Cumulative Irritancy Potential of Adapalene Cream 0.1% Compared With Adapalene Gel 0.1% and Several Tretinoin Formulations

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Thirty-one subjects (8 males and 23 females; mean age, 49.8 years) were enrolled in a single-center study to assess the irritancy potential of adapalene (Differin® cream 0.1% and Differin gel 0.1%) and tretinoin (Avita® cream 0.025%, Retin-A® cream 0.025%, Retin-A® cream 0.05%, Retin-A Micro® gel 0.1%, and generic cream 0.025%) as compared with white petrolatum when applied under occlusive conditions. All test materials were applied randomly under occlusion to sites located on the upper area of the subject's back under protective patches. All patches were applied to the same sites unless the degree of reaction to a test product or the adhesive necessitated removal (grade 3). Each test material was applied daily, Monday through Friday, for approximately 24 hours, with the Friday patches left in place over the weekend. Twenty-six of the 31 subjects (84%) completed the study. No subject discontinued because of an adverse event. Five subjects voluntarily discontinued the study early for reasons unrelated to study treatment (4 subject request and 1 lost to follow-up). In the statistical comparison of the 7 test products, the mean cumulative irritancy index of both adapalene cream 0.1% and gel 0.1% was statistically significantly (P<.05) lower than for all of the tretinoin products used and was not significantly higher than the negative control product (white petrolatum).

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Adapalene is a naphthoic-acid derivative with retinoid activity that is effective for the treatment of mild to moderate acne vulgaris.[1,2] Previous studies have shown adapalene gel to be significantly less irritating than either tretinoin cream or gel under both occlusive and nonocclusive conditions.[3-6] Adapalene cream was formulated in a moisturizing base to help relieve the dryness associated with topical retinoid therapy.

The cumulative irritancy assay (patch test) is designed to assess the irritation potential of topically applied materials. The irritation is caused by direct damage to the epidermal cells, and no immunologic (allergic) mechanism is involved. Results from this standard assay are widely accepted to be indicators of irritation.[7]

Materials and Methods

Study Design—This single-center study used a randomized, negative-controlled, investigator-blind, intrasubject comparison design involving healthy subjects meeting specific inclusion/exclusion criteria.

Table 1.

Irritation Classification

Mean Cumulative Irritancy Index	Product Classification
<0.25	Nonirritating
0.25–1 (noninclusive)	Slightly irritating
1–2 (noninclusive)	Moderately irritating
2–3 (noninclusive)	Very irritating

Table 2.

Demographic Data and Skin Phototypes

	All Products (N=31)
Age, y	
Mean (range)	49.8 (21–75)
Gender, n (%)	
Male	8 (26)
Female	23 (74)
Race, n (%)	
White	30 (97)
Hispanic	0 (0)
Other	1 (3)
Skin phototype, n (%)	
I	5 (16)
II	8 (26)
III	9 (29)
IV	7 (23)
V	2 (6)

Seven test products, adapalene (Differin® cream 0.1% and Differin gel 0.1%) and tretinoin (Avita® cream 0.025%, Retin-A® cream 0.025%, Retin-A® cream 0.05%, Retin-A Micro® gel 0.1%, and generic cream 0.025%), were compared with white petrolatum (negative control) and randomized for application to 8 sites on the upper area of the back of each subject. Occlusive patches containing the products were applied daily, Monday through Friday, for 3 weeks. The patches applied Monday through Thursday each remained in place for 24 hours, and the Friday patch remained in place over the weekend for 72 hours. Each subject signed an informed consent form.

A total of 31 subjects were enrolled and analyzed for safety evaluations. Twenty-six subjects (84%) completed the study. All subjects received all 7 test products and the control. Skin reactions (erythema score±other local reaction) were assessed on the patch test areas before each evening application of test products. The erythema grading scale was as follows: no reaction, 0; barely visible erythema, 0.5; mild erythema, 1; moderate erythema, 2; and severe erythema, 3. Other concomitant cutaneous reactions (eg, dryness, cracking, peeling) on test sites were noted, including adhesive reactions.

The subjects' backs were photographed before each reading. When an irritation reaction to the product was rated 3, product application was discontinued for the incriminated site. When an irritation reaction to the adhesive prohibited patching at a particular site, all product applications at those sites were discontinued.

Safety and Tolerability Assessment—For evaluating the cutaneous tolerance, a cumulative irritancy index (CII) was calculated for each treatment group and subject as follows: CII=sum of irritation scores/number of readings. The following conventions were applied for the CII calculations: baseline score at day 1 was excluded from the calculation; when the erythema reaction was rated 3 for any site, application was discontinued for the incriminated site, and a score of 3 was inputted for the remaining readings (last observation carried forward).

Individual CII values were averaged across subjects to obtain a mean CII (MCII) for each treatment. According to the MCII values, each product could be classified into the irritation classes as shown in Table 1. CII values were submitted to an analysis of variance with effects for subject, zone, and product.

Results

Demographic data and skin phototypes are shown in Table 2. Results are summarized in Table 3 and the Figure. The 2 adapalene products were similar in irritancy, and neither product showed a statistically significant difference when compared with the white petrolatum (negative control). Both adapalene products were significantly ($P<.05$) less irritating than any of the tretinoin products.

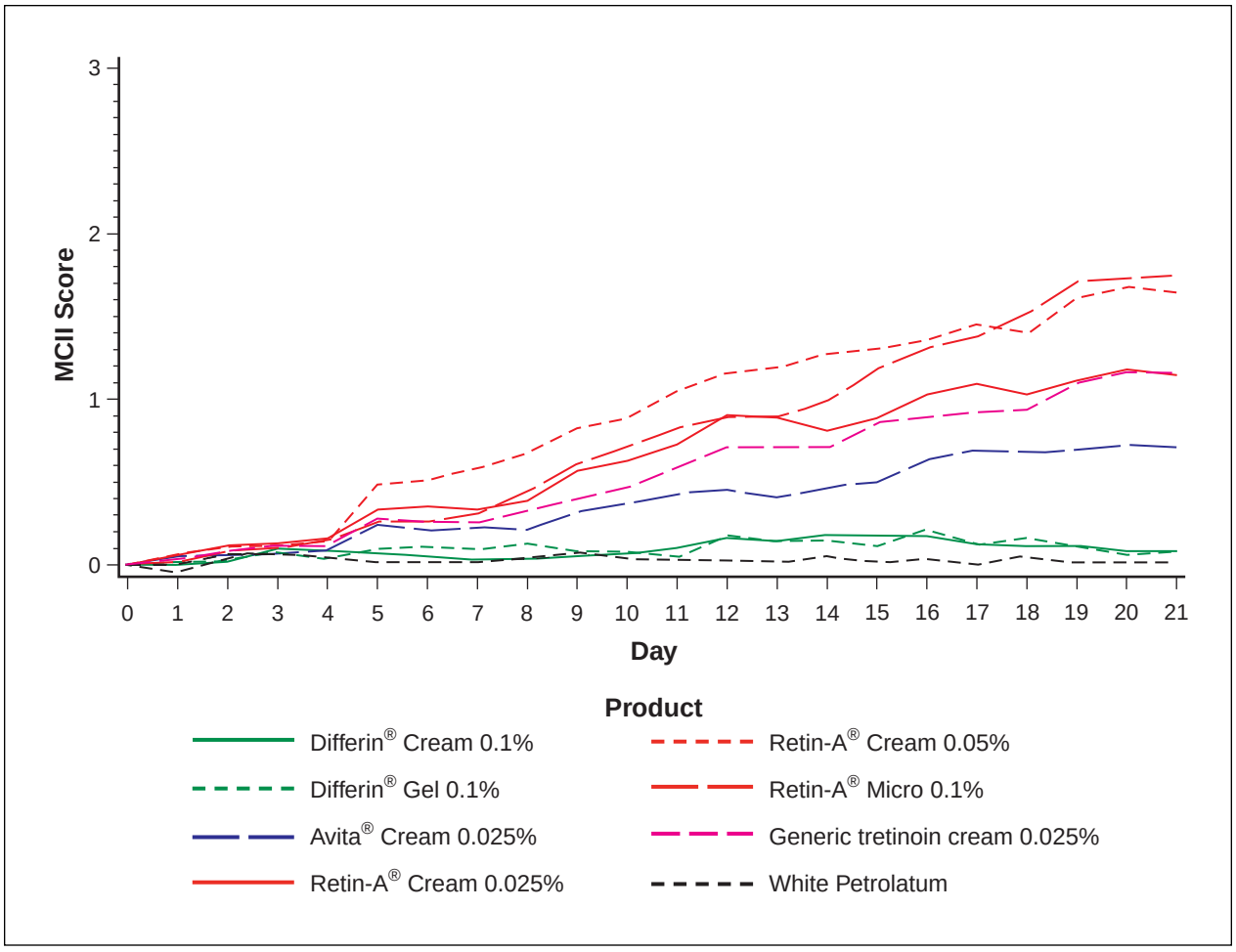
The incidence of product-related adverse events (eg, patch discontinuation due to severe erythema)

Table 3.

Results of Mean Cumulative Irritancy Index (MCII) by Study Product

Study Product	Mean MCII (SD)	Statistical Grouping*
White petrolatum	0.03 (0.06)	A
Adapalene (Differin®) cream 0.1%	0.09 (0.19)	A
Adapalene (Differin) gel 0.1%	0.10 (0.14)	A
Tretinoin (Avita®) cream 0.025%	0.39 (0.31)	B
Generic tretinoin cream 0.025%	0.57 (0.36)	B, C
Tretinoin (Retin-A®) cream 0.025%	0.66 (0.40)	C, D
Tretinoin (Retin-A®) cream 0.05%	0.93 (0.58)	E
Microsphere (Retin-A Micro®) gel 0.1%	0.81 (0.45)	D, E

*MCIIs with the same letter are not statistically significantly different ($P>.05$) from each other but are different from MCIIs of other letters.



Mean cumulative irritancy index (MCII) scoring over a 21-day patch test.

ranged from 6% to 32% for the tretinoin products, with the largest rate observed for the microsphere gel 0.1% product. The Figure demonstrates the mean irritation scores by reading number compared with the test products.

Conclusion

Both adapalene cream 0.1% and gel 0.1% showed significantly less dermal irritancy in repeated occlusive applications compared with all of the tretinoins, including the generic cream 0.025%. The 2 adapalene products were similar as to dermal irritancy when compared with white petrolatum, the negative control product.

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