The Effect of Vehicle Formulation on Acne Medication Tolerability

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Combination acne medications provide enhanced treatment opportunities. A commonly used acne therapy may combine a topical antibiotic with benzoyl peroxide (BPO) to prevent antibiotic resistance while optimizing control of microcomedone formation with a retinoid. Unfortunately, this combination of highly efficacious medications may cause irritation because of the inherent skin irritancy of BPO and retinoids. The present study was undertaken to determine if vehicle optimization of a clindamycin-BPO formulation could increase the tolerability of an added retinoid. Forty-six women with mild to moderate facial acne were enrolled in a 3-center, institutional review board–approved, 2-week, split-face study to compare an optimized vehicle (glycerin and dimethicone) clindamycin-BPO formulation with a traditional clindamycin-BPO formulation, with tretinoin cream 0.025% applied to the entire face. The use of the optimized vehicle clindamycin-BPO formulation in combination with tretinoin cream 0.025% resulted in significantly less erythema and dryness on evaluation days 4, 7, and 14 (P<.05), as assessed by the blinded dermatologist investigators. The incorporation of new vehicles into topical dermatologic medications allows medication combinations with enhanced tolerability.

Cutis. 2008;82:281-284.

New methods are presently available to formulate topical dermatologic medications. Originally, prescription creams, ointments, and lotions were designed to deliver medication to the skin surface and enhance penetration. The simplest combination of ingredients that solubilized the drug was selected partly to decrease development time and production costs. There was no need to evaluate the drug for skin tolerability because formulation technology had not developed to the point where aesthetics could be optimized. While drug research was continuing in the pharmaceutical industry, vehicle formulation was progressing in the cosmetic industry. Most currently marketed facial moisturizers are essentially vehicles. Combining the tolerability and aesthetics of a facial moisturizer with the efficacy of a prescription drug leads to formulation optimization. This new concept is now entering the realm of topical dermatologic medications.

One of the more commonly prescribed preparations for the treatment of inflammatory and comedonal acne is a clindamycin 1%–benzoyl peroxide (BPO) 5% gel. The combination of these 2 ingredients kills *Propionibacterium acnes* (clindamycin) and provides comedolytic activity (BPO).[1,2] However, the combination is more efficacious than either ingredient alone, as the BPO prevents antibiotic resistance to the clindamycin.[3,4] The addition of another topical medication, such as a retinoid, could address the issue of microcomedone formation, treating yet a third component of acne. Unfortunately, many patients cannot tolerate twice-daily

Accepted for publication August 16, 2007.

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This study was supported by an unrestricted educational grant from Stiefel Laboratories, Inc. Dr. Draelos is a researcher for Stiefel Laboratories, Inc. Dr. Callender is a consultant for, is on the advisory board and speakers bureau for, and has received research grants from Stiefel Laboratories, Inc. Dr. Young received a research grant from Stiefel Laboratories, Inc. Dr. Dhawan is a consultant for Stiefel Laboratories, Inc.

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facial application of a clindamycin-BPO preparation and nightly application of tretinoin. The inherent irritancy of the retinoid, enhanced by the BPO, creates a red, itchy, flaky face that is poorly tolerated by patients.

The facial irritancy experienced with this combination can be addressed in several ways. One solution is to apply the clindamycin-BPO preparation and the retinoid together at night followed by a moisturizer. The moisturizer can provide an environment for barrier repair, counteracting the damage induced by the medications. Another solution is to use a mild cleanser to minimize barrier damage. However, neither of these solutions may be workable. The moisturizer may not be acceptable to individuals with oily skin. Furthermore, the cleanser may not remove enough sebum to keep the growth of *P acnes* under control. A final solution may be to alternate nightly use of clindamycin-BPO preparation and the retinoid; however, this regimen may decrease product efficacy because of reduced application. The modern solution to this problem is to optimize the vehicle of the medication to prevent barrier damage to the greatest degree possible.

A newer clindamycin-BPO medication was developed with a modern, cosmetically suitable vehicle containing glycerin and dimethicone. Both ingredients are complementary because the glycerin attracts water to the skin, while the dimethicone prevents the water from being lost to the atmosphere.[5] Humectants are substances that attract water and are widely used in therapeutic skin moisturizers. Glycerin is known as a humectant.[6] Under conditions with ambient humidity exceeding 70%, it is possible for glycerin to draw water from the atmosphere, which is not desirable in a topical dermatologic preparation because the cream or gel would become sticky shortly after application. For this reason, high concentrations of glycerin are not used. It is more desirable for the water to be drawn from the deeper epidermal and dermal tissues to rehydrate the stratum corneum. However, glycerin is not a good stand-alone vehicle ingredient in a medication that may exacerbate barrier damage because the water attracted by the glycerin will be rapidly lost to the environment through the damaged barrier.[7]

Dimethicone frequently is combined with glycerin to create an artificial occlusive barrier to retard water loss from the skin surface to the atmosphere until barrier repair can occur. For this reason, dimethicone is a key moisturizing ingredient and forms the basis for all oil-free moisturizers because it is not a vegetable or mineral oil. From a dermatologic standpoint, dimethicone is the ideal skin barrier enhancer because it is hypoallergenic, noncomedogenic, and nonacnegenic.

Dimethicone is one of the substances that forms the family of silicones. Silicone was developed in the 1930s when Franklin, Hyde, and McGragor discovered a method of extracting pure silica from raw quartzite, converting it to dimethyl silicone. Silicone originates from silica, which is found in sand, quartz, and granite. It derives its properties from the alternating silica and oxygen bonds, known as siloxane bonds, which are exceedingly strong.[8] These strong bonds characterize the chemical structure of silicone and account for the tremendous thermal and oxidizing stability of silicone. Silicone is resistant to decomposition from UV radiation, acids, alkalis, ozone, and electrical discharges.[8] The silicone used in topical dermatologic preparations is an odorless, colorless, nontoxic liquid. It is soluble in aromatic and halocarbon solvents but poorly soluble in polar and aliphatic solutes. Because silicone is immiscible and insoluble in water, it is used in a variety of skin preparations for enhancing the skin barrier. It functions as a nongreasy occlusive agent, putting a thin water-impermeable film over damaged skin that exhibits increased transepidermal water loss. The film maximizes the environment for barrier repair, which is necessary for the healing of xerotic and dermatitis skin conditions. It also creates an artificial barrier until the skin can repair itself. Lastly, it increases skin smoothness by functioning as an emollient to fill in gaps where damaged corneocytes are missing from the stratum corneum. This quality is known as emolliency and makes the skin feel soft to the touch, an important aesthetic quality to patients.

In combination with glycerin, dimethicone is an ideal agent for incorporation into acne medications because of the moisturizing and barrier-enhancing benefits as well as its ability to smooth desquamating skin scale during the early stages of facial retinization. The improvement in skin appearance from dimethicone combined with glycerin may increase compliance among patients with acne who are concerned about their appearance.

The present study was undertaken to evaluate a dimethicone vehicle–optimized clindamycin-BPO acne preparation in combination with tretinoin cream 0.025% compared with a traditional clindamycin-BPO acne preparation with tretinoin cream 0.025%. The goal was to determine if a cosmetically enhanced vehicle could decrease the erythema, dryness, and scaling commonly associated with the use of multiple acne medications.

Methods

Forty-six women 21 years and older with any Fitzpatrick skin type were enrolled in this institutional review board–approved 2-week investigator-blinded study after properly completing the consent process. The research was conducted at 3 separate geographic sites in North Carolina, Maryland, and California. The participants were required to have mild to moderate facial acne, defined as a minimum of 8 inflammatory papules and/or pustules, a minimum of 8 and a maximum of 100 noninflammatory open and/or closed comedones, and no more than 1 nodulocystic lesion. Women of childbearing potential were required to have a negative urine pregnancy test result at baseline and to practice an effective method of contraception throughout the study. No individuals with facial skin disease or hypersensitivity to any of the study product ingredients were enrolled in the study.

All participants underwent a 14-day washout period following enrollment. During this time, use of topical acne medications was not permitted and facial care was standardized using a designated nonmedicated bar soap. Systemic acne treatments, corticosteroids, and oral antibiotics were not to be used 30 days prior to study initiation. Participants were not permitted to initiate or discontinue oral contraceptives during the study or for 30 days prior to study enrollment. No sunscreens or facial moisturizers were allowed during the study.

Following the washout period, participants were asked to apply tretinoin cream 0.025% to the entire face each evening. Participants were randomized to apply the optimized vehicle clindamycin-BPO formulation to the right side of the face and the traditional clindamycin-BPO formulation to the left side of the face, or vice versa. Each clindamycin-BPO formulation was applied 60 minutes after the tretinoin cream 0.025% in the evening. Participants were evaluated at baseline and days 4, 7, and 14.

At baseline, participants were asked to rate their skin sensitivity on a 5-point scale (0=I do not have sensitive skin; 1=my skin is minimally sensitive; 2=my skin is mildly sensitive; 3=my skin is moderately sensitive; 4=my skin is extremely sensitive). Participants also were asked to evaluate their local skin tolerance for each side of their face separately at each visit on a 4-point scale in terms of erythema and dryness (0=none; 1=slight; 2=some; 3=very) and pruritus and burning (0=none; 1=slight; 2=moderate; 3=strong). Participants completed a questionnaire regarding their perception of each product in terms of preference and cosmetic acceptability. The investigators evaluated each participant's acne severity at baseline, including inflammatory and noninflammatory acne lesion counts and nodulocystic lesion counts. Both sides of the face were evaluated separately for erythema, dryness, and peeling (0=none; 1=slight; 2=some; 3=very) by the investigators at baseline and days 4, 7, and 14.

Statistical significance was defined as $P<.05$. Changes from baseline in investigator scores were evaluated using an analysis of covariance with effects for treatment and baseline value. The frequency of tolerance scores were compared using the Fisher exact test. Finally, the participant questionnaires were assessed using a binomial test for product preference and the Fisher exact test for cosmetic acceptability questions. The safety measure was the analysis of adverse events.

Results

A total of 43 of 46 participants completed the 2-week study. Three participants withdrew from the study and were lost to follow-up. The enrolled participants were white (27/43 [63%]) and black (16/43 [37%]) with a mean age of 32 years. All of the participants were women. At enrollment, the participants had a mean inflammatory acne lesion count of 14 and a mean noninflammatory acne lesion count of 24.

The investigators noted better tolerability for the optimized vehicle clindamycin-BPO formulation compared with the traditional clindamycin-BPO formulation at multiple time points. At days 4, 7, and 14, there was a statistically significant decrease in erythema and dryness with the optimized vehicle clindamycin-BPO formulation ($P<.05$). Additionally, significant reductions in peeling were seen at days 4 and 7 with the optimized vehicle clindamycin-BPO formulation ($P<.05$).

The participants noted significantly less dryness at days 4 and 7 with the optimized vehicle clindamycin-BPO formulation ($P<.05$). Burning also was significantly reduced at day 4 with the optimized vehicle clindamycin-BPO formulation ($P<.05$). Overall, significantly more participants (65% [28/43]) thought the optimized vehicle clindamycin-BPO formulation was gentler to the skin ($P<.05$). Both products were believed to be equally cosmetically acceptable.

There were no significant safety differences between the 2 tested clindamycin-BPO formulations; however, the safety profile was better for the optimized vehicle clindamycin-BPO formulation.

Comment

Dermatologic medicine is experiencing the development of new medications that combine therapeutic and cosmeceutic benefits. In the present study, the

vehicle for the medication became an active ingredient to deliver skin benefits as well as the active drug. Vehicles are no longer simply meant to solubilize the drug and function as a penetration enhancer; now they are intended to deliver the drug as well as maintain or enhance the skin barrier. Dimethicone is a major multifunctional ingredient that is able to act as an occlusive moisturizer, emollient, and artificial barrier. It is an active ingredient labeled as a skin protectant in many over-the-counter formulations, including lip balms, hand creams, and ostomy care products. The combination of glycerin and dimethicone provides a robust humectant and occlusive vehicle formulation for the delivery of acne medications. The formulation studied in this research contained both glycerin and dimethicone. It was compared with a nonbarrier-enhancing formulation with the same active ingredients (clindamycin and BPO) in participants using tretinoin cream 0.025% nightly. The results demonstrated that both the blinded investigators and the participants noted a statistically significant reduction in dryness with the optimized vehicle clindamycin-BPO formulation as opposed to the traditional clindamycin-BPO formulation after 4, 7, and 14 days of use ($P<.05$). This finding may be attributable to the inclusion of glycerin and dimethicone.

This research demonstrates the value of creating dermatologic medications with enhanced tolerability. In many ways, tolerability is a measure of the ability of the drug and vehicle to maintain the integrity of the stratum corneum barrier composed of protein-rich corneocytes and intercellular lipids. Topical medications that damage this barrier will be perceived as less tolerable than those medications that maintain or enhance the barrier. Poor tolerability, as observed in clinical practice, often leads to treatment noncompliance. Therefore, for optimal therapy, the goal of modern topical dermatologic medications should be to make both the drug and the vehicle work synergistically to heal the skin.

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