Efficacy and Safety of 12-week Treatment with Fenofibrate• 300 mg in Thai Dyslipidemic Patients

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Background : *High levels of low density lipoprotein (LDL) cholesterol is a known major factor in atherosclerosis. In addition to LDL-cholesterol, an increase in the triglycerides-rich lipoprotein and a decrease in HDL- cholesterol increase the risk of coronary artery disease. Fenofibrate, a fibric acid derivative, is highly effective in reducing serum triglycerides and LDL-cholesterol and produces a modest increase in HDL-cholesterol. The present study was done to evaluate the efficacy of fenofibrate at 300 mg daily on serum lipid profiles and to study the drug safety and tolerability of fenofibrate in Thai patients.*
Material and Method : *Forty patients with elevated serum total cholesterol, LDL cholesterol were recruited for 12 weeks of 300 mg per day of fenofibrate therapy. Blood analysis for lipid profiles, liver function test, creatinine and muscle enzyme were done at the begining and end of the study.*
Results : *The mean baseline total cholesterol, LDL- cholesterol, triglycerides and HDL- cholesterol were 249 mg/dl, 160 mg/dl, 325 mg/dl and 43 mg/dl respectively. Significant changes of all lipid parameters from baseline were observed after 12 weeks of treatment. Reduction of serum total cholesterol, LDL- cholesterol and triglycerides were 16, 23, and 41 percent respectively. Increased serum HDL- cholesterol of 14 percent was also observed. One patient withdrew from the trial due to chest pain. Two asymptomatic elevated transaminase were detected during the study.*
Conclusion : *Fenofibrate• at 300 mg per day is effective and safe in treating Thai patients with dyslipidemia.*

Keywords : *Fenofibrate, Dyslipidemia, Thai patients*

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Coronary artery disease (CAD) is now a leading cause of morbidity and mortality in the Thai population. High levels of low-density lipoprotein (LDL) cholesterol are a known risk factor for the development of CAD. Treatment of hypercholesterolemia seems to decrease the rate of coronary events, the magnitude of the preventive effect being proportional to the degree of LDL-cholesterol reduction[1]. In addition to LDL-cholesterol, low levels of high-density lipoprotein (HDL) cholesterol predict an increased incidence of CAD, independent of other risk factors, including LDL-cholesterol levels[2-4]. Data from Framingham Heart Study showed that the optimal HDL-cholesterol levels for men and women are more than 45 mg/dl and 55 mg/dl, respectively[5]. The risk of CAD increases by 25 percent for every 5 mg/dl that HDL-cholesterol decreases below 45 mg/dl [6]. Thus, a drug that can produce a large increase in HDL-cholesterol while at the same time reducing LDL-cholesterol may be a valuable treatment option. The fibric acid derivatives are hypolipidemic drugs that decrease total cholesterol and triglycerides concentrations and increase HDL-cholesterol. Fenofibrate, another fibric acid derivative, was introduced into clinical practice in 1975 and has been widely used

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in hyperlipidemic patients. Data from many clinical trials show that total plasma cholesterol levels are reduced by approximately 20 to 25 percent, whereas triglycerides levels of Frederickson type IIb and Type IV patients are reduced by 40 to 60 percent[7]. The present study aimed to evaluate the efficacy of fenofibrate at 300 mg daily on the serum concentration of total cholesterol, LDL-cholesterol, triglycerides and HDL-cholesterol in Thai patients with hyperlipidemia and to study the drug safety and tolerability of the locally manufactured fenofibrate in a Thai population over 12 weeks of active treatment.

Material and Method

This open-labeled multicenter study was carried out in 3 hospitals in Thailand (Bhumibol Adulyadej Hospital, Pramontkutkalo Hospital and Royal Thai Police Hospital). The study protocol was approved by the Ethics review Committee at each center. Each patient enrolled in the trial provided, informed written consent. The study was conducted according to the principle of Good Clinical Practice.

Patients

Patients of either sex aged between 35 and 75 years with dyslipidemia were eligible if dietary restriction for an adequate duration had failed to reduce serum LDL-cholesterol or triglycerides to the desired level and drug treatment was felt necessary by their primary physicians. Patients were excluded if any of the following conditions applied: receiving concomitant treatment with other lipid lowering drugs or drugs likely to interfere with fenofibrate, known hypersensitivity to fenofibrate, condition associated with secondary hyperlipidemia (uncontrolled diabetes mellitus, nephrotic syndrome, hypothyroidism, Cushing syndrome, cholestasis, chronic renal failure and alcohol abuse), hepatic function disorders (including hepatitis, cirrhosis and other hepatopaties with AST or ALT > 2 times the upper normal limit of the laboratory, or gamma-GT > 3 times normal), impaired renal function with serum creatinine more than 2.0 mg/dl, clinically significant active cardiac diseases, pregnant women or women of childbearing age not using adequate contraception, and/or breast feeding.

Study Design and Treatment

A 3 weeks observation period (wash out period) was followed by 12 weeks of active treatment. At the first screening visit, blood analysis of individual patients was done for lipid profile, blood urea nitrogen, creatinine, liver function test, complete blood count and creatine phosphokinase. After the patients had been advised to continue with hypolipidemic diet and not to consume alcohol for 3 weeks, second blood samples were drawn. If the serum LDL-cholesterol or triglycerides met the criteria mentioned above, the patients were enrolled in the present study. According to the lipid parameters obtained, the patients were divided into subgroups for analysis by the following classification:

1. Type IIa: Serum total cholesterol $\geq$ 250 mg/dl and triglycerides < 200 mg/dl
2. Type IIb: Serum total cholesterol $\geq$ 250 mg/dl and triglycerides $\geq$ 200 mg/dl
3. Type IV: Serum total cholesterol < 250 mg/dl and triglycerides $\geq$ 200 mg/dl

Fenofibrate was administered at a dosage of 300 mg daily for 12 weeks. The patients were instructed to return to the clinic after 6 and 12 weeks of treatment, or earlier if they developed any adverse effects. The pill count was done at each visit for compliance assessment. At the 6 and 12 week visit, the third and fourth blood analysis were done.

Statistical Method

Results were demonstrated as mean $\pm$ standard deviation or percent where appropriate. Student's t-test was used to compare the continuous data. A p-value of < 0.05 was considered statistically significant.

Results

Of the total 40 patients enrolled, 26 were men (65%) and the mean age was 56 $\pm$ 15 years (ranging from 35 to 75 years). The mean body weight and body mass index were 66 $\pm$ 12 kg and 25 $\pm$ 4 kg/m^2, respectively. The baseline characteristics of all patients are shown in Table 1.

One of the 40 patients enrolled in the study dropped out because of loss to complete follow up. Thus, 39 patients, 10 with phenotype IIa, 11 with phenotype IIb and 18 with phenotype IV hyperlipoproteinemia, completed the entire study (Table 1). Statistical analysis was made with the results obtained from these patients.

Efficacy

Treatment Effects on Lipid Parameters in Total Population

The baseline lipid data for the total population and the various subgroups studied are shown in Table 2.

Table 1. Demographic data and prevalence of risk factors in the total sample and relevant subgroups

	Total Population	Patients with type IIa	Patients with type IIb	Patients with type IV
No. of patients	39	10	11	18
Age (yr)*	55±12	54±14	57±12	54±13
Sex:male (%)**	26 (66)	6 (15)	7 (18)	13 (33)
Weight (kg)*	66±12	64±16	61±11	68±10
BMI (kg/m^2)*	25±4	25±5	24±3	25±3
Risk factors for CAD; number of case (%)**				
Hypertension (%)	15 (38)	4 (10)	4 (10)	7 (18)
Smoking (%)	3 (8)	1 (3)	2 (5)	0
History of CAD (%)	12 (31)	1 (3)	4 (10)	7 (18)
Family history of CAD (%)	2 (5)	2 (5)	0	0
Type II DM (%)	8 (21)	3 (8)	1 (3)	4 (10)

* Mean ± SD, ** % base on total population

The mean baseline of total cholesterol and LDL-cholesterol level were 249 ± 49 mg/dl and 160 ± 58 mg/dl, respectively. The mean total cholesterol level was significantly reduced to 209 ± 37 mg/dl after 12 weeks of treatment. The mean LDL-cholesterol level was significantly lowered to 124 ± 37 mg/dl at week 12. The mean percentage reduction was 16 percent for total cholesterol level and 23 percent for LDL-cholesterol level.

The mean baseline of triglycerides was 325 ± 160 mg/dl and was significantly reduced to 193 ± 100 mg/dl after 12 weeks of fenofibrate therapy. For HDL-cholesterol, the mean baseline was 43 ± 10 mg/dl and was significantly increased to 49 ± 9 mg/dl after 12 weeks, equal to 14 percent increment.

The effects of fenofibrate therapy on the lipid parameters are shown in Table 2.

Treatment Effects in the Different Subgroups

Study subjects with various phenotype hyperlipoproteinemia (Type IIa, IIb and IV) were analyzed separately to assess whether drug effects were similar in comparison with the overall study population. In all subgroups, fenofibrate therapy caused significant reduction in total cholesterol, LDL-cholesterol and triglycerides (Table 2). HDL-cholesterol was significantly increased after 12 weeks of treatment.

The effect of fenofibrate therapy was more pronounced in those whose baseline LDL-cholesterol or triglycerides level were high (Table 3 and Fig. 1). HDL-cholesterol increment was also higher in patients whose baseline levels were low.

Tolerability

There were 3 cases who had adverse events, one case of chest pain and another 2 cases of myalgia.

Table 2. Baseline (Pre-treatment) lipid level and the effect of fenofibrate 300 mg (Post-treatment) in total population and relevant subgroups

	Total Popu-lation	Patients with type lla	Patients with type llb	Patients with type IV
No. of patients	39	10	11	18
Total cholesterol				
Pre-treatment**	249±49	279±48	254±38	234±47
Post-treatmen**	209±49	217±48	210±38	201±47
% change*	-16	-22	-17	-14
LDL-cholesterol				
Pre-treatment**	160±58	206±57	148±35	149±59
Post-treatmen**	123±58	138±57	124±35	113±59
% change*	-23	-33	-16	-24
Triglycerides				
Pre-treatment**	325±160	169±62	324±99	392±183
Post-treatmen**	191±160	104±62	187±99	231±183
% change*	-41	-38	-42	-41
HDL-cholesterol				
Pre-treatment**	43±10	44±9	45±8	41±12
Post-treatmen**	49±10	54±9	49±8	47±12
% change*	+14	+23	+9	+15

*p-value < 0.001 ** mean in mg/dl ± SD

Table 3. Effects of fenofibrate 300 mg dialy on various lipid parameters as a function of baseline values

Category (mg/dl)	Number	Baseline	12 weeks	Δ(%) (mg/dl)	P-value (mg/dl)
LDL< 160	22	121±33	118±28	-2.5	0.55
LDL 160-190	6	173±9	123±12	-28.9	0.001
LDL> 190	11	232±37	138±57	-40.5	<0.001
HDL≤ 35	15	33±2	42±7	27.3	<0.001
HDL> 35	24	49±8	52±8	6.1	0.83
TG ≤ 200	11	158±45	100±30	-36.7	0.001
TG > 200	28	390±139	232±92	-40.5	<0.001

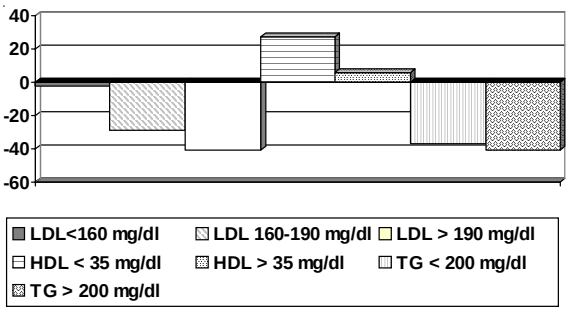

Fig. 1 Percent change from baseline levels

All of them still continued to take fenofibrate and developed no symptoms after the subsequent follow up period except one case who had to discontinue the drug because of chest pain and withdrew from the study.

Asymptomatic elevation of serum transaminase was noted in 2 study subjects during treatment with fenofibrate. In all cases the increase were less than threefold.

Discussion

The main objective of the present study was to evaluate the efficacy and tolerability of locally manufactured fenofibrate (Lexemin) on lipid profile in Thai dyslipidemic patients. The results of the present study demonstrate that fenofibrate at 300 mg dosage beneficially modified the lipid profile of Thai patients with dyslipidemia.

Fenofibrate therapy produced a significant reduction in lipid parameters after 12 weeks of therapy. Serum total cholesterol, LDL- cholesterol and triglycerides reduction of 16, 23 and 41 percent, respectively and increased serum HDL-cholesterol of 14 percent was observed in the total population. The results of the present study are compatible with those in studies using the same dosage of fenofibrate in which total cholesterol reduction in patients with type IIa and type IIb hyperlipoproteinemia was reduced by 16 to 30 percent and 10 to 30 percent, respectively[8,9]. LDL-cholesterol decreased by 17 to 29 percent in type IIa patients and by 2 to 29 percent in type IIb patients. Triglycerides were reduced by 30 to 67 percent in type IIb patients and by 35 to 60 percent in type IV patients. Finally, increment of HDL-cholesterol of 0 to 40 percent and 0 to 20 percent in type IIa and IIb patients was reported in previous trials, respectively.

At present, the standard therapy for patients with hypercholesterolemia is the use of statin, irrespective of initial LDL-cholesterol levels[10-13]. However, in certain forms of primary hyperlipoproteinemia, such as familial (type III) dysbetalipoproteinemia or endogenous (typeIV) hypertriglycerides, fenofibrate are the drugs of choice. Patients with combined hyperlipoproteinemia (typeIIb) may respond better to fibrate than to statin. The results observed in the presented study subjects with type IIb hyperlipoproteinemia when treated with fenofibrate support this notion. In addition, statin exert a limited, dose-independence increase in HDL-cholesterol of about 5 percent compared with placebo[3]. In the present study, fenofibrate 300 mg daily showed an increasing HDL-cholesterol by 14 percent in the total population and 23 percent in type IIa patients[12].

The study treatment was well tolerated, with only one patient discontinuing treatment due to an adverse event.

In conclusion, the present study showed that locally manufactured fenofibrate (Lexemin) in 300 mg daily dosage was highly effective in lowering total cholesterol, LDL- cholesterol and triglycerides in Thai dyslipidemic patients and induced a large significant increase in HDL-cholesterol, and was well tolerated.

References

1. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD. Cholesterol reduction yields clinical benefit: impact of statin trials. Circulation 1998; 97: 946-52.
2. Wilson PW, Abbott RD, Castelli WP. High-density lipoprotein cholesterol and mortality. The Framingham Heart Study. Arteriosclerosis 1988; 8: 737-41.
3. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 1989; 79: 8-15.
4. Assmann G, Schutte H, von Eckardstein A, Huang Y. High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAm experience and pathophysiological implications for reverse cholesterol transport. Atherosclerosis 1996; 124 Suppl: S11-20.
5. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998; 97: 1837-47.
6. Castelli WP, Anderson K. A population at risk: Prevalence of high cholesterol levels in hypertensive patients in the Framingham Study. Am J Med 1986; 80: 23-32.
7. Blane GF. Review of European clinical experience with fenofibrate. Cardiology 1989; 76 Suppl 1: 1-13.
8. Blane GF. Comparative toxicity and safety profile of fenofibrate and other fibric acid derivatives. Am J Med 1987; 83: 26-31.

9. Brow WV, Dujovne CA, Farquhar JW, et al. Effects of fenofibrate on serum lipids. A multicenter, double-blind study of the lipid-lowering effects of fenofibrate in patients with type II hyperlipidemia. Arteriosclerosis 1986; 6: 670-8.
10. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS (Air Force/Texas Coronary atherosclerosis Prevention Study). JAMA 1998; 279: 1615-22.
11. Shepherd J, Cobbe SM, Ford L, et al (West of Scotland Coronary Prevention Study Group). Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Eng J Med 1995; 333: 1301-7.
12. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S) Lancet 1994; 344: 1383-9.
13. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigation. N Engl J Med 1996; 335: 1001-9.

ประสิทธิภาพและความปลอดภัยของการใช้ยาฟีโนไฟเบรทเพื่อลดระดับไขมันในผู้ป่วยไทย

บรรหาร กออนันตกูล, นูกูล เจียมอนุกูลกิจ, ชุมพล เปี่ยมสมบูรณ์, อิทธพร คณะเจริญ, จิรพันธ์ ชวาลตันพิพัฒน์

ภูมิหลัง *: ระดับไขมันแอลดีแอลคลอเลสเตอรอลในเลือดสูงเป็นปัจจัยเสี่ยงที่สำคัญของโรคหลอดเลือดหัวใจ นอกจากระดับไขมันแอลดีแอล พบว่าผู้ป่วยที่มีระดับไขมันไตรกลีเซอร์ไรด์สูงและไขมันเอชดีแอลต่ำ จะมีความเสี่ยงต่อการเกิดโรคหลอดเลือดหัวใจสูงขึ้น ยาในกลุ่มฟีโนไฟเบรทมีประสิทธิภาพสูงในการลดระดับไขมันไตรกลีเซอร์ไรด์ และแอลดีแอลในเลือด นอกจากนั้นยังสามารถเพิ่มระดับไขมันเอชดีแอลได้ด้วย*

วัตถุประสงค์ *: เพื่อประเมินประสิทธิภาพของการใช้ยาฟีโนไฟเบรท Lexemin ในขนาด 300 มิลลิกรัมต่อวันต่อระดับไขมันในเลือด รวมทั้งประเมินความปลอดภัยของการใช้ยาที่ผลิตในประเทศในผู้ป่วยไทย*

วิธีการศึกษา *: ผู้ป่วยที่มีระดับไขมันคลอเลสเตอรอลและแอลดีแอลในเลือดสูงซึ่งจำเป็นต้องได้รับการรักษาด้วยยาในกลุ่มฟีโนไฟเบรท จำนวน 40 ราย ได้รับยาในขนาด 300 มิลลิกรัมต่อวันเป็นเวลา 12 สัปดาห์ และทำการติดตามผลการรักษาและความปลอดภัยของยาโดยการตรวจเลือด*

ผลการศึกษา *: ระดับไขมันคลอเลสเตอรอล, แอลดีแอล, ไตรกลีเซอไรด์ และเอชดีแอล ก่อนการรักษาเท่ากับ 249, 160, 325 และ 43 มิลลิกรัมต่อเดซิลิตร ตามลำดับ พบว่ายาฟีโนไฟเบรทในขนาด 300 มิลลิกรัมต่อวันสามารถลดระดับไขมันคลอเลสเตอรอลได้ร้อยละ 16 แอลดีแอลได้ร้อยละ 23 และไตรกลีเซอไรด์ลดลงได้ร้อยละ 41 หลังใช้ไป 12 สัปดาห์ และหลังการรักษาสามารถเพิ่มระดับไขมันเอชดีแอลได้ร้อยละ 14 ระหว่างการศึกษาพบผลข้างเคียงในผู้ป่วย 1 ราย และผลเลือดผิดปกติโดยไม่มีอาการจำนวน 2 ราย*

สรุป *: ยาฟีโนไฟเบรทในขนาด 300 มิลลิกรัมต่อวันมีประสิทธิภาพและปลอดภัยในการรักษาผู้ป่วยที่มีระดับไขมันสูงในผู้ป่วยไทย*