N 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 pancellular reduction in bronchoalveolar lavage cytology at 04.00 hours and a reduction in the overnight fall in forced expiratory volume in 1 second (FEV1). 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-inflammatory agents for asthma and are increasingly recognised as having a more rapid onset of action than was previously thought. They have been shown to be of modest benefit in acute asthma4 and, moreover, single doses of inhaled steroids have a protective effect on the bronchial response to exercise5 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. Nocturnal 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.

Informed consent was obtained from all patients. The study was approved by the Ethics Committee of the University of São Paulo Medical School at Ribeirão Preto, Brazil.

METHODS

Subjects

Ten patients with steroid naive moderate asthma and nocturnal asthma participated in a randomised, double blind, placebo controlled, crossover trial. Participants spent three nights in the laboratory, one week apart. On each night they underwent spirometric testing at 16.00 hours and received one of the three treatments (placebo, beclomethasone 1000 µg, or fluticasone 1000 µg) delivered by metered dose inhaler. Spirometric tests were repeated at 04.00 hours the following morning.

Results: Following placebo administration the mean (SE) overnight fall in FEV1 was 0.65 (0.27) l compared with –0.02 (0.13) l following fluticasone (p=0.019) and 0.23 (0.12) l following beclomethasone (p=0.048 v placebo).

Conclusion: A single dose of inhaled steroid (within the therapeutic range) reduced the fall in FEV1 in patients with nocturnal asthma when administered at 16.00 hours. Nocturnal worsening of asthma is a useful model for testing inhaled steroid activity in a single night study.

Results

Fall in FEV1 (l) = pre-BD FEV1 (16.00 hours) – 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
Rapid effect of inhaled steroids on nocturnal worsening of asthma 633

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.9 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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