

The Tolerability of Topical Tretinoin and Oral Minocycline Hydrochloride With and Without Anti-inflammatory Skin Care Products



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Acne is a common dermatologic condition requiring a variety of treatments, depending on the severity of the disease. Acne is diverse in its presentation, depending on the location of the follicular plug, and consists of noninflammatory lesions, inflammatory lesions, or both. The noninflammatory lesions, consisting of open and closed comedones, are due to follicular plugs high in the follicular ostia, amenable to topical therapy.¹ The most effective therapies are those that both improve follicular keratinization and decrease the formation of microcomedones. The one topical agent that is able to function optimally in both of these capacities is the retinoid tretinoin.²

Despite proven efficacy in the treatment of comedonal and mild inflammatory acne, topical tretinoin is not well accepted by patients because of its inherent irritation. The first 2 weeks of therapy are marked by erythema, desquamation, stinging, and burning. This is caused by the effect of hypervitaminosis A on the skin, a phase of treatment known as retinization.³ Many acne patients discontinue tretinoin therapy during the first 2 weeks, citing poor tolerability.⁴ A novel approach to improve compliance with topical tretinoin is combining aesthetically pleasing topical skin care products with prescription acne therapy. Thus, the drying effect of tretinoin can be offset by providing patients with a well-formulated cleanser and moisturizer and codispersing these with prescription tretinoin.

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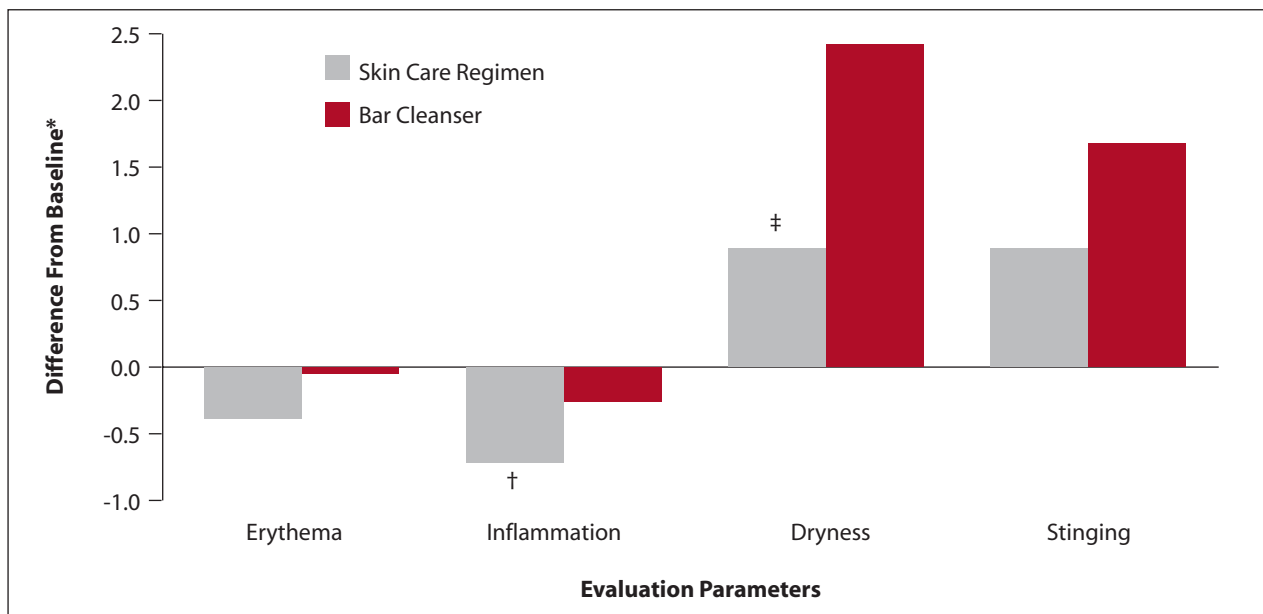
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Topical tretinoin may be prescribed along with an oral antibiotic for the treatment of moderate to severe inflammatory acne. A commonly utilized antibiotic is minocycline hydrochloride, known for its anti-inflammatory and antibacterial effects.⁵ This study was designed to evaluate the tolerability of topical tretinoin 0.025% cream in combination with oral minocycline hydrochloride for the treatment of moderate to severe acne when combined with a variety of specially formulated skin care products to include a moisturizer, cleanser, facial wipe, serum, and mask.

Method

Forty subjects older than 14 years presenting with a clinical diagnosis of moderate to severe acne (defined as a minimum of 15 inflammatory lesions, 25 noninflammatory lesions, and fewer than 3 cysts) were enrolled in a single-center, single-blind study. The 40 subjects were randomized into 2 balanced groups at baseline. Group 1 used topical tretinoin 0.025% cream at bedtime and the accompanying moisturizer and cleanser twice daily in combination with 50 mg of oral minocycline hydrochloride pellet-filled capsules twice daily. A facial wipe and serum were provided for use as needed along with a mask to be used once weekly. Group 2 used a synthetic detergent bar cleanser and received 50 mg of oral minocycline hydrochloride pellet-filled capsules twice daily along with a nightly application of topical tretinoin 0.025% cream. No additional skin care products were allowed or provided.

At baseline, the blinded investigator performed a relevant medical history and examination of each subject. Male and nonpregnant, nonlactating female subjects who signed an institutional review board–approved informed consent form were enrolled in the study. The blinded



Investigator-noted difference from baseline tolerability assessment of subjects using topical tretinoin 0.025% cream in combination with 50 mg oral minocycline hydrochloride and a skin care regimen and subjects using topical tretinoin 0.025% in combination with 50 mg oral minocycline hydrochloride and bar cleanser. The difference from baseline calculation means that a more negative number or lower number is indicative of superior performance. A well-constructed skin care regimen has statistically reduced the incidence of inflammation and dryness following the initial 2 weeks of facial retinization. Asterisk indicates difference in scores on an ordinal scale where 0=none, 1=minimal, 2=mild, 3=moderate, 4=moderately severe, 5=severe; dagger, $P=.039$; double dagger, $P=.005$.

investigator assessed acne severity and skin appearance for erythema, inflammation, dryness, and stinging on an ordinal 6-point scale. The ordinal scale was defined as follows: 0=none, 1=minimal, 2=mild, 3=moderate, 4=moderately severe, and 5=severe. Digital photography with a 3-point head restraint was also completed. Noninvasive measurements consisting of dermospectrophotometry, transepidermal water loss ([TEWL] measuring water leaving the skin), and corneometry (measuring the concentrated water in the skin) were obtained in duplicate from both cheeks of each subject. Subjects returned to the research center at week 2 to repeat all assessments and conclude the tolerability study.

The goal of the study was to evaluate the effect of the specially designed and concomitantly dispensed skin care products on subject tolerability. The cleanser, designed to minimize facial dryness induced by tretinoin, contained mild synthetic surfactants in combination with the anti-inflammatory agents green tea and ubiquinone. The moisturizer contained aloe vera, green tea, and a dipeptide along with glycerin to minimize scaling and redness. The facial wipe, designed for use away from home and packaged in a disposable foil pouch, contained water in combination with the water-attracting moisturizers glycerin, sodium pyroglutamic acid, panthenol, and sodium hyaluronate. A serum was also included to decrease skin

inflammation and contained bisabolol, a chamomile extract, silymarin, and green tea. Finally, the algae and glycerin mask was used once weekly to decrease skin dehydration. These products were designed to prevent the compliance issues associated with the first 2 weeks of tretinoin use by minimizing erythema, desquamation, stinging, and burning.

Results

Of the 40 subjects enrolled, 37 subjects completed the 2-week tolerability study. Two subjects withdrew from the study because of oral minocycline hydrochloride side effects. One subject was lost to follow-up and could not be contacted following study enrollment. No adverse events occurred during the study.

After 2 weeks of using topical tretinoin 0.025% cream, the blinded investigator noted a statistically significant reduction in inflammation ($P=.039$) and dryness ($P=.005$) resulting from using the skin care system as compared to using the bar cleanser alone (Figure). No statistically significant differences were noted in terms of patient-reported stinging. The noninvasive assessments of corneometry and TEWL showed no statistically significant difference between the 2 skin care groups. Dermospectrophotometry measurements did not show any statistically significant increase in erythema.

COSMETIC CONSULTATION

Comment

The study validated the novel concept of developing complementary skin care products to codispense with efficacious prescription oral and topical acne therapies. This new approach to acne treatment rose out of the recognition that skin care products have a profound cutaneous effect with the ability to enhance or detract from prescription therapy. For example, topical tretinoin 0.025% cream represents one of the most effective topical therapies for prevention of microcomedones, the acne-initiating lesion. Many adolescents and young adults discontinue tretinoin within the first 2 weeks of use because of the unwanted side effects of dryness, flaking, and redness; however, 2 weeks is an insufficient duration of use to appreciate the therapeutic benefits. This study examined a codispensed cleanser and moisturizer designed to complement retinoid side effects. The mild surfactant cleanser was able to effectively remove sebum without damaging the skin barrier, as evidenced by the lack of change in corneometry and TEWL measurements during the study. The lack of barrier damage was also prevented by the glycerin-rich moisturizer. Glycerin is a humectant that attracts water to rehydrate the retinoid-induced keratinocyte desquamation. The addition of aloe vera gel, containing the anti-inflammatory methyl salicylate, and the dipeptide, which provides a protective film over the skin's surface, further prevents retinoid damage.

One of the major reasons that acne therapy can be ineffective is lack of compliance. Many adolescents are sporadic in their use of tretinoin because of the side effects discussed previously, which prevent patients from completing the facial retinization phase of treatment. The use of a complementary cleanser and moisturizer, rather than patient self-selected products, may enhance compliance, thus improving the results of acne therapy.

In addition to the codispensed cleanser and moisturizers, the study also provided oral minocycline hydrochloride pellet-filled capsules and a specially formulated facial wipe, serum, and mask. These latter 3 products were designed to provide a complete skin care regimen when combined with the cleanser and moisturizer. The

facial wipe was developed to appeal to the busy adolescent who needs a mild, self-contained, all-in-one cleanser and moisturizer to use after school or following athletic practice. The facial wipe is a woven fiber pad containing water that removes dirt from the face. The facial wipe also contains a mixture of humectants, glycerin, sodium pyroglutamic acid, panthenol, and sodium hyaluronate that attracts water and smoothes down desquamating corneocytes. The facial wipe and its packaging can be easily disposed of after use.

The serum and mask were dispensed with oral minocycline hydrochloride. The serum is a mild moisturizer containing a botanical anti-inflammatory blend of bisabolol, silymarin, and green tea. These ingredients are designed to minimize the erythema associated with both acne and retinoid dermatitis. This botanical combination is frequently used in cosmetic products designed for sensitive skin because ingredient-induced irritation can be minimized. The mask builds upon this concept by providing further assistance with retinoid dermatitis by rehydrating the skin with glycerin and algae humectants.

After 2 weeks of using topical tretinoin 0.025% cream, the blinded investigator noted a statistically significant reduction in retinoid-induced inflammation ($P=.039$) and dryness ($P=.005$) from using the skin care system as compared to using the bar cleanser alone. Thus, the use of complementary codispensed skin care products may improve the tolerability of topical tretinoin 0.025% cream when used in combination with oral minocycline hydrochloride.

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