Lipoprotein profile in long term theophylline administration in children with asthma

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SUMMARY

Atherosclerosis in childhood has a slowly progressive course and its clinical features usually become prominent in middle ages. Hypercholesterolemia is one of the major risk factors for the development of atherosclerosis. A clear correlation exists between hypercholesterolemia in childhood and atherosclerotic lesions extending into adulthood.

In this study, we evaluated the effect of slow release theophylline (SRT) treatment on plasma lipid profile and assessed the risk for atherosclerotic coronary heart disease in children with bronchial asthma. Group 1 consisted of 15 children with a mean age of 10.8 ± 3.19 years who received SRT for bronchial asthma for a mean period of 9.13 ± 2.17 months. Group 2 was composed of 15 children with a mean age of 11.40 ± 3.78 years and followed up for bronchial asthma, who received no SRT treatment. Group 3 comprised 15 children with a mean age of 9.00 ± 3.76 years and no history of asthma or wheezing. In all patients lipid profiles were assessed by measuring levels of plasma triglyceride, total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) apolipoprotein A (Apo-A) and apolipoprotein B (Apo-B). In group 1, the mean total cholesterol level was 175.53 ± 24.36 mg/dl, LDL-C level was 91.00 ± 24.07 mg/dl and Apo-B level was 87.27 ± 12.74 mg/dl after SRT treatment. In group 1, group 2 (control group with asthma) and group 3 (the non-asthmatic control group), the mean plasma lipid level after SRT treatment was significantly higher than that before SRT treatment. In conclusion, long-term SRT treatment in children with bronchial asthma may alter lipid profile and may increase the risk for developing atherosclerotic coronary heart disease.

Key words: Lipoprotein profile. Slow release theophylline.

Allergol et Immunopathol 2002;30(2):79-84.

INTRODUCTION

The coronary artery disease (CAD) is one of the major causes of death in USA and other industrialized countries (1). Autopsy studies demonstrated that the pathologic process responsible for coronary heart disease originated in childhood. Strong Mc Gill et al studied 4,737 cadavers of both sexes, and showed that atherosclerotic plaques were found in the coronary arteries of children who died about the age of 10 years (2, 3). The development of CAD is associated with a variety of risk factors, which include elevated plasma cholesterol levels, hypertension, cigarette smoking, diabetes, and a positive family history of CAD (1).

It has been suggested that hypercholesterolemia is a significant factor in the development of atherosclerosis, and that there is a correlation between the hypercholesterolemia in childhood (total cholesterol, high LDL-C level, low HDL-C level) and the stage and extent of atherosclerotic lesions (4-6). The knowledge of the association between altered plasma lipid profile and the future development of atherosclerosis among the pediatric population led the National Cholesterol Education Program and American

Pediatric Academy to improve cholesterol screening programs to determine individuals in early terms, who were predisposed to atherosclerosis, and to recommend a reduction in the amount of cholesterol and saturated fat in the diet of whole population (7, 8).

Theophylline was used as a xanthine derivated diuretic drug at first and after its bronchodilator effect was understood, it has been used in the treatment of bronchial asthma and chronic obstructive lung disease for about fifty years. The development of methods giving more sensitive blood levels in regulating the optimal dose and the production of slow releasing theophylline capsules led to the enhancement of the importance of this drug in the treatment of asthma (9). Other natural sources of xanthines such as coffee, cacao and tea, which contain cafeine, seem to increase serum cholesterol and LDL-C levels and therefore increase the risk of coronary artery disease. In addition, theophylline, used extensively in treatment of asthmatic children, could lead to similar variations.

In this study, plasma lipid profile of the asthmatic children treated with SRT for a long time was evaluated and the result were compared with the plasma lipid profiles of two control groups, including asthmatic children not treated with SRT and non-asthmatic children.

MATERIALS AND METHODS

Children followed for bronchial asthma in Pediatric Allergy Department of Dokuz Eylül Universty School of Medicine were enrolled in the study. The patients with asthma in Group 2 received no SRT treatment for at least three months. All children in both groups were taking salbutamol preparations orally or by inhalation for the control of acute asthmatic symptoms and some of the patients received cromolyn sodium for profilactic purpose.Children who were treated with systemic or inhaled corticosteroid therapy were excluded from the study.

Children hospitalized in the pediatric surgery ward for elective herniotomy, and circumsicion without a history of asthma or wheezing were included in the study to serve as nonasthmatic control subjects (Group 3). Detailed knowledge about the study was given to the parents of the children. After, a complete medical history was elicited from the parents. Children with acute illnesses or chronic diseases other than asthma, or with a family history of diabetes mellitus, cardiovascular or renal diseases, or known hyperlipidemia (defined as levels over 200 mg/dl) among parents or siblings were excluded.

The mean duration of SRT therapy was 9.13 ± 2.17 (7-12) months. After 12 hours of overnight fasting, plasma lipid profile was determined from venous blood samples of children included in the study. In the first group plasma lipid levels were measured for two times as before and after SRT treatment. In the second and third group, plasma lipid levels were measured once.

In addition, blood samples were obtained (once a month) after two hours of the last theophylline dose in children treated with SRT to determine blood theophylline levels. Theophylline measured by using an enzyme-multiplied immunoassay technique (EMIT) supplied by Behring-Syva (COBAS MIRAS, UK). The sensitivity of the Emit 2000 theophylline specific assay was 0.75 μg/mlt. Therapeutic range of theophylline is 10-20 μg/mlt.

In all patients blood glucose levels and andropometric measurements were detected in our study.

Apolipoprotein A and Apolipoprotein B levels were measured by Nephelometric Beckman Array protein system (Normal ranges: Apo A for male, 94-178 mg/dlt, Apo A for female, 101-199 mg/dlt, Apo B for male 52-109 mg/dlt, Apo B for female 49-103 mg/dlt). Plasma triglyceride, total cholesterol, HDL-C and LDL-C levels were determined with Randox kit by Boehringer-Mannheim Mitachi 742-200 autoanalyser (Normal ranges: Plasma triglyceride 30-190 mg/dlt, total cholesterol 140-200 mg/dlt, HDL-C 35-60 mg/dlt and LDL-C 100-130 mg/dlt).

As Statistical Methods, Kruskal Wallis Variance analysis was used to calculate the statistical significance of differences among the lipid profiles, demographic and anthropometric variables of the three groups. To determine gender difference between the groups Chi-square test was used.

RESULTS

Each groups comprised of fifteen children making a total of 45 children enrolled in the study. The characteristics of the three groups are shown in table I.

There were no significant difference in age, gender, weight, height, skin-fold thickness, and arm circumference of the three groups ($p > 0.05$).

The mean serum theophylline concentration of children in group 1 was 12.5 ± 2.57 μg/ml. There was no correlation between the duration of SRT therapy, theophylline levels and the lipoprotein levels. The mean serum glucose levels were 73.55 ± 18.91 mg/dl in Group 1, 75.87 ± 7.76 mg/dl in Group 2, and

Table I

Some characteristic of children with asthma treated with SRT or not treated with SRT and children without asthma

Demographic and anthropometric findings	Population			
	Group 1 (n = 15)	Group 2 (n = 15)	Group 3 (n = 15)	p*
Age (year)	10.8 ± 3.19	11.40 ± 3.78	9.00 ± 3.76	NS
Gender (M/F)	7/8	10/5	10/5	NS
Height (cm)	142.33 ± 15.76	143.33 ± 18.94	140.00 ± 18.01	NS
Weight (kg)	37.9 ± 13.24	37.77 ± 12.42	34.20 ± 12.83	NS
Triceps skin-fold (cm)	10.67 ± 3.30	10.19 ± 3.95	11.55 ± 5.85	NS
Arm circumference (cm)	21.43 ± 3.15	18.81 ± 4.04	18.93 ± 5.04	NS

Values (except ratios and p values) are expressed as mean ± SD.
NS: Not significant.
*Significance of differences among groups.

78.00 ± 6.76 mg/dl in Group 3, and no significant difference was found between these levels ($p > 0.05$).

The plasma lipid profiles of children in group 1 before and after SRT treatment was shown in table II. The mean triglyceride, total cholesterol, LDL-C and Apo B levels after SRT treatment were measured higher than the levels before treatment in group 1, which was statisticaly significant. The ratio of Apo A to Apo B levels after treatment with SRT was lower than the ratio before treatment and this was also statistically significant.

No statistically significant difference was observed between the level of plasma lipids before SRT treatment in group 1 and the other groups (table III).

When plasma lipid levels after SRT treatment in group 1 was compared with other groups total cholesterol, LDL-C and Apo B levels were higher in group 1 which was statisticaly significant (table IV).

Table II

Mean plasma lipid profiles of children in group 1 (before and after SRT treatment)

Lipid profile	Population		
	Before	After	p*
Trigliserid (mg/dl)	80.13 ± 38.58	91.67 ± 41.22	< 0.05
Total Cholesterol	134.0 ± 18.31	175.53 ± 24.36	< 0.05
HDL-C	58.40 ± 33.09	58.33 ± 9.39	> 0.05
LDL-C	70.73 ± 18.96	91.00 ± 24.07	< 0.05
Apolipoprotein A	145.53 ± 24.48	146.27 ± 23.56	> 0.05
Apolipoprotein B	72.81 ± 15.05	87.27 ± 12 74	< 0.05
LDL-C/HDL-C	2.12 ± 0.63	2.67 ± 0.63	> 0.05
Apo A/Apo B	2.09 ± 0.60	1.71 ± 0.39	< 0.05
Total Cholesterol/HDL-C	2.78 ± 0.83	2.87 ± 0.73	> 0.05

Values (except p values) are expressed as mean ± SD.
*Significance of differences among groups, by analysis of variance.

DISCUSSION

Our results showed that children receiving SRT therapy have higher total serum cholesterol levels than the recommended values of the National Cholesterol Education Program and American Academy of Pediatric (7, 8). The Bogalusa Heart Study group determined a positive correlation between the serum total cholesterol level and the degree of involvement of the aortic wall with fatty streaks. The group with cholesterol levels between 140 and 170 mg/dl had approximately 25 % involvement, whereas the group with levels greater than 200 mg/dl had approximately 50 % involvement (10). We found the plasma total cholesterol level as 175.53 ± 24.36 mg/dl in children receiving long term SRT treatment. This level was significantly higher than in the other two groups.

Theophylline is used extensively in children with bronchial asthma. It has been realized that other antiasthmatic drugs administered in conjunction with SRT treatment affect the lipid profile (11). Because of the metabolic effects on lipid profile of corticosteroids, children receiving systemic or inhaled corticosteroid therapy were not included in the study. Beta 2 agonist drugs were used by some patients in Group 1 and 2 for control of acute asthmatic attacks and some patients used prophylactic cromolyn treatment. However, no differences have been reported in the lipid profile by these drugs (11).

The alteration in plasma lipid composition in patients receiving long-term SRT treatment could be re-

Table III

Mean plasma lipid profiles of children in groups 1 (before SRT teratment), 2 and 3

Lipid profile	Population			
	Group 1	Group 2	Group 3	p*
Trigliserid (mg/dl)	80.13 ± 38.58	65.47 ± 28.33	66.13 ± 22.67	> 0.05
Total Cholesterol	134.0 ± 18.31	137.13 ± 26.15	126.73 ± 23.89	> 0.05
HDL-C	58.40 ± 33.09	52.86 ± 14.04	46.73 ± 15.49	> 0.05
LDL-C	70.73 ± 18.96	69.43 ± 22.92	66.40 ± 22.55	> 0.05
Apolipoprotein A	145.53 ± 24.48	143.60 ± 23.89	127 ± 33.77	> 0.05
Apolipoprotein B	72.81 ± 15.05	71.58 ± 16.59	71.29 ± 13.28	> 0.05
LDL-C/HDL-C	2.12 ± 0.63	1.39 ± 0.67	1.59 ± 0.78	> 0.05
Apo A/Apo B	2.09 ± 0.60	1.84 ± 0.62	1.84 ± 0.62	> 0.05
Total Cholesterol/HDL-C	2.78 ± 0.83	2.62 ± 0.92	2.92 ± 0.92	> 0.05

Values (except p values) are expressed as mean ± SD.
*Significance of differences among groups, by analysis of variance.

lated to the lipolytic effect of theophylline (12). Theophylline enters the adipose tissue, inhibits the phosphodiesterase enzyme and increases the intracellular cAMP. cAMP activates the hormon sensitive lipase, which increases lipolysis. Thus, the serum free fatty acid, triglyceride, glycerol and cholesterol levels increase (13, 14).

In previous studies, an increase in plasma free fatty acid concentration was found in adults and in animals following caffeine intake (12, 15). In a study related to the effects of long-term administration (4 weeks) of theophylline to low birth-weight infants with apnea of prematurity on plasma lipids showed that this kind of treatment did not change plasma lipids (16). Although high plasma HDL-C levels prevent the deposition of vascular cholesterol and development of atherosclerosis, the elevation of LDL-C level, which is the major carrier of cholesterol leads to the early development of atherosclerosis and is a major risk factor for cardiovascular disease. Susceptibility of LDL-C to lipid peroxidation increases its atherogenic potential. This is due to the fact that the oxidative and peroxidative forms of LDL-C could not be removed from the plasma via LDL receptors in normal cells, and accumulates in the atherosclerotic lesions via alternative receptors of the macrophages and endothelial cells, thus, stimulating the hypertrophy of blood vessel wall.

In our study, even though total cholesterol and LDL-C levels were significantly elevated in children

Table IV

Mean plasma lipid profiles of children in groups 1 (after SRT teratment), 2 and 3

Lipid profile	Population			
	Group 1	Group 2	Group 3	p*
Trigliserid (mg/dl)	91.67 ± 41.22	65.47 ± 28.33	66.13 ± 22.67	> 0.05
Total cholesterol	175.53 ± 24.36	137.13 ± 26.15	126.73 ± 23.89	< 0.05
HDL-C	58.33 ± 9.39	52.86 ± 14.04	46.73 ± 15.49	> 0.05
LDL-C	91.00 ± 24.07	69.43 ± 22.92	66.40 ± 22.55	< 0.05
Apolipoprotein A	146.27 ± 23.56	143.60 ± 23.89	127 ± 33.77	> 0.05
Apolipoprotein B	87.27 ± 12 74	71.58 ± 16.59	71.29 ± 13.28	< 0.05
LDL-C/ HDL-C	2.67 ± 0.63	1.39 ± 0.67	1.59 ± 0.78	> 0.05
ApoA/ Apo B	1.71 ± 0.39	1.84 ± 0.62	1.84 ± 0.62	> 0.05
Total Cholesterol/HDL-C	2.87 ± 0.73	2.62 ± 0.92	2.92 ± 0.92	> 0.05

Values (except p values) are expressed as mean ± SD.
*Significance of differences among groups, by analysis of variance.

given long term SRT treatment, the plasma triglyceride, total cholesterol, HDL-C, LDL-C, Apolipoprotein A and Apolipoprotein B levels among the children in three groups were found in normal limits recommended by Cholesterol Education Program and American Pediatric Academy (17). They are also within the normal ranges for Turkish and American children and adolescents (17, 18).

In our study, since the long-term SRT treatment increased the total cholesterol and LDL-C levels, the risk of atherosclerotic coronary heart disease in these children may be higher, and we concluded that the effects of such mild changes in levels of total plasma cholesterol during long term SRT treatment on the risk of developing atherosclerotic heart disease in adulthood warrant long term follow up studies.

RESUMEN

La arteriosclerosis en la infancia experimenta un desarrollo progresivo lento y su descubrimiento clínico se suele producir en la edad madura. La hipercolesterolemia es uno de los mayores factores de riesgo en el desarrollo de arteriosclerosis. Existe una relación definida entre la hipercolesterolemia en la infancia y la prolongación de las lesiones arterioscleróticas en la edad adulta.

En este estudio hemos evaluado el efecto de un tratamiento con teofilina de liberación prolongada en un perfil de lípido plasmático y hemos descrito el riesgo de arteriosclerosis coronaria en niños con asma bronquial.

Quince niños con una edad media de 10,8 ± 3,19 años y que recibieron TLP durante un tiempo medio de 9,13 ± 2,17 meses contra el asma bronquial fueron clasificados como grupo 1; 15 niños con una edad media de 11,40 ± 3,78, expuestos a un seguimiento por asma bronquial y que no recibieron el tratamiento con TPL fueron clasificados como grupo 2; 15 niños con una edad media de 9,00 ± 3,76 años que no presentaban un historial de asma ni de disnea sibilante fueron clasificados como grupo 3.

Los perfiles de lípidos se cuantificaron con mediciones de los niveles de triglicéridos en plasma, colesterol total, lipoproteínas de alta densidad (LAD), lipoproteínas de baja densidad (LBD), apolipoproteína A (Apo-A) y apolipoproteína B (Apo-B) a todos los pacientes objeto de este estudio.

El nivel medio de colesterol total se determinó en 175,53 ± 24,36 mg/dl, el nivel de LBD en 91,00 ± 24,07 mg/dl y el nivel Apo-B en 87,27 ± 12,74 mg/dl en el primer grupo tras el tratamiento con TPL. El nivel medio de lípidos en plasma tras el tratamiento con TLP fue significativamente más alto que el nivel medio de lípidos antes del tratamiento en el Grupo 1, en el Grupo 2 (grupo de control con asma) y en el Grupo 3 (grupo de control sin asma).

En conclusión, el tratamiento con TLP a largo plazo en niños con asma bronquial puede alterar el perfil de lípidos y puede incrementar el riesgo de padecer cardiopatías coronarias por arteriosclerosis en los niños con asma bronquial.

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Palabras clave: Perfil de lipoproteína. Teofilina de liberación prolongada.

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