الطرائق العلاجية لهذا المرض تتراوح من تغيير في نمط الحياة إلى إستعمال أدوية كيميائية متنوعة وإعتماداً على دراسات حديثة تضمنت إعطاء خليط دوائي من الـ fibrate – statin ولكنها ارتبطت بزيادة نسبة ظهور تأثيرات دوائية جانبية كاعتلال في وظائف الكبد والعضلات وإرتفاع الكلفة العلاجية , لذا فقد إقترحنا وبحثنا في دراستنا السريرية هذه لعلاج مرض إرتفاع الدهون المختلط استعمال خليط الـ lovastatin – clofibrate بين يوم وآخر (الـ clofibrate في يوم والـ lovastatin في يوم آخر وعلى التوالي) بدلاً من نظام الخلط الدوائي التقليدي اليومي ولنفس الدوائين . قارنت الدراسة بين سلامة وكفاءة وكلفة النظامين العلاجيين ولفترة متابعة استمرت ثلاثة أشهر .

اشتملت الدراسة على (44) مريض مصابين بإرتفاع الدهون المختلط , اكمل الدراسة (40) مريض (20) منهم (10 ذكور و 10 إناث) استلموا النظام العلاجي الجديد (بين يوم وآخر) كمجموعة رقم (1) وكان مدى أعمارهم وأوزانهم (40-65) سنة , (62-85) كغم على التوالي . الـ (20) مريض الآخرين (10 ذكور و 10 إناث) استلموا نظام الخلط العلاجي التقليدي اليومي كمجموعة رقم (2) وكان مدى أعمارهم و أوزانهم (67-42) سنة , (65-89) كغم على التوالي . شارك في الدراسة (10) أشخاص أصحاء و اعتبروا كمجموعة سيطرة لمقارنتها بالمجموعتين العلاجيتين (1) و (2) .

تضمنت الفحوصات المختبرية قياس مستوى الكولسترول الكلي , الكليسيرول ثلاثي الأحماض , البروتينات الدهنية واطئة الكثافة وعالية الكثافة كمؤشر على مدى كفاءة الأدوية الخافضة للدهون بينما مثل قياس مستوى الانزيمات (SGOT , SGPT , CK) مؤشر على مدى سلامة هذه الأدوية . اجريت الفحوصات قبل البدء بالعلاج (يوم الصفر) وبعد ثلاثة أشهر من العلاج ولكلا المجموعتين العلاجيتين .

لوحظ عدم وجود فرق معنوي في نسب التغيرات الحاصلة على مستويات الدهون في الدم بين المجموعتين العلاجيتين . وإن مستويات الدهون إنخفضت إلى مستوياتها الطبيعية ولجميع المرضى المشاركين في الدراسة . لوحظ إرتفاع متوسط مستويات إنزيم SGOT في المجموعتين العلاجيتين عما هو عليه في مجموعة السيطرة وكان الفرق معنوياً لكن مدى إرتفاعه في المجموعة (2) كان أكبر مما في المجموعة (1) . كما لوحظ إرتفاع متوسط مستويات أنزيم SGPT في المجموعة الأقل سلامة (2) عما هو عليه في مجموعة السيطرة حيث كان الفرق معنوياً . أما بالنسبة لمتوسط مستويات أنزيم CK فلم يرتفع بصورة كبيرة في كلا المجموعتين العلاجيتين مقارنة بمجموعة السيطرة لكن مدى إرتفاعه في المجموعة (2) كان أكبر مما هو عليه في المجموعة (1) . كما لوحظ أن الكلفة العلاجية في المجموعة العلاجية (1) إنخفظت بنسبة 50% مقارنة بمجموعة (2) . بينت الدراسة السريرية إمكانية تقليل التأثيرات الدوائية الجانبية والكلفة العلاجية لخليط الـ Statin – Fibrate مع المحافظة على كفاءته في خفض مستوى الدهون .

ABSTRACT

Mixed hyperlipidaemia is the most common form of hyperlipidaemias,where the patients have an elevation in both triglycerides and cholesterol levels with a high risk of atherosclerosis and chronic heart diseases. The therapeutic approach for this disorder described a range from nonpharmacologic lifestyle modifications to newly introduced pharmacologic options.Depending on the basis of recent reports involve fibrate - statin combination and associated with increase the incidence of side effects (myopathy, hepatotoxicity) and therapeutic cost, we suggest and investigate in our study a clinical trial for management of this metabolic disorder by using clofibrate and lovastatin on alternate days instead of the standard daily combination of the same drugs.

* Department of Pharmacotherapeutics , College of Pharmacy, Almustansiriya University, Baghdad – Iraq .

The study compares the safety, efficacy and cost of both therapeutic regimens for three months follow - up period. A total of 44 patients with a known mixed hyperlipidaemia were enrolled in this study. Of the 40 patients who completed the study, 20 (10 males, 10 females) received alternate - day therapy (group I), their age and weight ranges were (40-65) years and (62-85) Kg, respectively. The remaining 20 (10 males, 10 females) received every day therapy (group II), their age and weight ranges were (42-67) years and (65-89) Kg, respectively. Ten healthy age – matched control subjects (5 males , 5 females) .
The biochemical investigations involve measuring total serum cholesterol, triglyceride, LDL and HDL cholesterol levels as parameters of lipid - lowering agent efficacy; while SGOT,SGPT and CK levels as parameters of safety. All of these parameters were determined at baseline (day 0) and after three months of treatment for both therapeutic groups.
The study revealed that there was no significant difference between both treatment groups regarding the percent changes in lipid profiles from baseline values. These profiles had been returned to normal limits in all patients in both groups. The mean of SGOT levels for both treatment groups was significantly higher than that of control, but with group II the extent was more, while for SGPT levels group II only was significantly higher (less safety) than control one. With respect to CK levels and for both treatment groups, only slight elevation (not significant) occurred compared with control, but with group II the extent was more.With group I, the therapeutic cost was reduced by nearly 50% compared with group-II. By this clinical and biochemical trial, we decreased the side effects and cost of fibrate - statin combination while keeping their efficacy in lowering serum lipids.

INTRODUCTION :

Combined (mixed) hyperlipidaemia, associating hypercholesterolaemia and hypertriglyceridaemia, is a common metabolic disorder and has a genetic background but its phenotype is triggered by various predisposing factors such as obesity, type II diabetes and alcohol consumption .
This metabolic disorder is undoubtedly associated with an increased cardiovascular risk and thus deserves specific management[1] .
After diet failure, the first drug of choice for the treatment of mixed hyperlipidaemia remains controversial. Indeed, fibrates are more active on hypertriglyceridaemia, mainly by stimulating lipoprotien lipase (LPL) activity and promoting clearance of VLDL from plasma ; while statins are more active on hypercholesterolaemia by augmenting receptor - mediated clearance of LDL cholesterol generated from VLDL. Furthermore, monotherapy (Fibrate or statin alone) is generally incapable of normalizing the lipid profile in the presence of severe combined hyperlipidaemia[1,2,3] .
Both of the above pharmacological classes have their advantages and disadvantages. Ideally, a statin- fibrate combination would be most appropriate in order to act on the two components of such hyperlipidaemia, but such association therapy is not without problems including a potentially increased risk of side effects (myopathy, hepatotoxicity) and high cost. Thus, the controversial issue that remains to be addressed is whether these lipid - lowering benefits outweigh the potential risks of therapy and so, this combination must be used cautiously and with a continuous monitoring[1,4, 5] .
Rindone et. al..[6] found lovastatin administered every other day as a monotherapy to be effective on lipid levels. Their study included only 19 patients without any comparable group receiving the same drug every day.
Furthermore, the use of moderate statin doses combined with fibrate, or a temporary discontinuation, appear to have a relatively low incidence of myopathy[7]. So, and to alleviate problems encountered with this combination therapy, we used lovastatin and clofibrate on alternate days instead of the standard daily combination of the same drugs. We present the results of our study which compare the efficacy, safety and cost of this combination.

SUBJECTS AND METHODS :

Subjects :

This randomized clinical study initially consisted of 44 patients (mean age 55±10 years, 22 males and 22 females) with mixed hyperlipidaemia who were diagnosed and followed as out patients for three months by a specialist physician .

Patients were eligible to participate in the study only if at least 6-months period of monotherapy, in addition to a low- fat diet, failed to control their hyperlipidaemia. This failure was established by insufficient LDL cholesterol and triglyceride levels reduction according to National Cholesterol Education Program (NCEP) reports[8] Patients accepted for enrollment were characterized by the following measures :

. Elevated total cholesterol > 250 mg/dL .

. Elevated triglycerides > 250 mg/dL .

. Elevated LDL cholesterol ≥ 190 mg/dL in patients with < 2 risk factors .
≥160 mg/dL in patients with ≥ 2 risk factors .
≥ 130 mg/dL in patients with known CHD .

. HDL cholesterol 35-60 mg/dL .

To avoid any possible interactions with our study, the patient exclusion criteria were involved .

Patients with a history of congestive heart failure, acute myocardial infarction, secondary hyperlipidaemia , uncontrolled diabetes mellitus or hypertension and those with hepatic or renal disease .

. Pregnant , breast feeding and postmenopausal women receiving hormone replacement therapy .

. Hypersensitivity to statins or fibrates .

. Those use other medications which may increase the risk of myopathy (e.g. erythromycin and cyclosporine) and hepatotoxicity (e.g. isoniazid , methyldopa and phenothiazines) . patients on warfarin therapy were also excluded to avoid increased anticoagulant effect .

Ten healthy subjects were included in this study as a control group (5 males, 5 females) and were matched with patient groups .

Patients were randomized into two treatment groups :

Group I : twenty two patients received clofibrate (500 mg two times daily after,meals) every other day and lovastatin (20 mg at bedtime) on the days that clofibrate was not taken and for 3 months follow-up period.

Group II : twenty two patients received clofibrate (500 mg two times daily after meals) and lovastatin (20mg at bedtime) every day and for 3- months follow-up period .

All patients gave informed consent before the study entry and were maintained on dietary therapy according to the American Heart Association diet regimen [30% of energy from unsaturated fatty acids, 50% from complex carbohydrate and 20% from fish and chicken proteins][9].

The clinical and laboratory parameters (lipid profiles and enzymes activity) were determined at baseline before the initiation of therapy and at the end of 3-months for both groups. Patients were advised to report immediately unusual muscle pain, weakness or brown urine.

Methods:

The level of lipid constituents in the serum is much influenced by diet . Thus, the samples were taken from the patients after 12-hours fasting, since the elevated results caused by diet can not be distinguished from those resulted from abnormal lipid metabolism[10] .

After application of venous tourniquet, about 5 ml of blood was withdrawn using a plastic disposable syringe at day of enrollment (day 0, before treatment) and at the end of 3-months.

Each sample was transferred to a plastic centrifuge tube and left at room temperature for complete clotting of blood. Serum was aspirated after centrifugation at 1000 rpm for 10 minutes and kept in the freeze to be ready for doing the required analysis.
Total cholesterol[11] , triglycerides[12] , LDL[13] and HDL[14] levels were determined to reflect the efficacy of hypolipidaemic agents; while SGOT , SGPT[15] and CK[16] levels were determined to reflect the laboratory safety assessment.

Statistical Analysis:

All treatment decisions were based on the mean of two lipoprotein levels. If the first two measurements were different by > 30 mg/dL , a third test was obtained and the average of all three was used.
Data are expressed as mean ± SD or percentage and the student's " t " test was used for a statistical evaluation of significant difference between control and patient groups and confirmed by Analysis of Variance (ANOVA). A p-value of < 0.05 was regarded as significant

RESULTS :

Of the 44 patients initially enrolled with mixed hyperlipidaemia, 4 were lost to follow-up for reasons other than drug side effects and as the following :

. 1 male and 1 female from group I due to patient's own personal reasons.
. 1 male and 1 female from group II due to high therapeutic cost.

So, only 40 patients completed the 3-months follow-up period (20 on alternate day and 20 on every day regimen) . The demographic characteristics at baseline for patients and control subjects did not differ statistically Table(1).

Table 1 . Baseline characteristics of control and patient groups .

Baseline characteristics	Control N=10	Group I N=20	Group II N=20	p-value
Men/women	5/5	10/10	10/10	NS
Age (year):range	43-68	40-65	42-67	
Age (year):mean±SD	56±8	54±10	55±11	NS
Weight range (Kg)	60-87	62-85	65-89	
Occupation:				
Sedentary work	3 (30%)	7 (35%)	8 (40%)	NS
Manual work	7 (70%)	13 (65%)	12 (60%)	NS
Current alcohol drinking		1 (5%)	1 (5%)	NS
Current smoker		5 (25%)	4 (20%)	NS
Controlled hypertension		11 (55%)	10 (50%)	NS
Controlled diabetes mellitus		5 (25%)	6 (30%)	NS
History of CAD		7 (35%)	8 (40%)	NS
History of fibrates intake (as monotherapy)		8 (40%)	6 (30%)	NS
History of statins intake (as monotherapy)		12 (60%)	14 (70%)	NS

. Values are expressed as percentages or mean ± SD .
. N = number of subjects .
. Group I : alternate day of clofibrate – lovastatin therapy .
. Group II : every day of clofibrate – lovastatin therapy .
. NS = not significant (p>0.05) .

1. Lipid Profiles :

After 3 – months of treatment , as shown in table (2) , there was no significant difference between both treatment groups regarding the percent changes in lipid profiles from baseline values. These profiles had been returned to normal limits in all patients in both groups.

Table 2 . Effect of clofibrate – lovastatin combination on lipid profile levele (mg/dL).

Sampling time	Control n=10	Group I n=20	Group II n=20	P*	P**
Total serum cholesterol levels (mg/Dl)					
Baseline (pretreatment)		295±23	298±25	S	NS
	190±10				
Three months later (after treatment)		203±19	206±18	NS	NS
Serum triglyceride levels (mg/dL)					
Baseline (pretreatment)		366±96	373±77	S	NS
	190±10				
Three months later (after treatment)		203±19	206±18	NS	NS
Serum triglyceride levels (mg/dL)					
Baseline (pretreatment)		366±96	373±77	S	NS
	165±24				
Three months later (after treatment)		169±31	171±30	NS	NS
Serum LDL cholesterol levels (mg/dL)					
Baseline (pretreatment)		188±23	194±25	S	NS
	118±10				
Three months later (after treatment)		121±22	122±24	NS	NS
Serum HDL cholesterol levels (mg/dL)					
Baseline (pretreatment)		37±9	38±6	S	NS
	50±12				
Three months later (after treatment)		46±11	48±10	NS	NS

Data are expressed as mean ± SD
N= number of subjects
Group I : alternate day therapy
Group II : every day therapy

P* : patient groups versus control
P** : group I versus group II
S : significant ($p<0.05$)
NS : not significant ($p>0.05$)

2. Laboratory Safety Assessment :

After 3 - months of treatment ,as shown in table (3) , the mean of SGOT levels for both treatment groups was significantly higher than that of control, but with group II the extent was more, while for SGPT levels only group II was significantly higher (less safety) than control one.With respect to CK levels and for both treatment groups, only slight elevation (not significant) occurred compared with control, but with group II the extent was more.

Those drinking alcohol or walking for long distances in group II reflect an elevation in SGPT and CK levels > 3 fold the upper normal limits, respectively. GI- disturbances (nausea, vomiting and abdominal pain) also observed in group II patients only.(l0% of this group).

Table 3 . Effect of clofibrate – lovastatin combination on SGOT,SGPT&CK levels (IU/L) .

Sampling time	Control n=10	GroupI n=20	GroupII n=20	P*	P**	P***
SGOT levels (IU/L)						
Baseline (pretreatment)	16±7	19±4	18±6	NS	NS	NS
Three months later (after treatment)		23±20	26±24	S	S	NS
SGPT levels (IU/L)						
Baseline (pretreatment)	15±9	17±6	18±7	NS	NS	NS
Three months later (after treatment)		19±8	28±22	NS	S	S
CK levels (IU/L)						
Baseline (pretreatment)	60±33	64±30	63±34	NS	NS	NS
Three months later (after treatment)		67±32	70±35	NS	NS	NS

Data are expressed as mean ± SD
n= number of subjects
GroupI : alternate day therapy
GroupII : every day therapy

P* : group I versus control
P** : group II versus control
p***: group I versus group II
S : significant ($p<0.05$)
NS : not significant ($p>0.05$)

3. Therapeutic Cost :

Therapeutic cost of group II was two times that of group I after the end of three months treatment (table 4) .

Table 4 . Therapeutic cost consumed by each group after 3 months .

	Group I	Group II
Atromid – S	4500	9000
Medostatin	11250	22500
Total price	15750	31500

Data are expressed as Iraqi Dinar for each patient during 3 months .

DISCUSSION AND CONCLUSION :

According to our data at the end of three months follow - up period, there was no significant difference between both treatment groups (same efficacy) with regard to percent changes in serum lipids from baseline values and all lipid profiles (total cholesterol, triglycerides, LDL and HDL cholesterol) had returned to normal limits in all patients and in both treatment groups. These observed changes in lipid values in alternate - day therapy were consistent with the results of recent studies on the administration of simvastatin and fenofibrate as standard combination therapy (every day regimen) in patients with mixed hyperlipidaemia[17,18] .

The results revealed that , no patient had signs or symptoms of myopathy (myalgia and increase in CK levels > 10 fold the upper limit of normal) or hepatotoxicity. These results agree with the findings of Athyros G. et. al.[18], who studied the safety and efficacy of long term statin - fibrate combinations in patients with refractory familial combined hyperlipidaemia .

The levels of SGOT, SGPT and CK at baseline and for both patient groups were only slightly higher (not significant) than those of control. These results certainly clarified that the post medical history of monotherapeutic regimen (fibrate or statin, alone) does not induce serious adverse effects (hepatotoxicity or myopathy) when compared with combination therapeutic regimen of the same drugs[19,20] .

According to the data after three months of treatment, the mean of SGOT levels for both therapeutic groups was significantly higher than that of control but the extent of elevation in group II was more than that of group I (the safest group) ; while for the mean of SGPT levels, only group II was significantly higher (less safety than group I) than control one. These results document the finding that statin- fibrate combination could increase the risk of hepatotoxicity, taking in consideration the therapeutic dose[21] .

However , the mean of CK levels after the end of the follow-up period for both therapeutic groups remained within the normal limits (as need longer duration for CK levels to rise markedly) in spite of slight elevation compared with control levels. The extent of this elevation with group II was more than that of group I (the safest group). This slight elevation consistent with the previous studies which documented that the statin-fibrate combination could increase the incidence of myopathy[22,23,24] .

In the every day therapeutic regimen of the present clinical trial (group II), alcohol drinking (5% of this group) and walking for long distances (10% of this group) had been shown to elevate the levels of SGPT and CK more than three folds the upper limit of normal (ULN) respectively; while with respect to alternate- day therapy (group I) ,this marked elevation in SGPT and CK levels had not been shown in patient taking alcohol or those walking for long distances. These results agree with the finding that excessive alcohol intake and heavy exercise could increase the risk of hepatotoxicity and myopathy respectively for patients on daily regular doses of statin- fibrate combination[25,26] .

Generally, however, patients who received this combination regarding both therapeutic regimens should advice to avoid alcohol consumption and strenuous muscular work otherwise, monitoring of adverse effects and dosage adjustment may be required .

Although combination therapy was more effective in reducing LDL than monotherapy but, on the basis of cost per percentage of LDL- reduction ,combination therapy was frequently less cost- effective than monotherapy. Therefore, and with alternate- day group of our study, as the drug doses were reduced to a half ,the cost of therapy was reduced nearly 50% and patient compliance increased compared to that of every day group where 10% of this group was lost due to a high therapeutic cost of statin- fibrate combination regimen .

Thus , conclusions deduced are :

1-Lovastatin (20 mg) given on alternate days with clofibrate (1 gm) is as effective as the every day combination of the same drugs at the same doses in lowering plasma total cholesterol, triglycerides, LDL-cholesterol and increasing HDL- cholesterol levels.

2-Alternate- day therapy is associated with better tolerance and safety .
3-Alternate-day therapy is associated with less therapeutic cost than every day combination regimen.
However , the use of clofibrate now is limited due to concern over long – term serious side effects , notably a suspicion of causing malignant neoplasms , cholelithiasis and pancreatitis[10] . Therefore , our plan for the future is to have another attempt on using a combined antihyperlipidemic therapy replacing clofibrate by a more safe drug .

REFERENCES :

1. Scheen AJ. Treatment of combined hyperlipidemia : fibrate and /or statin. Rev- Med-Liege. 1999; 54(7) : 583-7 .
2. Glueck SR., Oakes N., Speirs J., Trasy T., Lang J. Gemfibrozil- lovastatin therapy for primary hypercholesterolemia .Am J Cardiol 1992 ; 70 : 4-9 .
3. Da Col PG., Fonda M., trscare M. Tolerability and efficacy of combination therapy with simvastatin plus gemfibrozil in type II refractory familial combined hyperlipideamia .Curr Ther Res 1993 ; 94 : 13-20 .
4. Shepherd J. Fibrates and statins in the treatment of hyperlipidaemia: an appraisal of their efficacy and safety. European Heart Journal 1995 ; 16 : 5-13 .
5. Feher MD., Foxton J., Banks D., Lant AF., Wray R. Long- term safety of statin -fibrate combination treatment in the management of hypercholesterolemia in patients with CAD. Br Heart J. 1995 : 74 : 14-17 .
6. Rindone IP., Achacosa R., Bledsoe R. Effect of lovastatin administered every other day on serum LDL cholesterol > 160 mg/dL. Am J Cardiol 1995 ; 76 : 312-313 .
7. Pasternak RC, Smith SC., et al. Clinical advisory on the use and safety of statins. Journal of American College of Cardiology 2002 ; 40 : 568-573 .
8. Classification, prevalence, detection and evaluation in : National Cholesterol Education Program : 2nd report of the expert panel on detection, evaluation and treatment of high blood cholesterol in adults. National Institutes of Health Publication. 1993 : 11-22 .
9. Dietary therapy and physical activity in: National Cholesterol Education Program: 2nd report of the expert panel on detection, evaluation and treatment of high blood cholesterol in adults. National Institutes of Health Publication. 1993 : 111-125 .
10. Walker R., Edwards C. Clinical Pharmacy and Therapeutics, 2nd Ed., Churchill Livingstone, London; 1999 : 327-345 .
11. Richmond W. Preparation and properties of cholesterol oxidase from No cardio SP. and its application to enzymatic assay of total cholesterol in serum . Clin. Chem. 1973,19,1350 .
12. Fossati Pand Principe L. Serum triglyceride determined colorimetrically with an enzyme that produce hydrogen peroxide . Clin. Chem. 1982,28(10),2077 .
13. Friedwald WT , Levy RJ. , Fredrickson DS. Estimation of the LDL cholesterol in plasma with out the use of preoperative ultracentrifuge . Clin. Chem 1972,18,499 .
14. Burstein M.and Schdnich HR. As cited by Biomerieux Kit (France) . J. Lipid Res. 1970,11,583 .
15. Reitman S. and Frankel S. As cited by Randox Kit (UK) . Am. J. Clin. Path. 1957,28,56 .
16. Hess . JW , etal . As cited by Randox Kit (UK) . Amer. J. Clin. Path. 1968,50,89 .
17. Ellen RI., McPherson R. Long- term efficacy and safety of fenofibrate in the treatment of combined hyperlipidemia. Am J Cardiol 1998; 81(4A): 60B- 65B .
18. Athyros VG., Papageorgion AA., etal .Safety and efficacy of long-term statin-fibrate combinations in patients with refractory familial combined hyperlipidemia. Am J Cardiol. 1997; 80: 608-613 .
19. Rosenson RS. , Frauenheim WA. Safety of combined pravastatin- gemfibrozil therapy. Am J Cardiol 1994 ; 74 : 499-500 .
20. Iliadis EA., Rosenson RS. Long-term safety of pravastatin-gemfibrozil therapy in mixed hyperlipidemia. Clin Cardiol 1999 ; 22 : 25-8 .
21. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002 ; 346 : 1221-31 .
22. Katzung BG. Basic and Clinical Pharmacology, 4 th Ed., Appleton& Lange, California; 1989 : 419-430 .

23. George CF., Wood NL. British National Formulary, number 34(Ed.), British Medical Association, London; 1997 : 118-120 .
24. Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. JAMA 1990; 264: 71-75 .
25. Thompson PD, Zmuda JM, Domalik LJ, Zimet RJ, Staggers J, Guyton JR, Lovastatin increases exercise- induced skeletal muscle injury. Metabolism 1997; 46: 1206-10 .
26. Shek A., Ferrill MJ. Statin -fibrate combination therapy. Ann- Pharmacother. 2001; 35(7-8): 908-17 .