Prevention and management of glucocorticoid-induced side effects: A comprehensive review

A review of glucocorticoid pharmacology and bone health

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Learning objectives
After completing this learning activity, participants should be able to describe key features of glucocorticoid pharmacology and anticipate, prevent, and manage complications of glucocorticoid use affecting bone health.

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Systemic glucocorticoids are an essential therapy for a range of conditions, but their multiple side effects can produce significant morbidity for patients. The objective of this review is to discuss these side effects while addressing 3 questions: 1) What dose and duration of glucocorticoid therapy should prompt concern for individual side effects?; 2) How should clinicians counsel patients about these complications?; and 3) How can these problems be prevented or managed? To accomplish these objectives, we have created a series of tables and algorithms based on a review of relevant data to guide counseling, prophylaxis, and management of 11 glucocorticoid side effects. The first article in this 4-part continuing medical education series begins with a review of glucocorticoid pharmacology followed by a discussion of bone health (ie, osteoporosis and osteonecrosis). (J Am Acad Dermatol 2017;76:1-9.)

Key words: glucocorticoids; medication monitoring; osteonecrosis; osteoporosis; pharmacology; side effects; steroids.

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Please note that infectious and other complications of steroid use will be discussed in the third and fourth installments of this Continuing Medical Education feature in the February 2017 issue of the *JAAD*.

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GLUCOCORTICOID PHARMACOLOGY

Key points

- **Glucocorticoids are selected based on therapeutic efficacy and side effect considerations, properties that depend on pharmacokinetic and pharmacodynamic parameters**
- **Understanding these parameters may help clinicians manage glucocorticoid side effects for their patients**

There are many options when prescribing glucocorticoids. Prednisone, prednisolone, methylprednisolone, and dexamethasone are all commonly used oral formulations. High-dose pulse glucocorticoid therapy may be required in clinical emergencies or for severe, uncontrolled disease, often in the form of intravenous (IV) methylprednisolone. High-dose dexamethasone may be required in the case of central nervous system emergencies for its enhanced central nervous system penetration.[1] In dermatology, pulse IV methylprednisolone is an option for patients with severe pemphigus vulgaris, pyoderma gangrenosum, and systemic lupus erythematosus. Intraarticular and intralesional formulations, such as triamcinolone acetonide or methylprednisolone acetate, are appropriate for certain conditions. Our glucocorticoid side effect pretreatment screening, ongoing monitoring, and counseling recommendations are shown in Table I.

Glucocorticoids exert their effect by binding to the glucocorticoid receptor, which translocates to the nucleus and targets gene transcription.[2] Nongenomic mechanisms are thought to explain the efficacy of pulse-dose glucocorticoid therapy, because these doses are generally greater than the saturation dose for the glucocorticoid receptor.[1] Oral glucocorticoids are well absorbed after administration and show variable degrees of binding to corticosteroid-binding globulin and albumin.[1] Only free, unbound drug can interact with the glucocorticoid receptor.[1] Prednisone and prednisolone both have dose-dependent pharmacokinetics because of nonlinear protein binding, while methylprednisolone and dexamethasone do not have this same dose-dependency.[1]

Glucocorticoids require a carbon-11 hydroxyl group in order to have activity.[3] The enzyme 11β-hydroxysteroid dehydrogenase controls the availability of glucocorticoids for binding to receptors. Type 1 dehydrogenase converts inactive to active drug and has its greatest activity in the liver.[1] For this reason, topical glucocorticoids, such as cortisone, must be 11-hydroxyl compounds in order to be effective. Cortisone is an 11-keto compound that has no activity topically. The enzyme is also responsible for converting prednisone to its active form, prednisolone. Type 2 dehydrogenase is found in mineralocorticoid target tissue.[1]

Systemic glucocorticoids are divided into short-, medium-, and long-acting formulations on the basis of adrenocorticotropic hormone suppression after a single dose.[3] The potency of glucocorticoids is determined by affinity for the intracellular glucocorticoid receptor and duration of action.[3] There is only a weak correlation between circulating half-life, potency, and duration of action.[3,4] Glucocorticoid potencies and duration of action are shown in Table II.

These concepts in pharmacology help explain the therapeutic and adverse effects of systemic glucocorticoids. For example, patients with low protein states are at increased risk of adverse effects from prednisone therapy because the amount of circulating unbound drug is increased.[1,4-6] The dose-dependent availability and clearance of prednisone and prednisolone accounts for the decreased side effects (and diminished efficacy) of alternate-day dosing.[6] Meanwhile, not all individuals metabolize drugs at the same rate; those who are slow metabolizers may suffer increased side effects.[7]

Certain diseases and drug–drug interactions alter glucocorticoid pharmacokinetics.[1] Altered pharmacokinetics are reported in patients with liver disease, renal failure, nephrotic syndrome, severe obesity, and inflammatory bowel disease, but the direction of effect is not necessarily the same for each glucocorticoid.[1] For example, in patients with severe liver disease, the conversion of prednisone to prednisolone is impaired. This effect may be partially offset by a decreased rate of elimination of prednisolone, but it may be prudent to use the active metabolite prednisolone preferentially over prednisone in these patients.[3,6] In patients with severe systemic diseases, it is wise to confer with the patient's other providers before prescribing glucocorticoids.

Clinicians should also be aware of other medications taken by the patient. The coadministration of CYP450 enzyme inducers increases the clearance and decreases the half-life of glucocorticoids, while enzyme inhibitors decrease clearance and increase half-life.[1] Complete lists of CYP450 inducers and inhibitors are readily available, and clinicians are encouraged to review all drug–drug interactions before prescribing new medications.

Glucocorticoid side effects are not limited to systemic oral or intravenous therapy. Injected glucocorticoids vary in their absorption, but high potency injections, or multiple injections that result in glucocorticoid accumulation, can cause systemic side effects. This is true of intramuscular injections, which can increase the risk of adrenal suppression