Adverse effects of topical glucocorticosteroids

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Topical corticosteroids were introduced into medicine about 50 years ago. They represent a significant milestone in dermatologic therapy. Despite encouragement to report observed adverse drug reactions, the clinical practice of reporting is poor and incomplete. Likewise, adverse effects and safety of topical corticosteroids are neglected in the medical literature. The authors provide an updated review of their adverse-effect profile. Children are more prone to the development of systemic reactions to topically applied medication because of their higher ratio of total body surface area to body weight. Cutaneous adverse effects occur regularly with prolonged treatment and are dependent on the chemical nature of the drug, the vehicle, and the location of its application. The most frequent adverse effects include atrophy, striae, rosacea, perioral dermatitis, acne, and purpura. Those that occur with lower frequency include hypertrichosis, pigmentation alterations, delayed wound healing, and exacerbation of skin infections. Of particular interest is the rate of contact sensitization against corticosteroids, which is considerably higher than generally believed. Systemic reactions such as hyperglycemia, glaucoma, and adrenal insufficiency have also been reported to follow topical application. The authors provide an updated review of local and systemic adverse effects upon administration of topical corticosteroids, including the latest FDA report on the safety of such steroids in children. (J Am Acad Dermatol 2006;54:1-15.)

Learning objective: At the completion of this learning activity, participants should be familiar with topical corticosteroids and their proper use.

Topical corticosteroids were introduced into dermatologic therapy in 1952, when topical hydrocortisone was successfully employed in the treatment of selected dermatoses by Sulzberger and Witten.[1] The availability of glucocorticosteroids marked the most important milestone in dermatologic therapy ever achieved, owing to potent anti-inflammatory and antiproliferative effects.[2] However, the same mechanisms of action responsible for the improvement of dermatologic inflammatory conditions can cause adverse effects. The first reports about adverse effects of topical corticosteroids became available in 1955 after the use of fludrocortisone.[3]

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HPA: hypothalamic-pituitary-adrenal

GUIDELINES FOR THE SELECTION OF AN APPROPRIATE TOPICAL GLUCOCORTICOSTEROID

Common indications

To meet the challenges of a plethora of different indications, topical corticosteroids of varying strength have been produced. Low- to medium-potency agents generally are used to treat acute inflammatory skin lesions of the face and intertriginous areas, whereas highly potent agents are often required to treat chronic, hyperkeratotic, or lichenified lesions on the palms and soles. Most preparations are applied once or twice daily. Greater frequency of application may be necessary for the palms or soles, because the product is easily removed during normal activities such as walking and hand washing, and penetration is poor owing to a thick stratum corneum. Every-other-day or weekend-only application may be effective in the treatment of several chronic conditions. Lower-potency agents are preferentially used in infants and the elderly because of concerns about an increased surface-to-weight ratio and increased skin fragility, respectively.

Vehicle and absorption

The vehicle in which the topical corticosteroid is formulated influences the absorption and potency of the drug.[4] Ointment bases are preferred for infiltrated, lichenified lesions, as they enhance penetration of the drug by means of their occlusive effect and increase the hydration of the stratum corneum. The addition of propylene glycol increases the solubility of corticosteroids in the vehicle, further improving the agent's availability and potency on the skin. Creams are preferred for acute and subacute dermatoses and are used on moist skin or intertriginous areas.

Absorption has been demonstrated to vary not only among individuals but with respect to anatomical location.[5] For example, while absorption on the forearm is poor (1%), the scalp absorbs around 4% and the scrotum up to 35% of applied drug (Fig 1).[5,6] Likewise, the groin, maxillae, neck, and face absorb increased amounts of topical corticosteroids and are thus more likely to develop local side effects.[7,8] The reasons for this difference in absorption are not entirely clear, but in vitro studies have shown that the variable percutaneous absorption is caused by the thickness of the stratum corneum and its lipid composition.[5] Penetration varies between eyelid and plantar skin about 300-fold (Fig 1).[5] The absorption of topical corticosteroids is usually determined in healthy volunteers without atopic dermatitis,[6] whereas in the clinical setting, topical corticosteroids are usually applied to diseased skin. In atopic dermatitis there is a defective epidermal barrier,[9,10] and the penetration of topical corticosteroids is 2 to 10 times greater than that through healthy skin.[11] For this reason, the skin of delicate sites such as the eyelids is much more likely to atrophy from even mild-potency topical corticosteroids. In addition, this phenomenon helps explain why application of mild-potency topical corticosteroids to the eyelids may result in serious local adverse effects such as glaucoma.[12-14]

Common challenges of topical corticosteroid use

It is therefore likely that while short-term use of particularly the less potent topical corticosteroids is central in the treatment of exacerbations of atopic dermatitis, long-term or repeated use of even mild-potency topical corticosteroids may be of greater concern. Under such circumstances and especially when the patient is a child or the area to be treated involves delicate skin (eg, portions of the face, especially around the eyes), alternative, steroid-free therapeutic options would be useful. In addition, even when the use of topical corticosteroids is appropriate, the fears among patients about the use of topical corticosteroids practically limits the use of and compliance with treatment.[15,16] This situation remains despite considerable efforts over many years by clinicians and manufacturers to explain the value of topical corticosteroids.

Chemical characteristics

Chemical substitution at certain key positions is able to modify the potency of corticosteroids. For example, halogenation at the 9-α position enhances the potency by improving activity within the target cell and decreasing breakdown into inactive metabolites.[17] Along the same lines, masking or removing the hydrophilic 17-dihydroxyacetone side chain or the 16-α-hydroxy group will increase the molecule's lipophilicity, thus enhancing penetration through the stratum corneum.[17]

HUMAN MODELS OF TESTING CORTICOSTEROID EFFICACY AND STRENGTH

Vasoconstriction test

Corticosteroid strength has been classified according to the vasoconstrictor assay, which is based on the extent to which the compound induces cutaneous vasoconstriction ("blanching effect") in normal human subjects (Table I).[18] The vasoconstriction test was established in 1962 to roughly estimate the efficacy of topical corticosteroids.[19,20] It represents an unspecific and simple in vivo test, although the phenomenon of vasoconstriction is not linked to the receptor-mediated activity of steroids. However, the exact cause of this vasoconstriction remains unknown. On applying a defined quantity (eg, 5 mg) of the corticosteroid preparation to a defined skin area, the vasoconstriction is assessed visually or by means of infrared reflection photometry, thermal conductivity, or laser Doppler velocimetry.[21]

Ultraviolet erythema test

The inhibitory effects of topical corticosteroids on an experimentally elicited erythema were examined with the ultraviolet erythema test.[22] The respective topical corticosteroid is applied 24 hours prior to ultraviolet A or ultraviolet B light exposure. The erythema is induced by applying the threefold minimal erythema dose. Seven hours after ultraviolet exposure and administration of topical corticosteroid, the extent of the erythema is scored and the treated sites are compared with the untreated ones.

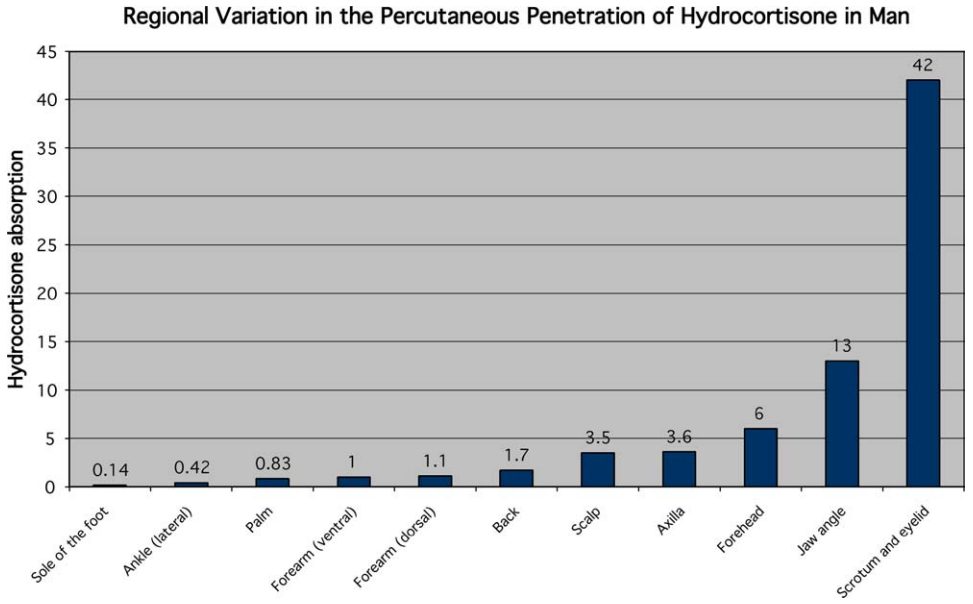

Fig 1. Regional variation in percutaneous penetration of hydrocortisone in human beings, according to Feldmann and Maibach[5] and Wester and Maibach.[6]

Pyrexial erythema test

The local reaction to an intracutaneous injection of a bacterial pyrogen such as purified lipopolysaccharide of *Salmonella abortus equi* is used as an inflammation model for human skin.[23] At injection of a defined quantity of the lipopolysaccharide, the local inflammation with and without application of topical corticosteroid is evaluated at 12 hours.

Skin atrophy test

The atrophy test is an important addition to the anti-inflammatory tests, since it can be used to determine those corticosteroids that have only a slight antiproliferative effect (atrophogenic potential). With the use of the Duhring chamber (a dome-shaped silicone reservoir), the corticosteroid to be tested is applied to the same skin area for 3 weeks under occlusion.[24] At that point, the resulting atrophy and the extent of telangiectasia are evaluated by means of a defined score.

Other tests

Other test systems include the ammonium hydroxide blister tests,[25] the stratum corneum test,[24] the skin thickness measurement,[26] the acne induction test,[27] and the assessment of endogenous cortisol production.[21,28,29] The psoriasis plaque test, the poison ivy test, and the contact eczema inhibition test are only of historic value.[21,30] Others, such as skin thickness assessment by means of ultrasound[31] or early detection of glucocorticoid-specific epidermal alterations with skin surface microscopy,[32] also are only rarely used. There are no data on interassay consistency among the individual assays.

ADVERSE EFFECTS OF TOPICAL CORTICOSTEROIDS

Despite the legal obligation to report to regulatory agencies observed adverse drug reactions, the clinical practice of reporting is rather poor and incomplete. It is estimated that the majority of the moderate to severe side effects will never be reported to regulatory authorities, especially since the drug in question was introduced a long time ago. The available databases (www.fda.gov/cder/drug/default.htm) suggest that only life-threatening side effects were reported or published. Therefore, any summary of adverse events that follow application of the respective drug is limited.

During the era when corticosteroids were the mainstay of topical therapy for inflammatory diseases, the unlimited use of these compounds was recognized to be hazardous. Local as well as systemic adverse effects have been documented. Children are more prone to develop systemic reactions to topically applied medication because of their higher ratio of total body surface area to body weight (about 2.5- to 3-fold that of adults). However, the thicknesses of the stratum corneum and its structural components, such as keratins and lipids, have been found not to be statistically different from those in adults.[33] Under normal conditions, up to 99% of the applied topical corticosteroid is removed form the skin by rubbing, washing off, and exfoliation, and only 1% is

Table I. Potency ranking of selected topical corticosteroid preparations

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)
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, 0.1% (Halog)
	Mometasone furoate ointment, 0.1% (Elocon, Ecural)
	Triamcinolone acetonide ointment, 0.5% (Kenalog)
Class 3 (potent)	Amcinonide cream, lotion, 0.1% (Cyclocort)
	Betamethasone valerate ointment, 0.01% (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)
	Halcinonide ointment, 0.1% (Halog)
	Triamcinolone acetonide ointment, 0.1% (Aristocort A)
	Triamcinolone acetonide, cream 0.5% (Aristocort-HP)
Class 4 (midstrength)	Betamethasone valerate lotion, 0.01% (Valisone, Luxiq)
	Desoximetasone cream, gel 0.05% (Topicort-LP)
	Fluocinolone acetonide cream, 0.2% (Synalar-HP)
	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)
Class 5 (midstrength)	Betamethasone dipropionate lotion, 0.05% (Diprosone)
	Betamethasone valerate cream, 0.01% (Valisone)
	Fluocinolone acetonide cream, 0.025% (Synalar)
	Fluocinolone acetonide oil, 0.01% (Dermasmoothe/FS)
	Flurandrenolide cream, 0.05% (Cordran)
	Fluticasone propionate cream, 0.05% (Cutivate)
	Hydrocortisone butyrate cream, 0.1% (Locoid)
	Hydrocortisone valerate cream, 0.2% (Westcort)
	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)
	Prednicarbate 0.1% cream (Dermatop)
	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

therapeutically active.[34] However, this small percentage of percutaneously absorbed corticosteroid can exert systemic adverse effects, while cutaneous adverse effects may also result from the transient presence of topical corticosteroid.

Local adverse events of corticosteroid use are far more prevalent than systemic reactions.[34,35] A myriad of possible adverse effects of topical glucocorticosteroids have been reported (Table II). Tachyphylaxis is characterized by decreasing efficacy of corticosteroids during continued treatment that frequently necessitates topical corticosteroids of greater potency. In the experimental setting, tachyphylaxis can be quantified by means of the vasoconstrictor assay

Table II. Adverse effects of topical corticosteroids

Atrophic changes
Steroid atrophy
Telangiectasia
Striae
Purpura
Stellate pseudoscars
Ulceration
Easy bruising
Infections
Masked microbial infections (tinea incognito)
Aggravation of cutaneous candidiasis, herpes or demodex
Reactivation of Kaposi sarcoma
Granuloma gluteale infantum
Ocular changes
Ocular hypertension
Glaucoma, cataract
Pharmacologic effects
Steroid rebound, steroid addiction, tachyphylaxis
Miscellaneous
Steroid acne
Perioral dermatitis
Steroid rosacea
Hirsutism
Hyperpigmentation
Hypopigmentation
Photosensitization
Rebound flare (psoriasis)

and inhibition of fibroblast proliferation.[19,20] Due to the tissue becoming less sensitive (tachyphylaxis), preparations that are more potent are frequently being used to achieve comparable effects,[36] yielding more severe undesired effects.

Atrophy

All topical steroids have been shown to cause skin atrophy, albeit to a variable degree.[26,37] This phenomenon is reflected in increased transparency and shininess of the skin, as well as the appearance of striae.[6,38] The factors that influence the degree of skin atrophy include age, body site, potency of topical corticosteroid, and the presence of occlusion. Atrophy from topical triamcinolone acetonide was first reported by Epstein et al.[38] Atrophy has now been recognized as the most common adverse effect of topical corticosteroid therapy (Fig 2).[39] Topical application of corticosteroids can cause atrophy, not only because of the suppressive action on cell proliferation but also because of inhibition of collagen synthesis. Dermal atrophy is probably caused by decreased fibroblast growth and reduced synthesis of collagen and acid mucopolysaccharides.[40]

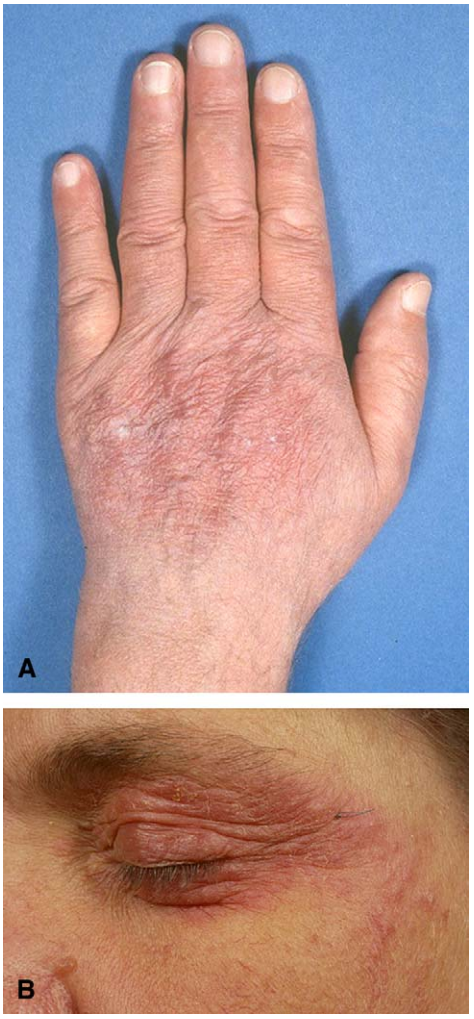

Fig 2. **A**, Steroid atrophy on the dorsum of the left hand with hyperpigmentation as a consequence of easy bruising caused by rarefaction of connective tissue. Stellate pseudoscars and increased wrinkling are also apparent in this 37-year-old man. **B**, Thickened lichenified skin, severe epidermal atrophy, and erythema after inappropriate use of high-potency corticosteroids on the eyelids. A yellow crust indicates that impetigo contagiosa (streptococci) on the upper eyelid is also present.

Intertriginous areas are particularly susceptible, probably owing to thinner skin, increased moisture, elevated temperature, and partial occlusion provided by the skin in these sites.

Telangiectasia

In addition to atrophy, corticosteroids stimulate human dermal microvascular endothelial cells,[41] leading to the occurrence of telangiectasia. This condition is characterized by an abnormal dilatation of capillary vessels and arterioles.

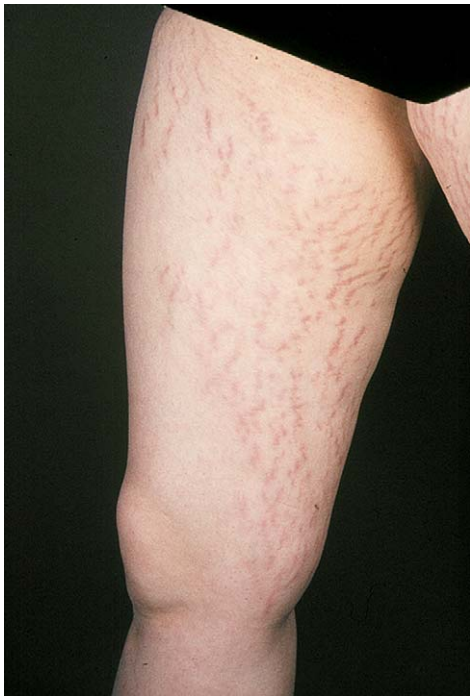

Fig 3. Striae distensae rubrae as a sign of topical corticosteroid abuse on the right thigh in a nonobese 27-year-old man.

Epidermal barrier disturbance

Moreover, subtle changes occur in the epidermal barrier upon topical corticosteroid application, as evidenced by decreased formation of lipid lamellar bodies and delayed barrier recovery (ie, increased transepidermal water loss).[42,43] This effect, which may theoretically worsen barrier impairment in atopic dermatitis and psoriasis, seems to be outweighed by reducing inflammation and permitting barrier repair.

Striae

Striae (rubrae distensae) are visible linear scars that form in areas of dermal damage, presumably during mechanical stress (Fig 3).[44] They develop with an initial inflammation and edema of the dermis, followed by the deposition of dermal collagen along the lines of mechanical stress.[45] Histologically, striae represent scar tissue and therefore, once developed, are permanent. Striae due to corticosteroid abuse should be distinguished from those that occur during excessive weight gain and pregnancy.

Steroid rosacea

Dermatoses of the face are usually steroid-sensitive and do not require potent formulations. The classical history of steroid rosacea begins in a middle-aged woman with intermittent papules and pustules that are initially controlled with steroids of low potency (Fig 4). Subsequently the lesions may reappear and prompt the continued use of greater-potency topical corticosteroid.[46]

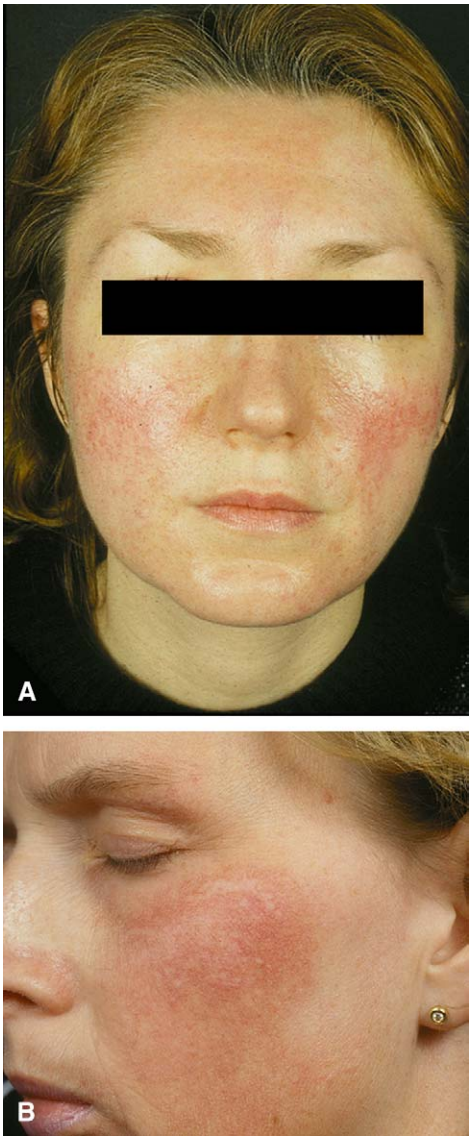

Fig 4. **A**, Long-term inadvertent use of corticosteroids for treatment of perioral and cheek dermatitis. **B**, Closer view of the left cheek showing atrophic skin and white scarring, along with telangiectases after uncontrolled use of high-potency steroids for 9 months.

Acne

Topical steroids can rapidly induce an acneiform eruption.[27,47-49] These authors attributed the acnegenic effect to the degradation of the follicular epithelium, resulting in extrusion of the follicular content (Fig 5). While steroids initially lead to the suppression of inflammatory papules and pustules,

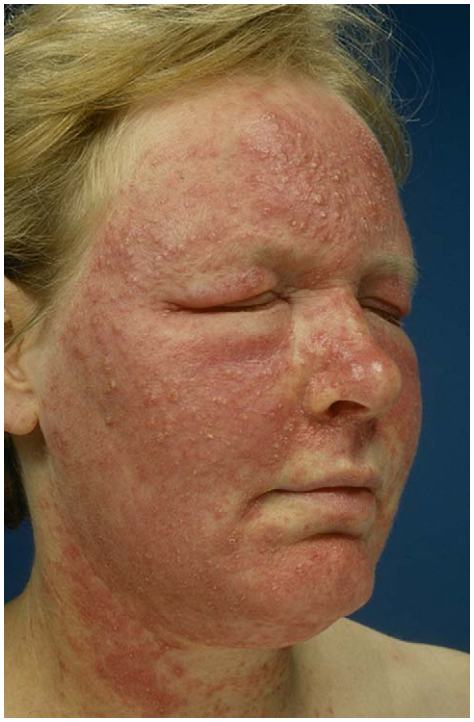

Fig 5. Steroid acne on the face characterized by pustules, erythema, and several open and closed comedones on the forehead. Free margins around the vermilion border are apparent.

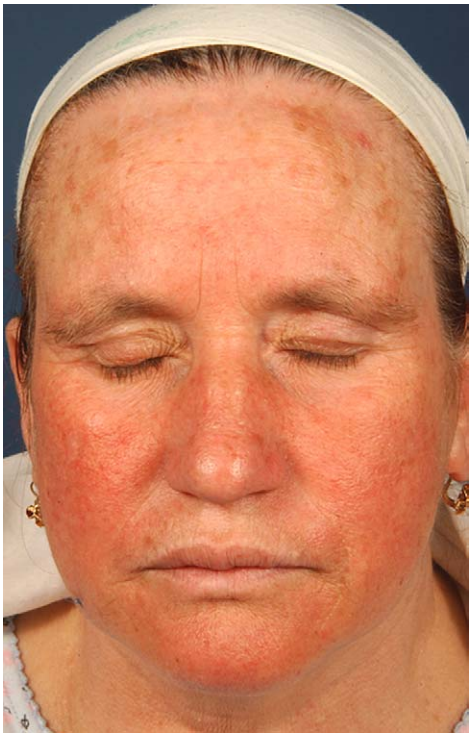

Fig 6. Steroid abuse in a patient with atopic dermatitis showing generalized facial erythema, patchy hyperpigmentation on the forehead, increased atrophy, and wrinkles around the eyes. This patient has continued treatment with stronger derivatives because of loss of effect (tachyphylaxis).

they become more resistant upon recurrence, producing the clinical picture of topical corticosteroid—induced acnelike lesions.

Perioral dermatitis

Steroid-induced perioral dermatitis has been described as a facial eruption that occurs in females and is composed of follicular papules and pustules on an erythematous background that begin in a perioral distribution, with prominent sparing of the skin adjacent to the vermilion border in women (Fig 6).[50] Though perioral dermatitis has been most frequently observed in young women, it has also been seen in men and children.[51] It is caused by the long-term use of potent corticosteroids on the face.

Steroid addiction

Corticosteroid addiction has been described as an ongoing inadvertent use of potent topical corticosteroid applied mostly to the face.[46] Patients who become addicted are continuing treatment because of concerns that acne, rosacea, perioral dermatitis, or telangiectasia may flare up when treatment is withdrawn.[52,53] Some cases may also present as the "red burning skin syndrome."[54] To distinguish erythroderma due to steroid withdrawal from chronic eczema, the serum nitric oxide levels may be used.[54]

Hypertrichosis

Steroids promote the growth of vellus hair by means of an unknown mechanism.[55] Reports of local and disseminated hypertrichosis caused by topical steroids are rare.[56,57] Variable degrees of hypertrichosis remain a more common manifestation of systemic corticosteroid use. The darker hairs may persist for months after withdrawal of steroids.

Hypopigmentation

While hyperpigmentation after intralesional injection of steroids has been well documented,[58] decreased pigmentation after topical use is quite common though frequently unnoticed (Fig 7). Americans of sub-Saharan African lineage are particularly affected. It has been postulated that steroids probably interfere with the synthesis of melanin by smaller melanocytes, leading to patchy areas of hypopigmentation.[58] Those lesions are generally reversible upon discontinuation of steroid therapy.

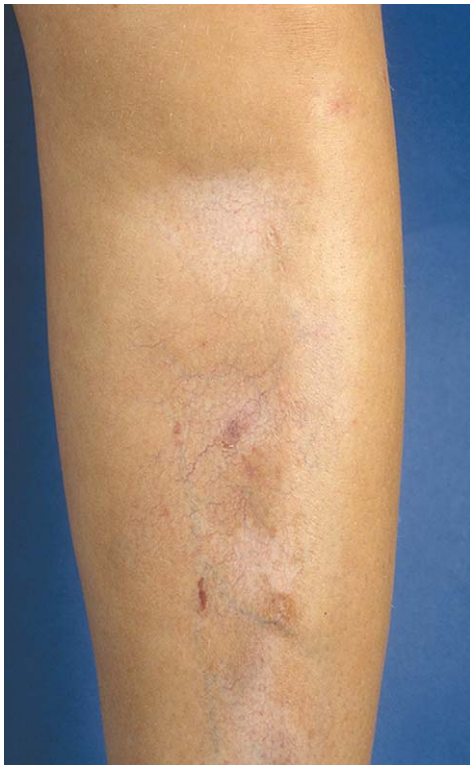

Fig 7. Hypopigmentation and hyperpigmentation due to easy bruising, as well as increased telangiectases and atrophy on the left forearm.

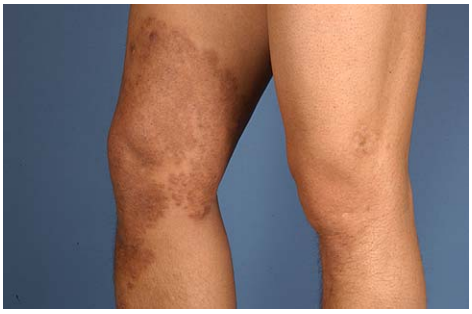

Fig 8. Tinea incognito of the leg. This patient underwent treatment with corticosteroids that masked the diagnosis of tinea.

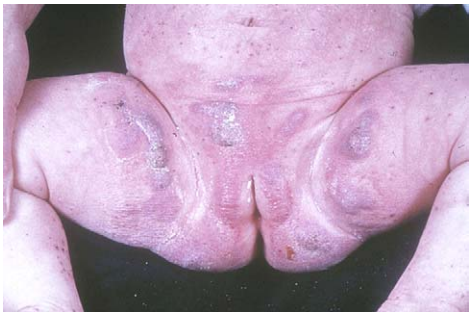

Fig 9. Severe granuloma gluteale infantum in a 2-year-old child who underwent treatment for diaper dermatitis. Succulent red to livid granulomatous plaques appear on the thighs, the buttocks, the vulva, and the lower portion of the abdomen. *Candida albicans* was cultured from the inguinal fold.

Purpura, stellate pseudoscars, and ulcerations

These consequences arise when severe steroid-induced dermal atrophy and loss of intercellular substance occur, causing blood vessels to lose their surrounding dermal matrix. The resulting lesions resemble actinic damage in the elderly (Fig 2, *A*). The resulting fragility of dermal vessels leads to purpuric, irregularly shaped, hypopigmented, depressed scars (Fig 7).[59] These stellate pseudoscars most frequently develop over the extremities, mostly on severely atrophic, telangiectatic purpuric skin (Fig 2, *A*). True ulceration from continued abuse of corticosteroids has also been reported.[52]

Aggravation of cutaneous infections

Mucocutaneous infections are common during treatment with corticosteroids and often occur early in therapy.[60,61] The incidence of skin infections varies but is probably between 16% and 43%.[60] Infections include tinea versicolor, onychomycosis due to *Trichophyton* and *Candida* species, dermatophytosis, and disseminated cutaneous *Alternaria* infection.[60] The term *tinea incognito* was coined to describe marked tinea infections that were transformed into unrecognizable cutaneous eruptions (Fig 8).[62] The corticosteroid therapy suppresses inflammation, while the fungal or bacterial growth flourishes. Similar effects of topical corticosteroids on prolongation or mitigation of herpes simplex, molluscum contagiosum, and scabies infection have also been reported.[63] Granuloma gluteale infantum is a persistent reddish-purple, granulomatous, papulonodular eruption that rarely occurs on the buttocks, thighs, or inguinal fold in children (Fig 9). It is a well-known consequence of diaper dermatitis that is being treated with corticosteroids.[64] Reactivation of Kaposi sarcoma is an additional concern.[65]

Delayed wound healing

The effects of corticosteroids on wound healing refer to those in keratinocytes (epidermal atrophy, delayed reepithelialization), fibroblasts (reduced collagen and ground substance, resulting in dermal atrophy and striae), vascular connective tissue support (telangiectasia, purpura, easy bruising), and impaired angiogenesis (delayed granulation tissue formation).[66]

Contact sensitization to topical corticosteroids

Contact hypersensitivity to topical corticosteroids may be a cause of persistence or worsening of skin diseases. Several multicenter studies that have been performed to address this question yielded a prevalence of positive reactions to corticosteroids between 0.2% and 6%.[67-70] While contact sensitization to topical corticosteroids is generally rare, its risk increases with prolonged exposure and the selection of certain drugs.[70,71] It seems that nonfluorinated corticosteroids (eg, hydrocortisone, hydrocortisone-17-butyrate, and budesonide) result in a higher prevalence of corticosteroid contact allergy in comparison with fluorinated compounds.[72] Binding to the amino acid arginine as part of certain proteins seems to be a prerequisite for allergic reactions to corticosteroids.[73] Contact sensitization to topical corticosteroids has to be distinguished from hypersensitivity to other constituents, for example, lanolin, preservatives such as parabenes, and antibiotics.[69]

Results of patch testing showed tixocortol pivalate as an effective screening agent for sensitivity to hydrocortisone and its derivatives,[70] while budesonide was useful in detecting potential allergies to other corticosteroids, including triamcinolone derivatives. A classification scheme based on structural relation of the steroid molecule has been devised for cross-reactivity (Table III). This scheme, with the representative agents hydrocortisone (group A), triamcinolone acetonide (group B), betamethasone (group C), and hydrocortisone butyrate (group D), is useful for clinical tests of contact allergy to corticosteroids. It also seems reasonable to confirm sensitization with the repeated open application test.[74,75]

Alterations in skin elasticity and mechanical properties

Decreases in skin elasticity are rarely considered but are common complications of corticosteroid therapy.[76] Such alterations can be assessed easily by pulling skin and observing incomplete retraction upon cessation of mechanical stress. In addition, skin extensibility is defined as the ability of skin to be elongated due to rarefaction of connective dermal tissue.

Influence of sun and aging

The cutaneous effects of corticosteroids have to be distinguished from those related to aging, sun exposure, and sex hormones. Aging is characterized by dry, wrinkled, loose skin after the ages of 35 in women and 45 in men (Fig 10). The pathophysiology of skin aging is similar to the one that follows topical application of corticosteroids. A marked decrease in skin thickness, especially in light-exposed areas, and delayed skin recovery are noted.

Table III. Classification of topical corticosteroids by cross-reactivity*

Group A
Hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisolone, methylprednisolone, prednisone
Group B
Triamcinolone acetonide, triamcinolone alcohol, amcinonide, budesonide, desonide, fluocinonide, fluocinolone acetonide, halcinonide
Group C
Betamethasone, betamethasone sodium phosphate, desoximetasone , dexamethasone, dexamethasone sodium phosphate, fluocortolone
Group D
Hydrocortisone-17-butyrate, hydrocortisone-17-valerate, alclometasone dipropionate, betamethasone valerate, betamethasone dipropionate, prednicarbate, clobetasol-17-butyrate, clobetasol-17-propionate, fluocortolone caproate, fluocortolone pivalate, fluprednidene acetate

*From Coopman S, Degreef H, Dooms-Goossens A. Br J Dermatol 1989;121:27-34.

SYSTEMIC ADVERSE EFFECTS UPON TOPICAL ADMINISTRATION

Systemic adverse effects from cutaneous corticosteroids have also been described (Tables IV, V). The formation of glaucoma from the use of topical corticosteroids around the eye has been recognized as a rare but serious problem.[12-14,77] This finding is not surprising if one considers that the penetration of topical corticosteroids is up to 300 times greater through the eyelid than on other body sites.[5] While systemic corticosteroid therapy has been associated with cataract formation,[78] visual loss due to glaucoma has also been reported to follow topical facial use for extended periods.[79] However, due to insufficient reporting, incidence figures are scarce for these potentially more serious effects. Short-term enhancement of plasma cortisol levels upon topical application of hydrocortisone, though, has been detected.[80]

Suppression of the hypothalamic-pituitary-adrenal (HPA) axis

Several studies have shown the potential for hypothalamic-pituitary-adrenal (HPA) axis suppression from potent topical corticosteroids.[81] As little as 2 g per day of clobetasol propionate, 0.05% cream, can cause a decreased morning cortisol level after

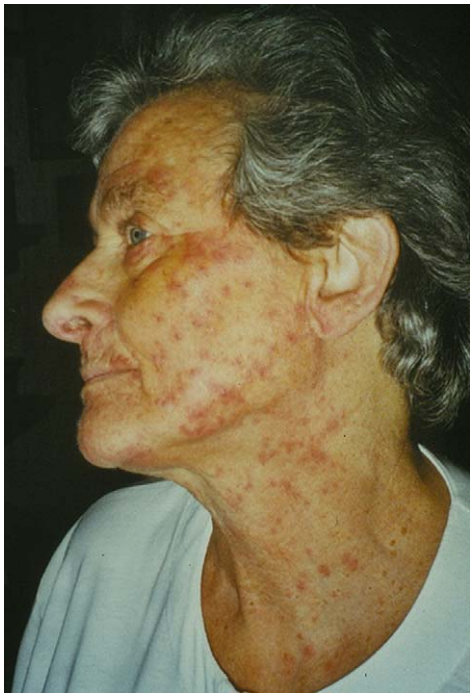

Fig 10. Photoaged skin showing increased bruising, brownish discoloration of the skin, and scarring in a 74-year-old woman with atopic dermatitis.

only a few days.[82,83] Along the same lines, iatrogenic Cushing syndrome has been associated with the use of topical corticosteroids.[84,85] In rare cases, corticosteroid-related Addison crises have caused death.[86] In addition, retarded growth in children exposed to long-term potent and superpotent topical formulations is possible.[87] Topical corticosteroids can also precipitate or exacerbate hyperglycemia.[88] For prevention, the use of less than 50 g per week of potent corticosteroids has been suggested.[89]

While all effective topical corticosteroids possess the potential to suppress the HPA axis,[87,90-92] an increase in steroid penetration has been shown to augment the potential for HPA suppression, especially in children with atopic dermatitis.[93-95] Application of corticosteroids to large surface areas, occlusion, higher concentrations, or more potent derivatives directly increase the risk of HPA suppression.[96] The advent of superpotent derivatives such as clobetasol propionate, betamethasone dipropionate, and diflorasone diacetate have an increased ability to suppress adrenal function. As little as 14 g/wk of clobetasol propionate ointment may induce suppression in children,[96] while 49 g/wk of betamethasone dipropionate was required to significantly reduce plasma cortisol levels. With the majority of patients with HPA suppression having exclusive laboratory test abnormalities, several cases of severely impaired stress responses have been reported, especially in children who have undergone treatment with high-potency topical corticosteroids.[87,97] The reactivity of the HPA axis can be assessed with the adrenocorticotropin hormone test, which has been described elsewhere[98] and wherein plasma cortisol levels are measured prior to and after a bolus administration of 250 μg (25 units) of synthetic α-1-24-adrenocorticotropic hormone. Recovery from steroid-induced adrenal insufficiency is time-dependent and occurs spontaneously. The administration of topical corticosteroids has also led to iatrogenic Cushing syndrome.[84,99] Complications of this syndrome occur only at prolonged exposure to excessively large doses of topical glucocorticosteroids.

Table IV. Rare systemic adverse events of topical glucocorticosteroids[106]

Endocrine	Cushing disease, moon face, centripetal obesity, buffalo hump, striae distensae
Metabolic	Glucose intolerance (hyperglycemia), osteopathy (fractures or aseptic necroses such as those of the femoral head), adrenocortical suppression, decreased growth rate
Electrolyte balance	Edema, hypocalcemia, hypertension
Ocular	Posterior subcapsular cataract, glaucoma

Adapted from Weaver J. Postmarketing safety review—PID D010141. Drugs: Topical corticosteroids. Bethesda, MD: FDA, July 9, 2001.

Hyperglycemia and diabetes mellitus

Significant percutaneous absorption of glucocorticosteroids may result in hyperglycemia and the unmasking of latent diabetes mellitus by means of a multifactorial mechanism (increasing transport of alanine, an important substrate for gluconeogenesis in the liver,[100] increasing the activity of rate-limiting enzymes,[101] and causing relative insulin resistance).[102] Consequently, systemically absorbed topical glucocorticosteroids may precipitate or exacerbate hyperglycemia,[88] especially in patients with preexisting hepatic disease.

Mineralocorticoid effects

While topical glucocorticosteroids have minimal or no mineralocorticoid activities, hydrocortisone—the natural glucocorticoid of the adrenal cortex—prednisolone, and prednisone, as well as 9-α-fluoroprednisolone, have measurable mineralocorticoid activity.[103] Prolonged treatment may

Table V. Reported severe adverse events that follow topical corticosteroid use

Drug	Reported adverse effect	Reference no.
Budesonide	Intraocular pressure changes (up to 30%)	115
	Irritation, itching, burning (up to 1%)	116
	Contact dermatitis (100 of 7,238)	117
Hydrocortisone	Pseudotumor cerebri (benign intracranial hypertension or elevated intracranial pressure)	118, 119
	Cataract	77
	Glaucoma	79
	Contact dermatitis (74 of 7,238 patients)	114, 117
Triamcinolone acetonide	Cushing syndrome	120, 121

Table VI. Topical corticosteroid products licensed for use in pediatric patients in the United States, by age limitation

Age limitation	Drug
>1 y	Alclometasone dipropionate cream and ointment
	Prednicarbate emollient cream
>2 y	Mometasone furoate monohydrate cream
>6 y (for up to 4 wk)	Fluocinolone acetonide topical oil
>3 mo (for up to 4 wk)	Fluticasone propionate cream
>12 y	Betamethasone dipropionate ointment, cream, gel, lotion and in combination with clotrimazole
	Clobetasone propionate cream, ointment, solution, gel

lead to associated edema and possible hypocalcemia.

SPECIAL ASPECTS IN PEDIATRIC PATIENTS

Because the skin of children is particularly sensitive,[104,105] the British National Formulary emphasizes that children are particularly susceptible to side effects. The organization recommends that in general, topical corticosteroids be avoided in children or, if necessary, used with great care and for short periods. A variety of topical corticosteroid products is licensed for use in pediatric patients (Table VI).

Recently a postmarketing safety review has been released by the FDA's Center for Drug Evaluations and Research, which assessed the 24 most frequently used topical corticosteroids in pediatric patients aged 0-18 years.[106]

In that summary was an assessment of 202 reports of adverse events associated with the use of topical corticosteroids in this patient population.[106] The children whose data were analyzed for the FDA report had a mean age of 7.7 years and a mean time to onset of lesions of 169.3 days. Most adverse events were reported between 1987 and 1997. The censoring date for analysis was May 2001. Betamethasone-containing products were most frequently implicated in reports of adverse reactions (79.4%). The combination of betamethasone dipropionate and clotrimazole cream was used in 52 (25.7%) cases, and triamcinolone acetonide in combination with nystatin cream was used 18 times. All other analyzed topical corticosteroids were used in less than 10 cases. Most frequently, the drug was applied to the

Table VII. Reported adverse events in pediatric patients, according to the FDA report

Event	Frequency (n = 202)*
Local irritation	66
Skin depigmentation or discoloration	30
Striae or skin atrophy	30
Cushing syndrome	6
Growth retardation	5
Hyperglycemia (diabetes)	5
Scarring	5
Staphylococcal infection	5
Genital hypertrichosis	4
Hirsutism	4
Rosacea	4
Acne	3
Glaucoma	3
Hypersensitivity reaction	3
Adrenal insufficiency	2
Bruising	2
Fungal infection	2
Gynecomastia	2
Perioral dermatitis	2
Mental status or mood change	2

*Several other adverse events occurred in fewer than 2 reports and are not listed here.

Table VIII. Optimal use of topical corticosteroids

Appropriately potent compound to achieve disease control
Continuation with a less potent preparation after sufficient response
Reduction of frequency of application (alternate-day therapy; weekend use)
Continuation of daily application with the weakest effective preparation
"Tapering off" treatment upon complete healing
Particular care in treating children and the elderly, especially at certain locations (eg, scrotum, face, flexures, and area around eyes)

face and neck (n = 40); buttock, groin, or genitals (n = 32); legs or feet (n = 22); arms or hands (n = 19); head or scalp (n = 12); trunk (n = 8); entire body (n = 4); or axilla (n = 2). In 79 adverse event reports, no localization was stated.

Of these 202 cases, the frequency of adverse events was reported (Table VII). While local irritation and reactions at the sites of application were most frequently reported, numerous systemic adverse events were also noticed. Among these systemic changes, striae cutis distensae, Cushing syndrome, growth retardation, hyperglycemia, hirsutism, glaucoma, and adrenal insufficiency were most significant. The most severe outcome of topical corticosteroid treatment in this survey consisted of hospitalization (n = 14), disability (n = 5), life-threatening illness (n = 1), and death (n = 1). The authors concluded that long-term application of topical corticosteroids in high-risk settings (eg, application to gluteal folds, genitals, and groin areas in young patients) should be limited. In addition, topical corticosteroids should not be continued when the dermatoses failed to improve.

Prescription of topical corticosteroids

A recent study indicated that pediatricians frequently prescribed combination products (eg, corticosteroid and antibiotic),[107] while they only infrequently prescribed single-agent high-potency topical corticosteroids. In particular, fixed combinations of betamethasone and clotrimazole were frequently prescribed.[108] As expected, pediatricians preferred low-potency (56.3%) over high-potency (5%) or medium-potency derivatives (28.7%).[107,109] In addition, these combination products tend to be used for diaper rash and are therefore occluded by the diaper. This study highlighted the importance of monotherapy and the thoughtful use of preparations in small children and babies.

Prevention of adverse effects

Guidelines and suggestions regarding the use of topical corticosteroids have been provided to prevent their misuse.[110,111] Possible measures to prevent side effects include the use of lower-potency steroids, application only in the morning, and alternate-day treatment (reducing tachyphylaxis and avoidance of occlusion; Table VIII).[112] Steroid-induced atrophy may be prevented with the use of topical tretinoin without lessening the steroid anti-inflammatory effect.[37] Topical keratolytics, such as salicylic acid, may be used simultaneously for thickened plaques, obviating the need for high-potency steroids and facilitating substitution with lower-potency ones. A recent study of 18 children has confirmed that weaker concentrations of topical corticosteroids under occlusion had comparable high efficacy but were associated with a lower risk of HPA axis suppression.[94,96] Systemic toxicity after topical administration seems to be more frequent in patients with renal and hepatic disease.[88,91] On the other hand, laboratory studies often revealed adrenal suppression in the absence of clinical signs. The frequency and severity of local adverse events must be kept in mind.

CONCLUSIONS

For many patients, the intermittent use of topical corticosteroids is highly effective, bears little risk, and is relatively inexpensive.[35] However, when the inflammatory disease remains recalcitrant or affects particularly sensitive areas, the repeated use of potent such steroids is not desirable for extended periods. In addition, patients may have genuine concerns about these agents that lead to noncompliance, even where treatment with them is appropriate. Thus a significant proportion of patients does not receive adequate treatment.[15,16] Patient education by the physician is important to dispel fears and ensure the safe use of topical corticosteroids.

The ideal, skin-selective corticosteroid will be difficult to develop because the intracellular receptors that are responsible for corticosteroid efficacy are also responsible for the various manifestations of adverse events.[2,113] Selective glucocorticoid receptor agonists capitalize on the recent finding that conventional glucocorticoids affect gene expression by means of 2 distinct mechanisms. Seventy percent of

the therapeutic effects are mediated by transrepression, while an equal proportion of glucocorticoid adverse effects are mediated by transactivation. Selective novel glucocorticoid receptor ligands that demonstrate relative dissociation between transrepression and transactivation have recently been developed and await clinical tests.[122]

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