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Combined treatment of hypercholesterolemia of renal transplant allograft recipients with fluvastatin and gemfibrozil

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Abstract The aim of this study was to investigate the safety and efficacy of combined treatment with fluvastatin (F) and gemfibrozil (G) in hypercholesterolemic renal transplant recipients (RTR). Ten hypercholesterolemic (total cholesterol [TC] > 220 mg/dl) RTR (7 men) with mean age 44 years (range 25–56 years) who remained hypercholesterolemic after 3 months of treatment (period A) with fluvastatin (40 mg/d) continued taking the same dose of F plus G (600 mg/dl) for another 3-month period (B). Serum total cholesterol, high density lipoprotein cholesterol (HDL-C), LDL cholesterol (LDL-C), triglyceride, serum creatinine (creatinine phosphokinase (CPK), serum glutamic-oxaloacetic transaminase (SGOT), and serum glutamate pyruvate transaminase (SGPT) were measured before treatment and at the end of periods A and B. Mean TC levels were 360.30 ± 62.42 mg/dl, 324.10 ± 100.53 mg/dl, 270.80 ± 67.77 mg/dl; mean LDL-C levels were 259.33 ± 71.43 mg/dl, 219.60 ± 81.31 mg/dl, 189.70 ± 65.51 mg/dl; mean HDL-C levels were 37.10 ± 11.68 mg/dl, 39.80 ± 13.21 mg/dl, 41.00 ± 12.94 mg/dl; mean triglyceride levels were 354.60 ± 183.29 mg/dl, 349.30 ± 242.94 mg/dl, 207.00 ± 85.35 mg/dl before treatment and at the end of periods A and B, respectively. There was a statistically significant fall of serum TC ($P = 0.002$), LDL-C ($P = 0.016$), and triglyceride ($P = 0.029$) levels at the end of periods A and B. Kidney and liver function did not change. F and G combined treatment is safe and useful in patients who do not respond satisfactorily to monotherapy with F. Gemfibrozil augments the effect of F on TC, LDL-C, and triglyceride levels.

Key words Renal transplantation · Fluvastatin · Gemfibrozil · Hyperlipidemia

Introduction

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-Co-A) reductase have gained a fundamental role in the treatment of hypercholesterolemia of renal transplant recipients (RTR) [1, 2]. Although these drugs have been found to be relatively safe so far, rare adverse effects on skeletal muscle have been described in patients receiving cyclosporine [3, 4]. Fluvastatin, a new, completely synthetic HMG-CoA reductase inhibitor, has been used successfully to treat hypercholerolemia of RTR [5, 6]. Also, fibrate derivatives have been shown to reduce serum lipid levels effectively in a large number of patients [7, 8]. Particular attention has been focused on myopathy associated with HMG-CoA reductase inhibitors in combination with gemfibrozil [2, 9]. Gemfibrozil is a fibrate derivative that has been shown to reduce serum lipid levels effectively in RTR [10]. The combination of fluvastatin with gemfibrozil has been shown to be safe and effective in the general popu-

Table 1 Effect of fluvastatin alone or in combination with gemfibrozil on the lipid profile of hyperlipidemic renal transplant recipients (*HDL* high density lipoprotein, *LDL* low density lipoprotein)

	Before treatment (mg/dl)	After fluvastatin (mg/dl)	After fluvastatin + gemfibrozil (mg/dl)
Total cholesterol	360.30 ± 62.42	324.10 ± 100.53	270.80 ± 67.77*
HDL-cholesterol	37.10 ± 11.68	39.80 ± 13.21	41.00 ± 2.94
LDL-cholesterol	259.33 ± 71.43	219.60 ± 81.31	189.70 ± 65.51**
Triglycerides	354.60 ± 183.29	349.30 ± 242.94	207.00 ± 85.35***

Analysis of variance, ANOVA, for repeated measures: * $P = 0.002$, ** $P = 0.016$, *** $P = 0.029$

lation [11]. From one point of view, the combination of gemfibrozil with fluvastatin should be an asset in the treatment of hyperlipidemia resistant to monotherapy with fluvastatin of RTR taking cyclosporine. This view is supported by this report.

Patients and methods

During 1997–1998, 28 RTR were put on fluvastatin treatment (40 mg/day) because of hyperlipidemia (serum total cholesterol TC > 220 mg/dl) that did not respond to a 3-month low lipid diet and weight loss. Thirteen of them who completed the 3 months of therapy (period A) and did not respond to it were put on combined treatment with fluvastatin (40 mg/day) plus gemfibrozil (600 mg/day) for another 3-month period (period B). Three of them were excluded from the study [one because he stopped treatment, another because of raised serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT) levels as a result of alcohol consumption, and the third because she was hospitalized with congestive heart failure and fever].

These patients 7 men, 3 women) with a mean age of 44.24 ± 13.32 years (range 25–56 years) attended a regular follow-up at monthly intervals at the outpatient department of our clinic. Their primary renal disease was chronic glomerulonephritis (GN) in 2, chronic pyelonephritis in 2, polycyctic kidney disease in 1, FSGN in 1, membranous GN in 1, and unknown etiology in 3. They had been on triple or quadruple sequential drug immunosuppression (methylprednisolone 0.10–0.08 mg/kg bw, CsA 2–4 mg/kg bw, and azathioprine 0.5–1.5 mg/kg bw or mycophenolate mofetil 5–15 mg/kg bw, and five of them had received antihypnocyte (ALG) induction therapy). They were transplanted 4.85 ± 2.34 years before commencement of hypolipidemic therapy, and their baseline serum creatinine was 1.35 ± 0.48 mg/dl and their body weight was 71.50 ± 11.45 kg. Four of them had proteinuria ranging from 0.20 to 0.8 g/24 h. There was no liver disease, myopathy, thyroid disease, or pregnancy. During the study the patients were following the steady diet already described [1].

Total cholesterol, triglycerides, high density lipoprotein (HDL)-cholesterol, serum creatinine, SGOT, SGPT, creatinine phosphokinase (CPK), uric acid, total serum protein, serum albumin and 24-h urine protein were measured before the treatment and at the end of periods A and B. LDL – cholesterol was measured indirectly by the Friedwald equation (LDL – cholesterol = total cholesterol – HDL-cholesterol – 1/5 triglycerides). The laboratory methods used for the above measurements have already been described [1].

Analysis of variance (ANOVA) for repeated measures was used for statistical analysis (statistical package SPSS, version 7.5 for WINDOWS). The differences were considered to be statistically significant when $P < 0.05$.

Results

Lipids. Lipid levels at baseline, after 3 months of treatment with fluvastatin (period A) and after 3 months of treatment with a combination of fluvastatin and gemfibrozil (period B) are given in Table 1. After 3 months of therapy with fluvastatin, there was a fall of total cholesterol, LDL-cholesterol, and triglycerides by 10.05%, 15.33%, and 1.5%, respectively, and an elevation of HDL-cholesterol by 7.27%. The combined treatment with gemfibrozil with fluvastatin for 3 months caused a fall of total cholesterol, LDL-cholesterol, and triglycerides from baseline levels by 24.85%, 26.85%, and 41.63%, respectively, and an elevation of HDL-cholesterol by 10.51% (Table 2). ANOVA for repeated measures over time showed that there was a statistically significant fall of total cholesterol ($P = 0.002$), LDL-cholesterol ($P = 0.016$), and triglycerides ($P = 0.029$). The rise o HDL-cholesterol was not significant.

Serum creatinine. Serum creatinine, uric acid, total serum protein, and albumin levels at baseline and at the end of periods A and B are given in Table 3. The measurement of serum creatinine showed that renal function remained stable during periods A and B. Also, no significant change in uric acid, total serum protein, serum albumin and 24-h urine protein was noticed.

Creatine phosphokinase. No significant change of creatine phosphokinase, SGOT, and SGPT levels at baseline and the end of periods A and B was noticed (Table 4).

Table 2 Change of lipids (%) of renal allograft recipients after treatment with fluvastatin alone or in combination with gemfibrozil

	After fluvastatin treatment	After fluvastatin + gemfibrozil treatment
Total cholesterol	– 10.05%	– 24.85%
HDL-cholesterol	+ 7.27%	+ 10.51%
LDL-cholesterol	– 15.33%	– 26.85%
Triglycerides	– 1.5%	– 41.63%

Table 3 Laboratory values in renal allograft recipients after treatment with fluvastatin alone or in combination with gemfibrozil

	Before treatment	After fluvastatin	After fluvastatin + gemfibrozil
Serum creatinine (mg/dl)	1.35 ± 0.48	1.36 ± 0.47	1.42 ± 0.43
Uric acid (mg/dl)	7.32 ± 0.94	7.66 ± 1.38	7.38 ± 0.84
Total protein (g/l)	7.09 ±0.61	7.12 ± 0.94	7.14 ± 0.89
Serum albumin (g/l)	4.35 ± 0.71	4.41 ± 0.93	4.44 ± 0.76
Proteinuria g/24-h	0.4 ± 0.27	0.37 ± 0.12	0.40 ± 0.21

ANOVA for repeated measures, P = NS

Table 4 Biochemical values in renal allograft recipients after treatment with fluvastatin alone or in combination with gemfibrozil (*CPK* creative phosphokinase, *SGOT* serum glutamic-oxaloacetic transaminase, *SGPT* serum glutamate pyruvate transaminase)

	Before treatment	After fluvastatin	After fluvastatin + gemfibrozil
CPK (ul/l)	47.8 ± 11.80	51.10 ± 11.84	50.00 ± 12.11
SGOT (u/l)	18.10 ± 3.98	17.00 ± 3.85	18.90 ± 3.47
SGPT (u/l)	19.30 ± 4.57	20.80 ± 7.22	19.80 ± 7.85

ANOVA for repeated measures, P = NS

Discussion

It is already known that cyclosporine has no significant effect on the pharmacokinetics of fluvastatin [12, 13] and that the pharmacokinetics of fluvastatin and gemfibrozil do not change when given concomitantly to members of the general population with dyslipidemia [14]. Despite the fact that fluvastatin [6] and gemfibrozil [10] do not affect cyclosporine levels, we used the lowest possible dose of fluvastatin (40 mg/d) and gemfibrozil (600 mg/d) because the pharmacokinetics of these three drugs are not known when given concomitantly in RTR.

The combination of fluvastatin and gemfibrozil produced a significant reduction of total cholesterol, LDL-cholesterol, and triglycerides (Table 1) and was more efficacious than fluvastatin alone. The major action of gemfibrozil when it was added to fluvastatin treatment was a lowering effect on the triglycerides level (Table 2). The fall of the triglycerides level with fluvastatin therapy was small, and this is in agreement with our previous experience with lovastatin [1].

The administration of fluvastatin for 3 months and the combined treatment of fluvastatin plus gemfibrozil for another 3 months were not associated with signs of muscle damage. Parameters of muscle damage are considered to be a rise of serum CPK, leg pain, and myalgias. CPK levels at the end of treatment with fluvastatin alone or combined with gemfibrozil did not show any significant change from the pretreatment levels (Table 4). No leg pain or myalgias were noticed.

Liver function as checked by serial measurements of SGOT and SGPT levels during the period of the study did not change (Table 4). Total protein, serum albumin, and 24-h protein output remained stable during periods A and B.

Serum creatinine levels did not show a significant elevation at the end of treatment with fluvastatin alone or combined with gemfibrozil when compared with those before treatment (Table 3).

In conclusion, combined treatment with fluvastatin and gemfibrozil of RTR who take cyclosporine and do not respond satisfactorily to fluvastatin monotherapy is effective and safe. The knowledge of the pharmacokinetics of fluvastatin and gemfibrozil given at the same time in patients taking cyclosporine may allow the use of higher doses of these drugs in the future.

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