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Amany Mohamed Abd Al-Aziz
El-Buhouth Street (Previously,
El- Tahrir St.), Dokki Cairo,
Egypt, Postal Code, 12311

Tel: +2027622603, +2023624425
Fax: +2027622603

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Theophylline Therapy and the Risk of Atherosclerotic Coronary Heart Disease in Asthmatic children

[1]Amany M. Abd Al-Aziz, [2]Amal A. Abou El-Ezz and [3]Mona A.M. Awad

In this research, we evaluated the effect of Slow Release Theophylline (SRT) therapy on lipoprotein a, cholesterol and triglycerides in children with bronchial asthma to asses their risk for atherosclerotic coronary heart disease. The study included 38 asthmatic children (26 males and 12 females) aged 6-13 years (mean±SD was 8.37±2.17) receiving SRT, mean duration of therapy was 10±2.5 mo. (Group I). Another 30 asthmatic children of the same age and sex but not receiving SRT (Group II) were included. Twenty healthy children of the same age and sex, not asthmatics, were recruited in the study as controls (Group III). All children were subjected to history taking, medical examination and assessment of serum level of lipoprotein a (Lp a), total cholesterol (Tc), HDL-c, LDL-c, VLDL-c and triglycerides. Theophylline level was assessed in the Group I. No statistically significant difference was found between asthmatics receiving SRT and controls as regards Lp (a), Tc, HDL-c, LDL-c, HDL-c/LDL-c, VLDL-c or triglycerides. HDL-c and HDL-c/LDL-c was significantly higher in asthmatics receiving SRT than asthmatics that did not ($p = 0.002$ and 0.009, respectively). No correlation was detected between serum theophyllin level and different lipid parameters apart from triglycerides and VLDL-c levels (was significantly positively correlated ($r = 0.57$, $p = 0.04$)). So, we can conclude that slow release theophylline therapy did not appear to alter lipid profile of asthmatic children receiving it and those children are not at increased risk for atherosclerotic coronary heart disease.

Key words: Asthma, theophylline, lipids, cholesterol, lipoprotein (a)

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[1]Department of Pediatrics, National Research Centre, Dokki, Cairo, Egypt
[2]Department of Pediatrics, Faculty of Medicine, Cairo University,
[3]Department of Clinical Pathology, National Research Centre, Dokki Cairo, Egypt

INTRODUCTION

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 (Uzuner *et al*., 2002).

Risk factors that have been identified for arteriosclerosis of the coronary arteries are hyperlipidemia and a decrease in high density lipoprotein cholesterol (HDL-c) level (Onaka, 1993) and increased low-density lipoprotein cholesterol (LDL-c). Lipoprotein a (Lp a) is a unique lipoprotein which is considered as an additional risk factor (independent of LDL-c) for Coronary Heart Disease (CHD) (Natoobhai and Sailesh, 1997). Some considered it a coronary risk factor only in the presence of traditional risk factors (Barghash *et al*., 2004). Its clinical importance is derived from its role in atherogenesis (Bahar *et al*., 2003). Lp (a) contributes to atherothrombotic risk by multiple mechanisms that include impaired fibronolysis, increased cholesterol deposition in the arterial wall and enhanced oxidation of low density lipoprotein cholesterol (Stein and Rosenson, 1997).

The previous data has raised the interest to screen children for hypercholesterolemia (Yagupsky *et al*., 1992). The American Heart Association (AHA) recommended in July 2002 that children should have checked their blood cholesterol by the age of five (Marshall *et al*., 2002).

Coffee drinking has been associated with increased serum cholesterol level in some, but not all studies (Sun *et al*., 2001). Theophylline, structurally an almost identical methylxanthine, is a bronchodilator utilized for many decades as bronchial asthma therapy, may induce similar changes. Theophyllin remained the most widely prescribed anti- asthma drug worldwide in spite of other anti asthma medication (Barnes and Pauwels, 1994). The prevalence of asthma among Egyptian children aged 3-15 years was estimated to be 8.2% (Kheders, 1998; EL-Hefny *et al*., 1991).

In this study we tried to evaluate the effect of Slow Release Theophylline (SRT) therapy on different lipid parameters (lipoprotein a, cholesterol and triglycerides) in children with bronchial asthma to asses their risk for atherosclerotic coronary heart disease.

MATERIALS AND METHODS

The study included 38 asthmatic children (26 males and 12 females) aged 6-13 years (mean±SD was 8.37±2.17) receiving SRT (Group I) for at least 4 months before the study. Another 30 asthmatic children of the same age and sex but not receiving SRT (Group II) for at least 4 months before the study were also included. All asthmatic cases were recruited from allergy clinic, pediatric hospital-Cairo University, Cairo-Egypt. Asthma duration was between 3-12.5 years. All patients were receiving other asthma therapy (B2 agonist's preparation by inhalation or orally for the control of acute symptoms and inhaled corticosteroid therapy). Another 20 healthy children of the same age and sex were included in the study as a control group (Group III). All controls were recruited from pediatric clinic, National Research Centre. They have no symptoms or signs of bronchial asthma or family history of allergic diseases. The study done in the period, from February 2005 till December 2005.

All children were subjected to complete medical history (children with acute illnesses or chronic disease, or a history of cardiovascular, renal, liver disease or known history of hyperlipidemia or diabetes mellitus were excluded. Children with positive family history of premature CHD were also excluded). All patients and control were subjected to physical examination, including anthropometric measures (height, weight and calculation of body mass index (those with BMI >95th centile for age and sex were excluded), general examination (those with hypertension were excluded). System examinations with special emphasis on the respiratory system were performed. Measurement of Peak Expiratory Flow Rate (PEFR) using Mini-Right peak flow meter. The best reading from three forced expirations was recorded.

Skin prick tests were performed using a battery of common environmental allergens (Dome Hollisteir extracts) for asthmatic children. Chest X-rays were done to exclude any other chest condition.

Laboratory investigations: (Done at Clinical pathology laboratory, National Research Centre, Cairo, Egypt). After overnight fasting, blood samples were obtained from all children. Complete blood picture (for eosinophilic count) was assessed. Serum was separated by centrifugation and stored at -20°C. Total serum IgE was assessed for all children using IMx Microparticle Enzyme Immunoassay (MEIA).

Lipid parameters including total serum cholesterol (Tc), HDL-c, LDL-c, triglycerides and Lipoprotein (a) (Lp a) were assessed for all children. Total serum cholesterol and Lipoprotein cholesterol contents were determined by the enzymatic-calorimetric method using cholesterol esterase, cholesterol oxidase, peroxidase and a chromagen (Allain *et al*., 1974). For measuring HDL-c, the major lipoproteins were precipitated using heparin-Mn (II) Leaving only HDL-c in solution. The precipitated

lipoproteins were sedimented by centrifugation and the clear HDL-c containing supernatant recovered for cholesterol analysis. LDL-c was calculated {Total cholesterol TC- (HDL-c + triglycerides/5)}. HDL-c/LDL-c was calculated. There is no simple direct way to measure VLDL-c so, it is usually calculated as percentage of triglycerides level (VLDL-c = triglycerides/5) (Mayo, clinic, 2006).

Serum triglycerides levels were determined by the enzymatic-calorimetric method using lipoprotein lipase-glycerokinase, glycerophosphate oxidase and a chromogen, as described (Fossati and Prencipe, 1982).

Lipoprotein a was measured using INNO test Lp (a), an enzyme immunoassay (ELISA) from IMMUNOGENETICS with a monoclonal anti Lp (a) as the solid phase antibody and a sheep anti- apoB polyclonal antibody labelled with horse radish peroxidase.

For those receiving SRT therapy (Group I), blood sample was obtained at the time of the expected peak serum theophyllin concentration (12 h after evening dose or 9 h after a morning dose at a steady state). Theophylline level was assessed in this group to check drug level and to ensure compliance among those children receiving it. Serum theophylline level was measured by a competitive fluorescence polarization immunoassay (TDX; Abott Laboratories Diagnostic Division, North Chicago, III).

Statistical analysis: SPSS for windows, version 7.0 computer program was used for statistical analysis. A p-value of less than 0.05 was considered statistically significant. One-way analysis of variance followed by post-hoc comparisons procedures were used to compare between 3 or more independent means. The t-test was used to compare between 2 independent means. Non parametric tests: Kruskal-Wallis Test and Mann-Whitney U-test were used when parametric tests couldn't be used. Pearson Correlation Coefficient r was used to measure the linear relationship between two quantitative, normally distributed variables, while Spearman's rho correlation coefficient was used when data were not normally distributed or have ordered categories.

RESULTS

The clinical and biochemical characteristics of all studied cases presented as ranges (Min and Max) and percentage were summarized in Table 1. The mean age (years) for cases receiving SRT was 8.37±2.17, for cases not receiving SRT was 9.1±1.97 and for controls was 8.78±2.3 (Not presented in the Table). The mean duration for asthma (years) was 6.71±2.57 in group receiving SRT and 6.33±2.92 in group not receiving it (Not presented in

Table 1: Clinical and biochemical characteristics of all studied cases

	Group I: Asthmatics receiving SRT (n = 38)		Group II: Asthmatics without SRT (n = 30)		Group III: Control (n = 20)	
Variable	Min	Max	Min	Max	Min	Max
Age (year)	6.00	13.00	6.00	13.00	6.00	12.0
Duration of illness (year)	3.00	12.50	3.00	12.00		
Lab. investigations						
Eosinophilic count (c/cumm)	44.00	1474.00	89.00	870.00	40.00	324.0
Serum IgE (IU mL^{-1})	100.00	3073.00	317.00	650.00	12.00	128.0
Lipoprotein a (mg dL^{-1})	7.40	78.80	13.70	106.70	18.00	63.0
Total cholesterol (mg dL^{-1})	125.00	219.00	138.00	177.00	125.00	250.0
HDL-c (mg dL^{-1})	24.00	56.00	13.00	29.00	23.00	66.0
LDL-c (mg dL^{-1})	81.00	158.00	95.00	167.00	83.00	187.0
HDL-c/LDL-c	0.18	0.54	0.09	0.26	0.14	0.6
VLDL-c (mg dL^{-1})	10.00	32.00	12.60	23.00	12.00	40.0
Triglycerides (mg dL^{-1})	50.00	163.00	63.00	115.00	60.00	200.0
Serum theophylline (μg mL^{-1})	8.19	16.80				
	No.	(%)	No.	(%)	No.	(%)
Sex						
Male	26	68.40	13	43.33	12	60
Female	12	31.60	16	56.67	8	40
Severity						
Mild persistent	4	10.50	6	20.00		
Moderately persistent	34	89.50	24	80.00		
Family history of atopy						
Positive	10	26.30	10	33.30		
Negative	28	73.70	20	66.70		

SRT Slow Release Theophyllin, HDL-c high density lipoprotein cholesterol, LDL-c low density lipoprotein cholesterol, VLDL-c very low density lipoprotein cholesterol

Table 2: Skin tests for common inhalant and food allergens among all asthmatic children

		Group I (n = 38): asthmatics receiving SRT		Group II (n = 30): asthmatics without SRT	
Skin tests		No.	(%)	No.	(%)
House dust	Positive	34	89.5	20	66.7
	Negative	4	10.5	10	33.3
Dust mite	Positive	6	15.8	0	0.0
	Negative	32	84.2	30	100.0
Dermatophagoid. Farinea	Positive	28	73.7	22	73.3
	Negative	10	26.3	8	26.7
Dermatophagoid. Petronyssinus	Positive	8	21.1	10	33.3
	Negative	30	78.9	20	66.7
Alternaria	Positive	22	57.9	8	66.7
	Negative	16	42.1	22	73.3
Aspergillus	Positive	0	0.0	4	13.3
	Negative	38	100.0	26	86.7
Cladosporium	Positive	8	21.1	4	13.3
	Negative	30	78.9	26	86.7
Cat hair	Positive	6	15.8	6	20.0
	Negative	32	84.2	24	80.0
Cockroach	Positive	16	42.1	10	33.3
	Negative	22	57.9	20	66.7
Egg	Positive	12	31.6	18	60.0
	Negative	26	68.4	12	40.0
Milk	Positive	6	15.8	4	13.3
	Negative	32	84.2	26	86.7
Banana	Positive	0	0.0	2	6.7
	Negative	38	100.0	28	93.3

SRT: Slow Release Theophyllin

Table 3: Correlations between lipid parameters and different variables among asthmatic children

		Age (year)		Duration of the disease (year)		IgE (IU mL^{-1})	
Lipid parameters		GP I	GP II	GP I	GP II	GP I	GP II
Lipoprotein a (mg dL^{-1})	r	-0.34	0.17	-0.55	-0.06	0.14	0.54
	p	0.28	0.63	0.06	0.86	0.66	0.11
Tc (mg dL^{-1})	r	0.41	-0.64	0.06	-0.50	0.03	0.59
	p	0.15	0.049	0.83	0.14	0.93	0.07
HDL-c (mg dL^{-1})	r	0.39	0.26	0.00	-0.33	0.18	-0.08
	p	0.20	0.47	1.00	0.35	0.58	0.82
LDL-c (mg dL^{-1})	r	0.29	-0.20	0.22	0.39	-0.16	0.14
	p	0.35	0.57	0.49	0.26	0.63	0.69
HDL-c/LDL-c	r	0.11	0.26	-0.11	-0.34	0.14	-0.21
	p	0.73	0.47	0.73	0.34	0.66	0.57
VLDL-c (mg dL^{-1})	r	0.59	0.26	0.06	0.15	0.51	-0.08
	p	0.03	0.47	0.83	0.68	0.06	0.82
Triglycerides (mg dL^{-1})	r	0.59	0.26	0.06	0.15	0.51	-0.08
	p	0.03	0.47	0.83	0.68	0.06	0.82

*$p<0.05$: Significant, Tc: Total cholesterol, HDL-c: High Density Lipoprotein cholesterol, LDL-c: Low Density Lipoprotein cholesterol, VLDL-c: Very Low Density Lipoprotein cholesterol, GP: Group

the Table). The mean duration for use of theophyllin therapy (SRT) was 10±2.5 months and its mean serum level was 13.5±3.25 mcg mL^{-1} (Not presented in the Table).

Skin tests details for common inhalant and food allergens for asthmatic children were summarized in Table 2.

Details of different lipid parameters among all studied groups were shown in Fig. 1. No statistically significant difference was detected between asthmatics receiving SRT and controls as regards all lipid parameters lp (a), Tc, HDL-c, LDL-c, HDL-c/LDL-c, VLDL-c or triglycerides. Asthmatics without SRT had significant lower Tc level than controls ($p = 0.02$) and also less than asthmatics with SRT but not statistically significant. Both asthmatics with SRT and controls had significant higher levels of HDL-c and HDL-c /LDL-c ratio than asthmatics not receiving SRT ($p = 0.002$ and 0.009, respectively).

Triglycerides and VLDL-c were significantly positively correlated with age in group receiving SRT ($p = 0.03$). Total cholesterol was significantly positively correlated with age in group not receiving SRT ($p = 0.049$) (Table 3).

Table 4 showed the corrletion between SRT and different lipid parameters in group receiving SRT. Theophyllin level was only significantly positively correlated with triglycerides and VLDL-c ($r = 0.57$, $p = 0.04$).

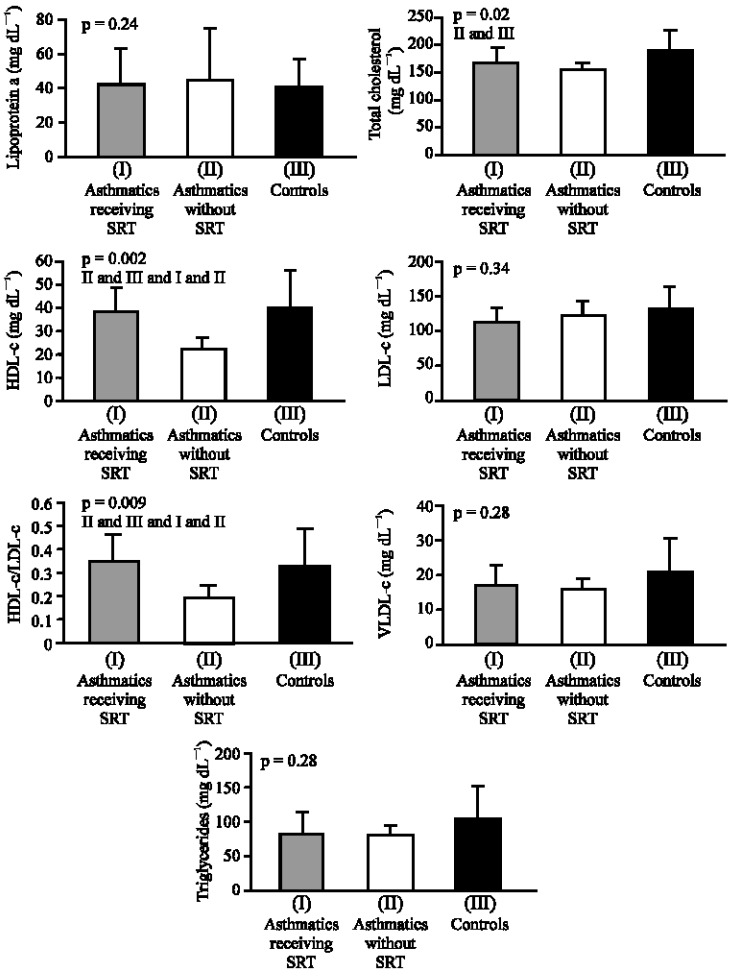

Fig. 1: Lipid parameters among studied groups. HDL-c = High Density Lipoprotein cholesterol, LDL-c = Low Density Lipoprotein cholesterol, VLDL-c= Very Low Density Lipoprotein cholesterol. X-axis: Represent studied groups and Y-axis: Represent lipid parameters

Table 4: Correlation between Theophylline level and lipid parameters

Lipid parameters	Correlation coefficient	Serum theophylline (mg mL^{-1})
Lipoprotein a (mg dL^{-1})	r	0.09
	p	0.78
Total cholesterol (mg dL^{-1})	r	0.26
	p	0.37
HDL-c (mg dL^{-1})	r	0.48
	p	0.11
LDL-c (mg dL^{-1})	r	0.01
	p	0.97
HDL/LDL	r	0.35
	p	0.27
VLDL-c (mg dL^{-1})	r	0.57
	p	0.04*
Triglycerides (mg dL^{-1})	r	0.57
	p	0.04*

*p<0.05: significant

Low density lipoprotein cholesterol (LDL-c) was statistically significantly lower in male asthmatics (110.40±15.89) than female asthmatics (133±27.92) (p = 0.02). High density lipoprotein cholesterol (HDL-c) were higher in male asthmatics (33.66±11.99) than female asthmatics (24.29±8.02) but not statistically significant (p = 0.07) (Not presented in Table).

DISCUSSION

Determination of metabolic effects of theophylline on lipid parameters may contribute to the under standing of the effects of other methyl-xanthines, including caffeine on lipid metabolism. Several studies had demonstrated a clear association between heavy drinking of coffee or other caffeine consumption and increased risk of coronary artery disease (Grobbee *et al*., 1990). A dose- response relation between coffee consumption and both total cholesterol and LDL-c was identified (Sun *et al*., 2001).

Cholesterol level in our study showed no statistical difference between asthmatics receiving SRT and controls

but it was significantly lower in asthmatics not receiving SRT than controls (p = 0.02) and less than asthmatics receiving SRT but didn't reach statistical significance (Fig. 1). This agreed with (Shenoi *et al*., 1992). Yagupsky *et al*. (1992) reported higher levels of Tc in asthmatics receiving theophylline therapy. Uzuner *et al*. (2002) found increased total cholesterol in asthmatics receiving SRT than controls (contrary to our result) and than asthmatics with no SRT (agreed with our result). In our study cases and controls were not homogenous as regards socioeconomic status and geographical area and hence general diet may be the cause of lowering of Tc in asthmatics not receiving SRT.

Low density lipoprotein cholesterol is the major cholesterol carrier. It acts as a transporter for cholesterol and triglycerides to various cells and tissues throughout the body (Alexander *et al*., 2006). Too much LDL-c in blood can slowly build up in the wall of arteries feeding heart and brain, together with other substances; it can form hard deposits (AHA, 2006). LDL-c showed no statistical significant difference between asthmatics receiving SRT and controls or those not receiving SRT in our work (Fig. 1). This agreed with Schanen *et al*. (2005) in adults and Bahar *et al*. (2003) in cases with Obstructive Lung Disease (OLD) as they found no difference between cases and controls. On the contrary Uzuner *et al*. (2002) found increased mean LDL-c in patients receiving SRT and concluded that long term SRT may increase the risk for atherosclerotic CHD.

High density lipoprotein cholesterol binds and removes cholesterol from the cell membranes and its level relates negatively to the risk of atherosclerotic coronary artery disease in adults (Hamsten, 1988). No statistically significant difference was found between asthmatics receiving SRT and controls as regards HDL-c and HDL-c/LDL-c (Fig. 1). HDL-c and HDL-c/LDL-c were significantly lower in Group II (not receiving SRT) than Group I (receiving theophyllin) and than controls (p = 0.02 and 0.009, respectively) (Fig. 1). On the contrary (Shenoi *et al*., 1992) found higher HDL-c in asthmatics than controls. Bahar *et al*. (2003) found no difference between cases with obstructive lung disease and controls. This controversy could be explained by different dietary habits or geographical distribution. Another explanation is that, in our study, HDL-c in male asthmatics were higher (33.66±11.99) than female asthmatics (24.29±8.02) but not statistically significant (p = 0.07) and most of Group I and III were males which may explain higher HDL-c among them than Group II. Also, increase percentage of males in Group I and controls than Group II (Table 1) with significant lower LDL-c in males (110.40±15.89) than females (133±27.92) (p = 0.02) could explain higher HDL-c/LDL-c in Group I and controls. Sammal *et al*. (1988) had shown that acute bacterial and viral infections in adults cause decrease in HDL-c in acute phase. HDL-c level is decreased in all species during acute-phase response (Hardardottir *et al*., 1995). Also stress-like acute myocardial infarction and burns had been reported to cause decrease in HDL-c and Tc levels (Clpin and Price, 1988). The previous data (viral infections and stress) could explain reduction of HDL-c in Group II than controls but did not explain the difference between Group I and II. The rise in HDL-c and HDL-c/LDL-c in Group I may reflect effect of SRT. It was reported that theophyllin at serum concentration 10-20 $\mu g\ mL^{-1}$ range modestly increase total cholesterol from 140-160 mg dL^{-1}, HDL-c from mean 36-50 mg dL^{-1} and HDL-c/LDL-c from mean 0.5-0.7 (Purdue Pharmaceutical Product, 2004). Yagupsky *et al*. (1992). found significant higher HDL-c in asthmatics receiving SRT, with conclusion that SRT don't increase atherosclerotic risk. Group II had very low HDL-c (Table 1 and Fig. 1) by the American standards, in age Group 1-14 the normal level is 35-84 mg dL^{-1} (John and Michael, 1992) so, SRT may protect asthmatics against atherosclerosis.

No statistical significant difference was found between asthmatics (receiving SRT or not) and controls as regards triglycerides (Fig. 1). This agreed with Bahar *et al*. (2003) among cases with obstructive lung disease.

Lipoprotein (a) excess has been identified as a powerful predictor of premature atherosclerotic vascular disease in several studies (Mohler and Rader, 2000) and elevated plasma lipoprotein (a) and cardiac events showed a modest but significant association in various clinical studies (Buechler *et al*., 2001). In our work Lp (a) showed no statistical significant difference between asthmatics receiving SRT and controls or asthmatics not receiving theophyllin (Fig. 1). This disagreed with Yagupsky *et al*. (1992) as they found higher Lp (a) with SRT therapy and Mutius *et al*. (1998) who reported that serum lipoprotein (a) was positively related to asthma. Plasma levels of Lp (a) are genetically determined and increase slightly with age and vary by race (Joseph and Frolkis, 1999) which may explain variability in results.

Only age was positively correlated with triglycerides level in Group I (p = 0.03) and cholesterol level in Group II (0.049) (Table 3) as eating more fat increase by ageing.

In conclusion, slow release theophylline therapy did not appear to alter lipid profile of asthmatics receiving it and those children are not at increased risk for hypercholesterolemia or premature atherosclerotic coronary heart disease than general population.

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