ACO HUD NORDIC AB is the leading skin care company in the Nordics. Covering the range from topical pharmaceuticals to exclusive skin care products, our product portfolio offers both width and depth. With research and laboratory in-house, we develop safe products with modern formulations for the Nordic consumer.

Through our knowledge and evidence based approach we add value within the skin care sector. With transparency as a key word for all our work, we frequently present and publish the results of our research.

This booklet contains scientific publications on ACO's research within the field of dermatology. Clinical studies on our medicinal products as well as review articles are presented.
EMOLLIENTS IN GENERAL

NEW! PREVENTION OR PROMOTION OF DRYNESS AND ECZEMA BY MOISTURIZERS?
M Lodén.

The use of moisturizers is almost instinctive and is also routinely recommended to reduce the likelihood of developing dryness and eczema. However, recent findings demonstrate that treatment with creams may increase the risks for eczema. Symptoms of dryness may appear in normal skin and the skin susceptibility to outside stressors may increase. Moisturizing creams contain a great variety of ingredients, some of which are found in the stratum corneum. However, knowledge regarding the mechanisms of the impact of different ingredients on the skin is still lacking and, currently, it is a matter of trial and error to find the most suitable moisturizer for an individual.

The cosmetic properties and the simplicity to use the products are important parameters for adherence, but even more important are the effects on the skin barrier function. A defect in skin barrier function has been suggested as the major cause for atopic eczema. Increased rate of transepidermal water loss (TEWL) induces signals that stimulate normalization of the skin barrier function, but increased TEWL can also have pathological effects, which results in cutaneous abnormalities. Therefore, we propose TEWL to be a surrogate parameter for the changed risks for development of eczema by moisturizer treatment.

INCREASING QUALITY OF LIFE BY IMPROVING THE QUALITY OF SKIN IN PATIENTS WITH ATOPIC DERMATITIS
K Halvarsson & M Lodén.

Atopic dermatitis is a chronic relapsing inflammatory skin disease which usually starts during the first years of life. In patients with the disease, the quality of skin is severely affected, and this is closely linked to a reduced quality of life. An increasing prevalence of the disease has also been observed during recent years, which has been attributed to potential provocation factors in the environment. The environmental influence of the disease is complex, but the role of stratum corneum as a biosensor regulating the response to a variety of insults has been suggested as one crucial factor. Therefore, our daily hygiene and treatment of dryness are necessary measures to improve the quality of life and possibly reduce the frequency of the disease. Soaps as well as moisturizers show important differences in their impact on barrier function.
Moisturizing creams marketed to consumers often contain trendy ingredients and are accompanied by exciting names and attractive claims. Moisturizers are also an important part of the dermatologist’s armamentarium to treat dry skin conditions and maintain healthy skin. The products can be regarded as cosmetics, but may also be regulated as medicinal products if they are marketed against dry skin diseases, such as atopic dermatitis and ichthyosis. When moisturizers are used on the so-called dry skin, many distinct disorders that manifest themselves with the generally recognized symptoms of dryness are treated. Dryness is not a single entity, but is characterized by differences in chemistry and morphology in the epidermis depending on the internal and external stressors of the skin. Patients and the society expect dermatologists and pharmacists to be able to recommend treatment for various skin conditions upon evidence-based medicine. Upon completing this paper, the reader should be aware of different types of moisturizers and their major constituents. Furthermore, s/he will know more about the relief of dryness symptoms and the functional changes of the skin induced by moisturizers.
CANODERM

NEW! TREATMENT WITH A BARRIER-STRENGTHENING MOISTURIZING CREAM DELAYS RELAPSE OF ATOPIC DERMATITIS: A PROSPECTIVE AND RANDOMIZED CONTROLLED CLINICAL TRIAL.


Standard treatment of atopic dermatitis (AD) is based on topical glucocorticosteroids or calcineurin inhibitors to treat flares combined with moisturizer treatment to alleviate dry skin symptoms. Patients with AD have an abnormal skin barrier function, and strategies for reducing the risks for eczema would be to repair the barrier or prevent barrier dysfunction. The objective of this study was to explore the time to relapse of eczema during a 26-week maintenance treatment with a urea containing moisturizer compared to no treatment (neither medical nor non-medicated preparations) after successful clearing of atopic lesions. The moisturizer has previously been shown to improve skin barrier function. Patients applied betamethasone valerate (0.1%) on eczematous lesions during a 3-week period. Those with cleared eczema entered a 26-week maintenance phase, applying the moisturizer or leaving the previously affected area untreated. Upon eczema relapse, patients were instructed to contact the clinic and to have the relapse confirmed by the investigator. Fifty-five patients entered the study and 44 patients were included in the maintenance phase (22 using moisturizer twice daily and 22 using no treatment). Median time to relapse for patients treated with moisturizer was > 180 days (duration of the study) compared with 30 days for the no-treatment group. Sixty-eight per cent of the patients treated with the moisturizer and 32% of the untreated patients remained free from eczema during the observation period. Maintenance treatment with a barrier-improving urea moisturizer on previous eczematous areas reduced the risk of relapse to approximately one third of that of no treatment.

NEW! MOISTURIZERS CHANGE THE mRNA EXPRESSION OF ENZYMES SYNTHESIZING SKIN BARRIER LIPIDS.


In a previous study, 7-week treatment of normal human skin with two test moisturizers, Complex cream and Hydrocarbon cream, was shown to affect mRNA expression of certain genes involved in keratinocyte differentiation. Moreover, the treatment altered transepidermal water loss (TEWL) in opposite directions. In the present study, the mRNA expression of genes important for formation of barrier lipids, i.e., cholesterol, free fatty acids and ceramides, was examined. Treatment with Hydrocarbon cream, which increased TEWL, also elevated the gene expression of GBA, SPTLC2, SMPD1, ALOX12B, ALOXE3, and HMGCS1. In addition, the expression of PPARG was decreased. On the other hand, Complex cream, which decreased TEWL, induced only the expression of PPARG, although not confirmed at the protein level. Furthermore, in the untreated skin, a correlation between the mRNA expression of PPARG and ACACB, and TEWL was found, suggesting that these genes are important for the skin barrier homeostasis. The observed changes further demonstrate that long-term treatment with certain moisturizers may induce dysfunctional skin barrier, and as a consequence several signaling pathways are altered.
LONG-TERM TREATMENT WITH MOISTURIZERS AFFECTS THE mRNA LEVELS OF GENES INVOLVED IN KERATINOCYTE DIFFERENTIATION AND DESQUAMATION.


In a recent study, we showed that long-term treatment with two different moisturizers affected TEWL in opposite directions. Therefore, we decided to examine the effect of these moisturizers on the cellular and molecular level. In a randomized controlled study on 20 volunteers, epidermal mRNA expression of genes essential for keratinocyte differentiation and desquamation after a 7-week treatment with two moisturizers was analyzed. Treatment with one test moisturizer increased gene expression of involucrin, transglutaminase 1, kallikrein 5, and kallikrein 7, while the other moisturizer affected only expression of cyclin-dependent kinase inhibitor 1A. Thus, moisturizers are able to modify the skin barrier function and change the mRNA expression of certain epidermal genes. Since the type of influence depends on the composition of the moisturizer, these should be tailored in accordance with the requirement of the barrier of each individual patient, which merits further investigations.

COST-EFFECTIVENESS OF A BARRIER-STRENGTHENING MOISTURIZING CREAM AS MAINTENANCE THERAPY VS. NO TREATMENT AFTER AN INITIAL STEROID COURSE IN PATIENTS WITH ATOPIC DERMATITIS IN SWEDEN – WITH MODEL APPLICATIONS FOR DENMARK, NORWAY AND FINLAND.


Atopic dermatitis (AD) affects health and quality of life and it has great impact on both health-care costs and costs to the society. The objective of this study was to develop a model to analyse the cost-effectiveness of a barrier-strengthening moisturizing cream as maintenance therapy compared with no treatment after initial treatment with betamethasone valerate in adult patients with AD in Sweden. A further aim was to apply a similar health-economic analysis for Denmark, Norway and Finland. A Markov simulation model was developed including data from three sources: (i) efficacy data from a randomized controlled trial including patients with moderate AD treated with either a moisturizing cream or no treatment, (ii) resource utilization and quality of life data, and (iii) unit prices from official price lists. A societal perspective was used and the analysis was performed according to treatment practice in Sweden. The model simulation was also applied for Denmark, Norway and Finland with inclusion of country-specific unit costs. Sensitivity analyses were performed to test the robustness of the results. The results from the present analyses of treatment for patients with moderate AD indicate that maintenance treatment with a moisturizing cream during eczema-free periods could be cost-effective in a societal perspective. Similar results were obtained for Sweden, Denmark, Norway and Finland. According to the analysis, treatment with a moisturizing cream was found to be a cost-effective option compared with no treatment in eczema-free periods in adult patients with AD in the four Nordic countries.
THE EFFECT OF TWO UREA-CONTAINING CREAMS ON DRY, ECZEMATOUS SKIN IN ATOPIC PATIENTS. I. EXPERT, PATIENT AND INSTRUMENTAL EVALUATION  
A-C Andersson, M Lindberg & M Lodén.  

The management of atopic dermatitis includes moisturizing creams, although scientific studies of their influence on the skin are scarce. In the present randomized, double-blind study, the effects of a new moisturizing cream were compared with those of an already registered medicinal cream in the treatment of dry eczematous skin in atopic patients, using multiple methods. The new cream contained 5% urea as active substance and the established licensed cream contained 4% urea and 4% sodium chloride as active ingredients. The new cream was studied in 25 patients and the established cream was tested in 23 patients. The patients were asked to apply the cream to dry, eczematous areas at least once daily for 20 days. At inclusion in the study and after 15 and 30 days of treatment the severity of the skin was evaluated by a dermatologist, assessed by the patients and measured in terms of transepidermal water loss (TEWL) and skin capacitance. Both groups improved during the study, but no statistically significant differences between them were found. This multiparametric approach covers different aspects of skin dryness and provides the possibility of evaluating treatment effects in a cost-effective way.

DIFFERENCES AMONG MOISTURIZERS IN AFFECTING SKIN SUSCEPTIBILITY TO HEXYL NICOTINATE, MEASURED AS TIME TO INCREASE SKIN BLOOD FLOW  
C Duval, M Lindberg, A Boman, S Johnsson, F Edlund & Marie Lodén.  
Skin Research and Technology 2003; 9: 59-63.  

A wide range of branded and generic moisturizers is frequently used for the prevention and treatment of dry skin. The influence of the moisturizers on the skin permeability is pertinent to the understanding of their therapeutic efficacy. The aim of the present study was to compare the effect of two moisturizers on the skin permeability barrier, assessed as skin reactivity to a vasodilating substance. The study was parallel, randomized and double blind on 53 healthy volunteers. One of the creams contained 5% urea, whereas the other contained no humectant but had a high lipid content. The participants were instructed to apply the cream twice daily for three weeks on the volar aspect of one of their forearms. The skin was then exposed to hexyl nicotinate, which induces vasodilatation. The time-course and magnitude of the microvascular changes in the two skin areas were monitored with a non-invasive optical technique (laser Doppler flowmetry) with two measuring probes. The lag-time between application and initial response was significantly longer for the urea-treated site compared with the other cream. Furthermore, the time for maximum response was shorter for the lipid-rich cream than for its placebo. The study shows differences in action between moisturizers, which may influence the skin susceptibility to other irritants and allergens in the environment.
CHANGES IN SKIN BARRIER FUNCTION FOLLOWING LONG-TERM TREATMENT WITH MOISTURIZERS, A RANDOMIZED CONTROLLED TRIAL

Moisturizers are commonly used by patients with dry skin conditions as well as people with healthy skin. Previous studies on short-term treatment have shown that moisturizers can weaken or strengthen skin barrier function and also influence skin barrier recovery. However, knowledge of the effects on skin barrier function of long-term treatment with moisturizers are still scarce. The aim of this study was to investigate the impact of long-term treatment with moisturizers on the barrier function of normal skin, as measured by transepidermal water loss (TEWL) and susceptibility to an irritant, and to relate those effects to the composition of the designed experimental moisturizers.

Volunteers (n=78) were randomized into five groups. Each group treated one volar forearm for 7 weeks with one of the following preparations: (i) one of three simplified creams, containing only a few ingredients in order to minimize the complexity of the system; (ii) a lipid-free gel; (iii) one ordinary cream, containing 5% urea, which has previously been shown to decrease TEWL. The lipids in the simplified creams were either hydrocarbons or vegetable triglyceride oil, and one of them also contained 5% urea. After 7 weeks, treated and control forearms were exposed for 24 h to sodium lauryl sulphate (SLS) using a patch test. TEWL, blood flow and skin capacitance of both SLS-exposed and undamaged skin were evaluated for 24 h after removal of patches. Additionally, a 24-h irritancy patch test of all test preparations was performed on 11 volunteers in order to check their possible acute irritancy potential. Changes were found in the barrier function of normal skin after 7 weeks of treatment with the test preparations. The simplified creams and the lipid-free gel increased TEWL and skin response to SLS, while the ordinary cream had the opposite effect. One of the simplified creams also decreased skin capacitance. All test preparations were shown to be non-irritant, both by short-term irritancy patch test and by measurement of blood flow after long-term treatment. Moisturizers influence the skin barrier function of normal skin, as measured by TEWL and susceptibility to SLS. Moreover, the effect on skin barrier function is determined by the composition of the moisturizer. The ingredients which influence the skin barrier function need to be identified, and the mechanism clarified at the molecular level.
**CANODERM**

**EFFECTS OF PRETREATMENT WITH A UREA-CONTAINING EMOLLIENT ON NICKEL ALLERGIC SKIN REACTIONS**

N Kuzmina, M Nyrén, M Lodén, F Edlund & L Emtestam.

The aim of this study was to evaluate the effect of a moisturizer containing urea on nickel-sensitized volunteers patients and five controls (non-sensitized volunteers) applied such a moisturizer on the volar side of one forearm twice daily for 20 days, while the other forearm served as the control. After treatment with the moisturizer, patch tests with 0%, 0.5% and 2% NiSO₄ in petrolatum were applied in a randomized manner on each arm. After 72 h, the skin reactions were blindly evaluated by clinical scoring and by measuring transepidermal water loss and electrical impedance. After treatment, the baseline transepidermal water loss values were lower and the baseline magnitude impedance index values were higher on the pretreated forearm. According to clinical scoring and measurements with the two physical measurement techniques, the degree of the patch test reactions was equal. All control subjects had negative nickel tests. We concluded that the skin reactivity to nickel in nickel-sensitized patients is not significantly affected by use of the urea-containing moisturizer.

**IMPROVEMENT IN SKIN BARRIER FUNCTION IN PATIENTS WITH ATOPIC DERMATITIS AFTER TREATMENT WITH A MOISTURIZING CREAM (CANODERM®)**


Patients with atopic skin show a defective barrier function both in rough and in clinically normal skin, with an increasing risk of developing contact dermatitis. Moisturizing creams are often used in the treatment of dry skin. The purpose of this study was to investigate the influence of treatment with a urea-containing moisturizer on the barrier properties of atopic skin. Fifteen patients with atopic dermatitis treated one of their forearms twice daily for 20 days with a moisturizing cream. Skin capacitance and transepidermal water loss (TEWL) were measured at the start of the study and after 10 and 20 days. On day 21 the skin was exposed to sodium lauryl sulphate (SLS) and on day 22 the irritant reaction was measured non-invasively. Skin capacitance was significantly increased by the treatment, indicating increased skin hydration. The water barrier function, as reflected by TEWL values, tended to improve (P=0.07). And the skin susceptibility to SLS was significantly reduced, as measured by TEWL and superficial skin blood flow (P<0.05). Thus, it seems that certain moisturizers could improve skin barrier function in atopics and reduce skin susceptibility to irritants. The mechanism and the clinical relevance need further investigation.
Moisturizers are used daily by many people to alleviate symptoms of clinically and subjectively dry skin. Recent studies suggest that certain ingredients in creams may accelerate the recovery of a disrupted barrier and decrease the skin susceptibility to irritant stimuli. In the present single-blind study, a moisturizing cream was tested for its influence both on barrier recovery in surfactant-damaged skin and on the susceptibility of normal skin to exposure to the irritant sodium lauryl sulphate (SLS). Parameters measured were transepidermal water loss (TEWL) and skin corneometer values, indicating degree of hydration. Treatment of surfactant-damaged skin with the test cream for 14 days promoted barrier recovery, as observed as a decrease in TEWL. Skin corneometer values also normalized more rapidly during the treatment. In normal skin, use of the test cream significantly reduced TEWL after 14 days of treatment, and irritant reactions to SLS were significantly decreased. Skin corneometer values increased after only 1 application and remained elevated after 14 days. In conclusion, the accelerated rate of recovery of surfactant-damaged skin and the lower degree of SLS-induced irritation in normal skin treated with the test cream may be of clinical relevance in attempts to reduce contact dermatitis due to irritant stimuli.
MINIDERM

A DOUBLE-BLIND STUDY COMPARING THE EFFECT OF GLYCERIN AND UREA ON DRY, ECZEMATOUS SKIN IN ATOPIC PATIENTS
Acta Dermato-Venerologica 2002; 82: 45-47.

Moisturizing creams have beneficial effects in the treatment of dry, scaly skin, but they may induce adverse skin reactions. In a randomized double-blind study, 197 patients with atopic dermatitis were treated with one of the following: a new moisturizing cream with 20% glycerine, its cream base without glycerine as placebo, or a cream with 4% urea and 4% sodium chloride. The patients were asked to apply the cream at least once daily for 30 days. Adverse skin reactions and changes in skin dryness were assessed by the patient and a dermatologist. Adverse skin reactions such as smarting (a sharp local superficial sensation) were felt significantly less among patients using the 20% glycerine cream compared with the urea-saline cream, because 10% of the patients judged the smarting as severe or moderate when using glycerine cream, whereas 24% did so using urea-saline cream (P<0.0006). No differences were found regarding skin reactions such as stinging, itching and dryness/irritation. The study showed equal effects on dry skin as judged by the patients and the dermatologist. In conclusion, a glycerine containing cream appears to be a suitable alternative to urea/sodium chloride in the treatment of atopic dry skin.

THE INFLUENCE OF A CREAM CONTAINING 20% GLYCERIN AND ITS VEHICLE ON SKIN BARRIER PROPERTIES
M Lodén & C Wessman.

Glycerin is widely used in cosmetics as well as in pharmaceutical formulations, mainly as humectant. In vitro studies have shown glycerine to prevent crystallization of stratum corneum model lipid mixture at low room humidity. Whether this may affect the skin barrier function during repeated application of glycerine in a cream base to normal skin is not known. Therefore, the influence of a cream containing 20% glycerin was compared with its placebo cream in a bilateral, double-blind study on 17 healthy volunteers. The effect was evaluated as influence on hydration with a corneometer and on skin barrier function. Skin barrier function was assessed as permeability to water with an evaporimeter (transepidermal water loss; TEWL) and as sensitivity to an irritating surfactant by measuring the biological response (measured as TEWL and skin blood flow). Ten days treatment of normal skin with 20% glycerine significantly increased skin corneometer values, indicating an increased hydration. However, our study failed to show an influence of glycerine on human skin, in terms of TEWL and skin sensitivity to SLS-induced irritation.


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**SUBMITTED ORIGINAL SCIENTIFIC PUBLICATIONS AND REVIEWS**


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