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The Relationship Between Serum Levels of Theophylline by Peak Expiratory Flow, Asthma Symptoms and Side Effects in Patients Treated with Inhaled Corticosteroids.

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ABSTRACT

Asthma is a respiratory disease with clinical symptoms such as, chest wheeze, chest tightness and shortness of breath. Theophylline has been consumed from many years ago for the treatment of respiratory diseases. 62 asthma patients under study were consuming a treatment regime with a high dosage of inhaling corticosteroid and a low dosage of theophylline as slow release tablets. Before the start of the study and 4 weeks after the prescription of theophylline, the patients were questioned about the improvement in the symptoms (coughing, shortness of breath and phlegm) and the PEF was determined with a peak flowmeter. The patients were also questioned about their experience with each of the side effects during the period of theophylline prescription. At the end of the study, the serum concentration of theophylline was measured by the HPLC method. The analysis of the changes of evening PEF revealed significant differences before and after the theophylline consumption (from 322.75 L/min (74.19%) to 351.18 L/min (80.67%), P<0.001). The expected relation between PEF and PEF % with the serum concentration of theophylline was not considerable (respectively P: 0.467 and P: 0.204. We understood that with the addition of low-dosage of theophylline to the treatment regime of the asthma patients who despite the treatment with inhaling corticosteroids were symptomatic, there will be an improvement in the symptoms and in the PEF of the patients. Adding to that no dangerous side effect was reported during this period.
Keywords:

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INTRODUCTION

Asthma is a respiratory disease with clinical symptoms such as chest wheezing, shortness of breath and chest tightness. Two main characteristics of this disease are being inflammatory and bronchoconstriction. The inflammation is controlled with the daily usage of steroids and the bronchoconstriction is controlled with β_2 receptor agonists [1]. Long term asthma causes the deformation of the airways and refractory asthma [2]. According to the WHO, around 235 million people worldwide are affected with this disease. Asthma is the most common disease in children. This disease is not specific to countries with low incomes, and is common in all countries regardless of their economic status. But more than 80% of the fatalities caused by this disease occur in low income countries [3]. The causes of Asthma have not been identified completely and the most important risk factor for this disease is a combination of genetic predisposition and environmental exposure to respirable particles that cause allergies and inflammation. Other driving factors such as cold weather, emotional arousal such as anger and fear, physical activity and even taking certain medications such as aspirin, NSAIDs, beta-blocker medication can be effective in causing asthma. Urbanization of societies has also been effective in increasing asthma [2], [4].

The identification of the diagnosis to asthma is with physical checkups, the symptoms observed, investigating the parameters (forced expiratory volume in 1 sec), FEV_1 (peak expiratory flow) PEF gained from Spirometry test, radiography scanning from the chest, measuring the biomarker etc. [4]. The aim of asthma treatment is to enable patients to live without symptoms and the drugs and prevent them from dealing with asthma driving factors. Physician and patient participation is an essential part of treatment [2]. Four stages of drug therapy are available based on disease level from mild to severe illness, which all contain an appropriate daily dose of inhaled Glucocorticosteroids. β_2 agonists, leukotriene receptor antagonists and long-acting and slow-release theophylline as simultaneous treatments are recommended, while antibodies against IgE are a new treatment option in cases of severe asthma that are refractory to treatment. inhaled β_2 agonists, Aminophylline, corticosteroids, adrenaline, and oxygen, and so on are consumed in cases of acute asthma attacks [2].

Theophylline (Dimethyl xanthine) has been used for respiratory diseases for many years. This substance is found naturally in tea and coffee beans in a very minute amount. Its use in these diseases is as Bronchodilator that is consumed with high dose of theophylline and this high dose leads to side effects [5]. The Bronchodilator mechanism of medicine that occurs in high densities is because of its role in inhibition of phosphodiesterase3 Enzyme that leads to relaxation of smooth muscles of the respiratory tract. In recent years anti-inflammatory effect of theophylline has been observed which is because of the inhibition effect of phosphodiesterase 4 and activation of Histone diacetylate (HAD), activation of histone diacetylate causes the expression genes of inflammatory mediators to be turned off. theophylline also decreases resistance to Corticosteroids through this mechanism that is worthwhile in severe asthma treatment. Anti-inflammatory effect of this medicine occurs in lower concentrations [6]. There is a close relation between theophylline effect and blood concentration in plasma while in concentrations less than 10 mg/L its bronchodilator effect is low and in concentrations above 25 mg/L the advantages are not considered because of the side effects. Its non-bronchodilator effects normally occurs in concentration below 10 mg/L. Appropriate dose to acquire proper treatment concentration of theophylline in patients is different because of the difference in its clearance [5]. Despite the widespread use of theophylline in the world, this drug is considered as a second line treatment and as an adjuvant therapy for patients with uncontrolled asthma. With the increase in the use of β_2 inhaling agonists as a bronchodilator and inhaled corticosteroids as anti-inflammator, the use of theophylline was decreased [5], [6].

Numerous studies have shown that the low-dosage of theophylline besides inhaling corticosteroids have better effect on the FEV_1 of patients compared to doubling the usage of inhaling corticosteroids. Since the effect of theophylline on the lungs has been very low in these studies, the positive effect of theophylline on patients has been related to the its anti-inflammatory effect. Also the improvement in the lung function of asthma patients who smoked was also displayed [7], [8]. Elixir and simple tablet form of medicine is absorbed faster but is not desirable because of high concentration fluctuation of fluticasone in plasma. Using sustained release form of theophylline leads to a constant speed of medicine absorption and reaching to a constant

blood concentration in 12-24 hours. For its bronchodilator effect, using 200-400 mg of medicine twice a day is advised but for anti-inflammatory effect, half of this amount is enough.

The main limitation in using theophylline is because of relating high frequence to adverse effect. Undesirable effects of theophylline is usually related to plasma concentration specially in doses over 20 mg/L, however such complications may be experienced in low densities by patient. Most common complications of the medicine include: headache nausea, increased gastric acid secretion and reflux which can be because of inhibition effect of medicine on phosphodiesterase enzyme, and paroxysm and cardiac arrhythmia in high concentrations which is due to the antagonistic effect on adenosine receptors [9] , [10] .

MATERIAL AND METHODS

This study was implemented as a clinical study and a group of patients were considered before and after the investigations. 62 Asthma patients aged from 19 – 85 were under study whom all had the Asthma conditions based on the Asthma diagnostic criteria according to EPR3 published by NIH [4]. The patients were selected from the Imam Khomeini hospital belonging to Ahvaz Jundishapur University of Medical Sciences, Ahva, Iran.

The recruited patients had asthma symptoms 6 weeks before the study and were under treatment of high dose of inhaled corticosteroids and received inhaled β_2 agonist if necessary. These patients also had PEF more than 50% of expected amount with at least 15% variability in PEF. All selected patients did not haveexacerbation symptoms 6 weeks before the study [11].

All the patients with severe illnesses, alcoholics and drug addicts were omitted from the study group. The patients received oral corticosteroid, Cromolyn Sodium or Ketotifen throughout the study. The treatment regime through the study included high dosage of inhaling corticosteroids (1000 µg Beclomethasone di propionate or 1000 µg Beclomethasone propionate twice daily) in combination with low-dosage of theophylline as slow-released tablets with dose of 6 mg / Kg / d in two separate doses.

Before the start of the study and 4 weeks after the prescription of theophylline, the patients were questioned about the improvement in the symptoms (coughs, phlegm and shortness of breath) and the PEF was determined with a peak flowmeter.

The improvements of the symptoms in the patients was graded as (weak, average, good and excellent) in the questionnaires and the amended peak flow for each person based on sex, age and height as a percentage of the expected PEF was measured. At the end of the study, the serum concentration of theophylline (with a 5 ml serum sample, 12 hours after receiving the drug) in the HPLC method (Kanuar company, Germany) and UV detector was implemented.

At the end of the study period, the patients were questioned about their experience with any of the side effects during the prescription of theophylline. The side effects included; restlessness, dizziness, insomnia, headache, anxiety, palpitations, tremor, nausea, vomiting, diarrhea, anorexia, stress, heart pain, seizures, itching, redness or rash and desquamation.

Finally, statistical analysis was performed using SPSS software version 23. The relation between serum concentrations of theophylline, with each side effect was evaluated using t-test for each independent sample. The PEF and PEF% improvement expected, was investigated by using t-test for paired samples. Rating of the improvement in patient's symptoms was evaluated with Wilcoxon ranking test.

RESULTS

In this study, from the 62 patients under study, 34 cases (54.8%) were females and 28 cases (45.2 %) were males. The overall details of the patients are available in table 1. The analysis of the evening PEF changes had considerable differences between before and after the theophylline consumption (from 322.75 L/min (74.19%) to 351.18 L/min (80.67%), P<0.001). The relation between PEF and expected PEF% changes with serum concentration of theophylline was not significance (respectively, P= 0.467 and P= 0.204).

The improvement in the symptoms ranked from weak, average, good and excellent with grades 1 to 4 are depicted. At the end, the theophylline consumption had a considerable change (from 3.2% weak), 25.8% (average), 6.56% (good), 14.5% (excellent) to 0.0% (weak), 6.5% (average), 51.6% (good) and 41.9% (excellent) : P<0.001). The average serum level of theophylline was 4.69 mg/L with a standard deviation of 3.92 mg/L (table 2). The average serum concentration of theophylline in patients was measured at 4.9 mg/L in those who experienced side effects and 4.58 mg/L in the rest of the patients. This difference was not statistically meaningful. Moreover, there was no significant correlation between any of these symptoms and the serum levels of theophylline (Fig.1). In this study, 20% of the patients with gastrointestinal symptoms and 40% have reported central nervous system side effects. Cardiovascular complications were reported in 4% of patients.3% of patient experienced dermatologic side efffec and there was no side effect in 24% of patient(Fig 2).

Table 1: Average and standard deviation of age and BMI

Title	Average	Standard deviation	Number
Age (year)	41.82	16.21	62
BMI(kg/m2)	26.15	5.56	62

BMI: Body mass index

Table 2: Distribution of theophylline serum concentration

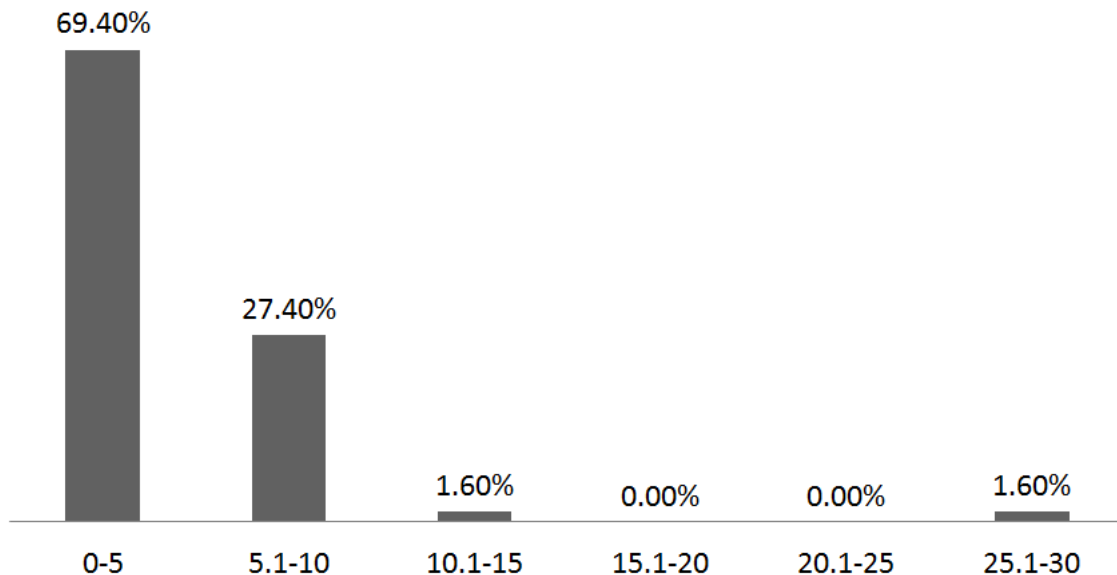| Number of cases	62
Average	4.69
Middle	3.70
Standard deviation	3.92
Minimum	0.30
Maximum	26.90

Figure 1- Distribution of theophylline serum concentration (mg/l) in sera of the patients
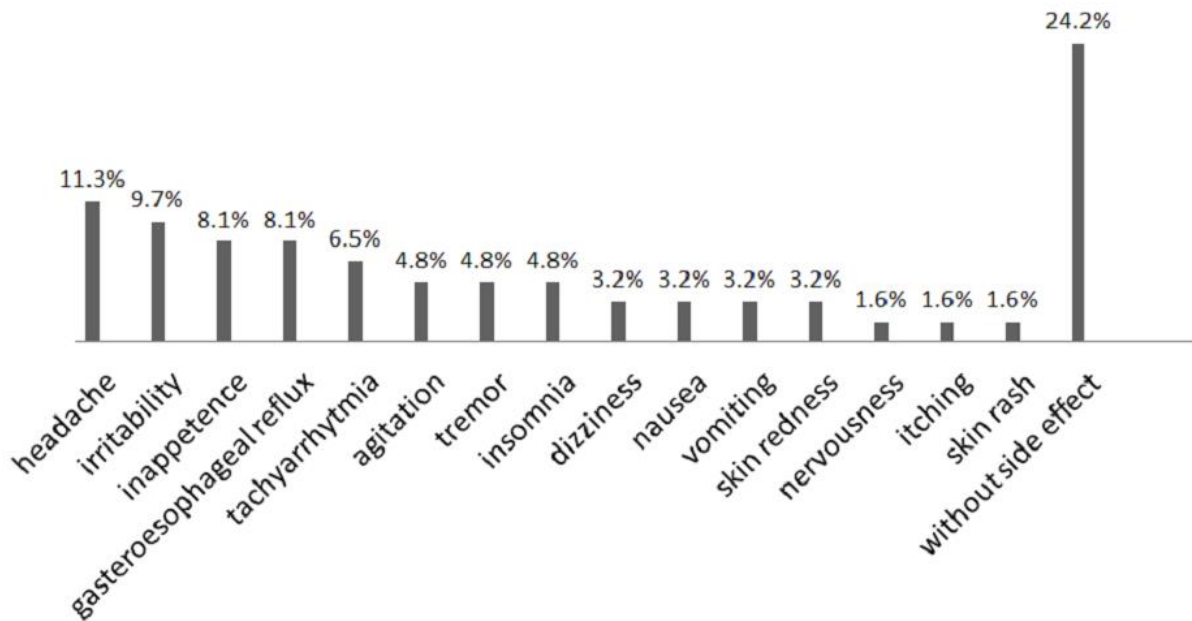
Figure 2- Abundance of side effects in patients treated with theophylline

DISCUSSIONS AND CONCLUSIONS

The limitations and side effects of theophylline are due to its narrow therapeutic index [12]. The beneficial impact assessment of theophylline, at lower levels than this range, led to the safer and more effective application of theophylline. The reason for assessment of side effects in our patients was increasing safety and ensuring treatment. We understood that with adding low doses of theophyllinetheophylline to the treatment regime of patients with asthma who were symptomatic despite treatment with inhaled corticosteroids, patients have improvement in symptoms and PEF. In addition, no serious side effects were reported in this period. Some research assessing the similar cases are as the following:

In Japan, Kenji Baba et. al., studied 17 patients with a treatment combining of inhaled beclomethasone and theophylline after stopping the theophylline. Daily symptoms, peak flow, spirometry tests, peripheral blood eosinophil levels between 1-3 weeks for three months after the discontinuation of theophylline were evaluated. 12 patients experienced asthma exacerbation, but 5 other patients did not show any symptoms. Experience in FEV_1 in patients with asthma exacerbation and CV% gradually reduced until the asthma exacerbation and the extent of the decline in the first week is much more compared to the third week. The V_{25} / HT decreased in both groups, but the rate of decline was higher in exacerbation group. The peripheral blood eosinophil's did not change during testing. The rapid decline in FEV_1 and CV% after discontinuation shows that the bronchodilator effect of theophylline on smooth muscles is more than its anti-inflammation effect. The results of this study suggest that theophylline has as much importance on the peripheral airways as it has on the central airways. Blood concentration of theophylline in the blood of these patients was 5 – 10.5 mg / ml [13]. In our study, patients PEF in the evening increased from 193 / 75% to 677 / 80% and the average serum level of drug was 4.69 mg / mL .

In 2005, Yan Wang et al compared the effects of inhaled corticosteroids combined with slow-released theophylline and doubled dose of inhaled corticosteroid in asthma treatment on 41 patients. Patients were in two groups. The first group consumed 500 μg Beclomethasone propionate, twice a day and the second group used 250 μg beclomethasone propionate twice a day besides 0.2g slow-released theophylline for 6 weeks. At the beginning and the end of the period, the patient's lung function were tested and sputum samples were tested to be checked for the number of cells and the IL-5 and assessing the cortisol levels in plasma. At the end of the study, FEV_1 and PEF significantly increased in both groups (P<0.05) and the amount of β-agonists, and

the symptoms also significantly (P<0.01) decreased. The amount of eosinophil in sputum and IL-5 (P<0.05) decreased. Between the two groups in terms of the reduction in these parameters and also cortisol levels, there was no significant difference. The study suggests that the use of theophylline with Beclomethasone dose can be considered for the treatment of asthma, rather than doubling the dose of Beclomathasone [14]. In our study, similar results were obtained with the addition of theophylline to the treatment regime.

Another study to evaluate the effectiveness of inhaled corticosteroid use in combination with a low-dose theophylline as a treatment for moderate asthma was conducted by Zhonghua yi xue za zhi et al., on 280 patients with asthma in 2011. Patients in the control group used 400 µg of inhaled budesonide daily and theophylline tablets (0.1g three times a day) and control with use of 300 µg inhaled budesonide plus Formoterol were studied. The study period was 6 months and at the end of the period, FEV_1 %, IL-4, IL-5 and IgE levels in the patients were measured and compared to levels before the study period. In each group, there was improvement in the factors measured and in the conditions of the patients observed, but no meaningful difference was observed between the two groups (P≥0.05) [15]. The findings of this study correspond to those of our study.

A study to compare adding theophylline to the treatment regime of inhaled corticosteroid and doubling dose of inhaled corticosteroids took place by Ukena et. al. in Germany on 133 patients with asthma. The study lasted for six weeks on 69 patients treated with a daily dose of 400 µg Beclomethasone bupropion and theophylline and 94 patients which were treated with a daily dose of 800 µg Beclomethasone bupropion. Serum theophylline levels measured in these patients is 10.1± 4.2 mg/.L. The lung function of the patients was measured by PEF and FEV_1 which both significantly increased and change of PEF reached less than 30%. This study also suggests theophylline besides inhaled corticosteroids as a proper treatment of moderate asthma [16]. Moreover, Spears et. al., studied the effect of adding a low-dose theophylline to the inhaling Beclomethasone treatment regime of asthma patients with a history of smoking. In this study, 68 patients were divided into three groups with three treatment regimes; 1- with a daily dose of inhaling Beclomethasone of 200 µg, 2- theophylline with a daily dose of 400 mg, and 3- taking both medicines together in 4 weeks. The results were obtained through pulmonary function tests and asthma control questionnaire (ACQ).. Prevalence of headache in all 3 groups was the same but gastrointestinal complications in theophylline consumers were more than others. The results of this study shows that using theophylline with low dose beside inhaled corticosteroid will have a better effect in improving pulmonary function in smoking asthma patients compared to using only inhaled corticosteroid which is in accordance with the results of current study [17].

Sohei Makino et al. had also published the results of a prospective study about evaluating of theophylline in Asthma and COPD. This study was performed on 3921 asthma patients in 66 institute all over Japan for 1 month. No serious effects was observed in patients while 54 patients reported unserious complication that have been at the beginning of the study and at the same time with Macrolide antibiotics use [18].

In the study of Melamedd, theophylline toxicity in ambulatory asthmatic adults under long-term treatment with theophylline was investigated to determine predictive value and incidence of adverse effects of theophylline.. 46 among 483 studied cases, serum concentrations were more than 20 mg/L [19]. None of symptoms were sensitive predictor for increasing level of theophylline. In Meamedd study there was no relation between serum concentration of theophylline and side effects.

In conclusion, low dose of theophylline is effective in improving symptoms and PEF of asthma patients who are still marked despite treatment with inhaled corticosteroids. However, theophylline serum concentration has revealed that there is no specific relation among any of side effects and the symptoms improvement or PEF. Therefore, appropriate monitoring of theophylline concentration is recommended for treatment.

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