

## INVESTIGATIVE REPORT

# Effects of Pretreatment with a Urea-containing Emollient on Nickel Allergic Skin Reactions

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**The aim of this study was to evaluate the effect of a moisturizer containing urea on allergic contact dermatitis. Twenty-five nickel-sensitized 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% NiSO<sub>4</sub> 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. Key words: urea; allergic contact dermatitis; transepidermal water loss; electrical impedance.**

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Nickel is the most prevalent contact allergen among women. The overall percentage of nickel allergic hypersensitivity is estimated at 13% in unselected populations and up to 40% among female patients in dermatology clinics (1). Avoidance of nickel in the workplace environment and private life may reduce exposure and thus sensitization. Among protective measures, wearing gloves, using barrier creams and moisturizers have been suggested. There is no clear difference between barrier creams and moisturizers/emollients. Both types of skin care products may influence the intensity of the irritant (2, 3) and allergic contact reactions (4). Although some creams are

selectively effective against certain irritants (5, 6), the same cream may have the opposite effect depending on the way it is applied (2, 7). Moreover, some humectants as active ingredients of moisturizers may affect the susceptibility of skin to irritants (8, 9). In allergic contact dermatitis, chelating agents in protective barrier creams abrogate positive patch test reactions in nickel-sensitized subjects (10). Therefore, moisturizers should be evaluated as regards their content, method of application and efficacy.

Urea has never been tested concerning its ability to protect the skin of sensitized patients from developing allergic contact dermatitis (ACD). The purpose of this long-term study was to evaluate how pretreatment with a cream containing a moderate amount of lipids and urea as the humectant affect the skin's response to nickel in persons with a known allergy to nickel.

## MATERIALS AND METHODS

### Participants

A total of 25 women (mean age 44.8 years, range 18–65) with nickel allergy took part in the study. The inclusion criterion was a positive patch test to nickel or a history of persistent reactions to nickel within the past 2 years. Three patients also had ACD to cobalt and one to PPD-mix (derivates of *p*-phenylenediamine). Apart from the nickel allergy, their previous or present clinical diagnoses were: diabetes (2 patients), urticaria (1), asthma (1), atopic dermatitis (4) and hand eczema (1). Participants with current active eczema were excluded. Five healthy women without nickel allergy (mean age 47 years, range 41–61), served as controls. Written informed consent was obtained from all the participants, and the local ethics committee approved the study.

### Test product

The cream tested (Canoderm®, ACO Hud AB, Stockholm, Sweden) contained 5% urea in an oil-in-water emulsion, pH was about 5. Other ingredients, here named in descending order, were aqua, caprylic/capric triglyceride, propylene glycol, hydrogenated canola oil, cetearyl alcohol, glyceryl polymethacrylate, dimethicone, paraffin, sodium lactate, carbomer, glyceryl stearate, PEG-100 stearate, polysorbate 60, lactic acid, propyl-paraben and methylparaben. Canola oil is a component of the product since it has been suggested to have beneficial effect in SLS-induced contact dermatitis (11). The lipid content

of the product is 22%. The weight of the moisturizer tubes was measured before and after the treatment.

#### Nickel challenge

We pipetted 50 µl of the 0.5% and 2.0% nickel sulphate in petrolatum into large aluminium chambers (12 mm in diameter, Finn Chambers, Boule Nordic AB, Stockholm, Sweden), which were randomly applied to each forearm, using Pirilä's method (12). Petrolatum and an empty chamber served as controls.

Clinical scoring was done in accordance with the ICDRG guidelines: 0, macroscopically negative; 1, erythema; 2, erythema and oedema; 3, erythema, oedema and/or vesicles (13).

#### Equipment and measurements used for evaluation

Transepidermal water loss (TEWL) was measured with DermaLab® equipment (Cortex Technology, Hasund, Denmark) (14).

Electrical impedance (IMP) was determined with a skin spectrometer, model SciBase II (SciBase AB, Huddinge, Sweden). This instrument records impedance spectra, both magnitude and phase, at 31 logarithmically distributed frequencies in the range of 1 kHz to 1 MHz in an area below the probe, as described elsewhere (15). In brief, we used four indices to represent changes with frequency in the four main aspects of IMP in the complex number space:

- Magnitude index,  $MIX = \text{abs}(Z_{20 \text{ kHz}}) / \text{abs}(Z_{500 \text{ kHz}})$
- Phase index,  $PIX = \text{arg}(Z_{20 \text{ kHz}}) - \text{arg}(Z_{500 \text{ kHz}})$
- Real part index,  $RIX = \text{Re}(Z_{20 \text{ kHz}}) / \text{abs}(Z_{500 \text{ kHz}})$
- Imaginary part index,  $IMIX = \text{Im}(Z_{20 \text{ kHz}}) / \text{abs}(Z_{500 \text{ kHz}})$ .

It has been proposed that the impedance of the skin, among other factors, is affected by certain changes of stratum corneum: the state of hydration (16), changes in lipid content (17) and number of cell layers (18).

#### Procedure

The study was randomized and single-blind. The subjects were asked to apply a 5-cm long string (approx 1 g) of the cream and rub it in on the volar aspect of the randomized forearm twice daily for 20 days. The other untreated forearm served as the control. On the following day, the subjects were asked to wash both of their arms, thus obviating interference by the cream residues on the skin surface. Four sites on the mid-volar aspect of each forearm were marked with ink to ensure correct placement of the chambers. The patch tests were done for 24 h. Then, the patches were removed and the skin was gently cleaned and washed with running water. The investigator was blinded as regards the sites, which were marked as 1–4. The readings were made before (day 0) and 72 h after the patches had been applied (day 3)—i.e. 48 h after removing them—in the following order: visual scoring, TEWL and IMP. Before the IMP measurement, the skin was moistened for 60 s with physiological saline to reduce the normally high impedance of the surface of the stratum corneum. All measurements were made in a draught-free room, after at least 20 min rest.

#### Statistics

Paired statistical tests were used to compare the moisturizer pretreated arms with the untreated symmetrical controls. The statistical analysis was done using the Wilcoxon matched pairs

test for continuous data (physical measurement techniques) and the Sign rank test for ordinal data (visual scoring). Since the aim of the study was to determine the effect of pretreatment with an emollient on skin reactivity, delta was calculated as the difference between the data obtained by physical measurement techniques (TEWL and IMP) on the pretreated and untreated sides before (day 0) and after (day 3) exposure to allergen. We also compared delta on day 0 and that on day 3 with the Wilcoxon matched pairs test separately for each physical measurement technique. A significance level of  $p < 0.05$  was chosen.

## RESULTS

The study was done in April–May 2003. The average air temperature in the laboratory was 22.9°C (range 22–25°C), relative humidity 32.8% (range 24–46%) and the average amount of cream used was 28.8 g (range 7–45 g; determined by weighing the tubes before and after the study).

#### Clinical assessment

Twenty-three patients in the nickel-allergic group had a positive reaction to NiSO<sub>4</sub> after 72 h. Two patients were excluded: one had a doubtful positive reaction and one had a delayed response on day 7 of the study. Three patients had severe allergic reactions together with the formation of blisters and erosions on day 3. In these cases, no evaluation with the equipment was done for technical reasons. The reaction to 0.5% NiSO<sub>4</sub>, as evaluated by visual inspection, tended to be greater on the pretreated forearm than on the forearm that had not been pretreated ( $p = 0.15$ ) (Table I). No difference was found in the reaction to 2% NiSO<sub>4</sub> ( $p = 0.68$ ) (Table I). In the healthy control group, all subjects had negative reactions to NiSO<sub>4</sub>.

#### Transepidermal water loss

The mean baseline TEWL values obtained from the pretreated forearm were significantly lower than those from the untreated forearm ( $p < 0.001$ ) (Fig. 1). The difference between delta TEWL was not statistically significant as regards 0.5% or 2% NiSO<sub>4</sub> ( $p = 0.59$  and 0.27, respectively). We found no significant differences

Table I. Results of visual scoring of patch tests to 0.5% and 2% NiSO<sub>4</sub> ( $n = 25$ ) on pretreated and untreated forearms on day 3

Scores	Pretreated		Untreated	
	0.5%	2%	0.5%	2%
0	5	3	9	4
1	3	1	4	3
2	5	6	3	3
3	12	15	9	15

Erythema was scored as 1; erythema and oedema as 2 and erythema, oedema and/or vesicles as 3.

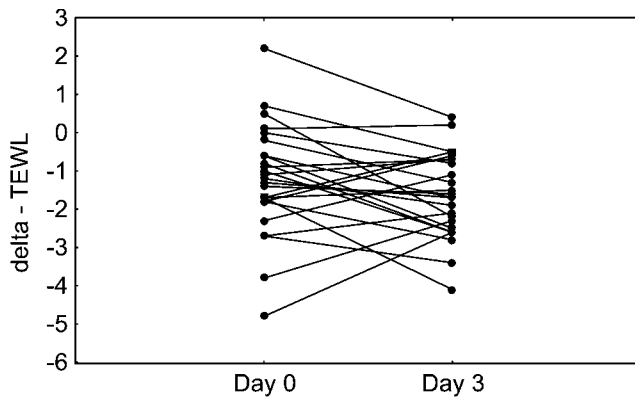


Fig. 1. Delta values of transepidermal water loss (TEWL) (differences between pretreated and untreated forearms) on day 0 before application of 0.5% nickel sulphate and 72 h after application. Each line represents a single patient ( $n=20$ ). On day 0 the values were significantly lower on the pretreated side ( $p<0.001$ ); no significant changes as a result of testing with  $\text{NiSO}_4$  on day 3.

in skin reactivity to nickel on forearms in the healthy control group, as evaluated by TEWL measurements.

#### Electrical impedance

On day 0, we found a significant difference between the MIX indices on both sides, i.e. higher values on the moisturizer pretreated forearm ( $p<0.001$ ) (Fig. 2). The delta MIX index showed no change from day 0 to day 3 ( $p=0.32$  for 0.5% and  $p=0.16$  for 2%  $\text{NiSO}_4$ ). This was also true of other impedance indices. No significant differences were noted in skin reactivity to nickel between the moisturizer-treated and untreated forearms in the healthy control group, as assessed by IMP measurements.

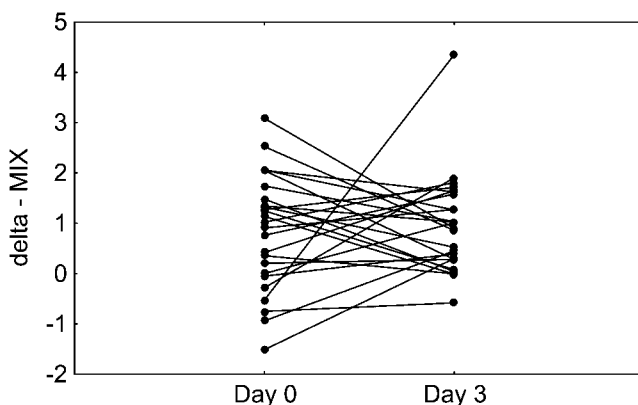


Fig. 2. Values of delta electrical impedance index (MIX) (differences between pretreated and untreated forearms) on day 0 before application of 0.5% nickel sulphate and 72 h after application. Each line represents a single patient ( $n=20$ ). On day 0 the values were significantly higher on the pretreated side ( $p<0.001$ ); no significant changes as a result of testing with  $\text{NiSO}_4$  on day 3.

## DISCUSSION

Surprisingly few reports deal with the effect of pretreatment with moisturizers on the development of experimentally induced ACD. Recently, in a randomized study by Zachariae et al. (4), 12 nickel-sensitized patients underwent treatment of one of their forearms with a lipid-enriched moisturizer for 7 days. The authors noted an increase in hydration of the skin, without an effect on its water barrier function on the pretreated forearm. These effects of the treatment were followed by more marked skin reactivity after challenge with 1%  $\text{NiCl}_2$  in aqueous solution for 24 h when evaluated with clinical scoring and physical measurement techniques where pretreatment with moisturizer did not affect the nickel response 24 and 72 h, respectively, after application. Such discrepancies with our findings may be explained by the fact that the authors used another type of allergen (1%  $\text{NiCl}_2$  vs 0.5% and 2%  $\text{NiSO}_4$  in the present study), and different vehicle (water vs petrolatum) and moisturizer (lipid-rich moisturizer vs one with a moderate amount of lipids in our study) (4). The opposite results have also been reported in 45 patients sensitized to nickel—i.e. a marked protective effect of chelating creams in the prevention of nickel-induced ACD (10).

Despite the development of many physical measurement techniques for the evaluation of patch tests, clinical scoring must still be regarded as a reliable method that shows good agreement among trained medical staff. All models for the classification of allergic patch test reactions are based on the same morphological features: erythema, infiltration, papules, vesicles and bullae. We used a standard scoring system, which classifies all reactions with the development of vesicles as 3+. According to this scale, we found on the pretreated side a tendency to an increase in the skin's response to the threshold concentration of nickel (0.5%). However, the intensity of the response to a higher concentration of nickel was not demonstrated by our methods, probably because of the greater likelihood of inducing a definite allergic reaction with formation of vesicles.

We found a surprisingly poor agreement between clinical scoring and TEWL, which is in line with previous reports (19). This accords with our recent observation that the development of an allergic reaction to nickel is not followed by an increase in TEWL values within 3 days (20). In this study, we aimed at evaluating the ability of visual scoring, TEWL and IMP techniques to distinguish between ACD (induced by an aqueous solution of  $\text{NiSO}_4$ ) and irritant contact dermatitis (induced by SLS) (20). We selected nickel-sensitized patients with both types of reactions that were of similar appearance and severity and the readings were made before applying the substances (day 0) and on days 3 and 7.

Non-invasive instruments are designed to detect various physical parameters; each instrument evaluating different aspects of the skin's response. While TEWL directly measures the water loss from the skin, IMP mainly detects the mobility of charge carriers and polar entities, determined by various factors, such as hydration, lipid content, number of cell layers in the horny layer, size of the corneocytes, and some properties of the deeper skin layers (21). In line with previous reports, the treatment effects in our study included a decrease in TEWL (9) and an increase in MIX values (22). Further, both types of instruments (TEWL and IMP) showed similar reactivity on the pretreated and untreated sides. These instruments have the advantage of being sensitive, objective methods for evaluation of the skin's condition. However, in three very severe reactions with the formation of bullae and erosions, no evaluation with the equipment was done, since complete sterilization of the probes was not part of the procedure. Indeed, visual scoring was the single method that permitted the inclusion of all observations.

In conclusion, we found that the severity of an ACR was not affected by pretreatment with a moisturizer containing urea, although the response tended to be visually greater on the pretreated forearm. As described by Hachem et al. (23), and more recently by Zachariae et al. (4), some moisturizers may increase the susceptibility of skin to certain allergens. The reason may be that stratum corneum saturated with water becomes more permeable to hydrophilic substances.

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