Efficacy and safety of oral low dose Theophylline in Jordanian patients with stable Chronic Obstructive Pulmonary Disease treated at King Hussein Medical Center

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ABSTRACT

Objective: To assess the efficacy of adding Slow-Release Theophylline to the regular treatment of Chronic Obstructive Pulmonary Disease (COPD) patients. The safety of Theophylline was also assessed as a secondary endpoint.

Methods: Prospective observational study of one hundred and nine patients, with moderate to very severe COPD, and treated in the pulmonology clinic at King Hussein Medical Center, between August 2014 and March 2015. Exclusion criteria included: acute exacerbation of COPD within the last 3 months; use of oral corticosteroids within the last 4 weeks; upper or lower respiratory tract infection within the last 4 weeks; recent unstable angina or arrhythmias; epilepsy; concurrent use of medications that might interact with Theophylline and excessive alcohol consumption. After enrolment, Forced Expiratory Volume in the first second (FEV1) and Forced Vital Capacity (FVC), oxygenation at rest using 2 different pulse oximeters and level of disability assessed by the Medical Research Council dyspnoea scale were evaluated. A fixed dose of oral Theophylline was added to their regular treatment, as Theophylline (Quibron-T SR) 300 mg slow-release capsules once daily. The patients were followed up after 4 weeks, when the measurements were repeated. The patients were also evaluated for any side effects related to Theophylline. The pre and post-Theophylline data were compared. The safety profile of Theophylline was assessed by recording side effects related to the drug, any serious side effects, or Theophylline withdrawal.

Results: Out of the 109 patients in our study, 96(88%) were males, and 13(12%) were females. Their mean(±SD) age was 69.0±7.8 years(range 46-83 years). After 4 weeks of added Theophylline, there was a statistically significant improvement in FEV1 from 53.3±10.4 to 56.4±10.1 (% predicted mean±SD) ($p= 0.03$) and FVC from 70.4±10.0 to 73.1±9.8% ($p= 0.05$). 61% of the patients showed improvement in dyspnoea, with a significant improvement in the MRC score from 3.8±0.8 to 3.2±0.8 ($p<0.0001$). The patients also showed an increase in saturation from 93.6%±2.3 to 93.8%±2.0, though this was not statistically significant ($p= 0.490$). 5 patients (5%) had side effects related to Theophylline,though none were serious. The most common side effect was nausea (60%). None of the patients who developed side effects stopped using Theophylline during the study.

Conclusion: Theophylline produced a significant increase in the lung function of patients with moderate, severe and very severe COPD and significantly improved their disability caused by dyspnoea, without any serious side effects. Use of Theophylline in stable COPD patients should be weighed however against the risk of possible non-serious side effects, mainly nausea.

Keywords: Chronic Obstructive Pulmonary Disease, Efficacy,Theophylline.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a disease caused by a chronic inflammatory response of the airways to different noxious particles or gases, leading to persistent, progressive airflow limitation.[1] It is ranked as the sixth leading cause of death worldwide, and is expected to become the fourth leading cause of death in 2030.[2]

The role of Theophylline in the management of COPD remains controversial. The British Thoracic Society (BTS) guidelines regarding COPD management recommend the use of Xanthine derivatives as a last resort, because of modest bronchodilator effects and narrow therapeutic index.[3]According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, Theophylline is recommended as a third line option.[1]

However, despite the current guidelines, interest in the use of Theophylline in patients with COPD is coming back.[4] Many clinical trials have actually shown that Theophylline is useful in the management of stable COPD patients.[5,6] Other studies showed that Theophylline withdrawal causes worsening of the clinical condition in patients with COPD.[7] An important effect of Theophylline in COPD patients, is its ability to restore Histone Deacetylase (HDAC2) activity,[8,9] which is usually defective in these patients, thus reversing steroid resistance in alveolar macrophages, which will cause an enhancement in the anti-inflammatory action of Inhaled Corticosteroids (ICS) in patients with COPD.

In our study, the primary endpoint was to investigate the efficacy of adding Slow-Release Theophylline to the regular treatment of patients with moderate, severe and very severe COPD, treated in King Hussein Medical Center (KHMC). We assessed the effect of low dose Theophylline on lung function and oxygenation after 4 weeks of adding it to regular treatment, as well as its effect on disability caused by COPD. Side effects related to Theophylline were also monitored to assess its safety, as a secondary endpoint.

Methods

In this prospective observational study, 109 patients with stable, moderate, severe and very severe COPD, classified according to the GOLD guidelines regarding the degree of their airflow limitation,[1]who were treated in KHMC, were enrolled between August 2014 and March 2015. Approval of the ethical committee was obtained in order to carry out the study. None of the patients who were included had ever received Theophylline previously.Inclusion criteria were the following: age >45 years, current or former smokers, post bronchodilator FEV_1 / FVC <70%, moderate to very severe COPD and a diagnosis of COPD for >2 years. Exclusion criteria were as follows: history of acute exacerbation of COPD within the last 3 months;history of use of oral corticosteroids due to an unstable respiratory condition within the last 4 weeks; history of upper or lower respiratory tract infection within the last 4 weeks; recent unstable angina or arrhythmias; epilepsy; concurrent use of medications that might interact with Theophylline metabolism and excessive alcohol consumption.

During their initial visit before being enrolled in the study, the patients were informed about the aim of the study, and a written consent was obtained from all of them.

After being enrolled in the study, evaluation of the pulmonary function by spirometry was done for all the patients in their first visit. FEV_1 and FVC, as percentage of predicted, were measured and recorded. A qualified respiratory nurse was in charge of performing spirometry.At least three "acceptable" spirograms were done for each patient, after which "repeatability" criteria were applied.[10] The largest FEV_1 and FVC were reported after examining all of the acceptable curves. Also, oxygenation of the patients at rest was evaluated by recording oxygen saturation levels at room air, using 2 different pulse oximeters.Despite our knowledge that oxygenation status is more accurately assessed by Arterial Blood Gases (ABG's) results, because most of the patients refused

blood gas analysis, as it was perceived as invasive, made us settle for the oxygen saturation readings obtained through the pulse oximeter.

The enrolled patients were asked also to assess their level of disability using the Medical Research Council (MRC) dyspnoea scale,[11]as shown in TableI. Patients assessed their disability on a scale from 1 to 5, with"1" meaning that the patient is breathless only on strenuous exercise, and "5" meaning that the patient is too breathless to leave the house or breathless when dressing.

After assessing all the above mentioned parameters, the enrolled patients had a fixed low dose of Theophylline added to their regular treatment regimen, in the form of Slow-Release Theophylline (Quibron-T SR) 300 mg slow-release capsules once daily.

The patients were followed up 4 weeks after their initial visit in the clinic. During the follow-up visit, lung function was assessed by spirometry, and oxygen saturation recorded, and level of disability was reassessed using the MRC dyspnoea scale. The patients were also evaluated for any side effects related to Theophyllinethrough non-specific questioning, or spontaneous report. Adverse effects were classified as "non-serious" and "serious" side effects. Non-serious side effects included headache, nausea and vomiting, abdominal discomfort, restlessness, gastroesophageal reflux, and diuresis. Serious side effects referred to convulsions, cardiac arrhythmias, and death.

By the end of the 4 weeks period of the study, the pre and post-Theophylline data were compared, including FEV_1, FVC, Oxygen saturation and disability level, and statistical significance was calculated for each. The safety profile of Theophylline was assessed by calculating the number of patients who developed any side effects, whether or not any serious side effects took place or if any patients withdrew from the drug because of side effects.

Student's paired t-test was used for the statistical analysis. Continuous variables were expressed as mean±standard deviation; categorical variables were expressed as percentages. Level of statistical significance was defined as $p<0.05$.

Results

Patients diagnosed with COPD, in whom Theophylline was added to their regular treatment, were enrolled in this study. Of the 109 patients enrolled in our study, 96 patients (88%) were males and 13 patients (12%) were females. Their ages ranged between 46-82 years, with a mean age (±SD) of 69.0 years (±7.8).

After 4 weeks of adding oral Theophylline to their treatment regimens, patients showed a statistically significant improvement in their FEV_1, FVC and MRC score. There was also a slight increase in the Oxygen saturation, which did not reach statistical significance as shown in Table II.

Overall,67patients (61%) showed an improvement in disability, as assessed by the MRC score.A comparison between the characteristics of patients who showed an improvement in MRC score, and those who did not, is shown in Table III.

5 patients (5%) had side effects related to Theophylline. However, none of the patients had serious side effects.The most encountered side effect was nausea (60%), as shown in Fig.1. None of the patients who developed side effects stopped using Theophylline during the study.

Table I: Medical Research Council (MRC) dyspnea scale

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on the level or walking up a slight hill
3	Walks slower than most people of the same age on the level, or stops for breath while walking at own pace on the level
4	Stops for breath after walking about 100 Yards or after a few minutes on level ground
5	Too breathless to leave the house or breathless when dressing or undressing

Table II: Comparison between different variables before and after Theophylline

Variable	Pre-Theophylline	Post-Theophylline	*P*-value
FEV1(% predicted), mean±SD	53.3±10.4	56.4±10.1	0.0266
FVC(% predicted), mean±SD	70.4±10.0	73.1±9.8	0.0453
Oxygen saturation(%), mean±SD	93.6±2.3	93.8±2.0	0.490
MRC score, mean±SD	3.8±0.8	3.2±0.8	<0.0001

Table III: Comparison between different characteristics in patients who showed improvement in their disability and those who did not.

Variable	Patients who showed improvement in MRC score (n=67)	Patients who didn't show improvement in MRC score (n=42)
Age (years), mean±SD	67.7±8.0	71.1±7.0
Pre-Theophylline FEV1(% predicted), mean±SD	53.5±8.7	53.0±12.8
Pre-Theophylline FVC(% predicted), mean±SD	71.3±7.4	69.0±13.2
Pre-Theophylline Oxygen saturation(%), mean±SD	93.5±2.0	93.7±2.8
Post-Theophylline FEV1(% predicted), mean±SD	56.8±8.5	55.7±12.4
Post-Theophylline FVC(% predicted), mean±SD	74.1±7.7	71.5±12.9
Post-Theophylline Oxygen saturation(%), mean±SD	93.7±1.7	93.9±2.4

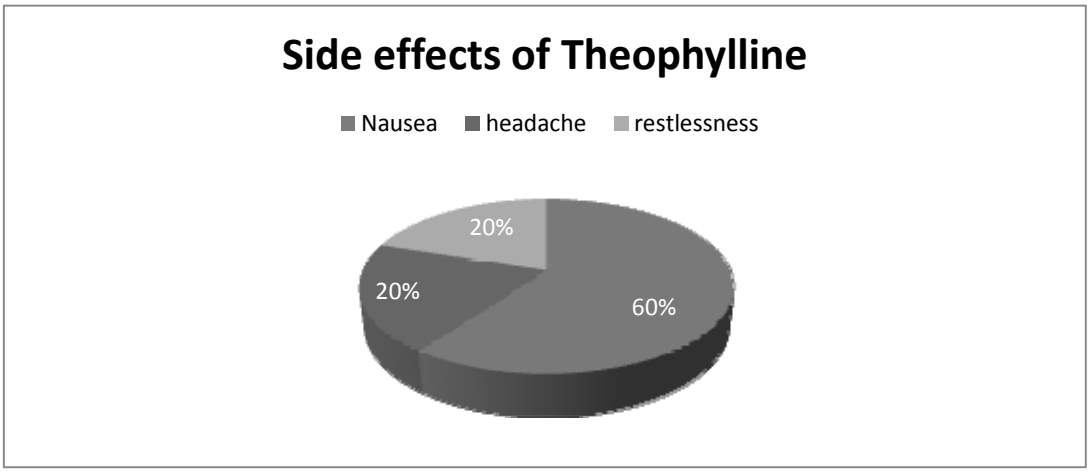

Fig. 1. Number and percentage of patients who developed different side effects related to Theophylline.

Discussion

Our study showed that after 4 weeks of oral Theophylline, in the form of Slow-Release Theophylline (Quibron-T SR) 300 mg once daily, added to regular treatment of patients with moderate to very severe COPD, there was a significant improvement in the pulmonary function. Both mean FEV1 and mean FVC showed a statistically significant increase (*p* values 0.0266 and 0.0453 respectively).

FEV_1, which is expressed in some studies in Litres and in other studies as percent of predicted, is the most common lung function variable assessed in clinical trials.[12] Many studies have shown that Theophylline causes a significant increase in the FEV_1 of COPD patients.[13-16] Giesselet *al*,[17] have actually shown in that Theophylline, in combination

with Salmeterol, causes greater improvement in FEV1 than either alone. However, some other studies have shown that Theophylline does not produce a significant increase in the FEV_1 in COPD patients.[18]

We also assessed the effect of Theophylline on the oxygenation of the patients with COPD. Oxygen saturation, as measured by pulse oximetry, before and after Theophylline addition, showed an increase after 4 weeks.Although, it did not reach statistical significance(*p* value 0.490).However, measuring the Oxygen saturation by a pulse oximeter is not the best way to assess changes in oxygenation, as it is insensitive to minor changes in arterial Oxygen partial pressure (PaO2). Better assessment of oxygenation, by measuring the Arterial Blood Gases (ABG's), is needed to interpret the effects of Theophylline on oxygenation of COPD patients more accurately.

Another variable that has been assessed in our study was the change in disability related to dyspnea after introduction of Theophylline. In our study, we adopted the MRC dyspnea scale as a method to evaluate the change in dyspnea. There was a significant improvement in the mean dyspnea score after 4 weeks of adding Theophylline (p value <0.0001). 61% of the patients enrolled in our study showed an improvement of their dyspnea score, while the remaining 39% did not notice any change. Patients who showed a significant change in their MRC score were younger than those who showed no significant response (67.7±8.0 Vs 71.1±7.0years±SD in non-responders).

Many other studies have also shown the significant effects that Theophylline addition has on improving the symptoms of patients with COPD.[16, 19, 20] including dyspnea and cough.

It is essential to emphasize, that even in some studies that did not show a significant improvement in the lung function after addition of Theophylline, significant improvement in the symptoms was observed.[21-23]There have been many proposed mechanisms to explain how Theophylline can improve the symptoms. Chrystyn*et al*,[24]studied the effect of oral Theophylline on patients with COPD. In their study, therapeutic levels of Theophylline led to a small increase in FEV_1 (13%), but a significant decrease in the trapped gas volume (64%).

A fall in trapped gas volume, which will lead to a similar fall in the functional residual capacity, is likely to have a beneficial effect on the mechanics of the diaphragm and chest wall muscles. An increase in diaphragmatic strength, [25] and an increase in the respiratory drive independent of the effect on lung function,[26]have been also shown to be important mechanisms through which Theophylline improves dyspnea in COPD patients.

In our study, we evaluated the safety of Theophylline use in COPD patients. We assessed the occurrence of any side effects caused by Theophyllineafter the 4 weeks, and whether or not any serious side effects took place. In our study, 5 patients out of the 109 patients enrolled in the study, (5%) developed side effects related to Theophylline administration. The most common side effect was nausea (60%), followed by headache (20%) and restlessness (20%). None of the patients developed any serious side effects. The low dose of theophylline used is a likely reason why there were no serious side effects. We used 300 mg compared to the standard dose of 400 mg/day, or more, for use as a controller.[27] None of the patients who developed the side effects, related to Theophyllineuse,stopped taking Theophylline during our study.

As the primary endpoint of this study was to assess the efficacy of Theophylline in COPD patients, safety of Theophylline was not surveyed thoroughly. We rather concentrated on the occurrence of serious side effects related to Theophylline, and whether or not the serious and non-serious side effects were severe enough to cause drug withdrawal by the patients.

Limitations of the study

Larger controlled studies need to be done in the future, in which two groups of patients, one receiving a placebo and the other

receiving Theophylline, are compared. These studies will improve our interpretation of the results, and provide more accurate data regarding the effects of Theophylline in COPD patients.

In assessing oxygenation of the patients enrolled in our study, we depended on the oxygen saturation measured by 2 different pulse oximeters.Better assessment of oxygenation, by measuring the PaO_2 in arterial blood sample, is needed to accurately interpret the effects of Theophylline on oxygenation of COPD patients.

Another limitation in our study is not measuring the Theophylline blood concentration levels. Future studies need to do so, in order to correlate the obtained results regarding the efficacy and safety of Theophylline, with its blood levels.

Conclusion

In our study, Theophylline was shown to cause a significant increase in the lung function of COPD patients, and to significantly improve their disability caused by dyspnea, without causing any serious side effects. Use of Theophylline in stable COPD patients should be weighed however against the risk of possible non-serious side effects, mainly nausea.

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