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Comparative tolerance of adapalene 0·1% gel and six different tretinoin formulations

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Summary Adapalene 0·1% gel (Differin® gel) is a recently introduced topical treatment for mild to moderate acne which has been demonstrated to be much better tolerated and at least as effective as tretinoin 0·025% gel. We compared the tolerance of adapalene 0·1% gel with six different formulations and concentrations of tretinoin. A total of 55 healthy human subjects were enrolled in two controlled, randomized, observer blinded, intraindividual comparison studies. In the first study, adapalene 0·1% gel was evaluated for its 21-day cumulative irritation potential compared with tretinoin 0·025%, 0·05% and 0·1% cream, tretinoin 0·01% and 0·025% gel, and petrolatum (control). In the second study, adapalene 0·1% gel was evaluated for its 21-day cumulative irritation potential compared with tretinoin 0·025%, 0·05% and 0·1% cream, tretinoin 0·1% gel microsphere, and petrolatum (control). In both studies, cumulative irritation scores helped to define three groups of common irritancy potential, with significant differences between each group. In study A, the three groups were in descending order of irritancy: tretinoin 0·1% cream and tretinoin 0·05% cream; tretinoin 0·025% gel, tretinoin 0·01% gel and tretinoin 0·025% cream; adapalene 0·1% gel and petrolatum (control). In study B, the three groups were in descending order of irritancy: tretinoin 0·1% cream; tretinoin 0·05% cream, tretinoin 0·025% cream and tretinoin 0·1% gel microsphere; adapalene 0·1% gel and petrolatum (control). The experimental results show that adapalene 0·1% gel is significantly better tolerated than any of six formulations of tretinoin, including two gels, three creams and a microsphere formulation, ranging in potency from 0·01% to 0·1%.

Adapalene 0·1% gel (Differin® gel) is a recently introduced naphthoic acid derivative with potent retinoic acid receptor agonist activity and anti-inflammatory properties. Adapalene has been demonstrated to be safe and efficacious in the topical treatment of acne[1,2] and to have a low skin-irritation potential.[3,4] Different multicentre clinical studies have shown that adapalene 0·1% gel is a much better tolerated and at least as effective a treatment of acne as tretinoin 0·025% gel.[5,6] The question arises if this better tolerance can also be demonstrated when adapalene 0·1% gel is compared with other concentrations and/or formulations of tretinoin.

We describe below the results of two different studies comparing the tolerance of adapalene 0·1% gel with tretinoin 0·025%, 0·05% and 0·1% creams, tretinoin 0·01% and 0·025% gels and tretinoin 0·1% gel microsphere.

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STUDY A

A twenty-one day cumulative irritancy assay in normal human subjects comparing adapalene 0·1% gel with three concentrations of tretinoin (0·025%, 0·05% and 0·1%) creams, two concentrations of tretinoin (0·01% and 0·025%) gels and a non-medicated control.

Subjects and methods

Before initiation of the studies, the protocol was approved by an independant ethics committee, and written formal consent was obtained from each subject.

Twenty-eight healthy volunteers (3 men and 25 women), aged 22–72 years, took part in this single-centre, controlled, randomized, observer blinded, intra individual comparison study. Exclusion criteria were as follows: individuals of less than 18 years of age; individuals with a sensitivity to any of the study materials; individuals with any visible skin disease at

the study site which, in the opinion of the investigator, would have interfered with the evaluation; individuals receiving systemic or topical drugs or medication, including the study materials which, in the opinion of the investigator, would have interfered with the study results; individuals currently treated for asthma; individuals with psoriasis and/or active atopic dermatitis/eczema; females who were pregnant, planning a pregnancy or nursing a child; individuals with a known sensitivity to cosmetics, skin care products or topical drugs as related to the products evaluated; individuals involved in any investigational protocol within 28 days prior to or during the study. The procedure employed was a modification of that described by Lanman *et al.*[7] and further modified by Phillips *et al.*[8] and Berger *et al.*[9] The duration of each subject's participation was 21 days. Five days a week, 0·2 g of each of the study materials (Differin® 0·1% gel, Retin-A® 0·025%, 0·05% and 0·1% creams, Retin-A® 0·01% and 0·025% gels and petrolatum) were applied in a randomized sequence to the midthoracic area of the back using a non-porous film adhesive bandage for occlusion. The patches were removed daily except on weekends. After removal, the sites were lightly wiped, then examined and graded for irritation 30 min later according to the following eight point scale: 0 = no visible reaction; 0·5 = papular or papulovesicular response and/or dryness without erythema; 1 = minimal/doubtful erythema; 1·5 = minimal/doubtful erythema accompanied by papular or papulovesicular response and/or dryness; 2 = definite erythema; 2·5 = definite erythema, accompanied by papular or papulovesicular response and/or dryness; 3 = definite erythema and definite oedema with or without vesicles; 3 = definite erythema with or without oedema and severe damage to epidermis characterized by crusting, superficial erosions or oozing. The maximum obtainable individual score was three. Should this score be observed at any point during the study, further patch evaluation on the concerned subject was terminated with respect to the product involved. The materials were then reapplied to the same site. Fifteen consecutive applications were performed during the 3 weeks of the study. Scoring was also made the day after termination of the study.

Data analysis

The cumulative irritation score for each subject and for each product was calculated by summing each individual's score for the product on each of the 15 evaluation days and adding six scores for saturdays and sundays equal to the scores obtained for the following mondays, then dividing by the total number of scores (21 scores for completed subjects). Statistical analysis was performed on the cumulative irritation scores. The data were analysed using the within-subject analysis of variance with factors for subject and product. Product comparisons were made at the 5% level based on Fisher's least significant differences.

Results

Of the 28 subjects enrolled, 27 completed the study. One subject discontinued after study day 11 for personal reasons. There were no adverse events reported. Table 1 summarizes the analysis of comparative cumulative irritation; mean cumulative irritation scores by product are shown in descending order. Statistically significant groupings are given on the right, with products labelled by the same letter not significantly different.

Figure 1 shows cumulative irritation associated with each product as a function of time while Figure 2 shows the mean cumulative irritation score for each product and Figure 3 shows for each product the proportion of subjects who discontinued the patch applications due to excessive irritation.

Based on the analysis of cumulative irritation scores, the study products fell approximately into three groups of common irritancy potential, in descending order of irritancy: Group 1: tretinoin 0·1% cream and tretinoin 0·05% cream; Group 2: tretinoin 0·025% gel, tretinoin 0·01% gel and tretinoin 0·025% cream; Group 3: adapalene 0·1% gel and petrolatum (control). Products within each group were statistically different from all other products of another group. Products within groups were not statistically different from each other, except for a marginal significance between tretinoin 0·025% gel and tretinoin 0·025% cream ($P = 0·05$). The irritation scores results showed a direct dose–

Table 1 Summary of product comparisons; mean cumulative irritation score (mean ± SD; $n = 27$)

Product	Score	Grouping
Tretinoin 0.1% cream	1.97 ± 0.34	A
Tretinoin 0.05% cream	1.84 ± 0.29	A
Tretinoin 0.025% gel	1.66 ± 0.42	B
Tretinoin 0.01% gel	1.65 ± 0.37	B, C
Tretinoin 0.025% cream	1.51 ± 0.34	C
Adapalene 0.1% gel	0.37 ± 0.38	D
Petrolatum (control)	0.34 ± 0.31	D

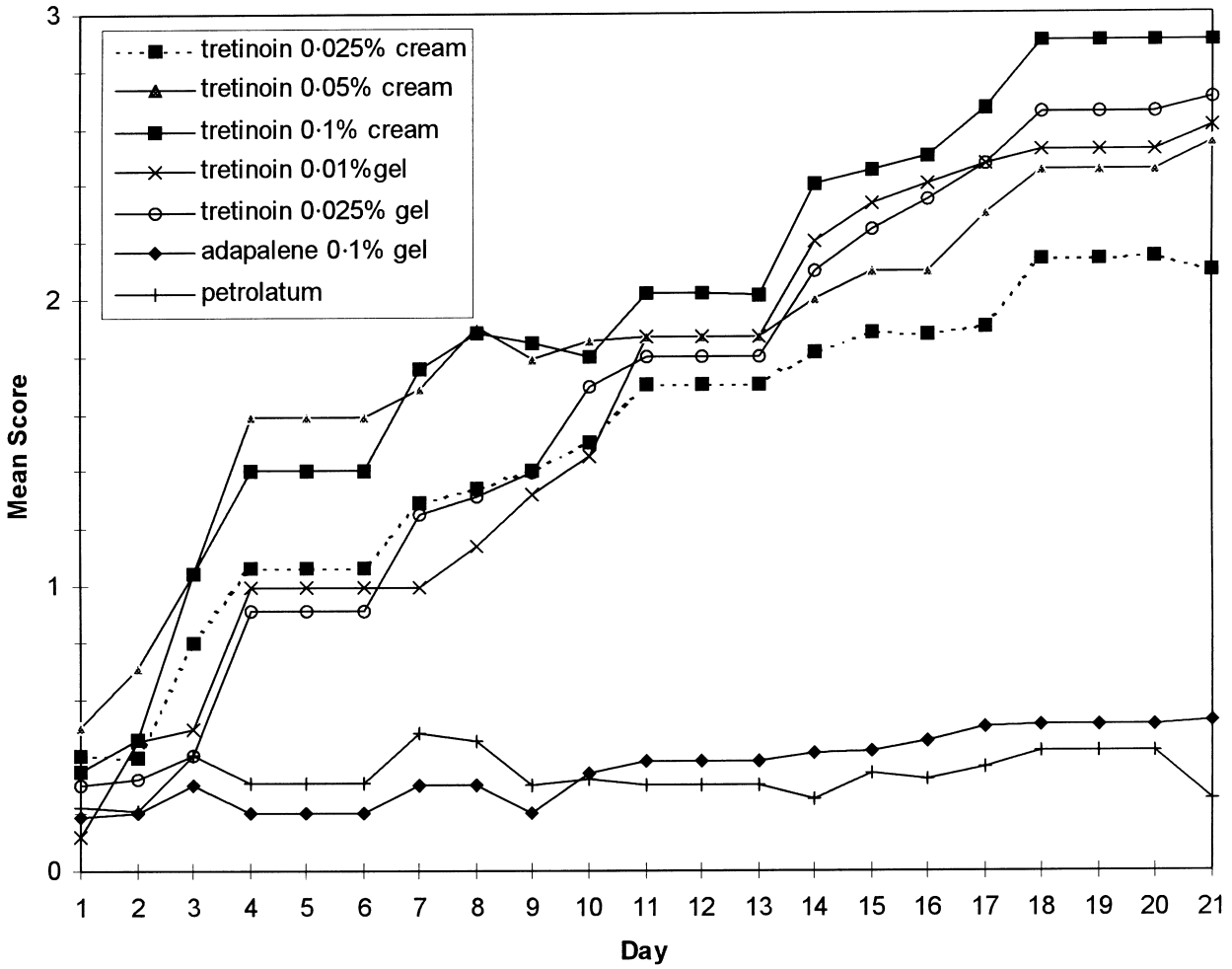

Figure 1. Mean Irritation Scores vs. Reading No. (time) by Treatment (All Completed Subjects, $n = 27$).

response relationship for the tretinoin products. At the same time, the cream formulation showed approximately equivalent irritancy to the gel formulation of the same potency.

STUDY B

A twenty-one day cumulative irritancy assay in normal human subjects comparing adapalene 0·1% gel with three concentrations of tretinoin (0·025%, 0·05% and 0·1%) creams, tretinoin 0·1% gel microsphere and a non-medicated control.

Subjects and methods

Twenty-seven consenting healthy volunteers (7 men and 20 women), aged 22–72 years, took part in this single-centre, controlled, randomized, observer blinded, intraindividual comparison study. The study protocol used to compare adapalene 0·1% gel with tretinoin 0·025%, 0·05% and 0·1% cream and tretinoin 0·1% gel microsphere was exactly the same as in study A.

Data analysis

Data analysis was performed using the same statistical methods as for study A.

Results

Of the 27 subjects enrolled, 26 completed the study. One subject discontinued after study day 1 for personal reasons. There were no adverse events reported. Table 2 summarizes the analysis of comparative cumulative irritation. Mean cumulative irritation scores by product are shown in descending order and statistically significant groupings are given on the right, with products labelled by the same letter not significantly different.

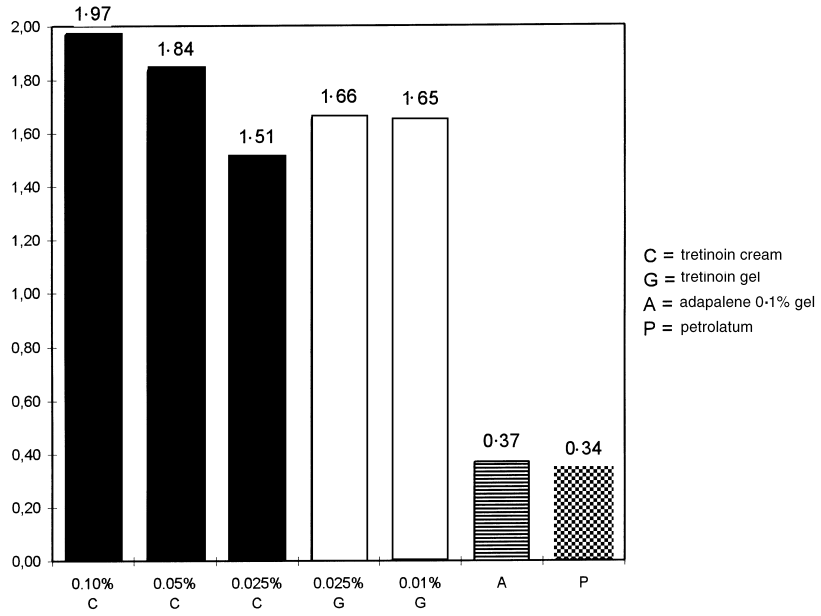

Figure 2. Mean cumulative irritation score by treatment (all completed subjects, $n = 27$).

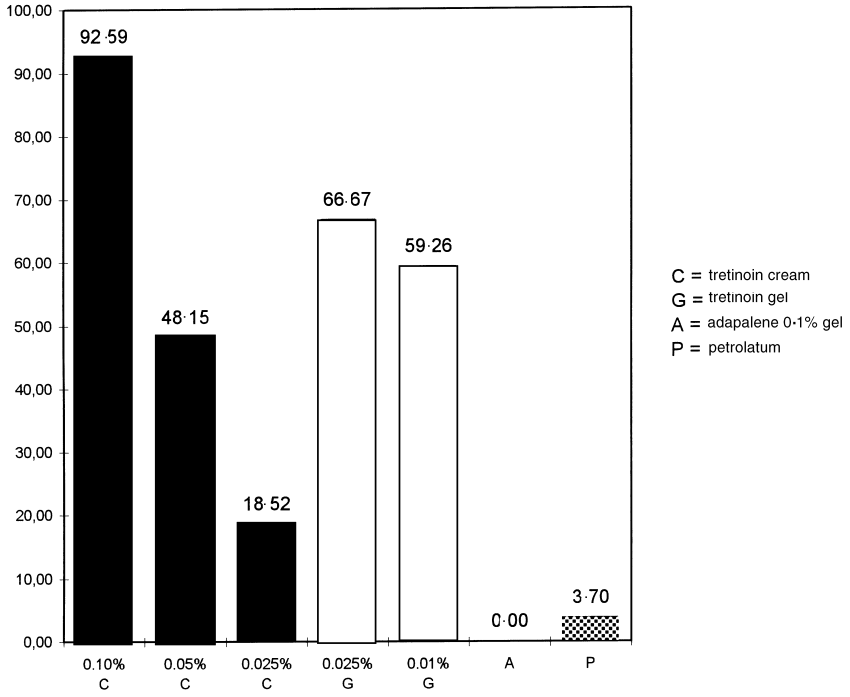

Figure 3. Percentage of subjects discontinuing patch by treatment (all completed subjects, $n = 27$).

Figure 4 shows cumulative irritation associated which each product as a function of time while Figure 5 shows the mean cumulative irritation score for each product. Figure 6 shows for each product the proportion of subjects who discontinued the patch applications due to excessive irritation.

Based on the analysis of cumulative irritation scores, the study products fell approximately into three groups of common irritancy potential, in descending order of irritancy: Group 1: tretinoin 0·1% cream; Group 2:

Table 2 Summary of product comparisons; mean cumulative irritation score (mean ± SD; $n = 26$)

Product	Score	Grouping
Tretinoin 0.1% cream	1.66 ± 0.38	A
Tretinoin 0.05% cream	1.31 ± 0.40	B
Tretinoin 0.1% gel microsphere	1.17 ± 0.52	B, C
Tretinoin 0.025% cream	1.12 ± 0.35	C
Petrolatum (control)	0.13 ± 0.33	D
Adapalene 0.1% gel	0.10 ± 0.29	D

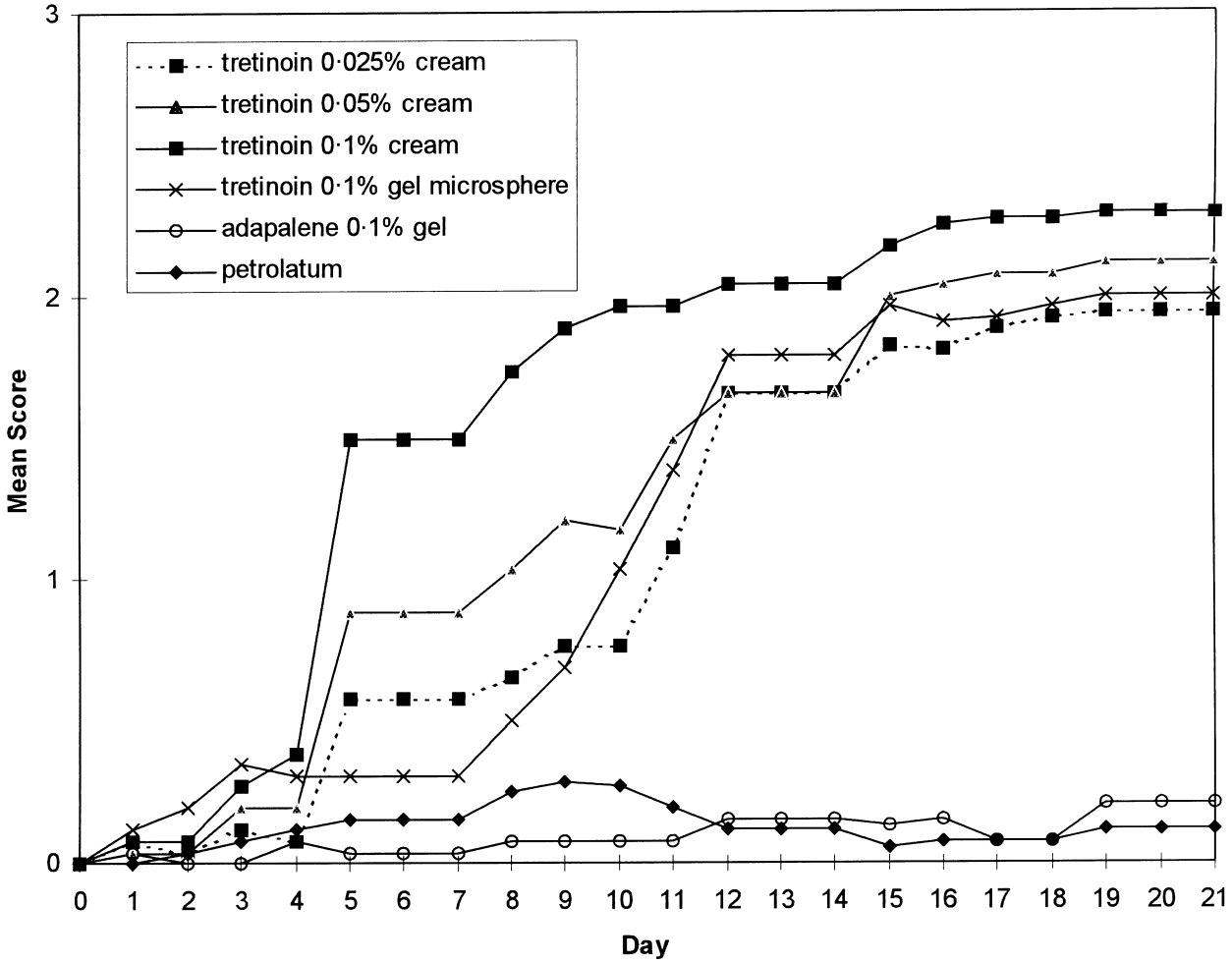

Figure 4. Mean Irritation Score vs. Reading No. (time) by Treatment (All Completed Subjects, $n = 26$).

tretinoin 0·05% cream, tretinoin 0·025% cream and tretinoin 0·1% gel microsphere; Group 3: adapalene 0·1% gel and petrolatum (control). Products within each group were statistically different from all other products of another group. Products within groups were not statistically different from each other, except for a marginal significance between tretinoin 0·05% cream and tretinoin 0·025% cream ($P = 0·05$). The irritation scores results showed a direct dose–response to the tretinoin products with 0·1% > 0·05% > 0·025%. Tretinoin 0·1% gel microsphere showed significantly lower irritancy potential than the tretinoin cream of the same potency.

Discussion

Under the given experimental conditions, we have shown that adapalene 0·1% gel was better tolerated than any of six different formulations of tretinoin (0·025%, 0·05% and 0·1% cream, 0·01% and 0·025% gel and tretinoin 0·1% gel microsphere).

In both studies, adapalene 0·1% gel appeared after 21 days of repeated occluded applications to be significantly less irritating than the six different formulations of tretinoin (including two gels, three creams and a microsphere formulation, ranging in potency from 0·01% to 0·1%) and no more irritating than petrolatum. In both studies, cumulative irritation scores helped to define three groups of common irritancy potential, with significant differences between each group. In study A, the three groups were in descending order of irritancy: tretinoin 0·1% cream and tretinoin 0·05% cream; tretinoin 0·025% gel, tretinoin 0·01% gel and tretinoin 0·025% cream; adapalene 0·1% gel and petrolatum (control). In study B, the three groups were in descending order of irritancy: tretinoin 0·1% cream; tretinoin 0·05% cream, tretinoin 0·025% cream and tretinoin 0·1%

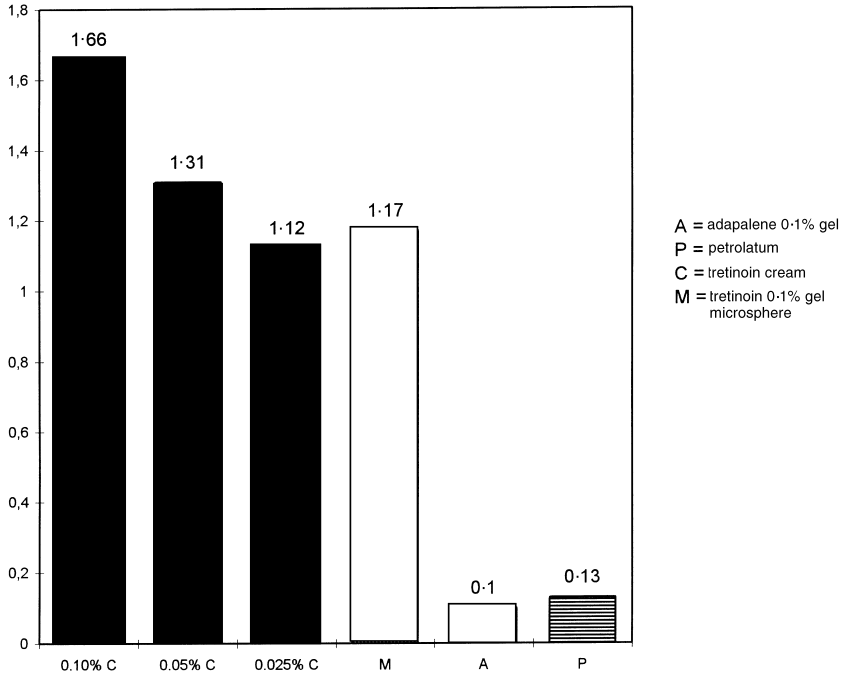

Figure 5. Mean cumulative irritation score by treatment (all completed subjects, $n = 26$).

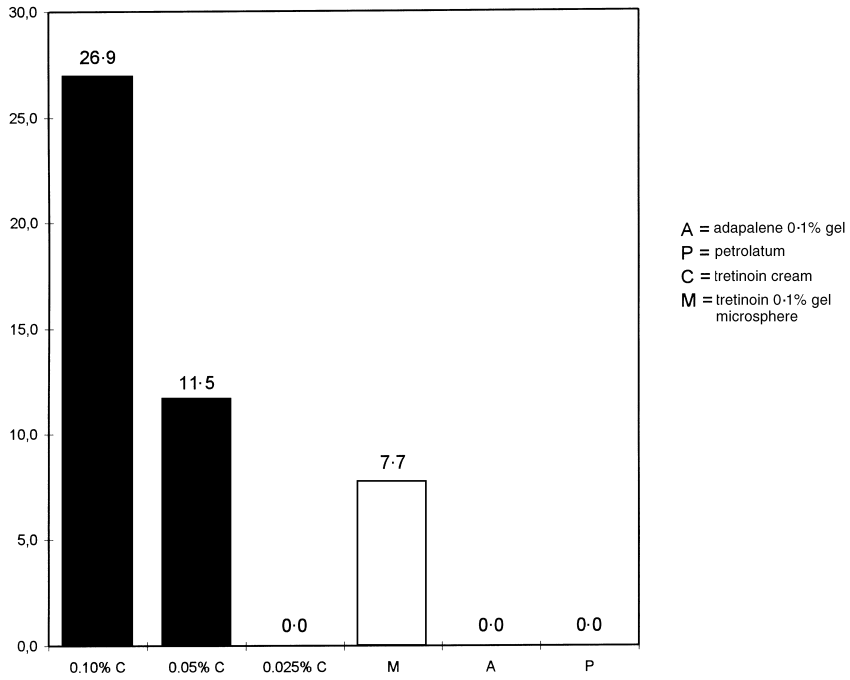

Figure 6. Percentage of subjects discontinuing patch by treatment (all completed subjects, $n = 26$).

gel microsphere; adapalene 0·1% gel and petrolatum (control). Besides demonstrating the optimal tolerance of adapalene 0·1% gel, these results, by showing a direct dose response to the tretinoin products, suggest that the irritancy induced by the tretinoin products comes mainly from the active agent itself, with the vehicle of lesser importance in the effect. Conversely, adapalene 0·1% gel, is no more irritating that petrolatum in these experimental conditions. This much better tolerance of adapalene 0·1% gel as compared with tretinoin may have different explanations. First, it can be explained by the unique receptor specificity of adapalene. As opposed to tretinoin, adapalene does not bind to cytosolic retinoic acid binding proteins (CRABP) and is relatively selective for the retinoic acid receptor β (RARβ) and somewhat for

the RARγ, while tretinoin binds to all three subtypes RARα, RARβ and RARγ.[10] Second, knowing that different retinoids may be cytotoxic for keratinocytes to a degree that does not necessarily correlate with receptor binding activity,[11] the more neutral adapalene molecule is probably less cytotoxic to keratinocytes than the long-chain organic acid, tretinoin. Third, it is possible that some of the breakdown products resulting from tretinoin degradation in the presence of light may be irritant. In contrast to tretinoin, adapalene does not break down in the presence of light.[12] Last, adapalene has well-demonstrated anti-inflammatory properties and has shown in an experimental model an anti-inflammatory activity comparable to indomethacin and betamethasone 17-valerate, whereas in the same conditions tretinoin was inactive.[10]

Our results show that these specificities of adapalene make it a better tolerated treatment than tretinoin whatever its formulation, particularly the microspheres. Knowing that, while being much better tolerated, adapalene 0·1% gel has demonstrated a comparable activity to tretinoin in acne vulgaris,[5,6] it clearly appears to have a better efficacy/tolerance ratio than tretinoin.

In conclusion our results show that adapalene 0·1% gel is better tolerated than any of six formulations of tretinoin, including two gels, three creams and a microsphere formulation, ranging in potency from 0·01% to 0·1%.

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