

Inhaled Corticosteroids in Obstructive Airway Disease

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Summary

Inhaled corticosteroids play an important role in the management of obstructive airway disease, by suppressing airway inflammation that is central to the pathophysiology of these conditions. In asthma there is strong clinical evidence supporting the use of inhaled corticosteroids in mild, moderate, and severe persistent asthma to improve lung function, reduce exacerbations, and prevent death. In chronic obstructive pulmonary disease, inhaled corticosteroids improve symptoms, reduce frequency of exacerbations and hospitalizations, and should be considered in patients with moderate-to-severe airflow limitation who have persistent symptoms despite optimal bronchodilator therapy. Though the adverse effects of corticosteroids are less when given via inhalation than when given systemically, nevertheless, the adverse effects are important and need to be considered. Newer inhaled corticosteroids with better pharmacologic properties are being developed and will probably be available in the near future. Key words: chronic obstructive pulmonary disease, asthma, corticosteroids, aerosols, administration, inhalation, metered-dose inhaler. [Respir Care 2007;52(7):852–858. © 2007 Daedalus Enterprises]

Introduction

With the recognition that chronic airway inflammation is central to the pathophysiology of obstructive airway

disease, namely asthma and chronic obstructive pulmonary disease (COPD), anti-inflammatory therapies, particularly corticosteroids, have gained widespread acceptance. Bordley and colleagues demonstrated in 1949 that intra-

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muscular injections of adrenocorticotrophic hormone were effective in treating asthma.¹ This was followed by the introduction of oral cortisone therapy for patients with difficult-to-control asthma.² Long-term oral corticosteroid use was a fairly common practice in the mid-to-late 20th century, but was associated with important systemic adverse effects. The breakthrough that revolutionized asthma therapy was the introduction of inhaled corticosteroids in 1972, initially as a means to reduce the dose of oral corticosteroids.³ However, with their clinical efficacy and good safety profile, inhaled corticosteroids took the place of oral corticosteroids and established themselves as a cornerstone in the management of asthma.

The use of inhaled corticosteroids in COPD is more controversial. With the success of inhaled corticosteroids in asthma, it was hoped that this could be replicated in COPD. Like asthma, COPD is characterized in part by chronic airway inflammation, and this provided the rationale for inhaled corticosteroids in COPD. However, it is now recognized that the inflammatory pathway in COPD differs markedly from that in asthma, and this translates to differences in response to treatment. Controversy and debate remain on the role of inhaled corticosteroids in COPD management. Nevertheless, the use of inhaled corticosteroids has been escalating, and they have been used in up to 65% of COPD patients in some population studies.⁴

There is a huge and growing body of literature on inhaled corticosteroids in asthma and COPD. In this paper we review the rationale for inhaled corticosteroids, currently available preparations, the latest evidence for inhaled corticosteroids in obstructive airway disease, and the risks of and some of the controversies about inhaled corticosteroids. This review will focus on the literature on the adult population.

The Rationale for Inhaled Corticosteroids in Obstructive Airway Diseases

Though both asthma and COPD are characterized by airflow limitation and chronic airway inflammation, from a cellular and molecular perspective there are several differences in their inflammatory pathways. The inflammatory process in asthma is characterized by eosinophils, mast cells, and CD4⁺ T lymphocytes, which produce the type-2 helper cytokines, interleukin 4, 5, and 13 (IL-4, IL-5, IL-13).⁵ These mediators recruit inflammatory cells and result in largely reversible airway hyperreactivity.

On the other hand, the nature of airway inflammation in COPD is different from that in asthma. COPD is characterized by an increase in macrophages, neutrophils, and CD8⁺ T lymphocytes, which occurs after exposure to noxious stimuli. Important mediators include IL-8 and tumor necrosis factor alpha. Largely irreversible structural

changes are seen in COPD, with alveolar destruction, airway scarring, fibrosis, and squamous metaplasia.⁶

Corticosteroids work by suppressing virtually every step of the inflammatory pathway. They do this by influencing multiple signal transduction and gene expression pathways. The most important action is switching off multiple activated inflammatory genes (that encode cytokines, chemokines, adhesion molecules, inflammatory enzymes, receptors, and proteins) by inhibiting histone acetyltransferases and recruiting histone deacetylases.⁷ In addition, corticosteroids may activate several anti-inflammatory genes and increase the degradation of messenger ribonucleic acid that encodes certain inflammatory proteins. At the cellular level, corticosteroids reduce the number of inflammatory cells in the airways by suppressing the production of chemotactic mediators and adhesion molecules (Fig. 1).⁸ By suppressing the number of eosinophils and inhibiting release of inflammatory products, they are especially effective in controlling eosinophil-associated inflammation that characterizes asthma.⁵

Although the neutrophil-predominant inflammatory process in COPD is often less responsive than is the eosinophil-predominant process in asthma, there are observations that offer the possibility that corticosteroid therapy may be useful as well. For example, corticosteroids may enhance β -agonist activity⁹ and may reduce the systemic inflammatory state induced by COPD.^{10,11} Despite these observations, many of the clinical trials have found minimal or no corticosteroid effects on lung function. One possible explanation for this discrepancy is that the chronic inflammatory state of COPD, as well as oxidative stress from continued tobacco smoke exposure, may impair corticosteroid receptors.¹² However, some data suggest that there is an asthma-like subgroup of COPD patients with bronchial hyperresponsiveness that may be more amenable to corticosteroid therapy.¹³ Also, pathological and biochemical patterns of inflammation during exacerbations, which involve the influx of various inflammatory cells and mediators and increase airway hyperresponsiveness, might be amenable to corticosteroid therapy.¹⁴

Inhaled Corticosteroids: Preparations and Modes of Delivery

Oral corticosteroids were used to treat obstructive airway disease prior to the introduction of inhaled corticosteroids. The major problem with oral steroids was the considerable systemic adverse effects. Inhalation of corticosteroids aims to maximize therapeutic efficacy while minimizing systemic adverse effects by delivering the drug directly to the site of action (the airways), thus limiting systemic absorption.

There are currently 6 inhaled corticosteroids preparations available to treat asthma in the United States:

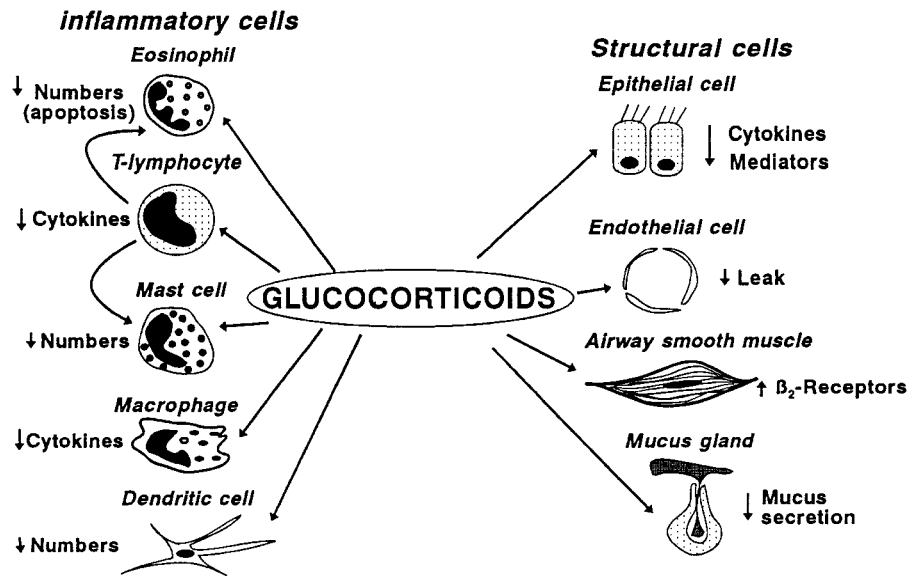


Fig. 1. Effects of corticosteroids on inflammatory and structural cells. (From Reference 8, with permission.)

Table 1. Inhaled Corticosteroid Preparations, Delivery Systems, and Dosages

Generic Name	Brand Name	Delivery System	Dose
Beclomethasone dipropionate	QVAR	HFA MDI	40 µg/puff or 80 µg/puff
Budesonide	Pulmicort Turbohaler	DPI	200 µg/dose
	Pulmicort Respules	Nebulizer suspension	0.25 or 0.5 mg/2 mL
Flunisolide	Aerobid	MDI	250 µg/puff
Fluticasone propionate	Flovent HFA	HFA MDI	44, 110, or 220 µg/puff
	Flovent Diskus*	DPI	50, 100, or 250 µg/dose
Mometasone furoate	Asmanex	DPI	220 µg/dose
Triamcinolone acetonide	Azmacort	MDI	100 µg/puff

* available in Europe

HFA = hydrofluoroalkane; MDI = metered-dose inhaler; DPI = dry powder inhaler.

beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate, and triamcinolone acetonide (Table 1). Several of these are also available in combination inhalers with long acting β agonists (eg formoterol and budesonide, salmeterol and fluticasone). It is important to realize that these agents are not equivalent; there are important differences in their pharmacokinetics and pharmacodynamic properties that affect their efficacy and safety. The higher-potency second-generation inhaled corticosteroids, such as fluticasone and mometasone, despite having properties that lower systemic bioactivity, can have adverse effects.¹⁵ The recent development of “designer” third-generation inhaled corticosteroids, such as ciclesonide, might exhibit a superior safety profile to currently available inhaled corticosteroids, and will be discussed later in this review.

Equally important are the delivery devices for inhaled corticosteroids. There are 3 principal devices: the metered-dose inhaler (MDI), the dry powder inhaler (DPI), and the nebulizer. Earlier MDIs used chlorofluorocarbons as propellants, which produced aerosols that were inefficiently delivered because of their relatively large particle size, resulting in as little as 10% lung deposition. Following ratification of the Montreal Protocol, non-ozone-depleting hydrofluoroalkane propellants are being introduced. The hydrofluoroalkane-based formulations have enhanced lung deposition¹⁶ because of their smaller average particle size and better aerodynamic properties. Hand-to-mouth coordination is required when using MDIs, and spacers are recommended to facilitate drug delivery.

DPIs are breath-actuated devices that may be easier for some patients to use because they do not require as much coordination. However, drug delivery depends on

the inspiratory flow generated by the patient.¹⁷ Also, DPIs produce larger particles, which results in high oral deposition.

Both MDI and DPI are effective methods of drug delivery, and a systemic review found no clear superiority of one over the other.¹⁸ Nebulized corticosteroids have been used especially in pediatric patients. However, there are no clinical data to suggest superior benefit from nebulized corticosteroids compared with hand-held inhaler with spacer device.¹⁹ It must be emphasized that good patient technique is key in ensuring optimal drug delivery to the airways, and careful selection of device based on the patient's profile is important.

The Evidence Base for Inhaled Corticosteroids in Asthma

There is a large evidence base for inhaled corticosteroids in asthma. Their benefit in improving pulmonary function and symptoms has been demonstrated in multiple studies. Population studies have also shown an effect in reducing exacerbations,²⁰ hospitalizations,²¹ and mortality.²² Several professional bodies, including the National Asthma Education and Prevention Program Expert Panel, recommend inhaled corticosteroids as the agent of choice for mild, moderate, and persistent asthma.^{23–26} Though the role of inhaled corticosteroids in the maintenance therapy of moderate-to-severe persistent asthma is well established, there remain several controversies.

Role in Acute Asthma

It was previously believed that the role of inhaled corticosteroids was predominantly in the long-term maintenance therapy of asthma, and that they were of limited usefulness in the acute setting. A Cochrane meta-analysis on inhaled corticosteroids in acute asthma in the emergency department supported this notion; it concluded that, though inhaled corticosteroids decrease hospital admissions compared to placebo, there was insufficient evidence that they improved symptoms or pulmonary function, or were as effective as systemic steroids.²⁷ Emerging data suggest that multiple doses of inhaled corticosteroids may be beneficial in the early phase of an asthma exacerbation.²⁸ However, systemic corticosteroids remain at present the treatment of choice in acute asthma.

Role in Mild Persistent Asthma

Previous National Asthma Education and Prevention Program guidelines recommended daily use of inhaled corticosteroids only for moderate to persistent asthma. These recommendations were extended to "mild persistent" asthma when the guidelines were revised in 2002.²⁶ There

is good evidence from several studies that inhaled corticosteroids are efficacious in controlling mild asthma and reducing exacerbations, notably the steroid treatment as regular therapy (START) trial²⁹ and the trial by O'Byrne et al on low-dose inhaled budesonide and formoterol in mild persistent asthma.³⁰ This was challenged by the improving asthma control trial by the Asthma Clinical Research Network, which suggested that daily inhaled corticosteroid treatment of patients with mild persistent asthma was only marginally better than intermittent treatment, with no differences in post-bronchodilator FEV₁ or exacerbations.³¹ The study indicated that patients with mild persistent asthma could be treated with intermittent courses of inhaled or oral corticosteroids, together with an action plan. Though minimizing exposure to corticosteroids is a good thing, there is concern that chronic airway inflammation is present even in patients with mild asthma and without anti-inflammatory treatment, and that remodeling may occur and lead to progressive decline in lung function.³² In addition, studies have suggested that early intervention with inhaled corticosteroids reduces the loss of FEV₁.³³

Combination Therapy With Long-Acting β_2 Agonists

Meta-analyses show that addition of long-acting β_2 agonists to moderate doses of inhaled corticosteroids in patients with asthma symptomatic at that dose results in significantly greater clinical benefit than increasing the dose of inhaled corticosteroids by 2-fold or more.^{34,35} However, there has been concern regarding the overall safety of long-acting β_2 agonists. A recent meta-analysis showed a small but significantly higher incidence of death and other major adverse outcomes in patients with asthma using long-acting β_2 agonists.³⁶ This led the U.S. Food and Drug Administration to issue a "black box" warning that "these medications may increase the chance of a severe asthma episode, and death when those episodes occur."³⁷ A prominent study in the meta-analysis was the salmeterol multicenter asthma trial,³⁸ which suggested that racial and genetic factors may be involved in these adverse outcomes. Others have argued that insufficient use of inhaled corticosteroids, and monotherapy with long-acting β_2 agonists may be the problems, because there were no significant differences between the 2 groups who used inhaled corticosteroids.³⁹

The Evidence Base for Inhaled Corticosteroids in COPD

No pharmacologic intervention has been shown to reverse the natural history of COPD, and treatment is generally aimed at alleviating symptoms, improving function, and reducing exacerbations and hospitalizations. There is

no doubt that a short course of oral corticosteroid therapy given during a COPD exacerbation improves lung function and reduces the relapse rate,⁴⁰ but the role of inhaled corticosteroids in COPD is controversial. Four large, long-term clinical trials that compared inhaled corticosteroids to placebo did not show any difference in the rate of decline in lung function.^{41–44} Two systematic reviews on this issue came to opposite conclusions.^{45,46} Currently, the only intervention that effectively slows the decline in pulmonary function is smoking cessation.

There have been some beneficial effects of inhaled corticosteroids demonstrated for other clinically relevant outcomes, such as symptoms, frequency of exacerbations, and hospitalizations. Guidelines recommend that inhaled corticosteroids be considered for patients with moderate-to-severe airflow limitation who have persistent symptoms despite optimal bronchodilator therapy.⁴⁷ This is based in part on the inhaled steroids in obstructive lung disease in Europe trial, which found fewer exacerbations in patients with severe COPD.⁴³ In the study by the Lung Health Study Research Group,⁴⁸ patients with moderate COPD had symptomatic improvement and reduced frequency of exacerbations with inhaled corticosteroids.

Inhaled Corticosteroids and COPD Mortality

Observational studies have found lower mortality and fewer rehospitalizations with inhaled corticosteroids,⁴⁹ and a meta-analysis of long-term trials found that inhaled corticosteroids significantly reduced mortality from all causes in patients with COPD.⁵⁰ This was prospectively studied in the “toward a revolution in COPD health” (TORCH) trial, which randomized more than 6,000 COPD patients to inhaled salmeterol plus fluticasone, salmeterol alone, fluticasone alone, or placebo.⁵¹ The findings were that the difference in all-course mortality between combination therapy and placebo did not quite reach statistical significance (12.6% vs 15.2%, $p = 0.052$). The study did show that combination therapy, as compared with monotherapy with long-acting β_2 agonists or inhaled corticosteroids, significantly reduced exacerbations, improved health status scores, and mitigated FEV₁ decline.

Risks of Inhaled Corticosteroids

The adverse effects of systemic corticosteroids are well known. Inhaled corticosteroids are generally associated with lower steroid blood levels and correspondingly less adverse effect.

A meta-analysis of randomized trials found no higher risk of loss of bone density or fractures,⁵² but previous observational studies had reported reduction in bone density.⁵³ There is a cumulative risk of cataracts⁵⁴ and a 1.44 odds ratio for glaucoma.⁵⁵ Other adverse effects include

bruising and local infections, such as candidiasis. Unlike the situation with systemic corticosteroid therapy, few data suggest any clinically important hypothalamic-pituitary-adrenal axis suppression, peptic ulcer disease, psychosis, hyperglycemia, or myopathy related to inhaled corticosteroids use.

A finding in the TORCH study that had not previously been reported in studies that involved inhaled corticosteroids was a higher rate of pneumonia among patients who received study medications that contained fluticasone propionate, despite fewer exacerbations.⁵¹ This finding requires further investigation to determine its importance.

Taken together, the data remind us that, although inhaled corticosteroids appear to have considerably fewer adverse effects, the adverse effects are important and need to be considered in the decision to give a patient inhaled corticosteroids.

New Developments in Inhaled Corticosteroids for Obstructive Airways Disease

Ciclesonide

Ciclesonide is one of the “designer” third-generation inhaled corticosteroids being developed with lung-deposition characteristics and intrinsic properties to optimize clinical efficacy. Ciclesonide is a prodrug, like beclomethasone dipropionate, which is activated by lung esterase and thus minimizes oropharyngeal effects. Its MDI formulation with a new hydrofluoroalkane propellant delivers smaller aerosol particles and therefore has better lung deposition. In addition, it is suitable for once-daily dosing, because it undergoes lipid conjugation within the lungs, has negligible oral bioavailability and high protein binding, and has rapid clearance, which reduces systemic effects.^{56,57} These properties may give ciclesonide a better therapeutic margin.^{58,59} Ciclesonide is awaiting U.S. Food and Drug Administration approval for use in asthma.

Using Biomarkers to Guide Treatment of Moderate Asthma

Fractional exhaled nitric oxide has been extensively investigated in asthma; it correlates with predominantly eosinophilic airway inflammation, and it is reduced by corticosteroids. The recent arrival of handheld portable nitric oxide analyzers may change asthma management. With fractional exhaled nitric oxide measurements, maintenance doses of inhaled corticosteroids may be significantly reduced without compromising asthma control.⁶⁰

Summary

Inhaled corticosteroids play an important role in the management of obstructive airway disease. In asthma, strong clinical evidence supports the use of inhaled corticosteroids in mild, moderate, and severe persistent asthma to improve lung function, reduce exacerbations, and prevent death. In COPD, inhaled corticosteroids improve symptoms, reduce the frequency of exacerbations and hospitalizations, and should be considered in patients with moderate-to-severe airflow limitation who have persistent symptoms despite optimal bronchodilator therapy. Though the adverse effects of corticosteroids are reduced when given via inhalation, nevertheless they are important and need to be considered. Newer inhaled corticosteroids with better pharmacologic properties are being developed and will probably be available in the near future.

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