Effective Reduction of Acne-induced Post-inflammatory Hyperpigmentation with the Human Tyrosinase Inhibitor Thiamidol (isobutylamido thiazolyl resorcinol)

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Abstract

Objective: Post-inflammatory hyperpigmentation (PIH) is a major cosmetic concern especially in individuals with darker skin complexion. Unfortunately, treatment with anti-inflammatory ingredients alone does not prevent the development of hyperpigmented spots. Recently, Thiamidol (isobutylamido thiazolyl resorcinol) was described as a very potent inhibitor of human tyrosinase. The objective of this research was to investigate the potential of Thiamidol-based formulations to prevent PIH induced by acne-induced epidermal wounding.

Methods: The effect of skin care formulations containing Thiamidol on acne-related PIH was investigated in two studies; a vehicle-controlled, double-blinded, randomized clinical study, and a clinical observational study. Both studies had a duration of 3 months and included assessments of clinical photography, clinical grading and melanin index measurements.

Results: Subjects' self-grading demonstrated that Thiamidol significantly improved the visibility of acne-induced hyperpigmentation compared to the vehicle treatment. A skin care regimen with Thiamidol significantly improved acne-related PIH over 12 weeks shown by Mexameter measurements, expert grading, self-grading and clinical photography.

Conclusion: Thiamidol represents a safe and effective ingredient for cosmetic products against post-inflammatory hyperpigmentation.

Materials and Methods

Test Formulations

For Study 1, the test product was an oil-in-water emulsion with Thiamidol and without SPF. For Study 2, volunteers utilized a skin care regimen consisting of three Thiamidol-containing products (Day Cream SPF 30, Night Cream and Dual Serum (Beiersdorf, Germany).

Study Design I: Treatment of Post-acne Hyperpigmentation in Fitzpatrick phototype V subjects with Thiamidol

This single-blinded, comparative, single-center clinical study was performed from June to October 2018 at Allergisa Pesquisa Dermato-Cosmética LTDA, Campinas SP, Brazil. The study was conducted in conformance with the Declaration of Helsinki principles, the applicable regulatory requirements, including Resolution CNS no. 466/12, and in the spirit of the Good Clinical Practices (Document of the Americas and ICH E6: Good Clinical Practice). Each subject provided written, informed consent and signed a photo release consent form authorizing the reproduction and distribution of any images collected during the study. A total of 77 female subjects (aged 18 to 40 years), Fitzpatrick skin phototype V with a history of acne with remaining hyperpigmentation in the formerly affected area with no inflammatory acne lesion in the test area but at least 4 hyperpigmented spots (on whole face), met the inclusion criteria and were enrolled in the study, 64 participants completed the study. Exclusion criteria comprised topical acne therapy, skin diseases vitiligo, psoriasis and atopic dermatitis, intake of corticosteroids, immunosuppressive and anti-histaminic drugs. Hormonal medication was not part of the exclusion criteria.

During the study, subjects were not allowed to apply skin-lightening products to the face. They were further asked not to change any cosmetic or personal hygiene daily routine habits (including sunscreen, if used). Also, volunteers were asked to refrain from intense UV exposure (sunbathing, tanning devices).

At study start (T0), subjects were assessed by a dermatologist, who also performed a clinical grading. The subjects additionally answered a self-grading questionnaire to evaluate their skin before the treatment. One frontal and two lateral digital images of the face were taken using a VISIA CR photo station (Canfield Imaging Systems, Fairfield, NJ) with a Canon Mark II 5D digital SLR camera (Canon, Tokyo, Japan). Subjects were instructed to apply the respective test formulations twice daily for 12 weeks over the entire face (with the exception of inflammatory lesions) according to the provided use directions. The test formulas were randomly distributed to the subjects, 39 subjects applied the Thiamidol compound and 38 subjects the vehicle. After 28 ± 2, 56 ± 2 and 84 ± 2 days of product application, subjects returned to the institute for evaluations. A dermatologist performed a control check of the acne status and a dermatological assessment of tolerance regarding possible sensations of discomfort. At the same points in time, subjects assessed their facial skin using the self-grading questionnaire. Subjects were requested to rate the visibility of hyperpigmentation compared to the surrounding facial skin by means of a scale ranging from 1 (clearly darker than surrounding, clearly defined–very well visible) to 10 (comparable color to surrounding, overlaps into its surrounding–barely visible). Additionally, 3 facial images per subject were taken.

Study Design II: Treatment of Post-inflammatory Hyperpigmentation related to acne in Fitzpatrick phototypes V and VI subjects with Thiamidol

This cosmetic clinical observational study was carried out at the dermatologist office of Prof. Ncoza Dlova, Durban, South Africa from September to December 2018. Ethics approval was obtained from the Pharma-Ethics Independent Research Ethics Committee, South Africa (Ref: 180419938). Subjects were screened for inclusion and exclusion criteria, and informed consent forms were signed by eligible participants. Volunteers also signed a photo release consent form authorizing the reproduction and distribution of any images collected during the study. 32 subjects (4 male and 28 female, aged 18 to 50 years) with acne-related post-inflammatory hyperpigmentation were enrolled in the study. Out of these, 29 completed the study. All volunteers were self-reported as of African ancestry and were classified as Fitzpatrick skin phototypes V (24 subjects) or VI (5 subjects). Exclusion criteria comprised acne medication, aesthetic procedures 6 months prior to enrollment, usage of depigmenting products 2 months before beginning of the study or topical medication for hyperpigmentation 30 days prior to study entry. Hormonal medication was not part of the exclusion criteria.
The subjects applied each of the three regimen products at home once daily (Dual Serum and Day Cream SPF 30 in the morning, Night Cream in the evening) for 12 weeks to the whole face according to usual skin care application habits. Participants were instructed to refrain from usage of any other creams for the duration of the study, except face cleanser and sunscreen, if used.

At baseline and again after 4, 8 and 12 weeks, the dermatologist determined the subjects' skin profile and performed a clinical grading of efficacy and objective irritation parameters. Also, dermatologist questionnaires and patient self-assessments were completed at baseline and after 4, 8 and 12 weeks. The investigator assessed skin evenness by means of the following 5-point scale: extreme (score 0), severe (score 1), moderate (score 2), slight (score 3) and absent (score 4). Also, the investigator evaluated the question: 'How do you rate the improvement of the overall skin condition of the patient?' using the 4-tiered rating scale (very good, good, moderate, none).

Subjects determined their facial skin condition by means of a scale ranging from 1 (poor) to 10 (excellent). In addition, clinical photography (Canon EOS 1Ds Mark III, objective lens EF 50 mm 2.5 Makro, Canon Inc. Tokyo, Japan) and skin color measurements of lesions and perilesional areas (Mexameter MX 18, Courage and Khazaka, Köln, Germany) were conducted at every visit.

Statistical Analysis

Study I

Comparisons between time points and initial time point were performed through Wilcoxon signed rank test. The bilateral hypothesis was used. Comparisons between treatments were performed through Mann-Whitney test. The bilateral hypothesis was used. For each time point, comparisons between the two treatments were performed via Mann-Whitney test using differences to baseline (T0). The bilateral hypothesis was utilized. For binary data, the two-sided binomial test for null hypothesis proportion p = 0.5 was performed to test if the relative frequency for one category differs significantly from 0.5. Statistical analyses were performed using the XLSTAT 2018 software.

Study II

The Wilcoxon signed rank test was used for the comparison of visits (two-sided hypothesis testing, significance level 0.05, adjustment for multiple testing with the Bonferroni-Holm method). The analysis of the data was performed using Stata/IC 14.2 for Windows.

Results

FIGURE 1. Treatment of Acne-induced Post-inflammatory Hyperpigmentation with Thiamidol. A. Representative images of subjects with acne-induced PIH at baseline and after 4, 8 and 12 weeks of treatment with the Thiamidol-containing formulation or the vehicle. **B.** Visibility of hyperpigmentation as determined by self-grading after 4, 8 and 12 weeks of treatment with the Thiamidol-containing formulation or the vehicle. Data are depicted as mean ± SD. Significant differences are marked in comparison to vehicle (*p < 0.05).

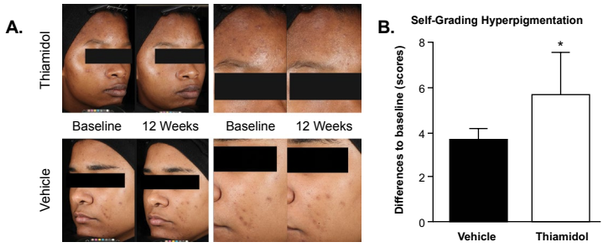

FIGURE 2. Treatment of Acne-induced Hyperpigmentation with three Thiamidol-based products. A. Representative images of a subject at baseline and after 4, 8 and 12 weeks of treatment with the Thiamidol-containing skin care regimen (Day Cream, Night Cream and Serum). **B.** Melanin index scores of lesional and perilesional skin after 4, 8 and 12 weeks of treatment. Data are depicted as mean ± SD. Significant differences are marked in comparison to baseline (***p < 0.001).

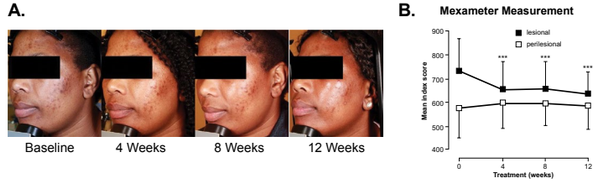

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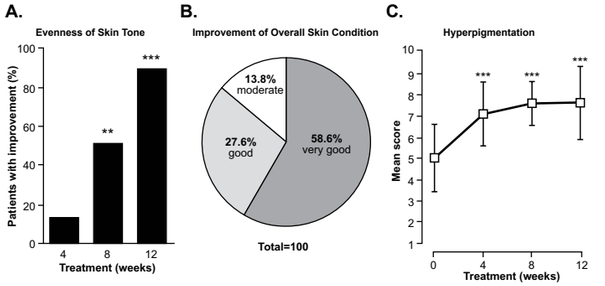
FIGURE 3. Expert rating and self-assessment of facial skin conditions.
A. Skin evenness as determined by the investigator at baseline and after 4, 8 and 12 weeks of treatment with the Thiamidol-containing skin care regimen (Day Cream, Night Cream, Serum). Data are depicted as mean ± SD. Significant differences are marked in comparison to baseline (**p < 0.01, ***p < 0.001).
B. Overall skin condition rated by the investigator after 12 weeks of treatment with the Thiamidol-containing skin care regimen. **C.** Subjective assessment of hyperpigmentation at baseline and after 4, 8 and 12 weeks of treatment with the Thiamidol-containing skin care regimen. Significant differences are marked in comparison to baseline (***p < 0.001).



Summary and Conclusions

- Post-inflammatory hyperpigmentation (PIH) is an extremely common skin condition which can develop at any age and is not gender specific
- Tyrosinase is a rate-limiting enzyme for melanogenesis; therefore, inhibition of tyrosinase activity remains a benchmark of hyperpigmentation therapy
- Recently, Thiamidol (isobutylamido thiazolyl resorcinol) has been identified as an effective inhibitor of human tyrosinase
- In acne-induced PIH (subjects with Fitzpatrick phototype V), Thiamidol treatment significantly reduced the visibility of hyperpigmentation after 12 weeks compared to a vehicle control, p < 0.05
- In an observational study, a 3-product regimen of Thiamidol-containing formulations (Day Cream with SPF 30, Night Cream, and Serum), we observed a significant improvement in melanin index score at Week 12 in the Thiamidol-treated group compared to vehicle control, p < 0.001
- In summary, Thiamidol significantly improved acne-related post-inflammatory hyperpigmentation in Fitzpatrick phototypes V and VI, an often difficult group to treat; additionally, Thiamidol was well tolerated by subjects
- These findings suggest Thiamidol is safe and efficacious and should be considered as a part of an overall regimen for the treatment of hyperpigmentation associated with acne-induced PIH

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