Effects of Azelaic Acid 15% Gel on Skin Barrier in Rosacea

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Patients with rosacea form a unique subset of individuals with sensitive skin. The redness, itching, stinging, burning, and chronic inflammation manifested as papules and pustules provide challenges in formulating both over-the-counter and prescription medications. Based on my experience, I estimate that approximately 50% to 75% of the calls made to cosmetic company hotlines regarding skin irritation are from individuals with rosacea. Thus, most large companies designing skin care products and cosmetics for sensitive skin will test their finished formulations on a population with rosacea prior to launching the products into a broader market. This challenge is even greater in the prescription realm, where drugs designed to treat rosacea must produce the desired clinical end point and also coexist with a vehicle designed for sensitive skin that delivers the bioactive molecule to the proper skin structure.

Designing a vehicle for the delivery of a medication for sensitive skin is indeed difficult. The vehicle must carry the drug to the skin in a form stable enough to achieve efficacy. Most vehicles must actually damage the stratum corneum to allow the drug to reach the target, which accounts for the incorporation of propylene glycol and fatty acids in many topical medications.[1] Barrier damage can be identified by patients as an increase in skin tightness and observed by the dermatologist as enhanced corneocyte desquamation.

This stratum corneum damage can be quantified in 2 ways, evaporimetry and corneometry. Evaporimetry measures increases in transepidermal water loss (TEWL) by utilizing 2 humidity meters at a known distance from the skin surface to gauge the water content of the skin vapors (Figure 1). If the skin barrier is damaged by topical medication, the amount of water loss will increase. Most topical drugs would not decrease TEWL, but a well-designed medication vehicle would be expected to remain barrier neutral. Complementary to evaporimetry is corneometry, which calculates changes in the skin's total water content. This is accomplished by applying a low-level electrical current to the skin. Water is the conductor, which transmits the current from the sending probe to the receiving probe. As the water content of the skin increases, electrical conductivity increases, along with the amount of electrical current (Figure 2). Continuous use of a well-constructed vehicle should not result in decreased corneometry readings.

This study was executed to evaluate the effects of the commonly prescribed topical rosacea medications azelaic acid 15% gel and metronidazole 1% gel on the sensitive skin of patients with rosacea by utilizing noninvasive and blinded-investigator assessments.

Method

This single-center study enrolled 50 female subjects ranging in age from 20 to 75 years who displayed mild to moderate erythematotelangiectatic rosacea, papulopustular rosacea, or both. Each subject signed an institutional review board–approved informed-consent form prior to enrollment in the study. All subjects underwent a 2-week washout period during which time they were instructed to use the provided study cleanser twice daily with no topical medications and no facial moisturizers. Subjects were randomized into 2 balanced groups. Group 1 applied azelaic acid 15% gel twice daily to one randomized side of the face for 2 weeks and nothing to the opposite side of the face for 2 weeks. Group 2 applied azelaic acid 15% gel once daily to one randomized side of the face for 2 weeks and metronidazole 1% gel once daily to the other side of the face for 2 weeks. Corneometry and TEWL measurements were made at the initiation of washout, baseline, and weeks 1 and 2.

TEWL measurements, an indicator of barrier damage, were made with an open-chamber evaporimeter. The difference in water vapor content between the 2 humidity meters as a measure of time represented the TEWL. Measurements were sampled at a rate of 5 inputs/s. The inputs were graphed as a real-time display and measured

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Dr. Draelos is a clinical investigator for, and this research was supported by an unrestricted educational grant from, Intendis GmbH.

Figure 1. This close-up view of the transepidermal water loss probe shows the humidity meters in the chamber through which the water vapor must flow to obtain an accurate measurement.

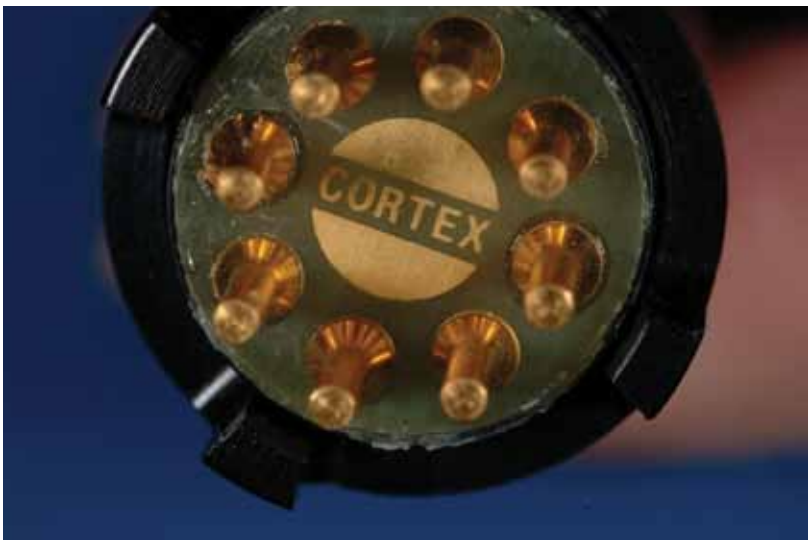

Figure 2. The corneometry probe consists of several pins used to measure the ability of skin to conduct electricity, an indirect measurement of cutaneous hydration.

as an average evaporative water loss rate over 20 seconds once steady-state conditions had been achieved.

Corneometry measurements were made with a pin probe designed to use electrical conductivity as an indirect measure of intracutaneous hydration. Increased water content is directly proportional to increased electrical conductance with water as the conductor.

A Mann-Whitney nonparametric 2-tailed test was used to evaluate the data with significance defined as $P \leq .05$ based on a 2-sided test.

Results

All 50 subjects successfully completed the study, and no adverse events occurred. The corneometry results were analyzed as change from washout, since the absolute numbers are not meaningful when compared among subjects. Higher corneometry measurements are consistent with increased skin hydration. At week 1, there was no statistically significant difference between group 1 and group 2. This indicates that none of the treatments functioned as a moisturizer after 1 week of use. However, at week 2, a statistically significant difference was seen between the groups treated with azelaic acid 15% gel once daily and twice daily and the group treated with metronidazole 1% gel. Better skin hydration that was statistically significant was observed in the azelaic acid 15% gel once-daily group ($P=.015$) and azelaic acid 15% gel twice-daily group ($P=.048$).

The TEWL measurements were also analyzed as change from washout. There was no change in TEWL at any point during the study in either group. Thus, none of the formulations or application schedules caused barrier damage.

The investigator assessed rosacea severity, erythema, desquamation, and irritation. No statistically significant increase in irritation or desquamation was seen in any of the 2 treatment groups. At the end of week 1, there were statistically significant decreases in erythema in the sides of the face treated with azelaic acid 15% gel once daily ($P=.007$) and metronidazole 1% gel ($P=.037$) when compared to the side of the face that received no treatment. Group 1 and group 2 showed no between-group differences in rosacea symptom improvement. All formulations as applied improved the signs of rosacea.

Comment

Ideal medications for the sensitive skin seen in patients with rosacea should be barrier neutral and slightly hydrating. This can be a challenge when formulating

a vehicle that provides adequate drug penetration in a stable form that is aesthetically pleasing. For difficult-to-dissolve drugs, such as metronidazole, this can be a challenge. Metronidazole is neither oil nor water soluble, requiring a sophisticated vehicle for delivery. This is accomplished through use of a β-cyclodextrin ring that has a polyhydric hydrophilic exterior surface for excellent water solubility and an interior hydrophobic cavity to enhance the solubility of metronidazole.[2] Azelaic acid, a particulate, is equally difficult to solubilize and requires the use of a gel that suspends the particles for delivery to the skin surface.[3] These interesting formulation challenges provided the impetus to investigate the effects of the vehicle on the facial skin barrier of rosacea patients.

No investigator-assessed change in barrier function, evaluated as an increase in desquamation or irritation, was noted after 2 weeks of applying azelaic acid 15% gel once or twice daily or applying metronidazole 1% gel. The TEWL measurements showed a slight increase in water loss as expected with a penetration-enhanced vehicle, but no statistically significant changes were noted. This indicates that both of the vehicles tested were barrier neutral and thus suitable for use by the sensitive-skinned patient with rosacea. Statistically significant improvement in skin hydration was observed after 2 weeks of once-daily and twice-daily applications of azelaic acid 15% gel as compared to 2 weeks of once-daily metronidazole 1% gel application. This finding may point to the increased moisturizing properties of the azelaic acid 15% gel vehicle. In summary, both formulations tested barrier neutral in a population of patients with rosacea.

References

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