Ethanol-Based Disinfectants Containing Urea May Reduce Soap Sensitivity

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Background: **The use of disinfectants is crucial to preventing the spread of nosocomial infections in health care workers. As many as 25 applications of hand disinfectants is a realistic default value during a working day. However, alcohol-based hand disinfectants may weaken skin barrier function and induce dryness and eczema, which decrease their acceptance.**

Objective: **To evaluate the effect of ethanol-containing disinfectants with 5% urea on skin barrier function and on sensitivity to an irritant soap (sodium lauryl sulfate [SLS]).**

Methods: **Twenty healthy volunteers treated one of their forearms twice daily for 17 days with an ethanol-containing gel with 5% urea. Two types of gels with urea were tested. Treatment was randomized to left or right forearm, and the contralateral forearm served as untreated control. Transepidermal water loss, skin capacitance (dryness), and sensitivity to SLS were evaluated.**

Results: **Twice-daily application of the urea-containing ethanol gels lowered transepidermal water loss, prevented dryness, and reduced sensitivity to SLS compared with the untreated control skin.**

Conclusions: **Improved barrier function using this ethanol gel with urea may have relevance in daily disinfectant procedures.**

The permeability barrier function of skin can be weakened by exposure to environmental stressors, such as solvents and irritants,[1,2]; changes in the skin microbiota (eg, colonization by *Staphylococcus aureus*)[3]; and internal factors, such as mutations in the filaggrin gene.[4,5]

In health care workers, the use of hand disinfectants is crucial to prevent the spread of nosocomial infections.[6,7] Different types of hand disinfection products are available, including hand rubs or wipes mainly based on alcohol as the active substance or hand washes, which contain, for example, triclosan or quaternary ammonium compounds as the active substances. Alcohol-based hand antiseptics contain ethanol, isopropanol, n-propanol, or 2 of these in combination. The antimicrobial activity of alcohols results from their ability to denature proteins, and products containing 60% to 80% alcohol are the most effective.

Because health care workers must clean their hands frequently, it is important that the products are both efficacious and safe for the skin. However, the tendency of products to cause skin irritation and dryness is a major factor influencing their acceptance and ultimate use by health care workers.[6] The European Chemical Agency has set a realistic default value of 25 applications of hand disinfectant per 8-hour working day, based on an estimated range of approximately 15 to 30 with an alcoholic hand rub per day per health care worker.[7] Alcohols, such as ethanol, enter the skin and remove measurable quantities of the lipid barrier material from the stratum corneum,[8] which is one explanation for the observed effect of ethanol as a barrier-deteriorating substance.[8] A recent study also showed alcohols to influence stratum corneum (SC) enzymes and keratinocytes and reduce the activities of kallikrein 5 and phospholipase A_2 in vitro, as well as damage skin condition and increase transepidermal water loss (TEWL) in healthy volunteers.[2] More than 25% of participants treated with ethanol 20 times per day dropped out of the experimental study because of skin irritation at day 12.

In our previous studies, we found that urea-containing creams improve skin barrier function in healthy volunteers,[9,10] as well as in patients with atopic dermatitis (AD).[11] Barrier-strengthening treatments reduce the risk of irritation[9,10,12] and relapse of eczema in AD.[13,14] The use of urea in formulations known to damage skin barrier function, such as disinfectant alcohols, could therefore be beneficial to health care workers in their daily disinfectant procedures. Ethanol might be the most commonly used alcohol in hand disinfectants because of more favorable properties, such as odor and toxicity, compared with the other alcohols. Therefore, this alcohol was used in the study.

The primary aim of the present study was to evaluate the influence of repeated applications of an ethanol gel (70% wt/wt) with 5% urea on skin barrier function (TEWL) and sensitivity to an

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irritant (sodium lauryl sulfate [SLS]). The contralateral arm served as the untreated control. A secondary aim was to study the influence of a more complex 5% urea-ethanol gel (also containing niacinamide [NA] and propanediol) on the same skin characteristics. Hand disinfectants usually contain emollient additives, but instead of the commonly used glycerin (triol), the current test product contained propanediol and NA as skin-conditioning substances. Transepidermal water loss, hydration (capacitance), and sensitivity to SLS were evaluated after twice-daily treatment for 17 days.

MATERIALS AND METHODS

Study Design

The study was monocentric, prospective, randomized, and bilateral, comparing the effect on the treated volar forearm with the corresponding untreated volar forearm, using blind evaluation (Table 1). The study was performed from February to November 2018. The 2 different gels were tested on 20 healthy volunteers. The simple ethanol gel (n = 12) contained 5% urea, 70% ethanol, carbomer, and water, and a more complex gel (n = 8) contained 5% urea, 70% ethanol, carbomer, NA, propanediol, and water (hereinafter abbreviated urea-NA-ethanol). The pH was adjusted to a value between 5 and 6 with piroctone olamine. Ethanol was denatured with denatonium benzoate and t-butyl alcohol.

To reduce variations due to left (lethal)–right (dominant) arm differences, allocation of the test products to the forearms was conducted consecutively according to a predetermined randomization scheme with randomly permuted blocks of fixed size. Unblinding was performed after closure of the database.

Volunteers

Twenty individuals, 5 men and 15 women (age, 24–85 years; mean, 56 years), who were not pregnant, and who considered themselves healthy, without signs of skin diseases on the forearm and with no known allergy to ingredients in the test product were included. The number of participants was based on the results from previous studies on urea where a similar number of included participants gave significant changes in TEWL,[9] which later also was confirmed as clinically relevant in delaying, for example, relapse of AD.[13,14] Informed consent was obtained from the volunteers, and the study was approved by the regional ethics committee in Stockholm. During the test period, the subjects were allowed to wash normally but not to use any other skin care products on their arms.

TABLE 1. Overview of Treatments and Evaluations

Activity	Inclusion	Day 8	Day 18	Day 19	Day 20
Informed consent	X				
TEWL	X	X	X		X
Capacitance	X	X	X		
Application of SLS			X		
Removal of SLS				X	
Visual evaluation					X
Erythema					X

Treatment

The participants were given the test product in an airless pump jar and asked to apply the gel twice daily, in the morning and in the evening, for 17 days in the middle of the volar forearm, on an area of approximately 20 to 30 cm^2. On the day of the visit to the clinic, no applications were to be done. Participants were given a diary to facilitate adherence to the treatment, and they were instructed to return their diary and container at the end of the study to verify compliance.

At inclusion, day 8, day 18, and day 20, the participants visited the clinic for skin analysis. The number of days could vary ±10% without further notice. At day 18, skin sensitivity was also challenged by exposure to a 1% aqueous solution of SLS (European Pharmacopoeia). Exposure of the skin to SLS (50 μL on one layer of filter paper in 12 mm inner diameter aluminum, Finn chambers) for 24 hours usually produces slight irritation with erythema, which may persist for some days.[10,12] The subjects reoved the SLS patches after 24 hours, rinsed the skin with water, marked the exposed area, and visited the laboratory the day after for evaluation of the SLS reaction (Table 1).

Measurements

After acclimatization of the volunteers for at least 20 minutes in the laboratory (temperature, <22°C; humidity, 20%–55%), the measurements were taken by the same expert in accordance with instructions given by the manufacturer and previous experiences.[12,15]

Measurement of TEWL was performed with an AquaFlux (Biox Systems Ltd, London, UK). After application of the probe onto the skin, the TEWL value was recorded in the computer until the SD of the values was 0.075 g/m^2h, after which the measurements were stopped (typically within 70 seconds). This value was used for further calculations. At inclusion and day 20, a single reading was taken, whereas triplicate readings were taken at days 8 and 18 to increase the precision in the readings.

Skin hydration was analyzed by measurement of skin capacitance with a Corneometer CM 825 (Courage+Khazaka electronic GmbH, Köln, Germany). The mean values from 5 readings were used in the calculations.

Skin color (erythema) was measured using DermaLab Combo (Cortex Technology, Hadsund, Denmark). The mean values from 4 readings were used in the calculations.

Before the noninvasive measurements, the degree of irritation on the SLS-exposed area was assessed visually on a scale ranging from 0 to 4 according to the European Society of Contact Dermatitis guideline on clinical scoring of acute SLS irritant reactions.[16] The scale was as follows: 0—negative: no damage; 0.5—doubtful: very weak erythema or minute scaling; 1—weak: weak erythema, slight edema, slight scaling and/or slight roughness; 2—moderate: moderate degree of erythema, edema, scaling, and/or roughness; 3—strong:

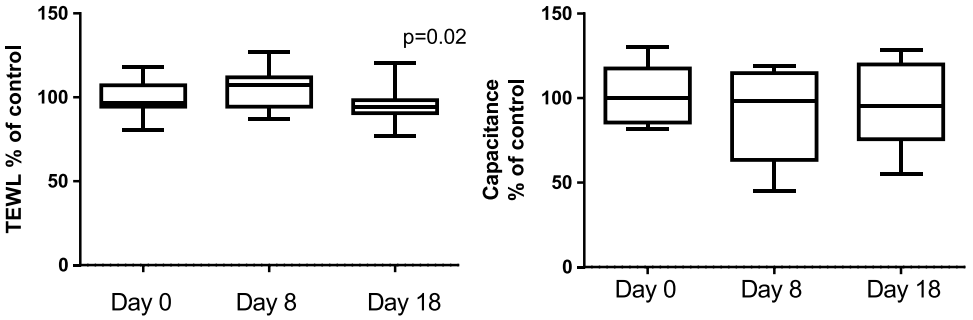

Figure 1. Transepidermal water loss and skin capacitance in urea-ethanol–treated skin as a percentage of the untreated control skin on volar forearm. Significantly lower TEWL was observed in treated skin compared with untreated skin at day 18 ($P < 0.02$, n = 12). No difference was seen in skin capacitance ($P = 0.52$ at day 18).

marked degree of erythema, edema, scaling, roughness; 4—very strong/caustic: as 3, with necrotic areas.

Calculations and Statistics

Median and descriptive statistics were applied to the data. The ratios (%) between the value in treated and untreated arm were calculated and presented using box plots where the bottom line of the box was the first quartile, and the top is at the third quartile value. A line was drawn across the box at the median. The whiskers are the lines that extend from the top and bottom of the box to the lowest and highest observation.

GraphPad Prism version 6.01 for Windows was used for calculations and graphs (GraphPad Software, San Diego, CA; www.graphpad.com). The Wilcoxon matched-pairs signed-rank test was used on paired data to test for differences between treated and nontreated control areas. $P < 0.05$ was considered as significant.

RESULTS

All included participants fulfilled the study. A full set of data was obtained on 17 participants. All data from 2 participants on day 8 were lost because of reasons not related to the treatment. In addition, one participant did not remove the patch after 24 hours but during the clinic visit at 48 hours; therefore, irritation was not evaluated for this participant. Irritation was followed up on the following day via telephone, and the treated skin showed less irritation than the untreated control skin, but these data were not included in the data presentations.

The mean daily consumption was 0.8 g (range, 0.3–1.0 g); that is, the daily dosing was between 10 and 50 mg/cm^2, but probably slightly less because of retention of the gel on the hand used to apply the gel.

Use of the urea-ethanol gel resulted in a lower TEWL at day 18 (Fig. 1). The median difference in TEWL was 0.49 g/m^{2}h (95% confidence interval, 0.14–0.80 g/m^{2}h) between the treated and untreated skin. Skin hydration, measured as capacitance, did not change with treatment with the urea-ethanol gel (Fig. 1; $P = 0.52$).

Challenging the skin with the surfactant SLS induced skin irritation, observed visually and as increased TEWL and redness (Table 2; Fig. 2). Visual evaluation of the irritation showed the skin treated with the urea-ethanol gel to be significantly less irritated than the untreated control skin (Table 2). The sum of the visual scores for irritation on urea-treated skin was almost half that of untreated skin (Table 2).

The urea-NA-ethanol gel also reduced TEWL (Fig. 3), and the median difference on day 18 between skin treated with the

TABLE 2. Visual Evaluation of the Degree of Irritation in the Skin Exposed to 1% Sodium Lauryl Sulfate After Treatment With the Urea-Ethanol Gel and the Urea-NA-Ethanol Gel for 17 Days

Scoring	Urea-Ethanol Gel (n = 12)	Urea-NA-Ethanol Gel (n = 7)
0	1 (1)	1 (1)
0.5	7 (1)	2 (0)
1	3 (4)	3 (2)
2	1 (5)	1 (3)
3	–	0 (1)
4	–	–
Sum	8.5 (14.5), 58.6%	6 (11), 54.5%
P	0.014	0.03

The table gives number of subjects with the defined scores in treated skin and untreated control skin (within parenthesis) and the percentage of the summed scores in the treated area compared with the untreated at day 20. The P value denotes the significance level between the gel-treated area and the untreated control area.

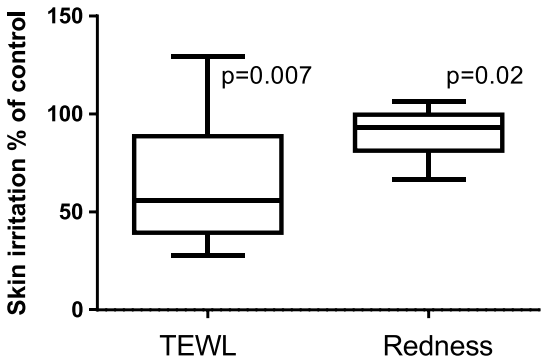

Figure 2. Skin irritation by exposure to SLS in areas treated with urea-ethanol as a percentage of the untreated control area. Significantly lower values in treated skin compared with untreated were recorded on day 20 (n = 12).

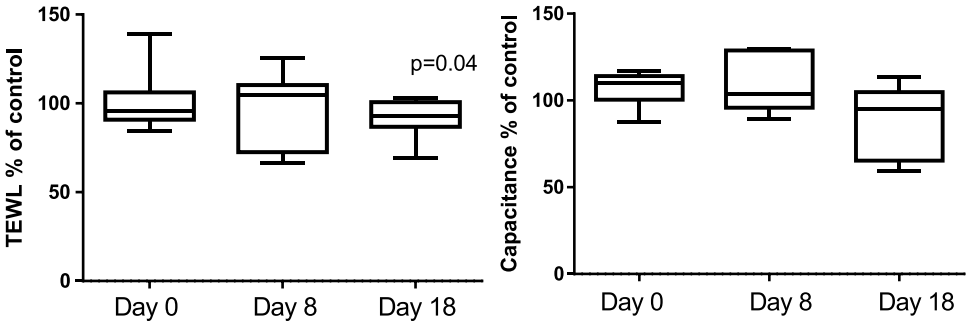

Figure 3. Transepidermal water loss and skin capacitance in areas treated with a urea-NA-ethanol gel as a percentage of the untreated control skin. Significantly lower TEWL was observed in treated skin compared with untreated skin (n = 8). No difference in skin capacitance ($P = 0.31$ at day 18).

urea-NA-ethanol gel and untreated skin was 0.95 g/m^{2}h (95% confidence interval, −0.25 to 5.1 g/m^{2}h). No significant differences in skin capacitance were noted ($P = 0.31$). Measurement of the irritation severity also showed significantly lower irritation in these areas compared with untreated skin (Fig. 4).

DISCUSSION

Strict adherence to recommended hand hygiene procedures is crucial to preventing the spread of nosocomial infections in health care workers. However, concerns about irritation and drying effects of alcohol are a major cause of poor acceptance of alcohol-based hand rubs in hospitals.[6] Proper hand hygiene also consumes a substantial part of the working time of hospital staff.[6] This makes it difficult for health care workers to achieve a balance between hygiene requirements, the risk of skin irritation, and the fulfillment of their workload.[6]

One strategy for reducing skin damage in health care workers has been to reduce exposure to irritating soaps and detergents and to promote the use of alcohol-based hand rubs, which are associated with less skin damage than disinfectant soaps. Among the alcohols, ethanol and isopropanol are reported to be less irritating than n-propanol and induce less increase in TEWL and expression of tumor necrosis factor α.[2] n-Propanol has also been shown to change corneocyte surface topography, which is associated with decreased SC hydration and a lower amount of skin "natural moisturizing factor" (NMF).[17] Natural moisturizing factor is mainly derived from the degradation of filaggrin, and the mixture includes urea, pyrrolidone carboxylic acid, lactic acid, amino acids, and salts. Mutations in the filaggrin gene are linked to skin barrier diseases, such as AD and ichthyosis.[4,5] These mutations and the level of filaggrin degradation determine the content of NMF in the SC.[3,18–20]

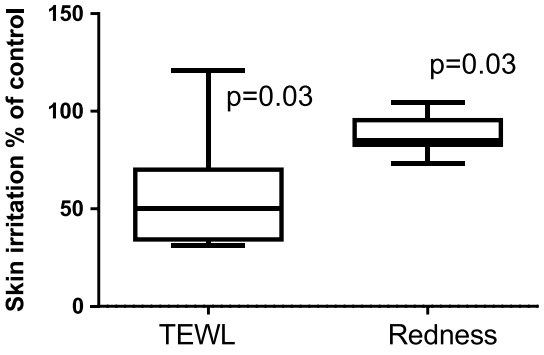

Figure 4. Skin irritation by SLS in exposed areas treated with urea-NA-ethanol gel as a percentage of the untreated control area, measured as TEWL and redness. Significantly lower values in treated skin compared with untreated skin (n = 7).

The reduction of NMF in the SC during exposure to n-propanol[17] suggests that replenishment of lost NMF by the use of hand rubs supplemented with NMF is a logical step to prevent dryness. However, whether ingredients other than urea in the NMF mixture will strengthen skin barrier function in a similar way to urea is not known. Additives in disinfectants vary, and their identity is seldom labeled on the container or in associated documents. One commonly used additive is glycerin, which is a well-known humectant but is not firmly linked to barrier improvement.[21,22] Furthermore, glycerin is reported to be an energy source for microbial growth,[23] to be decomposed into, for example, propanediol,[23] and to hamper the bactericidal efficacy of alcohol-based surgical hand rubs.[24] Contact allergy to alcohol-based hand rubs is rare, but fragrances, panthenol, lanolin alcohol, and menthol found in hand rubs may cause allergy.[25]

The finding that urea is one important NMF ingredient complies with previous clinical experiences where urea has been identified as a humectant and barrier-improving substance.[9–11,26] Moisturizing creams with urea reduce TEWL and skin sensitivity to surfactants in healthy skin[10,12] and reduce the risk of eczema relapse in patients with hand eczema[27] and AD.[13,14] Urea is reported to be a regulator of epidermal permeability barrier function[28] and improves barrier function by increasing the expression of antimicrobial peptide in a murine model of AD.[28] Urea is also proposed to protect against osmotic stress and retains the liquid crystalline phase of lipids at lower relative humidity caused by, for example, a dry environment or by freezing.[29] In addition, urea stimulates keratinocytes via 2 urea transporters (aquaporins), whereas inhibitors of these transporters block the downstream biological effects of urea.[30]

Therefore, based on previous findings on urea, it was considered more relevant to compare the urea-ethanol gel with untreated skin than to compare with a plain ethanol gel, because ethanol is expected to worsen the condition[2,6] and make skin more sensitive to the irritant SLS.

The findings of the present study that urea strengthens skin barrier function and increases skin tolerance to SLS when used in conjunction with ethanol are encouraging, because repeated use of disinfectants with ethanol is known to make the skin more prone to contact eczema.[2,8] The present study shows that urea as a lone additive to ethanol gel produces favorable effects and that the addition of NA and propanediol to the urea-ethanol gel retains the beneficial effects on the skin. Niacinamide is suggested to act as a barrier-enhancing substance by increasing the level of barrier lipids.[31]

In conclusion, twice-daily application of ethanol-containing gels with urea for 17 days was shown to keep the skin healthy, prevent dryness, reduce TEWL, and, more surprisingly, to decrease sensitivity to soaps. These findings may have relevance to daily disinfectant procedures in health care workers. However, further studies are needed to evaluate the value of urea in alcoholic hand rubs in the workplace and to also investigate the potential benefits of also adding NA and propanediol to disinfectants. Studies of this type are warranted to establish if products with different formulations yield similar results.[6]

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