

Corticosteroid Monograph

Local adverse effects of topical corticosteroid use are more prevalent than systemic reactions.³⁶

TABLE 216-1 Potency Ranking of Selected Topical Corticosteroid Preparations^a

GENERIC NAME	BRAND NAME
Class 1—Superpotent	
Betamethasone dipropionate 0.05% optimized vehicle	Diprolene gel/lotion/ointment
Clobetasol propionate 0.05%	Clobex lotion/spray Olux foam Temovate cream/emollient cream/gel/ointment
Diflorasone diacetate 0.05%	Psorcon ointment
Fluocinonide 0.1% optimized vehicle	Vanos cream
Flurandrenolide, 4 mg/cm ²	Cordran tape
Halobetasol propionate 0.05%	Ultravate cream/ointment
Class 2—Potent	
Amcinonide 0.1%	Cyclocort ointment
Betamethasone dipropionate 0.05%	Diprolene AF cream Diprosone ointment
Desoximetasone 0.25%	Topicort cream/ointment
Desoximetasone 0.5%	Topicort gel
Diflorasone diacetate 0.05%	Florone ointment Maxiflor ointment
Fluocinonide 0.05%	Lidex cream/gel/ointment
Halcinonide 0.1%	Halog cream/solution/ointment
Mometasone furoate 0.1%	Elocon ointment
Class 3—Potent, upper mid-strength	
Amcinonide 0.1%	Cyclocort cream/lotion
Betamethasone dipropionate 0.05%	Diprosone cream
Betamethasone valerate 0.1%	Valisone ointment
Diflorasone diacetate 0.05%	Florone cream Maxiflor cream Psorcon E cream
Fluocinonide 0.05%	Lidex E cream
Fluticasone propionate 0.005%	Cutivate ointment
Class 4—Mid-strength	
Betamethasone valerate 0.12%	Luxiq foam
Clocortolone pivalate 0.1%	Cloderm cream

Desoximetasone 0.05%	Topicort LP cream
Fluocinolone acetonide 0.025%	Synalar ointment
Flurandrenolide 0.05%	Cordran ointment
Hydrocortisone probutate 0.1%	Pandel cream
Hydrocortisone valerate 0.2%	Westcort ointment
Mometasone furoate 0.1%	Elocon cream/lotion
Prednicarbate 0.1%	Dermatop ointment
Triamcinolone acetonide 0.1%	Kenalog ointment
Class 5—Lower mid-strength	
Betamethasone dipropionate 0.05%	Diprosone lotion
Betamethasone valerate 0.1%	Valisone cream/lotion
Fluocinolone acetonide 0.025%	Synalar cream
Flurandrenolide 0.05%	Cordran cream, lotion
Fluticasone propionate 0.05%	Cutivate cream
Hydrocortisone butyrate 0.1%	Locoid lipocream
Hydrocortisone valerate 0.2%	Westcort cream
Prednicarbate 0.1%	Dermatop emollient cream
Triamcinolone acetonide 0.1%	Kenalog cream/ lotion
Class 6—Mild strength	
Alclometasone dipropionate 0.05%	Aclovate cream/ointment
Desonide 0.05%	DesOwen cream/lotion/ointment
	Tridesilon cream
Fluocinolone acetonide 0.01%	Synalar cream/solution
	Derma-Smoother/FS oil
Class 7—Least potent	
Topicals with dexamethasone, flumethasone, hydrocortisone	
Methylprednisolone, prednisolone	

^aIt is the general policy of this book not to use trade names. In this case, this rule is broken to facilitate easier reading.

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Atrophic Changes

Skin atrophy is the most common adverse effect of corticosteroid therapy. Dermal atrophy develops from the direct antiproliferative effects of topical corticosteroids on fibroblasts, with inhibition of collagen and mucopolysaccharide synthesis, resulting in loss of dermal support. Fragmentation and thinning of elastic fibers develop on the upper layers, whereas deeper fibers form a compact and dense network.³¹ As a result of these atrophic changes, there is vascular dilatation, telangiectasias, purpura, easy bruising, stellate pseudoscars (purpuric, irregularly shaped, and hypopigmented atrophic scars), and ulceration. Although atrophy is, to

some extent, reversible, formation of striae, visible linear scars that form in areas of dermal damage presumably during mechanical stress, are permanent.

Acneiform Reactions

The development or exacerbation of dermatoses of the face, including steroid rosacea, acne, and perioral dermatitis, is a well-known effect of topical corticosteroids. Although steroids initially lead to the suppression of inflammatory papules and pustules, patients become addicted because they notice that the lesions flare when treatment is withdrawn. This frequently leads to the continued use of greater potency topical corticosteroids. For these reasons, steroid use should be discouraged in the treatment of rosacea and perioral and periocular dermatitis. Prolonged corticosteroid treatment can also result in “steroid acne,” which is characterized by crops of dense, inflamed pustules in the same developmental stage. These lesions occur on the face, chest, and back.

Hypertrichosis

Hypertrichosis occurs rarely in women and children who apply potent corticosteroids to the face. The mechanism is still unknown.¹

Pigmentary Changes

Decreased pigmentation is a common side effect of topical steroid use. The pigment generally returns after discontinuation of therapy.

Development of Infections

Topical corticosteroids are responsible for exacerbating and/or masking cutaneous infectious diseases. The incidence of skin infection during corticosteroid therapy varies but is probably between 16 percent and 43 percent.³⁹ Tinea versicolor, disseminated *Alternaria* infection, and dermatophytosis, including tinea incognito (masked dermatophyte infection), can develop. Granuloma gluteale infantum, characterized by reddishpurplish granulomatous lesions on the diaper area, is a well-known complication of diaper dermatitis that is being treated with corticosteroids. *Candida albicans* is commonly recovered in these patients. Topical corticosteroids have also an effect on prolongation or mitigation of herpes simplex, molluscum contagiosum, and scabies infection.

Allergic Reactions

Persistence or worsening of skin diseases occurs as a result of contact hypersensitivity to topical corticosteroids. The prevalence to topical corticosteroid sensitization ranges between 0.2 percent and 6.0 percent, and increases with

prolonged exposure and the selection of certain drugs.^{36, 40,41} The allergen may be the vehicle, the preservative, or the steroid itself. Most topical steroid ointments are free of preservatives and are less likely than other topical agents and steroid creams to cause an allergic or irritant contact dermatitis. The most common preservatives that cause allergic contact dermatitis include parabens, polyethylene glycol, and benzyl alcohol (Table 216-3). Fragrance and local anesthetics are also sensitizers that may be included in the topical preparations.

TABLE 216-3 Potential Contact Sensitizers in Topical Corticosteroids

- Parabens
- Propylene glycol
- Benzyl alcohol
- Chlorocresol
- Ethylenediamine hydrochloride
- Isopropyl palmitate
- Polysorbate 60
- Stearyl alcohol
- The corticosteroid itself

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Systemic Adverse Effects

OCULAR EFFECTS

The development of glaucoma from the use of topical corticosteroids around the eye has been described.⁴⁶⁻⁴⁸ Prolonged corticosteroid use has also led to vision loss.⁴⁹

SUPPRESSION OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

Suppression of the HPA axis has been described with the use of potent topical corticosteroids. Iatrogenic Cushing syndrome, corticosteroid-related Addison crises, and retarded growth of children have all been described after prolonged use of potent topical corticosteroid preparations. A dose of 14 g/week of clobetasol propionate or 49 g/week of betamethasone dipropionate is sufficient to suppress plasma cortisol levels.¹⁷

METABOLIC SIDE EFFECTS

Increased glucose production and decreased glucose use induce hyperglycemia and may lead to diabetes mellitus.

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Systemic glucocorticoids can be administered intralesionally, orally, intramuscularly, and intravenously. The route and regimen are determined by the nature and extent of the disease being treated.

TABLE 225-2 Glucocorticoids

	EQUIVALENT GLUCOCORTICOID POTENCY (MG)	MINERALOCORTICOID POTENCY	PLASMA HALF- LIFE (MIN)	DURATION OF ACTION (H)
Short-acting				
Hydrocortisone (Cortisol)	20	0.8	90	12-Aug
Cortisone	25	1	30	12-Aug
Intermediate-acting				
Prednisone	5	0.25	60	24-36
Prednisolone	5	0.25	200	24-36
Methylprednisolone	4	0	180	24-36
Triamcinolone	4	0	300	24-36
Long-acting				
Dexamethasone	0.75	0	200	36-54

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RISKS AND PRECAUTIONS (Table 225-3)

Diet

Diet should be low in calories, fat, and sodium, and high in protein, potassium, and calcium. Protein intake is important to reduce steroid-induced nitrogen wasting.³⁴

Use of alcohol, coffee, and nicotine should be minimized. Exercise should be encouraged.

Infections

Patients with a positive PPD should be given prophylaxis with isoniazid.³⁵ Anergic patients should have a baseline chest x-ray to search for evidence of previous tuberculosis. Fevers or focal findings should be evaluated with appropriate cultures and diagnostic approaches. Some advocate use of Bactrim prophylaxis (1 DS Bactrim 3 days a week) against *Pneumocystis carinii* when patients receive concomitant cytotoxic therapy.²⁷

Gastrointestinal Complications

Although there is controversy about whether an increase in the incidence of peptic ulcer disease occurs in otherwise unaffected patients receiving GCs, there is almost a ninefold increase in patients taking both GCs and nonsteroidal anti-inflammatory agents.³⁶⁻³⁸ In patients with two or more risk factors (such as those taking nonsteroidal anti-inflammatory medications, a previous history of peptic ulceration, advanced malignant disease, or a total dose of GCs more than 1000 mg), prophylaxis may be considered. Prophylaxis can include antacids, H₂-receptor blockers (cimetidine, ranitidine, nizatidine, or famotidine with the evening meal), or proton pump inhibitors (Prilosec or Prevacid).

Adrenal Suppression

Patients receiving daily GC therapy for longer than 3 to 4 weeks must be assumed to have adrenal suppression that requires tapering of the GCs to allow for recovery of the HPA axis. Tapering is best performed by switching from a single daily dose to alternate-day doses, followed by a gradual reduction of the amount of the drug. The daily dose is first gradually tapered to 40 or 50 mg of prednisone. Then, either the dose can be kept constant on 1 day and reduced on the alternate day by 5-mg decrements down to 5 mg/day, or, the steroid dose can be increased on 1 day and reduced by a similar amount on the alternate day. More studies are needed to determine optimal tapering schedules.³⁹

TABLE 225-3 Prevention of Side Effects with Chronic (≥ 3 mo) Glucocorticoid Use

SIDE EFFECT	PREVENTATIVE MEASURES
Hypertension	Blood pressure (baseline; repeat with each visit).
Weight gain	Weight (baseline; repeat with each visit).
Re-activation of infection	Purified protein derivative, anergy panel at baseline (can be done up to 12 days after starting prednisone).

	Hepatitis screen. Consider <i>Pneumocystis carinii</i> pneumonia prophylaxis (Bactrim 1 DS three times a week).
Metabolic abnormalities	Electrolytes, lipids, glucose [baseline; repeat early after starting therapy; repeat annually; more frequent monitoring with known factors (e.g., diabetes, hyperlipidemias)].
Osteoporosis	Bone density (baseline; repeat annually if early bone prophylaxis done). Instruct about diet, exercise, other measures. Calcium and vitamin D supplementation. Start bisphosphonate for men, post-menopausal women. Evaluate post-menopausal women for hormone replacement therapy. Serum testosterone after treatment started in men; if low (< 300 ng/mL), check prostate specific antigen, prostate examination before starting testosterone replacement.
Eyes	Cataracts Slit-lamp examination (every 6-12 mo). Glaucoma Intraocular pressure examination (at 1 mo and every 6 mo).
Peptic ulceration	In patients with two or more risk factors, consider prophylaxis with an H ₂ -antagonist or proton pump inhibitor.
Suppression of hypothalamic-pituitary-adrenal axis	Single, early morning doses, preferably every other day. Check 8 A.M. serum cortisol before tapering prednisone < 3 mg/day. If < 10 µg/dL, repeat every 1-2 mo and maintain low prednisone dose until baseline cortisol adequate.

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After the prednisone dose is tapered to 5 mg on alternate days, the need for maintenance therapy must be assessed. The 8 A.M. plasma cortisol level is measured 4 weeks after the 5-mg dose has been reached. The morning dose of prednisone is held until the plasma cortisol level is determined. If the plasma cortisol level is less than 10 µg/dL, the alternate-day prednisone dose should be decreased by 1 mg every 1 to 2 weeks to a maintenance dose of 2 mg/day. Then the 8 A.M. plasma cortisol level should be rechecked every 2 months until it is greater than 10 µg/dL, at which point maintenance GCs can be terminated.⁴⁰ Recovery of the HPA axis can take longer than 9 months.⁴¹ At that point and at any point when the patient is receiving tapering doses of steroids, a stress caused, for example, by trauma, surgery, diarrhea, or fever more than 38°C (101°F) can precipitate acute adrenal insufficiency related to an inadequate stress response. Patients should wear bracelets or carry cards indicating

that they are receiving GCs. During such stressful situations, it is necessary to give high doses of GCs, generally 25 to 70 mg/day of prednisone or 100 to 300 mg/day of cortisol in divided doses.⁴² Patients must be educated about the need for stress coverage.

The amount of GCs to give for coverage for surgery should probably be individualized to the severity of the operation. Minor operations lasting less than 1 hour are associated with, at most, 50 mg/day (12.5 mg prednisone) of cortisol in response to the surgery. Moderate to major surgeries are associated with the production of 75 to 200 mg/day of cortisol.^{43,44} Thus, recent guidelines suggest that adrenally suppressed patients receive 25 mg of hydrocortisone equivalents for minor surgeries, 50 to 75 mg for moderate surgeries, and 100 to 150 mg for major surgery for 2 to 3 days, beginning when the patient is on call for surgery.⁴³ No trials have been done, and one recent study suggested even lower doses are adequate.⁴⁵

In general, adrenal insufficiency resolves within 1 year of the termination of GC therapy. An ACTH stimulation test may be performed after maintenance GCs are terminated to assess adrenal reserve. This test is performed in the office by determining a baseline cortisol level, giving an intramuscular injection of 0.25 mg of cosyntropin, and measuring the serum cortisol level again 1 hour later.⁴⁰ The adrenal response is suppressed if the serum cortisol level fails to increase by at least 5 µg/dL to a stimulated value 60 minutes later of more than 20 µg/dL. If adequate adrenal response to stress is demonstrated, there is less concern about the endogenous cortisol response to stress.²⁷ However, such a response is not a guarantee of adequate adrenal reserves if severe stress occurs, and many physicians would choose routine stress coverage with GCs without performing an ACTH stimulation test.⁴⁶

COMPLICATIONS

Complications associated with systemic GC therapy (Table 225-4)^{47,48} increase with higher doses, longer duration of therapy, and more frequent administration. However, osteoporosis and cataracts develop with alternate-day dosing, and avascular necrosis (AVN) can be seen after only short courses of GCs.

Osteoporosis

Osteoporosis occurs in 40 percent of individuals treated with systemic GCs; it is especially prominent in children, adolescents, and post-menopausal women.⁴⁹ Approximately one-third of patients have evidence of vertebral fractures after 5 to 10 years of GC treatment, but this proportion is higher in post-menopausal women.^{50,51}

Bone loss occurs most rapidly in the first 6 months of GC use, but continues at a slower rate after that, with loss of 3 percent to 10 percent of bone per year in many patients.^{49,52} Recent studies show that even low doses of prednisone (2.5 mg/day) adversely affect bone and increase vertebral and hip fractures.^{53,54} Some of the bone loss may be reversible after GCs are stopped, at least in the young.⁵⁵

Avascular Necrosis

AVN is manifested by pain and limitation of motion in one or more joints. There is intraosseous hypertension, leading to bone ischemia and necrosis.⁵⁹ It is likely that intraosseous lipocyte hypertrophy causes this intraosseous hypertension in persons taking GCs. In addition, GCs induce apoptosis of osteoblasts, likely contributing to AVN. Underlying diseases, such as systemic lupus erythematosus, increase the likelihood of steroid-induced AVN.⁶⁰ Studies suggest that many patients who develop AVN have either thrombophilia or hypofibrinolysis, which leads to thrombotic occlusion of venous outflow from the bone, decreased arterial perfusion, and subsequent infarction of bone.⁶¹

TABLE 225-4 Complications of Glucocorticoid Therapy

Central nervous system	<ul style="list-style-type: none"> • Pseudotumor cerebri and psychiatric disorders
Musculoskeletal	<ul style="list-style-type: none"> • Osteoporosis with spontaneous fractures • Aseptic necrosis of bone • Myopathy
Ocular	<ul style="list-style-type: none"> • Glaucoma and cataracts
Gastrointestinal	<ul style="list-style-type: none"> • Peptic ulceration • Intestinal perforation • Pancreatitis
Cardiovascular and fluid retention	<ul style="list-style-type: none"> • Hypertension • Sodium and fluid retention • Hypokalemic alkalosis • Atherosclerosis
Hypersensitivity reactions	<ul style="list-style-type: none"> • Urticaria • Anaphylaxis
Endocrinologic	<ul style="list-style-type: none"> • Suppression of hypothalamic-pituitary-adrenal axis • Growth failure • Secondary amenorrhea
Metabolic	

- Hyperglycemia and unmasking genetic predisposition to diabetes mellitus
- Non-ketotic hyperosmolar states
- Hyperlipidemia
- Alterations of fat distribution (typical cushingoid appearance)
- Fatty infiltration of the liver
- Drug interactions (decreased anticoagulant effect of ethyl biscoumacetate)

Fibroblast inhibition

- Inhibition of wound healing
- Subcutaneous tissue atrophy (striae, purpura, ecchymoses)

Suppression of host defenses

Immunosuppression, anergy

- Effects on phagocyte kinetics and function
- Increased incidence of infections

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Atherosclerosis

GCs enhance many risk factors that are associated with atherosclerosis, including arterial hypertension, insulin resistance, glucose intolerance, hyperlipidemia, and central obesity. It is thus not surprising that patients taking GCs have an increased risk of atherosclerosis.⁶² Patients with untreated Cushing disease have a four times higher mortality rate from cardiovascular complications, including coronary artery disease, congestive heart failure, and cardiac stroke.⁶³ The risk factors for atherosclerosis persist for at least 5 years after normalization of the serum cortisol level in Cushing disease, and similar findings may be true in those treated with chronic GCs.⁶⁴

Suppression of the Hypothalamic-Pituitary-Adrenal Axis

The HPA axis is rapidly suppressed after the onset of GC therapy. However, if therapy is limited to 1 to 3 weeks, the recovery of the HPA axis is rapid. Longer daily GC therapy is associated with suppression of the HPA axis for up to 1 year after therapy is terminated.⁴¹ Symptoms of adrenal suppression include lethargy, weakness, nausea, anorexia, fever, orthostatic hypotension, hypoglycemia, and weight loss. There also exists a steroid withdrawal syndrome, in which patients experience symptoms of adrenal insufficiency despite having an apparently normal cortisol response to ACTH. Symptoms most commonly include anorexia, lethargy, malaise, nausea, weight loss, desquamation of the skin, headache, and fever. Less commonly,

vomiting, myalgias, and arthralgias occur. These patients have adjusted to high levels of GCs, and symptoms disappear after the GCs are restarted. This problem can be treated by slower tapering of the GCs, often by 1 mg of prednisone every few weeks.⁶⁵

Drug Interactions

GCs are associated with a number of important drug interactions. Drugs such as barbiturates, phenytoin, and rifampin, which induce hepatic microsomal enzymes, may accelerate the metabolism of GCs.⁶⁶ Drugs such as cholestyramine, colestipol, and antacids impair absorption of GCs. GCs reduce the serum salicylate level and necessitate a higher dose of warfarin (Coumadin) for anticoagulation.

Immunologic Side Effects

GCs impair delayed-type hypersensitivity reactions because of their inhibition of lymphocytes and monocytes. Prednisone at daily doses of 15 mg or more suppresses the response to tuberculin, although it takes an average of 13.6 days for oral prednisone at 40 mg/day to inhibit the response to tuberculin.⁶⁷ Thus, even in situations requiring immediate use of prednisone, it is possible to perform simultaneously a PPD test and an anergy panel. Overall, there is an increased incidence of infections attributable to both the GCs and the immunologic changes related to the underlying disease.⁶⁸

Concerns during Pregnancy and Lactation

GCs cross the placenta, but they are not teratogenic. Exposed infants as well as breast-fed infants of mothers receiving GCs should be monitored for adrenal suppression and growth suppression. Based on animal experiments, there is some concern about the contribution of GCs to premature and lowbirth-weight infants with respect to neurodevelopment.⁶⁹

Concerns in the Pediatric Population

In the pediatric population, GCs cause growth retardation and early osteoporosis.⁷⁰ Growth retardation is caused by a direct action on cell metabolism, effects on calcium and phosphorus metabolism, and a decrease in growth hormone secretion, with inhibition of bone matrix formation. Growth retardation is not necessarily prevented by alternate-day GC regimens.⁷¹ Recent studies show that human growth hormone replacement has a significant effect on growth, as well as a significant effect on lean body mass.⁷² Immunization with live vaccines can be done if the duration of GC use is less than 2 weeks at any dose, if the dose of GC is less than

2 mg/kg or 20 mg/day of any duration, and if long-term alternate-day treatment with short-acting preparations is done. Immunization with live vaccines should not be done for at least 3 months after receiving high doses of GCs (greater than 2 mg/kg or greater than 20 mg/day) for more than 2 weeks.⁷³

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