

19782

DRUG THERAPY

ALEASTAIR J.J. WOOD, M.D., Editor

INHALED GLUCOCORTICOIDS FOR ASTHMA

PETER J. BARNES, D.M., D.Sc.

GLUCCORTICOIDS are the most effective therapy available for patients with asthma. They may be administered either orally or, much more safely, by inhalation. With the recognition that airway inflammation is present even in patients with mild asthma, therapy with inhaled glucocorticoids is now recommended at a much earlier stage.¹ However, despite their proved efficacy in the treatment of asthma, enthusiasm for their use has been tempered by concern about systemic side effects. Because of this concern, less effective therapies are often preferred, particularly for children.

MECHANISM OF ACTION

Molecular Mechanisms

Inhaled glucocorticoids are highly lipophilic. They rapidly enter airway cells, where they bind to cytosolic receptors. The glucocorticoid-receptor complexes then move quickly into the nucleus. There they bind to the glucocorticoid-responsive elements of genes, thereby either increasing or decreasing gene transcription. They also bind to, and disrupt the activity of, other transcription factors in the nucleus.² It is likely that the altered transcription of many different genes is involved in the anti-asthma effect of glucocorticoids, but the drugs' most important action may be to inhibit transcription of the genes for the cytokines implicated in asthmatic inflammation.²

Cellular Effects

Glucocorticoids may have direct inhibitory effects on many of the cells involved in airway inflammation in asthma, including macrophages, T-lymphocytes, eosinophils, and airway epithelial cells.³ In culture, the drugs decrease cytokine-mediated survival of eosinophils by stimulating apoptosis. This process may explain the reduction in the number of eosinophils in the circulation and airways of patients with asthma during glucocorticoid therapy,^{4,5} particularly the fraction of eosinophils with low density.⁶ Glucocorticoids may not inhibit the release of mediators of allergic reactions from mast cells, but they do reduce the number of mast cells within the airway.^{3,5} In addition to their suppressive effects on inflammatory cells, glucocorticoids may

also inhibit plasma exudation⁷ and mucus secretion⁸ in inflamed airways.

Effects on Inflammation

Inhaled glucocorticoids have antiinflammatory effects on the bronchial mucosa in patients with asthma. In patients treated with inhaled glucocorticoids for one to three months, there is a marked reduction in the numbers of mast cells, macrophages, T-lymphocytes, and eosinophils in the bronchial epithelium and submucosa.^{9,10} Furthermore, glucocorticoids reverse the shedding of epithelial cells and the goblet-cell hyperplasia characteristically seen in biopsy specimens of bronchial epithelium from patients with asthma.¹¹

Effects on Airway Hyperresponsiveness

By reducing airway inflammation, inhaled glucocorticoids consistently lessen airway hyperresponsiveness in adults and children with asthma.¹¹ Long-term treatment with inhaled glucocorticoids reduces airway responsiveness to histamine, cholinergic agonists, and allergens (affecting both early and late responses). Such treatment similarly lowers responsiveness to exercise, fog, cold air, bradykinin, adenosine, and irritants such as sulfur dioxide and metabisulfites. Inhaled glucocorticoid therapy not only makes the airways less sensitive to spasmogens, but also limits the maximal narrowing of the airway in response to a spasmogen.¹² The reduction in airway hyperresponsiveness may not be maximal until treatment has been given for several months.

The magnitude of the reduction varies, and airway responsiveness often remains abnormal. Although the treatment suppresses inflammation, it may be unable to reverse the persistent structural changes that underlie the disease.¹³

CLINICAL EFFICACY

Studies in Adults

Inhaled glucocorticoid therapy was initially introduced to reduce the need for oral glucocorticoids in patients with severe asthma. Several studies have confirmed that inhaled glucocorticoid therapy allows many patients to stop taking the drugs orally.¹³ Inhaled glucocorticoids began to be used for patients with milder asthma when the recognition grew that inflammation is present, even in the mild forms of the disease, from the onset of the illness.^{14,15} Inhaled glucocorticoids are now the appropriate first treatment for patients who need inhalation therapy with β_2 -adrenergic-receptor agonists more than once daily, as recommended in national and international guidelines.¹⁶⁻¹⁸ In patients with newly diagnosed asthma who were followed for two years, therapy with the inhaled glucocorticoid budesonide (600 μ g twice daily) reduced symptoms, reduced the need for inhalation therapy with β_2 -agonists, and improved airway function. In a parallel group treated with inhaled β_2 -agonists alone there was no significant change in symptoms or lung function.¹⁹ In another study, patients with mild asthma treated with a low

From the Department of Thoracic Medicine, National Heart and Lung Institute, Dovehouse St., London SW3 6LY, United Kingdom, where reprint requests should be addressed to Professor Barnes.

dose of inhaled budesonide (200 μ g twice daily) had fewer symptoms and showed progressive improvement in lung function during one year of therapy. Many became completely asymptomatic.²⁰ Although the effects of inhaled glucocorticoids on airway responsiveness may take several months to reach a plateau, the improvement in the symptoms of asthma is more rapid.²¹ High doses of inhaled glucocorticoids are now widely used to control more severe asthma. This treatment markedly reduces the need for oral glucocorticoid therapy and improves the control of more severe and unstable forms of the disease.²²⁻²⁴ Inhaled glucocorticoids are the treatment of choice in nocturnal asthma, which is a manifestation of inflamed airways, reducing both nighttime awakening and circadian variation in airway function.²⁵

Although inhaled glucocorticoids effectively control asthmatic inflammation, they must be taken regularly. The dose needed to maintain control, however, may decrease.²⁶ When therapy is discontinued, symptoms and airway responsiveness usually return to pretreatment levels.^{21,27}

Studies in Children

Inhaled glucocorticoids are equally effective in children. In an extensive study of children 7 to 17 years old, those using the drugs showed a marked improvement in symptoms, peak-expiratory-flow variability, and lung function as compared with a group receiving regular treatment with an inhaled β_2 -agonist. The effects were sustained for the 22 months of the study,²⁸ but the children's asthma worsened when the inhaled glucocorticoids were withdrawn.²⁹ Inhaled glucocorticoids are also effective in even younger children. For example, nebulized budesonide reduced the need for oral glucocorticoid therapy and also improved lung function in children under the age of three years.³⁰ In studies of preschool children and infants, glucocorticoids inhaled through a large-volume spacer also improved asthma symptoms and reduced the number of exacerbations.^{31,32}

Prevention of Irreversible Changes

Irreversible airflow obstruction develops in some patients with asthma. Although the pathophysiologic basis of this change is not understood, it is probably the result of chronic airway inflammation and may therefore be prevented by the use of inhaled glucocorticoids. The accelerated annual decline in lung function typical of patients with asthma has been slowed by such treatment.³³ Delaying the start of inhaled glucocorticoid therapy after diagnosis may lessen the overall improvement in lung function in both adults and children.^{27,34,35}

Reduction in Mortality

Since prospective studies are almost impossible to conduct because of the large number of subjects required, it is not known whether inhaled glucocorticoids reduce mortality from asthma. In a retrospective re-

view of mortality and prescribed anti-asthma medication, patients being treated with inhaled beclomethasone dipropionate received significant protection as compared with patients for whom an inhaled glucocorticoid was not prescribed (adjusted odds ratio, 0.1). The number of patients studied was small, however.³⁶

Effects on Chronic Obstructive Pulmonary Disease

Although the beneficial effects of inhaled glucocorticoids on patients with asthma are now well documented, the role of the drugs in the management of chronic obstructive pulmonary disease (COPD) is less apparent. The failure to improve airway obstruction of a short course (two to four weeks) of oral glucocorticoids serves to distinguish COPD from asthma. Treatment with inhaled glucocorticoids for three months failed to improve either the lung function or the airway responsiveness of patients with mild-to-moderate COPD,³⁷ although longer treatment had some beneficial effects.³⁸

Comparisons of Different Preparations

Several glucocorticoid preparations for inhalation therapy are now available, although not all of them are available in all countries (Table 1). There have been relatively few studies comparing the efficacy of the various preparations, and it is important to take into account the delivery system and the type of patients studied when such comparisons are made. Beclomethasone dipropionate, flunisolide, and triamcinolone are currently available in the United States, but there have been no studies comparing them. Budesonide, widely available in many countries, and beclomethasone are equally effective.³⁹

PHARMACOKINETICS

The pharmacokinetics of inhaled glucocorticoids determine the proportion of the inhaled drug that reaches

Table 1. Characteristics of Inhaled Glucocorticoids*

GLUCOCORTICOID	RELATIVE BINDING AFFINITY†	RELATIVE BLANCHING POTENCY‡	INHAILED DOSE μ g/puff
Beclomethasone dipropionate§	0.4	600	50, 100, 200
Beclomethasone monopropionate§	13.5	450	50, 100, 200
Triamcinolone	3.6	330	100
Flunisolide	1.8	330	250
Budesonide**	9.4	980	50, 100, 200
Fluticasone**	18.0	1200	25, 50, 125

*Adapted from Reed.⁴⁰

†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 μ g per 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 μ g, but 100 μ g is delivered by spacer. **Not available in the United States.

target cells in the airways as well as the fraction of the dose that enters the systemic circulation to produce side effects.¹⁰ Desirable properties in an inhaled glucocorticoid are high topical potency, low systemic bioavailability of the portion of the dose swallowed by the patient, and rapid metabolic clearance of any glucocorticoid that reaches the systemic circulation. After inhalation, a large proportion of the inhaled dose, 80 to 90 percent, is deposited on the oropharynx and swallowed. It is then available for absorption into the systemic circulation through the liver (Fig. 1). This fraction is markedly reduced if the glucocorticoid is administered through a large-volume spacer attached to a metered-dose inhaler. Rinsing the mouth after the use of a dry-powder inhaler will achieve the same effect. Between 10 and 20 percent of the inhaled drug enters the respiratory tract, where it is deposited in the airways and is available for absorption into the systemic circulation.

Most of the studies on the distribution of inhaled glucocorticoids have been conducted in normal subjects. Factors such as airway inflammatory disease, airway obstruction, the age of the patient, and concomitant therapy may all alter the disposition of the inhaled dose. There also may be important differences in the

metabolism of different glucocorticoids. Beclomethasone dipropionate, for example, is metabolized to the more active form, beclomethasone monopropionate in many types of tissues including lung tissue,¹¹ but there is no information about the formation, absorption, or metabolism of this metabolite in humans. Flunisolide and budesonide are subject to extensive first-pass metabolism in the liver so that less of these drugs reaches the systemic circulation.^{12,13} Little is known about the distribution of triamcinolone in the body. Fluticasone propionate has a low oral bioavailability, which reduces its systemic effects.^{14,15}

FREQUENCY OF ADMINISTRATION

When inhaled glucocorticoids were first introduced it was recommended that they be given four times daily. Administration twice daily is equally effective,¹⁶ although a schedule of four doses per day may be preferable for patients with more severe asthma.^{17,18} For patients with mild asthma, one dose per day may suffice.

LOCAL SIDE EFFECTS

Inhaled glucocorticoids have oropharyngeal side effects whose rate of appearance depends on the dose, the drug, and the patient's response to treatment.

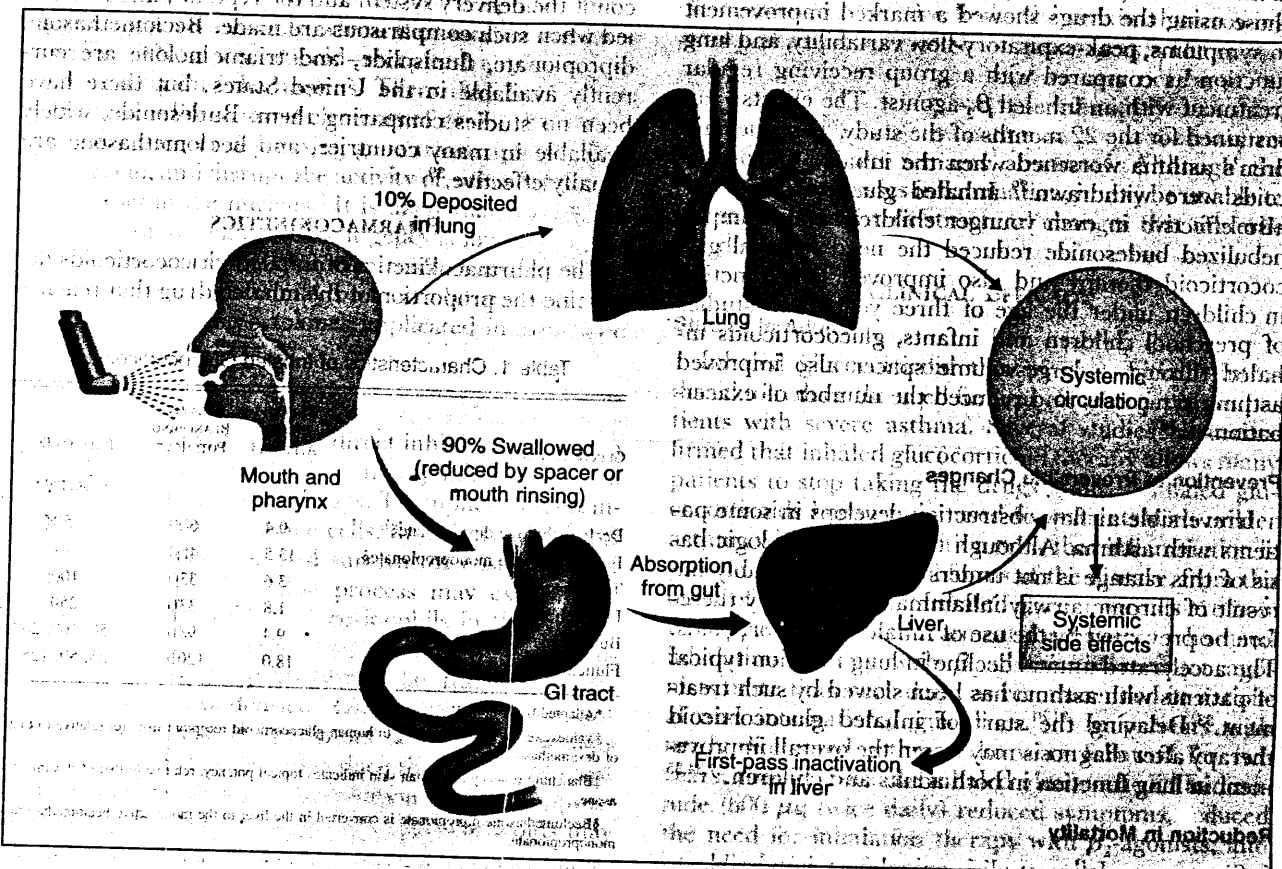


Figure 1. Pharmacokinetics of Inhaled Glucocorticoids.

These drugs reach the systemic circulation through either the gastrointestinal (GI) tract and liver (from the swallowed fraction) or the lung (from the inhaled fraction).

the frequency of administration, and the delivery system used.

Dysphonia

The most common side effect is dysphonia (hoarseness), which affects approximately one third of treated patients.⁵⁰ It may be due to myopathy of the laryngeal muscles and is reversible when treatment is stopped.⁵¹ It is not usually troublesome, but may be disabling in singers.

Oropharyngeal Candidiasis

Oropharyngeal candidiasis (thrush) may be a problem for some patients, particularly the elderly, and especially when the drug is given more than twice daily.⁵⁰ Use of a large-volume spacer protects against this effect by reducing the amount of inhaled glucocorticoid deposited in the oropharynx.

Other Local Complications

Inhaled glucocorticoids, even in high doses, do not increase the frequency of infections, such as tuberculosis, in the lower respiratory tract.^{52,53} The airway epithelium does not become atrophic, even after 10 years of therapy.⁵⁴ Cough and throat irritation, sometimes accompanied by reflex bronchoconstriction, may occur when inhaled glucocorticoids are given with a metered-dose inhaler. These symptoms are likely to be due to the surfactants, such as oleic acid, in pressurized aerosols. They disappear if a patient switches to an unpresurized, dry-powder inhaler.⁵⁵

SYSTEMIC SIDE EFFECTS

The efficacy of inhaled glucocorticoids in the control of asthma is undisputed. There are, though, concerns about their systemic effects, particularly because they are likely to be used for long periods and by children.⁵⁶ One major problem for researchers is deciding whether a measurable systemic effect has enough clinical importance to require long-term follow-up studies. As more sensitive biochemical tests of the systemic effects of glucocorticoids become available, such effects may be identified more often, but this will not mean that they are clinically important. Another difficulty lies in distinguishing the side effects of inhaled glucocorticoids from those of oral glucocorticoids since many patients are treated with both. The systemic effect of an inhaled glucocorticoid will depend on several factors, including the dose, the delivery system used, the site of delivery — gastrointestinal tract or lung — and the individual patient's response to the drug.

Effect of the Delivery System

The systemic effect of an inhaled glucocorticoid depends on the amount of the drug absorbed into the systemic circulation. As discussed above, approximately 80 to 90 percent of the dose inhaled from a metered-dose inhaler is deposited in the oropharynx, swallowed, and then absorbed into the circulation from the gastrointes-

tinal tract (Fig. 1). The use of a spacer markedly reduces oropharyngeal deposition, since large particles are retained in the device, but it may increase deposition of the drug in the lungs. Nevertheless, systemic effects are reduced if a spacer is used.⁵⁷⁻⁵⁹ For patients using dry-powder inhalers, rinsing the mouth similarly reduces systemic effects.⁵⁹ To reduce oral deposition and systemic absorption, all patients receiving a daily dose of not less than 800 μg of an inhaled glucocorticoid should, — depending on the type of inhaler — either use a spacer or rinse their mouths after inhalation. The portion of the inhaled dose that enters the lungs — and presumably creates the therapeutic effect — may also be absorbed into the systemic circulation. More efficient delivery to the lungs is thus accompanied by increased systemic absorption, but this is offset by a reduction in the dose needed for optimal control of airway inflammation. For example, a multiple dry-powder delivery system, the Turbuhaler, delivers approximately twice as much glucocorticoid to the lungs as other devices, but requires only half as large a dose.⁶⁰

Suppression of Hypothalamic-Pituitary-Adrenal Function

Glucocorticoid drugs suppress the function of the hypothalamic-pituitary-adrenal axis by reducing the secretion of corticotropin, which in turn reduces the secretion of cortisol by the adrenal glands. The degree of suppression depends on the dose, duration, frequency, and timing of glucocorticoid administration. Prolonged adrenal suppression may lead to reduced adrenal responses to stress, but there is no evidence that even high doses of inhaled glucocorticoids reduce a patient's plasma cortisol response to the stress produced by an exacerbation of asthma or by insulin-induced hypoglycemia.⁶¹ Basal secretion of corticotropin and cortisol may be evaluated by measuring plasma cortisol either in the morning or at several times during the day and night. The amount of cortisol excreted in the urine during 24 hours may also be measured.⁶² Other tests measure a patient's adrenal response after stimulation with cosyntropin, to assess adrenal reserve, or with insulin, to assess both adrenal and pituitary reserve.

Studies of pituitary-adrenal function in patients receiving inhaled glucocorticoids have had inconsistent results, some showing suppression and others no suppression. Many studies have been uncontrolled, and others are difficult to interpret because patients received prior therapy with oral glucocorticoids, which may affect the hypothalamic-pituitary-adrenal axis for several weeks.¹⁴ Beclomethasone and budesonide given in high doses (more than 1600 μg per day) by a conventional metered-dose inhaler cause a dose-related decrease both in morning concentrations of plasma cortisol and in 24-hour urinary cortisol excretion, although the values remain within the normal range.⁶³ However, when a spacer is used, a daily dose of 2000 μg of beclomethasone or budesonide has no effect on 24-hour urinary cortisol excretion.⁶⁵ Budesonide and fluticasone, at high doses (more than 1500 μg per day),

have less effect than beclomethasone on pituitary-adrenal function.^{65,66} In studies of children, inhaled flunisolide and triamcinolone, given in doses of up to 1000 μg per day, had no effect on 24-hour urinary cortisol excretion.^{67,68} Beclomethasone, given to children in doses of 800 μg or less, also left urinary cortisol excretion unchanged.^{69,70} In studies in which plasma cortisol was measured at frequent intervals, there was a small but significant reduction in nocturnal values when beclomethasone and budesonide were inhaled in doses as low as 400 μg per day.⁷¹ This response, however, was not related to dose for doses of inhaled glucocorticoids in the range of 400 to 1000 μg per day.⁷² Doses of 1500 μg per day have no effect on the adrenal responses to corticotropin or insulin-induced hypoglycemia.

Overall, in the absence of previous or concomitant treatment with oral glucocorticoids, inhaled glucocorticoids, in doses of 1500 μg per day or less in adults and 400 μg per day or less in children, have little if any effect on pituitary-adrenal function. Given the infrequency of pituitary-adrenal suppression, a low rate of glucocorticoid-related side effects would be expected and has proved to be the case.

Effects on Bone Metabolism

Glucocorticoids reduce bone mass directly by inhibiting bone formation, and indirectly by inhibiting the secretion of androgen in the pituitary-gonadal and adrenal systems and by limiting calcium absorption in the intestines and calcium reabsorption in the renal tubules, thereby causing secondary hyperparathyroidism.⁷³ Oral glucocorticoid therapy is a well-known cause of osteoporosis and an increased risk of vertebral and rib fractures, but there are no reports suggesting that long-term treatment with inhaled glucocorticoids is associated with an increased risk of fractures. Bone mineral density may be decreased by high doses of inhaled glucocorticoids, but their effect is confounded by the fact that patients taking these drugs also receive intermittent courses of oral glucocorticoids.⁷⁴ In a recent small study, the bone density of premenopausal women receiving inhaled glucocorticoids was slightly lower than that of age-matched normal subjects. However, there was no comparison with patients who had asthma but were not treated with glucocorticoids.⁷⁵

Several biochemical indexes have been used to assess the short-term effects of inhaled glucocorticoids on bone metabolism. Bone formation has been evaluated by measuring plasma concentrations of bone-specific alkaline phosphatase and osteocalcin. Bone resorption has been assessed by measuring urinary excretion of hydroxyproline, calcium, and pyridinium cross-links. In interpreting the results it is important to consider the age, diet, and physical activity of the patient. It is also necessary to choose appropriate control groups, because asthma itself may have an effect on some of the variables measured — for example, the plasma osteocalcin concentration.⁷⁶ Although inhaled glucocorti-

coids, even at doses of up to 2000 μg per day, have no effect on urinary calcium excretion, reversible dose-related suppression of plasma osteocalcin has been reported with beclomethasone and budesonide given by conventional metered-dose inhaler in doses of 2000 μg per day.^{77,78} Only high-dose beclomethasone increases urinary hydroxyproline excretion.⁸⁴ Given a large-volume spacer, even in doses of 2000 μg per day, neither beclomethasone nor budesonide had any effect on plasma osteocalcin concentrations in one study,⁶⁵ although some reduction was found in another.⁷⁸ Urinary excretion of pyridinium cross-links, a sensitive measure of bone and collagen degradation, is not increased by inhaled glucocorticoids (beclomethasone, in a dose of more than 1000 μg per day), even in patients also given intermittent courses of oral glucocorticoids.⁷⁴ In growing children, very low doses of oral glucocorticoids (for example, 2.5 mg of prednisolone per day) decrease plasma osteocalcin and increase urinary hydroxyproline excretion. Beclomethasone and budesonide, at doses up to 800 μg per day, have no effect.^{76,82}

Effects on Growth

There has been particular concern that inhaled glucocorticoids may cause stunting of growth. Asthma itself, like other chronic diseases, may result in poor growth and delay the onset of puberty.⁸³ The delay of puberty, however, may allow children with asthma to grow for a longer period, so that their final height is normal. This influence of asthma on growth makes it difficult to assess the effects of inhaled glucocorticoids in cross-sectional studies. Longitudinal studies have demonstrated no significant effect on statural growth of inhaled glucocorticoids in doses of up to 800 μg per day for up to five years of treatment.^{43,20,84} In a prospective, comparative study of inhaled beclomethasone (400 μg per day) and theophylline in children with mild-to-moderate asthma, there was no difference in height, although the children treated with beclomethasone grew more slowly.⁸⁵ However, it is not possible to relate changes in the rate of growth to final height; other studies have demonstrated that there is a catch-up period. In a longitudinal, three-to-five-year study of children two to seven years old, inhaled budesonide (200 μg per day) had no effect on growth.⁸⁶ A meta-analysis of 21 studies, including over 800 children, showed no effect of inhaled beclomethasone on height, even in children treated with higher doses for a long period.⁸⁷

Effects on Connective Tissue

Oral and topical glucocorticoids cause thinning of the skin, telangiectasia, and easy bruising. These probably result from a loss of extracellular ground substance within the dermis due to the drugs' inhibitory effect on dermal fibroblasts. There are reports of increased skin bruising and purpura in patients receiving high doses of inhaled beclomethasone, but the amount

of intermittent glucocorticoids they received is not known.^{88,89} Easy bruising linked to inhaled glucocorticoids is more frequent in elderly patients; there are no reports of this problem in children.

Cataracts

Long-term treatment with oral glucocorticoids increases the risk of posterior subcapsular cataracts, and there are a few reports of cataracts in patients taking inhaled glucocorticoids.¹⁴ In adults who received oral or high-dose inhaled glucocorticoids (or both), the prevalence of posterior subcapsular cataracts correlated with both the daily dose and the duration of oral glucocorticoid therapy, but not with the dose and duration of inhaled glucocorticoid therapy.⁹⁰ In a cross-sectional study of children taking inhaled beclomethasone or budesonide, no cataracts were found on slit-lamp examination, even in patients who had taken 2000 μ g per day for more than 10 years.⁹¹

Metabolic Effects

There is no evidence that inhaled glucocorticoids have clinically important metabolic effects. Fasting plasma glucose and insulin concentrations are unchanged after doses of beclomethasone of up to 2000 μ g per day in adults³⁹ and doses of budesonide of up to 800 μ g per day in children.⁹² In a group of patients with poorly controlled asthma, high-dose beclomethasone and budesonide surprisingly decreased insulin resistance and improved glucose tolerance, suggesting that asthma itself may lead to abnormalities in carbohydrate metabolism.⁹³ Neither beclomethasone (2000 μ g per day) in adults nor budesonide (800 μ g per day) in children had any effect on plasma cholesterol or triglyceride levels.^{39,93}

Hematologic Effects

Inhaled glucocorticoids may reduce the number of circulating eosinophils in patients with asthma,⁶ possibly because of an effect on local cytokine generation in the airways. They also may cause a small increase in circulating neutrophil counts.⁶⁵

Central Nervous System Effects

Despite the propensity of glucocorticoids to cause psychiatric disturbance — including emotional lability, euphoria, depression, aggressiveness, and insomnia — only eight patients have been described in whom psychiatric symptoms developed during inhaled glucocorticoid therapy.¹⁴

Safety in Pregnancy

There is no evidence that inhaled glucocorticoids have any adverse effects on pregnant women, their fetuses, the course of labor, or delivery.¹⁴ It is important to recognize, though, that poorly controlled asthma may retard intrauterine growth and increase the incidence of perinatal mortality, and that more effective

control of asthma with inhaled glucocorticoids may reduce these problems. Breast-feeding is not contraindicated for patients taking inhaled glucocorticoids, because these drugs are not present in milk.

COMPARISON WITH OTHER THERAPIES

No other therapy is as effective in controlling asthma as the use of glucocorticoids, but other treatments may reduce the need for high doses of the drugs in their inhaled form. Cromolyn sodium and nedocromil sodium are less effective in controlling asthma than inhaled glucocorticoids and need to be taken three to four times daily, although they may be useful for some patients.^{94,95} Cromolyn should be given before inhaled glucocorticoids are started in children, although it is important to recognize that the doses of inhaled glucocorticoids that provide equivalent asthma control (100 to 400 μ g per day) have no appreciable side effects, are cheaper, and need to be administered only twice daily. Nedocromil may reduce the need for inhaled glucocorticoids in patients who have problems with local side effects,⁹⁶ but cromolyn has no such sparing effect.

Conventional β_2 -agonists do not control asthma as effectively as inhaled glucocorticoids in either adults or children.^{19,27} The long-acting inhaled β_2 -agonist salmeterol, when added to 400 μ g of beclomethasone, appears to give equivalent, if not better, control of asthma than does an increase in the dose of beclomethasone to 1000 μ g per day.⁹⁷ Theophylline alone does not control asthma as effectively as inhaled glucocorticoids and produces more frequent side effects,⁸⁵ but it may have a useful additive effect.⁹⁸ Glucocorticoid inhalers may be more expensive than short-acting β_2 -agonists and theophylline, but their use can lead to savings in the direct costs of asthma treatment by reducing the numbers of medical consultations and hospital admissions.⁹⁹

CONCLUSIONS

Inhaled glucocorticoids are very effective in controlling the symptoms of asthma and in preventing exacerbations. Oral glucocorticoids may be equally effective but have many more side effects. Extensive studies conducted both in normal subjects and in patients with asthma of varying degrees of severity have demonstrated that inhaled glucocorticoids, irrespective of the preparation, have minimal systemic effects, even according to the most sensitive indicators, at doses of up to 400 μ g per day for children and up to 800 μ g per day for adults. At higher doses there is some evidence of systemic effects, although they are less noticeable with budesonide and fluticasone than with beclomethasone. Even at high doses (up to 2000 μ g per day) there is little evidence of any adverse effects. The small risk of adverse effects at high doses of inhaled glucocorticoids has to be set against the risks of not adequately controlling severe asthma. Since the systemic absorption of inhaled glucocorticoids may be reduced by the use of

spacer devices with metered-dose inhalers, and by mouth rinsing after the use of dry-powder inhalers, these should be used whenever doses of 800 μ g per day or more are needed to control asthma. In the future, it is possible that inhaled glucocorticoids with even fewer systemic effects will be developed.

REFERENCES

- Barnes PJ. Anti-inflammatory therapy for asthma. *Annu Rev Med* 1993;44:229-42.
- Barnes PJ, Adcock I. Anti-inflammatory actions of steroids: molecular mechanisms. *Trends Pharmacol Sci* 1993;14:436-41.
- Schleimer RP. Effects of glucocorticosteroids on inflammatory cells relevant to their therapeutic applications in asthma. *Am Rev Respir Dis* 1990;141:S59-S69.
- Laitinen LA, Laitinen A, Haahela T. A comparative study of the effects of an inhaled corticosteroid, budesonide, and of a β_2 -agonist, terbutaline, on airway inflammation in newly diagnosed asthma: a randomized, double-blind, parallel-group controlled trial. *J Allergy Clin Immunol* 1992;90:32-42.
- Djukanovic R, Wilson JW, Britten KM, et al. Effect of an inhaled corticosteroid on airway inflammation and symptoms in asthma. *Am Rev Respir Dis* 1992;145:669-74.
- Evans PM, O'Connor BJ, Fuller RW, Barnes PJ, Chung KF. Effect of inhaled corticosteroids on peripheral blood eosinophil counts and density profiles in asthma. *J Allergy Clin Immunol* 1993;91:643-50.
- Boschetto P, Rogers DF, Fabbri LM, Barnes PJ. Corticosteroid inhibition of airway microvascular leakage. *Am Rev Respir Dis* 1991;143:605-9.
- Shimura S, Sasaki T, Ikeda K, Yamauchi K, Sasaki H, Takishima T. Direct inhibitory action of glucocorticoid on glycoconjugate secretion from airway submucosal glands. *Am Rev Respir Dis* 1990;141:1044-9.
- Jeffery PK, Godfrey RW, Adelroth E, Nelson F, Rogers A, Johansson S-A. Effects of treatment on airway inflammation and thickening of basement membrane reticular collagen in asthma: a quantitative light and electron microscopic study. *Am Rev Respir Dis* 1992;145:890-9.
- Burke C, Power CK, Norris A, Condez A, Schmekel B, Pouller LW. Lung function and immunopathological changes after inhaled corticosteroid therapy in asthma. *Eur Respir J* 1992;5:73-9.
- Barnes PJ. Effect of corticosteroids on airway hyperresponsiveness. *Am Rev Respir Dis* 1990;141:S70-S76.
- Bel EH, Timmers MC, Zwiderman AH, Dijkman JH, Sterk PJ. The effect of inhaled corticosteroids on the maximal degree of airway narrowing to methacholine in asthmatic subjects. *Am Rev Respir Dis* 1991;143:109-13.
- Reed CE. Aerosol glucocorticoid treatment of asthma: adults. *Am Rev Respir Dis* 1990;140:S82-S88.
- Barnes PJ, Pedersen S. Efficacy and safety of inhaled corticosteroids in asthma: report of a workshop held in Eze, France, October 1992. *Am Rev Respir Dis* 1993;148:S1-S26.
- Barnes PJ. A new approach to the treatment of asthma. *N Engl J Med* 1989;321:1517-27.
- Guidelines for the diagnosis and management of asthma: National Heart, Lung, and Blood Institute, National Asthma Education Program Expert Panel Report. *J Allergy Clin Immunol* 1991;88:Suppl:425-534.
- International Asthma Management Project. International consensus report on the diagnosis and management of asthma. *Clin Exp Allergy* 1992;22:Suppl 1:1-72.
- Guidelines on the management of asthma. *Thorax* 1993;48:Suppl:S1-S24.
- Haahela T, Järvinen M, Kava T, et al. Comparison of a β_2 -agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991;325:388-92.
- Juniper EF, Kline PA, Vanzielegem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. *Am Rev Respir Dis* 1990;142:832-6.
- Vathenen AS, Knox AJ, Wisniewski A, Tattersfield AE. Time course of change in bronchial reactivity with an inhaled corticosteroid in asthma. *Am Rev Respir Dis* 1991;143:1317-21.
- Toogood JH. High-dose inhaled steroid therapy for asthma. *J Allergy Clin Immunol* 1989;83:528-36.
- Salmeron S, Guerin J-C, Godard P, et al. High doses of inhaled corticosteroids in unstable chronic asthma: a multicenter, double-blind, placebo-controlled study. *Am Rev Respir Dis* 1989;140:167-71.
- Lacronique J, Renon D, Georges D, Henry-Amar M, Marsac J. High-dose beclomethasone: oral steroid-sparing effect in severe asthmatic patients. *Eur Respir J* 1991;4:807-12.
- Wempe JB, Tammeling EP, Postma DS, Auffarth B, Teengs JP, Koeter GH. Effects of budesonide and bambuterol on circadian variation of airway responsiveness and nocturnal symptoms of asthma. *J Allergy Clin Immunol* 1992;90:349-57.
- Juniper EF, Kline PA, Vanzielegem MA, Hargreave FE. Reduction of budesonide after a year of increased use: a randomized controlled trial to evaluate whether improvement in airway responsiveness and clinical asthma are maintained. *J Allergy Clin Immunol* 1991;87:483-91.
- Haahela T, Järvinen M, Kava T, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994;331:700-5.
- van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, et al. Effect of 22 months of treatment with inhaled corticosteroids and/or β_2 -agonists on lung function, airway responsiveness, and symptoms in children with asthma. *Am Rev Respir Dis* 1992;146:547-54.
- Waalkens HJ, van Essen-Zandvliet EE, Hughes MD, et al. Cessation of long-term treatment with inhaled corticosteroid (budesonide) in children with asthma results in deterioration. *Am Rev Respir Dis* 1993;148:1252-7.
- Hengonvan P, Pedersen S, Godfrey S, Nikander K, Noviski N, Warner JO. Treatment of severe steroid dependent preschool asthma with nebulised budesonide suspension. *Arch Dis Child* 1993;68:356-9.
- Gleason JG, Price JF. Controlled trial of budesonide given by the Nebuhaler in preschool children with asthma. *BMJ* 1988;297:163-6.
- Biggaard H, Munck SL, Nielsen JP, Petersen W, Ohlsson SV. Inhaled budesonide for treatment of recurrent wheezing in early childhood. *Lancet* 1990;336:649-51.
- Dompeling E, van Schayck CP, Molema J, Folgering H, van Grunsven PM, van Weel C. Inhaled beclomethasone improves the course of asthma and COPD. *Eur Respir J* 1992;5:945-52.
- Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994;88:373-81.
- Selroos O, Backman R, Forsén K-O, et al. When to start treatment of asthma with inhaled corticosteroids? *Eur Respir J* 1994;7:Suppl. 18:151s, abstract.
- Ernst P, Spitzer WO, Suissa S, et al. Risk of fatal and near-fatal asthma in relation to inhaled corticosteroid use. *JAMA* 1992;268:3462-4.
- Watson A, Lim TK, Joyce H, Pride NB. Failure of inhaled corticosteroids to modify bronchoconstrictor or bronchodilator responsiveness in middle-aged smokers with mild airflow obstruction. *Chest* 1992;101:350-5.
- Kerstjens HAM, Brand PLP, Hughes MD, et al. A comparison of bronchodilator therapy with or without inhaled corticosteroid therapy for obstructive airways disease. *N Engl J Med* 1992;327:1413-9.
- Ebden P, Jenkins A, Houston G, Davies BH. Comparison of two high dose corticosteroid aerosol treatments, beclomethasone dipropionate (1500 micrograms/day) and budesonide (1600 micrograms/day), for chronic asthma. *Thorax* 1986;41:869-74.
- Szefer SJ. Glucocorticoid therapy for asthma: clinical pharmacology. *J Allergy Clin Immunol* 1991;88:147-65.
- Wurthwein G, Rohdewald P. Activation of beclomethasone dipropionate by hydrolysis to beclomethasone-17-monopropionate. *Biopharm Drug Dispos* 1990;11:381-94.
- Chaplin MD, Rooks W II, Swenson EW, Cooper WC, Nerenberg C, Chiu N. Flunisolide metabolism and dynamics of a metabolite. *Clin Pharmacol Ther* 1980;27:402-13.
- Ryrfeldt Å, Andersson P, Edsbacker S, Tonnesson M, Davies D, Pauwels R. Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid. *Eur J Respir Dis* 1982;Suppl. 122:86-95.
- Mollmann H, Rohdewald P, Schmidt EW, Salomon V, Derendorf H. Pharmacokinetics of triamcinolone acetonide and its phosphate ester. *Eur J Clin Pharmacol* 1985;29:85-9.
- Holliday SM, Faulds D, Sorokin EM. Inhaled fluticasone propionate: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in asthma. *Drugs* 1994;47:319-31.
- Meltzer EO, Kemp JP, Welch MJ, Orgel HA. Effect of dosing schedule on efficacy of beclomethasone dipropionate aerosol in chronic asthma. *Am Rev Respir Dis* 1985;131:732-6.
- Toogood JH, Baskerville JC, Jennings B, Lefcoe NM, Johansson S-A. Influence of dosing frequency and schedule on the response of chronic asthmatics to the aerosol steroid, budesonide. *J Allergy Clin Immunol* 1982;70:288-98.
- Malo J-L, Cartier A, Merland N, et al. Four-times-a-day dosing frequency is better than a twice-a-day regimen in subjects requiring a high-dose inhaled steroid, budesonide, to control moderate to severe asthma. *Am Rev Respir Dis* 1989;140:624-8.
- Jones AH, Langdon CG, Lee PS, et al. Pulmicort Turbuhaler once daily as initial prophylactic therapy for asthma. *Respir Med* 1994;88:293-9.
- Toogood JH, Jennings B, Baskerville J, Anderson J, Johansson S-A. Dosing regimen of budesonide and occurrence of oropharyngeal complications. *Eur J Respir Dis* 1984;65:35-44.
- Williams AJ, Baghat MS, Stableforth DE, Cayton RM, Shenoi PM, Skinner C. Dysphonia caused by inhaled steroids: recognition of a characteristic laryngeal abnormality. *Thorax* 1983;38:813-21.
- Brogden RN, Heel RC, Speight TM, Avery GS. Beclomethasone dipropionate: a reappraisal of its pharmacodynamic properties and therapeutic efficacy after a decade of use in asthma and rhinitis. *Drugs* 1984;28:99-126.