Cumulative Irritation Potential of Adapalene 0.1% Cream and Gel Compared With Tretinoin Microsphere 0.04% and 0.1%

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Despite the many beneficial effects of dermatologic applications, most of the current treatments for acne cause local irritation. The objective of this study was to compare the ability of the epidermis to tolerate adapalene 0.1% cream and gel and tretinoin microsphere in concentrations of 0.04% and 0.1%. A total of 31 subjects were enrolled in the study. The test products were applied under occlusive dressings on the upper back for approximately 24 hours, 4 times a week, and for 72 hours, once a week, for a period of 3 weeks. Skin reactions (erythema score plus other local reactions) at the product application sites were assessed 5 to 30 minutes after dressing removal.

Twenty-six subjects completed the study. A total of 10 subjects discontinued use of 1 or more of the test products because of irritation scores reaching severe or greater; all of these discontinuations were at sites treated with the tretinoin products.

The mean 21-day cumulative irritancy indices for adapalene 0.1% cream and gel were significantly lower (P<.01) than those for tretinoin microsphere 0.04% and 0.1% and not higher than that of the negative control product.

Cutis. 2005;75:238-243.

During the last 20 years, the number of topical and systemic drugs used in the treatment of acne vulgaris has been enriched. Topical new drugs have been discovered, and further development of already available formulations has improved both efficacy and safety.[1] Despite these beneficial effects, many retinoids and derivatives still cause local irritation, which is manifested as erythema and peeling of the stratum corneum.[2]

Adapalene, a naphthoic acid derivative with retinoid activity, is effective in the treatment of mild to moderate acne vulgaris. Adapalene gel 0.1% has been shown to be better tolerated than several tretinoin formulations.[3]

Tretinoin, an all-*trans*-retinoic acid used in the topical treatment of acne for more than 30 years, acts to normalize desquamation of follicular epithelium, promote drainage of comedones, and inhibit formation of new ones.[4,5]

Clinical studies have shown that patients treated with adapalene gel 0.1% had fewer incidents and less severe skin irritation than those treated with tretinoin 0.025% gel and creams.[6,7] Because of the known irritation potential of topical retinoic acid products, 2 new different formulations of retinoic acid, tretinoin microsphere 0.1% and 0.04%, were

Accepted for publication November 2, 2004.
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Dr. Dosik receives research grants from Galderma R&D, Inc. Mr. Homer is an employee of TKL Research, Inc, which was under contract with Galderma R&D, Inc. Ms. Arsonnaud is an employee of Galderma R&D, Inc. This study was supported by a research grant from Galderma R&D, Inc.
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Table 1.

Classification of Irritation

Mean Cumulative Irritancy Index	Product Classification
<0.025	Nonirritating
0.025–1 (noninclusive)	Slightly irritating
>1–2 (noninclusive)	Moderately irritating
>2–3 (noninclusive)	Very irritating

Table 2.

Demographics and Subject Disposition

	N=31
Age, y	
Mean±SD	39.7±12.0
Range	20–61
Gender, n (%)	
Female	29 (93.5)
Male	2 (6.5)
Race, n (%)	
White	24 (77.4)
Hispanic	7 (22.6)
No. of subjects who discontinued, n (%)	5 (16.1)
Because of an adverse event	0
At subject's request	3 (9.7)
Lost to follow-up	2 (6.5)
No. of subjects who completed, n (%)	26 (83.9)

developed to reduce the local irritation that occurs in the currently available tretinoin formulations and concentrations.

This present study was designed to compare, in a 21-day cumulative irritancy assay, the irritation potential of both adapalene 0.1% cream and gel with the new tretinoin microsphere in 0.1% and 0.04% formulations, with white petrolatum serving as a negative control.

The 21-day cumulative irritancy assay currently is used to assess the irritation potential of topically applied materials. Potential irritation is caused by direct damage to the epidermal cells; no immunologic (allergic) mechanisms are involved.[3] Results from this standard assay are widely accepted to be indicators of irritation.[8]

Methods

The study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments and in compliance with good clinical practice. Before entering the study, approval from an independent review board was obtained, and all subjects provided written informed consent.

Population—Subjects of any gender and race, aged at least 18 years, and with Fitzpatrick phototype I to IV were included in the study.[9] Female subjects had to have a negative urine pregnancy test at the beginning of the study.

Subjects with any surgical or medical condition (eg, history of atopic dermatitis, eczema, psoriasis) or with known sensitivities to any ingredients in the test products were excluded from the study.

In addition, subjects who did not conform to the washout period of between 1 and 12 weeks for topical and systemic medications (eg, oral corticosteroids, nonsteroidal anti-inflammatory drugs, salicylic acid >1 g/d, any oral retinoids) were excluded from the study.

Study Design—The design of this study is standard for the determination of the 21-day cumulative irritancy assay. The use of comparative treatments and a negative control product provided appropriate control in the study.

This was a single-center, active-controlled and negative-controlled, investigator-blinded, intraindividual comparison study, with randomized applications of study products to healthy subjects meeting specific inclusion and exclusion criteria.

To ensure the completion of 25 subjects, a total of 31 subjects were selected. All subjects received repeated applications of the 5 study products on the upper back under occlusive dressings for a period of

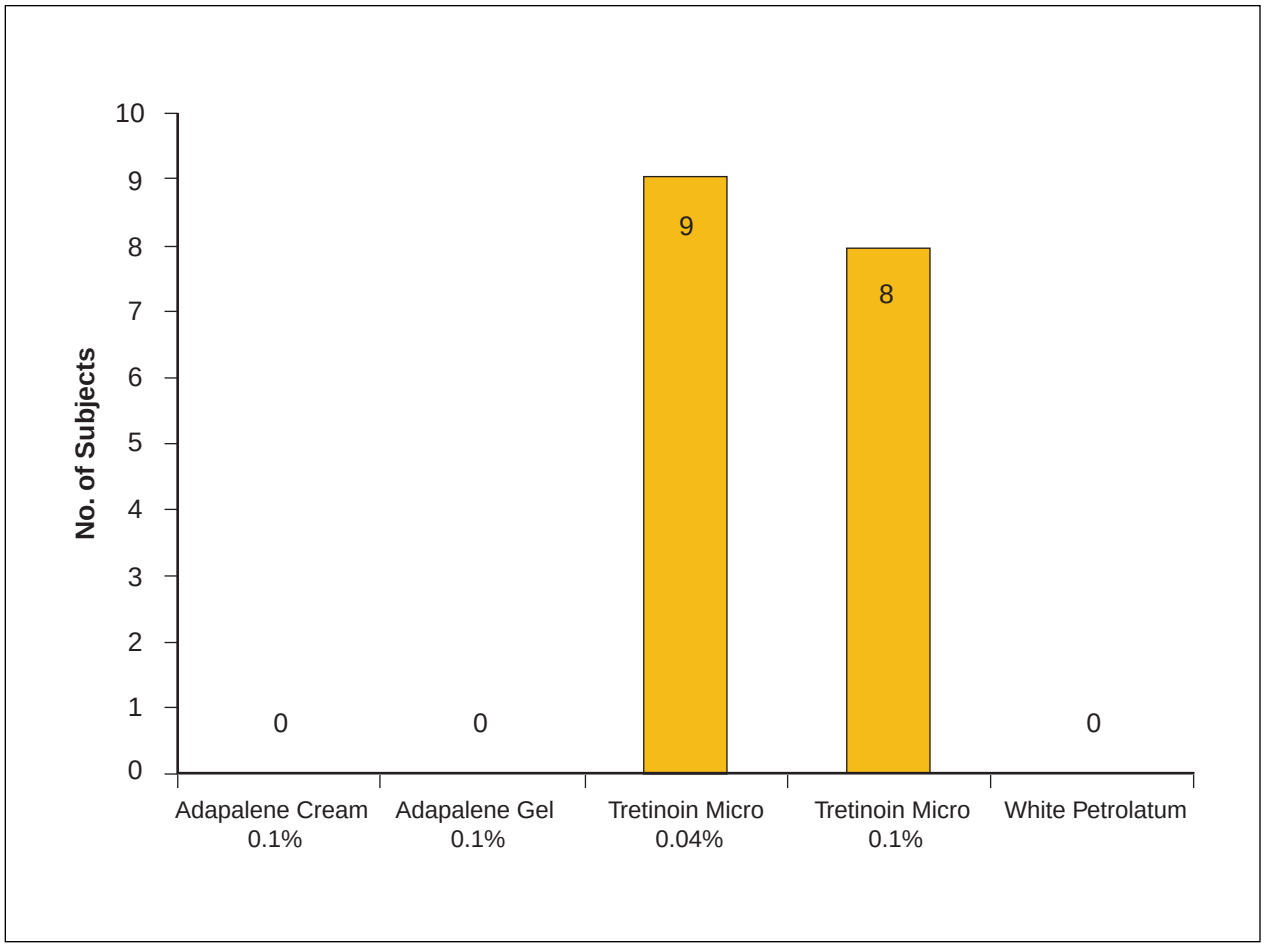

Figure 1. Discontinuation of treatment regimens during the course of the study.

Table 3.

Mean Cumulative Irritancy Index (MCII) by Tested Products

Study Products	MCII±SD	Differences			
		Adapalene gel 0.1%	Tretinoin microsphere 0.04%	Tretinoin microsphere 0.1%	White petrolatum
Adapalene cream 0.1%	0.05±0.15	−0.04	−0.67*	−0.62*	0.03
Adapalene gel 0.1%	0.09±0.16		−0.62*	−0.58*	0.08
Tretinoin microsphere 0.04%	0.71±0.46			0.04	0.70*
Tretinoin microsphere 0.1%	0.67±0.41				0.66*
White petrolatum	0.01±0.07				

*$P \leq .01$.

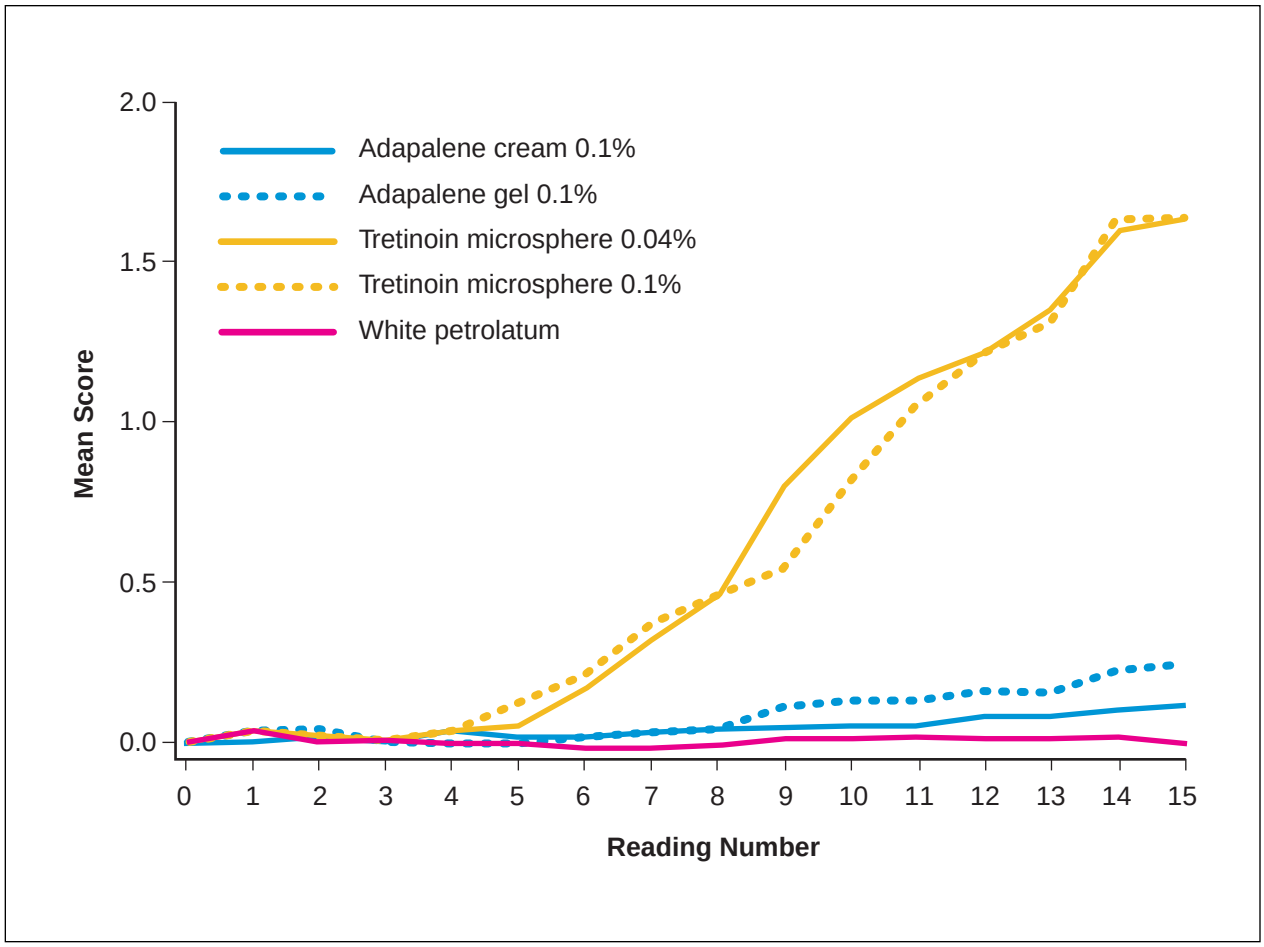

Figure 2. Mean individual treatment score for local tolerance by reading number.

3 weeks. The primary parameter of interest was an assessment of cumulative product irritancy, based on visual grading of erythema and other local skin reactions at the application sites.

At each visit, following the initial dressing application, skin reactions were assessed 15 to 30 minutes after removal of the product. When an erythema reaction related to a product received a score of 3 (severe) at 1 or more sites, product applications at the incriminated sites were discontinued. Likewise, if an irritation reaction was related to the adhesive, product applications at all sites were discontinued.

Test Products—Product applications were performed at the investigational site. Five zones (measuring 2×2 cm in diameter) were selected on the upper back of each subject, avoiding any moles, hairs, or nonflat areas. On initiation, each of the products was applied randomly to one of the zones on the upper back according to a predefined randomization schedule.

All efforts were made to keep the evaluator blinded to the identification of the products applied. Thus, the individual applying and removing the product was different from the individual evaluating the sites. The randomization list was kept from the evaluator.

Each zone was delineated with a cutaneous marker. The zones were designated by the numbers 1, 2, 3, 4, and 5 on one side of the spine. About 0.2 g of each product (adapalene 0.1% cream or gel, tretinoin microsphere 0.04 or 0.1%, and white petrolatum) was applied under an occlusive dressing (large Finn Chambers, a system that protects skin from rubbing against clothing), by a qualified member of the study site to its designated zone.

Dressings were applied at each visit and removed at the subsequent visit, approximately 24 hours later. However, those applied on Friday were left on for 72 hours over the weekend and removed the following Monday.

Furthermore, subjects were asked to avoid exposure to the sun, including sunbathing or other

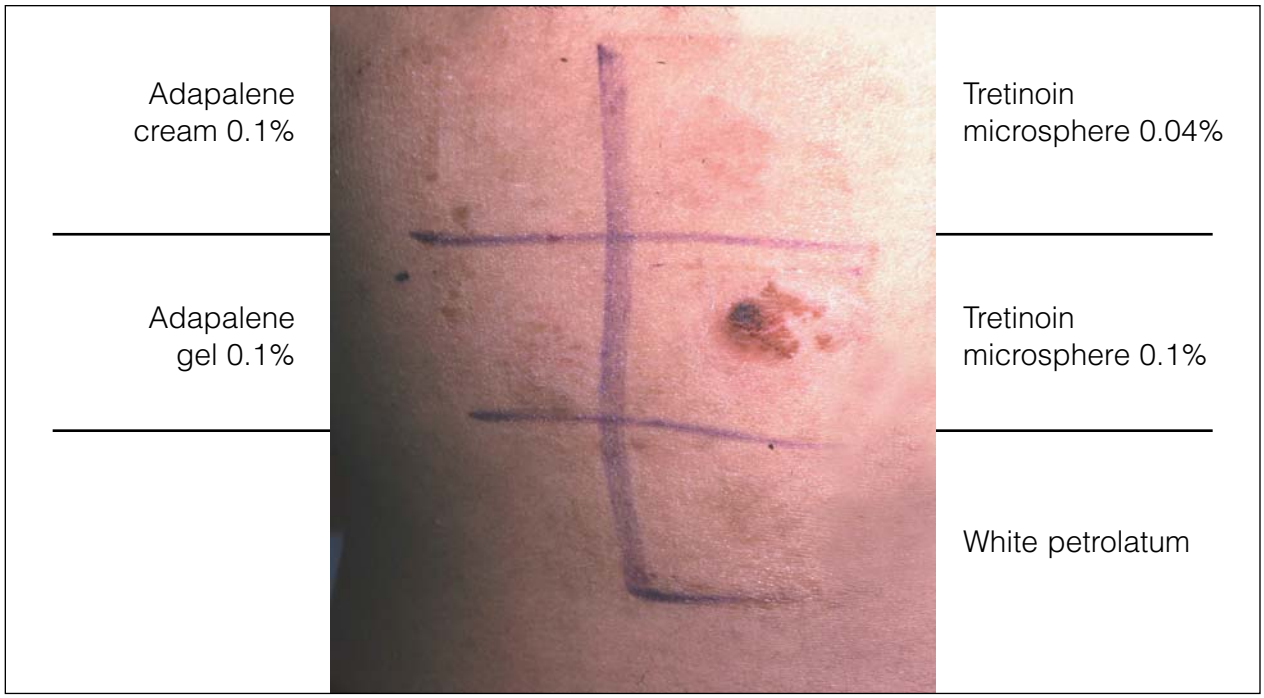

Figure 3. Example of irritation to test products after 14 days of application.

excessive exposure to UV irradiation (eg, tanning parlors); to avoid using any cosmetics on the study zone; and to avoid bathing or showering the upper back.

Clinical Evaluation—Evaluation visits took place every day except weekends. Each treated site on each subject's back was assessed for erythema and other local cutaneous irritation before the initial treatment application, and again at every study visit, approximately 15 to 30 minutes after dressing removal and before the following application.

Erythema was graded on a scale of 0 to 3, with 0 being no reaction and 3 being severe. If there was an erythema score of 3 (severe irritation) at a clinical evaluation or as described by the subject for any zone, product applications at the incriminated sites were discontinued and no longer scored.

Other local cutaneous irritation reported throughout the study included edema, papules, vesiculation, blisters, pustules, hyperpigmentation, weeping or oozing, and spreading of reaction beyond the test area evaluated.

When an irritation reaction related to the adhesive prohibited dressing at a particular site, all product applications at the treated sites were discontinued, and the scores carried forward to the end of the study. Safety was monitored through each individual's report of adverse events.

Statistical Analysis—Twenty-five subjects were considered an accepted sample size to evaluate the irritation potential of topical products that had already been tested in large populations. To account for possible dropouts, at least 30 subjects had to be enrolled to ensure the completion of 25 subjects. To allow a balanced design, this number is a multiple of the number of test products.

For evaluating the cutaneous tolerance, a cumulative irritancy index (CII) was calculated for each treatment and for each subject, as follows: CII equals the sum of irritation score and the number of readings. Classification of mean CII (MCII) is provided in Table 1.

To calculate the CII, the baseline score (day 0) was excluded from the calculation. When an irritation reaction was rated as 3 (severe) at any site, product applications at the incriminated sites were discontinued, and a score of 3 was imputed to the remaining readings (last observation carried forward). If product application was discontinued at a site because of a cause other than product irritation (eg, adhesive irritation), product applications at all sites were discontinued, and the last reading of each site was carried forward. If a subject missed a scheduled visit, the scores from the following visit were assigned to the missed visit.

CIIs were averaged across subjects to obtain an MCII for each treatment. CIIs were submitted to an analysis of variance with effects for subject, zone, and formulation. To adjust for multiple comparisons,

MCIIs were compared and formulations classified using the Tukey multiple comparisons procedure performed at the 1% and 5% significance levels. There was a maximum of 15 readings in the study.

Results

Population—Of the 31 subjects enrolled in the study, 26 (83.9%) completed the study. Table 2 shows demographics and subject disposition.

All female subjects of childbearing potential had to have a negative urine pregnancy test on enrollment in the study. No subjects had a medical history that precluded him or her from study participation.

Subjects received 15 applications of all study products for a period of 3 weeks. Exceptions to the full protocol-specified treatment regimen were 5 subjects who discontinued the study prematurely, 1 who missed one visit, 10 who discontinued treatment at specific application sites because of product-related irritation, and 1 who missed one visit and also discontinued treatment at specific application sites (Figure 1). No treatment-related adverse events were reported during the study.

The MCIIs ranged from approximately 0.05 to 0.71 for the 4 active test products. The lowest MCII was at sites treated with white petrolatum (0.01), and the highest MCII was at sites treated with tretinoin microsphere 0.04% (0.71).

Test Products—Both adapalene products and the white petrolatum were significantly less irritating than the tretinoin products ($P \leq .01$ and $P \leq .05$, respectively). Tretinoin microsphere 0.04% and 0.1% had MCIIs similar to each other (Table 3 and Figure 2). Figure 3 shows an example of irritation with tretinoin microsphere 0.1% after 14 days of application.

Individual reactions to the test products ranged from "no reaction" to "severe erythema with weeping or oozing." Reactions to white petrolatum did not exceed "mild erythema," and reactions to adapalene cream 0.1% did not exceed "mild erythema with a marked reaction to plaster." The most severe reaction observed in response to treatment with adapalene gel 0.1% was "moderate erythema," seen in one subject. Nine subjects discontinued treatment with tretinoin microsphere 0.04%, and 8 subjects discontinued treatment with tretinoin microsphere 0.1%, all because of limiting reactions.

Conclusion

In this study, adapalene gel and cream, both in a concentration of 0.1%, were shown to be less irritating than tretinoin microsphere in concentrations of 0.04% and 0.1%.

Acknowledgment—The authors would like to thank Patrick Göritz, Galderma R&D, Inc, for his support in writing this article.

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