CLINICAL INSIGHTS

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Cloderm® Cream (clocortolone pivalate 0.1%): A Moisturizing, Hydrating Formulation Enhances Epidermal Barrier Function

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The stratum corneum (SC) is a dynamic structure marked by multiple complex interactions and feedback loops.[1-4] Self-repair of the permeability barrier has been documented; i.e., the SC can quickly adapt and initiate natural physiologic recovery. Dysfunction of the SC is associated with specific disease states, perhaps most notably atopic dermatitis (AD), but also rosacea, psoriasis, and other inflammatory cutaneous disorders. More precisely, researchers and clinicians believe that AD may be driven in part by poor epidermal barrier function, perhaps as a result of impairments in the permeability, immune response, and antimicrobial barriers. Of note, patients with atopic dermatitis may have relative dysfunction of epidermal barrier function at all times, even during times of disease remission and in skin that clinically appears normal.[2,3,5] This dysfunction may be due to inherent filaggrin deficiency in atopic patients.

Over the last several years, due in part to therapeutic advancements as well as enhanced understanding of the epidermal barrier, treatment approaches for AD have increasingly incorporated "barrier repair" or, at least, "barrier enhancement." The emerging "Outside-In" theory[2] suggests that every AD patient requires application of a skin moisturizing regimen as an integral component of treatment. Other topical treatments, such as corticosteroids or immunomodulators, remain essential to patient care for the treatment of acute inflammation and the associated symptoms that occur during active flares. Ideally, these agents will confer their beneficial anti-inflammatory effects without contributing to further barrier damage. Data show that this is not always the case.

It has been shown that application of some topical corticosteroids can increase TEWL and potentially contribute to epidermal barrier dysfunction.[6,7] In mice, application of topical corticosteroids induced progressive increases in TEWL and a reduction in intercellular lipids in the SC.[7] It is now well known that even short-term use of topical corticosteroids can compromise epidermal barrier function and SC integrity by inhibiting epidermal lipid synthesis.[8] However, certain formulations of topical corticosteroids have been shown to improve skin hydration and reduce TEWL.[9,10] Perhaps the beneficial or detrimental effects of a given topical corticosteroid on TEWL have less to do with the corticosteroid itself than with the vehicle in which it is delivered.[11] Thus, treatment becomes an act of balancing the negative effects of the corticosteroid molecule itself on epidermal barrier versus the positive impact of the vehicle that delivers the molecule to the SC.

A recent study[12] assessed the effects of Cloderm® Cream (clocortolone pivalate 0.1%, Promius Pharma, LLC) on SC hydration and TEWL. A second study confirmed the results.[13]

STUDY RATIONALE: THE CLODERM CREAM VEHICLE

Cloderm Cream is formulated in a cream base with three ingredients that enhance the SC permeability barrier integrity. (Table 1) These are white petrolatum (an occlusive), mineral oil (an occlusive), and stearyl alcohol (a long-chain fatty alcohol humectant/emollient). Additionally, the cream vehicle does not contain the potential irritants lanolin or fragrance. It does not contain propylene glycol, which can produce cutaneous irritation or contact allergy in some patients when present in higher concentrations.[14] Propylene glycol, a penetration enhancer, is necessary in some topical corticosteroid formulations to facilitate delivery of the active molecule.[15] However, clocortolone pivalate is unique in that the substitution of the pivalate group

TABLE 1. CLODERM® CREAM INGREDIENTS	
Ingredient	**Function**
Clocortolone pivalate	Active ingredient
White petrolatum	Emollient/Occulsive
Mineral oil	Emollient/Occlusive
Stearyl alcohol	Humectant/Emulsifier
Purified water	Vehicle
Carbomer 934P	Thickener
EDTA	Chelating agent
Sodium hydroxide	pH adjuster
Polyoxyl 40 stearate	Emulsifier
Methylparaben, propylparaben	Preservatives
Lanolin-free, Propylene glycol-free, Fragrance-free	

at C-21 increases lipid solubility and thus enhances the permeability of the molecule through the stratum corneum without the help of penetration enhancers.[16]

STUDY DESIGN AND FINDINGS

In order to assess the effects of the formulation on skin moisture and TEWL, an *in vivo* study in healthy volunteers was designed. The study involved 18 healthy female volunteers, 23 to 55 years of age, with no skin disease other than dry skin on the volar forearms. Subjects did not use any moisturizing products or sunscreens for three days before the start of the clinical study. The study employed the Skin Trauma After Razor Shaving (STARS) bioassay. Dry shaving creates SC damage that results in increased TEWL and decreased skin surface hydration levels compared to normal skin sites. Subjects presented to the study site for dry shaving of two areas measuring 5cmx5cm on each volar forearm on Day 1. Subjects returned on Day 2, and five sites on the arm were identified for the study. Skin hydration was measured as capacitance using the Courage + Khazaka Corneometer® CM 825, and TEWL rate was measured using the cyberDERM RG1 Evaporimeter System on each area. These were considered the baseline scores. Then, each of three shaved sites received either Cloderm® Cream, Locoid® Lotion (hydrocortisone butyrate lotion 0.1%, Onset), or Locoid Lipocream® (hydrocortisone butyrate cream 0.1%, Onset). One untreated shaved site was used as damaged non-treated control and one non-shaved site was used as normal skin control. Measurements were repeated one hour, two hours, and four hours after treatment at all five sites; subjects were required to acclimate in an environmentally controlled room with the relative humidity maintained at less than 50 percent and temperature maintained at 19-22°C for 30-45 minutes prior to each set of measurements.

TEWL rates were significantly ($p<0.001$) decreased at one, two, and four hours post-treatment in the dry-shaved sites treated with Cloderm Cream or Locoid Lipocream, compared to the non-treated damaged control site. There were no statistically significant differences between Cloderm Cream and Locoid Lipocream at any time point. Locoid Lotion did not significantly decrease TEWL rates compared to non-treated damaged control site at any time point. Cloderm Cream and Locoid Lipocream reduced TEWL statistically significantly more than did Locoid Lotion. (Figure 1)

Skin surface hydration increased significantly ($p<0.001$) in all three treated sites, compared to the non-treated damaged control, but to different degrees. Cloderm Cream increased skin surface hydration significantly ($p<0.001$) better than did Locoid Lipocream and Locoid Lotion, at all timepoints. There were no significant differences in hydration levels between Locoid Lipocream and Locoid Lotion. (Figure 2)

DISCUSSION

The STARS bioassay is a useful approach to study the effects of products on damaged skin. Dry shaving creates enough skin damage to result in increased TEWL and decreased skin surface hydration compared to non-shaved skin sites. This experimentally induced minor trauma provides a useful model to determine the occlusive and/or moisturizing potential of topical products. One apparent weakness of this study may be the use of healthy volunteers rather than AD patients. However, the STARS bioassay in healthy volunteers provides a more uniform degree of cutaneous damage, hence a low variation in baseline TEWL and skin hydration measurements for all test sites. In contrast, use of lesional atopic skin with different degrees of involvement will provide highly variable baseline and subsequent assessments.

As expected, this study showed that one day after dry shaving (Day 2, pre-treatment), TEWL rates were greatly elevated relatively uniformly (percent relative standard deviation = 26%) in the dry-shaved sites compared to normal non-shaved skin. Similarly, skin surface hydration levels were greatly decreased relatively uniformly (percent relative standard deviation = 35%) in the pre-treatment dry-shaved sites. Thus, the low vari-

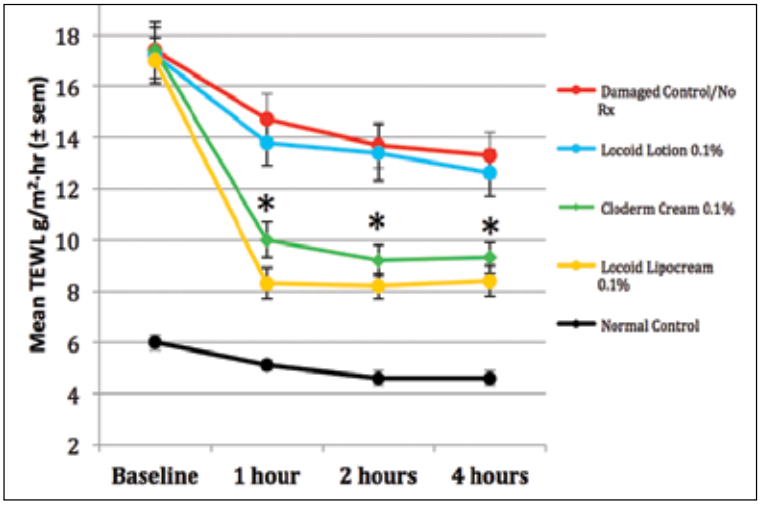

FIGURE 1. TEWL Results - * P < 0.001 compared to all other higher values

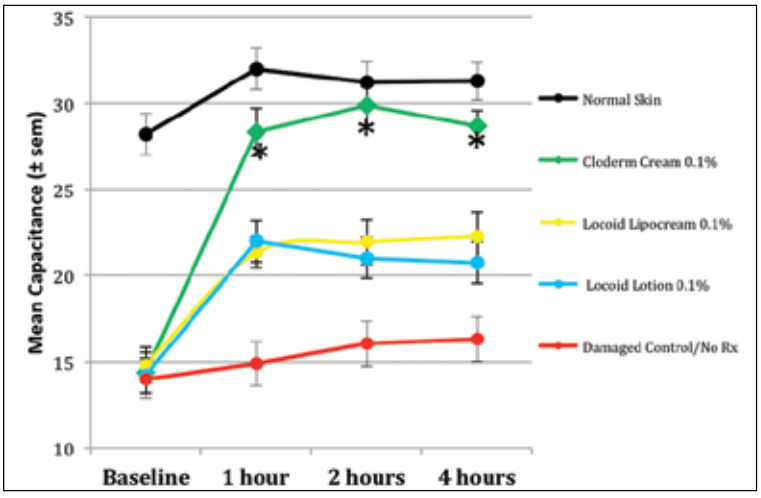

FIGURE 2. Skin Hydration Results - * P < 0.001 compared to all other lower values

ability of the data allowed a small sample size for the study and statistically significant results. Although a short-term study, the STARS bioassay in normal volunteers minimizes the confounding effects of the anti-inflammatory action of the steroid product on AD lesion healing and barrier dysfunction and thus characterizes the vehicle effect on enhancing barrier function quite accurately.

IMPLICATIONS FOR CARE

The products tested in this study all contain occlusive ingredients. As has been previously demonstrated, the relative benefit of occlusive ingredients within a given formulation can be variable.[16] TEWL results revealed that Cloderm Cream and Locoid Lipocream had comparable occlusive effect, while Locoid Lotion did not have significant occlusive effect compared to the control. However, application of Cloderm Cream to skin after razor shaving provided better hydration than did application of Locoid Lipocream or Locoid Lotion. This study shows that Cloderm Cream is an excellent skin moisturizer and its use enhances barrier function by providing occlusion and subsequent skin hydration. A second, identically designed study confirmed these results.

In the current clinical setting, where physicians approach management of AD in light of the "Outside-In" theory, it is important to select treatment options that will help to support the epidermal barrier for atopic dermatitis patients. When a mid-potency topical steroid is appropriate, the choice of Cloderm Cream helps skin hydration and enhances barrier function while effectively addressing the active inflammation and associated symptoms of atopic dermatitis. ■

Dr. Kircik is a consultant and speaker for Promius Pharma.

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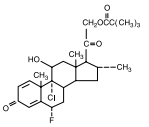
RxOnly

Cloderm® Cream, 0.1%
(clocortolone pivalate)

FOR TOPICAL DERMATOLOGIC USE ONLY–
NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE.
WARNING: KEEP OUT OF REACH OF CHILDREN

DESCRIPTION: Cloderm Cream 0.1% contains the medium potency topical corticosteroid, clocortolone pivalate, in a specially formulated water-washable emollient cream base consisting of purified water, white petrolatum, mineral oil, stearyl alcohol, polyoxyl 40 stearate, carbomer 934P, edetate disodium, sodium hydroxide, with methylparaben and propylparaben as preservatives.

Chemically, clocortolone pivalate is
9-chloro-6α-fluoro-11β,
21-dihydroxy-16α methylpregna-1,
4-diene-3, 20-dione 21-pivalate.
Its structure is as follows:



CLINICAL PHARMACOLOGY:
Topical corticosteroids share anti-inflammatory, antipruritic and vasoconstrictive actions.

The mechanism of anti-inflammatory activity of the topical corticosteroids is unclear. Various laboratory methods, including vasoconstrictor assays, are used to compare and predict potencies and/or clinical efficacies of the topical corticosteroids. There is some evidence to suggest that a recognizable correlation exists between vasoconstrictor potency and therapeutic efficacy in man.

Pharmacokinetics: The extent of percutaneous absorption of topical corticosteroids is determined by many factors including the vehicle, the integrity of the epidermal barrier, and the use of occlusive dressings.

Topical corticosteroids can be absorbed from normal intact skin. Inflammation and/or other disease processes in the skin increase percutaneous absorption. Occlusive dressings substantially increase the percutaneous absorption of topical corticosteroids. Thus, occlusive dressings may be a valuable therapeutic adjunct for treatment of resistant dermatoses.
(See **DOSAGE AND ADMINISTRATION**).

Once absorbed through the skin, topical corticosteroids are handled through pharmacokinetic pathways similar to systemically administered corticosteroids. Corticosteroids are bound to plasma proteins in varying degrees. Corticosteroids are metabolized primarily in the liver and are then excreted by the kidneys. Some of the topical corticosteroids and their metabolites are also excreted into the bile.

INDICATIONS AND USAGE: Topical corticosteroids are indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS: Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.

PRECAUTIONS: *General:* Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings.

Therefore, patients receiving a large dose of a potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression by using the urinary free cortisol and ACTH stimulation tests. If HPA axis suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid.

Recovery of HPA axis function is generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity.
(See **PRECAUTIONS**-*Pediatric Use*).

If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for the Patient: Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes.
2. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions especially under occlusive dressing.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests: The following tests may be helpful in evaluating the HPA axis suppression:
Urinary free cortisol test
ACTH stimulation test

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.

Studies to determine mutagenicity with prednisolone and hydrocortisone have revealed negative results.

Pregnancy Category C: Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dermal application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.

Nursing Mothers: It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are secreted into breast milk in quantities *not* likely to have deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use: Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing's syndrome than mature patients because of a larger skin surface area body weight ratio.

Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS:
The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings. These reactions are listed in an approximate decreasing order of occurrence:

Burning, Itching, Irritation, Dryness, Folliculitis, Hypertrichosis, Acneiform eruptions, Hypopigmentation, Perioral dermatitis, Allergic contact dermatitis, Maceration of the skin, Secondary infection, Skin atrophy, Striae, Miliaria.

OVERDOSAGE:
Topically applied corticosteroids can be absorbed in sufficient amounts to produce systemic effects (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION:
Apply Cloderm (clocortolone pivalate) Cream 0.1% sparingly to the affected areas three times a day and rub in gently.

Occlusive dressings may be used for the management of psoriasis or recalcitrant conditions.

If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted.

HOW SUPPLIED:
Cloderm (clocortolone pivalate) Cream 0.1% is supplied in 30 gram and 75 gram pump bottles, 45 gram and 90 gram tubes.

30 gram pump bottle	NDC-67857-804-30
75 gram pump bottle	NDC-67857-804-51
45 gram tube	NDC-67857-804-45
90 gram tube	NDC-67857-804-90

STORAGE:
Store Cloderm Cream between 15° and 30° C (59° and 86° F).
Avoid freezing.

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