Use of Inhaled Corticosteroids in Pediatric Asthma

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Summary. Inhaled corticosteroids reduce asthma symptoms and exacerbations, improve lung function, and reduce airway inflammation and bronchial hyperreactivity more effectively than other treatments. However, inhaled corticosteroids may be unable to return lung function and bronchial hyperreactivity to normal when introduced for moderately severe asthma. This finding highlights the need to improve treatment strategy in pediatric asthma. The natural progression of persistent asthma may lead to loss of lung function and chronic bronchial hyperreactivity for children and adults. There is evidence to suggest that asthma acts via a chronic inflammatory process that causes remodeling of the airways with mucosal thickening and smooth muscle hypertrophy. An optimal treatment strategy would be one aimed at reducing the ongoing airway inflammation. Inhaled steroids ameliorate the inflammation, whereas this has not been documented for any other treatment. Delayed introduction of inhaled steroids appears to result in reduced improvement in lung function compared with the early use of inhaled steroids. This improved response from the earlier use of inhaled steroids appears to be valid at any stage of the disease. Therefore, a change in treatment strategy toward earlier introduction of corticosteroids may impede airway remodeling, bronchial hyperreactivity, and airway damage. No other treatment has been found to affect the course of the disease. Systemic side-effects, particularly inhibition of growth in asthmatic children using inhaled corticosteroids, do not seem to be cause for concern. Growth retardation has not been reported when inhaled corticosteroid doses of $\leq 400 \mu g$ daily are individually tailored to each child’s needs. The ongoing change in treatment strategy toward the earlier use of inhaled steroids in childhood asthma, as reflected in current revisions of various treatment strategies, therefore seems well founded. Pediatr. Pulmonol. 1997; Supplement 15:27–33.

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INTRODUCTION

Revisions of the various international treatment strategies have gradually changed the attitude toward early use of inhaled steroids to emphasize their early introduction in childhood asthma. This development seems to be well founded in controlled trials and possibly may be developed even further.

SYMPTOM CONTROL

Comparative studies of inhaled corticosteroids and other treatments indicate that inhaled corticosteroids are more effective at reducing asthma symptoms and exacerbations, improving lung function, and reducing bronchial reactivity in children with asthma (irrespective of severity). Inhaled corticosteroids have been shown to be more effective than sodium cromoglycate,1,2 theophylline,3 short-4 and long-acting $\beta_2$-agonists5, as well as combinations of nonsteroidal treatments.6 Such superior effects were obtained with low-to-moderate doses of inhaled steroid. No controlled clinical studies have found any other drug to be more effective than inhaled steroids in controlling asthma morbidity. If control of disease is considered to be the control of asthma symptoms, improved lung function with minimized morbidity, and reduced number of exacerbations, this control is reliably obtained by inhaled steroids at any stage of the disease.

DISEASE CONTROL

Control of the disease may also be considered in terms of control of the underlying disease process. Can inhaled steroids also control the underlying disease process at any stage of disease? This question has been indirectly addressed in a Dutch study designed to compare the efficacy of inhaled steroids versus regular inhalation of a $\beta_2$-agonist. The effect of 22 months’ BUD treatment (200 $\mu g$, three times daily) on lung function was compared with that of placebo in 116 children aged 7–16 years old with moderate asthma.4 The children receiving BUD had significantly fewer asthma symptoms, better

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lungs function, and less bronchial reactivity compared with placebo. However, this study also ascertained that after 22 months of inhaled corticosteroid therapy lung function had returned to normal in only 40% of children. Similarly, bronchial reactivity only returned to the normal range in 26% of children receiving inhaled corticosteroid therapy.

In a separate study the effect of 12 week’s treatment with inhaled fluticasone propionate 100 μg twice daily was compared with placebo in 307 adult asthma patients with moderate asthma. Fluticasone propionate improved asthma symptoms and lung function, and reduced use of rescue medication. However, the percentage of patients who achieved normal lung function (>85% of predicted) was 10% in the placebo group compared with 28% in the fluticasone propionate group. Based on such evidence, inhaled steroids would seem to be unable to revert lung function and bronchial reactivity to normal if introduced late during the course of the disease.

These studies document the efficacy of inhaled corticosteroids in controlling morbidity of childhood asthma, but raise the questions of why does bronchial hyperreactivity persist in children with moderately severe asthma even after long-term treatment with efficient steroid therapy, and why does lung function not return to normal? Irrespective of how efficient inhaled steroids are at controlling asthma morbidity, they may not always be able to affect the underlying pathophysiology. It is possible that the lack of effect of inhaled steroids may be the result of abnormalities of airway function that precede the onset of wheezing. Narrower airways during childhood may increase the risk of developing asthma. This theory would imply that reduced lung function was a cause rather than a consequence of the asthma; hence, the condition may persist independent of asthma symptoms. An alternative explanation could be that despite control of symptoms, underlying inflammation could cause persistent airway narrowing. Evidence of persistent inflammation despite inhaled corticosteroid therapy has been reported. A third possible explanation could be that the disease process itself has caused irreversible airway damage with permanent ventilatory deficit and bronchial hyperreactivity. It is possible that the suboptimal response to inhaled steroids (in terms of persistently reduced lung function and bronchial hyperreactivity) is caused by a delay in antiinflammatory treat-ment, which allows uncontrolled airway inflammation to cause airway damage during the early stages of the disease. This finding would call for reappraisal of the positioning of inhaled steroids as second-line treatment in the present treatment strategy, and would suggest earlier introduction of treatment.

**IRREVERSIBLE AIRWAY OBSTRUCTION FROM PERSISTENT ASTHMA**

The natural course of persistent asthma may lead to irreversible airflow obstruction both in children and in adults. Retrospective studies have reported reduced lung function in symptom-free adults and adolescents with a history of asthma in childhood but no symptoms during recent years (compared with age-matched controls), although sequelae seem to disappear in adults remaining free of symptoms and medication since childhood. Asthmatic children with persistent asthma into adulthood have baseline lung function that is worse than healthy age-matched controls. In a short-term, prospective study, Backer and Ulrik reported significantly reduced lung growth in asthmatic children. A Dutch longitudinal study of adolescents monitored lung function in 269 teenagers every 6 months between 1978 and 1985, and reported a persistent reduction in FEV₁ of 0.2 L in males who reported puberty respiratory symptoms (this probably includes asthma, bronchitis, and pneumonia). Spirometry measurements have been found to worsen over time among children with persistent wheezing, or asthma. In the latter study, it could be predicted that a female who developed asthma at the age of 7 years would experience a 7% deficit in lung function by 15 years of age. The Melbourne cohort followed 247, randomly selected, 7-year-old children over 3 decades. Reduced lung function was found in children with persistent wheezing, and this correlated with the degree of wheezing. In addition, the resting airway obstruction in these asthmatic children increased with age. A prospective cohort of 10,792 children, aged 6 to 18 years, was examined annually between 1974 and 1989 in six United States cities. FEV₁ values were 6% lower, and FEF_{25–75} values were 17% lower, in white asthmatics with current symptoms. Martinez and coworkers studied 120 randomly selected infants during the first 6 years of life, and found a significantly reduced increase in lung function in those with persistent wheezing, and this approximated to 14% of the cohort. These findings would suggest that airway damage can result from persistent wheezing symptoms during childhood. Considering the prevailing treatment strategy in these studies, it is likely that the outcome reflects that of steroid-naive asthma patients. These childhood studies are in agreement with the findings of an increased rate of decline of FEV₁ found in adult asthmatics compared with

<table>
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<th>Abbreviations</th>
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<tr>
<td>BDP</td>
<td>Beclomethasone dipropionate</td>
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<tr>
<td>BUD</td>
<td>Budesonide</td>
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<tr>
<td>FEF_{25–75}</td>
<td>Forced expiratory flow in the middle section of the forced vital capacity</td>
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<td>FEV₁</td>
<td>Forced expiratory volume in 1 second</td>
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The thickened basement membrane reticular collagen cannot be reversed by inhaled corticosteroid treatment. This remodeling of the airways may reflect the irreversible airway damage previously discussed, which would point to the necessity of earlier preventative treatment.

EARLY INTERVENTION

Haahota et al. examined the effect of delayed intervention with inhaled corticosteroids in 74 adults with mild asthma. Subjects were randomized to receive either an inhaled corticosteroid or a \( \beta_2 \)-agonist for 2 years. After this period, those patients receiving the \( \beta_2 \)-agonist received the same inhaled corticosteroid treatment as the other group. Comparison of the two treatment groups revealed that those who were first treated with a \( \beta_2 \)-agonist for 2 years, and only subsequently treated with BUD, did not reach the same level of lung function and improved bronchial hyperreactivity within the third year as those who were treated with BUD from the beginning of the study had obtained during the initial study year. Overbeck et al. reported similar findings in adult patients who had asthma for a long period of time and found that the potential for inhaled steroid treatment to improve bronchial responsiveness was impaired in patients in whom treatment was delayed by 2 years.

In a 25-year follow-up study of young adult asthma patients, 21% had outgrown their bronchial hyperresponsiveness. Absence of bronchial hyperresponsiveness after 25 years was significantly associated with a shorter period between onset of asthma symptoms and specialized treatment of the disease.

Patients with mild symptoms treated only with bronchodilators as needed exhibited a significant worsening in spirometry measurements compared with patients with severe asthma treated with an inhaled steroid, as reported in a recent retrospective uncontrolled analysis of data from chart reviews. This finding may substantiate the deteriorating course of uncontrolled asthma and suggest that anti-inflammatory treatment should be started earlier. Delay in starting sodium cromoglycate, but not inhaled corticosteroids, had a negative effect on both clinical outcome and pulmonary function. This finding suggests treatment with sodium cromoglycate should be started early, but the findings need to be interpreted with caution based on the retrospective nature of the report.

In a controlled prospective study, the lung function of 216 asthmatic children, whose asthma history was well documented, was determined at 6-month intervals for 1–2 years before the study and 3–6 years after commencing treatment with an inhaled \( \beta_2 \)-agonist and an inhaled corticosteroid. After 3 years of treatment with an inhaled corticosteroid, children who started this therapy more than 5 years after the onset of symptoms had a

AIRWAY INFLAMMATION

There is evidence to suggest that the disease acts through a chronic inflammatory process, with thickening of the basal membrane and smooth muscle hyperplasia and hypertrophy causing airway remodeling. Bronchial hyperreactivity may be the result of such airway remodeling and may serve as a surrogate marker for the disease process. Several independent research groups have documented the features of chronic inflammation in the airways of newly diagnosed, steroid-naive, mild asthmatic adults. There is severe damage of the airway epithelium with areas of denudation and areas of regeneration, and the ratio of normal ciliated cells:goblet cells is decreased. Generalized significant edema and severe submucosal inflammation predominates, with an intense inflammatory reaction comprised of activated eosinophils, lymphocytes, plasma cells, and degranulated mast cells. Consistent features include thickening of the reticular membrane, hyperplasia, and hypertrophy of the bronchial smooth muscle and the mucous glands. In addition, collagen accumulates in the submucosa in asthma patients compared with normal controls. Such irreversible structural changes seem to develop early in the course of the disease. Basement membrane thickening has been described in asthmatic children, and shortly after onset of asthma.

Inhaled corticosteroids restore airway epithelium to normal and reduce the number of cells involved in inflammation; hence, these drugs have a disease modifying effect. In contrast, bronchodilator treatment reduces the symptoms but has no effect on the underlying inflammation. Cromones have also never been documented to modify airway inflammation.

healthy controls. Furthermore, this decline is most pronounced in those patients with the greatest degree of airflow obstruction, and with the greatest loss of lung function during the early years after diagnosis.

A recent study in Holland compared the outcome of treatment with inhaled BDP (200 \( \mu \)g twice daily) with that of salmeterol (50 \( \mu \)g twice daily) for 1 year in children with mild-to-moderate asthma. The improvement in lung function, decrease in bronchial reactivity, and decrease in number of exacerbations were all significantly greater for the inhaled BDP group compared with the salmeterol group. It is interesting to note that over the 1-year observation period, the control group exhibited a reduction in FEV\(_1\) as well as increased bronchial reactivity. It has been suggested that regular \( \beta_2 \)-agonist therapy may cause deterioration of asthma, but this is disputed, and the development may rather reflect deterioration of the uncontrolled airway inflammation. What is clear from these studies is that if asthma is not controlled it may lead to airway damage.
significantly reduced improvement in FEV\textsubscript{1} compared with those children who received the inhaled corticosteroid within the first 2 years after the onset of asthma. The group who received the inhaled corticosteroid therapy early after the onset of asthma were younger than the group who received therapy after a prolonged disease period. However, the negative correlation between the response to treatment and the years since onset of asthma was still present within a more narrow grouping of the children, according to delay of steroid treatment. These findings suggest that earlier intervention with inhaled corticosteroids may prevent airway damage that might otherwise occur during the course of childhood asthma. A similar study in adults with asthma reported the same negative correlation between time between onset of symptoms and start of steroid treatment and improvement in FEV\textsubscript{1}.40 Thus, it would appear that structural changes are more difficult to reverse once they have occurred than they are to prevent with prophylactic therapy. The additional ability of inhaled corticosteroids to modify the course of the disease and prevent airway damage would, therefore suggest, they should be used as first-line therapy in chronic asthma.

HOW EARLY IS EARLY?

The concept of early intervention should not be misinterpreted as a strategy to introduce inhaled corticosteroids “at the first sign of wheeze in small children with very mild episodic disease.”41 To date, there is insufficient data on the development of asthma and the disease modifying effect of inhaled steroids to recommend such a radical approach, and it is not known whether the natural course of mild asthma is to develop into severe asthma, which could call for such an aggressive approach. All studies on “early” intervention have been conducted in secondary or tertiary referral centers, and in most studies asthma had been established for some years. However, the same conclusion seems to emerge irrespective of the stage of the disease studied: in persistent asthma early intervention achieves better results compared with delayed intervention.

In the clinic it is not possible to separate patients with a self-limiting course of asthma symptoms from those who will continue to have persistent asthma symptoms. Finally, even children with a good prognosis should have the optimal treatment in the meantime.

Therefore, it seems logical to start all asthmatic children on inhaled steroids as soon persistent asthma symptoms appear, provided there is a continuous attempt to taper down the dose (Fig. 1). Such continuous down-titration of the minimal effective dose required to maintain the patient free of symptoms should mean that treatment is stopped in those who outgrow asthma, whereas those with persistent asthma will continue on inhaled steroids at the minimal effective dose allowing the treatment to modify the course of the disease.

The revisions of the international treatment strategy guidelines have clearly moved toward the increasingly earlier use of inhaled steroids, and it is possible that this progression has not come to an end.

SAFETY OF INHALED CORTICOSTEROIDS

In children, clinical side-effects of inhaled corticosteroids primarily focus on the risk of growth retardation. Children with mild, infrequent, episodic asthma should not receive regular treatment with inhaled steroids, as effectiveness has not been documented and reduced growth rate may occur. In a recent study, such a group of children was treated with a moderately high dose of inhaled steroid. Inhaled steroids had no effect on their normal lung function but did stunt growth,42 confirming that children not requiring regular inhaled steroids may experience side-effects of such overtreatment.

It is not justified to extrapolate the findings of studies of side-effects in subjects without established asthma to the risk of treating children with established asthma. In studies examining the systemic activity of inhaled steroids, healthy subjects had more pronounced adrenal suppression than asthma patients.43–46 This finding may be the result of a reduced lung dose, a reduced absorption, or an increased susceptibility of asthma patients compared with healthy controls.

It is important to note that many chronic diseases, including asthma, may themselves reduce the growth rate of children, and a significant relationship between inhibition of growth and asthma severity has been reported.6,47 It is, therefore, important to emphasize the need for individualized tailored dosing in the use of inhaled steroids. The majority of asthmatic children achieve a final height in the normal range.48 In a meta-analysis of 21 studies composed of 810 asthmatic children using inhaled corticosteroids to control asthma
symptoms and exacerbations, it was concluded that inhaled corticosteroids did not adversely affect their final height.\(^4\) This does not, however, exclude the possibility of increased susceptibility of certain individuals. Therefore, it is important to monitor growth as well as using the minimum effective dose.

The optimal clinical effects of inhaled corticosteroids are obtained in the majority of children with mild to moderate asthma with doses ranging from 100–200 \(\mu\)g daily, depending on the steroid and the inhalation device used.\(^1,5\) Increases in dose are not accompanied by proportional increases in effect, but increasing doses do result in increased systemic bioavailability (Fig. 2).\(^5\) Our treatment approach is, therefore, to start with a high dose for a short period to establish clinical control (induction therapy),\(^5\) and then titrate the dose down, often stopping treatment to establish whether the child requires regular inhaled corticosteroid treatment. Loss of control is followed by increasing the titrated dose to one that controls the asthma (maintenance therapy). Such a low-dose strategy is probably at the expense of patients experiencing more exacerbations than when on a continuous high-dose strategy, but allows for the inclusion of short bursts of high doses for exacerbations (relapse therapy) and means the overall use of steroids is minimized. In conclusion, there is no universal dose for a child; the dose for each child has to be individually and continuously titrated.

Clinical studies examining the risk of growth retardation in children receiving inhaled corticosteroids should determine the potential risk of this side-effect only after the minimally effective steroid dose has been individually tailored. Controlled trials reporting growth retardation have frequently used doses that appear inappropriate for the children being studied. Growth retardation has not been reported from tailored corticosteroid doses of \(\leqslant 400\ \mu\)g daily.\(^6\)

**CONCLUSION**

It would appear that asthma acts via a chronic inflammatory process resulting in mucosal thickening and airway remodeling. Hence, an optimal treatment strategy is one aimed at reducing ongoing airway inflammation. Low-dose inhaled corticosteroids reduce asthma symptoms and exacerbations, improve lung function, and reduce airway inflammation and bronchial hyperreactivity more effectively than any other treatment. Uncontrolled asthma may lead to irreversible loss of lung function and increased bronchial hyperreactivity, of which both can be ameliorated by earlier corticosteroid treatment. In moderately severe asthma, airway damage that is not reversible has often occurred. However, further progression is usually stopped by inhaled corticosteroids. There are no controlled data published to suggest that control of inflammation can be obtained by any other treatment, including cromones. Therefore, a change in treatment strategy toward the earlier introduction of corticosteroids may prevent airway remodeling, bronchial hyperreactivity, and airway damage. Inhaled corticosteroids do have some systemic activity, and concern over systemic side-effects in children focuses on possible growth retardation. However, growth retardation has not been reported when individually tailored inhaled corticosteroid doses of \(\leqslant 400\ \mu\)g daily are used. Furthermore, evidence is accumulating in support of the on-going change in treatment strategy for persistent childhood asthma to one of earlier use of inhaled steroids.

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