Treatment of Hyperlipidemia with Probucol Reduces Proteinuria in Puromycin Aminonucleoside-Induced Nephrotic Rats

T.	Tsutomu	Hirano ^a
J.C.L.	John C.L.	Mamo ^c
K.	Kayoko	Ohnami ^b
T.	Tetsuzo	Sugisaki ^b

^aFirst Department of Internal Medicine and ^bDepartment of Nephrology, Showa University School of Medicine, Tokyo, Japan; ^cDepartment of Physiology, University of Western Australia, Nedlands, Australia

Dr. Tsutomu Hirano, First Department of Internal Medicine, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142 (Japan)

Dear Sir,

Recently, it has been suggested that secondary hyperlipidemia resulting from nephrotic syndrome can exacerbate the primary renal disorder [1–3]. Diamond and Karnovsky [2] demonstrated that dietary cholesterol supplementation increased urinary protein excretion in puromycin aminonucleoside (PA)-induced nephrotic rats (PAN), concomitant with increased plasma cholesterol levels. PAN itself shows severe hyperlipidemia in the presence of remarkable proteinuria [4, 5]. This led us to speculate that treatment of hyperlipidemia with a hypo-lipidemic agent may attenuate PAN-induced proteinuria by inhibiting the vicious cycle. To investigate this we have studied the effects of Probucol, a potent cholesterol-lowering drug [6], on the rate of urinary protein excretion in PAN.

PA (100 mg/kg body weight) was injected intraperitoneally into male Wistar rats (150–160 g) and thereafter the animals were maintained on standard rat chow, or chow pellets containing 1% Probucol (kindly provided by Oot-suka Pharmaceutical, Osaka, Japan). Food and water were available ad libitum. Consumption of chow and body weight gain were identical for Probucol-treated and nontreated PAN (table 1). Ten days after PA injection, food was removed for a 24-hour period and total urine was collected. Blood samples were taken from un-anesthetized rats at the end of the 24-hour period from the tail vein. Plasma triglyceride, total cholesterol, phospholipid and apoprotein B (measured by an electroimmunoassay) were significantly increased in nephrotic rats, which were about 4–5 times higher than that in normal fasted rats (data not shown). Nephrotic rats receiving Probucol incorporated into their diet had plasma lipids and apoprotein B concentrations which were 50–65% lower than those in the nontreated nephrotic group (table 1). Urinary protein excretion was also significantly reduced in the Probucol-treated nephrotic rats compared to the nontreated nephrotic group (table 1). The mechanism by which Probucol reduced proteinuria is not understood. It may be a direct effect on glomerular filtration, or alternatively, be secondary to a lower concentration of plasma lipoproteins. The latter of these alternatives is supported by the fact that significant positive correlations existed between the severity of the proteinuria and plasma triglyceride, cholesterol

and apoprotein B levels (fig. 1). Kasiske et al. [3] reported that hypo-lipidemic agents, mevinolin or clofibrate, reduced proteinuria in obese Zucker rats. Our finding is comparable to their observation and supports the hypothesis

Table 1. Effects of Probucol treatment on PAN rats

Treatment
Body weight, g
Chow g/day
intake
Plasma concentrations, mg/dl

Proteinuria

TG
Chol PL
ApoB
mg/day
Nontreated, (n = 8) 1% Probucol, (n = 9)
188 ± 18 168 ± 30
14 ± 6 17 ± 6

165 ± 30 77 ± 30**
154 ± 13 128 ± 16 103 ± 30** 73 ± 29**
10 ± 2 6 ± 3**
343 ± 60
233 ± 122*

TG = Triglyceride; Chol = total cholesterol; PL = phospholipid; Apo B = apoprotein B. Data represent the mean ± SD. *p < 0.05, **p < 0.01.

Effect of Probucol on Proteinuria
359

200-
100 -

Fig. 1. The relationship between proteinuria and plasma lipid and apoprotein B concentrations. 0=Nephrotic rats; •=ne-phrotic rats treated with Probucol.

200
E 100
L
Q. I n n -
100 200 300 400 500

100 200 300 400 500 Proteinuria (mg/day)

$r=0.61$

“ $p < 0.01$

0

o • •,
1 I
• J

100 200 300 400 500

100 200 300 400 500 Proteinuria (mg/day)

References

- Moorhead JF, Chan MK, El-Nahas M, et al: Lipid nephrotoxicity in chronic progressive glomerular and tubulo-interstitial disease. *Lancet* 1982;ii: 1309–1311.
- Diamond JR, Karnovsky MJ: Exacerbation of chronic aminonucleoside nephrosis by dietary cholesterol supplementation. *Kidney Int* 1987;32:671–677.
- Kasiske BL, O'Donnell MP, Cleary MP, et al: Treatment of hyperlipidemia reduced glomerular injury in obese Zucker rats. *Kidney Int* 1988;33:667–672.
- Marsh JB, Sparks CE: Lipoprotein in experimental nephrosis: Plasma levels and composition. *Metabolism* 1979; 28:1040–1045.
- Furukawa S, Hirano T, Mamo JCL, et al: Catabolic defect of triglyceride is associated with abnormal VLDL in experimental nephrosis. *Metabolism*, in press.
- Barnhart JW, Sefranka JA, McIntosh DD: Hypocholesterolemic effect of 4,4'-(isopropylidenedithio)-bis-(2,6-di-*t*-butyl-phenol) (Probucol). *Am J Clin Nutr* 1970;23:1229–1233.
- Parthasarathy S, Young SG, Witztum JL, et al: Probucol inhibits oxidative modification of low density lipoprotein. *J Clin Invest* 1986;77:641–644.
- Diamond JR, Bonventre JV, Karnovsky MJ: A role for oxygen free radicals in aminonucleoside nephrosis. *Kidney Int* 1986; 29:478–483.

that secondary hyperlipidemia resulting from nephrosis may exacerbate the primary renal disorder.