Lipoprotein Profile in Long Term Theophylline Administration in Children with Asthma*

UZUN SÜRELİ TEOFİLİN ALAN BROŞİAL ASTIMLI ÇOCUKLARDA LİPOPROTEİN PROFİLİ

Özkan KARAMAN*, Nevin UZUNER, Nurten SAYDAM***, Gül GÜNER***, Dilek TEZCAN******

*Dokuz Eylül University Faculty of Medicine Department of Pediatric Allergy**
*Dokuz Eylül University Faculty of Medicine Department of Pediatric Allergy and Immunology***
*Dokuz Eylül University Faculty of Medicine Department of Biochemistry****
*Dokuz Eylül University Faculty of Medicine Department of Medical Biology*****

ÖZET

Ateroskleroz çocukluk çağında başlayıp yavaş ilerleyen ve klinik bulguları genellikle orta yaşlarda belirginleşen bir hastalıktır. Hiperkolesterolemi, ateroskleroz için majör risk faktörlerinden birisidir. Çocukluk çağındaki hiperkolesterolemi ile aterosklerotik lezyonların evresi ve yaygınlığı arasında ilişki saptanmıştır.

Amaç: Bu çalışmada yavaş salınan teofilin (SRT) tedavisi alan bronşial astımlı çocuklarda tedavinin plazma lipid profili üzerine etkisini ve aterosklerotik koroner kalp hastalığı riskini araştırdık.

Metod: Bronşial astım nedeniyle Pediatrik Allerji Bilim Dalı polikliniğinde izlenen yaşları 10.8 ± 3.19 yıl olan ve ortalama 9.13 ± 2.17 ay SRT tedavisi alan 15 çocuk grup 1, yaşları 11.40 ± 3.78 yıl olan ve SRT tedavisi almayan bronşial astımlı 15 çocuk grup 2 ve yaşları 9.00 ± 3.76 yıl olan astım ve wheezing öyküsü olmayan 15 çocukta grup 3 olarak sınıflandırıldı.

Çalışmaya alınan tüm çocukların plazma trigliserid, total kolesterol, HDL-C, LDL-C, Apo A ve Apo B düzeylerine bakılarak lipid profilleri değerlendirildi.

Bulgular: Grup 1'deki çocuklarda SRT tedavisinden sonra ortalama total kolesterol düzeyi 175.53 ± 24.36 mg/dlt, LDL-C düzeyi 91.00 ± 24.07 mg/dlt ve Apo B düzeyi 87.27 ± 12.74 mg/dlt olarak saptandı. Grup 1'de SRT tedavisinden sonra ortalama plazma lipit düzeyleri grup 1'de SRT tedavisinden önceki, grup 2 (astmatik kontrol grubu) ve 3'teki (non astmatik kontrol grubu) plazma lipit düzeylerinden belirgin yüksekti.

Sonuç: Bronşial astımlı çocuklarda uygulanan uzun dönem SRT tedavisi lipid profilini değiştirebilir ve bronşiyal astımlı çocuklarda aterosklerotik koroner kalp hastalığı riskini arttırabilir.

Anahtar sözcükler: Lipoprotein profili, yavaş salınan teofilin

Nevin UZUNER
Dokuz Eylül Üniversitesi
Tıp Fakültesi
Çocuk Sağlığı Hastalıkları ABD
Allerji Bilim Dalı
Tel:0232-2595959-3621
Fax:0232-2599723

SUMMARY

Atherosclerosis in during childhood, has a slowly progressive course and its clinical findings become prominent generally in middle ages. Hypercholesterolemia is one of the major risk factors in the development of atherosclerosis. There is a correlation defined between hypercholesterolemia in childhood and atherosclerotic lesions extending into adulthood.

Objective: In this study, we evaluated the effect of slow release theophylline (SRT)

* **Abbreviated:** SRT (slow release theophylline), HDL (high density lipoproteins), LDL (low density lipoproteins, Apo A (apolipoprotein A), Apo B (Apolipoprotein B), CAD (coronary artery disease)

treatment on plasma lipid profile and described the risk for atherosclerotic coronary heart disease in children with bronchial asthma.
Methods: Fifteen children with a mean age of 10.8 ± 3.19 years and receiving SRT for a mean time of 9.13±2.17 months for bronchial asthma were classified as group1; fifteen children with a mean age of 11.40 ± 3.78 years and followed up for bronchial asthma, who received no SRT treatment were classified as group 2; fifteen children with a mean age of 9.00 ± 3.76 years and had no asthma or wheezing history were classified as group 3.
The lipid profiles were assessed by the measurements of plasma triglyceride, total cholesterol, High density lipoproteins (HDL-C), low density lipoproteins (LDL-C) Apo- lipoprotein A (Apo-A) and Apo- lipoprotein B (Apo-B) levels in all patients enrolled in this study.
Results: The mean total cholesterol level was determined as 175.53 ± 24.36 mg/dl, the LDL-C level as 91.00 ± 24.07 mg/dl and Apo-B level as 87.27 ± 12.74 mg/dl in the first group after SRT treatment. The mean plasma lipid level after SRT treatment was significantly higher than mean plasma lipid levels before SRT treatment in Group 1, in Group 2 (control group with asthma) and in Group 3 (the non-asthmatic control group).
Conclusion: Conclusion, the long-term SRT treatment in children with bronchial asthma may alter the lipid profile, and may increase the risk of atherosclerotik coronary heart disease in children with bronchial asthma.
Key words: Lipoprotein profile, slow release theophylline

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 µgr/mlt. Therapeutic range of theophylline is 10-20 µgr/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 ($p>0.05$).

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*

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 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	p<0.05
Total Cholesterol	134.0 ± 18.31	175.53 ± 24.36	**p<0.05**
HDL-C	58.40 ± 33.09	58.33 ± 9.39	p>0.05
LDL-C	70.73 ± 18.96	91.00 ± 24.07	**p<0.05**
Apolipoprotein A	145.53 ± 24.48	146.27 ± 23.56	p> 0.05
Apolipoprotein B	72.81 ± 15.05	87.27 ± 12 74	**p<0.05**
LDL-C/ HDL-C	2.12 ± 0.63	2.67 ± 0.63	p>0.05
ApoA/ Apo B	2.09 ± 0.60	1.71 ± 0.39	**p<0.05**
Total Cholesterol/HDL-C	2.78 ± 0.83	2.87 ± 0.73	p>0.05

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

Table III. Mean plasma lipid profiles of children in groups1 (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	p>0.05
Total Cholesterol	134.0 ± 18.31	137.13 ± 26.15	126.73 ± 23.89	p>0.05
HDL-C	58.40 ± 33.09	52.86 ± 14.04	46.73 ± 15.49	p>0.05
LDL-C	70.73 ± 18.96	69.43 ± 22.92	66.40 ± 22.55	p>0.05
Apolipoprotein A	145.53 ± 24.48	143.60 ± 23.89	127 ± 33.77	p>0.05
Apolipoprotein B	72.81 ± 15.05	71.58 ± 16.59	71.29 ± 13.28	p>0.05
LDL-C/ HDL-C	2.12 ± 0.63	1.39 ± 0.67	1.59 ± 0.78	p>0.05
ApoA/ Apo B	2.09 ± 0.60	1.84 ± 0.62	1.84 ± 0.62	p>0.05
Total Cholesterol/HDL-C	2.78 ± 0.83	2.62 ± 0.92	2.92 ± 0.92	p>0.05

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

Table IV. Mean plasma lipid profiles of children in groups1 (after SRT teratment), 2 and 3.

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

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