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Consequences of systemic absorption of topical glucocorticoids

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In this issue of the *JAAD*, Kerner et al report blunted adrenal responses after the use of topical corticosteroids. While it is reassuring that laboratory values remained within the normal range in this particular study, the blunted responses serve as a reminder that systemic absorption of topically applied corticosteroids can have systemic implications. Topical corticosteroids can cause iatrogenic Cushing disease and adrenal suppression.^{1–5} Those at greater risk for medically significant adrenal suppression include infants and young children, those with an impaired cutaneous barrier, and those in whom highly potent corticosteroids are applied over large areas or under occlusion. Highly vascular areas, such as the ear canals and diaper area, have been associated with enhanced systemic absorption. Practical guidelines to reduce the effects of systemic absorption include pulse application of more potent corticosteroids (weekends only or 2 weeks on/1 week off), medication holidays, use of the minimal effective strength and dose of medication, and the use of steroid-sparing agents. We must be mindful that many patients with steroid-responsive dermatoses remain under-treated, and our role is to optimize patient outcomes while minimizing the risk of complications. The following commentary by Lynnette Nieman, MD, of the National Institutes of Health, focuses on topical corticosteroids and their potential to induce adrenal suppression.

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In a report entitled "Evaluation of the pituitary-adrenal axis function in patients on topical steroid therapy" in this issue of the *JAAD*, Dr Kerner and her colleagues examine the cortisol responses to exogenous ACTH after at least 2 weeks' administration of topical glucocorticoids.¹ Nearly 40% of patients had abnormal responses, confirming previous reports that topical glucocorticoids may be absorbed systemically in amounts sufficient to suppress pituitary-adrenal function. Unfortunately, the report does not list the various agents taken by the patients. However, since potency was associated with adrenal suppression, presumably class 2 or higher agents were taken in addition to class I agents (Table I).^{2,3}

Systemic glucocorticoid effects comprise a continuum from Cushing's syndrome to biochemical abnormalities without clinical importance.⁴ While full-blown Cushing's syndrome is rare, its components are recognized more often (Table II).⁵ In this setting the patient's physical appearance may reflect glucocorticoid excess, but laboratory results show adrenal insufficiency due to ACTH suppression. After the exogenous drug is stopped, there is a risk that the pituitary corticotropes will not "wake up" quickly. Such patients would present with symptoms of adrenal insufficiency (despite appearing cushingoid). The true rate of clinical adrenal insufficiency is not known and probably is higher than recognized, as the symptoms are nonspecific: tiredness, lassitude, joint aches and pains, and occasionally fever or anorexia. However, most patients must retain some cortisol production because death occurs rarely.

The current report raises questions about when practitioners should be concerned about adrenal suppression or Cushing's syndrome when prescribing topical glucocorticoids. The risk increases based on factors that include glucocorticoid potency (see Table I), the amount applied (affected body surface area is a surrogate measure), skin thickness and location (with eyelid and scrotum showing most penetration and the side of the foot the least), the presence of broken skin, the age of the patient (children have increased absorption), the use of occlusive dressings (which promote absorption), the type of vehicle (ointments increase penetration), and the duration of use.⁴

Cushing's syndrome has been reported most often in infants receiving a class 1 agent (usually clobetasol) for the treatment of diaper rash, often at higher doses and for longer periods than recommended.⁵ Clobetasol is not recommended for use at a weekly dose greater than 50 grams, for more than 2 weeks or in children younger than 12 years. Most adult patients with Cushing's syndrome have taken clobetasol in excess of these guidelines. However, less potent agents, such as betamethasone dipropionate 0.05% and mometasone furoate 0.1% have been implicated. One might anticipate that other agents might cause adverse effects if they were given long term to patients with characteristics that lead to increased absorption (eg, large surface area, broken skin, use of an occlusive dressing). Even relatively low doses of the class 1 agents (2 g/d for 2 weeks) have been associated with adrenal gland suppression.

Nonprescription bleaching creams often contain glucocorticoids and may lead to Cushing's syndrome or adrenal insufficiency. Although dermatologists do not prescribe these agents, patients may be seen because of associated skin atrophy, striae, or vitiligo.

The first step in preventing systemic adverse effects is to use the lowest glucocorticoid dose for the shortest period of time. When this is not possible, features of Cushing's syndrome should be sought. If these are present, adrenal insufficiency is likely when the drug is

discontinued. In the absence of systemic features, adrenal insufficiency is theoretically less likely but cannot be excluded.

Measurement of a morning serum cortisol level can be helpful. If this is less than 5 $\mu\text{g}/\text{dL}$, the patient likely has adrenal suppression.⁶ With ongoing administration of the topical agent, there is no need to administer an additional “replacement” dose of glucocorticoid. However, if the drug is stopped, one might choose to give a replacement dose of hydrocortisone (10–12 mg/M2) and taper this as the cortisol level rises.

Conversely, a morning cortisol value greater than 18 $\mu\text{g}/\text{dL}$ excludes clinically significant adrenal insufficiency. Intermediate values may require testing with synthetic ACTH (Cortrosyn). As in the current report, some investigators advocate a 1- μg dose. However, this dose may lead to falsely abnormal (low) responses. A cortisol response of 18 μg or more after a 250- μg dose excludes adrenal suppression with high certainty, although rare patients will have a falsely normal response.

If cortisol is not used to estimate the risk of adrenal insufficiency, patients should be counseled regarding its symptoms and encouraged to seek medical attention should these occur within a few days of discontinuing topical glucocorticoids.

In conclusion, although clinically significant systemic absorption of topical glucocorticoids is uncommon, it has important deleterious consequences. Mindful clinicians will consider this possible complication, particularly in high-risk patients.

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Table I**Classes of topical glucocorticoids based on potency^{2,3}****Class 1 (superpotent)**

Betamethasone dipropionate ointment, cream, 0.05% (Diprolene, Diprosone)
 Clobetasol propionate ointment, cream, 0.05% (Temovate, Dermoxin)
 Diflorasone diacetate ointment, 0.05% (Fluorone, Psorcon)
 Halobetasol propionate ointment, cream, 0.05% (Ultravate)
 Fluocinonide cream, 0.1%

Class 2 (potent)

Amcinonide ointment, 0.1% (Cyclocort)
 Desoximetasone ointment, cream, 0.25%; gel, 0.05% (Topicort, Ibaril)
 Diflorasone diacetate ointment, 0.05% (Florone, Maxiflor)
 Fluocinonide ointment, cream, gel, 0.05% (Lidex)
 Halcinonide cream, ointment 0.1% (Halog)
 Triamcinolone acetonide ointment, 0.5% (Kenalog)

Class 3 (potent)

Amcinonide cream, lotion, 0.1% (Cyclocort)
 Mometasone furoate ointment, 0.1% (Elocon, Ecural)
 Betamethasone valerate ointment, 0.1% (Valisone)
 Diflorasone diacetate cream, 0.05% (Florone, Maxiflor)
 Fluticasone propionate ointment, 0.005% (Cutivate)
 Fluocortolone cream, 0.25% (Ultralan)
 Fluocinonide cream, 0.05% (Lidex E cream, Topsyn)
 Triamcinolone acetonide ointment, 0.1% (Aristocort A)
 Triamcinolone acetonide, cream, 0.5% (Aristocort-HP)
 Desoximetasone cream, 0.05% (Topicort-LP)
 Betamethasone valerate lotion, 0.01% (Valisone, Luxiq)

Class 4 (mid-strength)

Fluocinolone acetonide ointment, 0.025% (Synalar)
 Flurandrenolide ointment, 0.05% (Cordran)
 Halcinonide cream, 0.025% (Halog)
 Hydrocortisone valerate ointment, 0.2% (Westcort)
 Mometasone furoate cream, 0.1% (Elocon, Ecural)
 Triamcinolone acetonide ointment, 0.1% (Kenalog)
 Fluocinolone acetonide cream, 0.025% (Synalar)
 Hydrocortisone valerate cream, 0.2% (Westcort)
 Desoximetasone emollient cream, 0.25%

Class 5 (mid-strength)

Betamethasone dipropionate lotion, 0.05% (Diprosone)
 Betamethasone valerate cream, 0.01% (Valisone)
 Fluocinolone acetonide oil, 0.01% (Dermasmoothe/FS)
 Flurandrenolide cream, 0.05% (Cordran)

Fluticasone propionate cream, 0.05% (Cutivate)
Hydrocortisone butyrate cream, ointment, gel 0.1% (Locoid)
Desonide ointment, 0.05% (Desowen, Tridesilon)
Prednicarbate 0.1% cream (Dermatop)
Fluocinolone acetonide cream, 0.25% (Synalar)
Triamcinolone acetonide lotion, 0.1% (Kenalog)

Class 6 (mild)

Alclometasone dipropionate ointment, cream, 0.05% (Aclovate)
Betamethasone valerate lotion, 0.05% (Valisone)
Desonide cream, 0.05% (Desowen, Tridesilon)
Fluocinolone acetonide cream, solution, 0.01% (Synalar)
Triamcinolone acetonide cream, 0.1% (Aristocort)

Class 7 (least potent)

Dexamethasone cream, 0.1% (Decadron phosphate)
Hydrocortisone, 0.5%, 1%, 2.5% (Hytone, others)
Methylprednisolone, 1% (Medrol)
Topical preparations with flumethasone, prednisolone

Table IIFeatures of Cushing syndrome seen with systemic absorption of topical glucocorticoids^{2,4,5}

Nontreated skin:
Violaceous striae greater than 1 cm in width
Facial plethora
Skin atrophy
Increased lanugo hair, especially on face (women)
Glucocorticoid acne
Weight gain
Abnormal fat distribution (temporal fossae, supra-clavicular, dorsocervical areas, "moon" face)
Hypertension
Irregular or absent menses
Irritability, impaired memory or cognition
Abnormal glucose tolerance
In children, decreased growth velocity