ORIGINAL ARTICLE

Study on Effectiveness of Low Dose Theophylline as Add-on to Inhaled Corticosteroid for Patients with Sulfur Mustard Induced Bronchiolitis

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Abstract

Background: Theophylline may reverse steroid resistance and decrease inflammation in patients with chronic pulmonary disease and sulfur mustard (SM) induced bronchiolitis. This study was designed to assess the effects of low-dose theophylline on improvement of pulmonary function tests (PFTs) of SM exposed patients.
Methods: In this comparative observational study, a group of SM-exposed victims during the Iraq-Iran war who were treated with oral slow releasing (SR) theophylline, salmetrol, fluxitide, omeprazole and NAC (study group) were compared to a group of age and gender matched SM-exposed patients who received same medications except oral SR theophylline (historical control group). PFTs were measured at the beginning of the study and after 8 weeks of the treatment.
Results: In total, 33 subjects in the study group and 27 subjects in the control group were studied. Mean (SD) age of all subjects was 51 (14.1) years. In the study group, on the 8th week post-treatment, PFTs decreased, though the differences of tests between before and after treatment were not significant. In the control group, all the tests decreased in the same period and these reductions were not also significant. However, the changes in PFTs were significantly different between the two groups. The results of most PFTs in the controls decreased in greater extents compared to theophylline treated patients. This shows that despite theophylline was unable to improve the patients; it was partially able to decelerate the reductions in PFTs.
Conclusion: Theophylline may not improve PFTs of SM exposed patients but it may decelerate the progress of the underlying respiratory disease. Further studies in this setting with higher doses of theophylline and longer term of evaluation are needed to better understand the pathophysiological mechanism of SM induced bronchiolitis and the effectiveness of the treatment with theophylline.

Keywords: Bronchiolitis; Mustard Gas; Spirometry; Steroids; Theophylline

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INTRODUCTION

Sulfur mustard (SM) is a bifunctional alkylating substance that was firstly used in the First World War and more recently during Iraq-Iran war as a potent chemical warfare agent (1). Even decades after exposure, exposed victims are suffering from airway hyper-reactivity, chronic bronchitis, bronchiectasis and bronchiolitis (1-4). At present, more than 40,000 Iranian victims are suffering from devastating chronic health impairments (1-3). These people have been treated and followed up for long periods of time, while overall healthcare costs have been raised (5).

The precise pathological mechanism of SM has still remained unclear. There are many findings showing that chemical induced bronchiolitis obliterans (BO) can be mentioned as the main pathology of lung injury. This can be due to a high level of oxidative stress, elastolysis and probable involvement of matrix metalloproteinases which may produce irreversible airway obstruction (6,7). Different treatments such as bronchodilators, corticosteroids, immunosuppressive, antibiotics, mucolytics, long-term oxygen therapy and physiotherapy have been used in this setting (4). Long-term administration of conventional medications such as corticosteroids has been shown discouraging (8). Thus, it is reasonable to look for a more effective combination of drugs and treatment protocols to achieve better outcomes.

The pathophysiologic basis of the disease is complex. Histone acetyltransferases (HAT) and histone deacetylase (HDAT) are the main enzymes responsible for regulating inflammatory gene expression. Targeted acetylation of histone tails is a dynamic process which occurs on actively transcribed chromatin (9). It plays an important role in allowing regulatory proteins to access DNA and is a major factor in the regulation of gene transcription (10). Although it is known that glucocorticosteroids can suppress inflammation by activating some anti-inflammatory genes, but principally they do this by repression of inflammatory genes and glucocorticosteroid

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receptor (GR) (7,11). The mechanism of GR repression of histone acetylation is direct inhibition of HAT activity and active recruitment of a histone deacetylase complex (HDAC) (12). In Chronic obstructive pulmonary disease (COPD) that is a corticosteroid insensitive disease; there is a reduction in HDAC activity and HDAC2 expression which may account for the amplified inflammation and resistance to the effects of corticosteroids (13).

High-dose theophylline has been classified as a bronchodilator, though there is increasing evidence that its low concentration may have immunomodulatory and anti-inflammatory effects (14,15). Theophylline can restore reduction of HDAC activity induced by oxidative stress. In addition, it may be able to reverse steroid resistance in COPD and other inflammatory lung diseases (13). The aim of this study was to assess the effects of low-dose theophylline added to an inhaled corticosteroid; long acting beta 2-agonists; azithromycin; omeprazole and N-acetyl cysteine (NAC) on improvement of pulmonary function tests (PFTs) of SM exposed patients.

METHODS

Study design and patients

In this comparative observational study SM exposed victims during the Iraq-Iran war were included. The documentation of SM exposure was based on the official certification issued by the Iranian Veterans (Janbazan) Foundation in Tehran.

Inclusion criteria were (a) documented exposure to SM and documented diagnosis of COPD due to exposure to mustard gas including histological evidence from previous biopsies, (b) impaired spirometric findings including less than 12% response to bronchodilators and (c) air-trapping in high resolution computed tomography (HRCT).

Exclusion criteria were (a) pneumonia and/or acute bronchitis, (b) smoking cigarettes or being a opioid abuser, (c) being under the treatment of other kinds of medications such as metformin for diabetes which could not be discontinued, (d) history of tuberculosis or lung resection, (e) history of serious adverse drug reaction to theophylline or other xanthine derivatives and (f) deterioration of clinical conditions during the course of the study.

This study received the approval of Ethical Committee of the Baqiyatallah University of Medical Sciences. Patients or their legal entourage gave informed written consent prior to the start of the study. Patients were free to quit at each phase of the study.

Treatment

Theophylline has been recommended as a standard anti-inflammatory treatment for COPD (16). In this study, a group of patients who were treated with oral slow releasing (SR) theophylline (250 mg twice a day), salmetrol(2 puffs twice a day), fluxitide (2 puffs twice a day), omeprazole (20 mg twice a day) and NAC (600 mg twice a day) were followed during 8 week therapy (study group). Their findings were compared to a group of age, gender and body mass matched patients who received same medications except oral SR theophylline for the same period of time (historical control group).

Assessments

All patients were visited by a general practitioner before and after the study and the respiratory manifestations of each patient including dyspnea, wake-up dyspnea, dry or productive cough, and hemoptysis were assessed.

Laboratory tests including hematology, blood chemistry and urinalysis were performed at the beginning and after the completion of treatment. Before the treatment is given, HRCT and pulmonary function tests (PFT) including peak expiratory flow (PEF), forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), forced expiratory flow 25% (FEF-25) and forced expiratory flow 75% (FEF-75) were performed on the participants. Chest HRCT scans were done with high-speed advantage scanner (General Electric Medical System, Milwaukee, Wisconsin, USA). Subsequently, all chest HRCT scans and other tests were reviewed by a radiologist and an expert pulmonologist in chronic bronchitis. The presence of air trapping was quantified and was considered to ascertain the BO only if it exceeded 25% of the cross-sectional areas of an affected lung, in at least one scanned level (17).

Statistical analysis

The changes of PFTs in both groups were compared by applying repeated measure ANOVA (General Linear Model) after 8 weeks. Within group comparisons of the values at each time point with baseline were also performed using t-test for the least squares mean of change. Analysis was performed by application of the SPSS software (SPSS Inc., Chicago, IL, USA). P-value of less than 0.05 was considered as statistically significant.

RESULTS

Sixty-eight patients were enrolled in this study. Five patients were excluded due to smoking cigarettes, acute bronchitis and history of adverse reaction to theophylline,

Table 1. Comparison of pulmonary function tests before and after treatment in study group

Test/Parameters	Pretreatment	Post-treatment	P value*
FVC	63.6 (20.6)	60.2 (19.6)	0.21
FEV1	67.2 (24.8)	63.6 (22.2)	0.29
FEV1/FVC Predicted	109.4 (14.6)	109.9 (14.6)	0.53
FEF-25	61.3 (34.5)	60.1 (31.4)	0.98
FEF-75	82.4 (41.4)	77.9 (35.9)	0.47
PEF	66.5 (29.7)	64.0 (26.6)	0.71

*Paired sample t-test was used.

erythromycin and cimetidine. Three patients refused to continue the follow-up. In total, 33 subjects in study group and 27 subjects in the control group were studied. Mean (SD) age of all subjects was 51 (14.1) years.

In the study group, on the 8th week post-treatment, PEF and most spirometric parameters decreased. However, the differences of these parameters between before and after treatment were not significant (Table 1). In the control group, all the tests decreased in the same period and these reductions were not also significant (Table 2).

Although the study group did not differ significantly from the control group regarding age, body mass index and gender characteristics, the changes in FEV1, FVC, FEF-25, FEF-75 and PEF were significantly different between the two groups (Table 3). In this regard, the results of FEV1 and FEF-75 were significantly less attenuated in the study group compared to the control group (P = 0.001, 0.004 respectively). In addition, the results of FEF-25 in study group improved while in the control group declined which the difference between them was significant (P = 0.002). However, the results of FVC and PEF were more significantly decreased in the study group compared to the controls (P < 0.001, = 0.003 respectively).

Although, the changes in ratio of FEV1/FVC-predicted were not significantly different between the groups, this ratio was reduced in the controls while it was improved in study group.

DISCUSSION

In this study, low dose theophylline as add-on to inhaled β2-agonist, NAC, azithromycin and omeprazole showed no improvement in PFTs of patients with SM induced bronchiolitis. The results of PFTs in both cases and controls decreased during 8 weeks. However, the results of most PFTs (FEV1, FEF-25, FEF-75 and FEV1/FVC) in the control patients who did not receive theophylline decreased in greater extents compared to theophylline treated patients. This shows that despite theophylline was unable to improve the patients; it was partially able to decelerate the reductions in PFTs.

Markham et al. reported that low-dose theophylline can decrease the need for inhaled corticosteroid therapy in patients with asthma by reducing eosinophil accumulation in bronchial tissue in patients with asthma (15). However, we did not evaluate corticosteroid dosage during this short period of study. Previous studies have shown that theophylline can be effective in the treatment and control of respiratory manifestations of patients with COPD by restoring decreased HDAC activity. In addition, it may be able to reverse steroid resistance in COPD and other

Table 2. Comparison of pulmonary function tests before and after treatment in the control group

Spirometric parameters	Pretreatment	Post-treatment	P value*
FVC	78.7 (18.5)	76.8 (18.2)	0.42
FEV1	88.0 (22.0)	84.3 (19.6)	0.16
FEV1/FVC Predicted	115.7 (8.4)	114.5 (9.0)	0.29
FEF-25	84.4 (28.2)	84.3 (28.2)	0.73
FEF-75	113.8 (51.1)	106.1 (42.3)	0.22
PEF	84.6 (22.2)	84.1 (23.9)	0.70

*Paired sample t-test was used.

Table 3. Comparison of demographic features and changes in pulmonary function tests between study and control groups

Parameters	Study group	Control group	P value
Age	52.0 (13.0)	49.9 (15.2)	0.57*
Body mass index	26.3 (4.1)	27.7 (4.4)	0. 23*
Female/male	14/19	13/14	0.42*
FVC; change	-2.8 (12.5)	-2.2 (14.1)	0.001**
FEV1; change	-2.6 (14.0)	-4.3 (15.4)	<0.001**
FEV1/FVC predicted; change	0.8 (7.3)	-1.5 (7.5)	0.06**
FEF-25; change	0.06 (15.5)	-1.2 (17.8)	0.002**
FEF-75; change	-3.0 (23.8)	-9.5 (39.4)	0.004**
PEF; change	-1.2 (18.8)	-1.1 (15.5)	0.003**

* Chi-Square test was used.
** Repeated measure ANOVA test was used.

inflammatory lung diseases. Thus, its combination therapy with an inhaled corticosteroid may reverse airway inflammation in patients with COPD and asthma (14-20). Correspondingly, Li et al. reported small dose of oral theophylline combined with low dose of inhaled glucocorticoids (beclomethasone dipropionate) might have the same effect as relatively higher dose of inhaled glucocorticoids on relief of clinical symptoms and bronchial responsiveness, without suppression on hypothalamic-pituitary-adrenal axis function (21). In addition, Wang et al. described both inhaled corticosteroids combined with SR theophylline and double-dose inhaled corticosteroids have the similar effects on asthma (22). Iioboshi et al. reported that 6 months of theophylline treatment seems to reduce airway inflammation in stable COPD patients (23). They showed that FEV1 increased, and neutrophil counts, tissue necrotizing factor-alpha and interleukin 8 levels in sputum reduced (23). Hansel et al. noted lower doses of theophylline is easier to use, side effects are uncommon and the problems of drug interaction are less; making the clinical use of theophylline less complicated. In addition, it may increase responsiveness to corticosteroids by reversal of the steroid resistance induced by oxidative stress and may even have a role in preventing progression of chronic airway diseases (24). Another study indicated that adding theophylline to usual treatment with inhaled bronchodilators provides additional benefits in stable COPD patients by reducing dynamic pulmonary hyperinflation, improving exercise tolerance; dyspnea and quality of life (25).

Some studies have shown an apparent role of inflammation on inducing COPD. Although inflammation of respiratory tissue can be induced from acute exposure to SM, it will not remain as the main finding throughout the disease course, as in later stages pleural thickening, BO and emphysema may develop (26). This may explain the reason that short term theophylline treatment was not able to improve respiratory findings in SM exposed patients.

Destructing and remodeling of small airways due to SM exposure in the chemical bronchitis seems to be a target for new therapeutic approaches. Theophylline may be helpful in remodeling small airways and/or enhancement of effectiveness of glucocorticoids and/or NAC and/or inhaled bronchodilator (24). Administration of theophylline can inhibit histone acetylation, activate GR and recruit HDAC2 and thus can increase efficacy of corticosteroids and also has a role to control inflammatory gene expression (24,27). On the other hand, it can inhibit lower esophageal sphincter pressure and cause gastroesophageal reflux (GER) in normal population (28). Also, in one study, it was shown that accession of GER in SM exposed victims is higher than normal adults (29). In addition, theophylline can increase gastric acid secretion (30).

In this study we noticed decrease of mean alterations of FEV1, FVC, and even FEV1/FVC in the group of patients receiving theophylline. This can be due to BO along with other pulmonary disorders that can be resulted from esophagitis in SM exposed patients (28). A previous study showed that repetitive microaspiration caused by GER may contribute to the exacerbation of various respiratory diseases, particularly development of BO syndrome. Hence, it seems that esophagitis plays a role in exacerbation of FEV1 in human cases (31). Nevertheless, we should consider that in the present study, all patients received a proton pomp inhibitor (omeprazole) during their treatment, though it seems that it has no inhibitory effect on GER and related outcomes especially in theophylline treated group.

LIMITATIONS

There may be several factors for elucidations in this study. The severity of the disease was not determined. Furthermore, data of the controls were retrospectively collected that can affect the accuracy of the data. Moreover, for a disease with an inflammatory background, more time is needed for a treatment to be effective. Therefore, the short period of evaluation can be another confounding factor. In addition, we only studied low dose theophylline and the potential effectiveness of higher doses of theophylline cannot be ruled out.

CONCLUSION

Theophylline may not improve PFTs of SM exposed patients but it may decelerate the progress of the underlying respiratory disease. GER as a side effect of theophylline may decrease the therapeutic effects of the drug. Further studies in this setting with higher doses of theophylline and longer term of evaluation are needed to better understand the pathophysiological mechanism of SM induced bronchiolitis and the effectiveness of the treatment.

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