The effects of gemfibrozil on hyperlipidemia in children with persistent nephrotic syndrome

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SUMMARY: Büyükçelik M, Anarat A, Karabay Bayazıt A, Noyan A, Özel A, Anarat R, Aydıngülü H, Dikmen N. The effects of gemfibrozil on hyperlipidemia in children with persistent nephrotic syndrome. Turk J Pediatr 2002; 44: 40-44.

Persistent nephrotic syndrome is frequently accompanied by severe hyperlipidemia, and this may pose a substantial risk for cardiovascular disease. Lipid-lowering drugs are prescribed by many nephrologists for adult patients but rarely for nephrotic children. The present investigation was designed to evaluate the safety and efficacy of gemfibrozil in nephrotic children. Eight girls and four boys aged from 5 to 17 years were enrolled in this study. They were all steroid and immunosuppressive resistant patients with nephrotic range proteinuria. Placebo was administered to five patients and gemfibrozil was administered to seven patients for four months. Blood samples were taken for the determination of cholesterol, triglyceride, low-density lipoprotein (LDL), high-density lipoprotein (HDL), BUN, serum creatinine (S_{cr}), ALT, AST, CPK, apolipoprotein A (apo A), apoliporotein B (apo B), and serum albumin levels during the initial and subsequent examinations. At the end of the fourth month, gemfibrozil reduced total cholesterol by 34%, LDL by 30%, apo B by 21% and triglycerides by 53% ($p < 0.05$). HDL cholesterol and apo A levels were not significantly altered. Renal function and urine protein excretion were not affected by gemfibrozil. In this study gemfibrozil therapy had no side effects and had favorable effects on the lipoprotein profile of nephrotic patients.

Key words: antilipid therapy, childhood, gemfibrozil, nephrotic syndrome.

Corticosteroids and cytotoxic drugs have dramatically improved the outlook for children with nephrotic syndrome, but resistance to treatment has raised interest in the short-and long-term effects of some important biochemical abnormalities that are secondary to primary disease. At this stage, attention is focused on hyperlipidemia, which is an important component of nephrotic syndrome[1]. This study was undertaken to investigate the safety and efficacy of gemfibrozil, one of the lipid-lowering agents, in nephrotic children resistant to therapy.

Material and Methods

Patients: This study took place in the Department of Pediatric Nephrology, Çukurova University Faculty of Medicine. Twelve patients between the ages of five and 17 (8 girls, 4 boys) were included in the study. All patients were resistant to prednisone, cyclophosphamide and dipyridamole treatment, subsequently received cyclosporine or chlorambucil, and showed proteinuria in the nephrotic limit (> 40 mg/m^2/hour). The patients were randomly divided into two groups. The average ages of Group I and II were 10.0 ± 3.9 years and 13.8 ± 2.5 years, respectively; the difference between these ages was not statistically significant. During the study period, the patients in Group I were treated with gemfibrozil which reduces the plasma cholesterol levels. The patients in Group II received a placebo instead. Group I consisted of seven children. These patients had received clinical treatment and follow-up for nephrotic syndrome for six to 36 months. One patient received levamisole as a third course of treatment. Renal biopsies were diagnosed as membranoproliferative glomerulo-nephritis in all patients. The children above seven years of age received 300 mg gemfibrozil twice daily

and younger patients received 150 mg gemfibrozil twice daily. During the study period, no special diet was followed; however, the patients were requested to stay within their regular diets. The patients in Group II (5 children) received a placebo. They were followed for nephrotic syndrome for 21 to 50 months under the regular therapy. As in the first group, all patients were resistant to prednisone, cyclophosphamide and dipyridamole treatment, and received cyclosporine or chlorambucil. Renal biopsies from four patients showed membrano-proliferative glomerulonephritis, and one showed focal segmental glomerulosclerosis. A placebo was administered at the same dose and at the same time as gemfibrozil. These patients were also requested to stay within their regular diets. The clinical characteristics of patients and controls are shown in Table I.

Prior to the start of the study, all patients and their parents were informed of the study goals, protocol and methodology, and their permissions were obtained. The duration of the study was set at four months.

Methods: During the study period, all patients were subjected to monthly examinations at the clinic for laboratory tests, and to determine adherence to the treatment course and side effects of the medication administered. Blood samples were taken for the determination of cholesterol, triglyceride, high-density liporotein (LDL), low-density lipoprotein (HDL), BUN, serum creatinine (S_{cr}) ALT, AST, CPK, apoliporotein A apolipoprotein B (apo A), (Apo B) and serum albumin levels during the initial and the subsequent examinations. A total of five sets of biochemical parameters were

Table I. Clinical Characteristics of Patient and Control Groups

Patient age (year)/sex	Antilipid treatment	C_{cr} (ml/min/1.73 m²)	Proteinuria (mg/m²/h)	Medications prior to antilipid treatment	Side effects of antilipid treatment	Other medications with antilipid treatment
10/M	gemfibrozil	55	200	prednisone, cyclophosphamide, dipyridamole, cyclosporine	None	None
9/M	gemfibrozil	60	45	prednisone, cyclophosphamide, dipyridamole, cyclosporine	None	captopril
5/F	gemfibrozil	60	61	prednisone, cyclophosphamide, dipyridamole	None	None
13/F	gemfibrozil	80	60	prednisone, cyclophosphamide, dipyridamole	None	prednisone
5/M	gemfibrozil	60	80	prednisone, cyclophosphamide, dipyridamole, cyclosporine, levamisole	None	prazosin, dipyridamole
13/F	gemfibrozil	60	47	prednisone, cyclophosphamide, dipyridamole, cyclosporine	None	dipyridamole, captopril
15/F	gemfibrozil	75	28	prednisone, cyclophosphamide, dipyridamole, chlorambucil	None	captopril
13/F	placebo	80	150	prednisone, cyclophosphamide, dipyridamole	None	captopril
13/M	placebo	61	94	prednisone, cyclophosphamide, dipyridamole, cyclosporine	None	prednisone
10/F	placebo	68	108	prednisone, cyclophosphamide, dipyridamole, chlorambucil	None	dipyridamole, cyclosporine
17/F	placebo	145	128	prednisone, cyclophosphamide, dipyridamole	None	None
14/F	placebo	70	115	prednisone, cyclophosphamide, dipyridamole, chlorambucil, cyclosporine	None	cyclosporine

C_{cr}: creatinine clearance.

obtained from each patient during the study period: at initial period and at first, second, third and fourth months. In addition, timed urine samples, taken over a 24 hr period, were analyzed for creatinine clearance (C_{cr}) and quantitative proteinuria.

Statistics: All biochemical values were determined as mean and standard deviation. The statistical evaluations were performed using Wilcoxon matched-pairs signed ranks test. Values of $p < 0.05$ were considered statistically significant.

Results

The statistical summary of the biochemical parameters obtained from blood and urine tests for each group is given in Table II. At the end of the fourth month gemifibrozil reduced total cholesterol by 34% from 378.1 ± 152.2 mg/dl to 247.0 ± 71.0 mg/dl, LDL by 30% from 266.0 ± 15.3 mg/dl to 161.7 ± 80.4 mg/dl, apo B by 21% from 266.0 ± 122.3 mg/dl to 210.0 ± 76.9 mg/dl, and triglycerides by 53% from 390.3 ± 280.5 mg/dl to 181.7 ± 68.8 mg/dl ($p < 0.05$). HDL cholesterol and apo A levels were not significantly altered. All other parameters for Group I and all parameters for Group II showed no statistically significant variations. All parameters in Group I showed statistically significant decreases during the course of treatment. The medication caused no significant side effects. There were positive correlations between cholesterol and LDL and apo B, and between LDL and apo B and HDL in Group I patients ($r = 0.9$, $r = 0.7$, $r = 0.5$, $r = 0.4$ respectively, $p < 0.001$).

Discussion

Hyperlipidemia is one of the common findings in children with nephrotic syndrome[1,2]. It may increase the cardiovascular risk and contribute to atherosclerotic complications and accelerated glomerular damage[3-6]. It has been demonstrated that reduction of hyperlipidemia by dietary or pharmacological means was protective in models of spontaneous and experimental glomerulosclerosis[7-9]. But, there is limited data in nephrotic children with lipid-lowering drugs.

Table II. Biochemical Parameters at the Beginning and End of Treatment

	Group I (n = 7)		Group (n = 5)	
	Month 0	Month 4	Month 0	Month 4
BUN (mg/dl)	19.4 ± 8.7	20.5 ± 9.2	22.2 ± 5.7	29.0 ± 15.2
S_{cr} (mg/dl)	0.9 ± 0.4	0.9 ± 0.5	0.8 ± 0.1	1.3 ± 0.5
C_{cr} (ml/min/1.73 m^2)	92.0 ± 21.9	87.7 ± 30.2	100.0 ± 22.4	80.2 ± 41.3
Total protein (g/dl)	5.0 ± 0.9	5.1 ± 1.2	5.6 ± 1.0	5.9 ± 1.2
Albumin (g/dl)	2.6 ± 0.6	2.5 ± 0.6	2.8 ± 0.5	3.0 ± 0.5
AST (U/L)	17.5 ± 14.3	18.8 ± 9.3	16.6 ± 3.9	20.8 ± 5.8
ALT (U/L)	7.5 ± 2.9	6.7 ± 3.3	8.4 ± 2.1	10.8 ± 2.1
CPK (U/L)	77.7 ± 50.2	86.7 ± 35.9	99.2 ± 61.4	93.4 ± 27.9
Apo A (mg/dl)	150.6 ± 22.3	156.5 ± 17.1	159.4 ± 36.7	147.0 ± 32.0
Apo B (mg/dl)	266.0 ± 122.3*	210.0 ± 76.9*	200.0 ± 83.0	173.6 ± 46.4
Cholesterol (mg/dl)	378.1 ± 152.2*	247.0 ± 71.0*	227.4 ± 52.1	205 ± 62.0
Triglyceride (mg/dl)	390.3 ± 280.5***	181.7 ± 68.8**	459.4 ± 281.3	413.0 ± 260.9
LDL (mg/dl)	266.0 ± 15.3*	161.7 ± 80.4*	140.4 ± 49.4	142.7 ± 34.9
HDL (mg/dl)	29.1 ± 8.3	43.1 ± 16.7	29.2 ± 11.6	31.0 ± 7.3
Proteinuria (mg/m^2/h)	156.0 ± 73.4	144.6 ± 73.0	161.4 ± 78.9	156.2 ± 56.0
U_p/U_{cr}	11.7 ± 7.9	11.4 ± 7.9	8.3 ± 4.8	7.0 ± 5.0

S_{cr} : Serum creatinine.
C_{cr} : Creatinine clearance.
Apo A: Apolipoprotein A.
Apo B: Apolipoprotein B.
LDL : Low-density lipoprotein.
HDL : High-density lipoprotein.
U_p/U_{cr}: Urinary protein/creatinine.
* $p < 0.05$.
** $p < 0.005$.
† All values are shown as mean ± one standard deviation.

Gemfibrozil is widely used in the treatment of nephrotic hyperlipidemia in adults but is sparingly used in children with persistent nephrotic syndrome[10,11].

Several clinical and experimental studies have reported that hypolipidemic drugs may cause improvement in deteriorated renal function[9,12,13]. However, some clinical studies demonstrated that the antilipidemic drugs have no effect on renal function[2,14]. In our study we could not find any significant difference between pre- and post-treatment values of BUN, S_{cr}, and C_{cr} in Group I and Group II patients. As in our study, some studies have demonstrated no regression in proteinuria with the treatment of hyperlipidemia[10,14].

Groggel et al.[10] demonstrated in adult nephrotic patients with gemfibrozil treatment that triglycerides decreased by 51%, plasma total cholesterol by 15% and LDL by 13%. HDL increased by 18%, apo A was unchanged, and apo B decreased by 26%. In our study, there were no significant differences in mean apo A levels before and after treatment in Groups I and II, but mean apo B, triglycerides and LDL values were significantly different at the beginning and end of the treatment in Group I. Mean apo B, cholesterol, triglycerides, LDL and HDL levels were not significantly different in pre- and post-treatment periods in Group II. There were no significant differences in mean HDL levels in both groups in pre- and post-treatment periods. Although mean HDL values were increased by 48% at the end of the treatment in Group I, the increase was not statistically significant. This effect is probably due to a stimulation of lipoprotein lipase, resulting in an increase in the clearance of triglyceride rich lipoproteins, as shown in previous studies[15-18]. Recently, it has also been revealed that fibrates activate peroxisome prolifetor-activated receptor alpha and there by alter the transcription of genes controlling lipoprotein metabolism[19,20]. Cholesterol level was significantly reduced by gemfibrozil in our study. Since all of the studies with this drug have been performed in adult patients, it is not appropriate to compare our results with them, because of the changes in lipid profile according to the age. Querfeld et al.[2] demonstrated that the mean concentration of triglycerides was reduced by 15%, plasma total cholesterol by 25%, LDL by 25%, LDL by 27% and HDL by 24%, as well as apo A by 19% and apo B by 21% with probucol, another hypolipidemic drug, in persistent childhood nephrotic syndrome.

Recent studies with lipid-lowering drugs have been successful without major side effects[5,11]. Groggel et al.[10] showed that gemfibrozil treatment caused no myalgia or muscle weakness. A temporary increase in mean CPK levels were found in only one patient, and this increase had improved with the continuation of the therapy; however, the changes in LDH, AST and ALT levels were not reported. We did not observe any side effects in our patients. There was no difference in CPK, AST and ALT levels before and after the treatment in either group.

In conclusion, this study shows that gemfibrozil therapy in children with corticosteroid and/or immunosupressive resistant nephrotic syndrome decreases the levels of cholesterol, triglycerides, LDL and apo B without significantly impacting renal functions and proteinuria. Since no changes were observed in the glomerular pathology that causes proteinuria, the improvement in hyperlipidemia can be attributed to the impact of gemfibrozil on the lipoprotein lipase enzyme. We still need a large multicenter and long-term trial to assess benefits and side effects of this type of therapy in children.

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