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Effects of a new topical combination on sensitive skin

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Synopsis

Using well-tolerated cosmetics or those with soothing effects is recommended to treat sensitive skin. However, we lack clinical studies. Two clinical trials were performed on sensitive skin in France and Thailand. The primary objective was to evaluate the preventive soothing effect. The secondary objectives were to evaluate the immediate soothing effect, product tolerance, and impact on quality of life. Evaluation methods included a stinging test and scoring erythema and stinging intensity. We also assessed tolerance, quality of life using the Dermatology Life Quality Index, and cosmetic qualities. The clinical trials were performed in France and Thailand to test efficacy in two different environments and on different ethnic skin. Interesting effects were observed in patients with sensitive skin in France and Thailand: a preventive soothing effect, a soothing effect on erythema, and an immediate soothing effect. *In vivo* biometrological, sodium lauryl sulfate, and capsaicin tests confirmed these data. A favorable effect on quality of life was also noted. The product was appreciated by volunteers for its efficacy, tolerance, and cosmetic qualities. A preliminary study on the effects on interleukin 8 was also included in the paper.

INTRODUCTION

"Sensitive skin" is defined as an erythema and/or unpleasant sensation (stinging, burning, pain, pruritus, and tingling) in response to multiple factors, which may be physical (UV, heat, cold, and wind), chemical (cosmetics, soap, water, detergents, and pollutants), and occasionally psychological (stress), or hormonal (menstrual cycle) (1–8). "Reactive," "overreactive," and "irritable" skin are synonyms of "sensitive" skin. The term "reactive skin" is more accurate than "sensitive skin," which may be confused with "sensitized skin" due to an allergic disorder, but "sensitive skin" is more commonly used.

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Sensitive skin is very frequent. In France, approximately 50% of individuals (59% of women and 41% of men) report having reactive skin (9). This patient-reported prevalence varies little across European countries (10), the United States of America (11), and Japan (12). Sensitive skin is clearly a very frequent cosmetic problem. Although the appearance of this kind of skin is normal in most cases, sensitive skin may occur in individuals who have another skin disorder (e.g., atopic dermatitis, seborrheic dermatitis, or rosacea) (9). The association with ethnicity is controversial (3,4,13). Three large epidemiological studies reported no "racial" differences when reporting sensitivity (11,14,15), most likely because races or ethnicities do not exist (16). On the other hand, cultural factors (10–12) are most likely crucial for defining sensitive skin, related symptoms, and lifestyle factors that may favor several triggering factors. For example, Japanese women react more intensely than German women, even though there is no difference in the sensory innervation of their skin (17). The role of phototype has also been suggested (18).

The debate is still out on how to treat sensitive skin. Using well-tolerated cosmetics or cosmetics with soothing effects, which decrease skin reactivity to insults, is recommended. In this study, we tested a cream made up of different compounds. Our aims were to have well tolerance, limit neurogenic and keratinocyte-induced inflammation, and reinforce skin barrier function in two different environments and on different ethnic skin (France and Thailand). Preliminary biological studies were also presented.

PATIENTS AND METHODS

PRODUCT

The tested cosmetic product (Sensibio Tolérance +®) is a cream containing sodium PCA (sodium l-pyrrolidone carboxylate; 1%) and Neurocontrol® (1.25%), a combination of RMX (rhamnose, mannitol, and xylitol, which are three carbohydrates) and a tetrapeptide [a transient receptor potential V1 (TRPV1) inhibitor].

In vitro studies. Human normal keratinocytes (HNK) from 3 different donors (Lonza, Belgium) were cultured (65,000 cells/well) with KBM [(keratinocyte basal medium) Lonza] and BPE (bovine pituitary extract), hEGF (human Epidermal Growth Factor), insulin, hydrocortisone, gentamicin, amphotericin B, epinephrine, and transferrin. The following day, the culture medium was replaced by the same medium supplemented or not with tested molecules (rhamnose, mannitol, xylitol and their association). After a 1-h incubation, tumor necrosis factor-α (TNF-α) (50 ng/ml) was added to induce interleukin 8 (IL-8) synthesis. After 24-h incubation, IL-8 amounts were measured by enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Bristol, UK).

Clinical studies. The primary objective was to evaluate the preventive soothing effect. The secondary objectives were to evaluate the immediate soothing effect, product tolerance, and its impact on quality of life.

The studies were performed by Dermscan in France and Thailand under the same conditions, with the same cosmetic product. Inclusion criteria were women aged 18 years or older, an I-II-III-IV phototype (Fitzpatrick scale), sensitive skin on their face, a

stinging test score ≥3, and patient consent. Exclusion criteria were: skin disease, known allergies, treatment for pain or itchiness, and the current application of another skin product or UV exposure.

The stinging test (19) was performed by applying 10% lactic acid (Sigma-Aldrich, Saint-Quentin-Fallavier, France) on one nasolabial fold and saline (Gifrer) on the other for 10 min. Each minute, the patient noted the intensity of unpleasant sensations using a four-point scale: none = 0, slight = 1, moderate = 2, severe = 3. The stinging score was calculated by adding scores taken after 2.5 min and 5 min of lactic acid application to the area. A score of 3/6 or higher was necessary for inclusion in the study. The stinging test was also used to evaluate the preventive effect on these patients by measuring the stinging score before treatment and after 4 weeks with two applications of the cream a day. An erythema score (from 0 to 4) was also used after the stinging test. To assess the immediate soothing effect, the stinging score was evaluated 2 min after applying a 10% lactic acid solution. Then, the product was applied and a stinging score was evaluated 5 and 15 min after this application.

Product tolerance was assessed by evaluating many criteria before treatment and after 4 weeks of treatment: edema, dryness, desquamation, roughness, vesicles, twinging, tingling, itchiness, or burning (none, very slight, slight, moderate, or severe).

Quality of life was evaluated using the Dermatology Life Quality Index (DLQI) before treatment and after 4 weeks of treatment. The DLQI is a health quality of life scale specifically designed for dermatological disorders (20). It includes 10 items, which focus on 6 dimensions: "symptoms," "daily activities," "leisure," "work," "personal relationships," and "treatment." A total score (between 0 and 30) is calculated and can be expressed as a percentage. The higher the score, the more quality of life is impaired. The health quality of life is considered "impaired" with a score of 6. It is "very impaired" with a score of 11. And it is "extremely impaired" with a score of 21 or greater (21).

Capsaicin and SLS Tests. This part of the study was performed in Poland by Dermscan (Ul. Kruczkowskiego 12, 80–288 Gdansk).

A capsaicin test was performed on women with dry and sensitive skin. After washing their nasogenian folds with 10% ethanol, increasing concentrations of capsaicin (from 10^{-3}% to 10^{-4}%) and 10% ethanol on the other fold were applied. Patients evaluated abnormal sensations on a scale from 0 to 5. A second evaluation was performed after 28 days by applying Sensibio Tolérance +® (Bioderma, Lyon, France) cream twice a day.

A sodium lauryl sulfate (SLS) test was performed by comparing the effects of (i) Sensibio Tolérance+® and 1% SLS, (ii) placebo, and (iii) placebo and 1% SLS. Placebo was a usual neutral basis made with water, glycerin, hydroxyethyl acrylate/sodium acryloyldimethyl taurate copolymer, isohexadecane, titanium dioxide, phenoxyethanol, chlorphenesin, polysorbate 60, alumina, and stearic acid.

Skin color was measured using Chromameter® (Konica Minolta, Singapore). Then, patch-tests were applied to normal forearm skin for 18 h. After removing the patches, the skin was washed and a new measurement was taken at 24 h.

Statistical analysis. Statistical analyses were performed using a *t*-test (Mann–Whitney test), a Student test, a Shapiro–Wilk test, and a Wilcoxon test, according to the quality of the data. Excel 2010 and SAS9.2 (SAS Institute, Cary, NC) softwares were used.

RESULTS

IN VITRO EFFECTS ON IL-8

The associations of Rhamnose 0.5%–mannitol 0.5%–xylitol 0.5% and rhamnose 0.05%–mannitol 0.1%–xylitol 0.1% associations inhibited IL-8 synthesis, respectively, from 24.8% ($p < 0.001$) and 22.2% ($p < 0.01$).

CLINICAL STUDY IN FRANCE

Thirty-three women were included in the study. The mean age was 47 (21–74) years. Sensibio Tolerance +® was applied by patients to the entire face twice a day for 28 days. The stinging score decreased from 4.3 (±0.2) to 1.7 (±0.4) after 4 weeks (−62%; $p < 0.0001$) (Fig. 1). An immediate soothing effect was showed by a decrease ($p < 0.0001$) in the stinging score after one application from 1.6 (±0.1) to 0.3 (±0.1) after 5 min (−80%), and to 0.03 (±0.03) after 15 min (−98.1%) (Fig. 2). The erythema score decreased from 2.5 (±0.1) to 1.8 (±0.2) after 4 weeks (−25%; $p < 0.0001$) (Fig. 3). The DLQI score decreased from 3.3 (±0.8) to 0.9 (±0.2) after 4 weeks (−74%; $p < 0.0001$). No pertinent side effects were noticed after 4 weeks of application. The patients gave a score of around 7/10 or 8/10 for the cosmetic qualities of the product and excipient (data not shown).

CLINICAL STUDY IN THAILAND

Thirty women were included in the study. The mean age was 39 (20–51) years. The cosmetic product was applied by patients to the entire face twice a day for 28 days. The stinging score decreased from 3.7 (±0.2) to 1.4 (±0.2) after 4 weeks (−62.2%; $p < 0.0001$) (Fig. 1). An immediate soothing effect was showed by a decrease ($p < 0.0001$) in the stinging score after one application of Sensibio Tolérance +® from 1.7 (±0.1) to 0.5 (±0.1) after 5 min (−70.6%) and 0.3 (±0.1) after 15 min (−82.4%) (Fig. 4). There was a significant difference ($p < 0.0001$) when the product was not applied: 1.7 (±0.1)

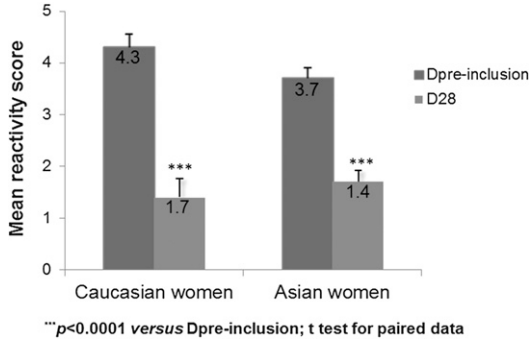

Figure 1. Preventive soothing effect.

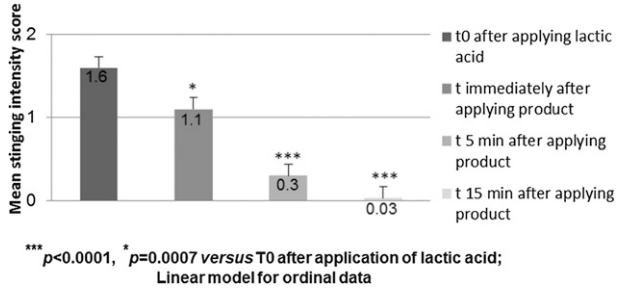

Figure 2. Immediate soothing effect on Caucasian skin.

to 1.2 (±0.1), then 0.7 (±0.2). Moreover, soothing effect duration was longer than that on the control side: 14.2 min versus 8 min (–44%, $p < 0.0001$). The erythema score decreased from 0.3 (±0.1) to 0.1 (±0.0) after 4 weeks, but no statistical analysis was applicable because less than a third of the patients had a variation between day 0 and day 28 (data not shown). The DLQI score decreased from 4.3 (±1.2) to 0.8 (±0.3) after 4 weeks (81.4%; $p < 0.001$). No pertinent side effects were noticed after 4 weeks of application. The patients gave a score of around 8/10 for the cosmetic qualities of the product (data not shown).

CAPSAICIN TEST

Twenty-two volunteers were included in the study. The mean age was 31 (18–64) years. After using the product twice a day for 28 days, the tolerated concentration of capsaicin increased from 1.10^{-4}% to $3.16.10^{-4}$% ($p < 0.01$), indicating that the tolerance threshold was higher.

SLS TEST

Twenty volunteers were included in this study. Twenty-four hours after using Sensibio Tolérance+®, redness significantly decreased ($p < 0.01$) by 79% compared with placebo and 1% of SLS. Photographs were taken in all cases. Patient number 7 at 24 h was given as an example (Fig. 5).

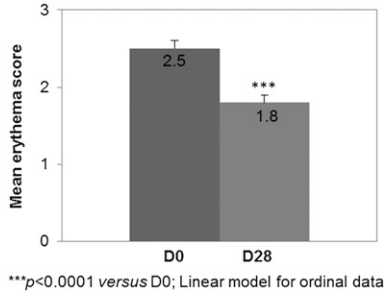

Figure 3. Soothing effect on erythema on Caucasian skin.

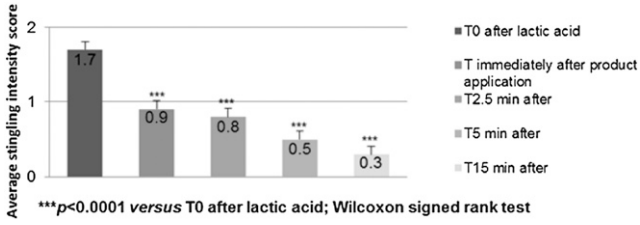

Figure 4. Immediate soothing effect on Asian skin.

DISCUSSION

Interesting effects of the cosmetic product in patients with sensitive skin were observed: a preventive soothing effect, an immediate soothing effect, and a soothing effect on erythema. SLS and capsaicin tests confirmed these data. A favorable effect on quality of life was also noted. The product was appreciated by volunteers for its efficacy, tolerance, and cosmetic qualities. These results were obtained in two different countries: France and Thailand.

Although the pathophysiology of sensitive skin remains unclear (22), the underlying mechanism is not immunological or allergic. There are not usually any histological abnormalities. Skin barrier function is altered in many patients, which may promote contact with triggering factors (23). Skin sensitivity may also cause dryness. Skin dryness and skin sensitivity could also be consequences of the same pathogenic mechanism when the two conditions are associated. Regular use of skin moisturizers seems to improve skin sensitivity (24). The role of "keratinocytic inflammation" is possible when cytokines are released. Abnormal sensations and vasodilatation strongly suggest the cutaneous nervous system's involvement (22). Neurotransmitters (25) may induce neurogenic inflammation after being released, when transient receptor potential (TRP) channels are activated (7). The main TRP is TRPV1, which is expressed by nerve endings and keratinocytes in the skin. Sensitive skin seems to be the result of a vicious cycle between neurogenic and "keratinocytic inflammation," with the release of neurotransmitters and cytokines.

Rhamnose is a monosaccharide which was previously known to decrease IL-8 secretion by inhibiting the interactions of T-cells with keratinocytes through intercellular adhesion molecule 1 (26). Mannitol and xylitol are polyols. Mannitol is also a hydroxyradical scavenger, which affects keratinocytes, for example, by inhibiting UV B–induced oxidative

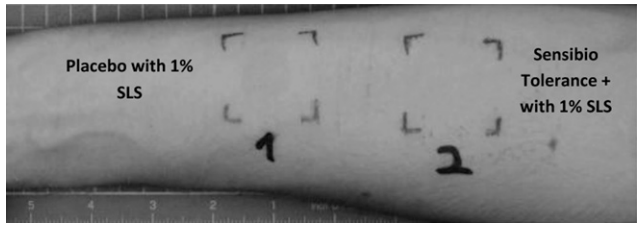

Figure 5. SLS test after 24 h: Patient number 7.

DNA base damage (27). Xylitol is also moisturizing and inhibits SLS-induced irritation (28). Our results suggest that the association of rhamnose, mannitol, and xylitol inhibits the TNF-α-induced production of IL-8. Among inflammatory cytokines that are released by keratinocytes, IL-8 is prominent and is especially involved in irritant dermatitis (29). Our results suggest that it is probably involved in the pathogeny of sensitive skins.

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