

# Etofibrate but not controlled-release niacin decreases LDL cholesterol and lipoprotein (a) in type IIb dyslipidemic subjects

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## Abstract

Etofibrate is a hybrid drug which combines niacin with clofibrate. After contact with plasma hydrolases, both constituents are gradually released in a controlled-release manner. In this study, we compared the effects of etofibrate and controlled-release niacin on lipid profile and plasma lipoprotein (a) (Lp(a)) levels of patients with triglyceride levels of 200 to 400 mg/dl, total cholesterol above 240 mg/dl and Lp(a) above 40 mg/dl. These patients were randomly assigned to a double-blind 16-week treatment period with etofibrate (500 mg twice daily, N = 14) or niacin (500 mg twice daily, N = 11). In both treatment groups total cholesterol, VLDL cholesterol and triglycerides were equally reduced and high-density lipoprotein cholesterol was increased. Etofibrate, but not niacin, reduced Lp(a) by 26% and low-density lipoprotein (LDL) cholesterol by 23%. The hybrid compound etofibrate produced a more effective reduction in plasma LDL cholesterol and Lp(a) levels than controlled-release niacin in type IIb dyslipidemic subjects.

## Key words

- Etofibrate
- Niacin
- Lipoprotein (a)
- Triglycerides
- Cholesterol

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## Introduction

Fibrates and niacin have been successfully used to reduce triglyceride plasma concentration, with the additional benefit of increasing the levels of antiatherogenic high-density lipoprotein (HDL) cholesterol. The two drugs have synergistic effects on triglycerides and HDL with a considerable reducing action on low-density lipoprotein (LDL) cholesterol. Moreover, it has been observed that the combination of the two drugs leads to a substantial reduction in coronary artery disease (CAD) events (1-4). The advantages

of this drug combination has led to the development of etofibrate in which clofibrate and niacin are covalently linked. In contact with plasma hydrolases, both constituents are gradually released, displaying a pharmacokinetic behavior similar to that of controlled-release formulations (5).

Some studies have shown that the traditional forms of niacin and fibrate could be of additional benefit by reducing plasma lipoprotein (a) (Lp(a)) levels (6-10). Lp(a) is an LDL-like lipoprotein, differentiated from LDL by the presence of an additional large protein molecule, the so-called apolipoprotein

tein (a) (apo(a)) which is linked to apo B through disulfide bridges (11-14). Similarly to LDL, a high Lp(a) concentration in plasma has been associated with the prevalence and severity of CAD (15-18). This may be due to several causes, one of them related to apo(a) homology with plasminogen, the zymogen of plasmin, that presumptively results in competitive inhibition of fibrinolysis (19-23). Lp(a) may also accumulate in the subendothelium where it binds with high affinity to extracellular matrix components (24). The effect of controlled-release forms of fibrates and niacin on Lp(a) levels has not been explored in all its relevant aspects. In the present investigation, we sought to compare the effects of etofibrate with those of controlled-release niacin on Lp(a) and plasma lipid profile in patients with type IIb dyslipidemia.

## Material and Methods

### Population

Thirty consecutive patients submitted to clinical evaluation at the coronary outpatient clinic of the Heart Institute were enrolled in this study. The inclusion criteria were plasma concentration of Lp(a) above 40 mg/dl, total cholesterol above 240 mg/dl and triglyceride between 200 and 400 mg/dl in the last two measurements. The exclusion criteria were liver, renal, metabolic, inflammatory or neoplastic disease, alcoholism or known hypersensitivity to niacin or etofibrate. Patients with unstable angina or myocardial infarction during the last 6 months and diabetic patients with plasma glucose above 135 mg/dl or HbA1c above 7.5% were also excluded. The step-one diet of the National Cholesterol Education Program (NCEP) of the American Heart Association was recommended to all patients three months before randomization. At randomization, all patients were taking only nitrates, whose doses were not changed during the study. The patients

were randomly selected for a double-blind treatment period with either 500 mg etofibrate (Tricerol<sup>®</sup>, Searle, São Paulo, SP, Brazil) or 500 mg polygel controlled-release niacin (Slo-Niacin<sup>®</sup>, Upsher-Smith Laboratories, Inc., Minneapolis, MN, USA) administered twice a day for a 16-week period. Etofibrate and niacin were placed in new vials labeled with the patient number and the vials were given directly to the patients by a research assistant. During the 4-week evaluation one patient in the etofibrate group and 4 in the niacin group did not return for study evaluation and were lost to follow-up. Thus, the final etofibrate group consisted of 14 subjects (12 males), mean age  $56 \pm 5$  years, and the niacin group consisted of 11 subjects (8 males), mean age  $57 \pm 7$  years. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of the Heart Institute and all subjects gave informed consent to participate in the study.

### Lipid and lipoprotein determinations

The first measurement after the diet period was considered to represent baseline values. Blood samples were obtained after a 12-h overnight fast, at baseline and after 4, 8, 12 and 16 weeks of treatment. Commercial enzymatic methods were used for the determination of total plasma cholesterol (CHOD-PAP, Boehringer-Mannheim Corp., Mannheim, Germany) and triglyceride concentration (Abbott Laboratories, North Chicago, IL, USA). HDL cholesterol was assayed by the same enzymatic method as for total cholesterol after precipitation of apo B lipoproteins with magnesium phosphotungstate. Very-low-density lipoprotein cholesterol and LDL cholesterol were calculated by the Friedewald formula (25). Plasma Lp(a) level was determined by radioimmunoassay using a kit supplied by Pharmacia (Uppsala, Sweden) (26). This assay is based on the determination of the apo(a) moiety of Lp(a).

### Statistical analysis

All data are reported as means  $\pm$  standard deviation. Plasma lipid variations were evaluated by analysis of variance (ANOVA). When the overall difference was statistically significant, differences within the evaluations were tested by the *a posteriori* Bonferroni test. Comparison between groups was performed by the Student *t*-test or Mann-Whitney test to analyze parametric and nonparametric data, respectively. Differences were considered significant when the probability value was  $<0.05$ .

### Results

There was no difference between the etofibrate and niacin groups regarding age, male/female ratio, frequency of smoking, hypertension, diabetes or body mass index values, and baseline plasma lipid and lipoprotein concentrations (Table 1). Table 2 shows the

mean results and percent variation of plasma lipid and Lp(a) concentrations. There was no significant difference between the plasma lipid and lipoprotein concentrations determined before admission to the study and at baseline after the dietary orientation period (Table 2). Both drugs reduced total cholesterol, VLDL cholesterol and triglyceride levels to the same extent and were equally effective in enhancing HDL cholesterol. However, etofibrate mark-

Table 1 - Baseline clinical characteristics.

The groups did not differ significantly.

	Groups	
	Etofibrate (N = 14)	Niacin (N = 11)
Age (years)	56 $\pm$ 5	57 $\pm$ 7
Male (N)	12	8
Body mass index (kg/m <sup>2</sup> )	26.7 $\pm$ 4	27.1 $\pm$ 3
Cigarette smoking (N)	3	2
Hypertension (N)	4	3
Diabetes mellitus (N)	1	2

Table 2 - Plasma lipid and lipoprotein (a) concentrations at admission to the study, baseline concentrations and concentrations after treatment with etofibrate (E) or niacin (N).

\*P<0.05 compared to group N. Data are reported as means  $\pm$  SD (mg/dl) and were analyzed by ANOVA.  $\Delta\%$ , Percent variation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

	Admission	Baseline	Weeks of treatment				$\Delta\%$	P
			4	8	12	16		
Total cholesterol								
E group	292 $\pm$ 38	295 $\pm$ 30	242 $\pm$ 43	223 $\pm$ 36	225 $\pm$ 32	220 $\pm$ 37	-26 $\pm$ 7	<0.0001
N group	297 $\pm$ 40	302 $\pm$ 41	268 $\pm$ 47	251 $\pm$ 38	256 $\pm$ 35	249 $\pm$ 37	-18 $\pm$ 5	<0.01
LDL cholesterol								
E group	201 $\pm$ 21	196 $\pm$ 17	168 $\pm$ 31	153 $\pm$ 23	153 $\pm$ 21	152 $\pm$ 25	-23 $\pm$ 4*	<0.0001
N group	203 $\pm$ 19	210 $\pm$ 22	198 $\pm$ 36	183 $\pm$ 26	185 $\pm$ 22	181 $\pm$ 26	-14 $\pm$ 7	0.07
HDL cholesterol								
E group	32 $\pm$ 5	33 $\pm$ 6	38 $\pm$ 5	47 $\pm$ 7	43 $\pm$ 5	44 $\pm$ 5	+33 $\pm$ 8	<0.0001
N group	32 $\pm$ 6	32 $\pm$ 7	37 $\pm$ 4	40 $\pm$ 5	43 $\pm$ 6	41 $\pm$ 3	+28 $\pm$ 8	<0.0001
VLDL cholesterol								
E group	60 $\pm$ 6	62 $\pm$ 7	35 $\pm$ 5	28 $\pm$ 4	29 $\pm$ 5	28 $\pm$ 5	-53 $\pm$ 4	<0.0001
N group	62 $\pm$ 5	62 $\pm$ 5	33 $\pm$ 4	28 $\pm$ 5	28 $\pm$ 5	28 $\pm$ 5	-54 $\pm$ 5	<0.0001
Triglycerides								
E group	294 $\pm$ 35	317 $\pm$ 39	170 $\pm$ 32	143 $\pm$ 29	145 $\pm$ 32	142 $\pm$ 36	-56 $\pm$ 9	<0.0001
N group	309 $\pm$ 49	304 $\pm$ 55	167 $\pm$ 37	141 $\pm$ 38	140 $\pm$ 37	139 $\pm$ 35	-55 $\pm$ 10	<0.0001
Lipoprotein (a)								
E group	51 $\pm$ 5	51 $\pm$ 4	47 $\pm$ 5	-	-	38 $\pm$ 6	-26 $\pm$ 5*	<0.0001
N group	49 $\pm$ 6	48 $\pm$ 5	49 $\pm$ 6	-	-	44 $\pm$ 5	-8 $\pm$ 3	0.08

Table 3 - Analysis of liver toxicity after treatment with etofibrate or niacin.

P>0.05 for all differences before and after treatment. ALT, Alanine aminotransferase; AST, aspartate aminotransferase.

	Etofibrate		Niacin	
	Before treatment	After treatment	Before treatment	After treatment
AST	12 ± 4	14 ± 5	13 ± 3	12 ± 3
ALT	18 ± 8	19 ± 10	20 ± 7	21 ± 6

edly reduced plasma Lp(a) concentration by 26% and LDL cholesterol by 23%, an effect not obtained with niacin. LDL cholesterol tended to be reduced by 14% in the niacin group but its reduction was not statistically significant (P = 0.07).

None of the patients who completed the study reported any side effects after either drug. However, since 5 patients were lost to follow-up, we cannot assure the absence of side effects. For the 3 diabetic patients included there was no clinically significant alteration in plasma glucose concentration after niacin (114 and 124 mg/dl before treatment and 116 and 112 mg/dl after treatment, respectively) or etofibrate (106 mg/dl before treatment and 111 mg/dl after treatment). Regarding liver toxicity, there was no significant increase in alanine aminotransferase or aspartate aminotransferase after treatment with either drug (Table 3).

## Discussion

It is apparent from our results that etofibrate is more effective as an LDL cholesterol-lowering agent than niacin alone. Likewise, comparing our data with those obtained in the literature after treatment with fibrates, it seems that etofibrate produced a greater LDL cholesterol reduction (27-29). The main mechanism whereby fibrates reduce LDL cholesterol is probably by increasing LDL removal from plasma (29). This fibrate effect could be a result of the reduction of apo CIII, achieved by the acti-

vation of peroxisome proliferator-activated receptors (30). Recently, it was reported that niacin accelerates hepatic intracellular post-translational degradation of apo B, resulting in decreased apo B secretion by hepatocytes (31). A trend towards LDL cholesterol reduction (P = 0.07) was observed in the niacin group, suggesting that the niacin moiety of etofibrate somehow contributed to the reduction of LDL cholesterol in the etofibrate group. Thus, it is possible that a combination of decreased synthesis and increased catabolism may account for the higher LDL cholesterol reduction observed in the etofibrate-treated patients.

Despite the structural similarity of Lp(a) to LDL particles and the presence of the LDL receptor ligand, i.e., apo B, only 25% of the plasma Lp(a) pool is removed by means of the LDL receptor (32). The presence of apo(a) is assumed to be the factor diminishing the affinity of Lp(a) for the receptor, since dissociation of the protein by cleavage of the disulfide linkages results in binding affinity similar to that of LDL (33). The apo(a) interference in the apo B binding domain of LDL receptor is probably the mechanism whereby lipid-lowering drugs that increase the expression of LDL receptors, such as statins, are ineffective in reducing plasma Lp(a) concentrations (6,34,35).

By an unknown mechanism of action, fibrate treatment and the use of estrogen as a contraceptive or for hormone replacement therapy consistently reduce plasma Lp(a) concentrations (6-8,36-39). Other drug therapies that have produced a significant reduction in Lp(a) concentration include niacin alone or in combination with a bile acid sequestrant or neomycin (9,10,40). Niacin reduces Lp(a) levels without affecting the fractional catabolic rate of the lipoprotein, suggesting that treatment with this drug decreases the rate of Lp(a) synthesis and not its removal from plasma (41). In the traditional form, niacin at 4 g/day decreased the plasma Lp(a) concentrations by 38% in hypercholesterolemic patients (9).

However, it is very difficult to maintain patient compliance with this dosage due to the side effects of niacin and lower doses of sustained-release niacin are more tolerable. Because of the pharmacokinetic behavior of the drug, lower doses of sustained-release niacin have also been suggested to have comparable effects on plasma lipid and lipoproteins in comparison with the regular doses of traditional niacin. Recently, some sustained-release forms of niacin have been shown to reduce Lp(a) (42,43). Nonetheless, this was not observed in the present study using treatment with a polygel controlled-release niacin. These contradictory results may be due to different study populations or to pharmacokinetic differences in these sustained-release forms. A comparative study of these sustained-release forms is necessary to unravel possible pharmacokinetic differences.

After contact with plasma hydrolases both constituents of etofibrate (clofibrate and niacin) are gradually released with a pharmacokinetic behavior similar to that of sustained-release forms. Therefore, the action of etofibrate on Lp(a) may either be caused by the fibrate moiety of the compound or by the

niacin moiety, since treatment with either drug administered alone causes this effect. Klör et al. (44) reported a 16.6% reduction of plasma Lp(a) levels after a short (one month) treatment period with 1 g/day etofibrate in patients with Lp(a) above 50 mg/dl. In our study, with the same dose we showed that a prolonged (4 months) treatment period may result in a greater (26%) Lp(a) reduction. Nevertheless, it should be pointed out that our patients had somewhat lower pretreatment Lp(a) values that might eventually have influenced the outcome of treatment.

Since the present study was not designed to determine the lipid-lowering effect of the NCEP step-one diet, we included patients that were already following the routine dietary orientation for CAD patients of the Heart Institute. Therefore, it is not unexpected that there was no difference in the plasma lipid concentrations determined before admission to the study and at baseline.

In conclusion, we observed that etofibrate was more efficient than polygel controlled-release niacin in reducing plasma LDL cholesterol and Lp(a) levels in patients with type IIb dyslipidemia and Lp(a) above 40 mg/dl.

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