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Research Article

The Efficacy and Side Effects of Gemfibrozil (Lopid) in Pediatric Patients with Primary Hypertriglyceridemia

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Abstract

Cardiovascular disease is a major cause of morbidity and mortality among industrialized countries. Dyslipidemia (especially elevated low density lipid (LDL), cholesterol, triglyceride (TG), and high density lipid (HDL) has been identified as an independent risk factor in the development of CVD [1]. Dyslipidemia is an increasingly prevent risk factor in children, concomitant with worldwide epidemic of obesity [2]. Early detection of affected children and appropriate intervention in terms of dietary manipulation, changes in sedentary lifestyle [5] and even drug therapy can halt or decrease the development of coronary heart disease and pancreatitis [3,4].

The cohort in this study acquired in a retrospective fashion from all patients seen in the endocrinology clinic over a period of 10 years that were placed on gemfibrozil as treatment for primary hypertriglyceridemia.

The most important finding of this study was that gemfibrozil reduced mean triglycerides 53.7% and increased HDL 31.8% in a pediatric population with primary hypertriglyceridemia. Gemfibrozil treatment was accompanied by a low level of adverse effects. However, the long-term benefit of lowering elevated triglycerides in children and adolescents remains unknown, except for prevention of pancreatitis.

The major implication of this study is that gemfibrozil significantly lowers triglycerides and raises HDL with reasonable safety in a pediatric population. However, this study did not establish criteria for initiating gemfibrozil therapy in a pediatric population.

Keywords: *Low Density Lipid (LDL); Cholesterol; Triglyceride (TG); High Density Lipid (HDL)*

Introduction

Cardiovascular disease is a major cause of morbidity and mortality among industrialized countries. Dyslipidemia (especially elevated low density lipid (LDL), cholesterol, triglyceride (TG), and low high density lipid (HDL) has been identified as an independent risk factor in the development of CVD [1]. Dyslipidemia is an increasingly prevent risk factor in children, concomitant with worldwide epidemic of obesity [2]. The recent surge of interest in the study of lipid and metabolism in children has stemmed from unequivocal evidence linking hyperlipidemia with premature heart disease and pancreatitis [3,4].

Early detection of affected children and appropriate intervention in terms of dietary manipulation, changes in sedentary lifestyle [5] and even drug therapy can halt or decrease the development of coronary heart disease and pancreatitis [3,4].

Background

The major circulating lipids are cholesterol, Triglycerides (TG) and phospholipids in which they are transported by lipoproteins (chylomicrons, VLDL, LDL, HDL) from one part of the body to another. Lipid disorders can occur as either primary or secondary to some underlying diseases. The primary dyslipidemias are associated with over production and/or impaired removal of lipoproteins which can be induced by an abnormality in ether the lipoprotein itself or the lipoprotein receptor [6,7]. Dyslipidemia is defined as total cholesterol, LDL-Cholesterol, TG, Apo-B, LP(a) levels above the 95th centile or HDL-cholesterol or Apo-A levels below the 10th centile for general population.

Hypertriglyceridemia is defined as plasma TG level above the 95th percentile for age and sex [8]. Primary hypertriglyceridemia is the result of various genetic defects leading to disordered triglyceride metabolism [9,10]. Secondary causes are acquired and may include high–fat diet, obesity, diabetes, pregnancy, uremia or dialysis, hypothyroidism, nephrotic syndrome, acromegaly, Cushing's syndrome, systemic lupus erythematosus, dysgammaglobulinemias, glycogen storage disease type I, lipodystrophy and drugs like estrogen, glucocorticoids, thiazide etc.

Familial chylomicronemia syndrome (FCS) is a disorder of lipoprotein metabolism due to familial lipoprotein lipase (LPL) or Apo protein C-II deficiencies (Apo-C-II) or the presence of inhibitors to LPL [6]. It is a very rare syndrome with prevalence of approximately 1 in 1 million for homozygous. It is relatively common for heterozygous approximately 1 in 500 [6]. The disease has been described in all races. To date, several hundred patients with LPL deficiency have been described [9-11]. FCS is the most dramatic example of severe hypertriglyceridemia. Almost all patients with fasting triglyceride level in excess of 1000 mg/dl (11.3 mmol.l) have FCS [8]. It manifests as eruptive xanthomas, acute pancreatitis, hepatomegaly, splenomegaly, foam cell infiltration of the bone marrow and lipemia retinalis. These patients usually have lipemic plasma due to marked elevation of TG and chylomicron levels [12-14].

Several mutations in the LPL gene located on chromosome 8p22 have been identified with LPL deficiency [15,16]. More than 50 missense and nonsense mutations have been identified. The majority of mutations are located on exons 3, 5 and 6 which are responsible for the catalytic coding region of the gene [10]. Apo C-II gene mutation has also been identified [17]. Other extremely rare genetic disorders can present with chylomicronemia and severe hypertriglyceridemia. Examples of these are: familial Apo AV deficiency, familial lipase maturation factor 1 (LMF 1) deficiency, and familial GPIHDLBP 1 deficiency.

The mainstay of treatment of infants and children with hypertriglyceridemia is dietary modification, control of other predisposing factors (obesity, DM), sedentary lifestyle and physical activity [6,8]. The basic principal of dietary modification is to provide enough calories for optimal growth with reduction of total saturated fat. During infancy period, breast milk should be stopped and modified fat formula like portagen milk is given. Medical treatment Gemfibrozil (Lopid) can be started if the dietary modifications failed [16,18]. Other drugs like nicotinic acid is the second choice which necessitates aspirin if skin rash appears.

Methods

The cohort in this study acquired in a retrospective fashion from all patients seen in the endocrinology clinic over a period of 10 years that were placed on gemfibrozil as treatment for primary hypertriglyceridemia.

Inclusion in the study required

1. Referral to the clinic between August 2002 and August 2012;
2. Age of younger than 14 years at the start of treatment;
3. Fasting triglyceride of at least 10 mmol/l; and
4. Treatment with gemfibrozil.

All consecutive patients meeting these criteria were included. Exclusion criteria:

1. Patients underwent plasma exchange.
2. Patients with combined hyperlipidemia.

The dose of gemfibrozil was 300 mg twice daily except in two young children who were prescribed 150 mg twice daily. All treated patients and parents were also advised of low fat diet and encourage exercise at each visit. Although this was a retrospective study, criteria for starting gemfibrozil remained consistent for the study duration. Data collected during pretreatment and on- treatment included age in years, height (cm), and weight (kg).

Total cholesterol, HDL, LDL, and triglycerides were recorded in all patients. LDL was computed from the Friedewald equation if the triglyceride level was < (4.5 mmol/l) = 400 mg/dL. Alanine aminotransferase and aspartate aminotransferase were reported only in patients with pretreatment and on-treatment values. Duration of treatment was recorded as elapsed time between the start of gemfibrozil pretreatment to the last clinic visit date. Other medications taken in addition to gemfibrozil were recorded.

Statistical analysis

Analysis was performed the IBM SPSS statistics version 20 (Chicago Illinois, USA), qualitative data was expressed as percentages, and continuous variables were expressed as the mean ± standard deviation or standard mean of error. Comparison of changes in lipid panels and other biomarkers such as Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatinine kinase (CK), was performed using Paired T-test.

Results

Under the inclusion criteria, the study population consisted of 47 patients started on gemfibrozil. Thirty-six patients had two sets of lipid data, pretreatment and post-treatment results with gemfibrozil will be included in the analysis.

Seven patients were excluded from the analysis because of lack of treatment data; two patients underwent plasma phoresis for an extremely high risk level of triglyceride but served to assess adverse effects of the medication and two patients lost follow up. Within the excluded patients, 6 did not report any adverse effects i.e. elevated liver enzymes or myopathy.

Possible adverse reactions were recorded in 6 patients. Five patients from the inclusive group had pain in the midback region. One patient from the excluded patients complained of muscle pain that disappeared after discontinuation of the medication. The latter patient was considered to have had true adverse effect from the gemfibrozil -CK > 1213 u/L.

Of the 36 patients included in the analysis, 50% (n = 18) were male, and 50% (n = 18) were females, 30.6% (n = 11) were age of 5 years or less, 27.8% (n = 10) were 6 to 10 years old, 22.2% (n = 8) were 11 to 15 years old, and remaining 19.4% (n = 7) were age of 16 years or more.

The Mean age of study population was 9.6 ± 5.8 years, and the mean duration on medication was 6.4 ± 4.41 years (Table 1).

Male	50%
Female	50%
Age (year)	9.6 ± 5.8
Treatment Duration (year)	6.4 ± 4.41
Lipid Panel	
Triglycerides (mmol/l ± SEM)	33.97±2.089
Total Cholesterol (mmol/l ± SEM)	7.55 ± 1.35
HDL (ul/l ± SEM)	0.67 ± 0.39
LDL-c (ul/l ± SEM)	0.78 ± 0.95
ALT (ul/l ± SEM)	23.45 ± 1.82
AST (ul/l ± SEM)	38.75 ± 1.93
CK (ul/l ± SEM)	108.45 ± 10.9

Table 1: *Baseline population characteristics (N = 36).*

The mean triglyceride levels decreased significantly by -18.33mmol/l with relative rate reduction of

53.7%, (P < 0.001).

Mean HDL increased significantly by 0.21 ul/l with increase relative rate of 33.1%, *P* < 0.001.

Total cholesterol levels decreased by 34.2% from 7.6 mmol/l (SEM 1.34) to 5 mmol/l (SEM 0.25) (*P*

= 0.0645).

Mean LDL decreased insignificantly from 0.86 mmol/l (SEM 0.21) to 0.73 mmol/l (SEM 0.13). (*P* =

0.39) (Figure 1).

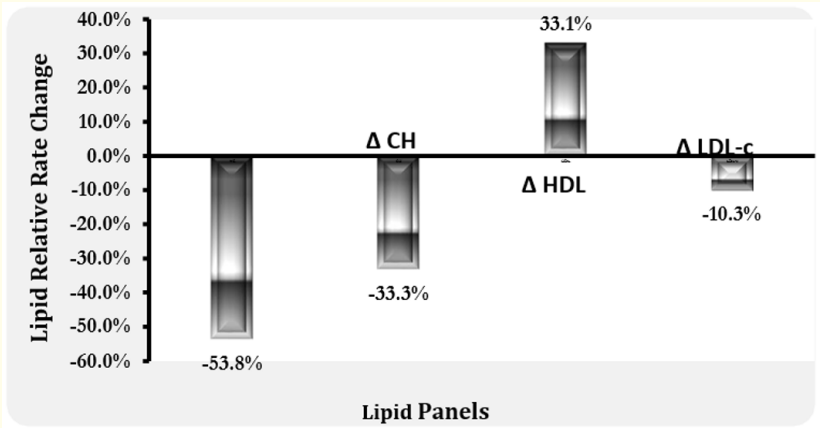

Figure 1

Additionally, for those patients who had pretreatment and on-treatment liver function tests (i.e. 36 patients), mean alanine aminotransferase, and aspartate aminotransferase liver enzymes increased from 23.46 to 25.6 mmol/l and 38.7 to 47.19 mmol/l, respectively ($P = 0.36$, $P = 0.017$).

CK increased insignificantly from 108.5 to 129.5 ($P = 0.068$) (Table 2).

	Baseline	Post Treatment	Mean Diff	95%CI	P value
Triglycerides	33.97	15.63	-18.33 ± 2.1 (mmol/l)	-14.0, -22.6	< 0.001*
Total Cholesterol	7.55	5.03	-2.51 ± 1.3 (mmol/l)	0.16, -5.1	0.064
HDL	0.66	0.87	+0.21 ± 0.05 (ul/l)	0.33, 0.10	< 0.001*
LDL	0.87	0.74	-0.13 ± 0.14 (ul/l)	0.18, -0.43	0.39
ALT	23.46	25.6	+2.15 ± 2.3 (ul/l)	6.9, -2.6	0.36
AST	38.75	47.19	+8.4 ± 3.4 (ul/l)	15.35, 1.53	< 0.017*
CK	108.45	129.54	+21.08 ± 11.0 (ul/l)	43.85, -1.68	0.068

Table 2: *Baseline and post-treatment data comparison.*

Discussion

The most important finding of this study was that gemfibrozil reduced mean triglycerides 53.7% and increased HDL 31.8% in a pediatric population with primary hypertriglyceridemia. Gemfibrozil treatment was accompanied by a low level of adverse effects. This study comprises the largest gemfibrozil intervention in a pediatric population.

However, the long-term benefit of lowering elevated triglycerides in children and adolescents remains unknown, except for prevention of pancreatitis. Values of fasting triglyceride levels < 10 mmol/l are considered sufficiently high to place patients at risk and should be treated to prevent pancreatitis, because with illness or dietary indiscretion, valus can rise to much higher levels.

Patient safety is of considerable importance when using any pharmaceutical product. In this study, we could only judge short-term adverse effects. Use of gemfibrozil resulted in muscle pain reported by one patient from the excluded patients. The medication was stopped for a while then resumed again without recurrence of muscle pain.

The other commonly known adverse effect associated with the drug is abdominal discomfort or pain, but none of our pediatric patients reported these symptoms.

Forty of forty-seven patients were known not have adverse events, but we had no information for two patients who could not be contacted. Long-term safety of gemfibrozil was not established by this study. This issue is important because medication started in childhood might be required for decades.

Limitations of this study include

1. limited treatment population size;
2. Seven patients failed to have pre-treatment laboratory values;
3. Two patients lost follow up;
4. It remains unclear whether the criteria utilized to start treatment with gemfibrozil were optimal. Future investigations are necessary to determine whether a triglyceride > 10 mmol/l should be changed to a different value in a pediatric population; and lastly,
5. Although the criteria for starting and following patients on gemfibrozil remained constant throughout the period of analysis, this was a retrospective study.

Conclusion

The major implication of this study is that gemfibrozil significantly lowers triglycerides and raises HDL with reasonable safety in a pediatric population.

However, this study did not establish criteria for initiating gemfibrozil therapy in a pediatric population.

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