Effect of oral bronchodilators on lung mucociliary clearance during sleep in patients with asthma

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Abstract

Background Lung mucociliary clearance rates are reduced during sleep in patients with asthma. Methylxanthines and β_2 agonists have been shown to enhance rates of lung mucociliary clearance. This study examined whether oral slow release bronchodilators may also have an effect on this clearance mechanism during sleep in patients with asthma.

Methods Nine patients with asthma with a mean(SE) age of 65(5) years and percentage predicted forced expiratory volume in one second (FEV₁ of 61(9)% participated in a double blind, placebo controlled, within subject crossover study to assess the effect of two weeks of treatment with salbutamol (Volmax; 8 mg twice daily) or theophylline (Phyllocontin; 350 mg twice daily) on lung mucociliary clearance during sleep. Lung mucociliary clearance rates were measured by a radioaerosol technique.

Results The observation period for radioaerosol clearance was approximately 0.3 hours before sleep, 6.0 hours during sleep and 0.6 hours after sleep. Mean mucociliary clearance rates for theophylline, placebo and salbutamol before sleep were: 39, 39, and 32%/hour respectively; during sleep: 11, 10, and 9%/hour respectively; and after sleep: 39, 32, and 35%/hour respectively.

Conclusion During sleep lung mucociliary clearance in stable asthma was reduced, which is in agreement with the group's previous findings. Treatment with controlled/slow release oral bronchodilators had no effect on this reduced rate of clearance associated with sleep.

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been shown to be enhanced by β_2 adrenergic drugs and methylxanthines.⁸⁻¹¹ Oral slow release bronchodilators are often prescribed to patients to treat nocturnal asthma.

We report a study in patients with asthma to compare the effects of controlled release salbutamol (Volmax, a β_2 agonist), theophylline (Phyllocontin Forte Continus, a methylxanthine), and placebo on overnight changes in lung mucociliary clearance.

Methods

PATIENTS

Twelve patients with asthma, six of whom were male, volunteered for the study. Three (two female) were withdrawn, two because of an exacerbation of their asthma (one during the run in period and the other during the salbutamol period), and the third because he was unable to manage without an oral bronchodilator during the run in period.

The patients who completed the study had a mean(SE) age of 65(5) years, percentage predicted FEV₁ of 61(9)% and a tobacco consumption of 12(5) pack years (seven ex-smokers and two non-smokers). Seven patients were receiving treatment with inhaled β_2 agonists and corticosteroids, three of whom were taking inhaled anticholinergic drugs. One other patient was receiving inhaled sodium cromoglycate only. The ninth patient was on no medication. Five of the patients were also receiving treatment with oral bronchodilators (four methylxanthines and one a β_2 agonist), which were discontinued for the one week run in period and for the duration of the trial. All nine patients had shown a 15% or greater reversibility of FEV₁ following the inhalation of 200 μ g salbutamol (n = 5), or a 20% or greater difference between the maximum and minimum peak expiratory flows (PEF) obtained for that day on at least two days where the PEF had been measured on seven consecutive days (n = 6), or both.

STUDY DESIGN

Salbutamol (8 mg twice daily), theophylline (350 mg twice daily) and placebo tablets were compared in a double blind, randomised, crossover study of seven weeks' duration. Patients underwent a one week run in period followed by three treatment periods, each of two weeks, which were not separated by wash

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Lung mucociliary clearance, one of the lung's host defence clearance mechanisms, is impaired in patients with airways disease.¹⁻⁴ Furthermore, lung mucociliary clearance has been shown to be reduced during sleep in healthy subjects⁵ and in patients with asthma,⁶ and this may contribute to the mucus plugging which is known to be present in the small airways of asthma sufferers.⁷

Tracheobronchial clearance rates have

out periods. Although the study design was such that the three treatment periods followed one another immediately, in practice this was not always possible because of previous commitments by the patients, or exacerbation of their asthma, or both. Those who had an exacerbation did not proceed into the next leg of the study until one month after the end of symptoms, or cessation of any oral corticosteroid treatment, or both. The patients were allowed to take their regular treatment throughout the study. The compliance with test medication was assessed by issuing a known number of tablets and counting those returned at the end of each treatment period. The last tablet was taken after the inhalation of radioaerosol, before sleep, and under supervision.

Informed written consent was obtained from each patient and the study was approved by the hospital's ethical subcommittee.

TRACHEOBRONCHIAL CLEARANCE

Tracheobronchial clearance was measured by an objective, non-invasive radioaerosol technique which has been described in detail elsewhere.¹² The initial deposition of the tracer radioaerosol was measured with two scintillation detectors placed midway along the sternum anteroposteriorly to the seated patients.¹³ A count was made immediately after inhalation and at approximately 0.3, 6 and 36 hours thereafter. Sequential counts of lung activity were recorded over a period of 20–25 minutes before sleep, and for approximately 40 minutes after the sleep period. For the periods before and after sleep a least squares fit to the count versus time data was used to estimate the clearance rate. For the sleep period the rate of clearance was calculated from the difference between mean readings at the beginning and end of that period. In each instance clearance was expressed in relation to the lung radioactive content at the start of the period in question.

The amount of radioaerosol present in the lungs at 36 hours was taken to be an estimate of alveolar deposition.¹⁴ The initial topographical distribution of the radioaerosol within the lungs was measured by a large field of view gamma camera linked to a computer

and expressed in terms of a penetration index.¹⁵

During the observation period any sputum samples produced were collected and weighed and their radioactive content measured.

PULMONARY FUNCTION

The FEV₁ for each patient was measured with a Vitalograph spirometer at the start of the study and during the half hour which preceded the inhalation of the radioaerosol on each study night. Predicted values were obtained on the basis of the patient's sex, age and height.¹⁶

STATISTICAL ANALYSIS

The data were analysed with the Wilcoxon signed rank sum test for matched pairs.¹⁷ The level of significance was taken at $p < 0.05$.

Results

The mean (SE) rates of compliance with trial medication were 99 (2)%, 98 (1)%, and 98 (3)% for placebo, theophylline, and salbutamol, respectively. Usage of other medication remained unchanged during the three periods. The mean (SE) alveolar deposition rates (18 (4)%, 26 (6)%, and 27 (6)%, respectively for placebo, theophylline, and salbutamol) and the mean (SE) penetration indices (0.29 (0.06), 0.38 (0.10), and 0.42 (0.12) respectively for placebo, theophylline and salbutamol) for the patients following the three treatments were similar. The percentage predicted FEV₁ values measured at the laboratory for each treatment were 53 (7)%, 55 (8)%, and 60 (9)% respectively for placebo, theophylline, and salbutamol ($p < 0.05$ for salbutamol *v* placebo).

The mean (SE) durations of the observation periods before, during, and after sleep following radioaerosol inhalation were 23(5), 350 (9), 38 (6); 18 (3), 342 (8), 36 (7); and 22 (3), 357 (8), 38 (8) minutes respectively for placebo, theophylline and salbutamol. The rates of clearance for the periods before, during and after sleep following the three treatments are shown in the figure. There were no significant differences in the rates of radioaerosol clearance from the lungs between the three treatments for the three periods. Within each of the three treatments the rate of clearance during sleep was significantly lower than the rates before and after sleep ($p < 0.01$).

Only one patient produced sputum during the observation period (placebo: 3.6 g containing 15% of the initial tracheobronchial deposition; theophylline: 2.0 g containing 31% of the initial tracheobronchial deposition).

Discussion

The rate of tracheobronchial clearance of deposited radioaerosol depends on its site of deposition within the lungs.¹⁸ In this study alveolar deposition and the penetration index

Mean (SE) tracheobronchial clearance rates for nine asthma patients before, during and after sleep following treatment with theophylline, placebo, and salbutamol.

for both bronchodilators and placebo were similar, so direct comparison of rates of tracheobronchial clearance between treatments is appropriate.

Tracheobronchial clearance comprises lung mucociliary clearance and cough. The contribution of productive cough in this study is small,¹⁹ so tracheobronchial clearance is likely to reflect lung mucociliary clearance itself. Enhancement of a depressed rate of lung mucociliary clearance, which is encountered in various lung diseases,¹⁴⁻²⁰ can be beneficial since a reduced residence time of bronchial secretions should lessen the risk of chest infections.²¹ If a bronchodilator is also shown to enhance clearance of secretions, this is an additional benefit of the drug. Salbutamol⁹ has been shown to enhance lung mucociliary clearance rates in chronic bronchitis when given topically from a metered dose inhaler, albeit at 2.5 times the normal recommended dose. Methylxanthines have been shown to enhance lung mucociliary clearance,²²⁻²³ and administration of 450 mg aminophylline twice daily for one week resulted in enhancement of mucus clearance in 75% of the study population.¹¹ Both β_2 agonists and methylxanthines have been reported to enhance ciliary beat frequency²⁴⁻²⁵ and mucus secretion,²⁶⁻²⁷ and this could influence lung mucociliary clearance.

During sleep lung mucociliary clearance rates have been shown to be reduced, both in healthy subjects⁵ and in patients with asthma.⁶ A pilot double blind crossover study on four asthma patients treated for one week with slow release aminophylline (450 mg twice daily) showed that three of the four patients had a faster clearance rate during sleep while on aminophylline than on placebo.²⁸ This study provides strong evidence that during sleep the rate of lung mucociliary clearance in asthma patients is slower than when the patients are awake, in agreement with previous observations.^{6,28} This retardation has been shown in normal subjects to be associated with sleep itself, and is not related to posture or circadian rhythm.⁵ Reduction of clearance of lung secretions during sleep, in addition to the already impaired lung mucociliary clearance in asthma patients,^{3,4} may well contribute to the early morning wheeze, cough, and dip in pulmonary function reported by such patients.

Our study has shown, however, that two weeks of treatment with an oral controlled release β_2 agonist or slow release methylxanthine does not enhance lung mucociliary clearance during sleep in patients with asthma. This finding contrasts with the observations reported with both these types of drugs in healthy subjects and in patients when awake,^{8,9,22-23} and must therefore be regarded as disappointing. Mucus secretion rates may decrease during sleep, thus lessening the load applied to the mucociliary escalator. Our data suggest that the asthma patients who fall asleep with partly blocked airways

are very unlikely to clear those airways during the night.

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