Adverse effects of topical glucocorticosteroids

Ulrich R. Hengge, MD,[a] Thomas Ruzicka, MD,[a] Robert A. Schwartz, MD,[b] and Michael J. Cork, MD[c]
Düsseldorf, Germany; Newark, New Jersey; and Sheffield, United Kingdom

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]

From the Department of Dermatology, Heinrich-Heine University Duesseldorf, Germany[a]; Department of Dermatology, New Jersey Medical School, Newark, New Jersey[b]; and the Dermatology, Division of Genomic Medicine, University of Sheffield Medical School, Sheffield, United Kingdom.[c]

Funding sources: None.
Conflict of interest: None identified.

Reprint requests: Ulrich R. Hengge, MD, Department of Dermatology, Heinrich-Heine-University, Moorenstrasse 5, D-40225 Düsseldorf, Germany. E-mail: ulrich.hengge@uni-duesseldorf.de.

0190-9622/$32.00

doi:10.1016/j.jaad.2005.01.010

Abbreviation used:
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.