The Effect of Ceramide-Containing Skin Care Products on Eczema Resolution Duration

Zoe Diana Draelos, MD

Eczema is a common dermatologic condition that affects children as well as adults and is related to a defective skin barrier, which is most commonly caused by damage to the intercellular lipids from improper selection of skin cleansers and moisturizers. A new concept in skin care is the incorporation of ceramides into therapeutic cleansers and moisturizers. Ceramides are important components of the intercellular lipids that are necessary to link the protein-rich corneocytes into a waterproof barrier that is capable of protecting the underlying skin tissues and regulating body homeostasis. This study evaluated the effect of both a multilamellar vesicular emulsion (MVE) ceramide-containing liquid cleanser and moisturizing cream plus fluocinonide cream 0.05% compared with a bar cleanser plus fluocinonide cream 0.05% in the treatment of mild to moderate eczema. The addition of an MVE ceramide-containing liquid cleanser and moisturizing cream to a high-potency corticosteroid enhanced the treatment outcome of mild to moderate eczema compared with the use of a bar cleanser and high-potency corticosteroid in reducing disease duration, time to disease clearance, and symptoms. Thus, skin care product selection can have an important clinical effect on the clearance of mild to moderate eczema.

Cutis. 2008;81:87-91.

Accepted for publication November 7, 2007.

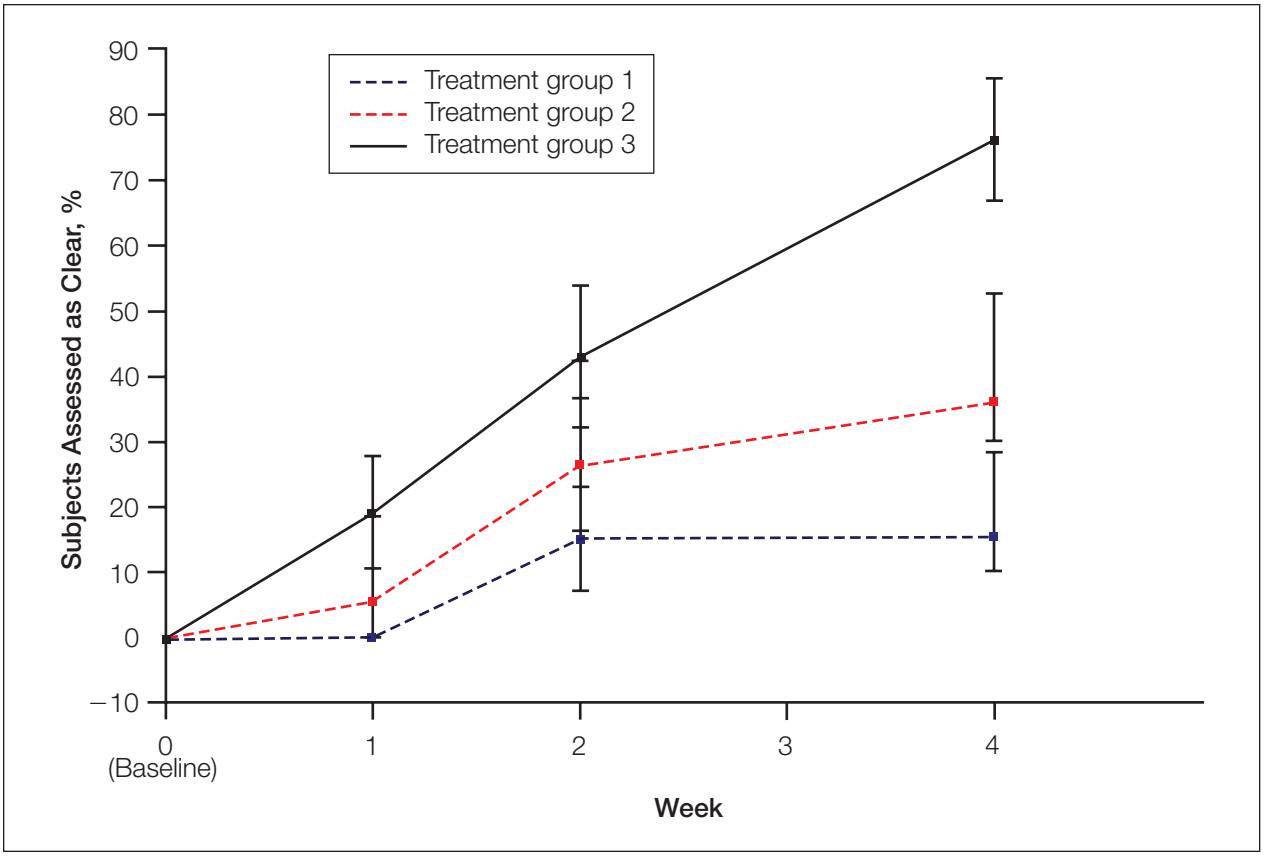
From Dermatology Consulting Services, High Point, North Carolina.

This study was supported by an unrestricted educational grant from Coria Laboratories, Ltd. The author reports no conflict of interest.

Correspondence: Zoe Diana Draelos, MD, 2444 N Main St, High Point, NC 27262 (zdraelos@northstate.net).

Eczema is a common dermatologic condition that is characterized by erythema, desquamation, papulation, lichenification, excoriation, and itching. It affects children as well as adults, both males and females, and is related to a defective skin barrier, which is most commonly caused by damage to the intercellular lipids from improper selection of skin cleansers and moisturizers. A new concept in skin care is the incorporation of ceramides into therapeutic cleansers and moisturizers. Ceramides are important components of the intercellular lipids that are necessary to link the protein-rich corneocytes into a waterproof barrier that is capable of protecting the underlying skin tissues and regulating body homeostasis.[1,2] With the availability of bioidentical synthetic ceramides 1, 3, and 6, ceramides can be effectively delivered to the skin through a time-released multilamellar vesicular emulsion (MVE) configuration.

MVE is a novel emulsion technology. An emulsion is created when water and oil are dissolved to form one continuous solution. Emulsions can be created either when water is dissolved in oil or when oil is dissolved in water. If the water is dissolved in oil, the oil is the highest concentration ingredient; if the oil is dissolved in water, the water is the highest concentration ingredient. MVE differs from both the traditional oil-in-water emulsion, whereby the oil is dissolved in water, and the traditional water-in-oil emulsion, whereby the water is dissolved in oil.[3] In MVE, there are concentric layers of oil-in-water emulsions, which are referred to as vesicles. The vesicles are unfolded when placed in contact with the skin surface to release ceramides; cholesterol; free fatty acids; phytosphingosine; and other moisturizing ingredients, such as dimethicone, glycerin, and hyaluronic acid, onto the skin surface.[4]



Percentage of subjects assessed as clear of disease over the duration of the study. Treatment group 1, fluocinonide cream 0.05% plus mild bar cleanser; treatment group 2, fluocinonide cream 0.05% plus multilamellar vesicular emulsion (MVE) ceramide-containing liquid cleanser; treatment group 3, fluocinonide cream 0.05% plus MVE ceramide-containing liquid cleanser and moisturizing cream. At week 4, $P=.155$ for treatment group 1 versus treatment group 2; $P=.0001$ for treatment group 1 versus treatment group 3; and $P=.024$ for treatment group 2 versus treatment group 3.

An MVE ceramide-containing moisturizer should provide more rapid barrier repair in eczematous skin conditions, yet this concept has never been clinically studied.

The primary goals in the treatment of eczema are the resolution of symptoms, primarily itching, stinging, and burning, and the return of the skin to a healthy attractive appearance. Both of these goals only can be accomplished when the barrier is fully repaired. The dermatologist must determine how to shorten the duration of barrier repair in the patient with eczema. Does barrier repair occur in the shortest time when the patient uses a high-potency topical corticosteroid and a mild bar cleanser? Alternatively, is the duration of barrier repair and symptoms shorter when a high-potency topical corticosteroid is combined with a ceramide-containing liquid cleanser? Is there added benefit to shortening the eczema duration and minimizing symptoms when both a ceramide-containing liquid cleanser and moisturizing cream are added to the high-potency topical corticosteroid?

This study was conducted to determine the value of an MVE ceramide-containing liquid cleanser and moisturizing cream in shortening the duration and symptoms of mild to moderate eczema when combined with a high-potency topical corticosteroid.

Methods and Materials

The 4-week Concordia Institutional Review Board (Cedar Knolls, New Jersey)–approved study enrolled 60 subjects aged 5 to 80 years with mild to moderate eczema. Subjects underwent a 4-week oral and topical eczema treatment washout period before study entry. At baseline, the investigator (a dermatologist) performed a brief medical history and physical examination of the subjects. Subjects with mild to moderate eczema, defined as the severity of eczema expected to exhibit reasonable clearing with a high-potency topical corticosteroid in 4 weeks, were enrolled if they met all inclusion and no exclusion criteria. Subjects were randomized to 1 of 3 balanced treatment groups of 20 subjects each. Treatment group 1 used fluocinonide cream 0.05%

Global Disease Severity by Treatment Group*

Treatment Group	Baseline Assessment	Treatment Week Assessment	Difference	*P* Value		
				Group 1 vs Group 2	Group 1 vs Group 3	Group 2 vs Group 3
Week 1						
Group 1	3.0	2.6	0.4	.012	.004	.272
Group 2	3.1	1.9	1.2			
Group 3	3.0	1.6	1.4			
Week 2						
Group 1	3.0	2.0	1.0	.442	.013	.063
Group 2	3.1	1.6	1.5			
Group 3	3.0	0.9	2.1			
Week 4						
Group 1	3.0	1.6	1.4	.0443	<.001	.087
Group 2	3.1	0.9	2.2			
Group 3	3.0	0.3	2.7			

*Treatment group 1, fluocinonide cream 0.05% plus mild bar cleanser; treatment group 2, fluocinonide cream 0.05% plus multilamellar vesicular emulsion (MVE) ceramide-containing liquid cleanser; treatment group 3, fluocinonide cream 0.05% plus MVE ceramide-containing liquid cleanser and moisturizing cream.

twice daily plus a mild bar cleanser as needed. Treatment group 2 used fluocinonide cream 0.05% twice daily plus an MVE ceramide-containing liquid cleanser as needed. Treatment group 3 used fluocinonide cream 0.05% twice daily plus an MVE ceramide-containing liquid cleanser as needed and an MVE ceramide-containing moisturizing cream twice daily.

Subjects were asked to use only the provided skin care products and medication on the eczematous areas. A demonstration of the study product application occurred at the research center to ensure that subjects properly applied the study medication. Subjects were given instructions and diaries to record the study product application that was appropriate for their treatment group. Subjects were required to demonstrate the first application of eczema medication before completing the baseline visit.

Blinded investigator assessments of global disease severity and signs and symptoms of eczema (erythema, desquamation, papulation, lichenification, excoriation, itching) were performed at baseline and weeks 1, 2, and 4, and rated on a 5-point scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe). A target site was selected for digital macrophotography.

Statistical analysis was performed on the intergroup differences from baseline at each visit and the signs and symptoms of eczema were tested for significance ($P \leq .05$) using a nonparametric Kruskal-Wallis test. If a significant difference across treatment groups was noted, paired comparisons were analyzed using a 2-tailed nonparametric Mann-Whitney test. Trends in the treatment groups across the duration of the study were tested using analysis of variance on rank-transformed data.

Results

All 60 subjects completed the 4-week study. No adverse events occurred and no tolerability issues arose with any of the study products as reported by either the investigator or the subjects. The study was designed to look at the additive benefits of fluocinonide cream 0.05% twice daily plus an MVE ceramide-containing liquid cleanser and moisturizing cream. Various data sets were generated.

Incidence and Time to Disease Clearance—The Kaplan-Meier method was used to evaluate the time to disease clearance based on investigator assessments (Figure). The incidence of clearing at week 4 increased from 15% with fluocinonide cream 0.05% plus the bar cleanser to 76% with fluocinonide cream 0.05% plus the MVE ceramide-containing liquid cleanser and moisturizing cream (P=.0001), and increased from 15% with fluocinonide cream 0.05% plus the bar cleanser to 37% with fluocinonide cream 0.05% plus the MVE ceramide-containing liquid cleanser (P=.155). The time to clearing was 3.0 weeks in treatment group 3 using fluocinonide cream 0.05% plus the MVE ceramide-containing liquid cleanser and moisturizing cream, 3.4 weeks in treatment group 2 using fluocinonide cream 0.05% plus the MVE ceramide-containing liquid cleanser, and 3.7 weeks in treatment group 1 using fluocinonide cream 0.05% plus the bar cleanser.

Global Assessment—The investigator assessed the global disease severity at baseline and weeks 1, 2, and 4 (Table). No statistically significant differences between the 3 treatment groups existed at baseline, which indicated that the treatment groups were well-balanced. By the end of week 1, concomitant use of fluocinonide cream 0.05% plus the MVE ceramide-containing liquid cleanser resulted in significantly better improvement in the global disease severity score compared with the use of fluocinonide cream 0.05% and the bar cleanser (P=.012). The increased improvement continued into week 2 but was not statistically significant. By week 4, there was again a statistically significant benefit to using fluocinonide cream 0.05% plus the MVE ceramide-containing liquid cleanser as opposed to the fluocinonide cream 0.05% plus the bar cleanser (P=.0443). Fluocinonide cream 0.05% used concomitantly with the MVE ceramide-containing liquid cleanser and moisturizing cream provided additional improvement from baseline at week 2 versus fluocinonide cream 0.05% plus MVE ceramide-containing liquid cleanser (P=.063).

Signs and Symptoms—The investigator assessed erythema, desquamation, papulation, lichenification, excoriation, and itching. For all signs and symptoms, treatment group 3 using fluocinonide cream 0.05% plus the MVE ceramide-containing liquid cleanser and moisturizing cream experienced the fastest onset and greatest improvement at all time points, followed by treatment group 2 using fluocinonide cream 0.05% plus the MVE ceramide-containing liquid cleanser, followed by treatment group 1 using fluocinonide cream 0.05% plus the bar cleanser. The improvements in erythema, desquamation, papulation, and lichenification were significantly greater at all time points in the 2 treatment groups using fluocinonide cream 0.05% plus the MVE ceramide-containing liquid cleanser compared with the treatment group using fluocinonide cream 0.05% plus the bar cleanser (P=.05). There was no difference between the 3 treatment groups for itching. There also was no difference for excoriation, but very few subjects demonstrated this finding, making the data irrelevant.

Comment

This study examined the benefits of adding an MVE ceramide-containing liquid cleanser and moisturizing cream to the traditional fluocinonide cream 0.05% used to treat mild to moderate eczema. Part of the enhanced efficacy of these skin care products is the unique construction of MVE and its interaction with eczematous skin. MVEs are manufactured using a cationic quaternary amine salt emulsifier, such as behentrimonium methosulfate. The active agents, such as ceramide, phytosphingosine, dimethicone, glycerin, and hyaluronic acid, are mixed into either the oil or water phase, depending on compatibility. High-shear mixing of the active agents with the emulsifier produces MVE. Behentrimonium methosulfate is the unique emulsifier that allows formation of the multilamellar concentric spheres of oil and water that trap the active agents in either the alternating lamellar lipid layers or within the aqueous sphere compartment. The structure of MVE can be appreciated with freeze fracture electron microscopy.

In addition to the distinctive MVE structure, the active agents that are delivered to the skin surface in a controlled-release manner are important. These active agents include ceramide, phytosphingosine, dimethicone, glycerin, and hyaluronic acid. Ceramides are produced in a rapid burst when skin barrier repair is initiated.[5] They also can function as occlusive agents, in combination with dimethicone, to decrease transepidermal water loss and provide an environment that is optimal for healing. Phytosphingosine, glycerin, and hyaluronic acid help to attract water to the epidermis and stratum corneum because they are classified as humectants. The newly hydrated stratum corneum retains the attracted water through the thin surface layer of the occlusive ceramides and dimethicone until barrier repair occurs and healing has been completed.[6] Thus, this combination of ingredients provides all of the elements necessary to facilitate the barrier repair process.

The healing facilitation induced by MVE technology was demonstrated in this study. The incidence of healing after 4 weeks of treatment with fluocinonide cream 0.05% and the bar cleanser can

be increased by 61% if the fluocinonide cream 0.05% is combined with an MVE ceramide-containing liquid cleanser and moisturizing cream. Similarly, the time to clearing can be reduced by 0.7 weeks with the latter treatment.

Conclusion

The results of this study demonstrate some interesting findings regarding the synergistic effects between topical prescription corticosteroids and over-the-counter skin cleansers and moisturizers. Both the physician and the patient want to achieve the fastest resolution possible of eczematous skin disease. This study demonstrated that comparable results can be achieved using either fluocinonide cream 0.05% and the bar cleanser for 4 weeks or fluocinonide cream 0.05% plus the MVE ceramide-containing liquid cleanser and moisturizing cream for 1 week. Careful selection of a cleanser and cream that are designed to speed skin barrier repair can decrease comparable healing time by 0.7 weeks, which may be expected because barrier repair must occur concomitantly with inflammation reduction for complete healing. Therefore, the addition of an MVE ceramide-containing liquid cleanser and moisturizing cream to a high-potency corticosteroid enhanced the treatment outcome of mild to moderate eczema compared with the use of a bar cleanser and high-potency corticosteroid in reducing disease duration, time to disease clearance, and symptoms. Thus, skin care product selection can have an important clinical effect on the clearance of mild to moderate eczema.

REFERENCES

1. Imokawa G, Akasaki S, Hattori M, et al. Selective recovery of deranged water-holding properties by stratum corneum lipids. *J Invest Dermatol.* 1986;87:758-761.
2. De Paepe K, Roseeuw D, Rogiers V. Repair of acetone- and sodium lauryl sulphate-damaged human skin barrier function using topically applied emulsions containing barrier lipids. *J Eur Acad Dermatol Venereol.* 2002;16: 587-594.
3. Espinoza R, inventor; HealthPoint, Ltd, assignee. Multivesicular emulsion drug delivery systems. US patent 6,709,663. March 23, 2004.
4. Gehring W, Wenz J, Gloor M. Influence of topically applied ceramide/phospholipid mixture on the barrier function of intact skin, atopic skin and experimentally induced barrier damage. *Int J Cosmet Sci.* 1997;19:143-156.
5. Yang L, Mao-Qiang M, Taljebini M, et al. Topical stratum corneum lipids accelerate barrier repair after tape stripping, solvent treatment and some but not all types of detergent treatment. *Br J Dermatol.* 1995;133: 679-685.
6. Zettersten EM, Ghadially R, Feingold KR, et al. Optimal ratios of topical stratum corneum lipids improve barrier recovery in chronologically aged skin. *J Am Acad Dermatol.* 1997;37(3, pt 1):403-408.