Glucocorticoids in Clinical Practice

Eileen G. Holland, PharmD, and A. Thomas Taylor, PharmD
Augusta and Athens, Georgia

The many unique features of glucocorticoids makes therapy with these steroids challenging. The anti-inflammatory potency, relative mineralocorticoid activity, plasma half-life, and route of administration of the synthetic cortisol preparations are compared. Because they produce profound anti-inflammatory and immunosuppressive effects, exogenously administered glucocorticoids are effective therapy for a variety of diseases and conditions. The appropriate dosing regimen is an adequate dose administered for a sufficient period to precipitate an acceptable response. It is impossible to predict the regimen that will suppress the hypothalamic-pituitary-adrenocortical (HPA) axis and thereby increase the risk of developing adrenal insufficiency during periods of stress. Until recovery of the axis is complete, patients require daily physiologic replacement doses; high-dose supplemental therapy may be required during a major illness or surgery. Once there are signs of improvement, the dosing regimen should be adjusted to a single morning dose, then to an alternate-day regimen, and, as soon as possible, the steroid should be discontinued. This tapering process maintains disease suppression while minimizing toxicity; however, it is often complicated by exacerbation of the disease and withdrawal symptoms. Potential complications associated with glucocorticoid therapy are numerous, involve all organ systems, and are potentially more devastating than the HPA axis suppression.
J Fam Pract 1991; 32:512-519.

For several decades glucocorticoids have been used extensively in the management of a wide spectrum of diseases. First isolated in 1935 by Kendall and co-workers, cortisone was administered to a woman with severe rheumatoid arthritis in 1948. Although the clinical improvement was dramatic, certain side effects became apparent.[1] During subsequent years, much information concerning the biochemistry, pharmacology, tissue effects, toxicity, and clinical use of glucocorticoids has accumulated. The mechanisms by which glucocorticoids exert their anti-inflammatory and immunosuppressive effects remain elusive, however. This article provides information necessary for clinicians to properly prescribe glucocorticoids.

Hypothalamic-Pituitary-Adrenocortical Axis

The hypothalamic-pituitary-adrenocortical (HPA) axis controls the amount of cortisone present in normal circulation (Figure 1). A hypothalamic hormone, corticotropin-releasing factor, stimulates the release of adrenocorticotropic hormone (ACTH), or corticotropin, which stimulates the adrenal cortex to secrete cortisol. Through a negative-feedback mechanism, an increase in circulating cortisol results in inhibition of corticotropin-releasing factor and subsequent ACTH secretion.[2] In humans, glucocorticoids are synthesized in a series of reactions that converts cholesterol to pregnenolone, to progesterone, and finally to cortisol.

In adults, about 20 mg of cortisol is secreted daily from the adrenal cortex. This secretion is considered the physiologic replacement amount. In children, about 12 mg/m^2 is secreted daily. The normal diurnal cycle results in peak cortisol levels in the morning with a gradual tapering off by mid to late afternoon.[1,3] During periods of acute stress, the adrenal cortex can secrete up to 300 mg of cortisol per day.[4,5]

Glucocorticoid Preparations and Routes of Administration

Several synthetic analogues of cortisol are currently available for systemic use. The anti-inflammatory potency, relative mineralocorticoid activity, and plasma half-life of

Submitted, revised, October 5, 1990.

From the University of Georgia College of Pharmacy, Athens, and Department of Family Medicine, Medical College of Georgia, Augusta. Requests for reprints should be addressed to Eileen G. Holland, PharmD, F1 1076, Medical College of Georgia, Augusta, Georgia 30912.

 ISSN 0094-3509

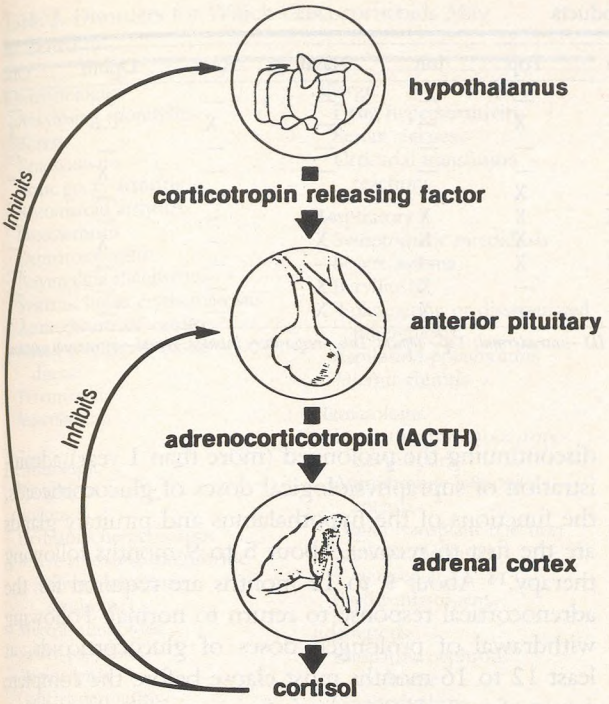

Figure 1. The hypothalamic-pituitary-adrenocortical (HPA) axis. The normal diurnal cycle of cortisone secretion begins with the release of corticotropin releasing factor from the hypothalamus which stimulates adrenocorticotropin (ACTH) secretion from the pituitary. ACTH stimulates the adrenals to release cortisol at a rate of about 20 mg per day with peak cortisol levels occurring in the morning. Through negative feedback, an increase in circulating cortisol (or its synthetic analogues) results in inhibition of this cycle.

commonly prescribed preparations are provided in Table 1. Since glucocorticoids are pharmacologically active until metabolized, agents with a prolonged half-life are associated with both increased anti-inflammatory potency and a greater degree of HPA axis suppression.[1,4] Nevertheless, when these agents are administered in equivalent anti-inflammatory doses, neither qualitative nor quantitative differences in the anti-inflammatory effects are evident.[6] Neither hepatic nor renal dysfunction appears to alter the pharmacokinetic disposition of glucocorticoids.[7] Cortisone and hydrocortisone are rarely employed for long-term anti-inflammatory therapy because they have the highest sodium-retaining properties.[1]

Prednisone and cortisone lack glucocorticoid activity until they are converted to prednisolone and cortisol in the liver.[1,8] Consequently, in patients with acute hepatitis or active chronic liver disease, availability of the active compound is assured by administering prednisolone rather than prednisone.[1,7,9] Similarly, an intra-articular injection of cortisone or its direct application to the skin is ineffective in the treatment of systemic disease because cortisone must be activated to cortisol by the liver.[8]

Table 1. Comparison of Glucocorticoid Preparations

	Equivalent Anti-inflammatory Dose (mg)	Sodium-Retaining Potency	Plasma Half-life (min)
Short-acting			
Cortisone	25	2+	30
Hydrocortisone (cortisol)	20	2+	90
Intermediate-acting			
Prednisone	5	1+	60
Prednisolone	5	1+	200
Methylprednisolone	4	0	180
Triamcinolone	4	0	300
Long-acting			
Dexamethasone	0.75	0	200
Betamethasone	0.6–0.75	0	300+

Glucocorticoids can be administered through a variety of routes to elicit either a systemic or local response (Table 2). Intravenous administration rapidly delivers high concentrations of the drug and is generally reserved for acute situations. Intramuscular administration is not often recommended because these depot preparations prolong HPA axis suppression.[7] If tolerated by the patient, oral administration is the preferred route. Because of both rapid and complete absorption from the gastrointestinal tract, dosing of oral and parental glucocorticoids is equivalent.[10]

Numerous products are available for topical and local administration. Local administration of glucocorticoids permits the delivery of high doses of active drug to the target tissue while minimizing the effects on other tissues and suppression of the HPA axis.[1,3,7] With all of these preparations, however, there is the potential for systemic absorption of the glucocorticoid and subsequent HPA axis suppression.

Numerous creams, ointments, and gels are available for direct application to inflamed or pruritic areas of the skin. Ophthalmic drops and ointments are used in conjunctivitis and other inflammatory conditions of the eyes. Inhaled preparations provide a direct, local action in the lungs and are used in patients with bronchial asthma who require chronic treatment with corticosteroids in conjunction with other therapy. Intranasal preparations provide symptomatic relief of seasonal or perennial rhinitis and may prevent the recurrence of nasal polyps. Intra-articular, intrasynovial, and intralesional administrations of glucocorticoids provide local effects with minimal systemic toxicity. These local injections are usually reserved for bursitis, tendinitis, and epicondylitis of the knee, ankle, wrist, elbow, shoulder, hip, and phalangeal

Table 2. Routes of Administration of Common Glucocorticoid Products

Drug	PO	IV	IM	SC	IA	ID	Top	Inh	Nasal	Rect	Ophth	Otic
Cortisone	X	—	X	—	—	—	—	—	—	—	—	—
Hydrocortisone	X	X	X	X	X	—	X	—	—	X	—	X
Prednisone	X	—	—	—	—	—	—	—	—	—	—	—
Prednisolone	X	X	X	—	X	—	—	—	—	—	X	—
Methylprednisolone	X	X	X	—	X	—	X	—	—	—	—	—
Triamcinolone	X	—	X	—	X	X	X	X	—	—	—	—
Dexamethasone	X	X	X	—	X	—	X	X	X	—	X	—
Betamethasone	X	X	X	—	X	X	X	—	—	—	—	—
Flunisolide	—	—	—	—	—	—	—	X	X	—	—	—
Beclomethasone	—	—	—	—	—	—	—	X	X	—	—	—

PO—oral; IV—intravenous; LM—intramuscular; SC—subcutaneous; IA—intra-articular; ID—intradermal; Top—topical; Inh—respiratory inhaler; Nasal—intranasal solution; Rect—rectal enema; Ophth—ophthalmic.

joints. Glucocorticoid retention enemas are used as adjunctive therapy in the treatment of ulcerative colitis.[1,4,7]

Mechanism of Action

The precise mechanism by which glucocorticoids exert their anti-inflammatory and immunosuppressive effects is complex.[11] The administration of glucocorticoids results in a transient increase in the number and proportion of circulating neutrophils while the concentration of other classes of leukocytes is diminished or unchanged.[6,11] Elevation of the neutrophil count is due to a combination of an accelerated release of mature neutrophils from the bone marrow and their decreased migration from the blood.[1] It has been proposed that suppressed leukocyte accumulation at the site of inflammation is the principal mechanism by which glucocorticoids exert their anti-inflammatory and immunosuppressive effects.[1,6] Additionally, glucocorticoids interfere with the function of the leukocytes present at the site of inflammation.[7]

HPA Axis Suppression

Administration of exogenous glucocorticoids in amounts greater than that needed for physiologic replacement results in HPA axis suppression and subsequent adrenal atrophy.[12] Because the demand for cortisol cannot be met by atrophic adrenal glands, potentially serious and even fatal complications arise when steroids are discontinued abruptly or a patient becomes acutely ill.[2] Indeed, suppression of the HPA axis will generally not be evident until the patient is subjected to major stress, such as that associated with surgery, trauma, infection, or severe emotional disturbances.[7]

Following the daily administration of the equivalent of 20 to 30 mg of prednisone for 1 to 4 weeks, biochemically demonstrable HPA axis suppression may persist for 1 year or more after treatment is discontinued.[13] After discontinuing the prolonged (more than 1 year) administration of supraphysiological doses of glucocorticoids, the functions of the hypothalamus and pituitary glands are the first to recover, about 5 to 9 months following therapy.[14] About 9 to 12 months are required for the adrenocortical response to return to normal. Following withdrawal of prolonged doses of glucocorticoids, at least 12 to 16 months must elapse before the complete return of normal homeostatic function, including responsiveness to stress.[8,14] The time course of recovery from smaller doses is not known.

In patients with decreased adrenal function due to atrophy, adrenocortical insufficiency can be avoided by administering daily physiological replacement doses (5 mg prednisone or its equivalent) until the adrenal function normalizes. In addition, for at least 6 months after discontinuing glucocorticoids, supraphysiological doses of steroids should be administered during periods of acute stress.[2,4,7]

Patients with documented or presumed decreased adrenal function should carry identification with them to alert medical personnel of their requirements for supplemental glucocorticoids during an emergency. In addition, patients with poor adrenal function who are at increased risk for becoming acutely ill because of concomitant disease states, social situations, or environmental conditions should be given a prefilled syringe containing 4 mg of dexamethasone to be injected intramuscularly if they are unconscious or unable to take medication by mouth.[2,3]

Indications for Glucocorticoids

Glucocorticoids are prescribed for a variety of inflammatory and immune-mediated diseases (Table 3). This diverse assortment of conditions affects nearly all organ systems and involves multiple etiologies. The goal of glucocorticoid therapy is not to eradicate the causative

Table 3. Disorders for Which Glucocorticoids May Be Beneficial

- Rheumatologic
  - Ankylosing spondylitis
  - Bursitis
  - Tenosynovitis
  - Acute gouty arthritis
  - Rheumatoid arthritis
  - Osteoarthritis
  - Dermatomyositis
  - Polymyalgia rheumatica
  - Systemic lupus erythematosus
  - Acute rheumatic carditis
  - Mixed connective tissue disease
  - Polymyositis
  - Vasculitidies
- Dermatologic
  - Pemphigus
  - Bullous
  - Dermatitis herpetiformis
  - Severe erythema multiforme (Stevens-Johnson syndrome)
  - Mycosis fungoides
  - Severe psoriasis
  - Angioedema
  - Contact dermatitis
  - Atopic dermatitis
- Ophthalmic
  - Allergic conjunctivitis
  - Keratitis
  - Herpes zoster ophthalmicus
  - Iritis
  - Uveitis
  - Optic neuritis
- Allergic
  - Drug hypersensitivity
  - Serum sickness
  - Urticarial transfusion reactions
- Respiratory
  - Symptomatic sarcoidosis
  - Severe asthma
  - Berylliosis
  - Fulminating or disseminated tuberculosis
  - Aspiration pneumonitis
  - Allergic rhinitis
- Hematologic
  - Idiopathic thrombocytopenia purpura
  - Autoimmune hemolytic anemia
  - Organ transplant rejection
  - Immune mediated cytopenias
  - Erythroblastopenia
- Edematous
  - Idiopathic nephrotic syndrome
  - Cerebral edema
- Gastrointestinal
  - Ulcerative colitis
  - Crohn's disease
- Miscellaneous
  - Chronic active hepatitis
  - Meningitis
  - Hypercalcemia
  - Adrenal cortical insufficiency

factor, but to minimize the sequelae while allowing the disease to run its natural course.[7]

Designing a Therapeutic Regimen

Designing an appropriate regimen is complicated. The preferred therapeutic strategy is dictated by the specific disease, the glucocorticoid preparation, and the patient.[1,7] For example, short-term glucocorticoid therapy of life-threatening diseases such as status asthmaticus provides dramatic improvement with few complications, while prolonged therapy of chronic inflammatory conditions can be associated with serious side effects.[1] Consequently, the severity of the disease, the anticipated dose and duration of therapy, and the immediate and future prognosis of the patient should be considered in determining the appropriateness of glucocorticoid therapy. Also, other therapeutic modalities that can delay the use of steroids or decrease the required dose should be used. Examples include aerosolized glucocorticoids for asthmatic patients and nonsteroidal anti-inflammatory agents in patients with rheumatoid arthritis.

The efficacy of specific regimens for certain conditions is proven; however, alternative agents, doses, and durations of therapy have not been studied to compare the efficacy of various other regimens. Consequently, there are no definitive guidelines that outline proper therapy in specific diseases. To assist clinicians in the daily therapeutic decision process, further research is needed to determine the agent of choice, the dosage, and the optimal duration of therapy for specific diseases.

A suitable dosing regimen for glucocorticoids includes a sufficient quantity of the drug administered over an adequate period to bring the inflammatory or immunologic reaction under control.[1] Therefore, the total daily dose is variable, depends on many factors, and can range from grams of methylprednisolone in acute organ transplantation rejection to 60 to 100 mg of prednisone in various hypersensitivity or autoimmune disorders. Admittedly, recommendations for administering glucocorticoids are vague; however, there are several important points to consider when prescribing these agents. Each of these is discussed separately.

Initiating Therapy

Once the decision has been made to administer glucocorticoids, therapy should be initiated with a dose sufficient to control the disease process.[1,7] By initiating therapy with a low dose, such as 10 to 15 mg of prednisone, one risks failure to induce optimal anti-inflammatory control. Consequently, to establish control, the dose must be increased and, by the end of therapy, a greater total dose may have been administered.[7] In general, patients with severe inflammatory illnesses known to be sensitive to glucocorticoids can be placed into remission with 1 mg/kg/d of prednisone, administered in one to three divided doses.[1]

The risk of HPA axis suppression and toxicity increases when multiple daily doses are administered or when long-acting agents are employed; however, toxicity does not develop if use is continued only until the acute disease process is alleviated.[1] Conversely, a single daily dose appears to be as effective as divided daily doses in controlling certain diseases, including rheumatoid arthritis, systemic lupus erythematosus, and polyarthritis.[8] The preferred regimen employs a short- or intermediate-acting agent administered once daily, in the morning. The early morning dose more closely resembles the natural diurnal cycle of cortisol secretion and results in less HPA axis suppression.[1,4,7]

Once there are subjective and objective signs of improvement, the dose and dosing interval should be

adjusted so that disease suppression will be maintained with fewest complications.[1] However, dosage reduction is chiefly determined and limited by the presence or absence of an exacerbation of the underlying disease.

Converting to Alternate-Day Therapy

Following conversion to a single daily dose, an effective way to continue the tapering process is to convert to alternate-day administration. Based on the hypothesis that the anti-inflammatory effects of glucocorticoids persist longer than the undesirable metabolic effects, alternate-day therapy provides a sufficient quantity of steroid to suppress disease activity while avoiding many of the complications associated with daily therapy.[1,4,8] Indeed, numerous studies have reported that alternate-day therapy resulted in the prevention or amelioration of adverse effects and HPA axis suppression while providing therapeutic effectiveness similar to that of daily therapy.[8]

Although alternate-day therapy can maintain remission in a disease process, this regimen is usually not capable of inducing a remission in patients with fulminant disease.[4,15] Therefore, alternate-day therapy should be considered a prophylaxis against exacerbations of a disease process that was originally controlled by daily steroid therapy.[1] The demonstrable benefits of alternate-day therapy occur only when steroids are used for a prolonged duration. If the anticipated duration of therapy is less than several weeks, there is no rationale for alternate-day therapy.[8]

To convert a patient to alternate-day therapy, the lowest daily steroid requirement should be determined. The optimal every-other-day dose is 2½ to 3 times the minimal daily dose. Generally, an intermediate-acting agent is administered as a total daily morning dose.[3,15] The dose on the "off" day should be gradually tapered by the equivalent of 2.5 to 5 mg of prednisone until the patient is on a true alternate-day regimen. Although the average daily dose on the alternate-day regimen may be 1½ times the previous daily dose, long-term complications will be minimized.[1,7]

The tapering of the alternate-day dose can continue until the minimum dose sufficient to control the disease process is reached or until the drug is discontinued. Ideally, the regimen will be converted to alternate-day therapy after the first week of treatment and, if possible, the glucocorticoid will be discontinued after another 3 weeks.[3] Too rapid tapering of glucocorticoid therapy, however, frequently results in reexacerbation of the disease.[16] The tapering process can be complicated not only by exacerbations of the underlying disease process, but also by withdrawal syndromes, which may mimic disease activity.[1,7,8,12] Typical glucocorticoid withdrawal symptoms include fatigue, weakness, arthralgia, anorexia, nausea, fever, weight loss, headache, desquamation of the skin, orthostatic dizziness and hypotension, fainting, dyspnea, and hypoglycemia.[1–3,7] These symptoms are transient and may be minimized by a more gradual tapering of the steroids.

Predicting HPA Axis Suppression

Clinical data do not provide adequate information to predict which glucocorticoid regimen places patients at risk for developing adrenocortical insufficiency under the stress of surgery or severe illness. Laboratory data indicate that 1 to 2 weeks of therapy can result in adrenal insufficiency.[8] Since the current data do not satisfactorily answer this practical question, more research is needed to define the situations in which patients are at greatest risk for developing HPA axis suppression.

Based on the available information, however, the following general guidelines may assist the clinician. Patients receiving the equivalent of 20 to 30 mg of prednisone daily for more than 1 week should be suspected of having HPA axis suppression. Patients receiving morning doses closer to the physiological range should be suspected of having HPA axis suppression after approximately 1 month of continuous therapy. If administered early in the day, physiological replacement doses of glucocorticoids are unlikely to cause HPA axis dysfunction.[8] Most important, the degree of HPA axis suppression may not be predictable; it depends on the patient, the disease state, and the dose, duration, frequency, time, and route of administration of the glucocorticoid.[2,4]

Testing the HPA Axis

When HPA axis suppression is suspected, the clinician has two alternatives. One is to treat the patient as though adrenocortical insufficiency is present. The other is to test the pituitary, hypothalamic, and adrenocortical reserves. A rapid test of adrenal function measures the 8:00 AM fasting plasma cortisol level. Once a level greater than 280 nmol/L (10 μg/dL) is sustained, therapy may be discontinued.[3] Effective provocative tests include insulin-induced hypoglycemia, metyrapone, lysine-vasopressin, and an ACTH test.[8] The first three tests are perhaps more sensitive indicators of HPA reserve, but are traumatic and cumbersome, and require hospitalization. The ACTH test correlates best with adrenocortical response to clinical stress.

The ACTH test is a reliable method of evaluating the HPA system before surgery in glucocorticoid-treated patients. The maximal response of the plasma-cortisol

level to ACTH corresponds to the maximal plasma cortisol level observed during the induction of general anesthesia and surgery.[8,13] Also, for patients receiving physiological replacement doses, this test enables the physician to periodically assess the function of the adrenal glands and determine when recovery is complete.

After withholding glucocorticoid therapy for 12 to 24 hours and determining a baseline plasma cortisol level at 8:00 AM, 250 μg of synthetic ACTH (cosyntropin) is administered intramuscularly. A repeat plasma cortisol is measured in 30 to 60 minutes. A normal response includes an increase in plasma cortisol of greater than 170 nmol/L (6 μg/dL) to a level of more than 550 nmol/L (20 μg/dL). An insufficient elevation of cortisol levels indicates adrenal insufficiency and the need for continued steroid supplementation during periods of stress.[2–4,8,13]

Complications and Contraindications

Although the primary focus of glucocorticoid therapy is on potential HPA axis suppression, decades of experience suggest that it is not as great a problem as is generally believed and is less hazardous than the other serious toxicities associated with steroid therapy[13] (Table 4). In addition, while potential complications of glucocorticoid therapy are numerous and involve all organ systems, it is important to emphasize that when steroids are used properly, complications can be minimized.

It is virtually impossible to predict which toxicities will appear in an individual; however, some patients may be at increased risk for certain side effects. The adverse effects can be classified as those that develop acutely and those that develop after long-term administration. Acute side effects such as central nervous system changes, fluid and electrolyte disorders, gastrointestinal upset, and impaired glucose tolerance may occur during the induction of anti-inflammatory control or during crisis therapy.[7] Generally, when high doses of steroids are tapered or stopped, these short-term effects lessen or disappear. Long-term side effects are more insidious in onset, occur in patients who receive daily steroids for months or longer, and are less likely to improve quickly after the drugs are discontinued.[7] Examples include a cushingoid appearance, growth retardation, hypertension, osteoporosis, and pancreatitis. Most important, the frequency and severity of all steroid-related complications can be reduced considerably by converting to alternate-day therapy.[1]

It is frequently stated that glucocorticoid therapy is associated with an increased prevalence of peptic ulcer or its recurrence or complications. In 1976, a retrospective analysis of 42 prospective, controlled investigations involving 5331 patients randomly selected to receive steroid (or ACTH) therapy or no therapy was conducted to determine whether this association is valid.[17] Proven peptic ulcers were found in 1.3% of the 2985 steroid-treated patients and in 0.8% of the 2346 control patients ($P > .05$). In addition, neither hemorrhage nor perforation of peptic ulcer occurred significantly more often in the steroid-treated group (all groups < 0.3%). In 1983, a similar analysis of 71 investigations involving 5961 patients was conducted.[18] The overall incidence of diagnosed ulcers was 1.8% in the steroid-treated patients and 0.8% in the control group ($P < .001$).

Obviously, this is a controversial topic, and it is difficult to determine whether there is a clinically important association between glucocorticoid therapy and peptic ulcer formation. Owing to their ability to induce tissue atrophy, however, glucocorticoids probably enhance the ulcerogenic potential of environmental factors and of other drugs. The risk of ulcerogenesis depends on

Table 4. Adverse Effects Associated with Glucocorticoid Therapy

- Adrenocortical excess
  - Buffalo hump
  - Hirsutism
  - Truncal obesity
- Musculoskeletal effects
  - Muscle wasting
  - Muscle pain
  - Muscle weakness
  - Delayed wound healing
  - Osteoporosis
  - Aseptic necrosis
  - Growth retardation
- Increased susceptibility to infection
  - Opportunistic pathogens: fungus, virus, bacteria, parasite
  - Recurrence of tuberculosis
  - Recurrence of chickenpox
  - Immunosuppression, anergy
- Cardiovascular and fluid disturbances
  - Hypernatremia
  - Edema
  - Hypokalemia
  - Hypokalemic alkalosis
  - Hypertension
  - Hypercalciuria
- Ocular effects
  - Posterior subcapsular cataracts
  - Exophthalmus
  - Glaucoma
- Endocrine effects
  - Hypercorticism
  - Amenorrhea
  - Decreased glucose tolerance
  - Hyperglycemia
  - Unmask genetic predisposition to diabetes mellitus
  - HPA axis suppression
- Gastrointestinal effects
  - Nausea
  - Vomiting
  - Anorexia
  - Increased appetite
  - Diarrhea
  - Constipation
  - Abdominal distension
  - Pancreatitis
  - Gastric irritation
  - Ulcerative esophagitis
  - Intestinal perforation
- Nervous system effects
  - Headache
  - Vertigo
  - Insomnia
  - Restlessness
  - Ischemic neuropathy
  - EEG abnormalities
  - Seizures
  - Euphoria
  - Mood swings
  - Depression
  - Anxiety
  - Psychoses
  - Pseudomotor cerebri
- Dermatologic effects
  - Acne
  - Skin atrophy and thinning
  - Striae
  - Increased sweating
  - Facial erythema
  - Angioedema
  - Petechiae
  - Ecchymosis
  - Easy bruisibility
  - Allergic dermatitis
  - Urticaria

the underlying disease and the dose administered. Risk appears to increase if the duration of therapy is longer than 30 days or if a total dose greater than 1000 mg of prednisone is administered.[17] Therefore, unless patients are receiving ulcerogenic agents, concomitant administration of antiulcer agents is not warranted. In addition, the efficacy of antiulcer therapy in preventing these ulcers has not been established.

The influence of glucocorticoids on host resistance to infection is also controversial. Patients with normal host defenses who are treated with low to moderate doses of glucocorticoids do not have an increased risk of infection.[1] Even these doses, however, can activate tuberculosis in patients with a subclinical course.[2] Conversely, high-dose steroids (defined as more than 50 mg of prednisone daily or its equivalent) for more than 2 weeks may result in opportunistic infections including those caused by *Aspergillus*, cytomegalovirus, *Pneumocystis carinii*, and herpes zoster.[6,7] One problem in determining the effect of glucocorticoids on host resistance to infection is that many patients receiving steroids already have decreased resistance due either to their disease state or to concomitant immunosuppressive therapy.[1,7] Alternate-day therapy may reduce the risk of infection.[4,6,8]

There are no absolute contraindications for the use of glucocorticoids. As always, however, the potential risks and benefits of therapy should be addressed, particularly if any of the following conditions are present: systemic fungal infections, diabetes mellitus, peptic ulcer disease, psychiatric difficulties, osteoporosis, or chronic infections such as tuberculosis.[1]

Monitoring Long-term Corticosteroid Therapy

It is essential that patients receiving corticosteroids on a long-term basis be monitored closely to detect early signs of toxicity. Early recognition of adverse effects may permit correction of the problem or prevent further progression to serious disease. A simple flow sheet that indicates when to perform physical examinations and laboratory tests may be devised to detect potential adverse effects associated with long-term corticosteroid therapy (Figure 2).

Monitoring Sheet for Long Term Corticosteroids Use

	Date	Date	Date	Date	Date	Date
Preparation and dose						
Monthly						
Weight						
Blood pressure						
Blood glucose						
Electrolytes and creatine						
Complete blood count (CBC)						
Oral mucosa exam						
Every 6 months						
Chest x-ray						
PPD with control						
Ophthalmology consult						
Rectal exam/hemoccult						
As appropriate						
Upper gastrointestinal (UGI) series						
Lateral thoracic spine x-ray						
Supplemental therapy: potassium diuretic estrogen calcium vitamin D isoniazid						

Figure 2. Example of a patient form used to ensure careful monitoring of long-term corticosteroid use.

Conclusions

Although glucocorticoids are frequently employed for the treatment of numerous inflammatory and immunologic disorders, there are no definitive guidelines that outline appropriate therapeutic strategies. For each disease, many questions remain unanswered, including the agent of choice, the appropriate dose and duration of therapy, and the best method for drug discontinuation. It is evident, however, that dosages should be sufficient to produce an appropriate anti-inflammatory response, be kept at the lowest effective level, and be tapered as soon as possible.

References

1. Kehrl JH, Fauci AS. The clinical use of glucocorticoids. Ann Allergy 1983; 50:2–10.
2. Koch-Weser J. Withdrawal from glucocorticoid therapy. N Engl J Med 1976; 295:30–2.
3. Kountz DS. An algorithm for corticosteroid withdrawal. Am Fam Physician 1989; 39:250–4.
4. Helfer EL, Rose LI. Corticosteroids and adrenal suppression; characterizing and avoiding the problem. Drugs 1989; 38:838–45.
5. Glick M. Glucocorticosteroid replacement therapy: a literature review and suggested replacement therapy. Oral Surg Oral Med Oral Pathol 1989; 67:614–20.
6. Fauci AS, Dale DC, Balow JE. Glucocorticosteroid therapy: mechanisms of action and clinical considerations. Ann Intern Med 1976; 84:304–15.
7. Claman HN. Glucocorticosteroids II: the clinical responses. Hosp Pract 1983; July:143–51.

8. Axelrod L. Glucocorticoid therapy. Medicine 1976; 55:39–65.
9. Powell LW, Axelsen E. Corticosteroids in liver disease: studies on the biological conversion of prednisone to prednisolone and plasma protein binding. Gut 1972; 13:690–6.
10. Ratto D, Alfaro C, Sipsey J, et al. Are intravenous corticosteroids required in status asthmaticus? JAMA 1988; 260:527–9.
11. Claman HN. Glucocorticosteroids I: anti-inflammatory mechanisms. Hosp Pract 1983; July:123–34.
12. Mortimer RH. Adrenal corticosteroid replacement therapy. Med J Aust 1985; 143:350–4.
13. Christy NP. HPA failure and glucocorticoid therapy. Hosp Pract 1984; July:77–89.
14. Graber AL, Ney RL, Nicholson WE, et al. Natural history of pituitary-adrenal recovery following long-term suppression with corticosteroids. J Clin Endocrinol Metab 1965; 25:11–6.
15. Laurens RG, Honig EG. Corticosteroids in treatment of asthma. South Med J 1986; 79:1544–53.
16. Lederle FA, Pluhar RE, Joseph AM, et al. Tapering of corticosteroid therapy following exacerbation of asthma: a randomized, double-blind, placebo-controlled trial. Arch Intern Med 1987; 147:2201–3.
17. Conn HO, Blitzer BL. Nonassociation of adrenocorticosteroid therapy and peptic ulcer. N Engl J Med 1976; 294:473–9.
18. Messer J, Reitman D, Sacks HS, et al. Association of adrenocorticosteroid therapy and peptic-ulcer disease. N Engl J Med 1983; 309:21–4.