Skin Research and Technology 2001; 7: 209–213
Printed in Denmark. All rights reserved

Copyright © Munksgaard 2001

Skin Research and Technology
ISSN 0909-752X

Instrumental and dermatologist evaluation of the effect of glycerine and urea on dry skin in atopic dermatitis

M. Lodén[1], A.-C. Andersson[2], C. Andersson[3], T. Frödin[3], H. Öman[3] and M. Lindberg[4]

[1]*ACO Hud AB, Stockholm,* [2]*Department of Dermatology, University Hospital, Uppsala,* [3]*Department of Dermatology, Linköping University Hospital, Linköping,* [4]*Department of Medicin, Occupational Dermatology, Karolinska Institute, Stockholm, Sweden*

Background/aims: Moisturising creams are useful treatment adjuncts in inflammatory dermatoses and have beneficial effects in the treatment of dry, scaly skin. The effects on dryness and skin permeability of a new moisturising cream with 20% glycerine was compared with its placebo and with a medicinally authorised cream with 4% urea (combined with 4% sodium chloride) in the treatment of dry skin.
Methods: Patients (n=109) with atopic dermatitis were treated for 30 days with a moisturiser in a randomised, parallel and double-blind fashion. Transepidermal water loss (TEWL) and skin capacitance were assessed instrumentally, and changes in the dryness of the skin were assessed by the dermatologist.
Results: No difference in TEWL was found between glycerine treatment and its placebo, whereas a lower value was found in the urea-treated area compared to the glycerine-treated area. No difference in skin capacitance was found. The clinical assessment of dryness showed urea to be superior to glycerine in treating the condition.
Conclusions: Moisturising creams are different, not only with respect to composition but also with respect to their influence on skin as a barrier to water in patients with atopic dermatitis.

Key words: moisturiser – dry skin – cream – emollient – permeability barrier – transepidermal water loss

© *Munksgaard, 2001*
Accepted for publication 28 January 2001

ATOPIC DERMATITIS is a common, chronically relapsing skin disorder, usually beginning in childhood. Moisturising creams are useful treatment adjuncts in such inflammatory dermatoses and have beneficial effects in the treatment of dry, scaly skin (1). However, although clinical experience suggests an important role for moisturisers, more scientific studies are considered essential to demonstrate possible differences in mechanism and effect (2).

Moisturising creams occlude the skin and contain humectants to increase its water content. Widely used humectants are urea, lactic acid, PCA and glycerine. Glycerine and urea diffuse into the stratum corneum (3–5) and increase the water-holding capacity of normal stratum corneum and of scales from psoriatic and ichthyotic patients (6–9). The humectants relieve clinical signs of dryness, such as scaling (10–12), and glycerine has also been shown to increase the rate of corneocyte loss from the superficial surface of human skin, probably due to an enhanced desmosome degradation (13). Glycerine has also been proposed to influence the crystalline arrangement of the intercellular bilayer lipids (14). The bulk of the bilamellar sheets of the lipids has been suggested to be in crystalline/gel domains bordered by lipids in a fluid crystalline state (15). In dry skin, the proportion of lipids in the solid state is suggested to be elevated, and glycerine may then help to maintain the lipids in a liquid crystalline state at low relative humidity (14).

The influence of glycerine on the intercellular lipids may have consequences for the permeability of the skin. Studies on normal skin show that a single application of an aqueous solution of glycerine reduces transepidermal water loss (TEWL) for some hours (6), whereas repeated application of 20% glycerine in a cream did not change TEWL or skin susceptibility to sodium lauryl sulphate (SLS) in a placebo-controlled study on normal skin (16). In tape-stripped and acetone-treated skin, a single application has been shown to decrease skin sensitivity to alkali, SLS and dimethylsulfoxide, but to increase the bioavailability of hexyl nicotinate (17). The other humectant, urea, has been found to decrease TEWL in normal and dry skin (8, 18–20) and to decrease skin sensitivity to SLS-induced irritation (18, 19), but to be a penetration enhancer for some drugs (21–23).

Although moisturisers with various compositions are used extensively on patients with atopic derma-

titis, controlled studies of their effects on dryness and skin permeability are few. The aim of the present study was to investigate the effect on dryness and skin permeability of a 20% glycerine cream and its placebo on patients with atopic dermatitis and to compare the effect with an established cream containing urea (4%) and sodium chloride (4%). The effect was judged by an expert (dermatologist) and measured as transepidermal water loss and skin capacitance.

Material and Methods

Subjects

The study was randomised, double-blind and performed on three parallel groups in February to April of the same year. In total, 110 patients (93 women and 16 men) with atopic dermatitis [according to criteria of Hanfin & Rajka (24)], but with no other significant concurrent illness and no known allergy to ingredients in the test creams, were included. One patient dropped out.

The mean age ± the standard deviation (SD) was 34±11 years in the glycerine group, 34±13 years in the urea group and 33±11 years in the placebo group. One area on the body was identified as dry by the dermatologist and was treated twice daily for 30 days with the cream. Among the 109 patients, the majority (87 patients) treated one area on the upper or lower forearm, 8 patients treated one area on the back, 8 treated the dorsal aspect of the hand and 6 treated one area on the leg. The patients were asked to replace their ordinary moisturiser by the test cream. The local ethics committees approved the study, and informed consent was obtained.

Test products

The glycerine cream contained 20% glycerine, aqua, petrolatum, canola, mineral oil, cetearyl alcohol, glyceryl stearate, dimethicone, PEG-100 stearate, glyceryl polymethacrylate, cholesterol, propylene glycol, methylparaben and propylparaben. Glycerine was replaced by water in the placebo cream. The urea cream contained 4% urea and 4% sodium chloride as water-binding substances in an oil-in-water emulsion, pH about 5. Other ingredients were paraffinum liquidum, PEG-5 glycerylstearate, cetyl alcohol, stearyl alcohol, stearic acid, trometamol, methylparaben, propylparaben, hydrochloric acid and water.

Evaluations

The expert assessment of severity of the dry skin was done at the start of the study and after 30 days, according to a newly proposed system for dry skin and ichthyosis (25). Scaling, roughness, redness and cracks (fissures) in the identified area were scored from 0 to 4, and the sum of the severity score was calculated (maximum 16). The same expert evaluated the patient at the start of and end of the study, and the evaluations were performed in the same room and with the same light conditions.

TEWL and skin capacitance were measured before the first application of the creams (i.e., at day 0) and at day 31. TEWL was quantified using an evaporimeter (Servomed, Kinna, Sweden) (26). The probe is equipped with a screen and grid to reduce air convection. The electrical capacitance, indicating degree of skin hydration (27, 28), was measured with a Corneometer CM-820 and CM-825 (Courage and Khazaka GmbH, Cologne, Germany). During measurements, noise and talk in the room were restricted. Measurements were made in a temperature-controlled room.

Calculations and statistics

Side-by-side box-and-whisker plots are used to display the data. The box is defined by the upper and lower quartiles and with the median marked by a subdivision of the box. The whiskers have a maximum length in terms of the interquartile range, and outliers are shown (Minitab Statistical Software, Minitab Inc., State College, PA, USA). A Spearman rank correlation (nonparametric) test was used to quantify the degree of linear association between the change in TEWL and the dryness score.

Statistical significances between the glycerine cream and the other two treatments were tested using the Mann-Whitney rank sum test. $P<0.025$ was con-

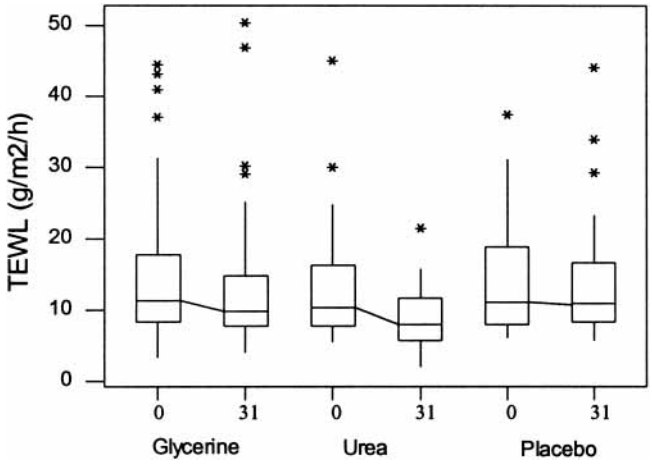

Fig. 1. Skin barrier function measured as TEWL at the start of the study and after 30 days of treatment with glycerine (n=*40), urea* (n=*35) and placebo* (n=*34).*

sidered as significant for each of the two comparisons to obtain an overall significance level of $P<0.05$.

Results

After treatment for 30 days, a significantly lower TEWL was found in the area treated with urea compared to the area treated with glycerine ($P=0.021$) (Fig. 1). No difference was found between the glycerine treatment and the placebo treatment ($P=0.419$). A lower value of the dryness score was also found in the area treated with urea compared to the area treated with glycerine ($P=0.024$), while no difference was found between the glycerine-treated area and the placebo-treated area ($P=0.419$) (Fig. 2). One patient in the glycerine group and four patients in the placebo group showed more dryness after the treatment period. No patient showed more dryness in the urea/sodium chloride group.

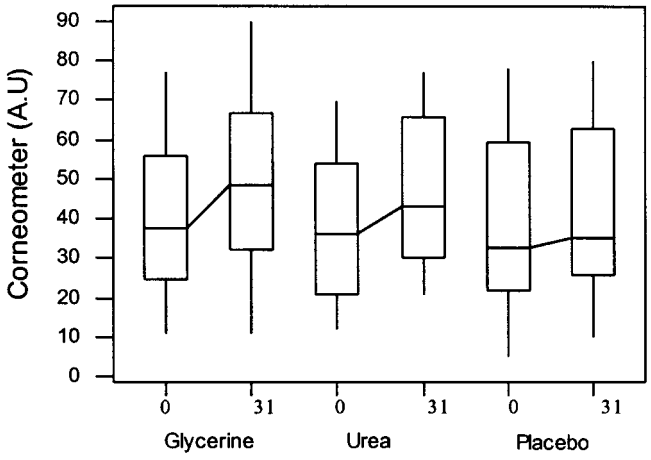

Fig. 4. Skin capacitance (A.U.) measured with a Corneometer at the start of the study and after treatment for 30 days with glycerine (n=*40), urea* (n=*35) and placebo* (n=*34).

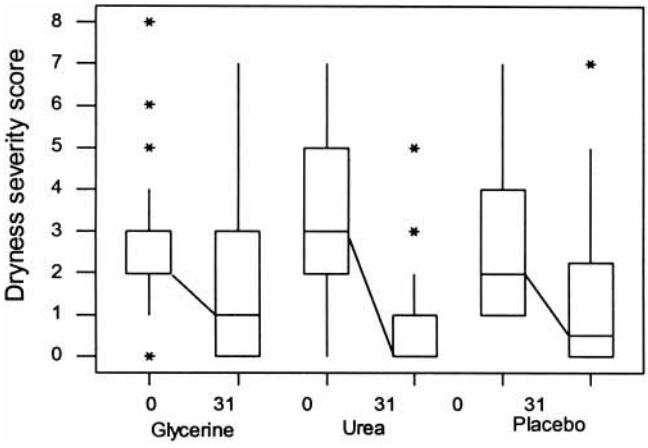

Fig. 2. Skin dryness severity score at the start of the study and after treatment for 30 days with glycerine (n=*40), urea* (n=*35) and placebo* (n=*34).

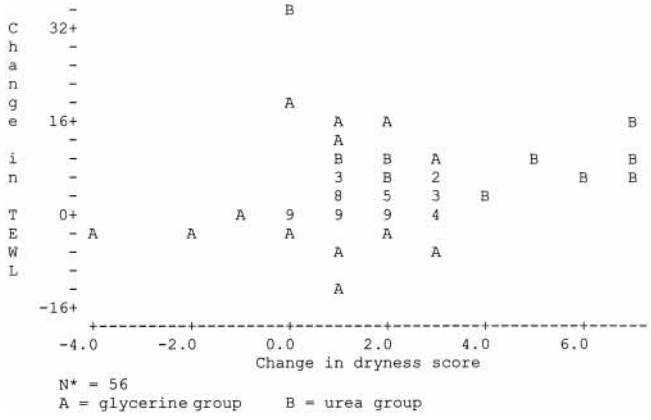

Fig. 5. Multiple scatter plot displaying the relationship between the change in TEWL and in dryness score (note: a positive change indicates improved skin). Glycerine is plotted with the symbol A and urea with the symbol B. If several points fall on the same spot, a count is given. If the count is over 9, a + is used.

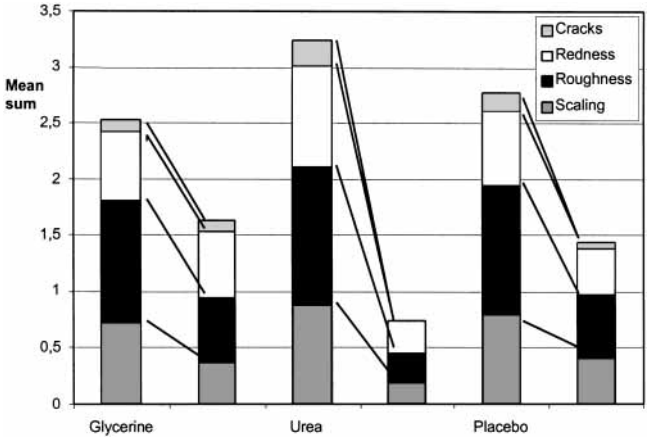

Fig. 3. The mean value of the sum of the dryness severity score and the mean value for the four parameters for dryness at the start of the study and after treatment for 30 days with glycerine (n=*40), urea* (n=*35) and placebo* (n=*34).

The analysis of possible influences on the four characteristics of dryness (scaling, roughness, redness and cracks) showed no obvious difference on scaling and roughness between the treatments (Fig. 3). However, glycerine might have had less influence on redness and cracks than the other treatments. In six patients redness increased and in seven redness decreased during treatment with glycerine. In the placebo group, four patients showed an increased redness, whereas no patients in the urea group showed increased redness at the end of the study.

No difference in skin capacitance was detected at day 31 between glycerine and urea, or between

glycerine and placebo, although the value tended to be higher in the glycerine-treated area than in the placebo-treated area at day 31 ($P=0.076$) (Fig. 4).

The association between the change in dryness score and the change in TEWL was significant ($r=0.332$, $P=0.0004$). The individual data from the areas treated with glycerine and urea can be observed in a multiple scatter plot (Fig. 5).

Discussion

The relationship between degree of skin dryness and TEWL is complex (29, 30). Elevated levels can be found both in hyperhydrated (31) and in dry skin, e.g., in atopic patients (32). The value is usually lowest in normal appearing skin. However, a low value may also be found in skin that appears to be dry, since the major permeability barrier may be confined to the lower part of the stratum corneum and the dryness to the outermost stratum corneum (30) – i.e., the defects can be localized at different depths of the stratum corneum. Therefore, a change in the appearance of dryness due to various treatments may not necessarily reflect a simultaneous change in TEWL.

In the present study, a significant relationship was noted between the improvement in clinical signs of dryness and reduction in TEWL. The clinical evaluation of dryness showed the improvement from glycerine treatment to be less pronounced compared to the improvement from treatment with urea/sodium chloride. However, this was not supported by the skin surface capacitance measurements, where no difference between the two areas was detected. Neither could we observe a statistically significant increase in capacitance in the glycerine-treated area compared to its placebo, which is in contrast to a previous study on normal skin, where higher capacitance levels were obtained after 10 days treatment (16). However, in the study on normal skin, paired comparisons were made, which give less variability and thus increases the possibility to detect statistically significant differences. Moreover, data from corneometer readings might be difficult to interpret. Corneometer measurements are claimed to reflect the hydration status of the skin, but can be influenced by other agents than water – for instance, by body hair and cream residues (33, 34). The active ingredients in the creams tested, urea and glycerine, can also induce changes in keratin dipole orientation and thereby affect the electrical properties of the skin (28).

No evidence of deterioration of the permeability barrier from glycerine treatment was found when TEWL for glycerine-treated and placebo-treated skin was compared, although glycerine has been proposed to be able to influence the structure of the bilayer lipids (14). A significantly lower TEWL was found in the urea-treated skin, than in the glycerine-treated skin. This is in accordance with previous findings where TEWL was reduced by treatment with urea-containing preparations, both in dry and in normal skin (8, 18–20, 35), whereas several urea-free moisturisers appear to cause no major changes in TEWL in dry or in normal skin (16, 18, 36–38). Other ingredients in topical preparations may also affect the skin barrier function. Five of the excipients in the emulsions have also been studied using non-invasive instruments, and no deterioration in skin barrier function could be detected following application of canola oil, petrolatum, stearic acid, glyceryl stearate or PEG-100 stearate to normal and surfactant-irritated skin (39, 40). Instead, canola oil reduced the damage in surfactant-irritated skin (40).

In conclusion, the chemical composition of moisturising creams is highly variable. The differences will inevitably cause differences not only in the hydrating power of the moisturisers but also in their influence on the skin barrier function. The results in the present study suggest that suitable formulations containing urea might be superior to glycerine-containing emulsions, if improvement in skin barrier function in dry atopic skin is considered important.

References

1. Marks R. How to measure the effects of emollients. J Dermatol Treat 1997: 8: 15–18.
2. Rycroft RJG. Occupational hand eczema: the role of emollients in treatment and prophylaxis. J Dermatol Treat 1997: 8: 23–24.
3. Wellner K, Wohlrab W. Quantitative evaluation of urea in stratum corneum of human skin. Arch Dermatol Res 1993: 285: 239–240.
4. Lodén M, Boström P, Kneczke M. The distribution and keratolytic effect of salicylic acid and urea in human skin. Skin Pharmacol 1995: 8: 173–178.
5. Batt MD, Fairhurst E. Hydration of the stratum corneum. Int J Cosmet Sci 1986: 8: 253–256.
6. Batt MD, Davis WB, Fairhurst E, Gerrard WA, Ridge BD. Changes in the physical properties of the stratum corneum following treatment with glycerol. J Soc Cosmet Chem 1988: 39: 367–381.
7. Swanbeck G. A new treatment of ichthyosis and other hyperkeratotic conditions. Acta Derm Venereol 1968: 48: 123–127.
8. Grice K, Sattar H, Baker H. Urea and retinoic acid in ichthyosis and their effect on transepidermal water loss and water holding capacity of stratum corneum. Acta Derm Venereol 1973: 53: 114–118.
9. Tagami H. Electrical measurement of the water content of the skin surface. Functional analysis of the hygroscopic property and water-holding capacity of the stratum corne-

um in vivo and technique for assessing moisturizing efficacy. Cosmet Toiletr 1982: 97: 39–47.
10. Fritz A. Investigation of Cortesal, a hydrocortisone cream and its water-retaining cream base in the treatment of xerotic skin and dry eczema. Curr Therap Res 1983: 33: 930–935.
11. Middleton JD, Roberts ME. Effect of a skin cream containing the sodium salt of pyrrolidone carboxylic acid on dry and flaky skin. J Soc Cosmet Chem 1978: 29: 201–205.
12. Dahl MV, Dahl AC. 12% lactate lotion for the treatment of xerosis. Arch Dermatol 1983: 119: 27–30.
13. Rawlings AV, Harding CR, Watkinson A, Banks J, Ackerman C, Sabin R. The effect of glycerol and humidity on desmosome degradation in stratum corneum. Arch Dermatol Res 1995: 287: 457–464.
14. Froebe CL, Simion A, Ohlmeyer H, et al. Prevention of stratum corneum lipid phase transitions in vitro by glycerol – an alternative mechanism for skin moisturization. J Soc Cosmet Chem 1990: 41: 51–65.
15. Forslind B. A domain mosaic model of the skin barrier. Acta Derm Venereol 1994: 74: 1–6.
16. Lodén M, Wessman C. The influence of a cream containing 20% glycerin and its vehicle on skin barrier properties. Int J Cosm Sc 2001: 23 (in press).
17. Bettinger J, Gloor M, Peter C, Kleesz P, Fluhr J, Gehring W. Opposing effects of glycerol on the protective function of the horny layer against irritants and on the penetration of hexyl nicotinate. Dermatology 1998: 197: 18–24.
18. Lodén M. Urea containing moisturizers influence the barrier properties of human skin. Arch Dermatol Res 1996: 228: 103–107.
19. Lodén M. Andersson AC, Lindberg M. Improvement in skin barrier function in patients with atopic dermatitis after treatment with a moisturizing cream (Canoderm®). Br J Dermatol 1999: 140: 264–267.
20. Serup J. A double-blind comparison of two creams containing urea as the active ingredient. Assessment of efficacy and side-effects by non-invasive techniques and a clinical scoring scheme. Acta Derm Venereol 1992: suppl. (177): 34–38.
21. Wohlrab W. The influence of urea on the penetration kinetics of vitamin-A-acid into human skin. Z Hautkr 1990: 65: 803–805.
22. Kim CK, Kim JJ, Chi SC, Shim CK. Effect of fatty acids and urea on the penetration of ketoprofen through rat skin. Int J Pharm 1993: 99:109–118.
23. Beastall J, Guy RH, Hadgraft J, Wilding I. The influence of urea on percutaneous absorption. Pharm Res 1986: 3: 294–297.
24. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol 1980: suppl. (92): 44–47.
25. Serup J. EEMCO guidance for the assessment of dry skin (xerosis) and ichthyosis: clinical scoring systems. Skin Res Technol 1995: 1: 109–114.
26. Pinnagoda J. Hardware and measuring principles: evaporimeter. In: Elsner P, Berardesca E, Maibach H, eds. Bioengineering of the skin: water and the stratum corneum. Boca Raton: CRC Press, 1994: 51–59.
27. Courage W. Hardware and measuring principle: corneometer. In: Elsner P, Berardesca E, Maibach H, eds. Bioengineering of the skin: water and the stratum corneum. Boca Raton: CRC Press, 1994: 171–175.
28. Potts RO. Stratum corneum hydration: experimental techniques and interpretation of results. J Soc Cosmet Chem 1986: 37: 9–33.
29. Lodén M, Lindberg M. Product testing. Testing of moisturizers. In: Elsner P, Berardesca E, Maibach HI, eds. Handbooks of skin bioengineering, vol. 1. Water and the stratum corneum. Boca Raton: CRC Press, 1994: 275–279.
30. Imokawa G, Akasaki S, Minematsu Y, Kawai M. Importance of intercellular lipids in water-retention properties of the stratum corneum: induction and recovery study of surfactant dry skin. Arch Dermatol Res 1989: 281: 45–51.
31. Blank IH, Moloney J, Emslie AG, Simon I, Apt C, The diffusion of water across the stratum corneum as a function of its water content. J Invest Dermatol 1984: 82: 188–194.
32. Lodén M, Olsson H, Axéll T, Linde YW. Friction, capacitance and transepidermal water loss (TEWL) in dry atopic and normal skin. Br J Dermatol 1992: 126: 137–141.
33. Lodén M, Hagforsen E, Lindberg M. The presence of body hair influences the measurement of skin hydration with the corneometer. Acta Derm Venereol 1995: 75: 449–450.
34. Lodén M, Lindberg M. The influence of a single application of different moisturizers on the skin capacitance. Acta Derm Venereol 1991: 71: 79–92.
35. Andersson A-C, Lindberg M, Lodén M. The effect of two urea-containing creams on dry, eczematous skin in atopic patients. I. Expert, patient and instrumental evaluation. J Dermatol Treat 1999: 10: 165–169.
36. Halkier-Sørensen L, Thestrup-Pedersen K. The efficacy of a moisturizer (Locobase) among cleaners and kitchen assistants during everyday exposure to water and detergents. Contact Dermatitis 1993: 29: 266–271.
37. Vilaplana J, Coll J, Trullás C, Axón A, Pelejero C. Clinical and non-invasive evaluation of 12% ammonium lactate emulsion for the treatment of dry skin in atopic and non-atopic subjects. Acta Derm Venereol 1992: 72: 28–33.
38. Serup J, Winther A, Blichmann CW. Effects of repeated application of a moisturizer. Acta Derm Venereol 1989: 69: 457–459.
39. Bárány E, Lindberg M, Lodén M. Unexpected skin barrier influence from nonionic emulsifiers. Int J Pharm 2000: 195: 189–195.
40. Lodén M, Andersson AC. Effect of topically applied lipids on surfactant-irritated skin. Br J Dermatol 1996: 134: 215–220.

Address:
Marie Lodén
ACO Hud AB
Box 622
SE-194 26 Upplands Väsby
Sweden

Tel: 46 8 6223651
Fax: 46 8 6223680
e-mail: marie.loden@acohud.se