A Randomized, Single-blind Comparison of the Efficacy, Tolerability and Cosmetic Acceptance of Propyless® or Fenuril® Treatment of Patients with Dry Skin

Jan Faergemann[1], Petter Olsson[2] and Åke Svensson[3]

[1]Department of Dermatology, Sahlgrenska University Hospital, SE-413 45 Göteborg, [2]Schering-Plough AB Stockholm, and [3]Department of Dermatology, University Hospital MAS, Malmö, Sweden. E-mail: jan.faergemann@derm.gu.se

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Sir,

Dry skin (xerosis) is characterized by pruritic, dry, cracked and fissured skin. Exposure to environmental irritants, water, soap, temperature changes or stress may contribute to dry skin, e.g. in atopic dermatitis (AD). An important factor in the pathogenesis of AD is a weakened skin barrier, which results in a drier and more sensitive skin (1). Effective repair and restoration of the skin barrier is therefore important in improvement of AD. Irritation of the skin is another important aggravating factor in AD.

Moisturizers can improve dry skin by increasing the water content of the stratum corneum and restoring the epidermal barrier function (2). The use of moisturizer has also been shown to decrease the use of high-potency topical corticosteroids in infants with AD (3). The composition of the moisturizer determines its properties, but still the mechanism at the molecular level remains to be clarified (4).

The moisture retention effect of propylene glycol is dependent on its ability to dry on the skin to a hygroscopic film that retains moisture by forming a barrier to the evaporation of water. It may also function by an osmotic mechanism. Moisturizers with urea have been shown to reduce the transepidermal water loss (TEWL) in patients with AD and ichthyosis and to make normal and atopic skin less susceptible to irritation caused by sodium lauryl sulphate, but sensitization caused by urea may reduce patient acceptance (5).

Common beliefs are that the drier the atopic skin, the more fat is needed in the moisturizer for an efficient treatment and also that a larger quantity of lotion than of cream is needed.

The primary objective of this study was to compare the cutaneous emulsion (lotion) Propyless® (based on propylene glycol) with the cream Fenuril® (based on urea and NaCl) with regard to the symptoms: smarting, stinging, itching and irritation in subjects with AD and dry skin on their lower legs.

METHODS

This study was performed from October to March at two dermatological departments in Sweden.

Patients, aged 18–70 years, with a diagnosis of AD as defined by Williams et al. (6) and with symmetrical dry skin on their lower legs, and who had given written informed consent prior to study entry, were eligible for participation in this study. Participants with active skin disease on the test areas were excluded, as were patients with an acute or chronic systemic illness of clinical significance or allergy to, or idiosyncrasy reaction to any of the two test formulations. Other reasons for exclusion from the study were use of oral corticosteroids, immunosuppressive drugs or other topical formulations in the test area.

This study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guideline for Good Clinical Practice. The trial was approved by the appropriate Independent Ethics Committee and the Swedish Medical Products Agency. Before enrolment, all patients signed informed consent.

All patients received one bottle of Propyless® cutaneous emulsion/lotion (480 g; 20% propylene glycol, Schering-Plough, Brussels, Belgium, Batch numbers: NUPC2L32, NUPC2L29, NUPC2H19, 03NNUPC102, NUPC2H18 and 03NUPC98) and one bottle of Fenuril® cream (400 g; 4% carbamide and 4% NaCl, ACO, Upplands Väsby, Sweden, Batch number: DK 011A) at randomization. The patients applied one formulation on each lower leg (according to randomization 1:1 ratio) twice daily for 2 weeks. The allocation of treatment was known to the patients but not to the investigator.

The patients assessed the effects of Propyless® lotion and Fenuril® cream with regard to the symptoms smarting, stinging, itching and irritation rated as 0: none, 1: very weak, 2: weak, 3: moderate or 4: severe. The severity was assessed at baseline and after 2 weeks of treatment.

At baseline and after 2 weeks of treatment the physician assessed the severity of dry skin in the patients using a Dry skin Area and Severity Index (DASI) (7). The DASI includes scoring of four signs (scaling, roughness, redness and cracks/fissures) normally scored at four different body regions (head and neck, upper extremities, trunk and lower extremities) according to a 0–4 categorical scale (0: absent, 1: slight, 2: moderate, 3: severe, 4: extreme). The total score is the sum of products of the severity scores from each of the areas affected in each body region. DASI is the sum of the four body regions. In this study, only the lower extremities were included, and therefore only the DASI score in this area was assessed. The change in DASI scores from baseline to end of treatment was summarized.

The evaluation of overall treatment effect of Propyless® lotion and Fenuril® cream was rated as: lotion > cream, lotion = cream or lotion < cream.

The patient cosmetic acceptability of the two formulations was assessed by the patients answering "yes" or "no" to four questions at the last visit (see Results).

TEWL was measured in a sub-group of 20 patients using an evaporimeter. The difference in TEWL between baseline and end of treatment was recorded and the difference between the two treatment groups was calculated (8).

Adverse events were solicited by non-specific questioning at the visits and were recorded in the case report form.

Statistical methods

Assuming a difference in subject assessment of symptoms of 25% (e.g. a total score of 12 and 16, respectively, and a standard deviation of 7.5) and $\alpha = 0.05$ and $\beta = 0.20$ (power 80%) a sample size of 57 was calculated to be needed.

The subjects were randomized into two groups (1:1) to apply Propyless® lotion on the right leg and Fenuril® cream on the left leg or vice versa. For treatment comparisons of score variables, Wilcoxon-Mann-Whitney tests were applied to the right-left differences of the two groups, with respect to the score changes over time, thereby adjusting for a potential right/left-effect and for baseline levels. Analysis of preference was performed by using a binomial test where a null hypothesis of equal preference rates for the two treatments corresponds to a probability of 0.5 (for subjects having any preference). All statistical comparisons were performed as two-sided at a significance level of 0.05. The statistical analysis tool was SPSS software (version 13.0; SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 56 patients with a mean age of 46 years (age range 19–72 years) were screened. One 72-year-old subject was included in the analyses according to the intention-to-treat-principle. A total of 70% of the patients were females and 98% were of Caucasian origin. One patient withdraw from the study before start of treatment. Fifty-five patients (98%) completed the study. The total amounts of Propyless® lotion and Fenuril® cream used during the study were similar.

Propyless® lotion resulted in statistically significantly less itching ($p = 0.046$) and irritation ($p = 0.014$). No statistical significance was observed for smarting ($p = 1.0$) or stinging ($p = 0.75$). The change in total score is displayed in Fig. 1. The change in total score was statistically significantly better for Propyless® lotion than for Fenuril® cream ($p = 0.049$).

In addition to patient's assessment, the investigator evaluated scaling, roughness, redness and cracks/fissures using the DASI. For all these parameters both treatments resulted in an improvement in a majority of the patients. There were no statistically significant differences between the two treatments with respect to the DASI evaluations.

The overall treatment effect of Propyless® lotion and Fenuril® cream was evaluated. In total, 69% of the investigators and patients rated the overall treatment effect of Propyless® as better (40%) or equal (29%) to that of Fenuril®.

For Propyless® lotion, 25% of the patients found it greasy and 22% answered that Propyless® lotion left a greasy film. For Fenuril® approximately 33% of the patients reported the cream to be greasy and to leave a greasy film. Ninety-three percent of the patients found Propyless® lotion easy to apply, compared with 80% for Fenuril® cream. A minority of the patients rated the odour as bad (9% for Propyless® lotion and 11% for Fenuril® cream).

No (Fenuril®) or almost no (decrease of 0.1 g/m^2×h for Propyless®) effect on TEWL was observed after treatment.

A total of three adverse events were reported during the study. One of these was serious due to hospitalization (severe stomach pain; assessed as not related to study treatment). The other two, non-serious, were itching of moderate intensity (assessed as possibly related to the study treatment, Propyless® lotion) and eczema of mild intensity (assessed as not related to study treatment).

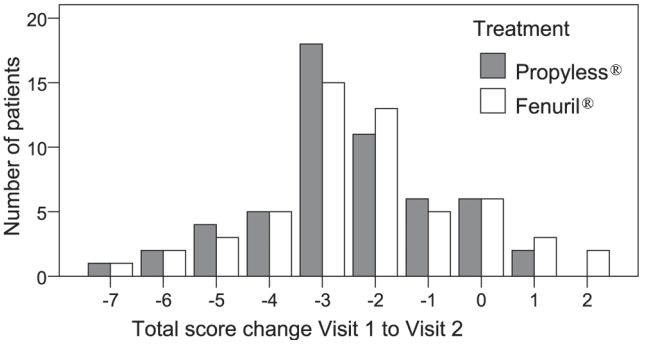

Fig. 1. Symptom score changes from visit 1 to visit 2. Negative values indicate improvement, zero values no change and positive values indicate worsening of symptoms ($p = 0.049$).

DISCUSSION

The primary objective of this study was to compare Propyless® lotion and Fenuril® cream with regard to smarting, stinging, itching and irritation. Propyless® lotion resulted in statistically significantly less itching and irritation, and the change in total score was statistically significantly better for Propyless® lotion. These results indicate that propylene glycol may be as active as urea as a humectant and less irritating than the combination of urea and NaCl.

For all studied parameters regarding cosmetic variables (greasiness, easiness to apply and odour) Propyless® lotion showed a better, though not statistically significant, patient acceptability.

TEWL has been reported to be a good indicator of stratum corneum skin water integrity (9, 10). This study was the first study evaluating the transepidermal water loss measuring TEWL after treatment with Propyless® lotion or Fenuril® cream. Only minor differences in TEWL values were observed within the same treatment and no statistically significant difference between Propyless® lotion and Fenuril® cream was observed while an improvement of other skin parameters such as itching and irritation was observed. Earlier studies showed a good correlation between TEWL in psoriatic skin lesions and the severity of psoriasis (11) while TEWL has not been confirmed to be a good measure of risk for hand dermatitis (12).

Although the TEWL results were not conclusive, the patients' assessments of symptoms and the investigator evaluation according to DASI confirmed that Propyless® lotion was at least as effective as Fenuril® cream in the treatment of dry skin associated with AD. The patient rating of the overall result showed a statistically significantly better result after treatment with Propyless® lotion.

Thus, in this study a greater fat content was not required in the moisturizer for an efficient treatment of dry skin, and the patients did not use a greater total amount of lotion than of cream.

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Conflict of interest: Petter Olsson is an employee of Schering-Plough AB, Sweden.

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