

USE OF INHALED CORTICOSTEROIDS IN THE TREATMENT OF CHILDHOOD ASTHMA

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SUMMARY : *In order to control asthma, we need to suppress the airway inflammation and reduce bronchial responsiveness. Clinically, the anti-asthma effect of inhaled corticosteroids (ICSs) is manifested by a reduction in asthma exacerbations, diurnal variation in lung function, and daily symptoms. The early use of ICS is supported by all current published guidelines, including the International Consensus Report, which emphasise the fundamental role of inflammation in the pathogenesis of asthma and the resulting need for anti-inflammatory therapy. Initially, a quite large dose is used, which is then reduced to the smallest dose that is able to control the symptoms. For most children, this will be possible at doses of 400 µg or less daily. At this dose, there is no convincing evidence of any systemic effects, even using the most sensitive tests. However, it is not known how long the anti-inflammatory treatment should be continued after remission.*

Key Words : *Childhood Asthma, Inhaled Corticosteroid.*

Inhaled corticosteroids (ICSs) have been used for the treatment of childhood asthma for more than 25 years (2). They act on intracellular glucocorticoid receptors which have high levels of expression in airway epithelial and endothelial cells. Their most important effect in asthma is likely to be inhibition of transcription of the cytokines IL-3 and IL-5, which in turn reduce recruitment of eosinophils and survival of mast cells in the lung airways. They may also have a direct effect on eosinophil chemotaxis and diapedesis, airway microvascular leakage and mucus gland production. Corticosteroids also increase the synthesis of lipocortin-1 which, by inhibition of phospholipase A2, reduces the production of arachidonic acid metabolites, such as leucotrienes and prostaglandins. Another important action of

these drugs in the treatment of asthma is the enhancement of beta-receptor responsiveness (2, 6, 7). The chronic inflammatory process in asthma may lead to permanent structural changes in the airways. The key to successful therapy is the prevention or suppression of these inflammatory processes. Recent biopsy studies in patients with asthma have now confirmed that ICSs reduce the number and activation of inflammatory cells in the airways (9).

Five different ICSs (beclomethasone dipropionate, budesonide, flunisolide, triamcinolone and fluticasone) with lung selectivity for topical use have been developed and proven to be effective in children. Although there are many studies that have dealt with the efficacy of individual ICS in asthma, no clinically important

differences between these drugs were found. Both the effect and side effects are related to the dosage rather than type of the ICSs used (7).

Unfortunately, we have no reliable non-invasive markers by which to assess airway inflammation or to judge the effect of treatment. Thus, the decision to start regular anti-inflammatory medication has to be made from the description of the frequency and severity of symptoms and the results of lung function tests. In order to ascertain its severity, chronic asthma has recently been divided into three groups: Mild-persistent, moderate, and severe asthma (6). Bronchial biopsy and bronchoalveolar lavage studies have demonstrated chronic inflammation in the airways, which is evident even in mild asthma and between the attacks (2). Therefore today, a stepwise approach to the treatment of mild-persistent childhood asthma is advocated with the first step being the use of safe anti-inflammatory agents such as sodium cromoglycate (SCG). However, long-term controlled studies indicate unequivocally that SCG is of significant clinical benefit in only 60-70 % of adults or children (8). Nebulized SCG improves asthma in preschool children but does not reduce hospital admission rates or severe wheezing after viral respiratory infections (3). Furthermore, it may have to be given three or four times a day which is inconvenient and difficult to sustain. Poor compliance with SCG therapy is an important cause of persistent morbidity from asthma (5). Despite these disadvantages, SCG retains its place as first line regular medication in mild persistent childhood asthma. Nedocromil, a newer medication, has been shown to improve pulmonary function in patients with mild to moderate asthma (6). It has not been extensively studied yet in children. If a child presents with severe symptoms or evidence of chest deformity, it is appropriate to give an ICS as the first regular medication. In this respect, asthma therapy should be individualized for each child.

Many controlled clinical trials have now established that ICSs are effective in improving lung functions and bronchial hyperreactivity, controlling asthma symptoms and reducing the frequency and severity of acute exacerbations (2, 6, 7, 14). In fact, ICSs are effective in all patients irrespective of age and asthma severity. It is surprising that treatment induced increases in pulmonary function tests are related to the interval

between the onset of asthma symptoms and the start of ICS therapy. Recent findings suggest that the effect of ICSs on lung functions are significantly greater when ICSs are started within two years after asthma is diagnosed, so that children who started early on ICSs have significantly better lung functions than do those in whom ICSs are not started until some years after the onset of asthma symptoms (1, 4). Importantly, these studies show that the level of control achieved seems to be greatest if ICS therapy is started early in the course of the disease. Early intervention with ICS seems to prevent the development of irreversible persistent structural changes such as basement membrane thickness and bronchial smooth muscle hypertrophy, that occurs over the time if the asthma is under-treated (10). This has not been shown for any other drug. For many years, ICSs were reserved for patients with only severe asthma. As experience was gained with ICS, they have now become first-line therapy in children with chronic asthma symptoms. The beneficial effect of ICSs has been clearly shown to be dose related. Once control of asthma has been achieved, the dose of ICS may be reduced in line with the recommendations of the international guidelines. In most school children adequate control of asthma can be obtained with prophylactic doses between 100 and 200 µg per day (1, 2, 4, 6, 7, 11). The next question is how long the therapy should be continued. Some short- and long-term studies in children and adult asthmatic patients show that treatment with ICS improves both symptoms and objective measures of lung function, but it does not cure asthma. Cessation of ICSs were followed by recurrence or increase in symptoms and a deterioration in lung functions (15). Treatment with the lowest dose should, therefore, be continued following symptomatic remission without the need of additional bronchodilator. In fact, some chronic asthmatic patients may be taking these drugs for many years.

The Unwanted Effects of ICSs

The advantage of administering corticosteroids by the inhalation route is that patients with asthma can benefit from corticosteroid treatment with less systemic unwanted effects. Although oropharyngeal candidiasis and dysphonia have been recognised as local complications of ICSs, both have a low incidence and are of no clinical importance in children (2, 7, 13). The systemic effect of an ICS depends upon the amount of the

drug which is systemically absorbed. The oropharyngeal deposition of ICS can be markedly reduced by the use of a spacer, by mouth washing or by new-dry-powder inhalers, so that the fraction inhaled into the respiratory tract becomes a relatively more dominating contributor (>85%) to the systemic fraction (7).

Most studies in children have shown that 24 h excretion of free cortisol, base-line serum cortisol, and responses to ACTH and metyrapone do not differ from those in controls after long-term treatment with ICS in doses up to 800 µg daily (2, 7). However, in a number of other studies, adrenal suppression was reported with the same doses (12). It seems likely that, in children as in adults, ICSs may lead to a slight dose-dependent suppression of base-line adrenal steroid production when administered in a high dose (>800 µg daily), but with preservation of its reserve capacity (13). This emphasises the importance of using the minimum dose (around 400 µg-day) compatible with good control of asthma in children.

Recent interest in the growth of asthmatic children has centered on growth failure as a potential side-effect of ICSs therapy. However, asthma is associated with delayed maturation. The asthmatic children who are not receiving ICS, may show a delayed growth velocity and a delayed bone age (2). Growth in stature is dependent upon the growth of the long bones of the leg as well as spinal growth. These two aspects of growth occur in tandem, although with different hormonal controls. In normal children, growth hormone is responsible for the proportionate increase in body segments whereas sex steroids have a greater effect on spinal growth. The effect of ICS on growth is not simply related to adrenal suppression. Therefore, the difference in growth pattern seems to be unrelated to the use of ICS, but appears to be more pronounced in children with severe asthma. Treatment with ICSs in daily doses up to 400 µg does not adversely affect long-term natural growth in children with asthma (6, 7). No other clinically important unwanted effects (osteoporosis, cataracts, psychic disturbances, several metabolic and hematologic changes) have so far been associated with ICSs in standard pediatric doses.

Conclusion

Inhaled steroids are an increasingly popular mode of treatment for children with asthma. They

improve lung function and symptoms and reduce bronchodilator usage. In order to avoid higher doses and more severe disease, they may be introduced at an early stage and at a lower dose in the disease process. In conventional doses, they appear to be very safe. Nevertheless, we must select our patients carefully, and one of the most important points to remember is that children are different from adults.

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