Corticosteroids are the most effective antiasthma drugs for patients experiencing exacerbations of asthma. Oral or inhaled corticosteroids are valuable as maintenance pharmacotherapy to prevent disabling wheezing, chest constriction, nocturnal wheezing dyspnea, and other symptoms of ineffectively controlled asthma. While the therapeutic dosages of systemically administered corticosteroid are very high in the presence of status asthmaticus in hospitalized patients, maintenance dosages of oral corticosteroids are far less and often consist of prednisone, 20 to 60 mg administered on alternate days. Effective inhalation of corticosteroids into the bronchi in stable patients permits reduction or discontinuation of oral corticosteroids. To address the use of corticosteroids in asthma, this manuscript will be divided into rationale, use, and problems.

Asthma as defined by the expert panel of the National Heart, Lung, Blood Institute, "is a lung disease with the following characteristics: (1) airway obstruction that is reversible (but not completely so in some patients) either spontaneously or with treatment; (2) airway inflammation; and (3) increased airway responsiveness to a variety of stimuli." Asthma causes a variable degree of bronchial obstruction, airway inflammation, and hypersecretion of mucus and over time, even the prednisone-requiring patient may experience disease remission, either lasting months or permanently. For the acutely wheezing patient with asthma, it is preferable to administer an effective dosage of oral or systemic corticosteroids rather than to withhold them. For ambulatory patients whose asthma is not managed satisfactorily with bronchodilators, cromolyn, and avoidance measures in patients with IgE-mediated asthma, inhaled corticosteroids usually provide effective control of asthma. Indeed, in some patients, inhaled corticosteroids provide effective antiasthma monotherapy.

Rationale for Corticosteroids

The administration of systemic corticosteroids helps reduce the inospital fatality rate from asthma. The administration of oral corticosteroids to acutely wheezing or otherwise symptomatic patients with asthma helps avoid emergency room treatment or recidivism to the emergency room. Parenterally administered corticosteroids, such as methylprednisolone or triamcinolone acetonide, provide a less desirable but at times essential route of administration of corticosteroids for some noncompliant patients. In the treatment of patients with status asthmaticus, improvements in expiratory flow rates require 6 to 12 h before significant changes can be documented. However, patients improve clinically and measurements will demonstrate reductions in functional residual capacity and residual volume. During the initial hours after parenteral corticosteroids have been administered along with beta-adrenergic agonists (and possibly theophylline), respiratory effort can be more efficient even if the FEV₁ has not yet improved.

A potent inhaled corticosteroid, budesonide, administered to patients with newly diagnosed mild asthma, was associated with more effective symptomatic control of asthma and reduced need for supplemental terbutaline as compared to patients treated with inhaled terbutaline. Bronchial hyperresponsiveness to histamine, as measured by the provocative concentration to cause a 15% decline in FEV₁, was 7.0 mg/ml in both groups initially. After 6 weeks, the budesonide-treated patients had reduced bronchial hyperresponsiveness. However, despite mean differences between groups, after 2 years, the budesonide-treated patients did not have significantly reduced bronchial hyperresponsiveness as compared to terbutaline-treated patients. Both groups of patients had experienced lessened bronchial responsiveness, for which one explanation is enrollment in a study and effective management of asthma. In another study with budesonide during 1 year of treatment, airway responsiveness improved an average of fourfold as compared with placebo-treated patients. Beclomethasone dipropionate and triamcinolone acetonide by inhalation help reduce nocturnal wheezing as well as minimize the need for other medications. Long-term treatment with inhaled corticosteroids resulted in reduced inflammatory cells in bronchial biopsy specimens in patients with asthma, but the patients had not lost their bronchial hyperresponsiveness. These data suggest that although on morphologic grounds based on biopsy results and clinically patients improve with inhaled corticosteroids, bronchial hyperresponsiveness persists.

In addition to the empiric observations justifying use of corticosteroids in asthma, many experimental findings suggest benefits that could rationalize their administration in the management of asthma. Corticosteroids are associated with reduction of bronchial mucosal edema, mucus accumulation, membrane stabilization (vascular and lysosomal), suppression of inflammation, and prevention of the late bronchoconstrictive response after allergen challenge. Some data support blockage of the early bronchial response if systemic corticosteroids have been administered for 1 week previously. Corticosteroids inhibit proliferation of mucosal mast cells but not their in vitro mediator release. Other effects of corticosteroids include reduction of peripheral blood and presumably pulmonary eosinophils, lymphocytes, basophils, and monocytes. There are experimental data demonstrating that corticosteroids in vitro increase the
actions of lipocortin, enzymes that inhibit action of phospholipase A₂. A reduction of eicosanoid production by corticosteroids via inhibition of phospholipase A₂ could contribute to their benefits in asthma.¹⁴ Corticosteroids increase beta-adrenergic receptor number and have as a major role, the reversal of beta-adrenergic refractoriness (sub-sensitivity) in status asthmaticus.¹⁵

**USE OF CORTICOSTEROIDS**

The administration of corticosteroids can be considered from the perspective of acutely symptomatic patients, ambulatory patients who have mild to severe symptoms, and as a modality for a diagnostic-therapeutic trial to determine reversibility of respiratory symptoms. In the treatment of patients who have presented themselves to the emergency department and have not improved with beta-adrenergic therapy, it is essential to administer effective doses of corticosteroids without further delay. Indeed, when a patient presents with acute severe asthma and displays findings such as nasal flaring, inability to speak a full sentence, use of accessory muscles of respiration or has a paradoxical pulse, systemic or oral corticosteroids should be administered along with other necessary therapy. Effective therapy includes hydrocortisone, 200 to 300 mg, or methylprednisolone, 40 to 50 mg intravenously with administration every 4 to 6 h. Alternatively, prednisone, 50 mg, can be given and repeated although the most effective dosage is unknown. There are virtually no data to support the administration of larger corticosteroid doses such as hydrocortisone, 1,000 mg every 6 h. The high-dose corticosteroids should be continued from several days to 1 week at which time most patients have improved greatly and can be converted to a single morning dose of prednisone, an inexpensive, short-acting corticosteroid. One method of use of corticosteroids is to discharge the patient recommending prednisone, 50 to 60 mg daily for 5 to 7 days. The patient should be examined and if the chest is clear and the patient is asymptomatic, a decision can be made as to whether continued prednisone is necessary or not. If the patient has required long-term or intermittent corticosteroids before the hospitalization, conversion to alternate day prednisone should be advised. The dose of prednisone should be taken in the morning to preserve integrity of the HPA axis. One effective strategy is to convert the prednisone to 50 to 60 mg on alternate days. The patient can be reexamined every 2 weeks and reductions of 5 to 10 mg tried.

Most patients with asthma can be managed with moderate dosages of alternate day prednisone, high dosages of inhaled corticosteroids, and beta-adrenergic agonists. Supplemental prednisone may be necessary during exacerbations of asthma but usually 1 week of daily prednisone is sufficient. In a comparison of patients whose asthma required daily prednisone vs patients tolerating alternate day prednisone, no differences were identified in terms of volume of distribution (about 0.6 L/kg), clearance (2.0 mL/min/kg), or elimination half life (about 210 min).¹⁴ These findings in well-characterized patients suggest that differences of prednisone will be explained by pharmacodynamic differences as yet unknown.

Pharmacotherapy alone is incomplete in the absence of consideration of triggering factors of asthma and their potential avoidance by the patient. For many patients, the administration of high-dose topical corticosteroids will permit reduction of oral corticosteroids or even their discontinuation. In the United States, beclomethasone dipropionate or triamcinolone can be administered up to 16 to 20 times per day, and flunisolide, 8 times daily, in patients over 12 years of age. Budesonide, a potent topical corticosteroid available in other countries, can be administered as 200 μg twice daily. A concentrated formulation of beclomethasone dipropionate containing 250 μg per actuation is not available in the United States but is 6 times as concentrated as the currently marketed products.

When a patient with asthma experiences occasional exacerbations, usually in the setting of an upper respiratory infection, a short effective course of prednisone can help prevent emergency department treatment and hospitalizations. The dosage is 40 to 60 mg daily in adults and in children, 2 mg/kg of body weight for several days.

Inhaled corticosteroids combined with beta-adrenergic agonists provide satisfactory control of asthma in ambulatory patients. As there is increasing emphasis on long-term use of inhaled corticosteroids, it necessitates physician awareness to teach and maintain appropriate inhaler technique.¹⁵ Some patients who cough with inspiration but otherwise are asymptomatic will require perhaps 4 to 7 days of prednisone, such that inhaled drugs can actually reach distal airways. Failure to recognize such "subclinical" asthma is one of the many explanations for disappointing results with inhaled corticosteroids.

Oral and inhaled corticosteroids may be administered as part of a diagnostic-therapeutic trial in patients with combined asthma and COPD where the contributions of each need to be determined. Also in cough equivalent asthma, corticosteroids may be the only therapeutic modality to relieve symptoms.

**PROBLEMS REGARDING CORTICOSTEROIDS**

Corticosteroids may be administered for asthma, even on a long-term basis and not produce dreaded adverse effects. Despite the widespread use of beta-adrenergic agonists, theophylline and cromolyn, in addition to appropriate avoidance measures, exacerbations of asthma may require intensified therapy that cannot be provided by currently available noncorticosteroid drugs. When daily corticosteroids are
required, it is advisable to administer a short-acting corticosteroid such as prednisone or methylprednisolone, although the latter is a costly alternative. If these agents are administered on a once daily schedule for 3 weeks or less, then abrupt cessation will not create adrenal insufficiency. If long-term oral corticosteroids are necessary to control severe asthma, alternate day prednisone is a useful approach. Pulmonary function is preserved for the 48-h period as is the morning serum cortisol and adrenal response to ACTH. Because some almost subclinical HPA suppression occurs as demonstrated by the metyrapone test, major stress necessitates additional corticosteroids. Some minor side effects of alternate day prednisone include appetite stimulation, acne in adolescents, hyperglycemia in predisposed patients, and prednisone-phobia either in physicians or patients. To try to minimize confusion, a patient information sheet may be utilized.

Long-term use of prednisone doses of even over 100 mg on alternate days results in avoidance of many serious adverse effects recognized with high-dose prednisone administered on a daily basis. For example, alternate day prednisone avoids serious infections, including those of bacterial, fungal, and granulomatous origin, Cushingoid obesity, hypertension, hyperglycemia (unless the patient is predisposed), poor wound healing or scar tensile strength, personality changes, and growth retardation in children. The latter assumes that asthma is managed successfully. There is a small incidence of posterior subcapsular cataracts that appears to be related to the total dosage of corticosteroids. Annual ophthalmologic examinations should be obtained. Some patients report symptoms of dyspepsia, but the risk of peptic ulceration in patients receiving oral corticosteroids is about the same as occurs in nonusers of corticosteroids (0.8 percent) or slightly greater (1.8 percent). The effects of alternate day or daily prednisone on skeletal mass depend on the disease being treated, duration and dosages used, presteroid bone mass, racial background, exercise patterns, and other medications (excessive thyroid replacement) or bone diseases. Supraphysiologic dosages of corticosteroids may cause loss of trabecular and cortical bone. However, vertebral fractures and profound bone loss are not inevitable consequences of long-term prednisone administration in patients with asthma. Efforts should be made to define other conditions that might impede normal remodeling of bone. Although calcium supplementation for postmenopausal women has not proved useful in some studies, as compared to estrogen replacement, in premenopausal women and men who are increasing their bone mass until age 45 years, adequate calcium should be used. For example, about 1,000 mg of element calcium is recommended per day in the absence of contraindications. Exercise should be encouraged and asthma managed to permit aerobic activities. In patients who have known osteopenia, additional modalities (etidronate) may be advised as it may be impossible to discontinue essential corticosteroids.

Inhaled corticosteroids have been effective and well tolerated in the United States since 1976. Most patients require 6 to 20 inhalations of beclomethasone dipropionate or triamcinolone acetonide daily. With currently available preparations, theoretical adverse effects such as bronchial mucosal atrophy, "reactivation" tuberculosis, and rubeola pneumonia in nonimmune subjects have not materialized. The topically active corticosteroids are metabolized quickly such that clinically important dysfunction of the HPA axis does not occur. The introduction of more potent inhaled corticosteroids, however, creates the possibility of systemic effects and suppression of serum cortisol or adrenal response to ACTH.

The 2 expected adverse effects from inhaled corticosteroids include Candida pharyngitis or laryngitis and dysphonia. Both conditions are reversible. Extension devices may help prevent recurrences in some patients.

Patients should realize that there may be times when oral corticosteroids may be required despite optimal use of topical corticosteroids. In this context, alternate day prednisone and inhaled corticosteroids are maintenance therapy in contrast to daily prednisone which is added therapeutically to prevent progressive deterioration of asthma during an exacerbation. The adverse effects of a 4 to 7 day course of prednisone during an asthma exacerbation are minimal compared to the benefits and include possible appetite stimulation, hypokalemia, hyperglycemia, acne (primarily in adolescents), and induction of prednisone-phobia. Measurement of serum prednisone concentrations, its metabolite, prednisolone, and cortisol has proved helpful to identify noncompliance. If a discussion with the patient or family does not improve compliance, depot corticosteroids may be administered after appropriate documentation in the medical record. The use of such long-acting corticosteroids should be restricted to cases where it is necessary to try to prevent an asthma fatality when the usual modalities have been unsuccessful.

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