Addition of Salmeterol or Theophylline to an Inhaled Corticosteroid Regimen in Patients With Severe Asthma

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Abstract

Objectives: The aim of this study was to compare the efficacy of addition of salmeterol or theophylline to an inhaled steroids regimen in the treatment of severe asthma.

Design: A crossover study.

Material and Methods: Fifteen patients (5 male, 10 female) aged 18 to 51 years were included in this crossover study. All patients were suffering from severe asthma and were on inhaled steroids (800-1000 mg/daily, fluticasone propionate). They were also taking inhaled short acting β_2-agonists as required. The patients were randomised; 8 patients received inhaled salmeterol (50 µg twice daily) and 7 received once-daily sustained release theophylline (400-600 mg/daily) for four weeks. At the end of this four-week period, the treatments were stopped for a week (wash-out period) and following this period, the treatments were interchanged. Outcome measurements (improved mean baseline FEV_1, increase in PEFR from baseline, mean morning and evening PEFR, decreased rescue medication, symptom-free days and nights) were compared in the two treatment groups at the end of the study.

Results: A greater but not significant increase in forced expiratory volume (FEV_1) was observed in the salmeterol group. Rescue medication was not required on 82.7% of the days during the treatment period in salmeterol patients and on 75.5% of the days in theophylline patients. The frequency of symptom-free nights was significantly higher in the theophylline group.

Conclusions: Salmeterol was found to be superior to theophylline in improving FEV_1 while theophylline was more effective than salmeterol in controlling nocturnal symptoms in asthma patients taking inhaled steroids.

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Introduction

Asthma is the most common chronic lung disorder and affects people of all ages. Poor patient education, poor patient-physician relationship, low socio-economic status, decreased access to medical care, overuse of adrenergic inhalers and failure to control inflammation of the airways during treatment are important factors in the management of asthma (1).

Theophylline and long-acting β_2-agonists are bronchodilators used in the treatment of severe asthma (1). The addition of once-daily theophylline or inhaled long acting β_2-agonists, when needed, provides clinical benefits to patients with severe asthma taking high doses of inhaled steroids and salbutamol (1,2).

The aim of this study was to compare the clinical efficacy of salmeterol or theophylline given in addition to high doses of inhaled steroids to patients with severe asthma.

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Table 1. Pulmonary functions in asthma patients treated with salmeterol or theophylline

		Salmeterol (mean±SD)	Theophylline (Mean±SD)
Baseline FEV_1	(L)	1.70±0.56	2.02±0.77
FEV_1 after treatment periods	(L)	2.60± 1.02	2.73±1.07
Differences in FEV_1	(L)	0.90±0.85	0.72±0.65
Comparison of differences in FEV_1 in salmeterol and theophylline groups		p>0.05	
Baseline FEV_1 %	(%)	54.73±13.98	61.67±13.63
FEV_1 % after treatment periods	(%)	81.67±22.61	83.80±20.54
Differences in FEV_1 %	(%)	26.93±20.48	22.13±18.50
Comparison of differences in FEV_1 % in salmeterol and theophylline groups		p>0.05	
Baseline PEFR	(L/min)	237.1±88.5	289.8±127.1
PEFR after treatment periods	(L/min)	417.3± 166.8	458.1±167.0
Differences in PEFR	(L/min)	180.1±139.9	168.3±152.6
Comparison of differences in PEFR in salmeterol and theophylline groups		p>0.05	
Baseline PEFR%	(%)	54.87±18.25	62.67±18.75
PEFR % after treatment periods	(%)	92.93±29.13	100.53±25.55
Differences in PEFR %	(%)	38.07±23.54	37.87±28.98
Comparison of differences in PEFR% in salmeterol and theophylline groups		p>0.05	

Table 2. Outcomes in asthma patients treated with salmeterol or theophylline

		Salmeterol (mean±SD)	Theophylline (Mean±SD)
Mean of morning PEFR	(L/min)	358.3± 94.3	346.1± 115.3
Mean of evening PEFR	(L/min)	359.4± 102.2	349.9± 127.2
Diurnal variation	(%)	0.14± 4.30	0.36±6.69
Frequency of symptom-free days	(%)	65.0± 34.5	70.3± 37.3
Frequency of symptom-free nights *	(%)	72.3± 33.4	80.1± 31.0
Frequency of days rescue medication needed	(%)	17.3± 27.4	24.5± 37.8
Frequency of adverse events	(%)	14.28	21.42

*p<0.05

Materials and Methods

Five male and 10 female patients, aged 18 to 51 years, with severe asthma (baseline FEV_1, 50% to 80% of predicted; 15% reversibility to inhaled salbutamol) were included in a crossover study. Informed consent was obtained from the patients. Approbation of the local ethics committee was taken. A total of 15 patients were randomly assigned to two groups, using a table of random numbers. Eight patients received inhaled salmeterol (50 µg twice daily) and 7 received once-daily sustained release theophylline (400-600 mg/daily) for four weeks in addition to their established regimen. All patients were on inhaled steroids (800-1000 mg/daily, fluticasone propionate) and also taking inhaled short acting β_2-agonists as required for symptom control.

Pulmonary function was measured at the beginning of each treatment period. A peak flowmeter was given to each patient and the patients were trained to use the peak-flowmeter. During each treatment period; the patients were asked to keep a twice daily record of their peak expiratory flow rates (PEFR), in the mornings and evenings. They were also asked to keep a record of symptoms occurring in the daytime and at night, number of rescue medication taken and side effects. If there was no restriction of daily activities and no wheezing or shortness of breath, this was accepted as a symptom-free day. If the patient had slept well and had not woken up with wheezing or shortness of breath, this was accepted as a symptom-free night.

At the end of the four-week treatment period, pulmonary functions were measured, and theophylline or salmeterol treatment was stopped for a week. After this wash-out period of one week, patients who had previously received salmeterol were started on theophylline and salmeterol was given to 7 patients received inhaled salmeterol (50 µg twice daily) and 8 patients received once-daily sustained release theophylline (400-600 mg/daily). After four weeks, the records kept by the patients were collected. Outcome measurements (improving mean baseline FEV_1, increase in PEFR from baseline, mean morning and evening PEFR, decreasing rescue medication, symptom-free days and nights) were compared in the two treatment groups.

In the group receiving theophylline, serum theophylline concentration was measured in each patient on the fifth day of treatment and the dose of theophylline was either increased or decreased accordingly. Serum theophylline concentration was also measured on the thirtieth day in order to control the theophylline level. Wilcoxon Matched-Pairs Signed-Rank test was used in the statistical analysis by SPSS packet program.

Results

Both salmeterol and theophylline treatment were found to have a significant effect in improving FEV_1 and PEFR over the four-week period ($p<0.01$). A greater increase in FEV_1 was observed in the salmeterol group (0.90 Lt, 26.9%) as compared to the patients receiving theophylline (0.72 Lt, 22.1%) but the difference between the two groups was not statistically significant (Table 1).

The mean values for daily morning and evening PEFR, diurnal variation in PEFR, and number of symptom-free days

were also not significantly different in the two treatment groups. Mean morning and evening PEFR values were 358 L/min and 359 L/min in the salmeterol group, while these values were 346 L/min, and 349 L/min in the theophylline group ($p>0.05$) (Table2).

The mean frequency of symptom-free days in patients receiving salmeterol was 65.0% during the four-week period compared to 70.3% for theophylline patients ($p>0.05$). The frequency of symptom-free nights (80.1%), on the other hand, was found to be significantly higher in the theophylline treatment group (72.3%) ($p<0.05$) (Table 2).
Rescue medication with salbutamol was not required in 82.7% of the days in the salmeterol patients, and 75.5% for the theophylline patients (Table 2).

A similar proportion of patients in each group experienced adverse events ($p>0.05$) However, adverse events were slightly less frequent in patients receiving salmeterol (14.3% versus 21.4%) (Table 2). Mild gastrointestinal symptoms occurred during the theophylline treatment. Adverse events leading to withdrawal were not observed in either group.
Serum mean theophylline concentration was 8.61±4.09 mg/L (min:4.28 mg/L; max:20.65 mg/L) on the fifth day. Mean theophylline level at the end of 30 days of theophylline treatment was 9.97±2.70 mg/L (min: 7.38 mg/L;max: 17.83 mg/L).

Discussion

According to international guidelines, patients with persistent severe asthma should receive long term daily anti-inflammatory therapy. If inhaled corticosteroids do not eliminate symptoms, sustained-release theophylline or long-acting inhaled β_2-agonists should be added to the treatment regimen (1,2). Theophylline and long-acting inhaled β_2-agonists are bronchodilators used in the management of asthma. Salmeterol is available in a metered-dose inhaler. Theophylline has a narrow therapeutic index, requiring individual dose titration and regular monitoring of serum theophylline concentrations to avoid adverse effects. There is increasing evidence that theophylline has anti-asthma properties other than bronchodilatation and that these non bronchodilatator effects are mediated by anti-inflammatory and immunomodulatory processes (3,4).

In this study, the efficacy of inhaled salmeterol (50µg twice a day) was compared with theophylline (400-600mg, once a day) taken for four a week period.

In many studies; salmeterol was found to be more effective than theophylline (5-7). Wilson et al reported that salmeterol was superior to theophylline in improving FEV_1 (6). In contrast, in a study carried out by Nutini et al. no significant differences in increasing FEV_1 were found between salmeterol and theophylline [8]. In our study; similar findings were observed. Although the increase in FEV_1 appeared to be greater with salmeterol, the difference was not statistically significant.

The difference in mean morning and evening PEFR values was not statistically significant in the two treatment groups ($p>0.05$). Similar findings were reported in different studies (6,8).

The frequency of symptom-free days was also similar in the two treatment groups (65% in salmeterol, 70% in theophylline group). These rates were somewhat higher than the rates reported by Davies et al (5).

On the other hand, salmeterol patients experienced significantly fewer symptom-free nights (72.3%) compared to the theophylline patients (80.1%), ($p<0.05$). This finding is in agreement with the results of the study by Lönnerholm et al. which showed that the protective effect of sustained-release theophylline lasts throughout the night and also relieves the early morning symptoms (9).

Rescue medication was required on 17.3% of the days for salmeterol patients and 24.5% for theophylline patients ($p>0.05$). In similar studies; salmeterol was reported to be more effective than theophylline in reducing rescue medication (5,10).

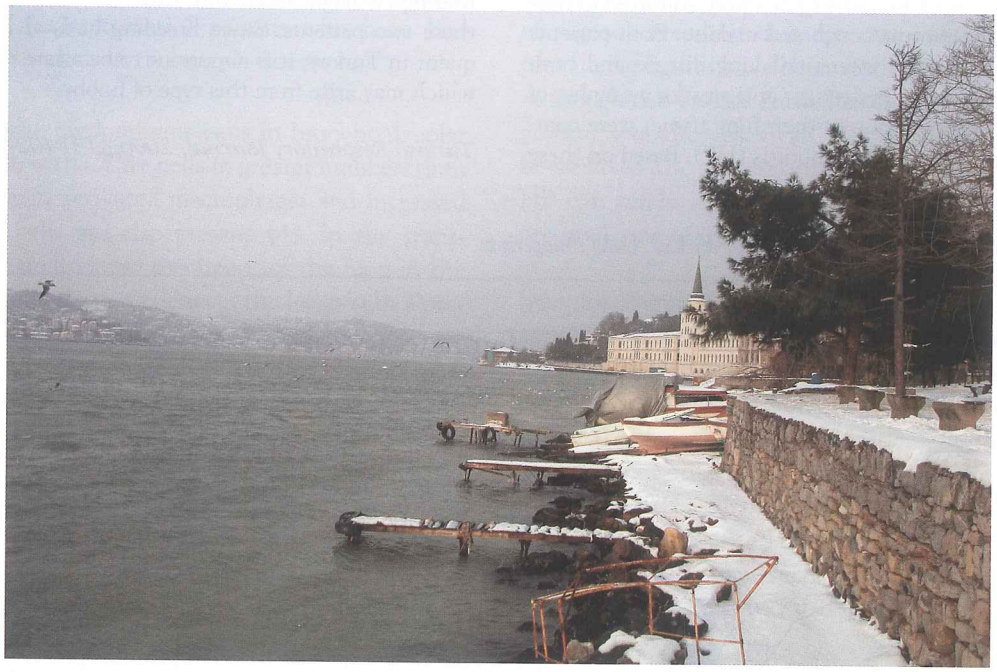
Although these can generally be avoided by appropriate dosing and monitoring, theophylline is known to have a potential for significant adverse effects (11). Adverse effects were reported in a higher proportion in theophylline treatment than salmeterol treatment in many studies (5,6,10). In our study, serum theophylline concentrations measured on the fifth day and on the thirtieth day were in the normal therapeutic range. Although adverse events were slightly less frequent in patients receiving salmeterol, the difference was not significant.

In conclusion, salmeterol and theophylline are both effective drugs in the treatment of severe asthma. Salmeterol appears to be slightly superior to theophylline in improving FEV_1 and once-daily sustained-release theophylline was found to be significantly more effective than salmeterol in controlling nocturnal symptoms in patients taking inhaled steroids.

References

1. Lawlor GJ, Tashkin DP: Asthma; in: Lawlor GJ, Fisher TJ, Adelman DC. (eds): Manual of Allergy and Immunology. Boston, Little, Brown and Company, third edition, 1995, pp 121-180.
2. Barnes PJ, Pauwels RA: Theophylline in the management of asthma. Time for reappraisal?. Eur Respir J 1994; 7(3): 579-591.
3. Kidney J, Dominguez M, Taylor PM, Rose M, Chun KF, Barnes PJ: Immunomodulation by theophylline in asthma: demonstration by withdrawal of therapy. Am J Respir Crit Care Med 1995; 151:1907-1914.
4. Jaffar ZH, Sullivan PJ, Castello JF. Effect of low dose theophylline

on lymphocyte profile in peripheral blood and bronchoalveolar lavage fluid (BAL) of asthmatic subjects. Am J Respir Crit Care Med 1994;4: 334.
5. Davies B, Brooks G, Devoy M: The efficacy and safety of salmeterol compared to theophylline: meta-analysis of nine controlled studies. Respir Med 1998; 2:256-263.
6. Wilson AJ, Gibson PG, Coughlan J. Long acting beta- agonists versus theophylline for maintenance treatment of asthma. Cochrane database of systematic Reviews 2000;2:1281.
7. Holimon TD, Chafin CC, Self TH. Nocturnal asthma uncontrolled by inhaled corticosteroids: theeophylline or long-acting beta 2 agoinsts? Drugs 2001;3: 391-418.
8. Nutini S, Martini T, Righi R. Long-term treatment of asthmatic patients with salmeterol vs. slow-release theophylline. Respir Med 1998; 4: 683-690.
9. Lönnerholm G, Foucard T, Lindström B. Combined treatment with sustained-release theophylline and b2-adrenoreseptor-stimulating agents in chronic childhood asthma. British Med J 1981; 282: 1029-1031.
10. Pollard SJ, Spector SL, Yancey SW, Cox FM, Emmett A. Salmeterol versus theophylline in the treatment of asthma. Annals of allergy, asthma & Immunology 1997; 5: 457-464.
11. Global strategy for asthma management and prevention, NHLB/WHO Workshop report 1995; 95:3659.



İstanbul in winter. Photography by Turgay Çelikel, MD, PhD