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octurnal worsening of asthma is a common and 
potentially fatal complication of asthma, and there is 
accumulating evidence that the inflammatory airway 
response is also increased at night. Studies on the ability 
of corticosteroids to block circadian recruitment of inflammatory 
cells have shown that a single dose of prednisone at 15.00 
hours resulted in a significant parcellular reduction in 
bronchoalveolar lavage cytology at 04.00 hours and a 
reduction in the overnight fall in forced expiratory volume in 
1 second (FEV,
1). Studies of the pathophysiology of nocturnal 
asthma therefore support a collaborative cellular mechanism 
of inflammation that is steroid sensitive but dependent on 
timing in addition to dosage. 1–3

Inhaled steroids are the most commonly used anti-
flammatory agents for asthma and are increasingly recog-
nised as having a more rapid onset of action than was previously thought. They have been shown to be of modest 
benefit in acute asthma 4 and, moreover, single doses of inhaled 
steroids have a protective effect on the bronchial response to 
exercise 5 and to allergen challenge. 6

We have investigated the inhibition of nocturnal worsening 
of asthma by a single high dose of inhaled steroid as a model 
for detecting the rapid effect of inhaled steroids using a highly 
active drug (fluticasone 1000 µg), a less potent drug (beclomethasone 1000 µg), and placebo.

METHODS

Subjects

Ten patients aged 19–45 years with a history of asthma were recruited from the general population. All had steroid naive 
moderate asthma with nocturnal worsening. They met the 
diagnostic criteria for asthma, with a concentration of <8 mg/ 
ml methacholine provoking a fall in FEV1 of 20% or more 
(PC20), and/or improvement in FEV1, by inhaled β2 agonist 
(200 µg albuterol) of >15% in the previous 6 months. Noctur-
nal asthma was defined as a fall in peak expiratory flow of 
>15% from bedtime to morning on at least four nights over a 
seven day period of testing. Patients were atopic with a 
positive skin prick test. Exclusion criteria were smoking 
history, other pulmonary disease, use of medication other 
than bronchodilator, and anti-inflammatory asthma therapy 
in the 4 weeks before entry into the study. In those with upper 
respiratory tract infection enrolment to the study was 
postponed for 6 weeks.

Study design

This was a randomised, double blind, placebo controlled, 
crossover trial to test the effects of a single 1000 µg dose of 
inhaled steroids on the nocturnal worsening of asthma. The study 
medications were fluticasone propionate and beclomethasone 
dipropionate. Both drugs and placebo were administered with the aid of a spacer and MDI.

The study consisted of three nights in the laboratory. One 
week was allowed between tests to prevent carryover effects. 
Patients were asked to withhold all asthma medications for 24 
hours before study measurements. On each occasion the 
patient arrived at the hospital at 15.30 hours and underwent 
spirometric tests before and after administration of an inhaled 
β2 agonist (200 µg albuterol). At 16.00 hours one of the three 
treatments was given. No medications were taken between 
16.00 and 04.00 hours, and the night was spent in the hospit-
 al. Spirometric tests were repeated at 04.00 hours.

Statistical analysis

The primary outcome was the fall in nocturnal FEV1, which was calculated from the pre-bronchodilator (pre-BD) 
measurement using the formula:

\[
\text{Fall in FEV1 (l)} = \text{pre-BD FEV1 (16.00 hours)} - \text{pre-BD FEV1 (04.00 hours)}
\]

Repeated measures analysis of variance (ANOVA) was used to 
compare the effects of the treatments. Data were expressed 
as mean (SE) values. A p value of <0.05 was considered 
significant.

RESULTS

The 10 subjects (six men) were of mean (SD) age 34 (3) years 
with FEV1 74.3 (5.1)% predicted and a bronchodilator
response of 22.7 (10.1)%. All were receiving an inhaled β₂ agonist; seven were also on a long acting β₂ agonist and two were on ipratropium bromide. No subject was taking theophylline.

The overnight fall in FEV₁, from 16.00 hours to 04.00 hours on each night is shown in fig 1. In the night following placebo administration the mean overnight fall in FEV₁ was 0.65 (0.27) l compared with −0.02 (0.13) l following fluticasone (p=0.019 vs placebo; 95% CI 0.135 to 1.208) and 0.23 (0.12) l following beclomethasone (p=0.048 vs placebo; 95% CI 0.003 to 0.847). The effect of beclomethasone was not significantly different from that of fluticasone (p=0.053; 95% CI −0.005 to 0.498). The negative value for the mean fall in FEV₁ on the night of fluticasone treatment indicates an increase in FEV₁.

DISCUSSION

A single dose of inhaled steroid reduced the fall in FEV₁ in patients with nocturnal asthma; both beclomethasone and fluticasone were tested with equivalent doses on a per mg basis. Since the potency of fluticasone is twice that of beclomethasone, we in fact evaluated two unmatched doses, one being half the other. Both inhaled steroids were different from placebo. The borderline statistical significance of the difference between the drugs is likely to relate to the small sample size. The study was not designed to distinguish between the two treatments because the medications may differ in their time response effects and the maximum effect of treatment was not investigated. A single dose of inhaled steroid (within therapeutic range) is therefore enough to prevent nocturnal worsening of asthma when administered at 16.00 hours.

An inflammatory events cascade occurs in asthmatic patients with nocturnal asthma which has its onset in the afternoon, making this a predictable phenomenon. Nocturnal asthma therefore offers a unique model for investigating the pathophysiology and treatment of asthma. The protocol described here can be used in various studies on inhaled steroids—for example, to test for side effects on the hypothalamic-pituitary-adrenal axis, to determine the site of action, and to compare potency. Moreover, acute effects of inhaled steroids have been shown to correlate with long term effects, which strengthens the relevance of this model.

There is evidence that the reported effect of steroids is derived from direct action in the lungs rather than from systemic activity. Currie et al. showed that fluticasone 1000 µg/day did not cause significant suppression of overnight urinary cortisol. Although the study was not designed as a large therapeutic trial, our data support the acute protective effect of a single dose of inhaled steroid on nocturnal asthma. We conclude that nocturnal worsening of asthma is a useful model for testing the activity of inhaled steroids.

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