Topical Corticosteroid Application and the Structural and Functional Integrity of the Epidermal Barrier

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Abstract

Topical corticosteroids are a very important part of the treatment of many skin disorders, especially eczematous dermatoses. When utilized properly and judiciously, these agents often achieve excellent results in clearing or markedly improving many dermatological disorders. As some studies have shown, topical corticosteroids, despite their ability to decrease inflammation through several mechanisms, induce abnormalities in lipid synthesis and intercellular bilayer structure in the stratum corneum, which appear to prolong epidermal barrier recovery. These adverse effects may contribute to earlier eczematous flaring if measures to provide barrier repair are not undertaken. In addition, although topical corticosteroids are applied only to sites affected by the skin eruption, the incorporation of "barrier friendly" excipients into the vehicle that improve stratum corneum permeability barrier function and integrity is very rational.

Introduction

Topical corticosteroids (TCS) are commonly used for the treatment of a wide spectrum of dermatoses associated with multiple inflammatory and immunological pathways, with certain pathways contributing to the pathophysiology of specific disease states.[1,2] The multiple anti-inflammatory modes of action induced by TCS after cutaneous application explain their ability to rapidly mitigate the signs and symptoms of inflammatory dermatoses, such as atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis, nummular dermatitis, seborrheic dermatitis, and chronic plaque psoriasis.[2,3] Since the 1952 publication about hydrocortisone (compound F), the first topically applied corticosteroid (CS) to exhibit therapeutic effects, several advances have led to the discovery of CS compounds that vary in potency. Additionally, there have been advances in vehicle formulations to help augment cutaneous bioavailability, improve adaptability for use on certain body sites, address barrier repair, and/or reduce skin irritation.[1–4]

TCS are efficacious for many different dermatological disorders due to multiple anti-inflammatory, antiproliferative, and immunosuppressive effects.[1,2] However, the various biological activities produced by TCS that induce these multiple and varied effects can also produce adverse effects (AEs), such as cutaneous atrophy and persistent erythema/telangiectasia formation.[1–3] These AEs are more likely to occur with prolonged use and/or unsupervised use. On a cellular level, TCS exert their biological effects by binding to cytoplasmic glucocorticoid receptors (GRs), which traverse into the nucleus. Within the nucleus, the TCS-GR complex binds to response elements within steroid-responsive genes, which induces either transrepression or transactivation of regulatory proteins.[1,2] Transrepression of cyclooxygenase-2 (COX-2), or specific cytokines, primarily modulates anti-inflammatory effects while many TCS-related AEs appear to be caused by transactivation of specific pathways.[1,2] For some disorders, such as eczematous dermatoses (i.e., atopic dermatitis) and seborrheic dermatitis, provided the potency of the TCS formulation is sufficiently

matched with the severity of the disease, TCS induce a rapid diminution of the predominant inflammatory cascades causing the eczematous eruption and associated pruritus. In other cases, the pathogenic pathways inducing inflammation and other disease manifestations (i.e., hyperproliferation) may be slower to respond, such as in plaque psoriasis. In any event, the use of TCS for so many disorders reflect the multitude of biological properties that CS exert on both the epidermis and dermis.[1–3]

Clinical Relevance of Impairments of the Epidermal Permeability Barrier

An important area that is commonly overlooked when discussing TCS therapy, especially for chronic inflammatory dermatoses, is the impact that TCS use exerts on the structural and functional integrity of the stratum corneum (SC).[5–8] However, before addressing if there are any relationships between TCS use and epidermal barrier impairments, it is important to first recognize that the "epidermal barrier" is a collection of many individual barrier responsibilities that are often inter-related.[5,6] The SC serves as the central focus of many epidermal barrier functions.[5–9] These include the permeability barrier, antimicrobial barrier, immune response barrier, and photoprotection barrier.[5,6] The SC permeability barrier is the function that is most commonly discussed as the control of epidermal water flux, content, and gradient is critical to maintaining the structural and functional integrity of the epidermis and preventing the adverse sequelae of faulty barrier self-repair mechanisms that persist if permeability barrier impairment is not corrected.[5–9]

How does prolonged SC permeability barrier impairment and propagation of self-repair mechanisms lead to xerotic and inflammatory skin changes and precipitation of eczematous dermatitis? When the SC is impaired, transepidermal water loss (TEWL) is increased and skin hydration is decreased.[5–8] This leads to decreased water content and disruption of the homeostatic water gradient within the epidermis, especially the SC, leading to impaired function of several water-dependent enzymes involved in normal desquamation and maintaining normal SC structure.[5–12] In response to the increase in TEWL, the epidermis initiates self-repair mechanisms to restore and maintain the SC permeability barrier.[5–8] First, there is an immediate release of stored lipids into the lower SC to help support the SC intercellular lipid bilayer, which functions to modulate TEWL.[5,6,13] There is also an upregulation of both epidermal physiological lipid production and the conversion of profilaggrin to filaggrin in the epidermal granular layer, which increases SC humectancy (water retention) by producing more filaggrin-derived natural moisturizing factors (NMFs) within the SC. However, another consequence of increased TEWL, that is often overlooked, is the increased production of "jump start" pro-inflammatory cytokines (i.e., tumor necrosis factor alpha [TNF-α], interleukin [IL]-1, IL-6) which induce inflammation and epidermal hyperproliferation.[5–9,14–20] If SC permeability impairment is not corrected by self-repair or exogenous application of a topical barrier repair formulation, increased TEWL continues and the compromise of the normal function and structure progresses and is amplified. This leads to visible dryness (xerosis), decreased skin elasticity and resiliency, fissuring, hyperkeratosis, and erythema secondary to inflammation (i.e., eczema craquele, eczematous dermatitis). Hence, eczematous dermatitis can be precipitated by compromise of the SC permeability barrier, which increases TEWL and decreases SC water content and ultimately causes a cascade of pathways that, if left unchecked, produce xerotic and eczematous dermatological disorders.[5–9,20–24]

Atopic skin/atopic dermatitis. In patients with atopic skin/atopic dermatitis (AD), there are innate impairments of SC barrier functions including the permeability barrier, antimicrobial barrier, and immune response barrier.[5–9,18,21,23] One major SC impairment in atopic skin that directly affects the permeability barrier, even when visibly normal between eczematous flares, are deficiencies in ceramides that are major components of the SC intercellular lipid bilayer, which control water flux and the magnitude of TEWL.[5–8,21–24] Another aberration that directly affects the SC permeability barrier, found in some patients with atopic skin/AD, is the presence of loss-of-function mutations in the filaggrin gene, which lead to decreased SC humectancy as production of NMFs is impaired.[9,18,25,26] Hence, patients with atopic skin are less capable of self-correcting and maintaining SC permeability function, which predisposes them to easier triggering of inflammation and eczematous flaring when TEWL is increased and allowed to persist.

Atopic skin/AD also exhibits diminished ability to detect and respond to certain microbial pathogens.[5,9] A decrease in some antimicrobial peptides (AMPs) that normally provide an important line of

TABLE 1. Disease state-associated impairments of epidermal barrier functions

DISEASE STATE	IMPAIRMENTS
ATOPIC SKIN/ATOPIC DERMATITIS[a-e]	• Decrease in ceramide subfractions in stratum corneum (SC) in both lesional and nonlesional skin • Reduced epidermal acid and neutral sphingomyelinase in atopic dermatitis (AD) in both lesional and nonlesional skin • Sphingomyelin deacylase activity increased in AD in both lesional and nonlesional skin (reduces ceramide) – Decrease in filaggrin due to loss-of-function filaggrin gene mutation results in decrease production of natural moisturizing factors (NMFs) – Reduction in multiple antimicrobial peptides increases susceptibility to bacterial colonization and cutaneous infections – Decreased expression of toll-like receptor-2 (TLR2) reduces ability to detect and respond to microbial pathogens – Colonization of skin and nares with *Staphylococcus aureus* with superantigen production (can trigger and/or prolong flare) – Dysregulation of innate and acquired immune response with hyper-responsiveness to cutaneous irritants and allergens (Th2 imbalance, Th2–Th1 shift) – Increase in certain neuropeptides (i.e., substance-P) in AD-affected skin
PSORIASIS[a,f,g]	• Abnormal disposition of lamellar bodies (LBs) in some psoriasis phenotypes • LBs in large quantity present in evolving plaque psoriasis, but many entombed in corneocyte cytoplasm resulting in impaired lipid deposition into the SC intercellular space • LBs contents secreted into SC intercellular space in chronic plaque psoriasis • Ceramide-1 decreased in psoriatic plaques compared to uninvolved skin and controls; correlated with increased TEWL • Increases in TEWL: erythrodermic > developing plaque > chronic plaque > nonlesional skin • Alterations in epidermal differentiation including changes in formation of the cornified cell envelope, increase in involucrin, decrease in filaggrin expression, increase in hyperproliferative keratins (K6, K16), and decrease in markers of terminal differentiation (K1, K10) • Increase in AMPs (less susceptibility to infection than AD)

[a]Del Rosso JQ, Levin J. The clinical relevance of maintaining the functional integrity of the stratum corneum in both healthy and diseased skin. *J Clin Aesthet Dermatol*. 2011;4(9):22–42; [b]Proksch E, Elias PM. Epidermal barrier in atopic dermatitis. In: Bieber T, Leung DYM, eds. *Atopic Dermatitis*. New York: Marcel Dekker; 2002:123–143; [c]DiNardo A,Wertz PW. Atopic dermatitis. In: Leyden JJ, Rawlings AV, eds. *Skin Moisturization*. 1st ed. New York: Marcel Dekker; 2002:165–178; [d]Cork MJ, Danby SG, Vasilopoulos Y, et al. Epidermal barrier dysfunction in atopic dermatitis. *J Invest Dermatol*. 2009;129:1892–1908; [e]Del Rosso JQ. Repair and maintenance of the epidermal barrier in patients diagnosed with atopic dermatitis: an evaluation of the components of a body wash-moisturizer skin care regimen directed at management of atopic skin. *J Clin Aesthet Dermatol*. 2011;4(6):45–55; [f]Ghadially R. Psoriasis and ichthyosis. In: Leyden JJ, Rawlings AV, eds. *Skin Moisturization*. 1st ed. New York: Marcel Dekker; 2002:166–178. [g]Nestle FO. Psoriasis. In: Gaspari AA, Tyring SK, eds. *Clinical and Basic Immunodermatology*. London: Springer-Verlag;2008:207–216.

innate defense against microbial colonization and infection and polymorphisms in toll-like receptor-2 (TLR2) that cause deficient detection of some bacterial organisms and impairment of permeability barrier repair, have been identified in atopic skin/AD.[27–34] These impairments noted in atopic skin/AD that allow *Staphylococcus aureus* and other microbial organisms to gain unopposed access to skin and proliferate in the presence of antimicrobial defense that is inherently deficient provide some rational explanation for the high prevalence of both *S. aureus* colonization (skin, nares) and cutaneous infection in atopic skin/AD.[5,6,9,27–34,84,85]

Psoriasis. Psoriasis is associated with SC abnormalities that differ from those seen in atopic skin and may vary depending on the type and

severity of psoriasis.[5,6,35] Although it is not known whether SC permeability barrier impairment correlates with precipitation of psoriasis, repair and maintenance of the SC permeability barrier is suggested to prevent the emergence of both xerotic and eczematous skin changes.[5,6,35–38] The morphological, physiochemical, and functional SC impairments associated with atopic dermatitis and plaque psoriasis are outlined in Table 1.

Effects of Topical Corticosteroids on Epidermal Barrier Structure and Function

Continuous application of a TCS to skin is well known to cause visible adverse changes related primarily to alterations in dermal matrix and vasculature, presenting as atrophy, purpura, telangiectasias, and irreversible striae.[1–3] Other morphological, physiochemical, and functional changes have been demonstrated in association with TCS use, which can have direct implications related to epidermal barrier functions. These include epidermal atrophy; reduction in keratinocyte size; decreases in ceramides, free fatty acids, and cholesterol; and increase in TEWL.[39,40] After as early as three days of application of topical clobetasol on both human and murine skin, subclinical adverse changes in the epidermis were noted that reflected deterioration in epidermal barrier homeostasis.[40] These included delayed barrier recovery, abnormal SC integrity and cohesion, and the global inhibition of lipid synthesis.

This aforementioned study that demonstrated TCS-induced epidermal changes also demonstrated barrier repair with improvement in SC cohesion and integrity after application of a physiological lipid-based moisturizer.[40] These observations suggest that use of topical barrier repair as an adjunct to TCS therapy is a rational approach to counter the adverse effects of the TCS on the SC permeability barrier that will be present upon discontinuation of the TCS. When a TCS is used without adjunctive barrier repair therapy, the impairments of the SC permeability barrier that are contributed by the TCS may serve as a trigger that precipitates an earlier eczematous flare as compared to when adjunctive barrier repair therapy is used concomitantly.

In another study, application of betamethasone valerate (BMV) to AD lesional skin normalized expression of filaggrin, an SC protein important for structure and production of NMFs, and loricrin, an important protein of the cornified envelope that provides structural strength to the SC.[41] However, BMV reduced the expression rate-limiting enzymes for SC lipid synthesis, involucrin, and small proline-rich peptides, the latter two involved with SC binding of ceramides. It appears that TCS, such as BMV, may alter some components of SC barrier repair, primarily those involving restoration of lipids.

In a second study evaluating application of BMV or triamcinolone acetonide to AD-affected skin for three weeks and separately to skin of mice with essential fatty acid deficiency, both TCSs produced marked reduction in several AMPs including human beta defensin (hBD)-2, hBD-3, psoriasin, and cathelicidin (LL-37).[42]

In a separate study, BMV applied to AD-affected upper arm skin for three weeks improved SC hydration and TEWL parameters, normalized epidermal differentiation, and reduced epidermal proliferation. However, electron microscopic evaluation indicated inconsistent extracellular lipid bilayers and only partially filled lamellar bodies after BMV treatment, again supporting that TCS application affects the primary lipid structure of the SC permeability barrier.[43] An additional study evaluating BMV application to murine skin applied for three days before tape stripping demonstrated that BMV markedly delayed barrier repair as compared to vehicle.[44]

In a study that evaluated biopsies taken from atrophic facial skin in patients who were treated with prolonged TCS application over a mean of 15 months (range 4 months–4 years), the effects of TCS versus control were assessed. The results demonstrated lower neutral lipid content, decreased SC (corneocyte) layers, increased TEWL, reduced numbers of intercellular lipid lamellae, and a decrease in membrane-coating granules in the granular layer in the TCS-treated facial skin.[45]

In a murine skin study, the untoward effects of TCS application on the SC permeability and antimicrobial barriers may be partially mitigated by the simultaneous use of a topical vitamin D analog. Topical calcitriol was shown to counteract the impairment of the SC permeability barrier and the antimicrobial barrier induced by TCS.[46] When compared to the control group, the addition of topical calcitriol to TCS therapy markedly improved TEWL, increased lamellar body activity, and significantly upregulated major enzymes involved in lipid synthesis (HMG-CoA fatty acid synthase, serine-palmitoyl transferase). To add, TCS application reduced AMP expression in murine skin, such as cathelicidin-related AMP (CRAMP) and mouse beta-defensin 3 (mBd3), with application of calcitriol, a vitamin D analog, reversing the reduction of AMP expression.[46]

TABLE 2. Effects of topical corticosteroids on epidermal barrier structure and function

APPLICATION	POSITIVE BARRIER EFFECTS	ADVERSE BARRIER EFFECTS
BETAMETHASONE VALERATE[41] LESIONAL SKIN (ATOPIC DERMATITIS)	• Normalized expression of filaggrin (producer of natural moisturizing factor, involved in normal epidermal differentiation) • Normalized expression of loricin (a protein of cornified envelope, contributes to stratum corneum structural support)	• Decreased expression of rate-limited enzymes involved in stratum corneum lipid synthesis • Reduced expression of involucrin and proline-rich peptides (involved in binding of ceramides in the stratum corneum)
BETAMETHASONE VALERATE[43] LESIONAL SKIN (ATOPIC DERMATITIS)	• Decreased transepidermal water loss • Increased epidermal hydration • Normalized epidermal differentiation	• Partially filled lamellar bodies • Inconsistent intercellular lipid bilayers

To summarize, application of TCS has been associated with contradictory effects on TEWL, with reported effects on the epidermis that have been reasonably consistent including delayed barrier recovery, decreased SC lipids, alterations of the intercellular lipid bilayer and lamellar bodies, and decrease in AMPs.[5–9,39–46] The clinical relevance of these TCS-induced epidermal changes may relate to incomplete reversal of subclinical pathophysiological changes that contribute to development of xerotic and eczematous changes with an increased potential for earlier disease recurrence. This concept supports the application of TCS formulated in "barrier friendly" vehicle formulations to lesional skin and adjunctive topical barrier repair therapy to lesional and nonlesional skin in AD, and possibly other eczematous dermatoses and psoriasis.[5,6,47–54] The morphological, physiochemical, and structural effects induced by TCS on the epidermis, especially the SC, are depicted in Table 2.

The Clinical Relevance of Topical Corticosteroid-induced Epidermal Changes and Effects on Barrier Functions

Due to multiple modes of action, application of a TCS of adequate potency produces a rapid onset of therapeutic activity for the treatment of eczematous dermatoses and seborrheic dermatitis, and is capable of improving or clearing plaques of psoriasis over a period of two to eight weeks depending on the agent used, plaque thickness, and severity.[1–3] However, once the TCS is discontinued, the challenge is to sustain control of chronic-recurrent dermatoses, such as AD and plaque psoriasis, as prolonged TCS use without adequate interruption is associated with adverse reactions, such as atrophy and striae, and possibly systemic effects with widespread application.

It has been shown in AD that continued application of a topical anti-inflammatory agent, such as a mid-potency TCS or topical calcineurin inhibitor, twice weekly to sites prone to repeated eczematous flares (i.e., antecubital, popliteal, neck, legs/ankles, wrists), along with widespread application of a barrier repair agent to address low-grade eczematous changes, xerosis, and underlying SC barrier abnormalities, markedly prolongs the duration between flares.[55,56] It is well recognized that properly formulated barrier repair therapy can reduce TEWL, restore SC hydration, replenish SC lipids, expedite SC permeability barrier repair, and reduce eczematous dermatitis.[5,6,48–54,57–59] Taking it one step further, in patients treated with a mid-potency TCS for three weeks to clear AD, those subjects who used topical barrier repair therapy over the ensuing 26 months demonstrated a median time to relapse of more than 180 days (duration of the study) compared with 30 days for those subjects who applied nothing over the follow-up period. Sixty-eight percent of the subjects using barrier repair therapy and 32% of the untreated patients remained free from eczematous flares during the 180-day observation period.[60]

There is some evidence suggesting that newer barrier repair formulations, which incorporate physiological lipids and other optimized components, offer some clinically applicable advantages over conventional moisturizers, although further study is needed.[5,6,21,48–53] The more recent specialized physiological lipid/ceramide-based products are believed to provide "moderate efficacy improvements" and may decrease the

likelihood of disease exacerbation.[61,62] There is some evidence to support that application of a well-formulated barrier repair therapy alone may concurrently improve both permeability barrier function and antimicrobial barrier function.[63,64]

In AD-affected human skin, a ceramide-containing barrier repair agent was equivalent to topical tacrolimus in restoring permeability barrier function (decrease in TEWL), improving the antimicrobial barrier (increase in antimicrobial peptides hBD-2 and LL-37), and reducing cytokines associated with AD (decrease in IL-4).[64] Application to AD-like murine skin of a mid-potency TCS formulated in a ceramide-containing physiological lipid vehicle was superior to the TCS formulated in a polyethylene glycol/ethanol vehicle in restoring epidermal barrier function, decreasing inflammatory cell infiltration, and reducing cutaneous adherence of *S. aureus* organisms.[63] Based on currently available data, incorporation of a barrier repair agent into the regimen with TCS therapy optimizes therapeutic effects when treating AD and may prolong the duration of clearance when continued after the TCS has been stopped. It may also be helpful to use a TCS that is incorporated into a "barrier friendly" vehicle formulation. For example, hydrocortisone butyrate 0.1% has been incorporated into a lotion formulation that contains no short-chain alcohols, contains safflower oil as a source of the physiological lipid linoleic acid, and utilizes long-chain fatty alcohols and emollients for spreadability and some occlusivity to replenish the barrier. This and other formulations that do not degrade the SC permeability barrier are important as a vehicle that disrupts the SC may interfere with clinical improvement. Additionally, as previously discussed, the deleterious effects of TCS on barrier function may be improved with the application of physiological lipids, which may be accomplished with a lipid-rich TCS vehicle in addition to barrier repair maintenance therapy.

Conclusion

Topical corticosteroids are a very important part of the treatment of many skin disorders, especially eczematous dermatoses. When utilized properly and judiciously, these agents often achieve excellent results in clearing or markedly improving many dermatological disorders. As their long-term use is associated with untoward effects, and their modes of action are primarily suppressive rather than curative for treatment of chronic inflammatory skin disorders, the incorporation of nonsteroidal topical approaches that are effective and safe for prolonged use is always welcome. As eczematous dermatoses, such as atopic dermatitis, are associated with impaired epidermal permeability barrier function as part of the pathophysiology of the disease state, barrier repair and maintenance are believed to be important components of therapy. As some studies have shown that topical corticosteroids, despite their ability to decrease inflammation through several mechanisms, induce abnormalities in lipid synthesis and intercellular bilayer structure in the stratum corneum, which appear to prolong epidermal barrier recovery and may be a source of earlier eczematous flaring if measures to provide barrier repair are not undertaken. Although topical corticosteroids are applied only to sites affected by the skin eruption, the incorporation of "barrier friendly" excipients into the vehicle that improve stratum corneum permeability barrier function and integrity is very rational.

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