

Clinical use of inhaled corticosteroids in asthma

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Asthma has been recognized to be a chronic inflammatory disease,¹ and inhaled corticosteroids appear to be a logical treatment option. Inhaled corticosteroids act locally in the airway, have proven efficacy, and are advocated for treatment of milder stages of asthma. However, this form of therapy is fraught with compliance problems and concerns about systemic side effects and cost. In the present context of overall increasing health-care costs, the choice of drug regimen for asthma should also be based on cost-effectiveness studies. At present very few data exist on the cost-effectiveness of inhaled corticosteroids as a class of drug in the care of patients with asthma. This review will examine and discuss these novel perspectives in asthma therapy.

EFFECT OF INHALED CORTICOSTEROIDS ON THE INFLAMMATORY RESPONSE

The molecular mechanisms of corticosteroid action have been extensively reviewed in this supplement and have also been reviewed recently by Barnes and Pedersen.² Glucocorticoids exert a direct inhibition on many of the cells specifically involved in bronchial inflammation.³ The major advantage of inhaled corticosteroids lies in their ability to control the number and local activation of inflammatory cells.⁴

Many clinical trials have proved the clinical efficacy of inhaled corticosteroids in treating all types of asthma. Accordingly, recently published guidelines recommend their use by patients with moderate and severe asthma.¹ In addition, because the presence of inflammation in bronchi has been documented in subjects with mild asthma⁵ and in newly diagnosed patients,⁶ antiinflammatory ther-

apy has been proposed to treat mild, persistent asthma.⁷ In patients with this type of asthma, nedocromil sodium or sodium cromoglycate might be a useful alternative to inhaled corticosteroids. Inhaled corticosteroids are considered the treatment of choice for patients who have only nocturnal symptoms type of asthma.⁸

In experimentally induced asthma, inhaled corticosteroids have been shown to decrease the severity of responses to both direct and indirect stimuli.⁹ In allergen bronchoprovocations in patients with dual reactions, pretreatment with a single dose of beclomethasone (200 µg) reduced both the late response and the increase in airway responsiveness induced by the challenge.¹⁰ This effect was more important when the duration of pretreatment was increased.¹¹ In addition, prolonged therapy for 1 month also conferred protection against the early response.¹¹

The effects of inhaled corticosteroids on airway responsiveness and clinical severity have been shown to be related to the dose,¹² the frequency of administration,¹³ and the duration of treatment.¹⁴ Thus high doses are usually recommended at the beginning of therapy, with subsequent tapering to the minimum maintenance dose able to control the symptoms.¹ Unfortunately, regular use of inhaled steroids is required to maintain efficacy.¹⁴ Discontinuation of treatment after 6 weeks resulted in a return to pretreatment values after only 1 week.¹⁴ Exacerbation of the disease might even occur after a few years of regular treatment.¹⁵ However, in some patients with very mild asthma, prolonged therapy with inhaled corticosteroids seemed to allow complete resolution of inflammation and persistence of an asymptomatic stage even after cessation of therapy for at least 3 months.¹⁶ This finding might be used as an argument for the early institution of therapy with inhaled corticosteroids for patients newly diagnosed with asthma in an attempt to prevent the development of long-lasting inflammation, which is more difficult to treat.

This clinical efficacy has been confirmed by pathologic studies. After 10 years of treatment with inhaled steroids, bronchial mucosal biopsies

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showed suppression of inflammation; however, areas of metaplasia persisted, along with bronchial hyperresponsiveness.¹⁷

For reasons that are unclear, compliance with inhaled corticosteroid therapy appears to be poor. In one study that compared the use of two non-bronchodilator drugs (lodoxamide, a cromolyn-like agent, and tiotropium pivalate, an inhaled corticosteroid), overall compliance was 37.3%. Compliance was similar in both treatment groups, and both underuse and overuse were observed. However, valid data were able to be obtained in only 6 of 34 patients,¹⁸ which highlights the difficulties inherent in compliant drug use in patients with asthma. These findings were confirmed in another study that compared administration of inhaled corticosteroids four times a day with administration twice a day.¹⁹ Compliance was worse in the group in which administration was four times a day, as might have been expected. This is unfortunate, because improvement in symptoms and peak expiratory flow rates have been shown to be greater with administration four times a day than with administration twice a day.¹³

Although generalization of these clinical trial findings to clinical practice with inhaled corticosteroids is obviously strained, the question is clearly one of compliance. The absence of immediate relief from administration of the drug, in contrast to bronchodilators, might be an important explanatory factor. Further studies are needed to assess the practical importance of this problem, because with a noncompliant patient exacerbation of the disease might occur despite prescription of an effective regimen.

PHARMACOLOGIC CHARACTERISTICS

Detailed pharmacokinetics of the available inhaled corticosteroids have recently been reviewed.² Inhaled drugs should have high topical potency, low systemic bioavailability, and rapid metabolic clearance of the fraction of the dose that is swallowed and that enters the portal and systemic circulation. After inhalation, 80% to 90% of a dose is deposited in the oropharynx and swallowed; this fraction is thought to be responsible for both local oropharyngeal and systemic side effects. Administration of the drug through a volume spacer markedly reduces this fraction. Only 10% to 20% of the total dose is ultimately deposited in the lower airways and responsible for the primary beneficial effect. An important fraction of this latter dose is again absorbed into the systemic circulation (Fig. 1).

Because most of the studies conducted for determining these pharmacologic characteristics have been carried out on healthy volunteers, the influence of anatomic and physiologic alterations resulting from asthma are unknown. Moreover, few studies have compared the efficacy of available preparations in patients with asthma. Two studies showed that the effectiveness of budesonide and beclomethasone was equivalent at doses that were low (400 $\mu\text{g}/\text{day}$),²⁰ moderate (800 $\mu\text{g}/\text{day}$),²⁰ and high (1500 $\mu\text{g}/\text{day}$).²¹ Fluticasone propionate, 200 $\mu\text{g}/\text{day}$, was shown to be as effective as beclomethasone dipropionate, 400 $\mu\text{g}/\text{day}$.²² The higher potency of fluticasone was confirmed at the high dose of 1500 $\mu\text{g}/\text{day}$.²³ The relative binding affinities, potency, and doses delivered are summarized in Table I.

CLINICAL ADVERSE EFFECTS

Sensitivity to side effects of inhaled corticosteroids varies between individuals. Evaluations of the occurrence and impact of side effects are further confounded by the fact that most patients have at some time in the past been treated with oral corticosteroids.^{2, 10} Concern about the occurrence of symptomatic side effects is legitimate because therapy with inhaled corticosteroids is usually contemplated for long periods, if not for an entire lifetime. However, extremely long follow-up is needed to describe the particular side effects that occur with such drug use. Therefore, no definite answer is available at present. A more detailed description of the side effects can be found in a recent review by Barnes and Pedersen.²

The well-known effects of oral corticosteroids on bone metabolism, with the resulting risk of fracture due to osteoporosis, have been a concern with inhaled corticosteroids. However, a recent study of patients receiving long-term inhaled corticosteroid therapy for asthma showed that, after 10 years of treatment and a lifetime dose of inhaled corticosteroids greater than 3 gm, women had normal or near-normal bone density and little or no increase in the risk of fracture.²⁴ However, daily doses higher than 2 mg/day reduced bone density slightly. This loss could be offset with estrogen therapy in postmenopausal women. Altogether, because these high doses are needed in only a few patients and because inhaled corticosteroids potentially decrease the need for oral prednisone therapy, long-term administration of inhaled corticosteroids appears to be safe. However, the risk:benefit ratio might vary according to the severity of the disease.

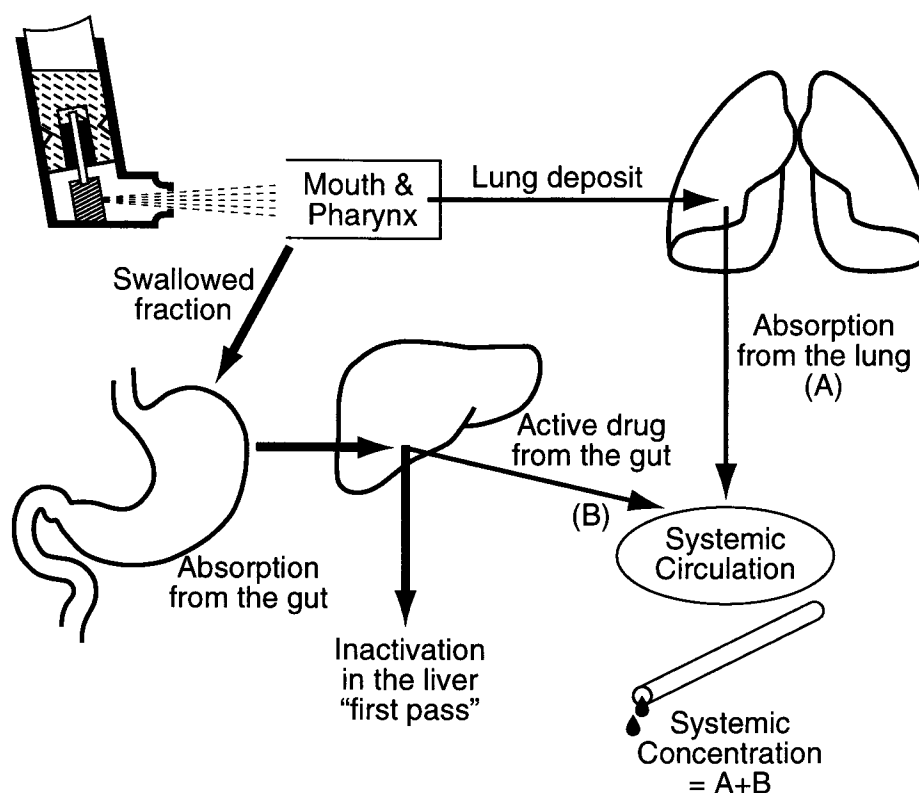


FIG. 1. The fate of inhaled steroids. The amount of an inhaled glucocorticosteroid that reaches the systemic circulation is the sum of the pulmonary and orally bioavailable fractions. The fraction deposited in the mouth will be swallowed, and systemic availability will be determined by absorption from the gastrointestinal tract and the degree of first-pass metabolism. The fraction deposited in the intrapulmonary airway is likely to be more or less completely absorbed in active form to the systemic circulation, because there is no evidence for any degree of metabolic inactivation in inhaled steroids currently being used. The systemic concentration will be reduced by continuous recirculation and inactivation in the liver. (Modified from Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma. *Am Rev Respir Dis* 1993;148:S1-26.)

High doses of inhaled corticosteroids suppress the hypothalamic pituitary adrenal axis, but without serious clinical consequences.^{2, 25} Inhaled corticosteroids at high doses also influence glucose and lipid metabolism²⁶; however, the clinical significance of these alterations is unknown.

In children, long-term administration of inhaled beclomethasone (400 µg/day) decreases linear growth.²⁷ Nonetheless, long-term data seem to indicate that lung development and functional capacity are improved and that final growth is unaffected.²⁸ These conflicting results require clarification.

There have been concerns regarding the risk of cataract formation as a result of inhaled corticosteroid use. This risk appears to be entirely related to prior use of oral corticosteroids.²⁹ Long-term administration of inhaled corticosteroids appears

to have an impact on the skin, resulting in purpura,³⁰ dermal thinning,³⁰ and easy bruising,³¹ especially in elderly patients.

Depending on the dose, the frequency of administration, and the delivery system used, local side effects of inhaled corticosteroids can be minimized. The most common side effect is dysphonia, resulting from steroid myopathy of the laryngeal muscles; this affects one third of patients and is reversible after discontinuation of treatment.³² Oral candidiasis frequently occurs but can be prevented by using a volume spacer, which reduces the amount of inhaled corticosteroid deposited locally. Rinsing the mouth after administration produces the same protective effect.² The pathology of the increased prevalence of oropharyngeal candidiasis is not understood.

The existence of these side effects emphasizes

TABLE I. Characteristics of inhaled glucocorticoids

Glucocorticoid	Relative binding affinity*	Relative blanching potency†	Inhaled dose, µg/puff
Beclomethasone dipropionate‡	0.4	600	50§
Beclomethasone monopropionate‡	13.5	450	—
Triamcinolone	3.6	330	100
Flunisolide	1.8	330	250
Budesonide¶	9.4	980	50, 100, 200
Fluticasone¶¶	18.0	1200	25, 50, 125

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*Values are for binding affinity to human glucocorticoid receptors in vitro, relative to that of dexamethasone.

†Blanching potency on human skin indicates topical potency, relative to that of dexamethasone.

‡Beclomethasone dipropionate is converted in the liver to the more active beclomethasone monopropionate.

§Larger doses (100, 200, or 250 µg/puff) are available in Europe, Asia, and Australia but are not yet available in the United States.

||The dose delivered by the metered-dose inhaler is 200 µg, but 100 µg is delivered by a spacer.

¶¶Not available in the United States.

the need to individualize therapy so as to follow closely the variations in treatment need, specific patient symptoms, and susceptibility to adverse effects. In particular, high-dose therapy with frequent drug administration should be used only in cases of acute exacerbation and should be reduced as soon as possible to the minimum maintenance dose capable of controlling the symptoms.¹

COST OF TREATMENT IN ASTHMA

In the year 1990, total outpatient care for asthma in the United States amounted to 1.5 million hospital visits and 6.5 million physician visits. Charges for these visits were \$129.2 million and \$193.3 million, respectively. Expenditures for medications amounted to \$712 million, corresponding to 3.3 million prescriptions for theophylline, 2.99 million for bronchodilators, and 1.15 million for corticosteroid preparations.³³ These numbers are likely to change because of the impact of the consensus guidelines for treatment that were published in 1992¹; however, no data are currently available. A retrospective study of the cost of outpatient treatment between 1977 and 1987 at

one facility in Switzerland showed that the overall cost remained the same.³⁴ The main explanation for this finding is that less expensive drugs, such as theophylline and oral prednisone, were replaced by more effective but more expensive inhaled corticosteroids, such as inhaled beclomethasone, which was introduced in this period.

Asthma has an economic impact not only on affected individuals but also on their families, the health-care system, and society as a whole.³⁵ These different perspectives should be kept in mind when assessing the results of studies on the cost of caring for patients with asthma.

Inhaled corticosteroids are most effective in treating asthma when combined with bronchodilators.² The economic consequences of such treatment have been addressed by only six papers, all of which used data on either beclomethasone dipropionate or budesonide. The first two studies addressed the impact of the use of high-dose budesonide (800 µg/day) for 5 years in 36 patients³⁶ and for 11 years in 14 counties in Sweden.³⁷ Both studies showed a reduction in inpatient hospital admissions and cost of care compared with the 2 years preceding the study.

The third study addressed the cost-effectiveness of doubling the budesonide dose from 400 µg/day to 800 µg/day in patients with mild to moderate asthma who were treated for 6 weeks with each regimen. No differences in symptoms and lung function were observed, and the costs were increased in the high-dose group.³⁸

The fourth study evaluated the cost-effectiveness of using budesonide to treat children, aged 1 to 3 years, who had persistent symptoms of asthma. Budesonide increased symptom-free days compared with placebo and reduced overall costs by £6.33 (about \$9.45) per symptom-free day gained.³⁹

The fifth study looked at the cost-effectiveness of adding inhaled corticosteroids to β_2 -agonist therapy for 12 months in children aged 7 to 16 years.⁴⁰ The combined regimen was more effective, but at an additional cost of \$83 per 10% increase in forced expiratory volume in 1 second and \$4.75 per symptom-free day gained.

Finally, inhaled corticosteroids (beclomethasone, 800 µg/day) and β_2 -agonists were shown to be more effective than β_2 -agonists and placebo or β_2 -agonists and ipratropium bromide in adults 18 to 60 years of age.⁴¹ However, the savings associated with inhaled corticosteroid use (\$175) were offset by the increased costs related to inhaled corticosteroids (\$376). The incremental cost-effectiveness ratio varied from \$200 per 10% improve-

ment in forced expiratory volume in 1 second to \$5 per symptom-free day gained. Altogether, from a societal perspective, treatment with inhaled corticosteroids led to increased productivity. If the economic benefits linked with this increased productivity were valued at more than \$42/day, this treatment brought net societal savings.⁴¹

All of these studies underscore the fact that cost-effectiveness studies can provide very different results depending on the severity of the disease, the endpoint chosen, and the type of costs and perspective taken. As a consequence, standardization is needed if meaningful information is to be derived from such studies.

CONCLUSIONS

Inhaled corticosteroids are a well-established treatment modality for asthma and are recommended in guidelines for the treatment of patients with moderate and severe asthma. These agents are effective despite variable problems with compliance and they do not present the systemic side effects of oral steroids, even when used for longer than 10 years. Therefore, benefits seem to outweigh risks in patients with moderate and severe asthma. The question of whether benefits outweigh risks for patients with mild asthma is disputable, in the absence of additional data, but the natural history of the disease and long-term data about the use of inhaled corticosteroids in patients with mild asthma should provide an answer to this question in the near future.

Inhaled corticosteroids are not inexpensive. Their cost-effectiveness seems to be established in patients with moderate to severe asthma when both direct medical costs and indirect costs, such as loss in productivity, are taken into account. Inhaled corticosteroids may be unaffordable for some patients who are in health-care systems in which the patient is responsible for the purchase of drugs used in an outpatient setting. These patients would have to rely on less effective treatment strategies with the ensuing risk of exacerbation of their disease, which leads to utilization of expensive health-care resources such as emergency department visits and hospitalizations.

In conclusion, more data on the costs of drug treatment are necessary, specifically regarding other types of medications used to treat patients with asthma. Furthermore, information is urgently needed on the cost-effectiveness of alternate interventions, such as patient education and the impact of specialist care. Education seems to be the most promising of these alternatives because it has the

potential to increase patient compliance and in turn decrease the amounts and numbers of drugs needed to control symptoms. This might be another way to improve the state of health and quality of life of patients with asthma while further decreasing the cost of therapy for the patients and society and the use of expensive health-care resources for this common disease.

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