

Clinical Research



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Comparison of Effects of Atorvastatin and Fenofibrate on Plasma Homocysteine, Folic Acid and Vitamin B12 Levels in Patients With Mixed Hyperlipidemia

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ABSTRACT

Objectives: Hyperhomocysteinemia is an independent cardiovascular risk factor. Lipid lowering agents such as fenofibrate have been reported to elevate plasma homocysteine levels. Atorvastatin is another kind of lipid lowering agent and there is not enough study investigating its effects on plasma homocysteine. In the present study we aimed to compare the effects of atorvastatin and fenofibrate on plasma homocysteine, folic acid and vitamin B12 levels.

Materials and Methods: Total of 43 patients were randomized into one of 2 groups: One of them (n=20) treated with atorvastatin, other (n=23) with fenofibrate for 3 months. After 1 and 3 months of treatment with these drugs, blood samples were collected and plasma lipids, folic acid, vitamin B12 and homocysteine levels were determined.

Results: Both of the lipid lowering agents significantly decreased plasma lipid levels. Atorvastatin group showed a significant reduction in total cholesterol and LDL-C than those in fenofibrate group. On the other hand, fenofibrate caused a greater reduction in triglyceride levels compared to the atorvastatin. There was no change in plasma folic acid and vitamin B12 levels after treatment with both of these hypolipidemic drugs. There was a significant increase in homocysteine levels after treatment with fenofibrate and atorvastatin, although fenofibrate was more effective than atorvastatin (36 and 15% respectively).

Conclusions: We conclude that increases in plasma homocysteine levels are a result of the known impairment of renal function caused by fenofibrate and a result of impairment of liver function caused by atorvastatin. ©2006, Fırat Üniversitesi, Tıp Fakültesi

Key words: Atorvastatin, fenofibrate, homocysteine, folic acid, vitamin B12

ÖZET

Hiperlipidemik hastalarda atorvastatin ve fenofibratın plazma homosistein, folik asit ve B12 vitamin düzeylerine etkilerinin karşılaştırılması

Amaç: Hiperhomosisteinemi bağımsız bir kardiyovasküler risk faktörüdür. Fenofibrat gibi lipid düşürücü ilaçların plazma homosistein miktarını arttırdığı bildirilmiştir. Atorvastatin diğer bir tip lipid düşürücü olup plazma homosistein üzerindeki etkileri yeterince çalışılmamıştır. Bu çalışmada atorvastatin ve fenofibratın plazma homosistein, folik asit ve B12 vitamin değerlerine olan etkilerini karşılaştırmayı amaçladık.

Gereç ve yöntem: Toplam 43 hiperlipidemik hasta iki gruba ayrıldı. Bir grup (n=20) atorvastatin ile, diğeri (n=23) fenofibrat ile 3 ay tedavi edildi. Tedavinin 1. ve 3. aylarında kan örnekleri alındı ve plazma lipitleri, folik asit, B12 vitamini ve homosistein düzeyleri ölçüldü.

Bulgular: Her iki lipid düşürücü ilaç plazma lipit düzeylerini önemli oranda düşürdü. Atorvastatin grubunda total kolesterol ve LDL-C miktarları fenofibrat grubundan daha fazla düşüş gösterdi. Diğer taraftan fenofibrat atorvastatinle karşılaştırıldığında trigliserid düzeyinde daha belirgin düşüşe neden oldu.

Her iki lipid düşürücü ilaç tedavisinden sonra folik asit ve B12 vitamin miktarlarında herhangi bir değişiklik gözlenmedi. Homosistein düzeyleri hem fenofibrat hem de atorvastatin tedavisinden sonra artış göstermekle beraber fenofibrat atorvastatininden daha etkili bulundu (sırasıyla, %36 ve %15).

Sonuç: Sonuç olarak plazma homosistein miktarındaki artışın fenofibratın neden olduğu renal fonksiyon bozukluğundan ve atorvastatinin neden olduğu muhtemel karaciğer fonksiyon bozukluğundan ileri geldiğini düşünmekteyiz. ©2006, Fırat Üniversitesi, Tıp Fakültesi

Anahtar kelimeler: Atorvastatin, fenofibrat, homosistein, folik asit, B12 vitamini

Homocysteine is a sulfur containing amino acid which is formed during the metabolism of methionine amino acid (1). Abundant epidemiological evidence has demonstrated that the presence of mild to moderate hyperhomocysteinemia is an independent risk factor for atherosclerosis in the coronary, cer-

ebreal, and peripheral vasculature (2,3). Hyperhomocysteinemia is a result of genetic as well as nutritional factors (4). Many factors including Vitamins B6 and B12, folic acid, fish oil, insulin and melatonin involve homocysteine metabolism (5-8). Particularly folate is the strongest nutritional and

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pharmacological determinant of plasma homocysteine concentrations (9). Therefore, hiperhomocysteinemia is accepted to be a treatable cardiovascular risk factor (10).

Hyperlipidemia is a major risk factor for atherosclerosis and cardiovascular disease (11-13). It is now well established that hyperlipidemia needs to be treated, especially in patients with a history of cardiac disease, including heart failure. Today, one of the most important classes of drugs for treating hyperlipidemia is the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (also known statins). Statins decrease all LDL sub fractions including small, dense LDL-C (14). Fibrates have an established role as lipid regulating drugs with marked TG lowering and HDL elevating effects, in addition to modest total and LDL-c lowering. Administration of fibrates has been reported to elevate plasma homocysteine levels (15-17). Folic acid supplementation prevents the elevation of plasma homocysteine in patients treated with fenofibrate (18). Whether this side effect of fenofibrate is due to its effect on renal function is not clear. There is one study comparing the effect of fenofibrate and atorvastatin on plasma homocysteine levels without determination of plasma folic acid and B12 vitamin, the main factors involving homocysteine metabolism (19).

Therefore, we conducted a trial in which the effects of fenofibrate and atorvastatin monotherapy on both plasma homocysteine and biochemical parameters were compared in patients with combined hyperlipidemia. We also aimed to study the levels of plasma folic acid and vitamin B12 and their relation to homocysteine levels in these subjects

MATERIALS AND METHODS

Sixty patients were included in the present study. The subjects ranged in age from 34 to 65 years old (mean 48 ± 7.5 years). A total of 43 subjects completed to evaluate the effects of atorvastatin and fenofibrate on plasma homocysteine, folic acid and vitamin B12 levels and other biochemical parameters.

Individuals taking scheduled medications concurrently (excluding oral contraceptives), those with significant medical histories, as well as smokers and pregnant females were excluded from the study. In addition patients who already treated with lipid-lowering drugs, or who had received dietetic advice for previously detected hyperlipidemia were also excluded. Plasma TSH and standard biochemical liver function tests (LFTs) were also performed, and patients excluded if these were not normal. Subjects were admitted to the clinical center, and physical examination and baseline laboratory measurements were obtained.

Patients were randomized into one of 2 groups: One of them treated with atorvastatin 10 mg daily for 3 months period (atorvastatin group) other with fenofibrate 200 mg daily for 3 months (fenofibrate group). Every group was composed with 30 subjects in the beginning of trial, but 20 patients in fenofibrate (10 women and 10 men) and 23 patients in atorvastatin group (11 women and 12 men) completed

Before starting to take lipid lowering agents and after 1 and 3 months of treatment with these agents, physical

examination was performed, body weight and blood pressures were measured and blood specimens were withdrawn between 08:00-10:00 a.m. following an overnight fast. Blood samples were collected and plasma samples were separated and stored at -20°C until analyzed.

Total Hcy levels were determined with an enzyme immunoassay kit (Axis-Shield AS, Oslo, Norway). Vitamin B12 and folic acid were determined by IMMULITE 2000 Analyzer using a Chemiluminescence kit (DPC, diagnostic Products Corporation, Los Angeles, CA).

Statistical Analysis

Biochemical and other parameters were compared for the whole group at 0, 1, and 3 months by means of ANOVA in conjunction with Bonferroni's t-statistics. The baseline and post treatment values of all parameters of two groups were compared by student t test. Results were presented as mean \pm SD. A level of significance of $P < 0.05$ was used.

RESULTS

The baseline and post treatment of 1 and 3 months values for lipid parameters are shown in table 1. After treatment both with fenofibrate and atorvastatin caused significant modification in plasma lipids. Atorvastatin group showed a significant reduction in total cholesterol and LDL-C than those in fenofibrate group (33, 30 vs. 21% and 40 vs. 27%; $p < 0.01$). On the other hand, fenofibrate caused a greater reduction in triglyceride compared to the atorvastatin (30 vs. 20%; $p < 0.05$). Atorvastatin caused a 16% reduction in HDL-C and the reduction in HDL-C was 13% in fenofibrate group

Fenofibrate significantly increased creatinin levels ($p < 0.01$) while atorvastatin lead to nonsignificant elevation in creatinin levels ($p > 0.05$). Fenofibrate induced a significant increase in uric acid levels both after 1 month and 3 months of treatment ($p < 0.05$; $p < 0.01$ respectively)

Baseline homocysteine levels were similar in both groups. After treatment for 1 month and 3 month with fenofibarete the levels of homocysteine progressively and significantly increased compared to the baseline levels ($p < 0.05$ after 1 month treatment and $p < 0.01$ after 3 month treatment). There was no significant elevation in homocysteine levels after 1 month treatment with atorvastatin but mild an significant increase in Hcy levels were found after 3 month treatment ($p < 0.05$).

Baseline plasma folic acid and vitamin B12 levels were similar in both groups. There were no changes in both folic acid and vitamin B12 levels after 1 and 3 months treatment with both hypolipidemic agents.

Treatment with atorvastatin for 3 months significantly increased plasma alanine aminotransferase (ALT) levels ($p < 0.05$) while fenofibrate lead to a mild and non significant increase in its concentration. Plasma aspartate aminotransferase (AST) levels were also increased with atorvastatin ($p < 0.01$) but no significant change was found in fenofibrate group.

Table I. Lipid and blood pressure levels in patients treated with atorvastatin or fenofibrate at pretreatment and after 1 or 3 months of treatment

	Pretreatment values	After 1 month of treatment	After 3 months of treatment
Cholesterol (mg/dl)			
Atorvastatin	249 ± 46	177 ± 35	166 ± 34***
Fenofibrate	255 ± 38	210 ± 35	201 ± 18***
Triglycerides (mg/dl)			
Atorvastatin	302 ± 62	263 ± 22**	240 ± 36** ^a
Fenofibrate	296 ± 30	235 ± 32	207 ± 30*** ^a
HDL-cholesterol (mg/dl)			
Atorvastatin	37 ± 8	38 ± 7	44 ± 9** ^a
Fenofibrate	40 ± 7	42 ± 6	46 ± 8* ^a
LDL-cholesterol (mg/dl)			
Atorvastatin	147 ± 42	99 ± 20	87 ± 19***
Fenofibrate	155 ± 36	117 ± 28	113 ± 24**
VLDL-cholesterol (mg/dl)			
Atorvastatin	61 ± 17	44 ± 11	38 ± 11*** ^a
Fenofibrate	57 ± 11	43 ± 08	40 ± 07**
Systolic pressure (mmHg)			
Atorvastatin	135 ± 16	129 ± 12	127 ± 12
Fenofibrate	132 ± 13	130 ± 10	126 ± 10
Diastolic pressure (mmHg)			
Atorvastatin	84 ± 9	84 ± 5	82 ± 4
Fenofibrate	83 ± 8	82 ± 7	80 ± 6
BMI			
Atorvastatin	29.20 ± 5	29.00 ± 5	29.00 ± 5
Fenofibrate	27.75 ± 4	27.72 ± 5	27.57 ± 4

*p<0.05, **p<0.01, ***p<0.001 vs pretreatment values; a: p<0.05 vs 1 month of treatment values

Table II. Plasma levels of homocysteine, folic acid, vitamin B12, uric acid, creatinin, albumin, ALT, AST amylase in patient treated with atorvastatin and fenofibrate at pretreatment and after 1 and 3 months of treatment

	Pretreatment values	After 1 month of treatment	After 3 months of treatment
Homocysteine nmol/ ml			
Atorvastatin	17.54 ± 4	17.95 ± 4	20.00 ± 5*
Fenofibrate	18.28 ± 4	23.20 ± 5**	25.98 ± 6***
Folic acid (ng/ml)			
Atorvastatin	5.96 ± 1.92	6.36 ± 2.23	6.12 ± 1.5
Fenofibrate	6.18 ± 1.9	5.61 ± 1.5	5.55 ± 1.6
Vitamin B ₁₂ (pg/ml)			
Atorvastatin	282 ± 39	287 ± 36	277 ± 33
Fenofibrate	275 ± 42	271 ± 37	269 ± 35
Uric acid (mg/dl)			
Atorvastatin	4.48 ± 0.6	4.45 ± 0.7	4.56 ± 0.8
Fenofibrate	3.0 ± 0.8	4.10 ± 0.9**	4.30 ± 0.8***
Creatinin (mg/dl)			
Atorvastatin	0.87 ± 0.1	0.93 ± 0.1	0.94 ± 0.2
Fenofibrate	0.79 ± 0.1	0.95 ± 0.1*	0.97 ± 0.2**
Urea			
Atorvastatin	31.30 ± 9	31.7 ± 9	35.00 ± 8
Fenofibrate	30.00 ± 7	35.5 ± 7	35.50 ± 8
Albumin (g/dl)			
Atorvastatin	4.5 ± 0.4	4.4 ± 0.3	4.5 ± 0.3
Fenofibrate	4.4 ± 0.4	4.6 ± 0.3	4.7 ± 0.3
ALT (U/L)			
Atorvastatin	30.12 ± 4	32.20 ± 5	38.00 ± 6*** ^a
Fenofibrate	29.00 ± 3	29.75 ± 3	33.25 ± 5
AST (U/L)			
Atorvastatin	24.50 ± 4	27.15 ± 3	33.00 ± 5*** ^a
Fenofibrate	26.00 ± 3	28.00 ± 4	28.50 ± 4
Amylase (U/L)			
Atorvastatin	42.45 ± 6	44.25 ± 6	43.60 ± 5
Fenofibrate	47.20 ± 5	45.30 ± 4	48.75 ± 6
Creatine Kinase (U/L)			
Atorvastatin	99.50 ± 20	100.20 ± 21	95.00 ± 18
Fenofibrate	106.25 ± 24	137.45 ± 30*	153.50 ± 32**

* p< 0.05, **p<0.01, ***p<0.001 vs pretreatment values; a: p<0.05 vs 1 month treatment values

DISCUSSION

The main goal of the present study was to determine whether there was any difference between the effects of two lipid lowering drugs, fenofibrate and atorvastatin, on plasma homocysteine concentration and folic acid and vitamin B12 levels which are main factors involving homocysteine metabolism. The efficiency of both agents in lowering lipid levels has been proven in large clinical trials (19-22). Recently it was shown that treatment with fibrates increases plasma homocysteine concentration (15-17). In accordance with these observations, present findings also demonstrate that homocysteine levels increase after fenofibrate treatment. In addition, we have also found that treatment with atorvastatin results a moderate increase in plasma homocysteine levels in hyperlipidemic patients. The increase was higher in fenofibrate group than in atorvastatin group (36 vs. 15%, $p < 0.01$). In contrast to the present result, Giral et al. (19) have shown that treatment with atorvastatin did not exert any significant effect on the plasma homocysteine levels.

One study reported that fenofibrate dramatically increases plasma homocysteine levels, though blood levels of vitamins were not reduced and they proposed that it may be related to the renal function (15). In the present study we also did not detect any change in vitamin B12 and folic acid concentration after treatment with both lipid lowering agents. The increase in homocysteine levels were not related with these vitamin levels. In addition Lipscombe et al. (23) reported that a group of patients showed a reversible deterioration in renal function while being treated with a fibrate for hyperlipidemia. The possible explanation for the fenofibrate-induced increase in homocysteine levels may

involve alteration in renal function. Indeed, in the present study uric acid and creatinin levels increased by the treatment with fenofibrate as reported previously (24). On the other hand, atorvastatin treatment did not show any significant effects on the concentration of uric acid and creatinin.

We have found a mild but significant increase in homocysteine levels after treatment with atorvastatin for 3 months but not 1 month. There are a few studies concerning atorvastatin and homocysteine. Giral et al. (19) reported that atorvastatin has no effect on plasma homocysteine levels. The increase in homocysteine levels was not related kidney function in the present study because uric acid, creatinin and albumin levels did not show any significant change after atorvastatin treatment. On the other hand, present findings show another important result which is the changes in ALT, AST and amylase levels with the treatment of atorvastatin but not of fenofibrate. Liver has a significant role in the regulation of plasma homocysteine levels (25) with the help of the essential vitamins, including folic acid and vitamin B12, the liver converts homocysteine back into methionine. Impaired liver function could be a determinant in the development of hyperhomocysteinemia (26).

In conclusion, elevated homocysteine levels are a risk factor for atherosclerosis. Plasma homocysteine levels increased in the hyperlipidemic patients while treating another cardiovascular risk factor, hyperlipidemia, both with atorvastatin and fenofibrate. The significant elevation by fenofibrate may be due to its side effect on renal function. On the other hand, atorvastatin lead to a mild increase in plasma homocysteine levels and it may be explained by its effect on liver function.

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