

Adrenal suppression in two patients with asthma treated with low doses of the inhaled steroid fluticasone propionate

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Inhaled steroids have been recommended as first-line therapy for asthma in both children and adults.¹ Treatment with low doses of inhaled steroids are generally safe, but studies with sensitive indices of pituitary-adrenal axis function indicate suppression in patients receiving inhaled steroids.² The clinical significance of the suppression of these biochemical indices of pituitary-

Abbreviation used

ECP: Eosinophil cationic protein

adrenal axis function remains to be determined. Fluticasone propionate is a relatively new inhaled steroid preparation, which has been suggested to have twice the potency of the older beclomethasone dipropionate but with fewer systemic side effects.³ Decreased growth in children with mild asthma treated with beclomethasone dipropionate at 400 µg per day compared with placebo controls has been described.⁴ We present two case reports of adrenal suppression with inhaled fluticasone propionate used at relatively low doses in the absence of any oral steroid.

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J Allergy Clin Immunol 1998;101:425-6.

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0091-6749/98 \$5.00 + 0 1/54/87174

CASE REPORTS

Case 1

An 8-year-old girl had asthma diagnosed at age 2 years. There were two hospitalizations, three visits to an emergency department, and four courses of oral prednisone between ages 2 and 4 years. At age 4 she was started on maintenance doses of cromolyn sodium. At that time, skin testing revealed sensitivity to cat, dog, horse, and ragweed allergens. There were no pets in the home, and no members of the household were smokers. Dust mite control was undertaken. She continued to have difficulty at times of viral illness, and beclomethasone dipropionate (400 µg/day) was used intermittently at these times. She did well on this regimen, having normal growth and requiring only one visit to an emergency department after spending a weekend at a cottage with a dog.

In March 1995, the family obtained a pet dog. Thereafter the patient exhibited symptoms such as daily cough, shortness of breath with exercise, and marked wheezing with viral illnesses despite treatment with 200 µg Beclomethasone per day, 1 mg ketotifen fumarate twice a day, regular inhaled salbutamol, and ipratropium bromide. Skin testing confirmed sensitivity to dog allergen, but the family declined to get rid of the pet. The patient started receiving 800 µg budesonide per day in two divided doses administered by turbuhaler (Astra Pharma, Inc., Mississauga, Ontario) to achieve control of symptoms. After 1 month, the budesonide was reduced to a maintenance dose of 400 µg per day, doubling the dose with onset of viral illness. After 3 months, when her growth had not changed from an initial 123 cm, she was switched from 400 µg budesonide per day to 250 µg fluticasone per day. After 5 months of treatment, she was noticed by her family to have developed a round face. An early morning cortisol level was less than 30 nmol/L (normal range, 140 to 720 nmol/L). Blood eosinophils were $0.17 \times 10^9/L$, and her serum eosinophil cationic protein (ECP) level was 11.1 µg/L. An adrenocorticotrophic hormone stimulation test showed a baseline value of 30 nmol/L, with a peak of 85 nmol/L. Growth was no more than 0.5 cm in the 5 months of treatment with fluticasone.

The patient was switched from inhaled fluticasone to 16 mg nedocromil sodium and 200 µg budesonide per day. The family continued to refuse to give up the pet dog. After 1 month, a fasting morning cortisol value was 310 nmol/L, and the patient had lost the cushingoid features. A blood eosinophil count was $0.66 \times 10^9/L$, and her serum ECP level had risen to 51.8 µg/L. After a further 1 month, when her height had only increased 1.5 cm over 1 year, the inhaled budesonide was discontinued. Clinically she seemed to do well on inhaled nedocromil sodium despite the presence of the dog. However, her blood eosinophil count had risen to $0.933 \times 10^9/L$, and sputum induced with hypertonic saline indicated continuing airway inflammation at 4.75% eosinophils (normal value, <3%). A methacholine challenge resulted in a PC20 of 0.60 mg/ml (normal value, >16 mg/ml). Her growth velocity improved to 4.2 cm over 7 months.

Case 2

A 32-year-old woman with a 5-year history of asthma was seen in July 1995. The patient had a history of seasonal allergic rhinitis since her teenage years and had been a smoker until 2 years before her first visit. Allergy skin test responses were positive to tree, grass, ragweed, dust mite, cat, rabbit, hamster, and guinea pig allergens. She had no pets, and dust mite control procedures were in place. Eight hundred micrograms of budesonide per day administered by turbuhaler was started, but control seemed clinically incomplete. In September 1995, the

patient was switched to 500 µg fluticasone propionate per day. Salmeterol xinafoate was added, and symptom control was good. In May 1996, the patient was assessed for endocrine problems because of excessive weight gain. Although she did not appear cushingoid, her serum cortisol was found to be low at 15 nmol/L and repeated at 16 nmol/L (normal range, 140 to 720 nmol/L). Other hormone levels were normal. The patient had never been treated with oral steroids. The fluticasone propionate was gradually reduced in favor of 16 mg nedocromil sodium per day in four divided doses. One month later, her serum cortisol level was normal at 272 nmol/L. Blood eosinophils were $0.142 \times 10^9/L$. A sample of sputum induced with hypertonic saline was insufficient for processing. Methacholine challenge resulted in a PC20 of 3.0 mg/ml while receiving salmeterol.

DISCUSSION

Inhaled steroids are the most potent antiinflammatory agent for suppression of eosinophilic inflammation in asthma, which can usually be achieved with safe doses. However, the two cases described indicate that clinically important systemic effects can occur even at relatively low doses of inhaled steroid. Case 1 showed a child who demonstrated poor growth velocity even on low doses of inhaled steroid (200 µg budesonide per day). Moreover, the data suggested that 250 µg of inhaled fluticasone had greater systemic suppression than 200 µg of budesonide (the former delivered by metered-dose inhaler and the latter by turbuhaler) with greater suppression of fasting cortisol levels and lower eosinophil and serum ECP levels with fluticasone (250 µg fluticasone per day: early morning cortisol level, <30 nmol/L; blood eosinophils, $0.17 \times 10^9/L$; and serum ECP, 11.1 µg/L vs 200 µg budesonide per day: early morning cortisol level, 310 nmol/L; blood eosinophils, $0.66 \times 10^9/L$; and serum ECP, 51.8 µg/L). Both patients had no evidence for other causes of adrenal suppression, and their cortisol levels normalized after discontinuing inhaled fluticasone. Both patients seemed to do well clinically while receiving nedocromil sodium, but sputum examination in the child suggested incomplete suppression of eosinophils in the airway. The results indicate that patients treated with regular inhaled steroids need to be monitored for potential systemic effects. They also suggest that even newer inhaled steroids such as fluticasone propionate, which are claimed to have fewer systemic effects, can on occasion be associated with such effects.

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