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Chemical stability of adapalene and tretinoin when combined with benzoyl peroxide in presence and in absence of visible light and ultraviolet radiation

B.MARTIN, C.MEUNIER, D.MONTELS AND O.WATTS
Galderma R & D, 635 route des Lucioles, BP67, 06902 Sophia Antipolis cedex, Valbonne, France

Summary Adapalene and tretinoin are molecules used in the topical treatment of acne vulgaris. Commercial formulations (adapalene 0·1% gel and tretinoin 0·025% gel) were mixed with equal volumes of commercially available benzoyl peroxide formulation (10% lotion) and subsequently exposed to light over 24 h. With and without exposition to light, adapalene exhibits a remarkable stability whereas tretinoin is very sensitive to light and oxidation. The combination of benzoyl peroxide and light results in more than 50% degradation of tretinoin in about 2 h and 95% in 24 h.

The combination of a topical retinoid (tretinoin, isotretinoin or adapalene) with a topical antibacterial is often prescribed in the treatment of acne vulgaris. The products most often used with retinoids are topical clindamycin, erythromycin or benzoyl peroxide. The latter is a widely prescribed antiacne treatment and is available even in combination with erythromycin. Because benzoyl peroxide is a strong oxidiser, the chemical compatibility of such combinations should be carefully considered. The aromatic and phenoxy adamantyl structure of adapalene is highly stable, whereas the polyenic chains of tretinoin are more susceptible to oxidation (Fig. 1).[1,2] Since the products that are used in combination with benzoyl peroxide, especially when used concurrently, are also exposed to light, the stability of both in the presence of daylight was added to the investigations.

Materials and methods

Compounds studied

Adapalene (Differin® 0·1% gel, lot 051019·6; Laboratoires Galderma, Levallois-Perret, France), tretinoin (Aberel® 0·025% gel dermique, lot S941; Laboratoire Cilag, Paris, France) and benzoyl peroxide (Cutacnyl® 10% lotion, lot 26001·6, Laboratoires Galderma) were obtained commercially.

Preparation of the mixtures and light exposure

Equal volumes of 10% benzoyl peroxide lotion and the retinoid gels were mixed. The mixtures were introduced into 10-mL plastic syringes and stored under inactinic light (monochromatic sodium lamp type NA 55 W, Osram) and actinic light (fluorescent lighting tubes for normal room lighting) over a 24-h period. At different intervals (approximately each hour during the first 5-h period), aliquots of each mixture were tested for their retinoid content.

Analysis

Adapalene HPLC assay was conducted using an ODS-RP18, 5 μm, 4 × 250 mm reverse phase column (MERCK®). Separation was achieved with tetrahydrofuran/acetonitrile/purified water/trifluoroacetic acid 360/430/210/0·2 (v/v) as mobile phase. Flow rate and detection were set, respectively, at 1 mL/min and 270 nm (see Fig. 2).

Tretinoin was analysed using the same column and acetonitrile/purified water/acetic acid 800/200/0·2 (v/v) as mobile phase. Flow rate and detection were set, respectively, at 1·8 mL/min. and 353 nm (see Fig. 3).

Analyses were performed in duplicate. Results are given as a percentage of the initial content.

Results

Under inactinic light conditions (irradiation without visible or ultraviolet (UV) wavelengths) both retinoids are stable. When tretinoin was examined in the presence of benzoyl peroxide, however, it was degraded to about 80% of initial content after 24 h.

When exposed to laboratory room light, the tretinoin content dropped rapidly. The combination of benzoyl

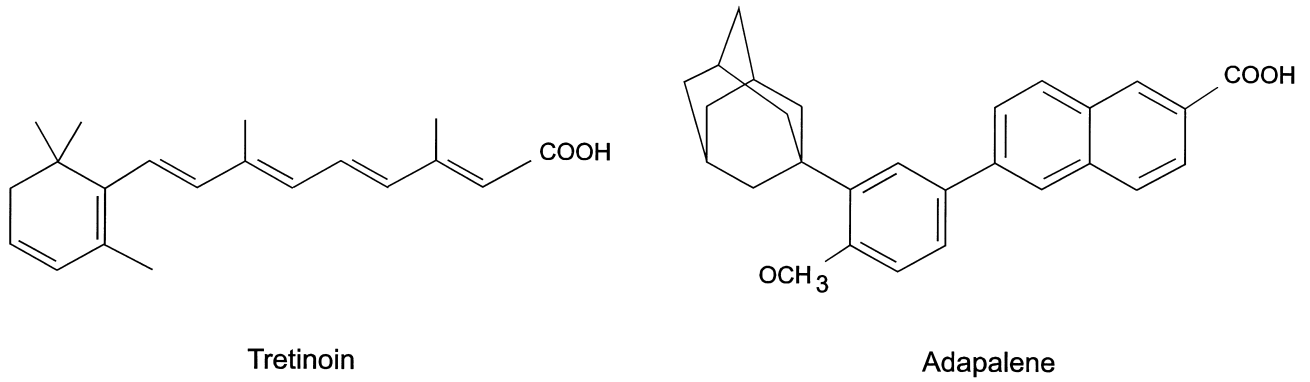

Figure 1. Chemical structures of the two retinoids.

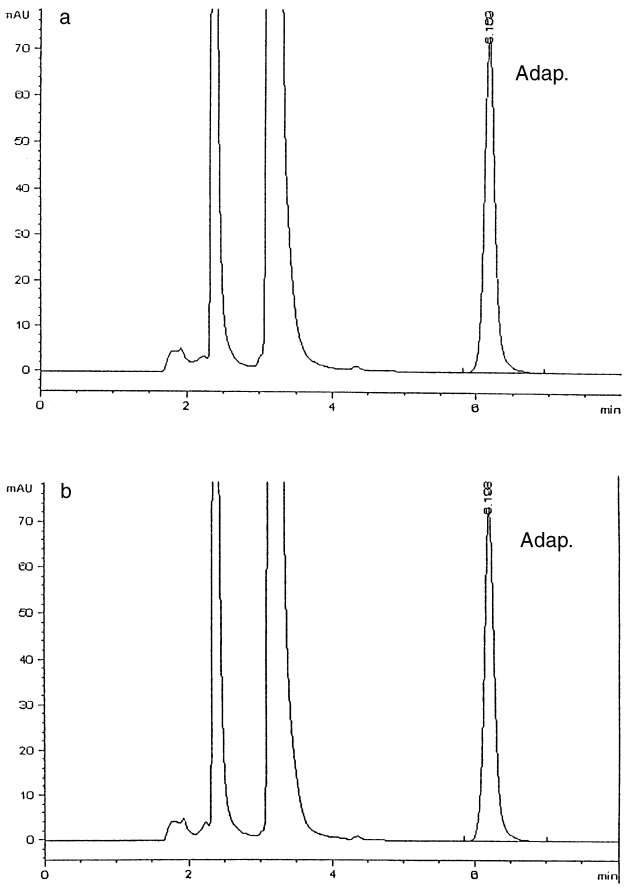

Figure 2. a: initial HPLC analysis of adapalene/benzoyl peroxide mixture. b: adapalene/benzoyl peroxide mixture after 24 h under fluorescent light. The two first peaks are assigned to benzoyl peroxide and excipient.

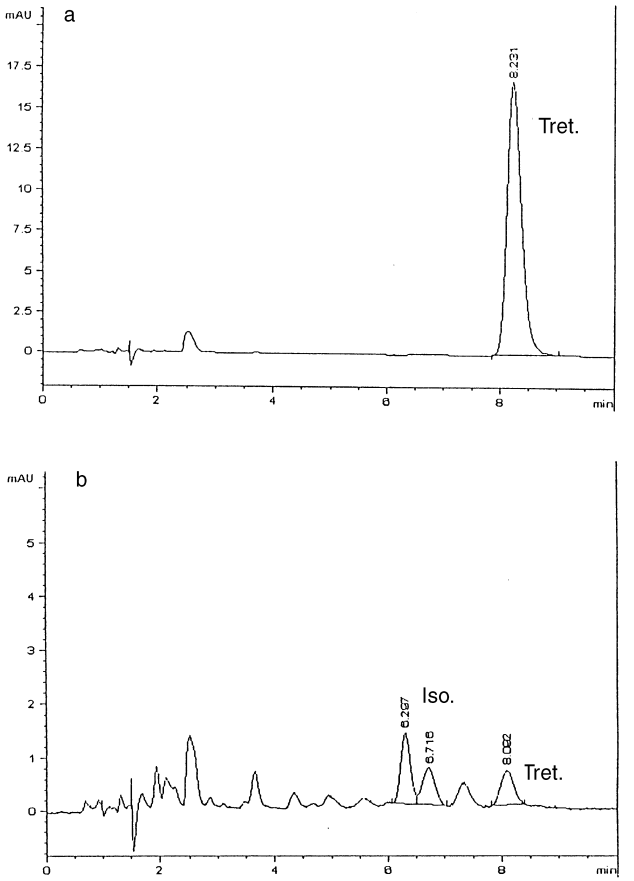

Figure 3. a: initial HPLC analysis of tretinoin/benzoyl peroxide mixture. b: tretinoin/benzoyl peroxide mixture after 24 h under fluorescent light.

peroxide and light gave more than 50% of degradation of tretinoin in about 2 h and 95% in 24 h.

Conversely, under all these conditions, adapalene was shown to be totally stable (see Figs 4 and 5).

Discussion

It is well known that tretinoin is very sensitive to oxidation and photo-isomerization.[2] As previously reported,[1] polyenic chains of tretinoin are very

sensitive to light compared to aromatic and phenoxy adamantyl moieties of adapalene.

Our results show that, under the conditions of the study, the photo-instability of tretinoin is potentiated by the presence of a strong oxidizing compound like benzoyl peroxide. Even in inactinic light conditions, the chemical instability of tretinoin is demonstrated with a degradation rate of about 80% after 24 h. Adapalene was found to be stable under all conditions studied for at least 24 h.

These results confirm previous findings of instability of topical tretinoin and isotretinoin in the presence of fluorescent light.[3] Whether these conditions can be extrapolated to clinical use needs to be further investigated, especially in the UV region. However, any topical preparation is to some extent exposed to various light sources. Degradation, as shown here, could have an influence on adverse events, especially cutaneous safety. The better cutaneous safety of adapalene compared to tretinoin, as shown in clinical studies,[4,5] could possibly be explained by its high stability

In clinical situations, a combination of two anti-acne products offering different mechanisms of action and targets, is an advantage for the prescriber and patients,

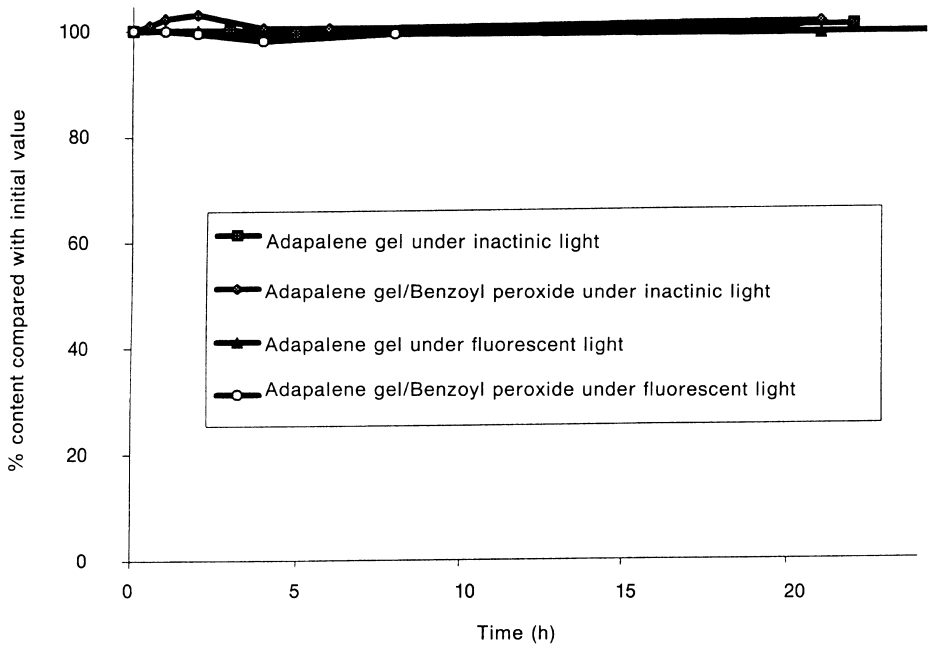

Figure 4. Stability of adapalene: effect of light and benzoyl peroxide.

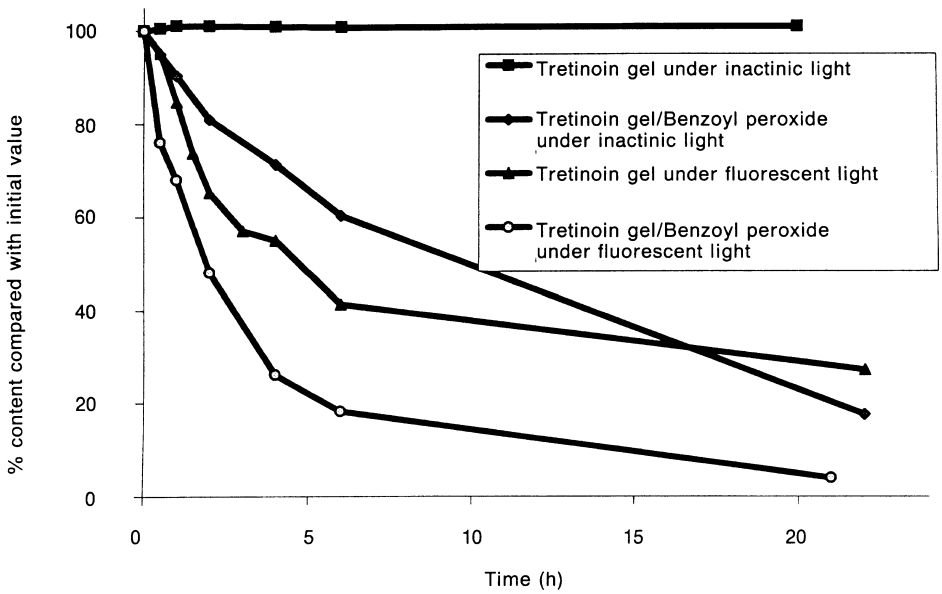

Figure 5. Stability of tretinoin: effect of light and benzoyl peroxide.

and therefore frequent clinical practice.[6,7] The chemical compatibility and stability of the associated products needs, however, to be taken into account. In a study in 25 healthy volunteers, the combination of adapalene and benzoyl peroxide was classified as non-irritant.[8] When considering the good tolerance of this combination and the results discussed above on stability to light and in the presence of benzoyl peroxide, adapalene 0·1% gel seems to offer very good stability and a good clinical tolerance in combination with benzoyl peroxide.

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