

Postgraduate course

Glucocorticoid therapy for asthma: Clinical pharmacology

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We are now well aware that inflammation plays an important role in the pathogenesis of asthma. This awareness comes at a time when we question the etiology of increased asthma prevalence and severity, as well as increased morbidity and mortality.¹⁻³ Questions are now being raised regarding techniques of asthma education, patient compliance, access to medical care, restructuring the approach to asthma treatment, and possible harmful effects of each medication. Therefore, each medication must be scrutinized very carefully for efficacy and adverse effects.

Glucocorticoids represent a group of extremely potent anti-inflammatory agents and are now highlighted as the treatment of choice for patients with persistent asthma.⁴ There are several excellent recent reviews available on glucocorticoid therapy for asthma.⁵⁻⁷ This review will focus on the rationale for the renewed interest in glucocorticoid therapy, recent information on glucocorticoid pharmacokinetics and pharmacodynamics, including the evolution of inhaled steroids, and an analysis of conditions that should be considered if patients fail to respond to glucocorticoid therapy.

RISING TO THE FOREFRONT

In the past, asthma was attributed primarily to spasm of airway smooth muscle, and emphasis was placed on bronchodilator therapy. It is now clear that asthma is an inflammatory disease that leads to edema, airway smooth muscle constriction, and obstruction of the airways with secretions. The inflammatory cells release mediators that cause significant airway hyperresponsiveness to various stimuli, such as histamine, exercise, and cold air.⁴ There is significant interaction among the various cell types and thus a need to use a medication with a wide spectrum of effect or one that modulates an essential target site.

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Abbreviations used

BHR:	Bronchial hyperresponsiveness
BDP:	Beclomethasone dipropionate
IC ₅₀ :	Plasma drug concentration that results in 50% suppression of the measured response
EET:	Effective exposure time-time that plasma drug concentration exceeds the IC ₅₀ value
FEV ₁ :	Volume in liters over the first second of a forced expiration
PC ₂₀ or PD ₂₀ :	Provocative concentration or dose of a bronchoconstrictor substance resulting in a 20% drop in FEV ₁
MDI:	Metered-dose inhaler
EOS:	Eosinophil
BMP:	Beclomethasone monopropionate
PEF:	Peak expiratory flow
BAL:	Bronchoalveolar lavage
BALF:	Bronchoalveolar lining fluid

After a single allergen exposure in a sensitive patient, there is a release of direct-acting mediators, primarily mast cell in origin, resulting in immediate bronchoconstriction and increased airway secretions. This response is referred to as the early phase pulmonary response. With significant exposure to allergen, there is also cell recruitment, including EOSs and neutrophils, that results in additional mediator release and sustained bronchoconstriction. This bronchoconstriction occurs several hours after the allergen bronchial challenge and is referred to as the late-phase pulmonary response. The release of mediators from these inflammatory cells results in epithelial lining damage and exposure of the airway receptors to irritant stimuli and bronchoconstrictors, such as histamine and methacholine. This resultant increase in airway hyperresponsiveness can last for several weeks to months after a single allergen challenge.⁸ From this model, it is assumed that multiple allergen challenges result in persistent airway inflammation through a cycle of continued cell recruitment and mediator release and consequent airway hyperresponsiveness. The clinical manifestations include episodic bronchoconstriction.

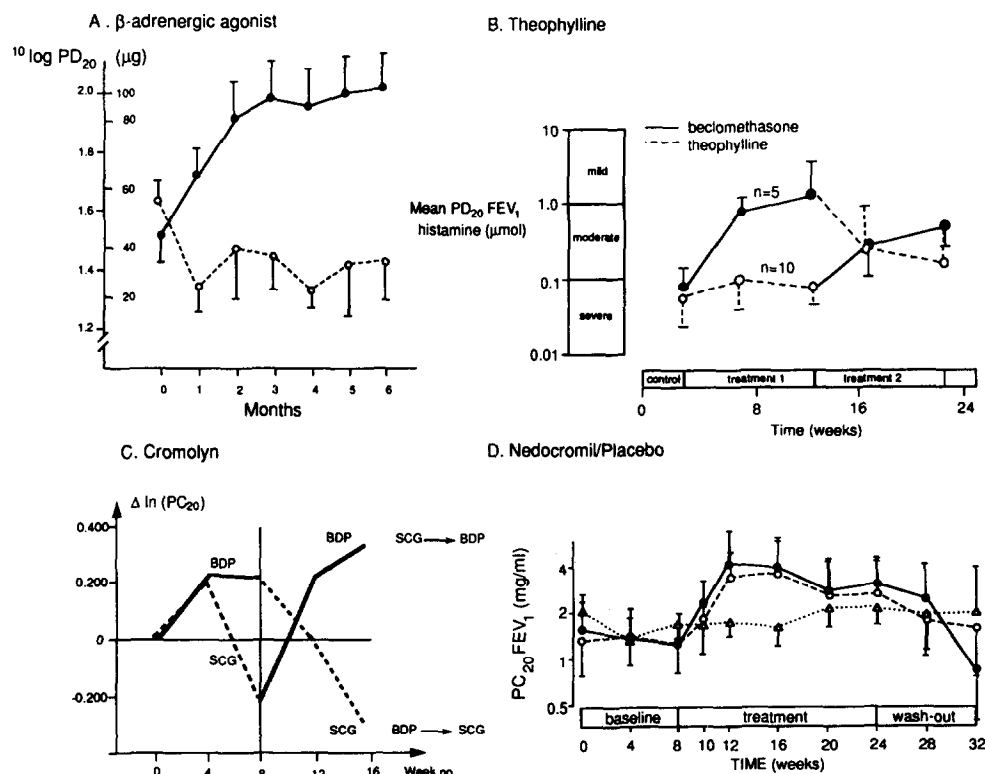
Effect of Inhaled Steroids on Airways Hyperresponsiveness:
Comparison to Other Asthma Medications

FIG. 1. **A.** Mean $^{10}\log PD_{20}$ methacholine ($\pm$ SEM) during 6 months of treatment with either inhaled budesonide, 200 μg ($\bullet$) ($n = 12$) or inhaled terbutaline, 0.5 mg ($\circ$) ($n = 7$) three times a day in children with asthma. Reprinted with permission from Mosby-Year Book, Inc. (Kerrebijn KF, et al. *J ALLERGY CLIN IMMUNOL* 1987;79:653-9). **B.** Mean PD_{20} histamine during crossover study in adults with asthma with beclomethasone dipropionate, 800 μg per day ($\bullet$), or sufficient oral theophylline ($\circ$) to maintain concentrations between 10 and 20 $\mu g/ml$. Reprinted with permission from American Lung Association (Dutoit JI, et al. *Am Rev Respir Dis* 1987;136:1174-8). **C.** Change in $\ln PC_{20}$ during crossover study in 38 adults with asthma with beclomethasone dipropionate, 200 μg twice daily (—) or sodium cromoglycate, 2 mg (---) four times a day for 8 weeks. Reprinted with permission from Mosby-Year Book, Inc. (Svendsen UG, et al. *J ALLERGY CLIN IMMUNOL* 1987;80:68-74). **D.** Geometric mean PD_{20} methacholine ($\pm$ SEM) before, during, and after treatment with either placebo (Δ) ($n = 8$), 4 mg of nedocromil ($\circ$) ($n = 9$), or 100 μg beclomethasone dipropionate ($\bullet$) ($n = 8$) four times a day for 4 months in 25 nonatopic adult patients with asthma. Reprinted with permission from American Lung Association (Bel EH, et al. *Am Rev Respir Dis* 1990;141:21-8).

tion, circadian variation in pulmonary function, and increased response of the airways to cold air, exercise, and environmental irritants.⁹

The severity of asthma can be correlated to a patient's medication requirement, pulmonary function, nocturnal symptoms, exercise lability, and airway response to histamine or methacholine.¹⁰ It is indeed remarkable that certain patients, despite aggressive glucocorticoid therapy, still have significant symptoms and airway hyperresponsiveness. Since it is now assumed that this may be related to the inflammatory

process, the primary goal of therapy should be to resolve inflammation.

Based on this concept of inflammation, the recent trend in asthma therapy is to combine a bronchodilator, primarily β -adrenergic agonists, with a non-bronchodilator antiasthma drug, either cromolyn or a glucocorticoid. Glucocorticoids are the most potent anti-inflammatory agents available for the treatment of asthma. Carryer et al.¹¹ are credited with the first use of cortisone acetate for the treatment of bronchial asthma, and this treatment became a source of rescue

therapy for patients with severe episodes of acute bronchospasm. For patients with severe asthma, it was then added to the treatment regimen for maintenance therapy. Because of the concern over potential adverse effects of systemic steroids, glucocorticoids suitable for inhaled administration were developed. When these are administered before an allergen challenge in a sensitized patient, glucocorticoids block the late-phase pulmonary response and the resultant increase in BHR.^{12, 13} Continued administration is effective in reducing the immediate pulmonary response to an allergen challenge.

Several studies highlight the unique properties of glucocorticoids in providing a sustained reduction in BHR with long-term treatment.¹⁴⁻¹⁶ Kerrebijn et al.¹⁵ reported a significant reduction in bronchial response to histamine (twofold to threefold change in histamine PC₂₀) in 11 of 12 allergic patients with asthma after treatment with budesonide at a dose of 200 µg three times per day for 6 months (Fig. 1, A). In contrast, there was no improvement observed in seven other patients with asthma treated in this parallel study design with β-adrenergic agonist therapy alone, terbutaline, 0.5 mg three times per day, for the same 6 month period. A similar effect was observed when an inhaled glucocorticoid, BDP, was compared to another bronchodilator, oral theophylline, in a double-blind, crossover study. In this study, 26 atopic patients with asthma were randomized to receive either BDP, 800 µg/day, or oral theophylline in a dose sufficient to maintain serum theophylline concentrations between 10 and 20 µg/ml for 10 to 12 weeks. After the first study period, patients were crossed over to the alternate treatment. Dutoit et al.¹⁷ reported that the degree of BHR improved within 3 weeks in the patients receiving inhaled steroid, whereas there was minimal change in patients receiving sustained-release theophylline twice daily (Fig. 1, B). The severity of BHR in the BDP-treated patients improved from the severe to the moderate range. Furthermore, when the patients receiving BDP were changed to theophylline, there was a deterioration in BHR.

A randomized, crossover study by Svendsen et al.¹⁸ compared the effects of cromolyn and BDP on pulmonary function and BHR in 38 atopic patients with asthma. Each patient received a 2-week run-in period, followed by 8 weeks of the first treatment and then 8 weeks of the alternate treatment. Cromolyn was administered in a dose of 2 mg four times per day and BDP, 200 µg twice daily, both by MDI. These authors observed that BDP increased FEV₁, FVC, and PEF, as well as PC₂₀ to histamine regardless of the order of treatment (Fig. 1, C). Cromolyn, however, was

most effective when it was administered as the first treatment. However, its effect on BHR was not sustained and not equal to the effect of inhaled BDP.¹⁸ When cromolyn was administered in the second study period, the improvement in pulmonary function and BHR obtained with BDP was not maintained.

A randomized, parallel design was used to compare the effects of nedocromil sodium and BDP on bronchial responsiveness to methacholine in 25 nonatopic subjects with asthma.¹⁹ After a run-in period of 2 months, the subjects received either nedocromil, 4 mg; BDP, 100 µg; or placebo, four times per day for 4 months. Methacholine PC₂₀ increased threefold in the patients receiving nedocromil or BDP after 8 weeks but did not improve with placebo (Fig. 1, D). Nedocromil is the only medication, other than inhaled glucocorticoids, that appears to provide a significant and sustained decrease in airway hyperresponsiveness. Only BDP demonstrated a significant improvement in FEV₁ and deep breath-induced bronchodilation, suggesting that the two drugs attenuate BHR by different mechanisms.

The proposed mechanisms of action for glucocorticoids in asthma include their effect on cell traffic (decreased peripheral blood EOSs, basophils, lymphocytes, and monocytes), altered chemotaxis (specifically neutrophils), impaired mediator synthesis and release, enhanced β-adrenergic receptor activity, and decreased vascular permeability.^{5, 6} However, these proposed mechanisms must be interpreted with caution because the evidence for their effect is based largely on *in vitro* studies, and these studies are usually conducted with isolated cells and glucocorticoid concentrations far exceeding those achieved *in vivo*. Furthermore, these glucocorticoid concentrations are maintained constant *in vitro*, vastly different than the circadian variation in glucocorticoid concentrations observed naturally and those obtained after oral doses administered in the morning. Very few of these proposed mechanisms have been supported by clinical studies. There are still many gaps in our knowledge regarding the precise mechanisms of action for glucocorticoids in the treatment of asthma.

There is only limited information regarding the long-term effects of inhaled glucocorticoids on resolving inflammation in asthma. Lundgren et al.²⁰ reported that after 10 years of treatment with inhaled glucocorticoids the number of inflammatory cells was significantly reduced compared to the number before treatment and similar to that of control biopsy specimens obtained from normal healthy control subjects. Despite the absence of inflammation and reduced epithelial damage during treatment, all patients still had

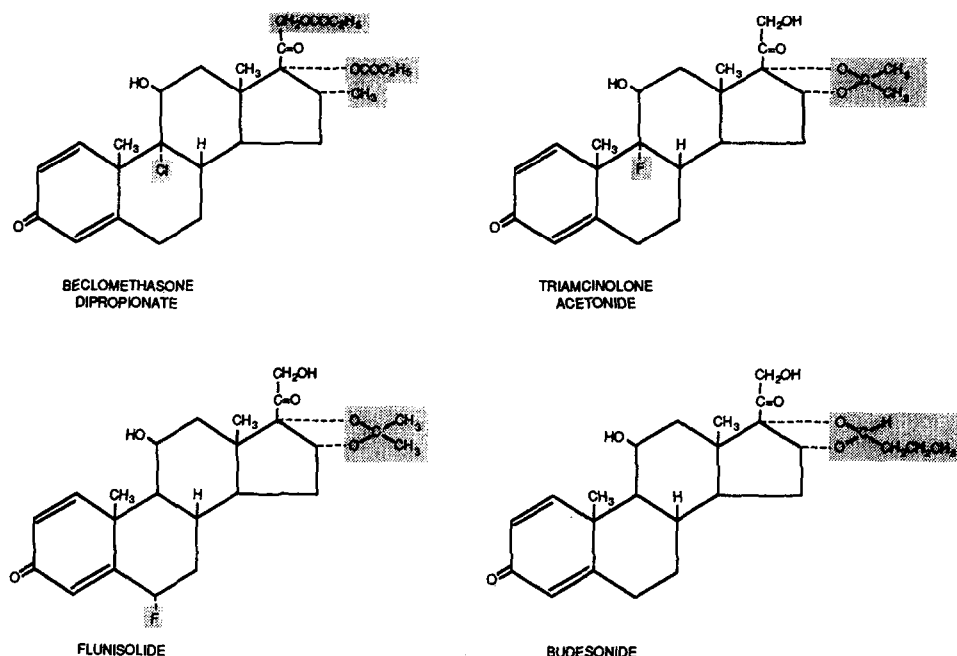


FIG. 2. Structure of inhaled glucocorticoids. Shaded areas indicate structural modifications designed to increase anti-inflammatory and topical potency.

BHR. This finding raises questions regarding the reversibility of certain pathogenic features of asthma. It also highlights the need for a marker of inflammation that is noninvasive and feasible for serial measurements to evaluate the effect of various methods of intervention.

RECENT ADVANCES IN GLUCOCORTICOID THERAPY

The principles of steroid therapy are well established and include the use of systemic glucocorticoids to optimize pulmonary function, an assessment of severity as the steroid dose is reduced, and an attempt to reduce the severity through the combination of bronchodilator and nonbronchodilator medications.²¹⁻²⁴ Monitoring patients with a peak flow meter can be useful in assessing severity and evaluating the effect of medication adjustments. It is also important to identify and minimize the effect of triggers, to develop a crisis plan for severe episodes of bronchoconstriction, and to review the course frequently, especially if the goals of treatment are not attained. Education of the patient and family is also extremely important. The dosing strategy applies larger and frequent doses in the presence of increased severity with a gradual reduction as control is established. Efficacy can be monitored by clinical symptoms, peak flow, pulmonary function tests, and possibly airway response to histamine or methacholine.

Systemic glucocorticoid therapy

Severe acute asthma, status asthmaticus, is treated with high-dose systemic glucocorticoids combined with frequent administration of inhaled β -adrenergic bronchodilator agents. Glucocorticoids can be administered by the parenteral route (methylprednisolone sodium succinate and hydrocortisone sodium succinate) or alternatively by the oral route (prednisone and methylprednisolone) that provide a rapid onset of action and a systemic effect. Methylprednisolone sodium succinate may be administered in a dose of approximately 1 mg/kg, intravenously, every 6 hours.^{24, 25} After resolution of severe obstruction, the steroid dose is reduced and administered by the oral route. The duration of treatment and tapering dose is dependent on the patient's response and past history.

Glucocorticoids are also recommended for the treatment of impending episodes of severe asthma when bronchodilator therapy is inadequate.^{26, 27} Prednisone, approximately 1 to 2 mg/kg/day, is administered orally once daily or in two to three divided doses for 3 to 7 days. There are no studies to date that compare the relative benefits of once-daily administration versus divided doses. The dose and duration of treatment is based on the patient's response and past history.

In patients with poorly controlled chronic asthma, oral glucocorticoids may be administered in a dosing schedule similar to that previously described to maximize pulmonary function. Once this goal is achieved,

TABLE I. Relative potencies of various glucocorticoids for inhalation therapy as measured by topical (inhibition of ear edema formation) and systemic effect (thymus involution) after topical and oral application to mice

	Topical anti-inflammatory potency	Systemic potency	Ratio between the topical and systemic potencies
Halogenated			
BDP	0.4	3.5	0.1
Triamcinolone acetonide	0.3	5.3	0.06
Flunisolide	0.7	12.8	0.05
Nonhalogenated			
Budesonide	1	1	1

Activity is expressed as relative potency in relation to budesonide.
Data compiled from publication by Brattsand et al. Eur J Respir Dis 1982;63(suppl 122): 62-73.

TABLE II. Maximum recommended adult and pediatric doses for available inhaled glucocorticoid preparations

Glucocorticoid	Adults			Children	
	µg/inhalation	Inhalations/day	mg/day	Inhalations/day	mg/day
BDP	42	20	0.84	10	0.42
Triamcinolone acetonide	100*	16	1.6	12	1.2
Flunisolide	250	8	2.0	4	1.0

Pediatric doses are described for children 6 to 12 years of age.
*200 µg per actuation but 100 µg retained in spacer.

the prednisone dose is tapered and may be supplemented and eventually replaced by inhaled glucocorticoids.²¹⁻²⁴

Inhaled glucocorticoids

Recent emphasis has been placed on the development of inhaled glucocorticoids, and the important property is topical potency. The biologic response to steroids is related to modification of the basic structure of the steroid molecule (Fig. 2). Structural modifications have successfully separated the mineralocorticoid from the metabolic and anti-inflammatory effects; however, it has not been possible to remove the metabolic effects and isolate the desired anti-inflammatory properties. Modifications at the 16 and 17 position significantly increase topical anti-inflammatory potency. It was previously believed that halogenation at the 6 or 9 position would increase topical potency, but in fact this has little effect, as evidenced by the absence of halogenation in budesonide. Halogenation, however, does increase systemic potency. Therefore, budesonide appears to have the highest

topical to systemic potency, based on limited comparisons, primarily animal studies.²⁸ The available inhaled glucocorticoids in the United States, BDP, triamcinolone acetonide, and flunisolide, appear to have similar topical to systemic potency ratios; however, more clinical studies are needed to clarify issues around comparative efficacy and toxicity (Table I). All three glucocorticoids are administered by a metered-dose inhaler. Unfortunately, there is no glucocorticoid approved for nebulized administration in the United States.

Budesonide is the most carefully characterized inhaled glucocorticoid based on the meticulous studies of Toogood et al.²⁹ Budesonide is a nonhalogenated glucocorticoid with high topical anti-inflammatory potency and low systemic bioavailability. An attempt was made to derive prednisone equivalents for the topical administration of budesonide. From these studies, an average 1 mg/day dose of budesonide produces an antiasthmatic effect equivalent to approximately 35 mg/day of oral prednisone in patients previously receiving steroid therapy and 58 mg/day in patients who

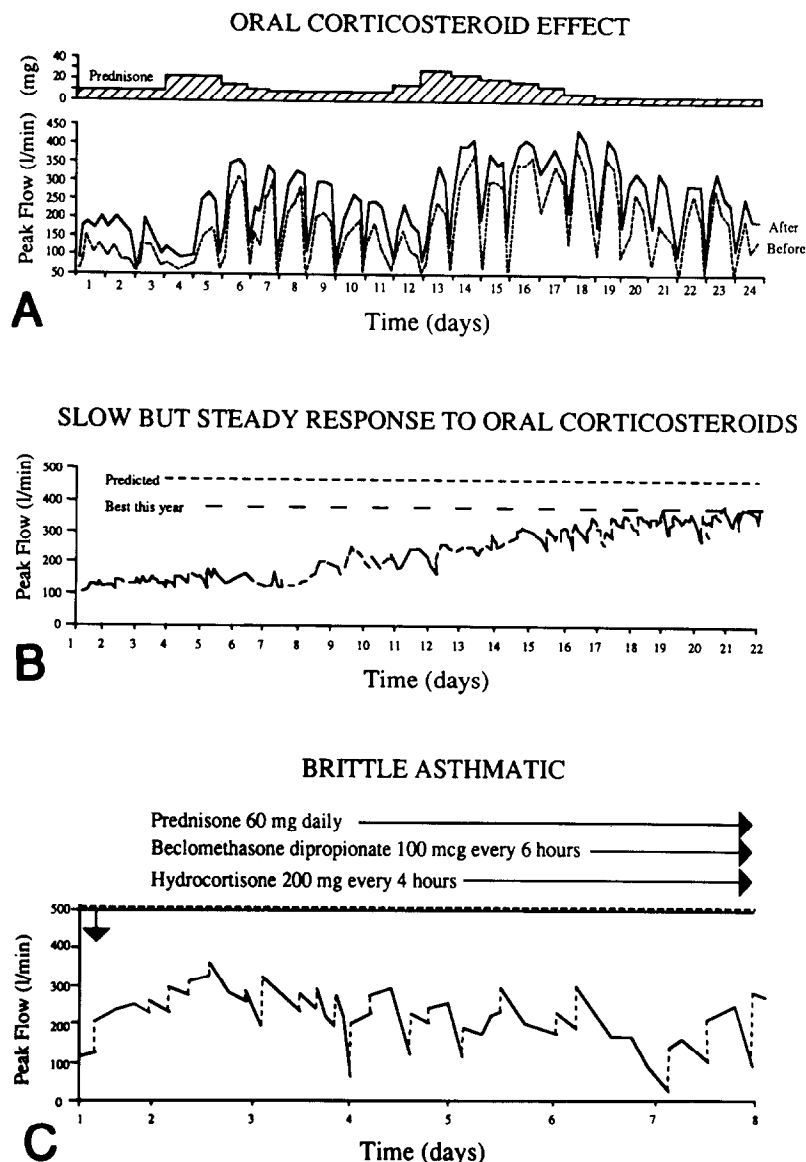


FIG. 3. Varying clinical response to systemic glucocorticoids as measured by PEF rates in individual patients. **A**, Peak flow improving with increased oral steroid dose and deteriorating with dose reduction; morning dip persists throughout. **B**, Slow but steady improvement, and optimal after 17 days of oral steroid. **C**, Unstable pattern, reversible with bronchodilator (*broken line*), but not responsive to oral and inhaled steroid. Reprinted with permission from Blackwell Scientific Publications, Oxford. Turner-Warwick M. Clinical patterns of responsiveness to corticosteroids. In: Kay AB, ed. *Asthma clinical pharmacology and therapeutic progress*. 1986:347-55.

have not received steroids. This dose of inhaled budesonide also produces a systemic effect on serum cortisol concentration equivalent to approximately 8.7 mg/day of prednisone. Administered in larger doses, up to 2.0 mg or more of inhaled budesonide per day, it may eliminate recurrent episodes of severe bronchospasm, even in patients with moderate to severe asthma.

Budesonide doses exceeding 1.84 mg/day in adults

may produce systemic effects on cortisol levels and eosinophil counts that are equivalent to, or more than, oral prednisone, 15 mg/day. The latter dose is associated with steroid complications, such as osteoporosis. More information is needed on prednisone equivalents, comparative efficacy, and toxicity for the inhaled glucocorticoids available in the United States, especially with long-term treatment. Furthermore, the systemic effect of inhaled steroids on serum cortisol

and EOSs may not represent meaningful clinical effects, and additional studies are needed regarding the effect of high-dose inhaled steroids on other steroid adverse effects, such as hypertension, osteoporosis, and cataracts, as well as carbohydrate and lipid metabolism.

Product information now is specific regarding maximum dosing guidelines for adults and children with the available inhaled glucocorticoids (Table II). For triamcinolone and flunisolide, the maximum recommended total daily dose is equivalent to 1.6 and 2 mg/day, respectively. For budesonide, the inhaled steroid with the highest topical to systemic ratio, this total daily dose is equivalent to 15 mg of prednisone per day, beyond which the risk for systemic effects increases significantly. Therefore, patients requiring doses of the inhaled glucocorticoids, approaching or exceeding 2 mg/day, should be monitored for adverse effects. These maximum dosing guidelines are even lower for children. This is not to say that adverse effects do not occur with lower doses. Capewell et al.³⁰ reported recently that adult patients with asthma, receiving inhaled BDP in total daily doses ranging from 1 to 2.25 mg/day, had decreased skin thickness (15% to 19% less) and a higher prevalence of purpura than that of a control group of patients who had never received inhaled or systemic glucocorticoids. Needless to say, more studies are needed in both adults and children to establish safety for doses that exceed the product recommendations, especially in the area of long-term systemic effects.

It has recently been recommended that inhaled glucocorticoids be used earlier in the course of persistent asthma. This appears appropriate in view of the evidence linking asthma to inflammation. Most patients respond very favorably to either bronchodilator therapy alone or combined bronchodilator and anti-inflammatory medications. Certain patients with severe asthma require continuous glucocorticoid therapy. In this era of questions related to the increased prevalence of asthma, failure to reduce hospital admissions, escalating cost of health care, and possible increase in asthma mortality, it is important to question the natural history of asthma and methods to control effectively its progression. There is also a need for long-term studies to assess the safety and efficacy of inhaled steroids in children, particularly in regard to growth and development, bone metabolism, and other adverse effects. Varsano et al.³¹ reported that 16 children with asthma, aged 3½ to 7 years, treated with budesonide, 200 µg/day by MDI and a spacer device for 12 months, had significant improvement in asthma control with no adverse effects in regard to growth, height, and adrenocortical suppression. Similar ob-

TABLE III. Potential mechanisms for poor response to glucocorticoid therapy

Other respiratory disorder, e.g., vocal cord dysfunction, cystic fibrosis, etc.
Overwhelming allergen exposure
Irreversible airway hyperresponsiveness
Poor compliance
Psychological disorder, e.g., panic-fear reaction, depression, etc.
Inadequate dose for severity of disease
Pharmacokinetic basis
Rapid metabolism
Poor distribution to site of action
Incomplete absorption from oral administration
Immunologic resistance
Glucocorticoid receptor down regulation
Abnormal glucocorticoid receptor or postreceptor phenomenon

servations were reported by Godfrey et al.³² after 3- to 5-year follow-up in 19 children who received BDP administered between the ages of 4.5 and 11.9 years. The overall mean dose of BDP was 400 µg/day. All children grew within a small percent of expected height, and no serious side effects were observed.

The efficacy and risk for adverse effects to inhaled steroids are related to the dose and frequency of administration, the specific glucocorticoid, and the systemic availability of the glucocorticoid. Very little is known regarding pulmonary distribution, retention, and metabolism of the inhaled glucocorticoids under clinical conditions. The systemic availability of the inhaled steroids can be influenced by the method of delivery, absorption from the lung and the intestinal tract, and metabolism, both in the lung and in the body. A spacer device improves the efficiency of drug delivered to the lung and also limits the amount of drug deposited in the oropharynx and eventually swallowed.³³ By limiting the amount of glucocorticoid swallowed, this will theoretically decrease the amount of drug systemically absorbed. However, Toogood et al.³⁴ demonstrated that the use of a spacer increased both the efficacy and the systemic effect of inhaled budesonide. This observation is probably related to improved delivery of the drug to the lung. Since budesonide is better absorbed from the lung as compared to the intestine, the relative systemic bioavailability was likely increased with the use of a spacer. This will be discussed further under glucocorticoid pharmacokinetics.

There are only a few studies that examine the effect of inhaled steroids at the site of action, namely, via bronchial biopsy. As previously mentioned, the study

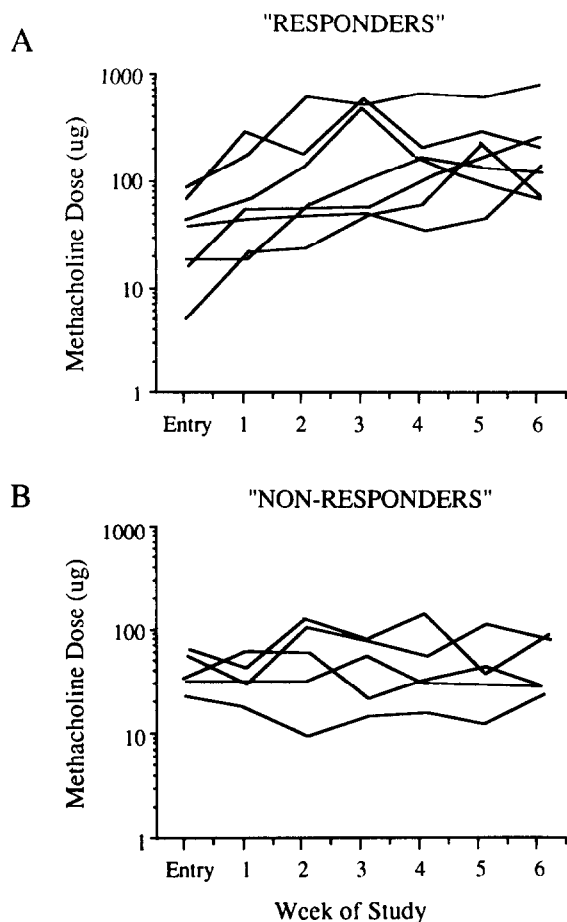


FIG. 4. PD₂₀ methacholine ($\pm$ SEM) during 6 months of treatment with inhaled budesonide, 200 μ g three times a day in children with asthma. **A**, Demonstrating initial improvement in seven patients with two of these patients revealing loss of improvement with time. **B**, No improvement in five other patients. Modified from Kerrebijn KF, et al. *J ALLERGY CLIN IMMUNOL* 1987;79:653-9.

by Lundgren et al.²⁰ identified significant resolution of inflammation after long-term treatment; however, bronchial hyperresponsiveness persisted. Long-term treatment appears to be indicated since increased airway hyperresponsiveness occurs after inhaled glucocorticoids are stopped (Fig. 1, *B* and *D*). Similar comparative information is needed with other non-bronchodilator asthma medications, such as cromolyn and nedocromil, to evaluate the effect on inflammation.

HIDDEN VARIABLES

In a very insightful review, Dr. Margaret Turner-Warwick³⁵ indicated the various ways patients respond to a course of oral glucocorticoid therapy. Some patients improve within 3 to 5 days, whereas other patients require 10 to 14 days to recover maximal pul-

monary function (Fig. 3). Indeed, with other markers of response, such as alteration in airway hyperresponsiveness, the response may be even slower. Juniper et al.³⁶ demonstrated that patients receiving inhaled budesonide at a dose of 400 μ g/day for 1 year had maximal improvement within the first 3 months. However, some of the patients were still progressing slowly at 1 year of treatment. Certain patients can be characterized as "brittle asthmatics" with variable pulmonary function despite aggressive courses of glucocorticoid therapy (Fig. 3).

Patients who require high-dose systemic steroid therapy are at significant risk for adverse effects, depending on the dose and duration of treatment. Remarkably, a proportion of these poorly responsive patients demonstrate minimal adverse steroid effects. Concerns have been raised regarding potential "steroid resistance" in patients with asthma. It is not clear whether this phenomenon is simply undertreated asthma, poor adherence to the treatment recommendations, a psychologic disturbance, irreversible airway hyperresponsiveness, an abnormality in glucocorticoid pharmacokinetics, or a cellular abnormality in key regulatory cells in the immune system (Table III).

A closer evaluation of the patients in Fig. 1, *A*, illustrating that inhaled budesonide reduces airway hyperresponsiveness,¹⁵ identifies several patterns of individual response, and this is graphically presented in Fig. 4. About one half of the patients responded to treatment, with a sustained reduction in airway hyperresponsiveness. Several of these patients, however, improved significantly initially and then gradually declined approaching the pretreatment measurement. The other one half of the patients had no change whatsoever in airway response to histamine.

Schwartz et al.³⁷ first suggested that some patients may be "resistant" to glucocorticoid therapy. They reported that certain patients who required >15 mg/day of oral prednisone to maintain some degree of asthma control had a diminished eosinopenic response to cortisol at 4 and 6 hours after the study dose, and accelerated plasma cortisol clearance, cortisol half-life, 87 minutes in resistant patients versus 144 minutes in control subjects. Kay et al.³⁸ Carmichael et al.,³⁹ and Poznansky et al.⁴⁰ also reported that certain patients may be "steroid resistant" based on their failure to demonstrate improvement in pulmonary function after a course of oral prednisolone, at least 20 mg daily for 1 week. As compared to responders, these apparent "steroid-resistant" patients were more likely to have a family history of asthma, longer duration of symptoms, a greater tendency toward nocturnal symptoms, and a greater degree of bronchial reactivity to methacholine. These charac-

teristics are frequently observed in severe asthma. The investigators proposed a defect in monocyte response to glucocorticoids.³⁸⁻⁴¹

Other investigators have proposed a generalized defect in tissue response to glucocorticoids, as indicated by vasoconstrictor response to glucocorticoids applied to the skin.⁴² Toogood et al.²⁹ commented that steroid response to inhaled and oral glucocorticoids could be differentiated, based on several additional features. Patients more likely to demonstrate breakthrough symptoms during glucocorticoid therapy could be differentiated from patients who did not, based on lower baseline pulmonary function (either FEV₁ or FVC), higher circulating EOS count, or higher peripheral monocyte count.

There is no question that the correct diagnosis, management of precipitants, appropriate use of conventional therapy, and adherence to the treatment regimen are basic tools to successful management. However, certain patients remain difficult to manage, raising questions about conditions that may alter response to glucocorticoid therapy. There is likely no single cause for failure to respond to steroid therapy, and the reason may vary among individual patients. Poor response could be related to a cellular defect in response to glucocorticoids or an abnormality in their absorption or metabolism of glucocorticoids. Although abnormal pharmacokinetics is not the explanation for all patients with apparent steroid resistance, it may play a role in certain individuals. The following section will summarize available information on glucocorticoid pharmacokinetics and pharmacodynamics and potential cellular mechanisms that could influence clinical response to glucocorticoids.

Pharmacokinetics and pharmacodynamics of systemic glucocorticoids

Structural modifications are applied to improve the potency and duration of glucocorticoid action. For example, the commonly administered oral glucocorticoid prednisone is inactive and must be converted to prednisolone by reduction at the 11-keto position. Methylprednisolone is active and differs from prednisolone by placement of a methyl group at the 6 α position. This minor structural modification alters the binding of methylprednisolone to transcortin, a corticosteroid-binding globulin, as well as susceptibility to changes in metabolism by other drugs. The structural modifications of inhaled steroids were previously discussed.

The magnitude and duration of effect of glucocorticoids is dependent on the structure of the glucocorticoid, absorption and distribution to the site of action, binding to the steroid receptor, and the elimination of

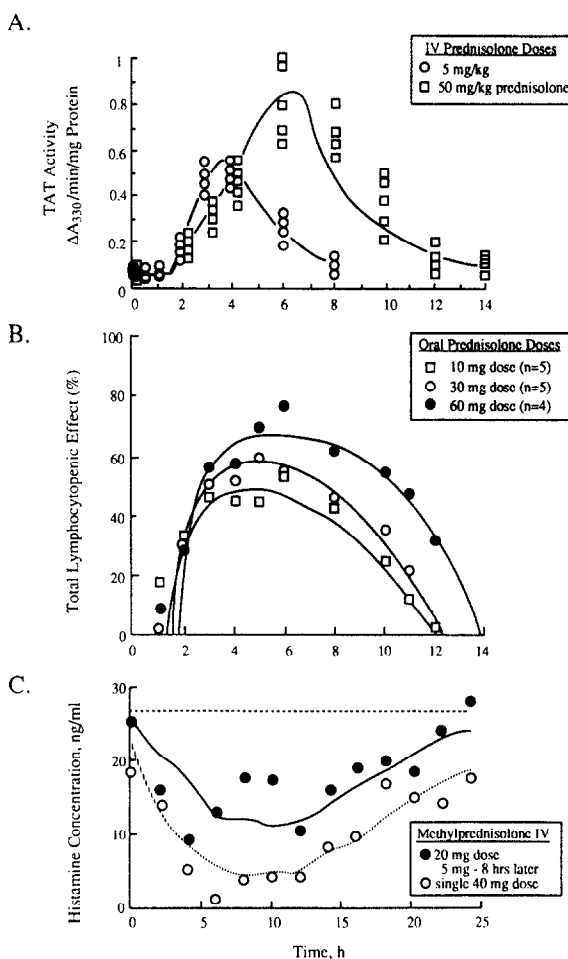


FIG. 5. Pharmacodynamics of glucocorticoids. **A**, Tyrosine aminotransferase activity in rat liver as a function of time before and after 5 ($\circ$) and 50 ($\square$) mg/kg of intravenous prednisolone. Symbols are experimental data and lines are least-squares regression lines. Reprinted with permission from Plenum Publishing Corp. Boudinot et al. *J Pharmacokin Biopharm* 1986;14:469-93. **B**, Mean data curves for total lymphocytopenic effect in relation to oral prednisolone dose in normal subjects. Reprinted with permission from American Society of Pharmacology Experimental Therapeutics. Oosterhuis B, et al. *J Pharmacol Exp Ther* 1987;243:716-22. **C**, Whole blood histamine concentrations for single subject after single 40 mg of intravenous methylprednisolone dose ($\circ$) and split dose of 20 mg followed by 5 mg 8 hours later ($\bullet$). Reprinted with permission from CV Mosby. Reiss WG, et al. *J ALLERGY CLIN IMMUNOL* 1990;85:1058-66.

the glucocorticoid.⁴³ Response to glucocorticoids can be studied in animal models to evaluate the effect of different dosing strategies. An enlightening feature of the animal model developed by Boudinot et al.⁴³ is derived from a measure of tyrosine aminotransferase activity as a marker. It was noted that a tenfold increase in dose does not produce a proportional increase in effect (Fig. 5, A). The maximum response is only

TABLE IV. Glucocorticoid pharmacokinetic and receptor binding parameters

Glucocorticoid	Half-life (hr)	Volume of distribution (l/1.73 m ²)	Clearance (ml/min/1.73 m ²)	Binding affinity*		References
				Human lung tissue	Rat skeletal muscle	
Cortisol	1.9 ± 0.11	70	425.5†	0.9	0.04	55
Prednisolone	3.25 ± 0.58	53.5 ± 13.5	198 ± 38	1.6	—	56
Methylprednisolone	2.58 ± 0.19	91.0 ± 9.9	384 ± 56.2	4.2	—	57
Dexamethasone	4.37 ± 1.16	33.4 ± 4.2	216 ± 21.5	1	1	58
BDP	15					59
Triamcinolone acetonide	1.46 ± 0.35	99.5 ± 27.5	753 ± 152	2.3	3.8	60
Flunisolide	1.6 ± 0.35	124.6 ± 21.8	960 ± 138			61
Budesonide	2.8 ± 1.1	301.3 ± 41.7	1395 ± 458		7.8	63

Data are compiled from various sources and presented as mean ± SD. Studies were conducted in normal adult subjects except for dexamethasone, which included adult subjects with asthma. Surface area was assumed to be 1.73 m² or 70 kg in adult subjects.

*Binding affinity relative to dexamethasone, derived from references 54 and 64.

†Estimated, based on available information on half-life and volume of distribution.

increased 50% and the duration of effect only increased twofold. An extension of this model is the observation that smaller doses administered more frequently are much more effective than large single doses.⁴⁴

Unfortunately, there are no good indicators of response at the cellular site of action for asthma, but certain pharmacodynamic observations identified in man with circulating leukocytes are, perhaps, correlated to the effect of glucocorticoids.⁴⁵⁻⁴⁷ With the lymphocytopenic effect of prednisolone as a marker, Oosterhuis et al.⁴⁷ observed a 33% increase in maximal response and a 20% increase in duration of effect with a sixfold increase in dose (Fig. 5, B).

Reiss et al.⁴⁸ used suppression of circulating basophils, measured as whole blood histamine, and plasma cortisol concentration to examine the pharmacodynamics of methylprednisolone. The drug was administered as a single 40 mg dose or as a split dose, 20 mg initially followed by 5 mg of methylprednisolone 8 hours later. The IC₅₀ value indicates the plasma methylprednisolone concentration that results in 50% suppression of the measured response. The EET is a mathematical parameter that indicates the time that the plasma methylprednisolone concentration exceeds the IC₅₀ value. The two measures of response used in this study can be categorized into a desirable response, suppression of circulating basophils or blood histamine, and an undesirable effect, suppression of plasma cortisol concentration.

The duration of blood histamine suppression as indicated by the EET is approximately 15 hours for both dosing schedules (Fig. 5, C). One interpretation of the clinical relevance of this study is that both regi-

mens provided only limited coverage and did not extend to the critical nighttime hours. The IC₅₀ for blood histamine suppression was very low, 5 ng/ml. In regard to an undesirable effect, suppression of plasma cortisol, the split-dose regimen caused less cortisol suppression than the single 40 mg dose. The EET for cortisol suppression was significantly lower for the split-dose regimen, 19.4 hours, as compared to the single dose, 28.5 hours, suggesting that the split-dose regimen has less risk for toxicity.

The IC₅₀ for cortisol suppression, 1 ng/ml, was even lower than the IC₅₀ for blood histamine suppression, 5 ng/ml. Although these measures are not a direct measure of the desired clinical effects of decreased inflammation and improved pulmonary function, they may provide an approximation. Other anti-inflammatory effects, such as reduced vascular permeability, are not measured here. The low IC₅₀ value for cortisol suppression is a concern and suggests that the critical concentration for adverse effects may be lower than the concentration for desirable effect. As with the beneficial effects, however, the IC₅₀ for cortisol may be very different in magnitude to the IC₅₀ for other adverse effects.

The investigators introduced the term "wasted drug" to indicate that glucocorticoid concentrations, significantly higher than the IC₅₀ values, likely do not enhance beneficial effect. They indicate that the duration of effect can be more successfully extended by use of a smaller total dose in a divided manner. The key point is that the dosing strategy is designed to maximize concentrations during the daytime hours. Extending the time of the second dose to a later time in the day might increase the risk for adverse effects,

especially if the IC_{50} value for undesirable effects is lower than the IC_{50} value for desirable effects.

A similar principle was proposed by Reinberg et al.⁴⁹ using a specially designed glucocorticoid preparation. A double-blind, randomized, crossover, placebo-controlled study compared two methods of steroid dosing and the consequent effect on pulmonary function. A preparation called Dutimelan 8-15 (DTM 8-15, Hoechst Italia, spa, Milan, Italy) was administered for 8 days according to the following regimen: at 8 AM, the patients received a tablet with 7 mg of prednisolone acetate and 4 mg of prednisolone alcohol; at 3 PM, a tablet with 15 mg of cortisone acetate and 3 mg of prednisolone alcohol; and at 8 PM, a placebo. On the alternate 8 days, they received placebo at 8 AM, and at 3 PM, a tablet consisting of 15 mg of cortisone acetate and 3 mg of prednisolone alcohol; and at 8 PM, another tablet with 7 mg of prednisolone acetate and 4 mg of prednisolone alcohol, a treatment labelled Rx 15-20. The 24-hour mean PEF (based on five measures per day for 8 days) and the morning pulmonary function were approximately 15% higher for the DTM 8-15 regimen as compared to the Rx 15-20 regimen. The investigators concluded that the steroid regimen at 8 AM and 3 PM, DTM 8-15, was more effective in the control of asthma than the steroid regimen administered at 3 PM and 8 PM. Unfortunately, the study did not compare DTM 8-15 to conventional therapy administered at 8 AM in a single dose. One of the disadvantages of DTM 8-15 is the fixed dose that limits individualization of treatment.

Reinberg et al.⁵⁰ also studied the effects of single doses of 40 mg of methylprednisolone administered intravenously at different times of the day, 3 AM, 7 AM, 3 PM, and 7 PM, in eight children with asthma. The mesor of the PEF during 24 hours was greatest after the steroid dose administered at 3 PM, as compared to the other three time periods, with the smallest change observed with the 3 AM dose. Systemic steroid dose administration is usually designed to minimize adrenocortical suppression; however, these investigators make the point that it may be necessary to extend the time of administration to achieve greater beneficial effect. They also believe that glucocorticoid doses can be maximized during the day to minimize the effect on the adrenocortical axis.⁵¹

Clinical pharmacology of inhaled glucocorticoids

Another approach to extending the effect of glucocorticoids is the inhaled route of administration. This strategy offers several advantages over oral therapy: delivery to the target site, low dose, high affinity

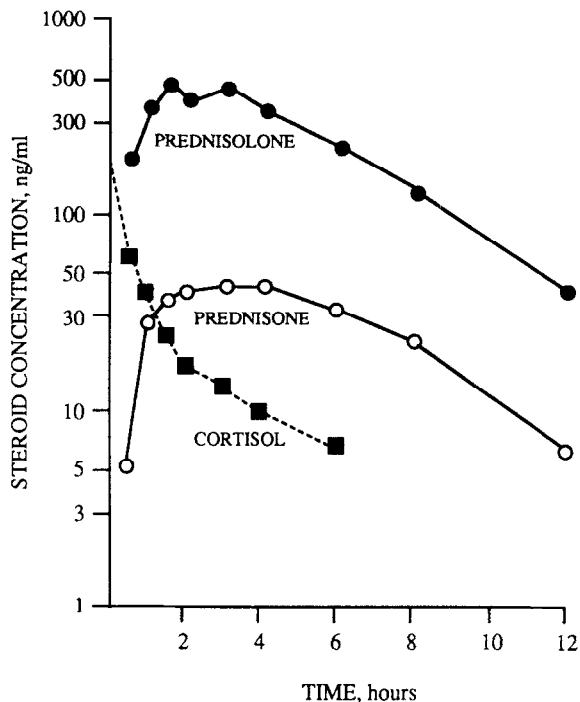


FIG. 6. Glucocorticoid plasma concentration-time profile of a human volunteer after a 50 mg oral dose of prednisone demonstrating conversion of prednisone to prednisolone and cortisol suppression. Reprinted with permission from Elsevier Science Publishers, New York (Rose JQ, Jusko WJ, eds. *Chromatography* 1979;162:280).

for the glucocorticoid receptor in a high concentration, and the feasibility of frequent dosage administration. Based on the previous discussion demonstrating the effect of split dosing⁴⁸ and the variability in effect related to the time of the dose,⁵⁰ perhaps the beneficial effect of inhaled steroids as compared to oral steroid dosing is related to the frequency of administration.^{29, 52} This finding is also consistent with the observations of Toogood et al.⁵³ demonstrating the benefit of four times per day of inhaled budesonide administration over twice daily administration, especially with asthma relapse. When the asthma is unstable, reducing the frequency of administration may necessitate increasing the total daily dose. However, it may be feasible to reduce the frequency of administration and total daily dose when the asthma is under good control. The following section will summarize the available information on pharmacokinetics of inhaled glucocorticoids. Unfortunately, the available data are from separate study populations, and there is no study conducted in the same study population with all inhaled glucocorticoids.

The most detailed information on inhaled glucocorticoid pharmacokinetics is available for bu-

desonide (Table IV). After intravenous administration of budesonide in healthy male volunteers, the plasma budesonide half-life was 2.8 ± 1.1 hours (mean $\pm$ SD), and plasma clearance was 1395 ± 458 ml/min/ 1.73 m².⁶³ The plasma protein binding for budesonide was $88.3\% \pm 1.5\%$ with negligible binding to transcortin. After oral budesonide administration, only $10.7\% \pm 4.3\%$ is absorbed, consistent with extensive first-pass metabolism, likely in the liver. From *in vitro* studies with human liver, two major metabolites were isolated, 6β -hydroxybudesonide and 16α -hydroxyprednisolone. These metabolites have one tenth to one hundredth the biologic activity of budesonide.⁶³ The disposition of these metabolites is not known.

Budesonide is a 1:1 mixture of two epimers that provides a relative binding affinity approximately seven times greater than dexamethasone. In glucocorticoid receptor binding and biologic activity measurements in skeletal muscle, differences were noted in the binding affinity and activity of the two epimers. The 22R-epimer was twice as active as the 22S-epimer, four times greater than triamcinolone, and 14 times greater than dexamethasone.⁶⁴

After inhalation with a spacer (Inhalet, 10 cm long tube), $72.8\% \pm 42.0\%$ is systemically available, after correction for the amount deposited in the spacer device and the oral cavity⁶⁵; $37.2\% \pm 9.2\%$ of the discharged dose was recovered from the spacer device, the actuator, and the subject's nostrils. Another portion, $4.2\% \pm 1.3\%$, was recovered from rinsings in the oral cavity. After inhalation, the plasma budesonide concentration peaked rapidly within the first 5 minutes of sampling time, and the plasma half-life of budesonide was 2.0 ± 0.2 hours. This combined with the high systemic availability of inhaled medication suggests that budesonide is not metabolized extensively in the lung. These studies were conducted with normal, healthy volunteers, and similar information in patients with asthma is not available.

Flunisolide pharmacokinetics are also well characterized. After intravenous administration in another study in 12 normal male subjects, aged 26 to 48 years, flunisolide half-life was measured as 1.6 ± 0.35 hours, and plasma clearance was 960 ± 138 ml/min/ 1.73 m². After oral administration, the systemic availability was measured as $20.1\% \pm 18.7\%$, suggesting extensive first pass metabolism similar to budesonide.⁶¹ The major metabolite is the 6β -hydroxy form of flunisolide, which is active but only three times as potent as hydrocortisone, and, after intravenous flunisolide, is detectable within 5 minutes, peaks within 0.5 to 1 hour, and has a half-life of 3.9 to 4.6 hours. Flunisolide is 320 times more potent than hydrocortisone in the systemic thymolytic

activity in rats and 180 times the anti-inflammatory activity of hydrocortisone.

When flunisolide was administered in another study group of 15 normal male subjects by bronchial inhalation via MDI without a spacer, the peak plasma flunisolide concentration occurred within the first hour, and the plasma half-life is 1.6 to 2 hours, identical to the after intravenous administration.⁶² This information suggests flunisolide was absorbed rapidly from pulmonary tissue. The systemic availability of flunisolide was 32% of the total dose actuated after bronchial inhalation and mouthwash after administration. The remaining dose was likely swallowed and extensively metabolized after absorption. After 2 mg of flunisolide daily by inhalation for 14 days, the plasma flunisolide concentrations were measured 12 hours after the dose and never exceeded 0.35 ng/ml. There was no indication of accumulation with time.

For triamcinolone acetonide, plasma half-life was 1.46 ± 0.35 hours, and plasma clearance was 753 ± 152 ml/min/ 1.73 m², as measured in eight normal volunteers after an intravenous dose. The metabolic pathways in man are not known, but in studies conducted in dogs, monkeys, and rats, the major metabolite is 6-hydroxytriamcinolone acetonide.⁶⁰ Relative to dexamethasone, triamcinolone acetonide binding to the glucocorticoid receptor is approximately three times greater in human lung tissue and rat skeletal muscle.^{54, 64} Information regarding the extent of systemic absorption after an oral and inhaled dose is not available.

There is only limited information on the disposition of BDP in man. BDP differs from the other inhaled glucocorticoids because it is metabolized to potent active metabolites.⁶⁵ In the skin-blanching technique, BDP is 500 times more potent than dexamethasone. A major metabolite of BDP is BMP, which has 360 times the potency of dexamethasone with this vasoconstrictor assay. BMP is then metabolized to beclomethasone, which is equally potent to dexamethasone. Early studies by Martin et al.⁵⁹ used an isotope form of BDP and identified an initial rapidly declining phase during the first 15 minutes after intravenous administration in man. This was followed by a slower declining phase with an approximate half-life of 15 hours; however, samples after 5 hours were attributed to polar metabolites. It appears that BDP is rapidly metabolized to BMP and subsequently metabolized to beclomethasone and other metabolites.

Additional metabolic studies based on human liver and lung slices demonstrated that BDP is metabolized rapidly to BMP in both the liver and the lung.⁶⁶ From these studies, it was concluded that, after inhaled administration, the BDP deposited in the oropharynx and subsequently swallowed would be transformed to

TABLE V. Glucocorticoid interactions with other medications

Glucocorticoid	Drug	Effect	Mechanism	Reference
Cortisol	β-Adrenergic agonist	Enhanced β-agonist response	Alteration of β-receptor affinity	73-76
	Phenobarbital	Increased elimination	Increased cytochrome P-450 activity	77,78
	Rifampicin	Decreased steroid effect	Increased elimination	79,80
Prednisolone	Antacids	Decreased steroid bioavailability	Possible physical adsorption to antacid	81
	Cimetidine	No effect		82-84
	Ranitidine	No effect		85
	Ketoconazole	Impaired elimination		86
	Oral contraceptives	No effect		87
		Increased steroid availability	Impaired elimination	
	Phenobarbital	Decreased steroid effect	Increased protein binding	
	Phenytoin	Decreased steroid effect	Increased cytochrome P-450 activity	70,88
Methylprednisolone	Carbamazepine	Decreased steroid effect	P-450 activity	
	Rifampicin	Decreased steroid effect	Increased steroid elimination	89,90
	Troleandomycin	No effect		71,72
	Cimetidine	No effect		91
	Diazepam	No effect		92
	Erythromycin	Impaired MPn elimination		93
	Ketoconazole	Impaired MPn elimination		94
	Phenobarbital	Probable diminished steroid effect	Increased cytochrome P-450 activity	70,88
	Phenytoin	Decreased steroid effect	Probable increased P-450 activity	89
	Carbamazepine	Decreased steroid effect		
	Rifampicin	Decreased steroid effect		
	Troleandomycin	Enhanced steroid effect	Partially related to impaired MPn elimination	95,96
Dexamethasone	Cimetidine	No effect		83
	Ephedrine	Enhanced elimination	Possible increased metabolism	97
	Phenobarbital	Increased dexamethasone elimination	Increased cytochrome P-450 activity	88
	Phenytoin	Increased dexamethasone elimination		98
	Theophylline	No effect		97

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BMP because it was absorbed from the gastrointestinal tract. From another study of BDP administered orally in man, it was concluded that approximately 90% of the drug was absorbed, based on the collection of urine and fecal metabolites⁶⁷; however, the plasma samples were not analyzed for the parent drug and active metabolites to quantitate systemic availability. Based on rapid metabolism of BDP to BMP in the lung slices, it was also suggested that inhaled BDP could be biotransformed to BMP as it was absorbed from the lung.⁶⁶ Unfortunately, there are no detailed studies of absorption, biotransformation, and subsequent disposition after intravenous, inhaled, and oral absorption in man, as previously summarized with budesonide and flunisolide. This information would be important to describe systemic availability of the parent drug and active metabolites.

There are some studies on biologic activity of inhaled and oral administration of BDP that have been used to attempt to quantitate systemic potency.⁶⁸ These studies include biologic markers of effect, such as changes in peripheral leukocytes after an administered dose and morning plasma cortisol suppression after a dose administered the previous evening. After oral administration, BDP in 2 to 4 mg doses produced the same or even greater effect than oral budesonide, 8 mg. After aerosol administration, it appeared that BDP had about twice the systemic potency of budesonide. In addition, vasoconstrictor studies in man confirmed the rank order of topical potency, presented in Table I, in which budesonide was approximately twice as potent as each of the other three inhaled glucocorticoids: flunisolide, BDP, and triamcinolone acetate.

Needless to say, there is a great need to compare the available inhaled steroids and all new forms under a standard set of conditions to quantitate, fully, systemic availability and consequent systemic effects. Studies are in progress to define these parameters. These studies will permit a better comparison of these medications, as well as a definition of the margin of safety, especially with doses >2 mg/day of inhaled glucocorticoids.

Therapeutic drug monitoring for glucocorticoids

The availability of glucocorticoid at the site of action and consequent pharmacologic effect is altered by conditions that affect absorption, distribution, and elimination. Glucocorticoids are primarily eliminated via metabolic pathways, and certain inhaled steroids, such as BDP, are metabolized in the lung before they are absorbed, thus reducing their systemic effect.

Pharmacokinetic parameters for clinically relevant glucocorticoids after intravenous administration are summarized in Table IV. Very little is known regarding individual patient differences in pharmacokinetics that may influence clinical response. Insight has been gained through the application of assay techniques to measure glucocorticoid concentrations in biologic fluids.

We measure plasma glucocorticoid concentrations to identify patients who are noncompliant or may have abnormalities in the absorption or elimination of systemic glucocorticoids. Our test is based on the observation that glucocorticoids administered systemically, for example, oral prednisone, are rapidly converted to the active form, prednisolone, with a peak concentration at approximately 2 hours. Prednisolone is then eliminated rapidly with a half-life of approximately 2 hours. We have established a data base of pharmacokinetic parameters in children and adults for comparison of patients in question.⁶⁹

Our own application of monitoring techniques has allowed us to identify several important principles. First, concomitant medications can induce or impair glucocorticoid elimination. For example, phenytoin and carbamazepine are potent inducers of prednisolone and methylprednisolone metabolism.⁷⁰ Phenobarbital has a variable effect, significantly affecting some patients but with little effect in other patients. Second, methylprednisolone is more susceptible to drug interactions than prednisolone, the active metabolite of prednisone. In the presence of anticonvulsant therapy, methylprednisolone elimination is increased fivefold, whereas prednisolone elimination is increased approximately twofold.⁷⁰ Similarly, methylprednisolone elimination is significantly impaired in the presence of troleandomycin therapy with no change in the elimination of prednisolone.^{71, 72} Additional glucocorticoid-drug interactions are summarized in Table V. Third, there are patients who for some reason fail to absorb glucocorticoids adequately.⁶⁹ A simple change to an alternative glucocorticoid, for example, prednisone to methylprednisolone, can make a difference in the amount absorbed and consequent clinical response. We have also identified patients who metabolize glucocorticoids very rapidly without any apparent reason. Fourth, knowing the time of the peak concentration and the concentration derived from a certain dose allows a measurement of patient compliance.

Finally, we know very little regarding the conditions that influence the distribution of glucocorticoid to the lung. An interesting observation recently reported by Yoss et al.⁹⁹ demonstrated that oral dosing

with dexamethasone, 4 mg twice daily for seven doses, had little effect on altering the synthesis of inflammatory mediators from stimulated macrophages obtained from BAL. In this study, macrophages obtained from BAL were isolated, cultured, and coin-cubated in vitro in the absence and presence of dexamethasone, 1 μ mol/L, for 24 hours. Inhibition of spontaneous and ionophore A23187/phorbol myristate acetate-triggered release of three major arachidonic acid metabolites, thromboxane B₂, leukotriene B₄, and 5-hydroxyicosatetraenoic acid, was observed in the presence of dexamethasone. Next, a similar procedure was conducted, but this time after treatment of five volunteers with oral dexamethasone in a single-blind, placebo-controlled, crossover protocol. There was no significant inhibition of the release of arachidonic acid metabolites from macrophages triggered *ex vivo*.

A curious observation was that several subjects had enhanced mediator release to the provocative stimulus after treatment with oral dexamethasone as compared to placebo treatment. These subjects also did not demonstrate the expected polymorphonuclear leukocytosis, suggesting absence of steroid effect or noncompliance with the study protocol. It could also be argued that the cell isolation procedure and in vitro incubation period result in loss of glucocorticoid activity; however, concern is raised regarding inadequate distribution of systemic steroid to the site of action. The observations also raise the question whether certain patients may have an altered cellular response to glucocorticoids.

If glucocorticoid concentration in BAL fluid adequately reflects distribution to the airways, then there may be differences among the various glucocorticoids. Braude and Rebusk^{100, 101} were the first to examine the question of glucocorticoid penetration into BALF. Besides reporting that cortisol concentrations in BALF were similar to plasma cortisol concentration, they reported that methylprednisolone was superior to prednisone in penetration into the bronchoalveolar space. Our own studies with a rabbit model confirm that methylprednisolone persists in higher concentrations in BALF than in prednisolone, both during continuous intravenous infusion and after single bolus infusions.^{102, 103} This is likely related to the physicochemical characteristics of methylprednisolone that results in a larger volume of distribution and longer half-life and mean residence time than prednisolone.^{57, 103} There is no available information regarding the differences in pulmonary tissue retention time for the various inhaled glucocorticoids. Combined with an analysis of anti-inflammatory effect,

investigation of steroid distribution in the lung could be important in understanding the differences among available glucocorticoids and also be useful in the design of improved topical steroids.

Immunologic resistance

Assuming compliance with the treatment regimen is adequate, failure to respond to glucocorticoid therapy could be related to overwhelming inflammation combined with an insufficient dose of medication. However, questions could be raised whether cellular resistance may result from drug-induced desensitization,¹⁰⁴ a genetic abnormality in the glucocorticoid receptor,^{105, 106} or a consequence of the inflammatory process. Certain mediators, such as interleukin-1, interferon- γ , and possibly other cellular mediators, can alter glucocorticoid response.^{41, 107, 108} Although the mechanism of action for interferon- γ is unknown, interleukin-1 decreases the density of glucocorticoid receptors. Clearly, additional work is needed to understand conditions that may influence response to steroid therapy.

Information regarding the molecular biology of glucocorticoid action is far too complex to address in this brief overview. Nevertheless, understanding the mechanisms of glucocorticoid action hold the key to insight for the control of the inflammatory response. Our recent investigation of patients with nocturnal asthma demonstrates a circadian variation in the degree of inflammation in certain patients with asthma.¹⁰⁹ Patients with nocturnal asthma have a heightened airway response to methacholine, increased number of inflammatory cells in BALF, along with decreased leukocyte β -adrenergic-receptor density and function, during sleep as compared to the waking hours.¹⁰⁹⁻¹¹¹ This has implications for the timing of anti-inflammatory as well as bronchodilator therapy.

FUTURE DIRECTIONS

In summary, most patients respond to a combination of bronchodilator and anti-inflammatory asthma therapy. With the increased emphasis on anti-inflammatory therapy, it now appears possible to minimize symptoms and normalize lifestyle in patients with mild to moderate asthma. Questions remain whether the inflammatory process and airway hyperresponsiveness can be reversed, even for those patients with severe asthma.

Although high-dose, short-term, glucocorticoid therapy is relatively safe in severe life-threatening disorders, long-term systemic glucocorticoid therapy has significant risk for adverse effects. Topical formula-

tions reduce the risk of adverse effects but are not sufficient in many patients. We can expect more aggressive use of glucocorticoid therapy, both inhaled and systemic. The safety and efficacy of high-dose inhaled glucocorticoids must be evaluated along with continued development of glucocorticoids with improved topical potency, ideally a steroid selective for inflammatory cells. It will also be important to understand the inflammatory process and to determine whether, indeed, there is circadian variation in inflammation and the potential implications with anti-inflammatory dosing strategy. Monitoring techniques, as well as the integration of pharmacokinetics, pharmacodynamics, and molecular biology, will be important in defining principles of individualized treatment. Perhaps the identification of anti-inflammatory cell products resulting from steroid hormone action will lead to the development of new therapeutic agents. The future is bright for exciting developments in understanding the pathogenesis and treatment of chronic asthma and a careful investigation of glucocorticoid pharmacology will no doubt contribute significantly.

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