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Evidence-Based Skincare:
The Importance of Offering Moisturization, Relief, and Protection in Common Skin Disorders

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Evidence-Based Skincare: The Importance of Offering Moisturization, Relief, and Protection in Common Skin Disorders

INTRODUCTION

ORIGINAL ARTICLES

Evidence-Based Skincare: The Importance of Offering Moisturization, Relief, and Protection in Common Skin Disorders

Over the past decade, seismic growth occurred in our basic understanding of the epidermal barrier function and its role in modulating skin health. With the increased attention to epidermal barrier function and strategies to help normalize it, the role of topical skincare and unique formulations designed to capitalize on this knowledge is now paramount. Given the robust armament that now enhances clinical space, there is also a greater demand for evidence supporting the claims that define "moisturization" or "barrier repair." The purpose of this supplement is to provide both the biological basis and clinical impact of several targeted products aimed at specific physiologic and pathologic states including aging skin, diaper dermatitis, occupational irritant dermatitis, and atopic dermatitis.

Even in the healthy aged population, chronologically expected changes occur, including the anatomy and functionality of the skin. The epidermis begins to thin, with an increase in transepidermal water loss and a noticeably dry and scaly skin surface. Furthermore, there is a steep decrease in stratum corneum lipids with age, resulting in a downturn in the level of ceramides further contributing to these changes. In their paper, "Efficacy of a Skin Condition-Adapted Solution for Xerosis and Itch Relief Associated With Aging" Ramsin and Friedman review the characteristic biological changes inherent in skin aging and review the data from several clinical trials utilizing products containing integral elements of the barrier, such as urea.

On the other end of the spectrum, neonates and infants are also burdened by unique biological and situational elements that predispose to irritant contact dermatitis. In his paper "Protective Effect of a Diaper Rash Ointment for Diaper Dermatitis," Dr. Peter Lio reviews the data from a multicenter open-label trial of 60 infants (1 - 36 months) with a known history of recurrent diaper dermatitis showing that an almond oil based ointment confers a protective effect from future episodes of diaper dermatitis, and improves dryness and suppleness of skin.

In a more regional focus, hand dermatitis is the most common occupational irritant and contact dermatitis, which has a major impact on quality of life in certain professional arenas. Dr. Laura Jordan reviews the ins and outs of occupational irritant contact dermatitis and provides a multi-faceted management approach in her paper "Efficacy of a Hand Regimen in Skin Barrier Protection in Individuals With Occupational Irritant Contact Dermatitis."

Lastly, Dr. Lio focuses on the role of moisturization in the disease prototype of itch and xerosis, in his paper "Efficacy of a Moisturizing Foam in Skin Barrier Regeneration and Itch Relief in Subjects Prone to Atopic Dermatitis." In this single center open label study, 26 adults previously diagnosed with AD without active lesions were treated with a single application of an anti-itch foam and reported immediate relief of clinical signs of AD, including pruritus as assessed by both the subjects and the investigators, among other data points, highlighting the important role of barrier repair/restoration in the management of this common and chronic inflammatory disease.

Certainly this supplement provides a whirlwind overview and evidenced based management strategies of cutaneous pathologies all unified by one theme – barrier disruption. Enjoy!

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Efficacy of a Moisturizing Foam in Skin Barrier Regeneration and Itch Relief in Subjects Prone to Atopic Dermatitis

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ABSTRACT

Introduction: Atopic dermatitis (AD) is characterized by impaired epidermal barrier with increased transepidermal water loss (TEWL). Scratching further compromises skin integrity, contributing to a cycle of inflammation. The objective of the present study was to investigate a topical anti-itch foam in improving skin barrier and itch.

Material and Methods: A single center open study was performed on 26 adults previously diagnosed with AD but without active lesions. One leg was treated with a single application of an anti-itch foam. Dryness, scaling, roughness, cracking, and signs of scratching were assessed before, 6, and 24 hours after application. Skin hydration was measured at 24 hours. The same product was applied twice daily for 7.5 days to the other leg, and skin hydration and TEWL were measured at baseline and on days 2, 8, and 10. Pruritus was assessed by volunteers and by a dermatologist.

Results: A significant increase in skin moisture ($P<0.001$) was measured 6 hours after a single application. Scores of dryness, scaling, roughness ($P<0.001$) and cracking ($P=0.002$) were significantly improved up to 24 hours after a single application. After a 7.5-day repeated application period, the anti-itch foam significantly reduced TEWL ($P<0.001$) compared to baseline. Skin hydration significantly improved ($P<0.001$) in the same time period. 48 hours after the last application, these improvements remained significant ($P<0.001$).

Conclusions: The anti-itch foam improved the skin barrier. It provided immediate relief of clinical signs of AD including pruritus. Moreover, it delivered a long-lasting moisturizing effect, comforting the skin, and improving overall skin condition.

J Drugs Dermatol. 2016;15(suppl 11):s77-80.

INTRODUCTION

Skin prone to atopic dermatitis (AD) is commonly characterized by an impaired epidermal barrier that results in increased transepidermal water loss (TEWL) and leaves the skin rough, dry, and itchy.[1] Subsequent scratching behavior further compromises the integrity of the skin, contributing to a cycle of inflammation.[2] This "itch-scratch cycle" fuels the disease and likely leads to increased penetration of irritants, allergens, and infectious agents that cause persistent inflammation in the skin and may actually lead to the development of other immunologic alterations.[2,3] Although the barrier defect has been considered a secondary phenomenon in some models,[4] the most modern conception of the disease suggests that skin barrier function is a fundamental component of AD that must be addressed.[5]

It is well established that appropriate moisturizers can help restore barrier function and alleviate symptoms of AD.[6,7]Further, topical anti-itch preparations provide direct relief of pruritus but also likely work to abate the itch-scratch cycle.[8]

The anti-itch foam preparation used in the study was formulated with glycerol, a powerful humectant which also has anti-irritant, barrier-restoring, and even antimicrobial effects, all of which make it an excellent choice in patients with AD.[9] Additionally, the foam contains a proprietary synthetic avenanthramide based on the active ingredient in colloidal oatmeal that possesses anti-irritant, anti-itch and antihistaminic properties.[10,11]Remarkably, this component has been shown to actually reduce redness and itch in irritated skin as a monotherapy.[12]

The objective of the present study was to investigate a topical anti-itch foam in skin barrier regeneration and itch alleviation.

MATERIALS AND METHODS

A single center open clinical study was performed. A total of 42 subjects were screened, and 26 subjects were enrolled (average age, 30.4; range, 21.6-44.7 years) with dry and pruritic skin who had previously been diagnosed with AD, but were without active lesions at enrollment (Table 1).

One leg was treated with a single application of an anti-itch foam. Clinical scores for dryness, scaling, roughness, cracking, and clinical signs of scratching were assessed by a dermatologist before, 6, and 24 hours after the application. In addition, skin hydration was measured at 24 hours.

The same product was applied twice daily for 7.5 days to the other leg. Skin hydration and TEWL were measured at baseline and on days 2, 8, and 10 by means of corneometry and tewametry. Volunteers assessed pruritus intensity during the study using

TABLE 1.

Demographic Data and Baseline Characteristics

		(N=26)
Age (years)	N	26
	Mean ± SD	30.4 ± 6.0
	(Min,Max)	(21.6,44.7)
BMI ($kg.m^{-2}$)	N	26
	Mean ± SD	24.4 ± 4.0
	(Min,Max)	(17.1,32.8)
Gender	N	26
	Female	20 (76.9%)
	Male	6 (23.1%)
Skin phototype	N	26
	II	1 (3.8%)
	III	22 (84.6%)
	IV	1 (3.8%)
	V	1 (3.8%)
	VI	1 (3.8%)

a visual analog scale. Pruritus severity was also assessed by a dermatologist based on evaluation of the skin and interview of the volunteers.

The intra-individual difference between before and after application was analyzed using either a Wilcoxon Signed Rank test or a paired Student t-test depending on the distribution of the population, testing the hypothesis of equality. The *P*-value was to be less than 0.05 to declare significance.

RESULTS

At day 1 (baseline), 100% of patients reported itching and scratching and 88% of patients reported redness. At day 8, 50% of patients (13/26) did not have any itching sensations, 58% of patients (15/26) reported not needing to scratch, and 88% of patients (23/26) did not have redness due to scratching.

Clinical scores of dryness, scaling, roughness ($P<0.001$), and cracking ($P=0.002$) were significantly improved up to 24 hours after a single application (Figure 1).

Corneometry after a single application of product showed that the skin hydration was significantly increased at 6 hours after application and returned to baseline by 24 hours after application (Figure 2).

For the 7.5-day repeated application period, the anti-itch foam significantly reduced TEWL ($P<0.001$) compared to baseline on and beyond day 2. Moreover, skin hydration significantly improved ($P<0.001$) in the same time period (Table 2). Forty-eight hours after the last application, these improvements still remained significant ($P<0.001$).

These results were further supported by volunteer self-evaluations: the itch intensity and urge to scratch was clearly diminished after just one week of product application. This was confirmed by the dermatologist via the pruritus severity assessments (Table 3).

Overall, 7 subjects experienced a total of 8 adverse events of mild to moderate severity. These included rhinopharyngitis, a common cold, headache, and stomach ache and were determined not to be related to the study product. No serious adverse events occurred during the study.

DISCUSSION

In the past decade, there has been an intense focus on the primacy of the skin barrier in the pathophysiology of AD, particularly with the description of mutations in the *FLG* gene encoding filaggrin, a key skin protein in barrier function.[13, 14] However, even in the absence of mutations in *FLG*, the presence of inflammatory mediators actually downregulates filaggrin production, resulting in a functionally impaired skin barrier.[15] At the same time there has been increased attention devoted to itch, the cardinal symptom of AD, but with noted unmet needs for this troublesome problem.[16]

FIGURE 1. Moisturizing foam demonstrates immediate effect on skin prone to atopic dermatitis following a single application.

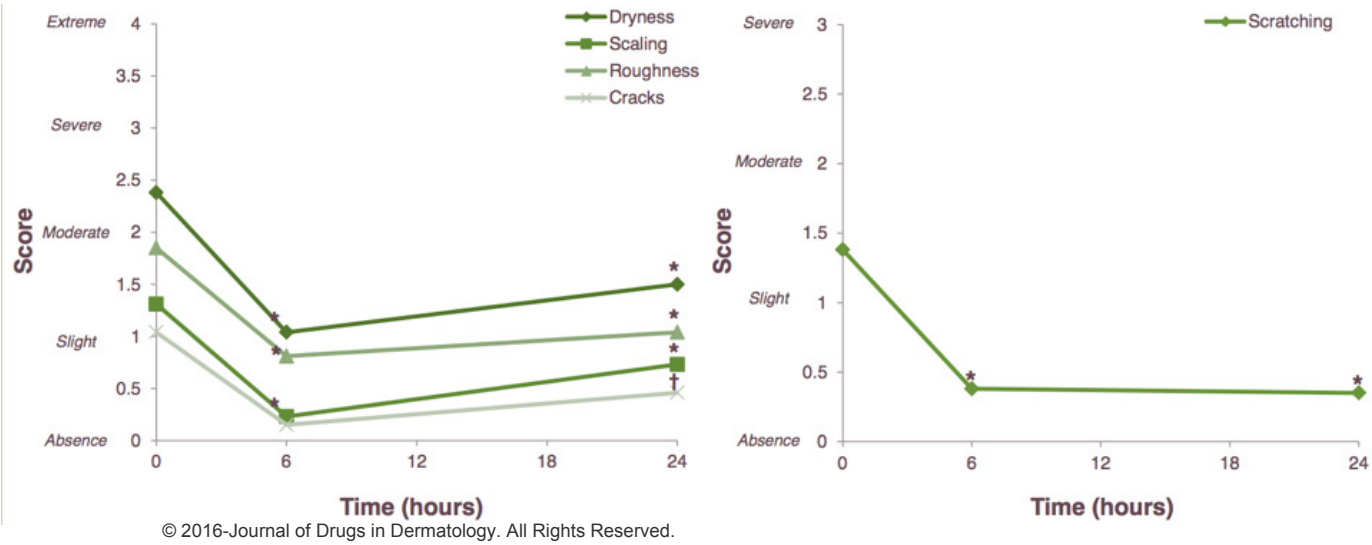
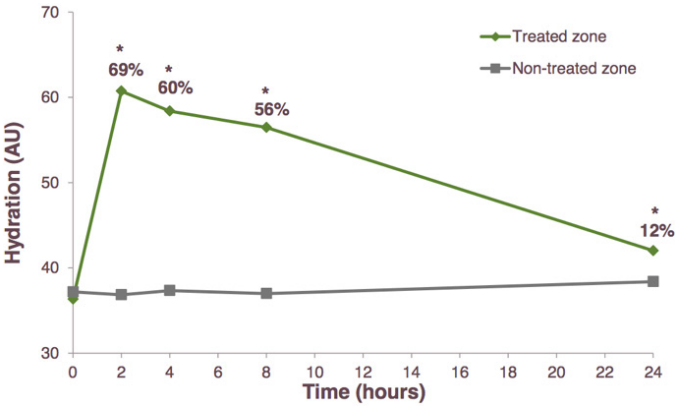


FIGURE 2. Moisturizing foam has an immediate effect on skin hydration after a single application on subjects with AD (n=20).



This study was conducted to assess the effect on skin moisturizing, skin barrier regeneration, and itch relief of an anti-itch foam. The anti-itch foam was demonstrated to strengthen the skin barrier, improving TEWL and corneometry significantly after one application and throughout the longer twice-daily application period. It provided an immediate relief of clinical signs of AD, including pruritus as assessed by both the subjects and the investigators. Moreover, it delivered a long-lasting moisturizing effect, comforting of the skin, and improvement of overall skin condition.

Associated itch was rapidly relieved and need to scratch significantly decreased within the first hours of the foam use. This anti-itch effect persisted for 48 hours after the last application. The early and durable anti-itch effect, the softening effect on the skin, and the cosmetic properties of the foam (easy to apply, rapidly absorbed) resulted in a 100% compliance.

In this study, it was shown that a twice-daily application of the foam induced a skin moisturizing effect detected from the first 24 hours. Following a 1-week treatment period, the skin remained moisturized 48 hours after ceasing product application. The moisturizing effect as assessed by corneometry was long-lasting as it was still observed after 6 hours following a single application but faded after 24 hours, justifying an at least twice-daily regimen. Clinical scores (dryness, scaling, roughness, cracks, and scratch signs) assessed by investigators however were all significantly improved at 24 hours after a single application.

Similarly, the regeneration of the skin barrier started as soon as 24 hours following the first application and this improvement was still significant 48 hours after the last product application.

In conclusion, in patients with dry, sensitive, and itchy skin prone to AD, the anti-itch foam applied twice daily for 7 days proved to have a very good moisturizing effect and to be able to repair a deficient skin barrier. Associated itch was rapidly and durably relieved and need to scratch significantly decreased as well. These suggest that the anti-itch foam product may play a role in managing symptoms of AD.

TABLE 2.

Biophysical Measurements Mean Values Over Time

	Time	N	Mean ± SD	Product effect[1]	Remanence[2] (48h)
TEWL	Day 1 (T0)	26	15.58 ± 7.63	-	
	Day 2	26	11.58 ± 5.54	**p<0.001**	
	Day 8	26	9.07 ± 5.50	**p<0.001**	
	Day 10	26	8.85 ± 3.38	**p<0.001**	p=0.949 (ns)
Corneometry	Day 1 (T0)	26	25.11 ± 8.94	-	
	Day 2	26	28.42 ± 7.71	**p=0.007**	
	Day 8	26	35.35 ± 10.53	**p<0.001**	
	Day 10	26	30.70 ± 9.43	**p<0.001**	**p<0.001**
pH	Day 1 (T0)	26	4.85 ± 0.47	-	
	Day 8	26	5.26 ± 0.65	**p=0.011**	

[1]Compared to baseline (TO)
[2]Compared to day 8

TABLE 3.

Mean Values of Pruritus Over Time

	Time	N	Mean ± SD	Product effect[1]	Remanence[2] (48h)
Intensity (assessed by the subject)	Day 1 (T0)	26	60.50 ± 15.71	-	
	Day 2	26	34.81 ± 23.65	**p<0.001**	
	Day 8	26	18.54 ± 16.82	**p<0.001**	
	Day 10	26	20.50 ± 21.75	**p<0.001**	p=0.562 (ns)
Severity (assessed by the investigator)	Day 1 (T0)	26	3.31 ± 0.84	-	
	Day 2	26	0.96 ± 1.28	**p<0.001**	
	Day 8	26	0.58 ± 0.81	**p<0.001**	
	Day 10	26	0.50 ± 0.86	**p<0.001**	p=0.835 (ns)

[1]Compared to baseline (TO)
[2]Compared to day 8

DISCLOSURES

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Efficacy of a Hand Regimen in Skin Barrier Protection in Individuals With Occupational Irritant Contact Dermatitis

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ABSTRACT

Background: Occupational irritant contact dermatitis (OICD) is a difficult and hard to manage condition. It occurs more frequently in certain occupations where contact with harsh chemicals, use of alcohol-based disinfectants, and frequent hand washing heightens the risk. Treatment for OICD includes patient education in addition to physical, topical, and systemic therapies.
Objective: To review the pathogenesis and treatment options for OICD and evaluate the efficacy of a selective skin-care regimen involving a hand protectant cream alone as well as combined with a repair cream and specific cleanser.
Materials and Methods: A single-center open study was performed comprising 42 healthy male and female adult volunteers prone to occupational irritant contact dermatitis due to frequent wet work or contact with detergents. Between day 0 and day 7, subjects applied a hand protectant cream as needed on both hands (at least twice daily). On days 7 to 14, subjects applied a hand protectant cream and cleanser as needed on both hands (at least twice daily) as well as a repair cream each evening. A diary log was given to each volunteer for application control and for a subjective evaluation of daily tolerability.
Results: In these subjects prone to occupational irritant contact dermatitis, the hand protectant cream applied during the initial 7-day period was effective in restoring the damaged skin barrier and improving the stratum corneum hydration.
A regimen that combined the hand protectant and repair creams with a specific cleanser during a further 7-day period allowed continued improvement of skin hydration and additional clinical benefits while respecting the skin barrier function.
Conclusion: The results of this study support the use of a 3-step approach for patients who are at risk of repeated exposure to external irritants.

J Drugs Dermatol. 2016;15(suppl 11):s81-85.

INTRODUCTION

Irritant contact dermatitis (ICD) is an inflammatory condition triggered by chemical stimuli on epidermal keratinocytes and skin barrier disruption, and both internal and external elements play a role in its pathogenesis.[1] The amount and period of time an individual is exposed to a trigger contributes to that individual's inflammatory response and type of ICD developed.[2] In acute ICD (AICD), an individual experiences dermatitis for less than 3 months which does not occur more than once per year.[3] AICD typically occurs as a result of accidental skin damage by brief contact with a strong irritant.[2] On the other hand, chronic ICD (CICD) lasts for greater than 3 months with 2 or more episodes per year, usually arising after recurrent skin exposure to irritating elements, resulting in minor damage when compared to AICD. In CICD, the skin fails to repair completely between exposures, leading to this more chronic dermatitis, which is most common in wet work occupations such as healthcare and hairdressing.[1,2,3]

Occupational ICD (OICD) is a form of ICD that occurs as a result of working conditions,[4] and hand dermatitis is the most common form of OICD. Childhood dermatitis is a significant predictive factor in the development of hand OICD, and hand washing is its greatest risk factor. Women are affected twice as often as men due to their increased exposure to water and other skin irritants. Hand dermatitis is accompanied by a considerable economic burden, poor long-term prognosis, and impaired quality of life. Locating and avoiding exposure to risk factors could lessen such consequences.[5]

Occupational skin diseases (OSD) are the second most common occupational diseases worldwide with OICD serving as the most frequent OSD, responsible for 77–95% of cases.[1] Globally, OICD affects 5 to 20 of 10,000 full-time workers per year.[6] Eighty percent of OICD occurs in 7 distinct professional groups: hairdressing, healthcare, metalworking, food industry, painters/decorators, construction industry, and cleaning professions.[7] Because OICD is not a life threatening disease, its potential impact on an individual's quality of life is frequently undervalued, and milder forms are often accepted as expected outcomes in certain occupations.[4,6]

Pathogenesis

OICD is a form of ICD, occurring in people who regularly come into contact with irritants during their workday. Such irritants can include chemicals (eg, detergents, organic solvents, disinfectants, water), physical factors (eg, mechanical friction, cold or

dry environment), and mechanical factors (eg, pressure, friction, abrasion).[2,6,8] Direct contact of the skin with an irritating factor can cause skin barrier disruption and a localized inflammatory reaction mediated by innate immunity, leading to OICD.[2,8] Chemical irritants can disrupt the skin barrier by removing lipids or hampering their organization within the stratum corneum. These irritants can also invade the epidermis, interfering with proper extrusion of lipids and harming keratinocytes, which subsequently respond with the release of pro-inflammatory cytokines such as IL-1α, IL-1β, TNF-α, GM-CSF, and IL-8.[1]

Upon recurrent exposure of mild irritants to an impaired skin barrier, reactivation of atopic dermatitis can occur, further worsening skin integrity.[1,6] Frequent exposure to water is a prevailing cause of skin barrier impairment, as indicated by increased transepidermal water loss (TEWL), a marker for barrier function, in such individuals.[9] Consequently, skin barrier impairment is the key step in OICD pathogenesis and is the hallmark of atopic skin.[1] Endogenous elements have also been found as risk factors for development of OICD such as the genetic mutation of the filaggrin gene (FLG) and history of atopic dermatitis during childhood.[2,6]

Treatment options

Treatment options for OICD include education as well as physical, topical, and systemic therapies. Patient education on the avoidance and substitution of irritating elements is recommended in addition to precautions from future outbreaks. Topical therapy options include emollients, corticosteroids, and calcineurin inhibitors while systemic treatments include acitretin, alitretinoin, azathioprine, cyclosporine, corticosteroids, and methotrexate. Patients also have the option for physical treatments such as UVB and PUVA.[3]

Prescribed medications may add to long-term health problems. For example, although topical corticosteroids can prove efficacious in the short term, continuous use beyond 6 weeks is not recommended as they can inhibit stratum corneum repair and induce skin atrophy, thus undermining long-term therapy success. Additionally, while systemic corticosteroids can improve symptoms in an acute reaction, they are not appropriate for use in chronic hand ICD due to their association with long-term side effects including osteoporosis, osteonecrosis, and immunosuppression. Similarly, long-term use of methotrexate is also associated with potential side effects including hepatitis, liver cirrhosis, and pulmonary fibrosis. Cyclosporine use requires careful monitoring and can also be linked with adverse effects such as nephrotoxicity, hypertension, and increased risk of infection. Of note, it is recommended that if the patient does not respond to cyclosporine therapy within 8 weeks, the medication should be discontinued.[3]

Non-pharmacologic treatment is ideal in the treatment of OICD with an emphasis on preventing occurrences.[6] For example, patients should avoid high-risk occupations and causative exogenous factors when possible as well as wear protective gloves and clothing.[1,3,6] For both primary and secondary prevention of OICD, skin care regimens including barrier creams, moisturizers, and cleansers, are encouraged.[1,3,6,11,12] The combined benefit of skin care and wearing gloves is widely recommended as the most important method for protection against OICD.[3,6] Skin protection education and training are an important part of secondary prevention.[1,3]

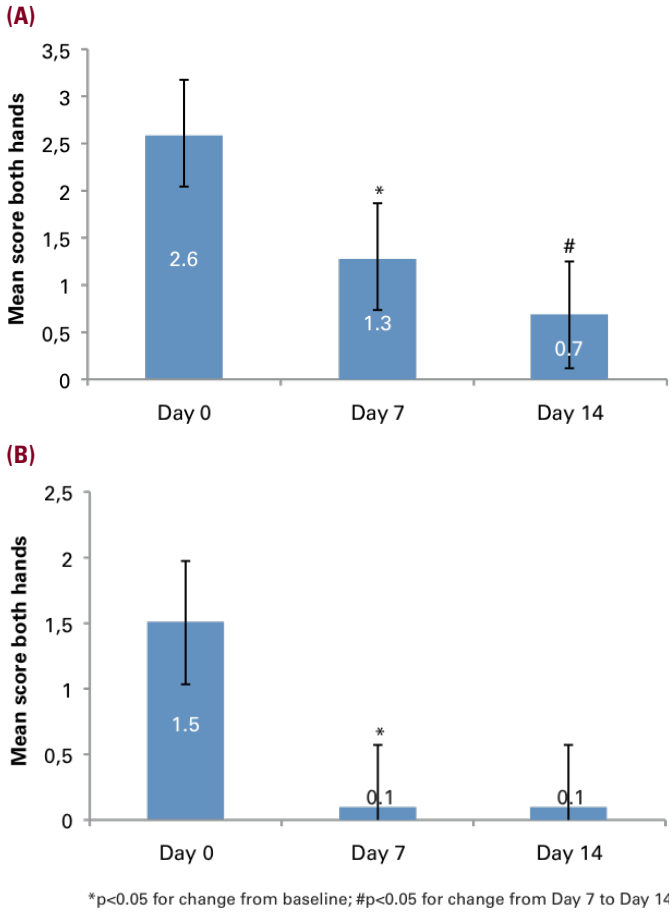
Formulation of skin care products should be carefully selected in the treatment of OICD. Products should be hydrating so that they may accelerate regeneration of the skin barrier and prevent recurrence of OICD.[7,8] They should be individualized to the patient in order to match their skin status, and products that are heavily stressful to the skin should be avoided. Application of these products is recommended after work and after cleansing.[7] Emollients in particular play a principal role in OICD treatment as they serve to normalize the abnormal epidermal barrier, and those with higher lipid content further hasten the healing process.[1,3] Further, regular use of barrier-strengthening skin moisturizers protects against irritants and prevents relapse.[13]

Glycerol is an ingredient widely used for its moisturizing and smoothing effects in different dermatological and cosmetic preparations. It penetrates the epidermis, delivering a moisturizing effect, depending on its concentration (commonly 5–10%). This humectant property hydrates the skin, especially the stratum corneum, aids in cutaneous elasticity, maintains and improves barrier function via reduction in TEWL, accelerates wound healing, and provides both antimicrobial and anti-irritant effects.[14] In a 2008 study, Breternitz et al. evaluated the application of glycerol-based emollient on 24 patients with mild to moderate atopic dermatitis (AD). Patients were treated for 4 weeks twice daily with a glycerol-based (20%) cream. The study found that stratum corneum hydration was significantly higher after glycerol-based application versus placebo at all time points, even remaining higher during washout, indicating a sustainable effect in AD.[15]

Paraffinum liquidum has also been applied to numerous topical applications, acting as both an emollient and an occlusive. A complex mixture of highly refined saturated hydrocarbons, this ingredient traps water in the SC, reducing TEWL and improving distensibility of the skin.[16,17,18] Further, skin softness is increased after use, more so than with wax esters, triglycerides, or fatty acids. It has a limited penetration into the skin and is mainly confined into the epidermal layers and thus considered safe for cosmetic application.[16]

Aluminum chlorohydrate is a commonly utilized aluminum compound found in cosmetic products, acting as an astringent, buffering agent, and antiperspirant. It coordinates is

FIGURE 1. Clinical scoring of (A) dryness and (B) itching on a 5-point scale from 0 (none) to 4 (severe) after 7 days. Protect cream followed by 7 days Protect, Cleanser, and Repair cream.



*p<0.05 for change from baseline; #p<0.05 for change from Day 7 to Day 14

bioaccessible for skin absorption, the FDA considers aluminum chlorohydrate use in topical products to be suitable for use and permitted in concentrations up to 25%.[19,20]

Limnanthes alba seed oil (also known as Meadowfoam seed oil) serves as a non-occlusive emollient which moisturizes the skin. It is rich in long-chain monounsaturated fatty acids and antioxidants. The long-chain fatty acids in this oil are akin to sebum, thus promoting their rapid absorption into the skin.[21]

Niacinamide has also been applied to cosmetic formulations. In vivo it has displayed anti-inflammatory, antipruritic, and antimicrobial properties.[22] Further, it reduces TEWL, improving barrier function. It has demonstrated anti-inflammatory effects in AD, psoriasis, rosacea, and acne vulgaris with topical formulations considered suitable for use in concentrations up to 5%.[22,23] In a 2005 study, Soma et al. investigated the topical application of nicotinamide 2% in 28 patients with atopic dermatitis and found a gradual time-dependent reduction in skin TEWL with a significant reduction between 0 and 8 weeks after treatment (P<0.05). A significant increase in stratum corneum hydration was evident in the nicotinamide group after 4 weeks (P<0.01) and after 8 weeks (P<0.01).[24]

MATERIALS AND METHODS

The ideal approach to managing OICD is a skin-care regimen that works to normalize the abnormal epidermal barrier and prevent relapse. To evaluate this treatment model, a clinical study was conducted from October through November 2015 as a single-center open study, comprising 42 male and female adult subjects with a history of occupational irritant contact dermatitis due to frequent exposure to water and detergents.

During Phase 1 of the study (between day 0 and day 7), subjects applied a hand protectant cream containing paraffinum liquidium as an emollient, aluminum chlorohydrate as an astringent, and glycerin as a humectant at least twice daily and more often if needed. The goal of this application was to create a protective barrier, decrease epidermal permeability, preserve hydration, and repair skin integrity. The role of the 5% aluminum chlorohydrate was to help prevent excess moisture accumulation under glove occlusion by plugging eccrine gland secretions and minimizing the extent to which irritants could penetrate the skin.

FIGURE 2. Subject assessment of (A) dryness and (B) itching (left hand) after 7 days Protect cream followed by 7 days Protect, Cleanser, and Repair cream.

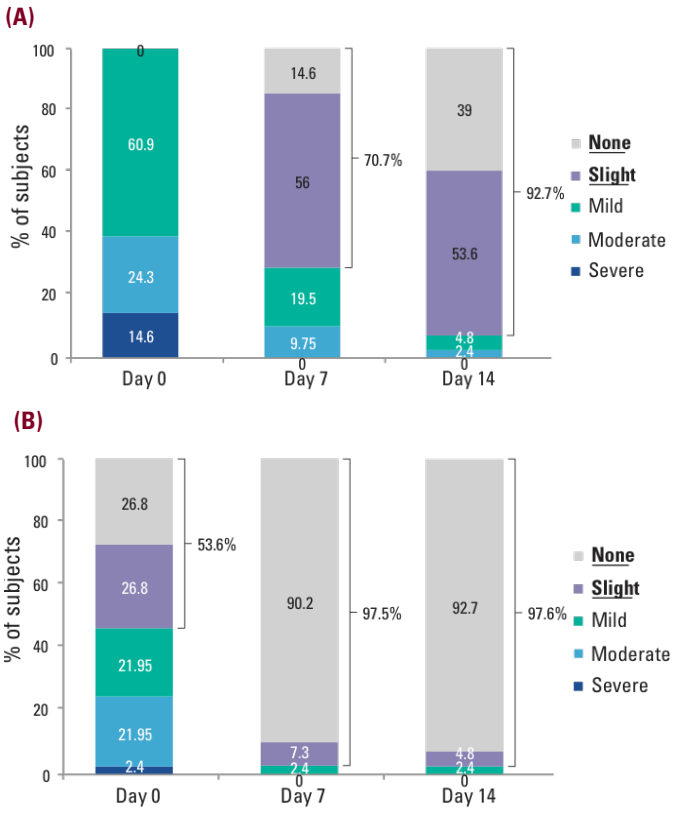
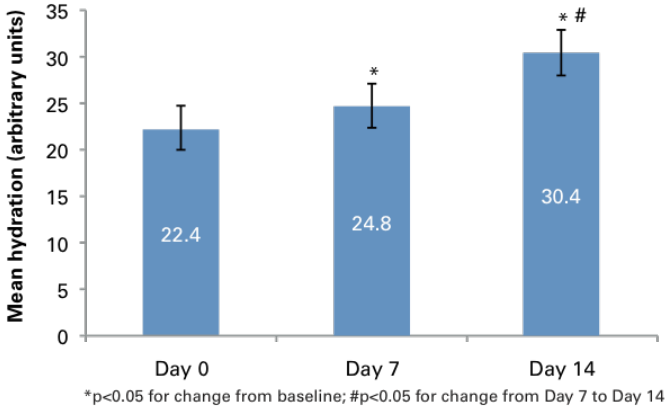


FIGURE 3. Mean hydration score as assessed by corneometer (arbitrary units) after 7 days Protect cream followed by 7 days Protect, Cleanser, and Repair cream.



*p<0.05 for change from baseline; #p<0.05 for change from Day 7 to Day 14

During Phase 2 of the study (between day 7 and day 14), all subjects applied the hand protectant cream and specific cleanser as often as needed (at least twice daily) and applied a repair cream nightly. The repair cream, designed for post-exposure use, was an oil-in-water cream formulated with skin conditioners and 29% lipids. It contained niacinamide (vitamin B_3), panthenol (pro-vitamin B_5), and tocopherol (vitamin E), ingredients which have displayed the ability to stabilize and improve epidermal barrier integrity by supporting the synthesis of barrier lipids, improving hydration, and enhancing anti-oxidative capacity, respectively. The purpose of this lipid composition was to act as an emollient, repairing skin barrier damage that occurs after exposure to common irritants.

Assessments were based on skin roughness, dryness, softness, discomfort, desquamation, fissure, erythema, burning, itching, edema and overall irritation. Each item was assessed on a 5-point scale (0=none, 1=slight, 2=mild, 3=moderate, 4=severe). Subjects in the study were also given a self-assessment questionnaire that allowed them to evaluate daily tolerability subjectively.

Corneometer and transepidermal water loss were included as biophysical measurements of hydration. Imaging via high-resolution UVA-light video camera and confocal microscopy were also utilized to assess treatment efficacy. Adverse events were collected during the study period, and tolerability was recorded in a subject diary.

RESULTS

Results from the clinical scoring illustrated a significant improvement (P<0.05) in skin roughness, dryness, softness, discomfort, desquamation, fissure, burning, and itching. Erythema and overall irritation decreased without reaching a statistical significance, and edema remained unchanged.

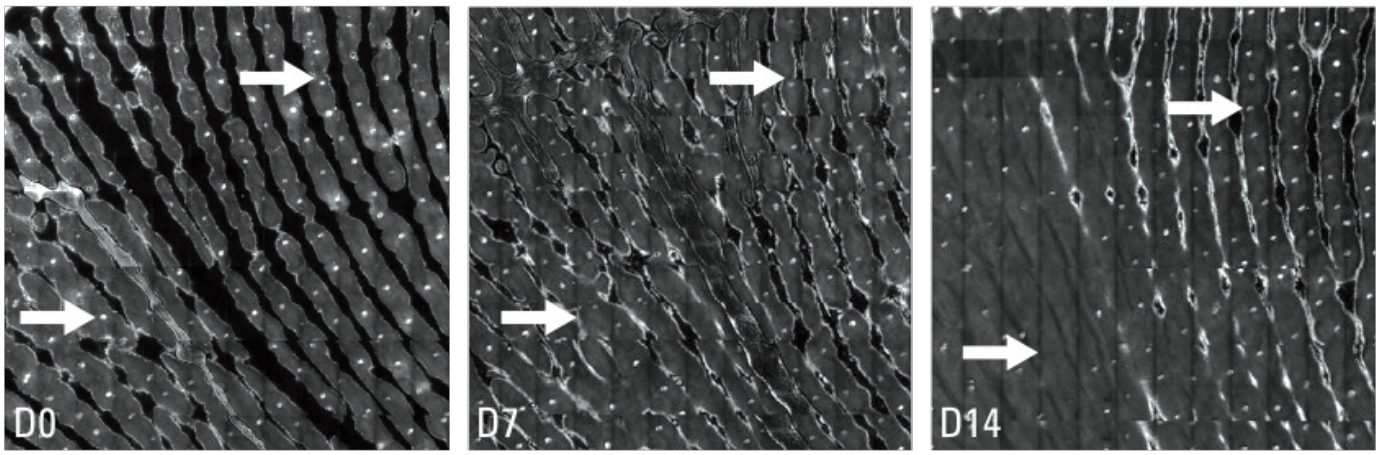
A marked improvement was observed by day 7 in roughness, dryness, softness, and skin discomfort, which continued to significantly improve (P<0.05) up to day 14. The mean dryness score decreased by 50% by day 7 from 2.6 to 1.3 (7 days use of the hand protectant cream) and further continued to decrease to 0.7 by day 14 (7 days with the hand protectant cream, specific cleanser, and repair cream; Figure 1a).

The mean itching severity score significantly decreased during the first week, and the effect was sustained up to day 14 (Figure 1b).

Subject Assessment

In those subjects prone to occupational irritant contact dermatitis, all had mild, moderate, or severe dryness on day 0 before application. After 7 days applying the hand protectant cream,

FIGURE 4. Confocol microscopy showing a visible decrease of the intensity of pores filled by the protect cream. D=day



70.6% of the subjects reported having none or only slight dryness (Figure 2a).

The proportion of subjects reporting having none or only slight itching was 97.5% on day 7 and 97.6% on day 14 (Figure 2b).

Skin hydration

Transepidermal water loss decreased by 5% on day 7 (P=0.012) and then remained stable, demonstrating that the cream respected the skin barrier function. Hydration had increased by 18.9% between baseline and day 7 (P=0.0142) and continued to improve by 30.7% from day 7 to day 14 (P=0.0199), giving an overall difference from baseline to day 14 of 55.4% (P< 0.05; Figure 3).

To further illustrate the improvements, confocal microscopy was performed on the palmar side of the hand. Images showed a decrease in the visibility of the sweat ducts on day 7 and day 14 and an enhanced hydration aspect (Figure 4).

Safety

All products were well tolerated with only 2 of the 41 subjects included in the safety population experiencing related adverse events (1 tingling sensation after the first application and 1 burning sensation after the first application).

DISCUSSION

Occupational contact dermatitis is the most frequent cause of occupational skin diseases with its subtypes comprising irritant contact dermatitis and allergic contact dermatitis.[1] Occupational irritant contact dermatitis most frequently occurs in individuals coming into regular contact with irritants during their workday.[2,6,8] Direct contact of an irritant with the skin can disrupt the skin barrier, causing a local inflammatory reaction mediated by innate immune system components and lead to OICD.[2,8] Diagnosis of OICD rests upon a multi-faceted approach and exclusion of other skin diseases as no specific diagnostic test currently exists.[1] OICD can have a significant negative impact on an individual's quality of life which is often discounted.[4,6] A variety of treatment options exist for OICD. However, emphasis on a preventative hand regimen is highly recommended as skin care products can help repair the skin barrier and prevent recurrence of OICD.[7,8] Emollients in particular are important for OICD prevention and repair as they are able to normalize the disrupted epidermal barrier.[1]

CONCLUSION

In these subjects prone to occupational irritant contact dermatitis, the hand protectant cream when applied alone during the initial 7-day period was effective in restoring the damaged skin barrier and improving the stratum corneum hydration. A regimen that combined the hand protectant cream, repair cream, and a specific cleanser during a further 7-day period allowed continued improvement of skin hydration and additional clinical benefits while respecting the skin barrier function. The result of this study supports the use of a 3-step approach for patients who are at risk of repeated exposure to external irritants.

DISCLOSURES

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Rapid Improvement and Protective Effects of an Almond Oil-Based Ointment for Diaper Dermatitis

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ABSTRACT

Introduction and Objectives: Newborns and babies are at risk of developing diaper dermatitis due to constant occlusion and exposure to irritants such as urine and feces. The aim of this study was to evaluate the clinical effectiveness of an almond oil-based ointment on diaper dermatitis in infants.

Material and Methods: A multicenter open-label trial of 60 infants (1-36 months) with a known history of recurrent diaper dermatitis was performed. The infants were clear at the time of enrollment. Inclusion criteria was a minimum of 3 episodes of rashes in the diaper area in the four weeks prior to enrollment. The almond oil-based ointment was used daily after each diaper change over 28 days, and data was recorded by the users (persons who applied the product) with daily report logs for the study duration including presence of diaper dermatitis, severity, as well as reports of teething and/or diarrhea. During each visit, a clinical evaluation was performed by an assessor (dermatologist or pediatrician) recording the degree of erythema, skin dryness, skin roughness to the touch, and skin suppleness using a scoring scale from 0 (null) to 9 (very severe). The users also performed an evaluation on product effectiveness and cosmetic qualities.

Results: Clinical evaluations showed no erythema, a significant decrease ($P<0.01$) in skin dryness, roughness, and a significant increase ($P<0.01$) in skin suppleness after 28 days of product application compared to initial state. During the course of the study, 90% of the subjects showed a decrease in frequency or total absence of diaper dermatitis. One-hundred percent of users rated the product to have a pleasant texture, a good protective effect, spreads easily, and does not irritate the skin. The scent was judged as pleasant by 95%, and for 75% of those applying the product, the texture was described as non-oily.

Conclusions: For newborns and infants regularly developing diaper dermatitis, the almond oil-based ointment appears to confer a protective effect from future episodes of diaper dermatitis, improves dryness and suppleness of skin, and is cosmetically acceptable by the users.

J Drugs Dermatol. 2016;15(suppl 11):s86-90

INTRODUCTION

Diaper dermatitis (DD) is a term used by clinicians to describe a wide range of inflammatory processes that occur in the diaper area.[1] DD is probably the most common cutaneous disorder in infancy and early childhood and is thought to account for nearly 20% of childhood dermatology visits and in up to 25% of children.[1,2,3]

There are a number of causes of DD including candida infections, allergic reactions, seborrheic dermatitis, bacterial infections, and rarer conditions such as zinc deficiency and Langerhans cell histiocytosis, but the most common cause by far is irritant dermatitis, fueled by contact with urine and feces.[4]

The Berg model of diaper dermatitis outlines the pathophysiology of irritant contact dermatitis in the diaper area and consists of the following contributing factors:

1. Increased moisture in the diaper area created by the occlusive effect of the diaper combined with the presence of feces and urine
2. Maceration of the skin and disruption of the skin barrier due to friction within the skin folds in the area
3. pH imbalance from the proteases and lipases found within feces as well as with bathing products
4. This elevated (more basic) pH results in abnormal skin flora, which in turn makes the skin more susceptible to infection by bacteria and fungus.[5]

Barrier creams, ointments, and pastes are often the first line treatments for DD and attempt to provide a water-repellent emollient or protective ointment to the skin.[6]The rationale for using a barrier cream or paste in the treatment or prevention of diaper dermatitis is that a thick occlusive cream or paste will help protect the skin from the increased moisture in the environment and thus support epidermal barrier function. While diaper care procedures aim to support skin barrier function, little is known about the effect of diaper creams on skin barrier function in infants. A study in 2014 investigated the skin barrier

function of diapered and non-diapered skin areas affected by DD in healthy infants and found that areas with DD had higher TEWL and skin pH than unaffected skin areas. Moreover, infants treated with diaper cream had lower TEWL and, interestingly, lower stratum corneum hydration, which may demonstrate protection against maceration.[7]

The aim of this study was to evaluate the clinical effectiveness and cosmetic acceptability of an almond oil- and soybean oil-based ointment on DD in children with recurrent irritant diaper dermatitis.

Almond oil has been used for its numerous health and beauty benefits since ancient times, with many traditions utilizing almond oil to treat dry skin conditions such as psoriasis and eczema, improve skin complexion, and promote soft healthy skin.[8] Almond oil remains sought-after for its rich concentration of oleic and linoleic essential fatty acids, and is used in the cosmetic industry for its penetrating, moisturizing, and restructuring properties.

Almond oil is a non-toxic, non-irritating, nonsensitizing and non-comedogenic, readily emulsifiable ester, which possesses some of the following properties and attributes:

- Imparts a dry lubricating feel in the presence of large amounts of mineral oil or petrolatum
- Superior solubiliser of lipophilic cosmetic raw materials
- High positive spreading coefficient
- Wetting agent and auxiliary suspending agent for water insoluble powdered products
- Stable to hydrolysis within a wide pH range of about 2–12.

There is theoretical concern for allergic potential as it is derived from a tree nut, however, only 1 known case of IgE sensitization is reported.[9]

Glycine Soja Oil (Soybean Oil) is derived from the seeds of the soya plant *Glycine max*. Soy extracts can be found in many cosmetic products, as numerous biologically active compounds have been identified in soybean.[10] Lipids, lecthins, and phytosterols enhance the skin barrier, while isoflavones impart an antioxidant effect.[11] In vitro studies have shown that soybean extracts stimulate collagen synthesis, initiate the elastin repair process, inhibit melanosome transfer, and have antioxidant/anti-inflammatory action; these properties reflected in the clinical benefits of topical soy formulations: anti-inflammatory, moisturizing, photorejuvenation/photoprotection, amelioration of fine lines, and skin lightening/brightening.[10]

METHODS

This was a multicenter open-label trial of 60 infants and children (1 to 36 months) with a known history of recurrent mild-to-moderate diaper dermatitis. The investigator group comprised 8 dermatologists and 2 pediatricians.

Inclusion criteria was a minimum of 3 episodes of rashes in the diaper area in the four weeks prior to enrollment but subjects were clear at the time of enrollment. The almond oil-based ointment was used daily after each diaper change over 28 days, and data was recorded by the users (person who applied the product) with daily report logs for the study duration including presence of diaper dermatitis, severity, as well as reports of teething and/or diarrhea. During each visit, a clinical evaluation was performed by an assessor (dermatologist or pediatrician) recording the degree of erythema, skin dryness, skin roughness to the touch, and skin suppleness using a scoring scale from 0 (null) to 9 (very severe). The users also performed an evaluation on product effectiveness and cosmetic qualities.

RESULTS

All 60 subjects completed the study. Fifty-three percent were female and forty-seven percent were male. The subjects' age ranged from 33 days to 3 years with an average of 11.1 months. The average number of diaper dermatitis episodes was 4.1 and the average duration for the study was 30 days. An average of 6.3 applications of the ointment per day was recorded (Table 1).

Clinical evaluations showed no erythema, a significant decrease ($P<0.01$) in skin dryness, roughness, and a significant increase ($P<0.01$) in skin suppleness after 28 days of product

TABLE 1.

Inclusion Environment Context (60 subjects)			
4 Weeks Prior to Inclusion in the Study	No	+/- SD	Avg No of Applications
Diaper changes per 24 hours	1856	3 - 12	7
Diaper rashes during prior 4 weeks	2561	1 - 14	4.1
Diaper dashes total duration (in days)	3527		4.5
Diaper rashes average intensity	0.596		1.5
Subjects' Distribution by Intensity	**Population**		**Population %**
Light	32		53%
Moderate	25		42%
Important	3		5%

TABLE 2.

Average Clinical Scoring (60 subjects; Comparison with initial state)				
Diaper Dermatitis	**Visit 1, Day 0 (Avg)**	**Visit 2, Day 28 (Avg)**	**Deviation Day 0**	**Significance**
Erythema	0	0	0	N/A
Skin Dryness	2.2	0.6	-1.6	*P*<0.01
Skin Roughness to Touch	2	0	-1.6	*P*<0.01

application compared to initial state. During the course of the study, 90% of the subjects showed a decrease in frequency or total absence of diaper dermatitis (Table 2 and Figure 1).

The product was well-tolerated with no adverse effects reported during the study.

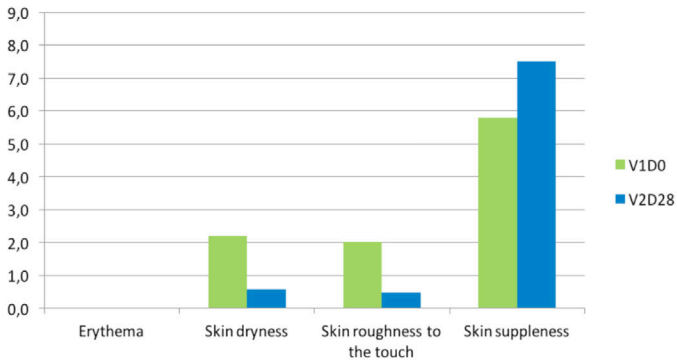
The statistical analysis used the Wilcoxon's test for paired series, for the intragroup evaluations comparison: the statistical treatment consists in determining if there is a significant difference between the individual data collected for the different evaluation times.

Wilcoxon's Test (two paired samples)

The Wilcoxon's test is a non parametric test allowing the comparison between two paired samples, in this case between the initial report at day 0 and the final report after day 28 (Table 3).

The secondary endpoint was cosmetic acceptability and user perception of the product. One-hundred percent of users rated the product to have a pleasant texture, a good protective effect, spreads easily and does not irritate the skin. The scent was judged as pleasant (95%), and for 75% of those applying, the product texture was described as non-oily. Ease of use was notable for 100% of respondents reporting that "the product acts gently", while 93% of respondents reported "the product ensures a daily protection against the diaper rash" (Table 4).

FIGURE 1. Graph of average clinical scoring evolutions in comparison with the initial state (60 subjects).



The analysis of the daily report logs concerns the occurrence of diaper rash episodes with an intensity scoring, and the reporting of teething or diarrhea. The results show, each week, a steady decrease of the number of teething (from 109 to 57), of diarrhea (from 23 to 5), and of diaper rash episodes (from 68 to 18). Similarly, concerning the declared diaper rash intensity, the average decreases from 0.6 to 0.1. Furthermore, the subjects' distribution by intensity level shows an increase of the population in the weakest level (null intensity: from 52% to 88% of the subjects) and a decrease of the population in the moderate level (from 12% to 3%). These results support the evidence of the product's protective effect.

An analysis of the preventive effect on the diaper rashes has also been carried out by comparison of the initial data "without product application" (ie, 4-week period prior to inclusion) with the final data "with product application" (after the 4-week application period). The results show a decrease of the cumulative number of episodes, observed on the 60 subjects sample (from 248 to 83), a decrease of the episode frequency (from 4.1 to 1.4), and a decrease of the average diaper rash intensity (from 1.5 to 0.7).

The statistical comparison of the final state compared with the initial state confirms these performances were trending toward significance with a significant difference (*P*<1%) in favor of the product.

TABLE 3.

Perception Rates for Cosmetic Qualities (60 subjects)			
Quotations	**Favorable**	**Unfavorable**	**Undecided**
The product has a pleasant texture	100%	0%	0%
The product has a pleasant scent	95%	5%	0%
The product has a good covering power	100%	0%	0%
The product does not irritate the skin	100%	0%	0%

DISCUSSION

The purpose of this multicenter open-label trial was to determine frequency and severity of diaper rash and the effectiveness and cosmetic acceptability of an almond oil-based topical product.

TABLE 4.

Analysis of Diaper Rashes Occurred (60 subjects)		
During the 4 Prior Weeks (preventative care)	Visit 1, Day 0 (without application)	Visit 2, Day 28 (with application)
Cumulated Number of Episodes for The 60 subjects sample	248	83
Episodes frequency	4.1	1.4
Diaper rash intensity	1.5	0.7
Subjects Distribution by Intensity Level		
Null	0 (0%)	21 (35%)
Light	32 (53%)	32 (53%)
Moderate	25 (42%)	6 (10%)
Important	3 (5%)	0 (0%)
Missing data	0 (0%)	1 (2%)

Compared to the initial state of the infants DD, the results indicated that the almond oil-based topical product was effective.

There are many types of barrier preparations available for both the prevention and treatment of DD. These may contain petroleum jelly, zinc oxide, dimethicone, and/or other occlusants and protectants. Some studies have shown that certain preparations are effective in treating DD,[12] while others have not found an effect of diaper creams on the frequency or severity of DD.[13]

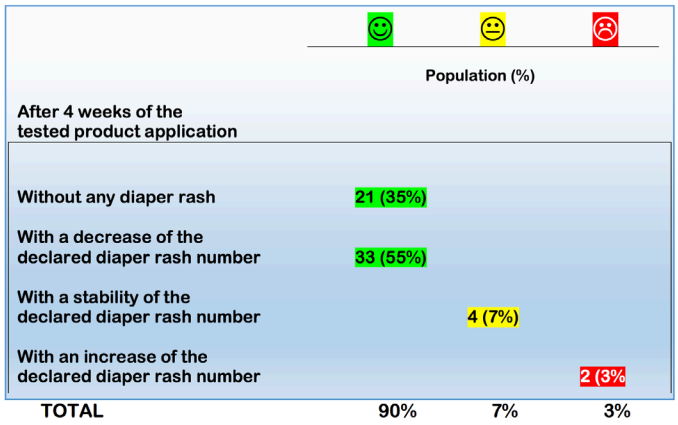
CONCLUSION

Newborns and infants frequently develop dermatitis in the diaper region and this likely reflects an impaired skin barrier in this area.[14] Supportive measures have been shown to restore the skin barrier, decreasing transepidermal water loss,[7] but literature reviews fail to identify a superior preparation for this task.[15]

In the present study, the almond oil-based ointment appeared to confer a protective effect against future episodes of diaper dermatitis, with 90% of the subjects showing a decrease in frequency or total absence of diaper dermatitis after using the ointment. In addition to this important finding, the significant decrease ($P<0.01$) in skin dryness and roughness, as well as the significant increase ($P<0.01$) in suppleness of skin, bolster the notion that barrier repair and maintenance are at play.

Correspondingly, the users also evaluated the product effectiveness according to 5 items. The results show that 100% of the users estimate that the product leaves the skin soft and hydrated. Ninety-eight percent also report that product efficiently protects the baby's bottom, and ninety-seven percent reported that the product leaves the skin more supple.

FIGURE 2. Subject distribution according to the evolution of the declared diaper rash number at day 28 (60 subjects).



The cosmetic aspects were judged and found that 100% of the users felt that the product does not irritate the skin, that its texture is pleasant, and that it was able to coat the skin well. The scent was judged as pleasant by 95% of users, while 75% reported that the product texture was not oily.

In sum, 97% of the users judged the product as overall satisfactory and 88% indicated they would purchase it.

The assessors have also evaluated the product. The obtained results show that for all the examined cases, both dermatologists and pediatricians felt that the product respects the skin hydration. Ninety-five percent of assessors reported that the product reduces diaper rash intensity and frequency.

Overall, these results support the efficacy of the diaper ointment for mild to moderate DD, making it a suitable choice for protective care against DD, in particular for children with a predilection to frequent dermatitis in the diaper area.

DISCLOSURES

Dr. Lio has served as a consultant/advisor and speaker for Valeant, Regeneron/Sanofi, and Pierre Fabre. He has served as a consultant/advisor for Anacor, AO Biome, Exeltis, Galderma, Johnson & Johnson, Theraplex, and Mission, and has received an honorarium for his work on this supplement sponsored by Galderma.

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Efficacy of a Skin Condition-Adapted Solution for Xerosis and Itch Relief Associated With Aging

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ABSTRACT

In recent decades, the stratum corneum (SC), has been recognized for its multifunctional role in maintaining the homeostasis of the human epidermal barrier. A better understanding of the SC's ability to act as its own biosensor in detecting dysfunction and integrating restorative actions can help identify the origin of certain skin conditions. A more holistic understanding of the morphological changes of the SC during the natural aging process and how it deviates in disease states can help bring about new treatment strategies.
Some important recent clinical studies point to new treatments and add to the existing body of research on corneobiology. These studies offer some explanation of and validation for the various ingredients incorporated into moisturizers and barrier repair devices aimed at treating pruritus and xerosis associated with the aging skin.

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INTRODUCTION

In the past half century, research has given increasing attention to the stratum corneum (SC). What was once thought of as a simple Saran™ Wrap-like layer of physiologically inactive cells is actually a remarkably dynamic layer serving a multitude of functions.[1] At just 10-20μm in thickness, the SC is now believed to be fundamentally involved in maintaining a variety of barrier functions, while impressively adjusting to extrinsic and intrinsic factors in order to sustain skin-barrier homeostasis.[2]

Since the stratum corneum is profoundly responsible in maintaining healthy skin, there has been significant motivation to better understand the mechanisms through which it protects the viable epidermis from offending pathogens, antigens, and irritants, as well as how the SC ensures adequate hydration in order to enable proper epidermal enzyme function and tactile perception.[2] Much of our understanding of the stratum corneum's functional structure is derived from observing various disease states in which key SC elements are dysfunctional or absent, and how a wide range of products may help restore those elements.[3,4]

Structure Meets Function: Epidermal Barrier and Hydration Homeostasis

To appreciate the dynamic nature with which the SC maintains skin barrier homeostasis, it is important to first adequately explore the morphological qualities and characteristics responsible for this thin but exquisitely active skin layer. Unique to the stratum corneum are the corneocytes: anucleated cells that have terminally differentiated from keratinocytes via a calcium dependent process, and are primarily composted of keratin macrofibrils (microfibril bundles made of hard keratin).[2,5] Conceptually, the SC is often described with a "brick and mortar" model: the corneocytes being the "brick," and the lamellar lipid membrane being the "mortar."[2] Furthermore, the corneocytes are protected by a cornified cell envelope, a highly cross-linked protein shell, and are held together by corneodesmosomes. The cornified envelope in combination with the keratin filaments contribute significantly to the flexibility and mechanical pliability of the SC.[5]

Biochemically speaking, the lamellar lipid membrane is made of ceramides (40-50%), free fatty acids (10-15%), and cholesterol (25%).[2] Ultimately, the components of this lamellar lipid mixture trace their roots back to the stratum spinosum layer, primarily from glycosylceramides, sphingomyelin, and phospholipids found in the lamellar bodies.[2] Collectively, the components in the lamellar lipid membrane are also pivotal in adding to the ability of the SC to minimize water loss and maintain homeostasis. Next, a closer inspection of the internal constituents of corneocytes further explains how the SC has such impressive abilities of maintaining moisture. Free amino acids, pyrrolidone carboxylic acid (PCA), urocanic acid, urea, and other electrolytes collectively make a hygroscopic "moisturizer" called natural moisturizing factor (NMF), which acts as a natural humectant in corneocytes.[2,3] Just as the lamellar lipid constituents can be traced back to the underlying stratum spinosum layer, the NMF hygroscopic components also trace back to an underlying layer: the stratum granulosum. Specifically, the keratohyalin granules of the stratum granulosum provide the filaggrin that eventually degrade to produce the components of the corneocyte NMF.[2]

The stratum corneum's dynamic morphological and biochemical features alone are a testament to the exquisite structural and functional interplay of this thin layer of skin. However, the true brilliance comes with observing how the SC's complex homeostatic mechanism is seemingly self-sustained.[2] In reality, the SC's homeostatic mechanism is a constant and iterative feedback loop, with no beginning or end point. However, at the heart of the schema is the SC's ability to detect subtle changes in its own hydration status and barrier integrity.[2] If exogenous or endogenous insults shift the SC into dyshomeostasis, a series of cascading signaling events are triggered in an attempt to shift it back to homeostasis. Though all the exact signaling pathways involved are still an active area of research, it is now widely recognized that serine-protease pathways are intimately involved in the signaling used to maintain epidermal permeability barrier homeostasis.[6] Once a shift is detected, serine-protease pathways in concert with other signaling events quickly cascade to initiate adaptive and compensatory responses in order to restore homeostasis.[2]

One prototypical example of a quick response to changes in the hydration or barrier status is evident with the stratum corneum's ability to rapidly increase the lamellar body secretions of precursor lipids.[2] These precursor lipids are then converted into major lipids, which are subsequently integrated into the intercellular lamellar lipid membrane. This process effectively increases the overall permeability barrier function by up to 20%. [2] Another response that the SC can initiate is an upregulation in the biosynthesis of all major epidermal lipids. These lipids are fundamental ingredients in the self-repair process, and are crucial in providing the ability to implement a rapid response.[2] Interestingly, the overall lipid content of the human SC decreases with age, causing a downturn in the efficiency of such responses. As discussed later, this ultimately plays an important contributing factor in the development of xerotic or pruritic conditions associated with aging. [7]

Morphological Changes Associated With Intrinsic and Extrinsic Skin Aging

With normal aging, the human epidermis begins to show morphological changes that span across the entire infrastructure of the skin.[8] The epidermis begins to thin, which leads to skin transparency, an increase in transepidermal water loss (TEWL), and a noticeably dry and scaly skin surface.[8] Furthermore, there is a steep decrease in SC lipids with age, resulting in a downturn in the level of ceramides.[5,9,10] In fact, it is now generally accepted that the total lipid content in the stratum corneum decreases by roughly 30% in the elderly.[5] This is particularly noteworthy since ceramide deficiency is associated with xerosis, and knowing this can be of great value in treatment modalities since ceramide replacement therapies have been shown to minimize the symptoms of dry, itchy skin.[4,7]

Though it is an oversimplified model, skin aging can be categorized into two often overlapping subcategories: intrinsic and extrinsic. Intrinsic aging is determined predominantly by one's genetic makeup, and drives the skin changes associated with normal aging.[8] An example of an intrinsic determinant of aging is the regional differences in lipid content and composition due to anatomical variation in the skin.[11] Another important intrinsic determinant is the role of ethnicity on aging since it has been shown that certain races have higher intercellular lipid content than others.[11] Both of these determinants of aging are particularly relevant to the greater scope of this review since variation in both the lipid content and composition profiles in the SC can have drastic effects on the skin barrier homeostasis (as discussed in the previous section).[2,11]

Unlike intrinsic aging, extrinsic aging is not genetically determined, and includes insults such as UV exposure, humidity, smoking, and diet that can cause cumulative damage to the skin over time.[8] For example, when the skin is in a low-humidity environment (<10%), it impairs the function of hydrolytic enzymes that are required for the proteolysis of filaggrin. This effectively decreases the amount of NMFs and causes the skin surface to become dry.[5] Taken from another perspective, if the SC were to become desiccated, the impaired hydrolytic enzymes would not be able to keep up with the required rate of corneodesmosome degradation. As a result, corneocytes build up and clump together instead of efficiently shedding, ultimately leading to visible scaling, roughness, and flaking.[2]

As previously discussed, the SC has a highly efficient mechanism in place to maintain the homeostasis of its environment. However, with repeated, recurrent, or chronic insults, the SC's arsenal of adaptive responses can become exhausted, eventually leading to skin pathologies.[2] In turn, this makes the stratum corneum more vulnerable to damage, especially if there are multiple insults happening in tandem. Furthermore, the rapid signal transduction pathways that are normally pivotal to the stratum corneum's ability to maintain homeostasis can work to the SC's detriment. This can happen especially if too many toxic insults coalesce, which will turn the signal transduction pathways into aberrant, amplified pathways that overshoot the desired responses. As a result, this can trigger inflammatory events, thus leading to greater epidermal depth involvement.[2] Over an extended period of time, this can cause epidermal hyperplasia, and retention hyperkeratosis as the stratum corneum cannot be exfoliated at a rate commensurate to the hastened epidermal turnover in a pro-inflammatory state.[12] As discussed in the next section, utilizing such knowledge can minimize trial and error, and would entail, for example, prescribing a keratolytic agent to combat an underlying hyperkeratotic process that is common in itchy, dry skin.[2,12]

Reverse Engineering a Skin-Adapted Solution

The SC's ability to detect subtle variations in its environment and subsequently implement restorative mechanisms is a testament to its unique ability to act as its own biosensor.[2] Gaining an understanding of the skin's natural adaptation mechanism in healthy skin and how it deviates in disease states can provide a wealth of knowledge in the treatment of skin conditions. Researchers can effectively use this knowledge to "reverse engineer" adaptive solutions for a whole host of dermatological disease states. While additional studies are needed, utilizing this reverse-engineering strategy in concert with existing translational ingredients is already yielding more efficient OTC treatments for patients suffering from xerosis and pruritis.[4,13]

As compared to traditional occlusive moisturizers predominantly comprised of nonphysiologic lipids, there are now a variety of ingredients used. Some of these ingredients include sorbitol, urea, lactate, and glycerin, which have NMF-like properties due to their humectant nature.[14] Utilizing these ingredients in concert with understood features of the SC's dynamic and restorative mechanisms have led to more effective moisturizing solutions. For example, the well documented lipid profile of ceramides (40-50%), free fatty acids (10-15%), and cholesterol (25%) found in healthy human SC has led to some newer moisturizers that contain an equimolar, ceramide-dominant composition that both replenishes and hypothetically stimulates their innate production.[2,3,12] These effective topical treatments underscore the value of formulating moisturizers with a good ratio of ingredients in contrast to a formula that is predominantly occlusive and/or humectant in nature and less likely to provide physiological barrier restoration.[2]

Recent Clinical Trials

The culmination of this knowledge has promising implications that can yield more effective topical solutions. A prime example of this is evidenced by a recent clinical trial of an investigational anti-itch lotion in a population of adults (aged ≥60) with dry to very dry skin on the body and marked dry and itchy skin on the legs. The results of this particular trial showed that the lotion had a rapid onset of action that significantly decreased itch intensity immediately after the first application, and showed complete relief in all test subjects after 8.5 days.[15]

As alluded to earlier, urea's humectant, as well as keratolytic, properties make it a useful monotherapy for conditions associated with dry, scaly skin, and has been shown to be effective in treating a range of conditions including: ichthyosis, xerosis, atopic dermatitis, tinea pedis, and contact dermatitis.[13] In fact, there have been a number of clinical trials in recent years that validate urea's therapeutic efficacy in a number of these skin conditions. In a double blind, randomized clinical trial, the use of 5% and 10% urea-containing moisturizers in patients suffering from atopic dermatitis were investigated. The study found that both concentrations improved the dry skin in patients suffering from atopic dermatitis and were also very well tolerated.[16]

Urea's effectiveness as a monotherapy on dry skin was recently further demonstrated. In a single center open study, the impact of a 10% urea moisturizer formulation on xerotic skin based on several biological profiles was investigated. The results of this study found that the product improved the skin barrier and skin capacitance, and even improved the visual skin dryness 1 week following the final product application.[17]

In one clinical trial, moisturizers containing either urea or glycerin were evaluated and compared on patients with atopic dermatitis, using TEWL, skin capacitance, and clinical changes as markers of biological impact. This study not only validated urea's efficacy in the treatment of atopic dermatitis but also suggested that urea may be superior to glycerin in the context of skin barrier function.[18] However, it is worth noting that this conclusion was made from urea's superior clinical assessment by dermatologists and instrumental TEWL findings, but the skin conductance, a marker for skin hydration, did not show a statistically significant difference for either the urea or glycine solutions compared to placebo.

In another more recent acceptability and objectivation study in France, a lotion containing glycerin was used to treat 28 adults aged ≥60 years old with dry to very dry skin on the body and marked dry and itchy skin on the legs. Improvements in the clinical assessments linked to skin aspect and skin sensation (B. Bisbal, unpublished data, November 2015) were shown. This same study showed subject satisfaction specific to dryness and skin aspect improvement to be overwhelmingly positive. The optimistic preliminary results in the aforementioned clinical trial conducted by B. Bisbal underscores the fact that polarizing statements regarding any single ingredient being better or worse is difficult to make.

To delve deeper, the efficacy of a lotion that utilizes urea as well as sodium lactate, dimethicone, and other emollient, humectant, and preserving ingredients for improving xerotic skin after two weeks of treatment was assessed. Follow-up studies showed the lotion had protective and moisturizing effects and the lotion was well-received by the surveyed test subjects across numerous categories such as the speed of absorption and skin calming effect (S. Bielfeldt, unpublished data, March 2016). Using this same lotion, a randomized, single-blind study of 33 senior adult patients was conducted for a 3-week treatment regimen to improve dry and itchy skin. The results also showed favorable clinical skin improvements and were statistically significant across numerous categories in the subject's assessments (S. Bielfeldt, unpublished data, February 2016).

Treatment Regimen

As discussed, there is a growing body of evidence in favor of urea's efficacy in treating xerotic skin. However, further investigations would certainly be useful in understanding how a well-balanced formulation of tried-and-true ingredients may serve as a more efficient approach to skin dryness and itchiness as opposed to monotherapy.

CONCLUSION

The SC's exquisite ability to act as its own biosensor is crucial for the maintenance of the skin's structural and functional integrity. Moreover, the SC's adaptive and complex homeostatic mechanisms are constantly active, even in healthy skin. Thus said, the SC's impressive ability to maintain homeostasis has its limits, as evidenced by epidermal changes observed with intrinsic and extrinsic aging. Specifically, aging brings a host of morphological changes to the human SC including thinning of the epidermis, an increase in TEWL, a decrease in native SC lipids, and an increased susceptibility to dry skin. In total, these changes promote and sustain xerosis and other age-associated symptoms in the skin that can be frustrating and, in some cases, debilitating to patients.

It is important for prescribers to be judicious in selecting a moisturizer that not only deposits deficient constituents to the SC but also creates a physiologically compatible environment that allows the skin to repair itself. A working knowledge of the SC's natural adaption mechanism and, more importantly, how it deviates from this in concert with translational ingredients, can yield more efficient OTC treatments for patients suffering from age associated skin conditions.

One ingredient in particular, urea, has been used to treat dermatological conditions for over a century. Though its mechanism of action is still not fully understood, it is widely accepted that its keratolytic and humectant properties increase SC hydration and combat the hyperkeratotic epidermal changes associated with the aging skin.

The importance of utilizing proven treatments in skin conditions can be best underscored with a quote taken from Dr. Albert Kligman's 1957 publication on urea: "it sometimes happens in the enthusiastic search for new therapeutic agents that some old stand-by has been overlooked, whose luster has worn off, but which none the less may have some useful application in moments when the miracle drugs falter. In the world of topical therapy, urea is such a drug".[13] Kligman's observations serve as a fundamental lesson in being judicious with time and resources in the context of translational research.

DISCLOSURES

RJ has no conflicts of interest to disclose. AJF consults for Galderma, Sanovaworks, Oakstone Institute, Loreal, La Roche Posay, Amgen, Aveeno, Valeant, Microcures, Nano Bio-Med, Biogen, Pfizer, Nerium, G&W Laboratories, Novartis, Occulus, Intraderm, Encore, Ferndale, Exeltis, and Promius.

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