Effects of the Nicotinic Acid Analogue Niceritrol on Lipoprotein Lp(a) and Coagulation-Fibrinolysis Status in Patients with Chronic Renal Failure on Hemodialysis

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Table 1. Effects of the 4-week administration of niceritrol on Lp(a), TAT, D-dimer and lipoprotein levels in 17 hemodialysis patients

Before

91.0 ± 4.7

77.4 ± 5.0

Results are means ± SE; p value by paired t test. 1 By Wilcoxon signed-rank test.

Dear Sir,

Atherosclerosis is reported to be accelerated in patients with chronic renal failure treated by hemodialysis [1]. Risk factors for it would include impaired lipoprotein metabolism and altered blood coagulation-fibrinolysis status. Some recent studies have shown that patients with chronic renal failure have an elevated plasma level of lipoprotein Lp(a) [2, 3], a low-density-lipoprotein-like lipoprotein having an additional protein component called Apo(a) [4]. An increased Lp(a) level is regarded as an independent risk factor for atherosclerosis in the general population [4]. High homology between Apo(a) and the kingle 4 domain of plasmin-ogen [5] may account for the proposed thrombogenic and atherogenic nature of Lp(a) [6]. Theoretically, Lp(a) competitively inhibits plasmin-mediated fibrinolysis [4]. So far, however, such a predicted suppression of fibrinolysis has not been clinically demonstrated in hemodialysis patients. To address this issue, we measured Lp(a) and coagulation-fibrinolysis parameters in hemodialysis patients before and after oral administration of niceritrol, a nicotinic acid analogue, which is known to lower Lp(a) concentration in nonuremic subjects [7].

The subjects were 17 (7 male and 10 female) nondiabetic hemodialysis patients. They were all Japanese. The mean (± SE) age was 58 ± 3 years and duration of hemodialysis treatment was 90 ± 15 months, respectively. The body mass index was 21.1 ± 0.5 kg/m². They received niceritrol (Pery-cit®, Sanwa Kagaku Kenkyusho Co. Ltd., Nagoya, Japan),

750 mg/day, for 4 weeks. Lp(a) was measured by ELISA [TintElize® Lp(a), Biopool, Umea, Sweden]. The thrombin-antithrombin (TAT) complex concentration was measured by ELISA (Enzygnost® TAT, Hoechst Japan Co. Ltd., Tokyo, Japan) as a sensitive index of blood coagulation. D-dimer, which is one of the degradation products of cross-linked fibrin, was measured by ELISA (Asserachrom® D-Di, Boehringer Mannheim Yamanouchi Co. Ltd., Tokyo, Japan) as a molecular marker for secondary fibrinolysis. Lipoproteins were assayed by ultracentrifugation as described

Apolipoprotein AI, mg/dl Apolipoprotein B, mg/dl

elsewhere [8]. Blood samples were drawn after an overnight fast before starting hemodialysis.

After

p value

114.4 ± 5.8

80.2 ± 6.3

0.0001

NS

Table 1 gives the results. Following the treatment, Lp(a) decreased by 33%. Niceritrol did not change the TAT plasma level, whereas it significantly increased D-dimer by 15%, TAT and D-dimer showed a positive correlation both at baseline and after niceritrol treatment, suggesting a dynamic balance between coagulation and secondary

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2000 -

After treatment $r = 0.654$ $P < 0.005$

ε

$w 1000i$

v, Φ

$\varepsilon^{3/4}$

$\hat{U}$

Before treatment $r = 0.557$ $P < 0.05$

$1 < r$

10

6 8

TAT (ng/ml)

Fig. 1. Correlation between TAT and D-dimer levels before and after niceritrol administration in hemodialysis patients. The slopes of the regression lines before and after treatment were significantly different ($p < 0.05$).

fibrinolysis (fig. 1). Interestingly, the slope of the regression line became greater after niceritrol treatment. The difference between the two slopes was statistically significant ($t = 2.234$, d.f. = 30, $p < 0.05$).

One of the postulated mechanisms for accelerated atherogenesis by Lp(a) is that Lp(a) could be a competitive inhibitor for plasmin as shown in vitro [4]. Previous studies failed

to show such an influence of Lp(a) on secondary fibrinolysis in a clinical setting [9]. In the present study, the 4-week administration of niceritrol was followed by a decrease in Lp(a), an increase in D-dimer and no change in TAT levels. Importantly, Lp(a) reduction by niceritrol treatment shifted the dynamic balance between coagulation and secondary fibrinolysis. Although there is still a possibility that niceritrol directly affected the blood coagulation system, our data can be interpreted to indicate that lowering Lp(a) attenuated the Lp(a)-mediated suppression of secondary fibrinolysis. Our observations clinically support the current concept that elevated Lp(a) interferes with the coagulation-fibrinolysis system, at least in hemodialysis patients.

References

Lindner A, Charra B, Sherrard DJ, Scribner BH: Accelerated atherosclerosis in prolonged maintenance hemodialysis. *N Engl J Med* 1974;290:697-701.

Parsy D, Dracon M, Cachera C, et al: Lipoprotein abnormalities in chronic hemodialysis patients. *Nephrol Dial Transplant* 1988;3:51-56. Shoji T, Nishizawa Y, Nishitani H, Yamakawa M, Morii H: High serum lipoprotein (a) concentrations in uremic patients treated with continuous ambulatory peritoneal dialysis. *Clin Nephrol* 1992;38:271-276.

MBewu AD, Durrington PN: Lipoprotein (a): Structure, properties and possible involvement in thrombogenesis and atherogenesis. *Atherosclerosis* 1990;85:1-14.

McLean JW, Tomlinson JE, Kuang W-J, Eaton DL, Chen EY, Fless GM, Scanu AM, Lawn RM: cDNA sequence of human apolipoprotein (a) is homologous to plasminogen. *Nature* 1987;300:132-137.

Hajjar KA, Gavish D, Breslow JL, Nachman PV: Lipoprotein (a) modulation of endothelial surface fibrinolysis and its potential role in atherosclerosis. *Nature* 1989;339:303-305.

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* 1989;226: 271-276.

Shoji T, Nishizawa Y, Nishitani H, Yamakawa M, Morii H: Impaired high density lipoprotein metabolism in uremic patients. *Kidney Int* 1992;41:1653-1661.

Sundell IB, Nilsson TK, Hallmans G, Hellsten G, Dahlen GH: Interrelationships between plasma levels of plasminogen activator inhibitor, tissue plasminogen activator, lipoprotein (a) and established cardiovascular risk factors in a North Swedish population. *Atherosclerosis* 1989;80:9-16.

Lp(a) and Coagulation-Fibrinolysis Status in HD Patients

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