

Inhaled corticosteroids: Current products and their role in patient care

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Glucocorticoids have multiple effects on almost all cells implicated in the inflammatory process. They exert their effects by binding to the glucocorticoid receptor located in the cytoplasm of target cells. This activation of the glucocorticoid receptor regulates the transcription of these target cells in ways that interfere with arachidonic acid metabolism, reduce microvascular leakage, inhibit cytokine production and secretion, interfere with the syntheses of leukotrienes and prostaglandins, and increase the responsiveness of β -receptors of the airway smooth muscle.¹

The effect of glucocorticoids on lymphocytes is to inhibit the production of IL-2 and IL-4 and to induce selective apoptosis, which causes cell death. They also reduce the number of eosinophils and neutrophils by inhibiting their influx in the late-phase response and decrease the number of tissue macrophages and monocytes by inhibiting the release of IL-1, interferon, tumor necrosis factor, and various enzymes. Their influence on mast cells is indirectly caused by their effect on the release of mast cell growth factors. Glucocorticoids also substantially reduce the number of circulating basophils. The combined effect of these multiple reactions on the various immunologic cells involved in the inflammatory process is a potent blockade of damaging mediator synthesis and release.

INHALED CORTICOSTEROIDS AS THE CORNERSTONE OF ASTHMA CARE

The current concept of airway inflammation as the principal factor in airway hyperresponsiveness and the known anti-inflammatory action of glucocorticoids establishes inhaled corticosteroids as the first line of treatment in asthma. A summary of their multiple effects is presented in Table I.

PROVEN EFFICACY OF INHALED CORTICOSTEROIDS: CLINICAL TRIAL RESULTS

The efficacy of inhaled corticosteroids has been proved in a number of recent clinical trials. In a double-blind, placebo-controlled, parallel-group, randomized, 1-year trial with an inhaled corticosteroid, Juniper et al.² found a fourfold improvement in bronchial hyperre-

Abbreviations used

CFC:	Chlorofluorocarbon
HFA-134:	Hydrofluoralkane 134
MDI:	Metered-dose inhaler

sponsiveness in patients receiving the drug, with a decrease in symptoms, exacerbations, and need for bronchodilators. In a similar study design conducted over a 2-year period, Haahtela et al.³ demonstrated comparable results by showing that inhaled steroids significantly improved bronchial hyperreactivity, peak flow measurements, symptom scores, and the need for supplemental bronchodilators.

The effect of inhaled beclomethasone therapy on airway mucosal inflammation in atopic asthma was further investigated by Djukanovic et al.⁴ in 10 symptomatic atopic asthmatic patients whose disease severity required preventative anti-inflammatory treatment. Endobronchial biopsies were obtained before and after 6 weeks of therapy with beclomethasone. This was the first prospective study investigating the effects of topical corticosteroids on inflammatory cells in the airway mucosa of symptomatic atopic asthmatic subjects. The authors demonstrated that 6 weeks of treatment with inhaled beclomethasone produced a significant ($p < 0.05$) reduction in epithelial and mucosal mast cells and eosinophils and submucosal T lymphocytes in parallel with a sevenfold decrease in airway responsiveness ($p = 0.001$).⁴

Dose dependence of inhaled corticosteroids

The value of low doses of inhaled corticosteroids in improving measures of maximal expiratory airflow, bronchial reactivity, and control of asthma symptoms and in reducing the frequency of exacerbations and the number of hospitalizations in patients with mild disease is well established. Furthermore, Haahtela et al.⁵ demonstrated that better long-term control of asthma was obtained with early treatment with an inhaled corticosteroid than with the use of a β_2 -agonist and that control of the disease in most patients could be maintained with a lower dose of the corticosteroid than initially was thought needed to normalize lung function.

It is believed that a delay in initiating inhaled corticosteroid therapy for patients with mild asthma may impair the magnitude of the response to therapy.⁵ This is believed to be due to the irreversible change, possibly related to remodeling of the airway wall, that occurs

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TABLE I. Actions of inhaled corticosteroids in asthma therapy

● Increased
— Number and responsiveness of β_2 -adrenergic receptors
● Decreased
— Inflammation
— IgE synthesis
— Histamine synthesis
— Eicosanoid release

when an inhaled corticosteroid is not given. It also is thought that this remodeling may be inhibited by the corticosteroid.⁶

COMPARISON OF INHALED STEROIDS

Although few studies have been conducted to compare the efficacy of the various preparations of inhaled corticosteroids, differences in pharmacokinetics determine the proportion of the inhaled drug that reaches target cells in the airways as well as the amount of drug that enters the systemic circulation. Desirable properties of an inhaled glucocorticoid include high topical potency, low systemic bioavailability of that part of the dose swallowed by the patient, the rapid metabolic clearance of any amount of the drug that reaches the systemic circulation, and minimal absorption through airways.

SIDE EFFECTS OF GLUCOCORTICOIDS

The most frequently reported side effects of inhaled steroids are local, involve the upper airway, and are caused by oropharyngeal deposition of the drug. The most common side effect is dysphonia, which is reversible on discontinuation of the drug. Oropharyngeal candidiasis is most predominant in elderly or immunocompromised patients, especially those with multiple dosing regimens. Other local complications include cough and throat irritation. The majority of these side effects can be eliminated by rinsing the mouth after drug administration and by using spacer devices that facilitate intrapulmonary deposition of the drug and diminish local upper airway deposition.

Systemic side effects associated with inhaled glucocorticoids are largely dependent on the type of delivery system used and the pharmacokinetics of the corticosteroid. When a corticosteroid is inhaled, a fraction of the drug is deposited in the oropharynx and subsequently swallowed. The amount of inhaled corticosteroid reaching the systemic circulation is the sum of the pulmonary and orally bioavailable fractions. Moreover, the systemic availability of the swallowed amount will be determined by absorption from the gastrointestinal tract and the subsequent degree of first-pass metabolism. Systemic side effects include thinning of the skin, bruising, adrenal suppression, decreased bone metabolism, and decreased growth.¹

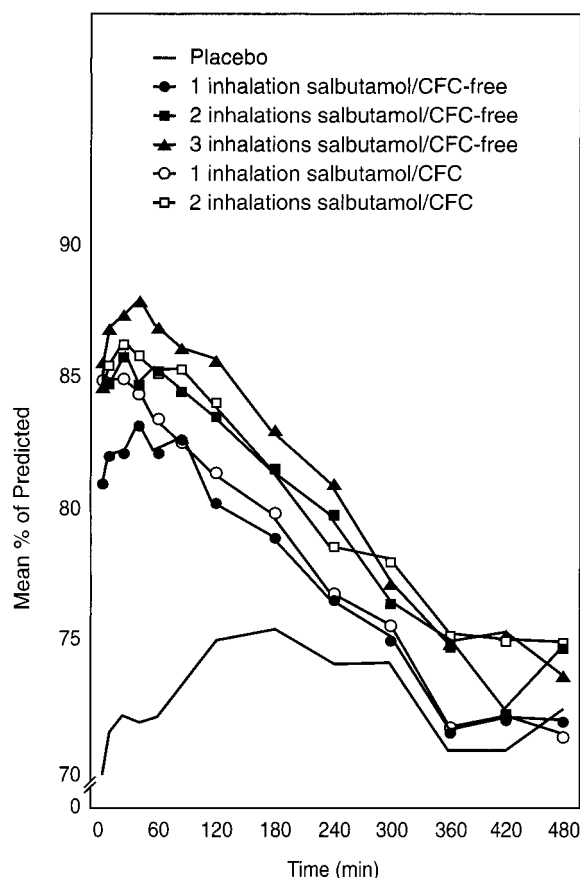


FIG. 1. Comparison of mean forced expiratory volume in 1 second data as a percentage of predicted value over time in 25 patients. Reprinted with permission from Dockhorn R, et al. *J Allergy Clin Immunol* 1995;96:50-6.

EFFECT OF THE DELIVERY SYSTEM

There are four ways to deliver inhaled corticosteroids: a metered-dose inhaler (MDI), an MDI with a large-volume spacer attachment, dry-powder inhalers, and nebulizers. Although MDIs, alone or with spacers attached, are the most common types of delivery systems, the accurate dispensation of a metered dose of the drug is deceptively difficult to accomplish. A large part of the problem is the coordination required to simultaneously inhale and actuate the MDI. This can result in excessive deposition of the drug in the oropharynx, which compromises drug delivery and deposition into the airways and contributes to the development of local and systemic side effects.

CFC-free MDIs

The worldwide ban on the use of chlorofluorocarbons (CFCs) as propellants initiated the development of alternatives that met the physical and chemical compatibility requirements of the drug and the aerosol. The ultimate goal of reformulation was to ensure continued availability of MDIs as a method of treatment while using a safe and effective system that addressed environ-

mental concerns. The development of hydrofluoroalkane 134 (HFA-134) met this objective.

In a preclinical toxicologic testing program of HFA-134, the European regulatory agency called the Committee for Proprietary Medicinal Products stated that there were no significant pharmacologic, toxicologic, or safety issues found during their review.⁷

The objective of a study presented to the Committee for Proprietary Medicinal Products was to determine if a dose of albuterol sulfate (known generically as salbutamol in Europe) in an HFA-134 propellant system was clinically comparable with albuterol sulfate in a CFC-propelled system. The primary objective measure was efficacy as assessed by forced expiratory volume in 1 second. The safety parameters were sitting heart rate and blood pressure, electrocardiogram, adverse events, physical examination, and clinical laboratory tests. Six treatment combinations were offered to 26 patients. A comparison of the mean forced expiratory volume in 1 second data for each of the six treatment groups showed that the albuterol/CFC-free system was clinically comparable to the albuterol/CFC system (Fig. 1).⁷

The safety and efficacy of the CFC-free propellant HFA-134 were further evaluated in a cumulative dose-response study conducted by Kleerup et al.⁸ They demonstrated statistically similar airway responses and side effects between the CFC and CFC-free preparations and determined HFA-134 albuterol to be a safe, effective, and equivalent substitute for CFC-albuterol.

CONCLUSIONS

Inhaled corticosteroids are currently the most effective anti-inflammatory medications for the treatment of asthma. Studies have demonstrated their efficacy in decreasing airway responsiveness, improving lung function, reducing symptoms, reducing the frequency and severity of exacerbations, and improving the quality of

life in patients with asthma. In severe or persistent asthma, long-term, high-dose regimens reduce the need for oral corticosteroids and therefore engender substantially fewer systemic adverse effects. The local side effects that are sometimes associated with inhaled corticosteroids can be minimized with the use of spacers and by rinsing the mouth after each use. Future developments in inhaled steroid therapy include concern with improving delivery systems, including use of CFC-free propellant systems.

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