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Beneficial effects of a skin tolerance-tested moisturizing cream on the barrier function in experimentally-elicited irritant and allergic contact dermatitis

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In experimentally-induced irritant (ICD) and allergic (ACD) contact dermatitis, an oil-in-water (o/w) cream was applied to investigate its effects on a disturbed barrier function compared to untreated physiological barrier repair. Transepidermal water loss (TEWL) measurements were performed. Before the start of the experiments, the skin tolerance of the cream was examined, revealing the non-irritating characteristics of the ingredients and the absence of any contact allergic patch test reaction. In the ICD study, sodium lauryl sulfate (SLS) patches were applied to the forearms of young female volunteers. Consequently, it was observed that repeated cream application (14 days, 2×/day) significantly improved the TEWL of SLS-damaged skin, leading to a complete recovery on day 15. In the ACD study, disruption of skin barrier function was obtained by a nickel-mediated contact allergy patch (CAP) test. The cream was then applied 2×/day for 4 consecutive days. Assessment of TEWL clearly showed that recovery of the disrupted skin significantly improved after cream application in comparison to untreated barrier repair.

Key words: skin barrier; skin tolerance; SLS treatment; contact allergy patch (CAP) test; TEWL; moisturizing cream; skin care products; irritant contact dermatitis; allergic contact dermatitis; occupational; prevention. © Munksgaard, 2001.

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Both clinical appearance and subjective feeling of a healthy skin are primarily determined by 2 factors, namely the skin lipids and the degree of hydration of the horny layer. 'Skin lipids' refer to the combination of lipids that constitute the barrier function of the stratum corneum (SC), including ceramides, free fatty acids and cholesterol and those of the hydrolipidic film which mainly originate from the sebaceous glands (1). The hydrolipidic film, an acidic water-in-oil (w/o) mixture, covers the SC and forms a natural layer on the skin which partly shields it from external aggressions such as cold, wind and microbial invasion. The barrier function on the other hand provides protection mainly against the intrusion into the skin of foreign substances and against excessive transepidermal water loss (TEWL) (2, 3).

The main goal of the present study was the assessment of the effect on the TEWL of a selected moisturizing body cream in an experimentally induced irritant (ICD) and allergic contact dermatitis (ACD) study design. The ICD was experimentally provoked by sodium lauryl sulfate (SLS), a well-known example of a molecule that damages the hydrolipidic mixture and disturbs the skin barrier function leading to a significant increase in TEWL (4). The ACD study concerned a nickel-mediated contact allergy patch (CAP) test carried out in sensitized volunteers. Recent data report on the presence of skin barrier malfunction in ACD as measured by increased TEWL values (5, 6). In both disturbed skin barrier conditions the outer epidermis is characterized by a rough and scaly appearance. Before the efficacy of the cream was tested, it was necessary to verify whether the product was harmless. Therefore skin compatibility

tests were carried out with the raw cosmetic materials as well as with the final product. This type of test was conducted in a sufficiently large population with a dermatological background. The studies were performed under ethical and standardized conditions as described in an ECVAM (European Centre for the Validation of Alternative Methods)/EEMCO (European Group for Efficacy Measurements on Cosmetics and Other Topical Products) workshop report on non-invasive methods (7).

Materials and Methods

Test product

The moisturizing cream was a non-ionic oil-in-water (o/w) emulsion containing 9% glycerin and 4% evening primrose oil (Oenothera Biennis). The ingredients, according to the International Nomenclature Cosmetic Ingredients (INCI), together with their functions, are listed in Table 1.

TEWL measurements

Assessment of skin barrier function was carried out by a TEWA meter TM 210® (Courage+ Khazaka electronic GmbH, Köln, Germany). In order to obtain reliable and reproducible results, measurements were done under standardized conditions according to Pinnagoda et al. (8) and Rogiers (9). Ambient conditions (room temperature of 20.2±0.2°C and relative humidity of 49.8±1.0%) were kept within a constant range. Volunteers rested for at least 15 min in this room before measurements were performed.

Skin compatibility tests in human volunteers

The cream, both scented and unscented, was examined for skin compatibility in 124 subjects who were previously diagnosed for positive contact allergic responses in 6 departments of dermatology in university hospitals (Leuven, Brussels, Jette, Louvain, Antwerp and Ghent, Belgium). Of these subjects, 25 had atopic dermatitis and 67 showed a positive reaction to 1 or more allergens of the standard series (i.e., the Belgian Contact and Environmental Dermatitis Group Patch Test Series) and/or other tested allergens (fragrance mix and Myroxylon Pereirae Resin). Patch tests (large Finn Chambers®, ∅ 20 mm, Epitest, Helsinki, Finland) with 15–20 mg of the substances were applied on the back and removed after 2 days (48 h). The tests were read a 1st time, 10 min after air drying. A 2nd reading took place after 3 (72 h) or 4 (96 h) days. An additional series, diluted in petrolatum (10), consisted of cetearyl alcohol (20%), allantoin (2%), 2-bromo-2-nitropropane-1,3-diol (0.5%), triclosan (2%), disodium EDTA (1%) and perfume Infant® (2% and 5%). These concentrations were higher than those present in the final product (e.g., perfume 0.1%). Repeated open application tests

Table 1. Qualitative composition of the moisturizing o/w cream

Ingredients	Functions
aqua	water phase of the emulsion
octyl stearate	co-emulsifying agent
glycerin (9%)	humectant; natural moisturising factor (NMF)
Oenothera Biennis (4%)	emollient
glyceryl stearate	co-emulsifying agent
dimethicone	silicone component; water resistant properties
behenyl alcohol	emollient
pentaerythrityl stearate/caprate/caprylate/adipate	emollient
allantoin	anti-irritant ingredient
ceteareth-20	non-ionic emulsifier
cetyl palmitate	co-emulsifying agent
tocopherol	anti-oxidizing agent
ascorbyl palmitate	anti-oxidizing agent
ceteareth-12	non-ionic emulsifier
cetearyl alcohol	co-emulsifying agent
parfum (Infant®)	fragrance
PEG-8	emulsion stabiliser; humectant
carbomer	thickening agent
disodium EDTA	chelating agent
ascorbic acid	anti-oxidizing agent
citric acid	anti-oxidizing and chelating agent
tetrahydroxypropyl ethylenediamine	neutralizing agent; pH adjuster
triclosan	antiseptic component
dichlorobenzyl alcohol	preservative
2-bromo-2-nitropropane-1,3-diol	preservative

Ingredients are listed according to INCI nomenclature, together with their main function.

(ROATs) with the cream were carried out in the subjects showing a positive or doubtful patch test reaction. 5 test subjects agreed to carry out a ROAT. A small quantity of the cream was applied to the skin 2 to 3×/day by means of a cotton swab near the fold of the elbow, this being done for a maximum of 7 days. Randomization of scented and unscented cream was made between both forearms. When a skin reaction (redness, papules, swelling or itch, etc.) became visible, the ROAT was immediately stopped.

Experimental design

ICD protocol. 12 white female volunteers signed informed consent (Fitzpatrick skin type II or III, mean age 23±3, ranging from 20 to 29 years). Only subjects with a non-pathological skin were allowed to participate in the study. Approval was obtained from the Ethics Committee of the AZ-VUB Hospital (Brussels, Belgium). The test subjects were asked not to clean the forearms with soap 1 week prior to the start of the experiment and during the term of the study, nor to apply cosmetic products. Baseline measurements were carried out on the volar side of both forearms. For that purpose 3 squares of 2×4 cm were demarcated and randomized between both forearms. ICD was provoked by a 24-h patch test with 1.25% (w/v) SLS aqueous solution (Sigma, St. Louis, MO, USA, 99% purity) on the 2 contralateral test sites. A filter paper (∅ 20 mm, pore size 200 μm, Sartorius®, Goettingen, Germany) was soaked with 160 μl of the solution and applied under occlusion (Dermalock® HDP Medical, Waasmunster, Belgium). The patches were fixed by self-adhesive Fixomull® Stretch (Beiersdorf, Hamburg, Germany). The 3rd test site was covered with a 'blank' patch with 160 μl of pure water and served as undamaged control skin. After removal of the patches, the forearms were rinsed with pure water. Assessment of the SLS irritation by TEWL was performed 24 h after air exposure. For 14 consecutive days, 0.03 ml of the test product was applied 2×/day, with an interval of 12 h, on 1 of the irritated skin areas. The symmetrical test area on the other forearm served as untreated SLS-damaged skin spot. The randomization was kept blinded for the investigator. Measurements were carried out on days 3, 8 and 15, each time 12 h after the last cream application.

ACD protocol. 12 white female volunteers between 21 and 40 years old (mean age 31±6 years), with a well-established history of nickel (Ni) contact allergy were selected for the experiment. Exclusion criteria were the presence of irritant contact dermatitis, atopic eczema and the use of locally applied and oral corticosteroids, retinoids or immunosupressive medications. All subjects signed informed consent. Approval was obtained from the Ethics Committee of the AZ-VUB Hospital (Brussels, Belgium). Before the start of the experiment, baseline TEWL measurements and clinical scoring for erythema and papulation (0=absent, 1=mild, 2=moderate, 3=important) were carried out. Subjects were asked to report itching according to the same scale. On both volar forearms, closed patch tests (large Finn Chambers®, ∅ 20 mm, Epitest, Helsinki, Finland) with a filter paper disk of ∅ 18 mm, were applied symmetrically. The patches contained 0.3 ml of 5% nickel sulfate in petrolatum. A 3rd patch, closely situated near the elbow, on either the left or right forearm, contained 0.3 ml physiological serum (0.9% NaCl) and served as untreated control skin. Patches were removed after 48 h and the test sites were subsequently cleaned with dry tissues. Forearms were kept open to the air for 24 h, followed by TEWL measurements and re-assessment of clinical scores (day 1). At that moment, a cream application period of 4 days (2×/day, 0.03 ml on an area of 2×4 cm) started on one of the Ni-insulted skin areas, while the other ACD spot was left untreated. Without revealing it to the investigator, the cream-treated site was randomized between subjects. Measurements and clinical evaluation were carried out on days 2 to 5, 12 h after the previous cream application.

Statistical analysis

The Wilcoxon signed-ranks test for paired observations was used to compare TEWL values (recorded at different time points) of cream-treated skin with those of the untreated control site and also for the comparison between baseline values and values obtained after either treatment or physiological barrier repair. This non-parametric test was also used when comparing the median values of the clinical scoring (sum of 3 parameters). $p<0.05$ was chosen as level of significance.

Results

Skin tolerance to the cream

Irritation. In the 124 tested subjects only 1 irritant test reaction was seen, both for the scented and the unscented cream. In this patient, suffering from atopic dermatitis with a highly irritable skin, a slight redness and scaliness was seen.

Contact allergy. No contact allergic reactions were observed to either the scented or the unscented cream. In 6 patients, 8 positive and 3 question-

Table 2. Mean TEWL values (n=12) of forearm skin before (t_1=0) and after (t_2=0) SLS irritation and 12 h after topical treatment on days 3, 8 and 15 (cream application 2×/day); results are expressed in g/h · m^2 (mean±SD)

Time (days)	SLS-damaged, untreated skin	SLS-damaged, treated skin	Undamaged, control skin	
t_1=0	7.5±1.1	7.4±1.1	7.4±1.1	
t_2=0	32.6±6.0	32.1±5.5	7.6±0.9	p>0.05 (NS)
	p>0.05 (NS)			
3	15.6±3.7	12.8±3.7	7.4±1.1	
8	13.0±1.9	10.2±2.0	7.5±1.1	
15	9.9±1.2	7.0±1.1	7.4±1.2	

able reactions were recorded to the following constituent ingredients: cetearyl alcohol (1), 2-bromo-2-nitropropane-1,3-diol (1 questionable), triclosan (1), Infant® perfume 2% (2+2 questionable) and Infant® perfume 5% (4). Among the 12 subjects showing hypersensitivity to fragrance mix, 4 showed an allergic reaction to the perfume Infant®. Out of the 12 subjects with a reaction to Myroxylon Pereirae Resin only 1 reacted to Infant® perfume. Although only 1 reaction to 2-bromo-2-nitropropane-1,3-diol was established and even interpreted as questionable, 6 patients showed an allergic reaction to formaldehyde, a decomposition product of this preservative.

Repeated open application tests. Of the 3 patients with a patch test reaction to cetearyl alcohol, 2-bromo-2-nitropropane-1,3-diol or triclosan, none reacted in the ROAT with the cream. 2 of the 4 subjects with a contact allergy to Infant® perfume agreed to carry out a ROAT. Both subjects showed an eczematous reaction to the scented cream, while no reaction was observed to the unscented cream.

Barrier recovery after SLS irritation

In Table 2, mean TEWL values before (t_1=0) and after (t_2=0) SLS treatment are given, showing the expected increase in water loss after SLS damage. After repeated application of the cream, significant differences in TEWL could be detected in comparison with the TEWL values of SLS-damaged, but untreated skin. As can be seen in Fig. 1, decreases in TEWL were statistically significant on days 3, 8 and 15. On day 15, 12 h after the last application of the cream, it was observed that repeated application of the test product supported the SLS-damaged skin to complete recovery. At that moment no significant difference could be detected between the treated test area and the undamaged control skin. At day 3, the normal physiological barrier repair of an SLS-damaged skin area already showed a barrier recovery of 50%. On day 15, in contrast to the cream-treated test spot, the TEWL values of the untreated skin still were significantly increased (\$\$, p<0.01), when compared to the undamaged control values.

Barrier recovery following Ni contact allergy

Mean TEWL values measured at baseline (BL) and after patch test removal (day 1) are given in Table 3, together with the values measured on days 2 to 5, 12 h after the previous cream application. As compared to BL, TEWL values measured on the ACD test spots (day 1) were significantly – equal for both spots – increased. The physiological serum patch (=control skin) did not elicit any clinical sign of contact allergy and the TEWL values measured on this test spot remained unchanged during the test period. TEWL values were also expressed as a percentage of the absolute values measured on control skin, arbitrarily set at 100%. Fig. 2 summarizes these results. It was shown that cream application, 2× daily for 4 days, significantly improved the barrier function on day 5. At that moment the TEWL values recorded were not significantly different from the baseline values (p>0.05). In contrast, compared to control skin,

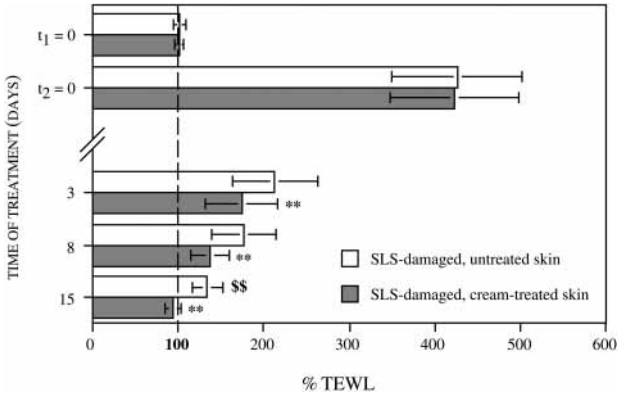

Fig. 1. The effect of the cream when topically applied to SLS-damaged forearm skin in comparison with physiological barrier repair. Mean values±SD (n=12) are presented, expressed as a percentage of the TEWL values measured on undamaged control skin, arbitrarily set at 100% (dashed line). TEWL measurements were carried out before (t_1=0) and after (t_2=0) SLS irritation. During a 14-day application period, measurements were performed 12 h after the last application of the cream on days 3, 8 and 15.
** (p<0.01) Significant difference between treated and untreated skin sites. **\$\$** (p<0.01) Significantly different results from values obtained before SLS irritation.

Table 3. TEWL values (g/h · m^2) and assessment of clinical scores (sum of 3 parameters) at baseline (BL) and after CAP test (day 1); cream application 2×/day during 4 days, evaluation 12 h after previous application on days 2 to 5; results are shown as mean±SD for TEWL and median for scoring (n=12)

	TEWL (g/h · m^2)				Clinical scores (sum)		
Time (days)	ACD skin Untreated	ACD skin Cream-treated	Control skin		ACD skin Untreated	ACD skin Cream-treated	Control skin
BL	9.0±1.3	9.1±1.3	9.2±1.4		–	–	–
1	20.4±8.2	20.6±8.6	9.0±1.6	$p>0.05$ (NS)	8	8 NS	–
	$p>0.05$ (NS)						
2	18.8±12.6	14.8±5.8	8.7±1.9		6	5*	–
3	14.6±7.7	11.5±3.5	9.1±2.3		3	3 NS	–
4	12.7±6.3	10.6±3.0	9.3±2.0		2	2 NS	–
5	12.3±6.2	9.6±3.3	9.0±1.8		1	1 NS	–

the TEWL measurements on the untreated ACD skin site remained elevated during the assessment period of 5 days. As can be seen in Table 3, visual scoring revealed a clinical ACD on day 1, which significantly diminished during the following days (median values going from 8 to 1, $p<0.001$). However, except for day 2, evaluation of clinical scores was considered equal for both cream-treated and untreated ACD test sites.

Discussion

Dry, rough and scaly skin requires more personal hygienic care than normal skin, which is usually well-hydrated with an intact hydrolipidic film and superficial barrier function. The inverse is often true for dry and damaged skin as seen in irritated or atopic skin (5, 11, 12). Moisturizing creams or body lotions are believed to exert beneficial effects and it has been clearly shown that, in the case of dry skin types, they increase SC hydration (13). Typical hydrating creams are non-ionic o/w emulsions containing natural moisturizing factors (NMFs) and mixtures of lipids of both mineral and vegetable origin (14). In previous work, the efficacy of different moisturizing creams has been tested for their hydrating potential using capacitance measurements and their effect on the barrier using TEWL measurements (15, 16). Consequently, the working hypothesis of our laboratory became as follows: a hydrating cream is considered to be efficient when its application on dry skin improves SC hydration and favours lower TEWL values. This hypothesis has been taken as the basic strategy to develop the skin care product used in the present study. When applied to elderly skin during a 14-day test (12 females, mean age 56±5 years old), a hydrating capacity of 30% and an effect on TEWL of 40% were measured (15). However, since the cream had to be tested on experimentally induced ICD and ACD, it was ethically necessary to run some additional skin compatibility tests prior to application (7). Of 124 tested subjects, there was only 1 with a mild irritant test reaction to the cream, whether scented or unscented. Therefore, the moisturizing product could be regarded as non-irritating. After patch testing, no contact allergic reactions were observed to either the scented or unscented version of the cream. Although 4 of the 12 subjects with a known perfume allergy reacted to a patch test with the Infant® perfume, none of them reacted to a patch with the scented cream. In the repeated open application test, none reacted to the unscented cream, while 2 subjects reacted to the scented cream. Therefore, precautions needed to be taken with regard to the incorporation of the perfume. Consequently, the cream applied in the experiments was chosen as unscented.

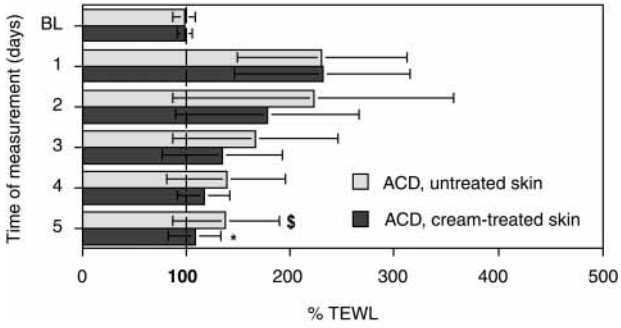

Fig. 2. Improvement of skin barrier recovery after ACD elicitation due to cream application on day 5 in comparison with physiological barrier repair. Results are presented as mean values±SD (n=12), expressed as a percentage of the TEWL values measured on undamaged control skin, arbitrarily set at 100% (dashed line). Statistical difference between treated and untreated skin sites, $p<0.05$ (*). $ ($p<0.05$). Significantly different results from baseline (BL) values.

In the 1st experiment, SLS was used as an irritant to provoke ICD. The exact mode of action of SLS is a subject of controversy but it is generally described that SLS exposure of the skin leads to partial delipidation, barrier damage and erythema

together with scaling (11). Too often, SLS still is a major component of liquid soaps and detergents and their frequent use is one of the main causes of the induction of ICD (17, 18). Alteration of the epidermal barrier function and subclinical skin injuries, as seen by higher TEWL values, are characteristic of ICD (12). After experimentally-induced skin damage, the regeneration process starts and a decrease in TEWL can be detected (3). In this study, it could clearly be shown that consecutive application of the hydrating cream supported barrier recovery before normal physiological barrier repair was completed. It is still unclear how topically applied cosmetic products are able to improve barrier properties and repair, but various reasons remain possible. It has been emphasized that the combination of hydrating ingredients with the (semi-) occlusive properties of various lipid components provides a 'shielding' effect and prevents water loss from the deeper layers (13, 19). Also, re-establishment of skin properties by addition of proper natural lipid components from the SC barrier, which can penetrate into the damaged superficial skin layers (20, 21), may occur. That barrier creams offer a protective effect against irritation is well described in the literature (22, 23). These studies showed that the TEWL values of skin sites previously treated with an occlusive barrier cream were significantly lower than those of untreated sites. As described by Hannuksela (14) and more recently by Lodén et al. (24), moisturizing products such as o/w emulsions can also prevent or reduce penetration and percutaneous absorption of irritants. The opposite, however, has also been reported, namely an increased skin susceptibility to irritants following a long-term pre-treatment period with a moisturizing cream (25). It was suggested that due to the fully hydrated SC, the latter became more permeable to hydrophilic irritants such as SLS. Indeed, it was found that the composition of the cream – which did not contain any NMFs or essential fatty acids – was not able, even after a 27-day application period, to decrease the TEWL by strengthening the barrier. So, there is no doubt that any clinical relevance in attempting the reduction of recovery of contact dermatitis is related to the composition of the moisturizing cream (24).

In addition, it is generally less known whether these dermatologic preparations are efficient in modulating skin exposure and vulnerability to allergens (5, 6). The CAP test carried out in the 2nd study created a standardized dermatitis implicating both immune and inflammatory mechanisms (26). Combined with TEWL measurements, this experimental model has been shown to be adequate for assessing skin barrier function and repair under ACD conditions (5, 27). The results of the ACD study design showed that application of the hydrating cream induced a more rapid recovery of the barrier function as measured by TEWL. An equal re-establishment of the initial clinical parameters of the skin studied was seen for both treated and untreated ACD conditions. However, when the clinical scoring was at its lowest level in the untreated ACD (day 5), the TEWL still remained significantly higher than its baseline value. This reflects subclinical skin barrier alterations at the late healing stage of physiological repair of ACD. After induction of the skin damage, the absolute TEWL values (Tables 1, 2) clearly indicated that SLS provoked a much severe barrier disturbance than the Ni-induced allergic reaction, as measured by TEWL. Although barrier restoration due to cream application was seen in both experimental models, the recovery of SLS-damaged skin took 14 days, whereas ACD returned to baseline values after 5 days.

It can be hypothesised that the positive effects observed after cream application are most likely related to the above-mentioned beneficial effects of moisturizing products on the hydration state and barrier function of the upper skin layers (16, 28). Due to the hydrating components and the barrier-restoring properties of the lipid phase, moisturizing creams may improve subclinical barrier alterations and consequently diminish the observed inflammatory reactions. This was also concluded by Lodén et al. (24), who emphasized that the mechanisms behind these effects still needed further investigation. Furthermore, the question was also raised whether classical anti-inflammatory therapeutics, widely applied in dermatology to decrease skin inflammation, could be beneficially combined with moisturizing creams to optimize the healing of ACD. Utilization of such a combination therapy could offer new methods for topical treatment of inflammatory dermatoses characterized by skin barrier malfunction. In this regard, Hachem et al. (27) already performed some experiments with topical corticosteroids combined with the same cream as used in the present experiments. In the healing process of ACD, they showed a synergistic phenomenon, leading to a decreased use of corticosteroids, thereby preventing their adverse effects on the skin (27).

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