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Effects of theophylline on CD4$^+$ T lymphocyte, interleukin-5, and interferon gamma in induced sputum of asthmatic subjects

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KEY WORDS asthma; theophylline; interleukin-5; interferon type Ⅱ; T-lymphocytes

ABSTRACT

AIM: To investigate the mechanism of anti-inflammatory action of theophylline on asthma. **METHODS**: Nineteen asthmatic subjects were administered 200 mg sustained-release theophylline twice daily for 4 weeks. The number of CD4$^+$ T lymphocytes, eosinophils, and the levels of interleukin (IL)-5 and interferon gamma (IFN-γ) in sputum pre- and post-administration were measured by direct immunofluorescene technique, Wright's stain and enzyme-linked immunosorbent assay, respectively. The symptom scores and lung function were also evaluated. **RESULTS**: Theophylline treatment significantly improved symptom scores and $FEV_{1.0}$, $FEV_{1.0}$% ($P < 0.05$) and reduced sputum eosinophils ($P < 0.01$) in asthmatic subjects. These were accompanied by a decrease in sputum IL-5 level ($P < 0.01$), but sputum CD4$^+$ T lymphocytes and IFN-γ had no significant change ($P > 0.05$). The mean (range) serum theophylline concentration in final steady state was 7.9 (3.9 - 12.9) mg/L. **CONCLUSION**: The anti-inflammatory action of theophylline in asthma may result from reduction of IL-5 production in the airways.

INTRODUCTION

Theophylline, a nonselective phosphodiesterase (PDE) inhibitor, has been used as a bronchodilator in the treatment of bronchial asthma for more than 50 years[1]. It is now widely believed to have additional actions beneficial to this disease, including anti-inflammatory actions[2]. Their studies show that theophylline treatment can reduce the level of eosinophil cationic protein (ECP) and activated eosinophil in sputum of asthmatic patients. The mechanism of anti-inflammatory action of theophylline in asthma is still unclear.

T lymphocyte number and activated T lymphocytes were increased in the bronchial mucosa in asthma[3,4], and these findings and the presence of detectable mRNA for interleukin (IL)-5 were related to disease severity[4]. The study by Walker *et al*[5] has shown that the level of IFN-γ decreases in bronchoalveolar lavage (BAL) fluid from asthmatic patients. Now it is thought that IL-5 can induce eosinophilia and IFN-γ may have therapeutic potential in allergic disease. Since PDE inhibitors impede, at least *in vitro*, the expression of IL-4 and IL-5 genes in Th2 cells[6] and theophylline inhibits proliferation of peripheral blood mononuclear cells and secretion of IL-4 and IL-5 from human Th2 cell lines[7], we hypothesized that modulation of CD4$^+$ T lymphocytes or cytokine production *in vivo* might underlie the anti-inflammatory actions of theophylline in asthma. In this study, we observed the effect of theophylline on CD4$^+$ T lymphocyte count and production of IL-5 and IFN-γ in induced sputum of asthmatic subjects and investigated their possible changes relating to eosinophils, symptoms, and lung function.

MATERIALS AND METHODS

Subject From May 2000 to April 2001, 24 adult asthmatic patients (11 males, 13 females) being treated in Department of Respiratory Disease of Wuhan University Renmin Hospital were entrolled in this study. The average age of the patients was 35 a. For the diagnosis of asthma the criteria in the Global Initiative for Asthma (GINA) was adopted[8]. Seven of the patients presented mild persistent asthma, nine patients moderate, and eight patients severe asthma. The mean baseline forced expiratory volume in ooe second ($FEV_{1.0}$) as a percentage of predicted normal ($FEV_{1.0}$%) was 68 % ± 16 %. All patients were demonstrated an over 15 %

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improvement in $FEV_{1.0}$ following inhaling 200 μg of salbutamol. Sixteen patients had positive allergy skin test. All patients had not taken theophylline, corticosteroids, or leukotriene antagonists within 6 weeks before initiation of this study. Ten healthy nonasthmatic and non-allergic subjects (medical students and hospital personnel, 4 males, 6 females) with a mean age of 35 a were also studied. None of the subjects (asthmatic patients or healthy individuals) had ever smoked cigarettes or had a history of cardio-pulmonary diseases other than asthma. All subjects had not experienced a respiratory tract infection at least 6 weeks prior to entry into the trial. The healthy subjects had no atopic constitution. The study was approved by the Institutional Ethic Committee of Wuhan University School of Medicine and written informed consent was signed by all subjects.

Study protocol All the patients were administered sustained-release theophylline tablet, each tablet contained anhydrous theophylline (1, 3-dimethyl-3, 7-dihydro-1*H*-purine-2, 6-dione 100 mg, Guangzhou Xinghua Pharmaceutical Ltd, China) at a dose of 400 mg/d (200 mg per time, *po*, bid) for 4 weeks. In the morning on the 4th day before breakfast and on the last day of the study, 4 h after dosing, the serum concentration of theophylline was detected using automated chemiluminescence system (ACS 180, USA), with a sensitivity of 0.3 mg/L – 40 mg/L. The patients kept daily records of their symptoms and the dose of used salbutamol throughout the study. Salbutamol aerosol [(*RS*)-2-(1, 1-dimethyl)-ethylamino-1-[4-hydroxy-3-(hydroxymethyl)-phenyl]-ethanol] inhalation, 100 μg per dose (Glaxo Wellcome, Chongqing, China) was permitted during the treatment if it was required. Before and at the end of the study, the measurement of lung function and induction of sputum with hypertonic saline were performed. On the first visit, allergy skin tests were performed. Subjects were instructed how to record symptoms and medications in a diary.

Clinical assessement Asthmatic subject characteristics were documented by questionnaire. The assessment of symptom scores was referred to the scoring key for asthma symptoms as given by Marks *et al*[9]. During the study period, subjects were asked to record two symptom scores on awakening and three scores before going to bed. The morning scores were for sleep disturbance due to asthma and morning chest tightness, and the evening scores were for frequency and severity of daytime asthma symptoms and cough. The mean of these scores was calculated and these were added and rescaled to yield a total symptom score of 10.

Spirometry was performed with a Vmax 229 spirometer (United States Sensor-Medics). $FEV_{1.0}$ and forced vital capacity (FVC) were recorded. The $FEV_{1.0}$ was also expressed as a percentage of the predicted values. Allergy skin tests were performed using the prick technique with 14 common allergen extracts.

Sputum induction and processing All subjects were premedicated with inhaled salbutamol 200 μg. Sputum induction was performed with an aerosol of hypertonic saline generated by Medix ultrasonic nebulizer (Clement Clarke International Ltd, Harlow Essex, UK) with 0.87 mL/min and particle size 5.58 μm aerodynamic mass median diameter using the method described previously[10]. The method was slightly modified by inhaling increasing concentrations of saline (3 %, 4 %, and 5 %) for 7 min each through a mouthpiece without a valve or nose clip. After each period of inhalation an $FEV_{1.0}$ was measured for safety. Subjects were asked to rinse their mouth and swallow the water and blow the nose to minimize contamination with saliva and post nasal drip. Then they were inducted to cough sputum into a sterile container.

Sputum was processed as previously described[11,12] with slight modification. Briefly, sputum was selected from saliva and dispersed using three volumes 0.1 % dithiothreitol (Sigma Chemical Co, USA). After 15 min gentle rocking, the cell suspension was filtered through a 48 μm-nylon gauze to remove cell debris and mucus, then centrifuged at 900 × *g* for 10 min. The supernatant fluid was aspirated and stored in two Eppendorf tubes at – 70 ℃ for later assay. The pellet was resuspended in a volume of PBS (NaCl 137 mmol/L, KCl 2.7 mmol/L, NaH_2PO_4 4.3 mmol/L, KH_2PO_4 1.4 mmol/L; 0.1 mol/L, pH 7.4), 200 – 600 μL depending on the macroscopic size, and a total cell count of leukocytes obtained in a modified Neubauer hemocytometer. The cell suspension 50 μL adjusted to 1.0×10^9/L were placed into cups LTP-C cytocentrifuge (Military Medicine Acadamy of Science, Beijing, China) and four cytospins were prepared at 225 × *g* for 1.5 min. Two slides were air-dried for eosinophil count, and two others were put into acetone for 10 min for examination of $CD4^+$ T lymphocytes.

Cell count and cytokine examination Eosinophil count was performed using Wright's stain. $CD4^+$ T lymphocytes were examined by direct immunofluorescene technique with FITC labeled CD4 mAb (Sigma Chemical Co, USA). Five hundred nonsquamous cells were

counted in Wright's-stained slides and immuofluorescene-stained slides and the results were expressed as a percentage of the nonsquamous count.

Determination of IL-5 and IFN-γ in the thawed supernatant was carried out by enzyme-linked immunosorbent assay (ELISA) using IL-5 and IFN-γ ELISA kit (Sigma Chemical Co, USA) according to the manufacturer's instructions. All sputum measurements were performed blindly to the clinical details.

Statistical analysis Results are expressed as $\bar{x} \pm s$. The classical t-test was used for the comparison of sputum level of IL-5 and IFN-γ. The t-test for paired observations were applied for the comparison of cytokine levels. Correlation coefficients were determined using Pearson's linear analysis. Statistical significance was set at a level of $P < 0.05$.

RESULTS

Clinical data A total of five asthmatic subjects withdrew from the study, so that 19 subjects from the theophylline group and 10 from the healthy group completed the study. Of those withdrawn from the theophylline group, one was unable to tolerate sputum induction, one developed intolerable dyspepsia attributed to theophylline, and three suffered an exacerbation of asthma associated with an upper respiratory tract infection. Theophylline treatment was accompanied by a decrease in the symptom scores of asthma (7.3 ± 1.3 *vs* 5.4 ± 1.6, $P < 0.05$). A small but significant increase in $FEV_{1.0}$% ($FEV_{1.0}$/FVC) was observed (63 % ± 15 % *vs* 69 % ± 14 %, $P < 0.05$). The $FEV_{1.0}$ was significantly increased (2.0 ± 0.7 *vs* 2.2 ± 0.9, $P < 0.05$), too. The mean final steady-state serum theophylline concentration was 7.9 mg/L (range 3.9 – 12.9 mg/L), which is below the currently regarded therapeutic range (10 – 20 mg/L).

Sputum cell counts Before theophylline treatment, eosinophils, lymphocytes, and $CD4^+$ T lymphocytes in sputum cytocentrifuge preparations of asthmatic patients were much higher than those of healthy subjects, but the percentage of macrophage was lower than that of healthy subjects. Low-dose theophylline treatment was accompanied by a decrease in the percentage of eosinophil, but it was still higher than that of healthy group; no change in the percentage of lymphocyte and $CD4^+$ T lymphocyte; a great increase in the percentage of macrophage (Tab 1).

Tab 1. Cell counts (%) in induced sputum of healthy subjects ($n = 10$), pre- and post-treatment asthmatics ($n = 19$). $\bar{x} \pm s$. $^bP < 0.05$, $^cP < 0.01$ *vs* healthy group. $^eP < 0.05$, $^fP < 0.01$ *vs* theophylline pre-treatment.

	Asthma group		Healthy group
	Pre-treatment	Post-treatment	
Eosinophil	31 ± 12^c	21 ± 10^{ef}	1.4 ± 0.7
Macrophage	26 ± 10^c	36 ± 12^{ce}	70 ± 6
Lymphocyte	9 ± 5^b	9 ± 5^b	1.8 ± 1.1
Neutrophil	31 ± 14	33 ± 17	22 ± 4
$CD4^+$ T lymphocyte	7 ± 4^c	7 ± 3^c	3.2 ± 1.4

Before theophylline treatment, the number of eosinophils in induced sputum was negatively correlated with $FEV_{1.0}$% of asthmatic patients ($r = -0.65$, $P < 0.01$, Fig 1).

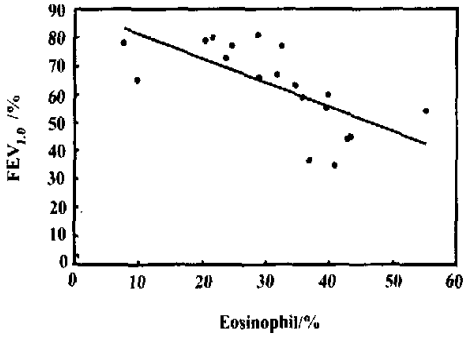

Fig 1. Correlation between the percentage of eosinophils in induced sputum and $FEV_{1.0}$% of asthmatic subjects before theophylline treatment. $n = 19$. $r = -0.65$. $P < 0.01$.

Sputum cytokine level The sputum IL-5 and IFN-γ levels in the control group were (15 ± 7) and (13 ± 5) ng/L, respectively, while the baseline sputum values of IL-5 and IFN-γ in asthmatic patients were (51 ± 31) and (11 ± 4) ng/L, ($P < 0.01$ and $P > 0.05$, respectively). The level of IL-5 was positively correlated with the percentage of eosinophils in induced sputum ($r = 0.85$, $P < 0.01$, Fig 2). The administration of theophylline for 4 weeks resulted in a substantial reduction in sputum IL-5 in all patients ($P < 0.01$). It must be noted that, although the use of theophylline was associated with a significant decline in sputum IL-5, the level continued to be significantly higher than control values ($P < 0.05$). There was no statistically significant difference between the pre-treatment and post-treatment in the level of IFN-γ in

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sputum of asthmatic patients (Tab 2).

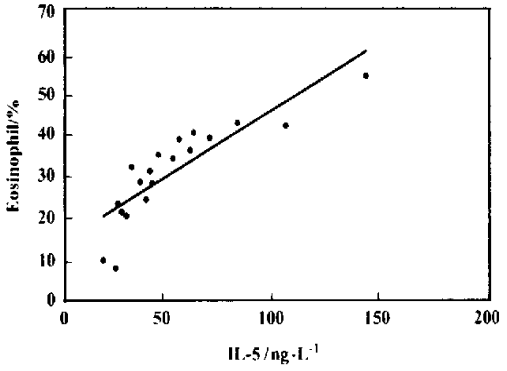

Fig 2. Correlation between the level of IL-5 and percentage of eosinophils in induced sputum of asthmatic subjects. $n = 19$. $r = 0.85$. $P < 0.01$.

Tab 2. The levels of IFN-γ and IL-5 in induced sputum of healthy subjects (n = 10), pre-and post-treatment asthmatics (n = 19). $\bar{x} \pm s$. $^bP < 0.05$, $^cP < 0.01$ *vs* healthy values. $^fP < 0.01$ *vs* theophylline pre-treatment values, respectively.

	Asthma group		Healthy group
	Pre-treatment	Post-treatment	
IL-5/ng·L^{-1}	51 ± 31^c	29 ± 18^{bf}	15 ± 7
IFN-γ/ng·L^{-1}	11 ± 4	12 ± 5	13 ± 5

DISCUSSION

In the study, it has been shown that symptom scores and lung function improvement in asthma after low-dose theophylline treatment was accompanied by a reduction in sputum eosinophilia and the level of IL-5 and no change was found in the number of CD4$^+$ T lymphocyte and the level of IFN-γ in sputum. These findings add further support to the concept of an anti-inflammatory role for this therapy. Although a causal link is not demonstrated, it is compatible with the hypothesis that the anti-inflammatory actions of low-dose theophylline in asthma depend at least in part on regulation of cytokine synthesis *in vivo*.

It is now well-recognized that inflammatory events play a central role in the pathogenesis of asthma[13]. The CD4$^+$ T lymphocyte is now believed to play a critical role in the allergic inflammatory response by enhancing the recruitment, growth, and differentiation of all other cell types involved in the response[14]. It performs its function by secreting several cykines. The CD4$^+$ T lymphocyte can be subdivided into two subsets based on their cytokine profiles and function, namely, Th1 and Th2 cell[15]. In our study, it was found that the proportion of CD4$^+$ T lymphocyte in sputum of asthmatic patients significantly increased, adding further evidence for upregulated T lymphocyte response in the asthmatic airways. In the study by Gerblich *et al*[16] analysis of blood and BAL lymphocytes in atopic asthmatics after allergen exposure have revealed that CD4$^+$ T lymphocytes are depleted in the circulation and sequestered in the lung. It was thought that the increase in CD4$^+$ T lymphocyte in the asthmatic airways was related to the selective distribution that may be determined by enhanced expression of ICAMs at the surface of T lymphocytes in the airway lumen[17]. Study performed with the murine model of OVA-induced airway inflammation has shown that Th1 cells are recruited early during the allergic response, whereas Th2 cell recruitment occurs later and is facilitated by Th1 cell[18]. It was speculated that the secretion of those Th2 cell-attracting chemokines MDC and I-309 by activated Th1 cells may favour the recruitment of Th2 cells. After 4 weeks treatment with oral theophylline (the mean serum theophylline concentration was 7.9 mg/L), our study showed that there was no change in the proportion of CD4$^+$ T lymphocytes in sputum. It suggested that low-dose theophylline had no effect on the number of CD4$^+$ T lymphocyte in the airways in patients with asthma. The study by Jaffar *et al*[19] has similar results to our study. Their study has shown that theophylline therapy appears to be associated with a reduction in the overall number of BAL CD4$^+$ T lymphocyte expressing activation marker but not a decrease in the proportion of these cells. All these suggested that the drug may have modulated the movement of both activated and nonactivated lung CD4$^+$ T lymphocytes equally.

IL-5 is of particular interest in the pathophysiology of asthma as it is associated with eosinophilia inflammation[20]. In our present study, this was also demonstrated. It was interesting that the observed reduction in the level of IL-5 in the sputum of asthmatic patients after oral theophylline treatment. The apparent reduction in the level of IL-5 was accompanied by a reduction in the number of eosinophils and improvement of asthmatic symptom and lung function. An inhibitory effect of theophylline on IL-5 might well be expected to inhibit recruitment of eosinophils to the airways. The

study performed by Ying *et al*[21] revealed that more than 70 % of IL-4 and IL-5 mRNA$^+$ cells are activated T cells in asthmatic airways with double immunocytochemistry *in situ* hybridization, but it has been demonstrated that those activated T cells exhibiting mRNA encoding for IL-3, IL-4, and IL-5 are of the Th2 phenotype[14,22]. Consquently, we considered that the inhibition of theophylline on IL-5 in the airway may be related to inhibition of Th2 cells which produced such "Th2-like" cytokine as IL-5.

IFN-γ has an immunoregulatory effect on various cells. IFN-γ may have therapeutic potential in allergic disease. In our study, it was observed that the level of IFN-γ in sputum was not changed after theophylline treatment. The result indicated that low-dose theophylline did not affect production of IFN-γ in the asthmatic airways. Since IFN-γ was considered to be produced by Th1 cells[23], we suspected that theophylline therapy had no impact on the secretion of Th1 cells.

It was noteworthy that in our study the number of eosinophils and the level of IL-5 in sputum of asthmatic patients were still higher than those of healthy subjects after 4 weeks treatment of oral low-dose theophylline. This result suggested that oral low-dose theophylline were not complete at modulating immunity and suppressing eosinophil inflammation in the airway of asthma. The study by Horiguchi *et al*[24] have demonstrated that after 8 weeks administration of theophylline, sputum and serum ECP decreased more markedly than that after 4 weeks administration, suggesting that the longer the period of treatment, the more distinct the anti-inflammatory effects of theophylline.

In conclusion, the results showed that asthmatic patients had increased sputum level of IL-5 and proportion of eosinophils, which were substantially supressed by a short-term administration of sub-bronchodilater dosage of theophylline. The findings support the current knowledge that theophylline exerts at least part of its anti-inflammatory action by affecting such particular cytokines as IL-5. It would, therefore, appear that theophylline may contribute to asthma control through its ability to reduce the cytokines, which are relevant to allergic mucosal responses.

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茶碱对哮喘患者诱导痰中 CD4⁺T 细胞、白介素-5 和干扰素-γ 的影响

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关键词 哮喘；茶碱；白介素-5；干扰素Ⅱ型；T-淋巴细胞

目的：研究小剂量茶碱抗哮喘炎症的可能机制。**方法**：19 名哮喘患者口服茶碱缓释片（200 mg，bid）治疗 4 周，观察治疗前后症状积分和肺功能变化，并分别采用直接免疫荧光技术、瑞氏染色和 ELISA 法检测治疗前后高渗盐水诱导痰中 CD4⁺T 细胞、嗜酸性粒细胞（Eos）及 IL-5 和 IFN-γ 的变化。**结果**：茶碱治疗可使哮喘患者诱导痰中 IL-5 水平和 Eos 数量显著下降（$P<0.01$），但 CD4⁺T 细胞数量和 IFN-γ 水平无明显变化（$P>0.05$）；患者症状及肺功能明显改善，$FEV_{1.0}$和 $FEV_{1.0}$%增加（$P<0.05$）。平均血浆茶碱浓度为 7.9 mg/L（3.9 – 12.9 mg/L）。**结论**：小剂量茶碱通过减少哮喘患者气道 IL-5 的产生而发挥抗炎作用。

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