

Editorial

Inhaled steroids and local side-effects

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Inhaled steroids are now the most important drugs for the treatment of asthma. Inhaled steroids reduce symptoms in children with asthma (1); improve quality of life in the children as well as their caregivers (2); improve lung function (3); and reduce levels of inflammation markers (4), bronchial responsiveness (5), and exercise-induced asthma (6, 7). In addition, it has been demonstrated that, as the use of inhaled steroids increased markedly in the Nordic countries from the late 1980s, the admission rate to hospital for acute asthma in older children started to decrease (8, 9), particularly for readmissions as compared to first admissions for acute asthma (10). Thus, the use of inhaled steroids in children with asthma has a beneficial effect upon the well-being of children and their families, as well as reducing community costs for asthma, by reducing admissions to hospital, the number of emergency consultations (1), and absence from work or school of patients, schoolchildren, and parents (11).

Despite these important effects of inhaled steroids upon asthma, clinicians have not reached general agreement on how early in life to start treatment with inhaled steroids. This is due to the general fear of the side-effects of inhaled steroids, and the systemic side-effect that has caused most concern in children is the possible reduction in growth velocity caused by these drugs (12), although recent reports have shown that asthmatic children employing inhaled steroids do reach their final target adult height (3).

The local side-effects of inhaled steroids upon the skin and mucous membranes of the respiratory tract and the oropharyngeal area are also well known, but have received much less attention than the systemic side-effects. These local side-effects include perioral dermatitis, oral candidiasis, hoarseness, dysphonia, cough during inhalation, and sensation of thirst.

In the present issue of *Allergy*, Dubus et al. report a multicenter observational study of local side-effects

caused by treatment with inhaled steroids (beclomethasone dipropionate or budesonide) in 639 asthmatic children 3 months to 16 years of age (13).

The mean duration of treatment with inhaled steroids was 15 months. As many as 61.5% of the children had at least one local side-effect. This is a higher rate than the reports of systemic side-effects caused by inhaled steroids, but it is also higher than the occurrence of local side-effects in most other reports. In most other studies, reporting local side-effects has been only a part of the study, and the focus most often has been on the effects of the drugs or on systemic side-effects. Few other studies have studied the local side-effects systematically as in the present study. One exception is the study by Williamson et al., who found that 58% of outpatients receiving an inhaled steroid reported throat symptoms or voice dysphonia compared to 13% of control subjects (14). These findings are in contrast to the report by Agertoft et al., who studied the occurrence of the local side-effect hoarseness in addition to posterior subcapsular cataracts and bruises. They did not find increased occurrence of any of these in 157 asthmatic children who had received a mean daily dose of 504 µg budesonide for 3–6 years (15).

The side-effects reported by Dubus et al. were cough during inhalation (39.7% of the patients), the sensation of thirst (21.9%), hoarseness (14.1%), dysphonia (11.1%), oral candidiasis (10.7%), perioral dermatitis (2.9%), and tongue hypertrophy in one patient (13). Cough and perioral dermatitis were found more often in younger children, and hoarseness in older children, but apart from these effects, the side-effects were not age dependent. Cough was found more often in children receiving beclomethasone dipropionate.

Association of the local side-effects with the inhalation device has been more extensively studied than differences between the different types of inhaled steroids. It is of interest that when subjects changed

from MDI beclomethasone dipropionate with chlorofluorocarbon as propellant to ultrafine particle beclomethasone with hydrofluoroalkane (HFA) as propellant, the number of adverse events decreased (16). In their report in the present issue of *Allergy*, Dubus et al. found that the use of a spacer, in comparison with the MDI only, influenced markedly the occurrence of cough for both drugs studied. Dysphonia was also more frequent when a MDI with spacer was used compared to Turbuhaler, MDI, or Autohaler alone. Hone et al. also looked into this in a thorough study of 20 asthma patients on high dose of inhaled steroids, 1 mg per day for 3 months. Already prior to starting inhaled steroids, more abnormality of the vocal cords was found in the asthmatic patients than the control group. However, this tended to improve rather than worsen during treatment with inhaled steroids (17). Selroos et al. (18) followed 154 adult asthma patients receiving inhaled steroids by MDI, and then changing to budesonide Turbuhaler for a further 2 years. Other patients received Turbuhaler as their first device. The patients rinsed their mouth with water after inhalation. After changing from MDI to Turbuhaler, the occurrence of local side-effects decreased from 21% to 6% because of the reduction of hoarseness (18).

In the study of Dubus et al., no cultures were made of *Candida*, but the diagnosis of oral candidiasis based upon clinical findings was made in 10.7% of subjects regardless of device (13). This agrees with the findings of Toogood et al. (19), who could not find any difference in local side-effects in using either the Turbuhaler or a MDI with Nebuhaler spacer for administration of budesonide. In contrast, with doses of budesonide from 0.4 to 2.4 mg a day, they found a dosage-dependent difference in oropharyngeal *Candida* colony count. However, Salzman & Pyszczynski reported less candidiasis when they used the beclomethasone MDI with spacer than the MDI alone (20).

Perioral dermatitis has occasionally been observed in

young children who use a face mask to take nebulized inhaled steroids (21). Dubus et al. (13) found perioral dermatitis in as many as 5.2% of children using a spacer device with face mask and in 14.3% of children using a nebulizer with face mask or a nebulizer only without mouthpiece. In this context, it is interesting to note that inhaled steroids may have an effect upon collagen synthesis in the skin. Budesonide in daily doses of 400 or 1600 µg reduced concentrations of procollagen types I and III propeptide in blister fluid (22).

Development of tongue hypertrophy has also been reported as a side-effect of inhaled steroids. Such tongue hypertrophy was found in three infants receiving inhaled beclomethasone. The condition resolved after cessation of inhaled steroids (23). The present study also reported one case of reversible tongue hypertrophy in a young child receiving inhaled budesonide (13). Most of the local side-effects reported in the present study, as well as in previous studies, are minor and of little consequence to the health of the child. Some of these local side-effects are dose dependent, and this underlines the necessity of finding the lowest effective dose of inhaled steroids. When local side-effects occur, changing to another inhalation device may help some patients.

Many patients and parents are afraid of the side-effects of inhaled steroids, and it has been shown that, even in a study, the compliance with therapy over a prolonged time period decreases markedly (24). Although the health effects of the local side-effects of inhaled steroids may be minor, these local side-effects may have an untoward effect upon the concordance (compliance) of the patients with the treatment, and thus upon the control of asthma. Therefore, factors such as dosage and inhalation device should also be considered, and precautions such as rinsing the mouth with water after inhalation and washing the face after inhalation when using a nebulizer or face mask, should be taken.

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