Pentaerythritol Tetranicotinate (niceritrol) Decreases Plasma Lipoprotein(a) Levels

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We determined the most effective dosage of pentaerythritol tetranicotinate (niceritrol) to reduce plasma lipoprotein(a) [Lp(a)] levels in 44 Japanese patients (16 men and 28 women; mean age, 59.2 ± 10.8 years) with hyperlipidemia types IIa, IIb, and IV. Patients received oral niceritrol at a dosage of 750 mg (3 tablets)/d for 8 weeks, followed by 1,500 mg (6 tablets)/d for 8 weeks. Administration of niceritrol 750 mg/d for 8 weeks decreased total and low-density lipoprotein (LDL) cholesterol in patients with type IIa hyperlipidemia and decreased triglycerides in patients with type IV hyperlipidemia, but did not affect Lp(a). However, niceritrol 1,500 mg/d for 8 weeks decreased Lp(a) in patients with initial Lp(a) levels greater than 30 mg/dL in addition to decreasing total and LDL cholesterol and triglycerides. These results suggest that the effective dosage of niceritrol to reduce the serum Lp(a) concentration in Japanese hyperlipidemic patients with a high Lp(a) level (≥30 mg/dL) is greater than 1,500 mg/d.

FIRST DESCRIBED IN 1963 by Berg,[1] lipoprotein(a) [Lp(a)] has recently been attracting great interest as an important independent risk factor for such atherosclerotic vascular diseases as ischemic heart disease and cerebrovascular disease,[2-8] although its impact is controversial.[9] Lp(a) concentration has been thought to be unrelated to clinical or biochemical parameters, but to be determined mainly by genetic variations.[10,11] The effectiveness of nicotinic acid, a commonly used lipid-lowering drug, in decreasing plasma Lp(a) levels was recently reported by Carlson et al.[12] This finding prompted us to investigate the effects of pentaerythritol tetranicotinate (niceritrol), the prodrug of nicotinic acid, on plasma Lp(a).[13,14] In this study, we determined the effective dosage of niceritrol to reduce plasma Lp(a) levels in Japanese patients with hyperlipidemia.

SUBJECTS AND METHODS

Subjects

Forty-four patients (16 men and 28 women; mean age, 59.2 ± 10.8 years) with hyperlipidemia were studied prospectively. Patients were required to have baseline serum triglyceride concentrations higher than 150 mg/dL or serum total cholesterol concentrations higher than 220 mg/dL, despite the dietary stabilization and life-style modification observed during a 6-week pretrial period, as proposed by the National Cholesterol Education Program.[15] Familial hypercholesterolemia, type I or III hyperlipoproteinemia, and secondary hyperlipoproteinemia were excluded. Clinical characteristics of the patients are listed in Table 1. The patients received oral niceritrol 750 mg (3 tablets)/d for 8 weeks and 1,500 mg (6 tablets)/d for a further 8 weeks after each meal according to the study protocol.

Measurements of Lp(a) and Lipids

Blood samples for the lipid profile were drawn after an overnight fast of longer than 12 hours before and at 8 and 16 weeks of treatment. Plasma Lp(a) was determined by an enzyme-linked immunosorbent assay (TintEliza Lp(a); Biopool, Umeå, Sweden), and serum lipid levels were measured by routine laboratory methods using autoanalyzers as previously described.[16]

Statistical Analysis

Conventional methods were used for calculation of the mean ± SEM and median values. Significance between variables before and after treatment with niceritrol was determined by the Wilcoxon signed-rank test.

RESULTS

Effects of Niceritrol on Plasma Total Cholesterol, Triglyceride, High-Density Lipoprotein Cholesterol, and Low-Density Lipoprotein Cholesterol Levels

In patients with type IIa hyperlipidemia, plasma total and low-density lipoprotein (LDL) cholesterol decreased significantly after 8 weeks of treatment with niceritrol 750 mg/d, and further decreases occurred after 8 weeks of treatment with niceritrol 1,500 mg/d (Table 2). Plasma triglyceride and high-density lipoprotein (HDL) cholesterol levels in type IIa hyperlipidemic patients were not changed by treatment with niceritrol (Table 2). Total cholesterol and LDL cholesterol concentrations of patients with type IIb hyperlipidemia were decreased by treatment with niceritrol, but the changes were not significant (Table 2). Plasma triglyceride level in type IIb hyperlipidemic patients was not changed by treatment with niceritrol. HDL cholesterol was increased after 8 weeks of treatment with niceritrol 750 mg/d in patients with type IIb hyperlipidemia (Table 2). In patients with type IV hyperlipidemia, total and LDL cholesterol did not change throughout treatment (Table 2). In patients with type IV hyperlipidemia, triglycerides decreased without significance after administration of niceritrol 750 mg/d for 8 weeks, and decreased with significance after 8 weeks' administration of niceritrol 1,500 mg/dL (Table 2). HDL cholesterol in patients with type IV hyperlipidemia increased significantly with niceritrol (Table 2).

Effects of Niceritrol on Plasma Lp(a) Levels

The effect of niceritrol on plasma Lp(a) levels was investigated with 43 patients entered in this study (N = 44). Table 3 shows the effects of niceritrol on serum Lp(a) level. In patients with an initial Lp(a) level greater than 30 mg/dL, the first 8 weeks of treatment with niceritrol at a

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Table 1. Clinical Characteristics of the Patients

Characteristic	Value (N = 44)
Age, yr (mean ± SE)	59.2 ± 10.8
Sex (n)	
Male	16
Female	28
Type of hyperlipidemia (n)	
IIa	23
IIb	14
IV	7

dosage of 750 mg/d did not affect Lp(a) significantly. However, niceritrol 1,500 mg/d decreased Lp(a) levels significantly after 8 weeks (median Lp(a) before, at 8 weeks, and after treatment, 44.0, 38.0, and 38.0 mg/dL, respectively). In contrast, neither the low (750 mg/d) nor the high (1,500 mg/d) dosage of niceritrol altered Lp(a) levels in patients with an Lp(a) level less than 30 mg/dL (median Lp(a) before, at 8 weeks, and after treatment, 13.5, 11.0, and 10.0 mg/dL, respectively). The mean and median reduction rate of Lp(a) in all patients at 16 weeks of treatment was 13.6% and 16.7%, respectively, and in patients with an initial Lp(a) level greater than 30 mg/dL, 25.0% and 18.4%, respectively. This significant decrease in Lp(a) levels was obtained during administration of niceritrol 1,500 mg/d. The initial Lp(a) level in type IIa hyperlipidemia is higher compared with levels in type IIb and type IV patients in this study, by accident. Reflecting this difference in the initial serum concentration, Lp(a) is significantly decreased by niceritrol in type IIa patients, but levels in type IIb or IV patients were not reduced in this study (Table 3).

Table 2. Effects of Niceritrol on Plasma Cholesterol and Triglyceride Levels (mean ± SEM, mg/dL)

Parameter	0 Weeks	8 Weeks	16 Weeks
TC			
All cases	253.2 ± 5.8	241.1 ± 5.8	236.6 ± 5.1†
IIa	263.5 ± 4.6	247.4 ± 5.6*	240.2 ± 6.6†
IIb	265.5 ± 11.2	257.4 ± 12	246.8 ± 8.4
IV	194.7 ± 7.2	191.0 ± 3.8	204.4 ± 11.2
TG			
All cases	165.3 ± 15.3	153.4 ± 15	156.5 ± 17
IIa	94.1 ± 5.3	106.4 ± 11	107.0 ± 11
IIb	242.6 ± 25.3	220.2 ± 36	232.1 ± 41
IV	244.7 ± 40.5	177.0 ± 28	167.7 ± 36*
HDL cholesterol			
All cases	52.3 ± 2.1	55.0 ± 2.3	54.5 ± 2.6
IIa	62.1 ± 2.3	63.2 ± 3.1	63.6 ± 3.7
IIb	43.5 ± 1.6	47.8 ± 1.9*	44.8 ± 2.5
IV	37.7 ± 4.0	42.5 ± 5.0*	43.9 ± 4.9*
LDL cholesterol			
All cases	167.9 ± 5.9	155.5 ± 5.4*	150.8 ± 5.2†
IIa	182.6 ± 5.0	163.0 ± 5.5†	155.2 ± 6.1‡
IIb	173.5 ± 10.9	165.5 ± 11.2	155.6 ± 11.0
IV	108.0 ± 6.4	113.1 ± 5.4	126.9 ± 11.9

NOTE. IIa, patients with pretreatment TC >220 mg/dL and TG <150 mg/dL; IIb, patients with pretreatment TC >220 mg/dL and TG >150 mg/dL; IV, patients with pretreatment TC <220 mg/dL and TG >150 mg/dL.

Abbreviations: TC, total cholesterol; TG, triglycerides.

*$P < .05$, †$P < .01$, ‡$P < .001$: *v* 0 weeks.

Table 3. Effect of Niceritrol on Plasma Lp(a) Level (mean ± SEM, mg/dL)

Group	0 Weeks	8 Weeks	16 Weeks
All cases (n = 43)	27.1 ± 3.9	26.4 ± 4.2	22.7 ± 3.5*
Lp(a) > 30 mg/dL (n = 13)	55.7 ± 8.3	52.7 ± 8.6	43.7 ± 8.4*
Lp(a) < 30 mg/dL (n = 30)	14.7 ± 1.6	13.7 ± 2.1	13.5 ± 2.0
IIa	37.4 ± 6.6	39.9 ± 7.3	32.8 ± 6.3*
IIb	18.4 ± 3.6	16.8 ± 4.3	16.4 ± 4.0
IV	12.0 ± 2.7	13.1 ± 3.9	11.4 ± 3.1

*$P < .01$ *v* 0 weeks.

DISCUSSION

The protein moiety of Lp(a) is composed of one molecule of apolipoprotein (apo) B-100, the major protein constituent of LDL, and one molecule of apo(a), a large glycoprotein attached to apo B-100 by a disulfide bond.[17-19] cDNA nucleotide sequence analyses have shown that apo(a) has a high degree of homology with plasminogen, a plasma protein involved in the fibrinolytic process.[20] Because of this homology, Lp(a) may compete with plasminogen, hence interfering with the thrombolytic process,[21,22] and may be a risk factor for coronary artery disease and cerebrovascular disease.[3-6,8,23] Recent reports have suggested that elevated Lp(a) concentrations are also associated with intermittent claudication[24] and intima-media carotid thickening[25] independent of other important risk factors for peripheral atherosclerosis. Therefore, reducing plasma Lp(a) may prevent peripheral atherosclerosis in addition to decreasing cardiovascular and cerebrovascular disease morbidity and mortality in patients with hyperlipidemia. However, Lp(a) cannot be decreased by the usual treatments for hyperlipidemia.[26-29] Alcohol,[30] nicotinic acid with or without neomycin,[12,31] α-tocopheryl nicotinate,[32] *N*-acetylcysteine,[33] and the anabolic steroid stanozolon[34] reportedly decrease Lp(a) concentrations. Niceritrol, the nicotinic acid ester (Fig 1) and a prodrug of nicotinic acid, is one of the few drugs that reduce plasma Lp(a) concentration.[13,14,35] It is gradually hydrolyzed and released as nicotinic acid in the body after absorption. So, the rate of adverse effects of niceritrol such as flushing of the face and gastrointestinal symptoms is smaller than that of nicotinic acid. A secondary and prolonged elevation of plasma free fatty acids is not observed after niceritrol administration, whereas it is observed after nicotinic acid.[36] However, the effective dosage of niceritrol to decrease plasma Lp(a) has not been clarified.

We studied the effects of niceritrol 750 and 1,500 mg/d on serum Lp(a). Administration of niceritrol 750 mg/d for 8 weeks did not affect plasma Lp(a) levels, although plasma total and LDL cholesterol levels were decreased in patients with type IIa hyperlipidemia (Table 2). However, Lp(a) in patients with an initial Lp(a) level greater than 30 mg/dL was decreased significantly by niceritrol 1,500 mg/d for 8 weeks (Table 3). These results suggest that niceritrol decreases plasma cholesterol at a dosage of 750 mg/d and that the effective dose of niceritrol to decrease plasma triglyceride in patients with type IV hyperlipidemia and Lp(a) is greater than 1,500 mg/d. Kazumi et al[37] reported that Lp(a) levels were decreased significantly by administration of niceritrol 750 mg/d for 8

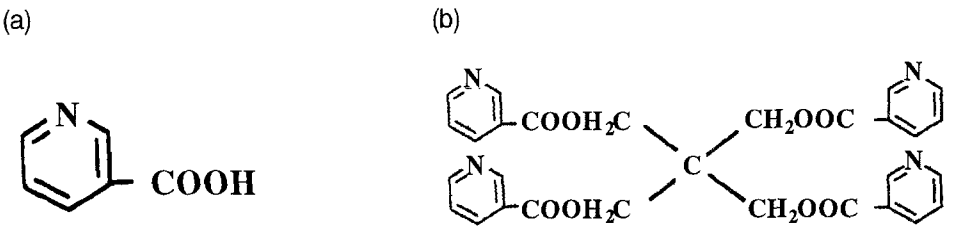

Fig 1. Structure of nicotinic acid (a) and niceritrol (b).

weeks and that no additional reductions were found even though the dose of niceritrol was increased to 1,500 mg/d in nonproteinuric non–insulin-dependent diabetes mellitus patients. Another report indicates the same result, although the disease etiology of the patients was not described.[38] The cause of the discrepancy between these two prior reports and our result is unclear, but subject differences might explain this. Our study was performed on patients with hyperlipidemia, and patients with diseases that can cause secondary hyperlipoproteinemia were excluded, so our result can be applied to only primary hyperlipidemic patients.

In patients with Lp(a) levels less than 30 mg/dL, niceritrol 1,500 mg/d did not induce serum Lp(a) reduction. These results are consistent with previous reports that significant reductions in Lp(a) occurred in 15 patients with initial Lp(a) values greater than 30 mg/dL, but not in seven patients with pretreatment values less than 30 mg/dL.[39] Other research also showed that niceritrol significantly reduced serum Lp(a) in patients with an initially high level (≥20 mg/dL).[14] Our findings are in agreement with these reports. This is clinically important, because individuals who have the highest risk due to high Lp(a) levels will benefit most from niceritrol.

The initial Lp(a) level in type IIa hyperlipidemia is higher compared with that in type IIb and type IV hyperlipidemia in this study. As far as we know, there is no report that suggests a relation between the serum Lp(a) level and the type of hyperlipidemia. So, it is thought that the high Lp(a) concentration in type IIa hyperlipidemia in this study is an accidental result. Reflecting this difference in the initial serum concentration, Lp(a) is significantly reduced by niceritrol in type IIa patients, but levels in type IIb or IV patients were not reduced in this study (Table 3).

In patients with type IIb hyperlipidemia, there were no significant decreases in plasma total and LDL cholesterol and triglyceride even if a tendency for a decrease in these plasma lipid was observed (Table 2). A large-scale study may prove the decrease in plasma cholesterol and triglyceride levels by treatment with niceritrol in patients with type IIb hyperlipidemia.

In conclusion, results of the present study suggest that administration of niceritrol 1,500 mg/d reduces plasma Lp(a) in Japanese hyperlipidemic patients with an Lp(a) level greater than 30 mg/dL, in addition to decreasing plasma total and LDL cholesterol in patients with type IIa hyperlipidemia and triglycerides in patients with type IV hyperlipidemia (Table 2), and that this therapy may decrease the risk of atherosclerosis.

REFERENCES

1. Berg K: A new serum type system in man: The Lp-system. Acta Pathol Microbiol Scand 59:369-382, 1963

2. Berg K, Dahlen G, Frick MH: Lp(a) lipoprotein and pre-β-lipoprotein in patients with coronary heart disease. Clin Genet 6:230-235, 1974

3. Dahlen GH, Guyton JR, Attar M, et al: Association of levels of lipoprotein Lp(a), plasma lipids, and other lipoproteins with coronary artery disease documented by angiography. Circulation 74:758-765, 1986

4. Genest J Jr, McNamara JR, Ordovas JM, et al: Lipoprotein cholesterol, apolipoprotein A-1 and B and lipoprotein(a) abnormalities in men with premature coronary artery disease. J Am Coll Cardiol 19:792-802, 1992

5. Hoefler G, Harnoncourt F, Paschke E, et al: Lipoprotein(a): A risk factor for myocardial infarction. Arteriosclerosis 8:398-401, 1988

6. Rosengren A, Wilhelmsen L, Erikssen E, et al: Lipoprotein(a) and coronary heart disease: A prospective study in a general population sample of middle aged men. Br Med J 301:1248-1251, 1990

7. Murai A, Miyahara T, Fujimoto N, et al: Lp(a) lipoprotein as a risk factor for coronary heart disease and cerebral infarction. Atherosclerosis 59:199-204, 1986

8. Zenker G, Koeltringer P, Bone G, et al: Lipoprotein(a) as a strong indicator for cerebrovascular disease. Stroke 17:942-945, 1986

9. Ridker PM, Hennekens CH, Stampfer MJ: A prospective study of lipoprotein(a) and the risk of myocardial infarction. JAMA 270:2195-2199, 1993

10. Boerwinkle E, Leffert CC, Lin J, et al: Apolipoprotein(a) gene accounts for greater than 90% of the variation in plasma lipoprotein(a) concentrations. J Clin Invest 90:52-60, 1992

11. Krempler F, Kostner GM, Bolzano K, et al: Turnover of lipoprotein(a) in man. J Clin Invest 65:1483-1490, 1980

12. Carlson LA, Hamsten A, Asplund A: Pronounced lowering of serum levels of lipoprotein Lp(a) in hyperlipidaemic subjects treated with nicotinic acid. J Intern Med 226:271-276, 1989

13. Nakahara H, Nakanishi T, Uyama O, et al: Niceritrol reduces plasma lipoprotein(a) levels in patients undergoing maintenance hemodialysis. Ren Fail 15:189-193, 1993

14. Matsunaga A, Handa K, Mori T, et al: Effects of niceritrol on levels of serum lipids, lipoprotein(a), and fibrinogen in patients with primary hypercholesterolemia. Atherosclerosis 94:241-248, 1992

15. The Expert Panel: Report of the National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults. Arch Intern Med 148:36-69, 1988

16. Hayahsi K, Ohtani H, Okura Y, et al: Hypolipidemic effect of beraprost sodium in patients with arteriosclerosis obliterans accompanied by hyperlipidemia. Curr Ther Res 55:1486-1491, 1994

17. Utermann G: The mysteries of lipoprotein(a). Science 246:904-910, 1989

18. Scanu AM, Fless GM: Lipoprotein(a): Heterogeneity and biological relevance. J Clin Invest 85:1709-1715, 1990

19. Sommer A, Gorges R, Kostner GM, et al: Sulfhydryl-selective fluorescence labeling of lipoprotein(a) reveals evidence for one single disulfide linkage between apoprotein(a) and B-100. Biochemistry 30:11245-11249, 1991

20. McLean JW, Tomlison JE, Kuang WJ, et al: cDNA sequence of human apolipoprotein(a) is homologous to plasminogen. Nature 330:132-137, 1987

21. Hajjar KA, Gavish D, Breslow JL, et al: Lipoprotein(a) modulation of endothelial cell surface fibrinolysis and its potential role in atherosclerosis. Nature 339:303-305, 1989

22. Lascalzo J, Weinfield M, Fless GM, et al: Lipoprotein(a), fibrin binding, and plasminogen activation. Arteriosclerosis 10:240-245, 1990

23. Kostner GM, Avogaro P, Cazzolalo G, et al: Lipoprotein Lp(a) and risk for myocardial infarction. Atherosclerosis 38:51-61, 1981

24. Molgaard J, Klausen IC, Lassvik C, et al: Significant association between low–molecular-weight apolipoprotein(a) isoforms and intermittent claudication. Arterioscler Thromb 12:895-901, 1992

25. Schreiner PJ, Morrisett JD, Sharrett AR, et al: Lipoprotein(a) as a risk factor for preclinical atherosclerosis. Arterioscler Thromb 13:826-833, 1993

26. Alber JJ, Canaba VG, Warnick GR, et al: Lp(a) lipoprotein: Relation to sinking pre-b lipoprotein, hyperlipoproteinemia and apolipoprotein B. Metabolism 24:1047-1054, 1975

27. Vessby B, Kostner G, Lithell H, et al: Diverging effects of cholestyramine on apolipoprotein B and lipoprotein(a). Atherosclerosis 44:61-71, 1982

28. Kostner GM, Gavish D, Leopold B, et al: HMG CoA reductase inhibitors lower LDL cholesterol without reducing Lp(a) levels. Circulation 80:1313-1319, 1989

29. Maeda S, Okuno M, Abe A, et al: Lack of effect of probucol on serum lipoprotein(a) levels. Atherosclerosis 79:267-269, 1989

30. Vaelimaeki M, Laitinen K, Ylikahrit R, et al: The effect of moderate alcohol intake on apolipoprotein A-I–containing lipoproteins and lipoprotein(a). Metabolism 40:1168-1172, 1991

31. Gurakar A, Hoeg JM, Kostner G, et al: Levels of lipoprotein Lp(a) decline with neomycin and niacin treatment. Atherosclerosis 57:293-301, 1985

32. Noma A, Maeda S, Okuno M, et al: Reduction of serum lipoprotein(a) levels in hyperlipidemic patients with a-tocopheryl nicotinate. Atherosclerosis 84:213-217, 1990

33. Gavish D, Brewer JL: Lipoprotein reduction by *N*-acetylcysteine. Lancet 337:203-204, 1991

34. Alber JJ, Taggart HM, Applebaum-Bowden D, et al: Reduction of lecithin-cholesterol acyltransferase, apolipoprotein D and the Lp(a) lipoprotein with anabolic steroid stanozolon. Biochim Biophys Acta 795:293-303, 1984

35. Sano R, Fujino A, Saito T, et al: Reduction by niceritrol treatment of serum lipoprotein(a) in normolipidemic patients with coronary artery disease. Tohoku J Exp Med 169:299-307, 1993

36. Svedmyr N, Harthon L: Comparison between the absorption of nicotinic acid and pentaerythritol tetranicotinate (Perycit®) from ordinary and enterocoated tablets. Acta Pharmacol Toxicol 28:66-74, 1970

37. Kazumi T, Yoshino G, Maeda T, et al: Effects of niceritrol on elevated serum lipoprotein Lp(a) levels in diabetic patients with or without overt proteinuria. Curr Ther Res 55:546-551, 1994

38. Segawa J, Sadayasu T, Nomura S, et al: Effects of niceritrol on plasma Lp(a) and fibrinolytic system. Eur Heart J 13:195, 1992 (abstr, suppl)

39. Kazumi T, Yoshino G, Shima F, et al: Niceritrol-induced reductions in serum lipoprotein(a) continue for one year. Curr Ther Res 54:550-552, 1993