Inhaled steroids: First line treatment of adult asthma


Corticosteroids are the most potent inhaled anti-inflammatory drugs for asthma treatment. This paper reviews the clinical evidence supporting the early use of inhaled steroids in asthma as a first line treatment. Inhaled steroids can probably alter the course of asthma, especially in mild asthmatics. Once they have been shown to improve control of asthma and even if the need for beta2-agonists is virtually nil, their use should be continued at low doses (ie, equivalent to 400 to 500 μg of budesonide or beclomethasone) for at least one year before attempting to reduce the dosage.

Key Words: Asthma. Inhaled steroids. Prophylaxis

O ver the past few years, many studies have highlighted the primary role of bronchial inflammation in the pathophysiology of asthma. While bronchodilators had been considered in the past as the main treatment of asthma, the emphasis is now on the control of inflammation in order to decrease airway obstruction and improve bronchial responsiveness.

To reduce airway inflammation and improve asthma control, the first step is environmental control such as elimination of relevant allergens and irritants such as cigarette smoke. However, this is usually not sufficient and the subject may require anti-inflammatory drugs, primarily steroids and secondarily sodium cromoglycate or nedocromil sodium. The aim of this paper is to evaluate the role of inhaled steroids as first line treatment in the control of asthma in adults.

CANADIAN AND INTERNATIONAL GUIDELINES

The present Canadian guidelines, drawn from two consensus meetings held in May and October 1990, were published by Hargreave et al in 1990 (1,2). Asthma control is defined by minimal (ideally none) airway obstruction and symptoms (ideally none) with little use of inhaled beta2-agonists. According to these guidelines, an adult asthmatic requiring as sole medication an inhaled beta2-agonist twice a day or less is considered to be well controlled (level 1). However, in the adult who requires a beta2-agonist more than twice but fewer than four times a day, is not awakened at night with asthma, and has normal spirometry, low dose inhaled steroids, equivalent to 400 to 500 μg per day of budesonide or beclomethasone, is recommended (level 2). Higher doses of inhaled steroids are given to those subjects who are more symptomatic, and additional medication may be added such as nedocromil, ipratropium bromide, theophylline and oral long-acting beta2-agonist (level 3). At the time these guidelines were prepared, inhaled long-acting beta2-agonists such as salmeterol and formoterol were not available. According to more recent international guidelines (3-5), asthma is not controlled if an asthmatic requires an inhaled beta2-agonist daily, and even at this early stage low dose

Correspondence: Dr André Cartier, Service de pneumologie-recherche, Hôpital du Sacré-Cœur de Montréal, 5400, boulevard Génér eau, Montréal, Quebec H2L 1C5. Telephone (514) 338-2796, Fax (514) 338-3123

Can Respir J Vol 2 Suppl A March 1995
inhaled steroids are suggested. The same guidelines, however, suggest that cromoglicate or nedocromil may be used instead of steroids. Canadian and international guidelines thus differ in their definition of asthma control in terms of the maximum doses of beta-agonists needed before low dose inhaled steroids are introduced. This is also reflected in the daily practice of Canadian physicians, with some giving inhaled steroids much earlier than others. This difference in prescription is likely to be related to the fear of the side effects of inhaled steroids; if they are used prophylactically (ie, to abolish symptoms and beta-agonist use), they should not induce more side effects than benefits. To answer this dilemma, we must determine in adults on the one hand the safe daily dose and on the other the minimal effective dose.

**IS THERE A SAFE DAILY DOSE OF INHALED STEROIDs?**

The adverse effects of inhaled steroids are related to their local action and their systemic absorption (6). At an equivalent therapeutic dose, inhaled steroids have much fewer systemic side effects than oral steroids but, as the dosage is increased, the absorption and thus the risk of significant adverse effects is increased. Locally, hoarseness and oral pharyngeal candidiasis are the most frequent side effects; the frequency of these effects is dose-dependent and is effectively diminished by the use of a spacer device for the metered-dose inhaler (MDI) (7) or by rinsing the throat for the Turbuhaler. Cough and bronchospasm are much less frequent adverse effects.

Toogood (6) recently published a review of the adverse side effects associated with the systemic absorption of inhaled steroids. The effect of the hypothalamus/hypothalamic-adrenergic axis, with diminished plasma or urinary cortisol, is seen at a dose usually higher than 1500 µg/day of beclomethasone or its equivalent, but a few subjects taking a lower dose, such as 600 to 1000 µg/day, may exhibit abnormal findings. Even if these biochemical changes have not been associated with any clinical manifestations, except in one odd case (8), they must be taken into consideration while prescribing inhaled steroids for prophylaxis. The use of spacer devices with the MDI or throat rinsing with the Turbuhaler effectively reduces systemic absorption (9,10). An effect on bone metabolism has not been documented at doses lower than 1000 µg/day, although diminution of serum osteocalcin has been observed in some subjects taking doses of 1000 µg/day. There is no effect on glucose metabolism but changes in plasma cholesterol and required insulin dosage are controversial. There is no evidence of a higher incidence of cataracts in association with inhaled steroids (11). Finally, physicians are aware of easy bruising associated with high doses of inhaled steroids (12), but at doses lower than 800 to 1000 µg/day this complication is rare.

Therefore, in adults we may consider doses of inhaled steroids equivalent to 400 to 500 µg/day of budesonide or beclomethasone to be clearly safe, as there is no evidence of any systemic absorption or potentially serious adverse effects. It is less clear, however, whether doses between 500 and 1000 µg/day are as safe for all patients.

**IS THERE A MINIMAL EFFECTIVE DOSE?**

It is well established that inhaled steroids at low doses can improve the control of asthma in most subjects (13,14). Furthermore, early introduction of inhaled steroids in asthma seems justified in view of the recent studies of Agero et al (15) in children and of Haatela et al (16) in adults. Both these studies showed that those asthmatics who are given inhaled steroids early have a better outcome in terms of airway function in comparison with those who receive inhaled steroids at similar doses but at a later stage. In addition, the availability of inhaled steroids at high concentration, such as beclomethasone at 250 µg/dose or budesonide at 200 or 400 µg/dose, allows physicians to give low dose steroids once or twice a day, thus improving patient compliance greatly.

Keeping in mind the upper safe limit of 500 µg/day of inhaled steroids, we will only consider subjects who are well controlled with this low dose. Juniper et al (17) have shown in a double-blind placebo controlled study that budesonide 200 µg bid can markedly improve asthma control in symptomatic subjects requiring bronchodilators regularly. Indeed, apart from reducing symptoms and the need for rescue bronchodilators, budesonide was associated with a significant reduction of nonallergic bronchial responsiveness not seen with placebo. This one-year study showed that the improvement in nonallergic bronchial responsiveness and in symptoms reached a plateau after six months. More interestingly, some subjects on budesonide became completely asymptomatic during the study period, requiring no more bronchodilators and normalizing their bronchial response to methacholine and exercise.

In theory, if one had followed the Canadian or international guidelines, inhaled steroids should have been reduced and even stopped as patients became symptomatic. However, studies on the effect of inhaled steroids on nonallergic bronchial responsiveness have clearly demonstrated that short-term administration (up to 6 weeks) of inhaled steroids is associated with only a transient improvement in bronchial responsiveness and symptoms (17-19). However, Juniper et al (20) have shown that budesonide 200 µg bid given for one year leads to a more prolonged improvement of symptoms and nonallergic bronchial responsiveness, even after it has stopped, some subjects saw a recurrence of their symptoms (mainly cough) after three months of cessation of budesonide. Furthermore, Osterman et al (21) have shown that 50% of subjects who had received budesonide for one year maintained their improvement in bronchial responsiveness six months after cessation of budesonide. Also, Haatela et al (16) showed that a higher dose of budesonide (1200 µg/day) was associated with a prolonged improvement of asthma control in at least 33% of asthmatics receiving placebo for one year after having received budesonide 1200 µg/day for two years in a double-blind study. These data are thus in favour of prolonged treatment.

Would half the dose of inhaled steroids be as effective in maintaining such a control of asthma? There are no published studies that have addressed this question. However, in a
double-blind placebo controlled study, doubling the effective dose of inhaled steroids was associated with improvement in symptoms, elimination of daily symptoms, diminution in rescue bronchodilator utilization twice a day of the concentrated formulations of beclomethasone or budesonide.

This clearly favours the use of inhaled steroids for improvement.

CONCLUSION

Although inhaled steroids are used as a first line treatment in asthma, inhaled betagonists are still the first choice to relieve symptoms, and every asthma should have a betagonist inhaler at hand for treating asthma symptoms. However, when a mild asthma subject requires a betagonist regularly and almost daily, he or she should receive at least a trial of low dose inhaled steroids at the equivalent dose of 400 to 500 µg/day of beclomethasone or budesonide. The trial should last for at least one year. If there is no improvement in symptoms or reduction in betagonist use, the steroids should be stopped. There are no studies that have examined the prophylactic use of inhaled steroids in this situation, whereas Juniper et al (13) have shown in patients in whom asthma control was improved there is a clear reduction in asthma exacerbations with the prophylactic use of inhaled steroids. On the other hand, if the administration of low dose inhaled steroids is associated with a significant improvement in symptoms, and even if there is almost no use of betagonist, it is justified to continue the inhaled steroids at the same dose in order to maximize the gain. The duration of treatment should be at least one year after which one may try to reduce the dose to one inhalation per day for five or six months, trying then to stop it, without hesitating to increase or reintroduce the steroid upon recurrence of symptoms.

In conclusion, the early use of low dose inhaled steroids as a first line treatment will improve the quality of life of asthmatics, the majority having only mild symptoms (24).

1. Juniper E, Kline PA, Vasconcellos MA, Richardson OE, Byrne P. Inhaled steroids. In: British Thoracic Society, The Paediatric Association, the Research Unit of the Royal Children's Hospital, the Royal Australian College, the Royal College of General Practitioners, the Practitioners in Asthma Group, the Health Association of Accredited and Emergency Medicine, and the British Paediatric Respiratory Group. Thorax, 1985;40:24-26.