

Irritancy of the skin disinfectant n-propanol

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Hand disinfection with short-chain aliphatic alcohols, so-called “rub-ins” is the method of choice for cross-infection prevention in health care environments, but their irritant potential is not well known. Skin tolerance is a major compliance factor, and a high proportion of health care workers suffer from low-grade irritant contact dermatitis. Therefore, assessment of the irritancy of the skin disinfectant n-propanol 60%, and comparative 100% and 0% solutions, was performed in the setting of experimental low-grade ICD. ICD was induced by overnight patch exposure to H₂O, and to 0.3% sodium dodecyl sulfate (SDS), in 12 probands, followed by repeated open exposure to the test substances. Outcome variables were transepidermal water loss (TEWL), and skin surface capacitance. On skin sites pre-irritated by SDS, all n-propanol concentrations (100%, 60%, 0%) increased TEWL. However, a clear divergence appeared between pure n-propanol, and the lower concentrations. In contrast to pure n-propanol, n-propanol 60% and 0% had no significant effect on TEWL on H₂O-pre-irritated skin sites. Capacitance of pre-irritated skin sites was increased by exposure to H₂O-containing n-propanol solutions (60% and 0%). These results show a clear difference between the irritant potential of n-propanol 100% on one side, and n-propanol 60% and 0% on the other side. The level of pre-existent skin irritation is a pertinent factor in susceptibility to irritation, as the irritant potential of n-propanol 60%, the concentration used in daily practice, and n-propanol 0% (water) became significant only on detergent-irritated skin. Thus, preventive skin care may be a constructive approach in increasing tolerance of modern hand disinfection practices.

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Recent surveys have documented poor compliance of health care workers with hygienic hand disinfection (1). Determinant factors for compliance with hand hygiene protocols are the required amount of time for the disinfection procedure, workload, and skin irritancy (1–4). In the context of alcohol-based hand disinfection being promoted as the cornerstone of cross-infection prevention in hospitals (5, 6), skin tolerance of these products is of crucial importance for both nosocomial infection prevention, and occupational health of health care workers. Several field studies indicate that alcohol-based hand disinfectants (short-chain aliphatic alcohols such as n-propanol or isopropanol, so called “rub-ins”) have a low irritation potential as compared to detergent-based products (7–15). On the other hand, health care workers often invoke “skin problems” as deterring them from good compliance with alcoholic hand disinfection (2, 3, 6), a perception that may be related to the stinging

sensation that alcohols induce upon contact with slightly abraded skin (16). Prevalence of irritant contact dermatitis of health care workers’ hands in hospitals varies between 20% and 70% (17, 18). Therefore, skin tolerance to alcoholic rub-ins may depend not only on the irritancy of the disinfectant itself, but on the level of pre-existing irritant contact dermatitis. In the present work, we have studied the irritant potential of different concentrations of n-propanol in an *in vivo* irritation model with experimentally induced low-grade irritant contact dermatitis.

Patients and Methods

The study protocol was approved by the institutional ethical committee. Study participants were recruited among medical students on a voluntary basis. The experiment was performed with 12 healthy subjects (8 female, 4 male, age range 23 to

31 years). 2 female subjects had an atopy score (19) suggestive of the presence of an atopic diathesis; none presented an eczematous skin condition.

Experimental induction of low-grade skin irritation

5 circular skin sites ($d=20$ mm) were selected as test areas on each volar forearm and numbered from 1 to 5 in a proximal-to-distal direction. On the non-dominant forearm, low-grade skin irritation was induced on skin sites 1 to 4 by overnight (14 h) patch exposure to a polypropylene plastic chamber (Hill Top° Research Inc, Miami, USA) containing a Webril° pad soaked with 0.1 ml of freshly prepared 0.3% sodium dodecyl sulfate (SDS) (99.9% purity, Sigma Chemical; St Louis USA). At the same time, sites 1 to 4 of the dominant forearm had an analogous patch exposure to distilled H₂O. The 5th, most distal skin site was exposed to an empty patch test chamber on both forearms. The patch test chambers were removed after 14 h.

Repeated open exposure test

After removal of the patch chambers, the skin sites were left open for 90 min, and subjects spent 30 min in the laboratory for acclimatization. After measurement of TEWL and capacitance, skin sites 1 to 3 on both forearms were exposed to the test substances as follows: site 1, 100% n-propanol; site 2, 60% n-propanol; site 3, n-propanol 0% (water). The control sites on each forearm (site 4, patch soaked with SDS or water; site 5, dry patch) were left unexposed after removal of the patch test chambers. The test substances were applied on skin sites 1 to 3 of both forearms by gentle friction with a cotton swab, one site after the other, in 10-s steps. Each exposure cycle lasted 30 min, i.e. 5 min of cumulative exposure for each of the 6 skin sites. After 3 cycles, each one of the 3 skin sites exposed on each forearm had thus received a cumulative exposure to the test substance of 15 min. Non-invasive measurements were performed on all 10 skin sites, 30 min after the end of each exposure cycle.

Measurement time points were as follows: M0, prior to patch test chamber application on day 0; M1, 90 minutes after removal of the patch chambers on day 1; M1/1, M1/2, and M1/3, 30 minutes after each exposure cycle on day 1; M2, on the following day after an exposure-free overnight interval. No emollients or detergents were applied on the forearms during the entire experiment.

Non-invasive measurements

All measurements, as well as the exposure cycles, were performed in a climatized laboratory (con-

stant 22°C, 40% relative humidity) according to existing guidelines (20, 21). We used the EP-2 Evaporimeter (Servo Med AB, Kinna, Sweden) for quantification of transepidermal water loss (TEWL), and the CM 810 PC Corneometer (Courage & Khazaka GmbH, Köln, Germany) for skin capacitance measurements.

Statistical analysis

Statistics were limited to non-parametric methods, due to the small sample size. For both skin capacitance and TEWL data-sets, the measurements at M1, M1/1, M1/2, and M1/3 were ranked, and a time trend was investigated (Page test). The overall effect of each test substance concentration was defined as the individual means of the 3 exposure cycles (M1/1, M1/2, M1/3). Basal measures were subtracted individually to control for the site effect. The data obtained with the different test substance concentrations were compared with a Wilcoxon matched-pairs signed rank test. Tests were performed at the 0.05 level; p-values were multiplied by 20 in order to correct for the non-independence of the tests (Bonferroni correction for multiple tests).

Graphics

The biometric measures are graphically represented by simple scatter plots of measures versus rank of the measurement. The medians by site are joined with a full line (exposure to n-propanol 100%, site (i)), dash-dot-dot-dotted line (n-propanol 60%, site (ii)), dashed line (n-propanol 0%, i.e. water, site (iii)), dash-dotted line (site 4, "wet" control, preirritation with SDS or water, but not further exposed to the test substances), and dotted line (site 5, "dry control", dry patch test chamber, i.e. no pre-irritation, no further exposure to the test substances). The symbols relate to the site number. Large TEWL values (over 60) were arbitrarily plotted as such with a full triangle mark.

Results

11 of 12 subjects completed the repeated open exposure test on SDS 0.3%, and H₂O -pre-irritated forearm skin. 1 non-atopic subject discontinued exposure during the 3rd exposure cycle due to stinging symptoms, occurring on the skin sites exposed to 100% and 60% n-propanol. These symptoms occurred on both forearms, i.e., irrespectively of the type of pre-irritation (SDS or H₂O). 1 subject presented extremely elevated basal TEWL values at M0, which were judged as artefactual and were removed.

Transepidermal water loss (TEWL)

Repeated open exposure of the SDS-pre-irritated skin sites to n-propanol 100%, 60%, and 0% (water) induced a significant TEWL-increase (Page; $p < 0.02$) (Fig. 1b). In contrast, on H₂O-pre-irritated skin sites, n-propanol 60%, and n-propanol 0% (water) failed to induce significant TEWL changes, while repeated open exposure to n-propanol 100% led to an increase in TEWL levels (Page; $p < 0.08$) (Fig. 1a). Overall, n-propanol 60% and n-propanol 0% (water) produced similar effects on TEWL, and this is observed with both types of

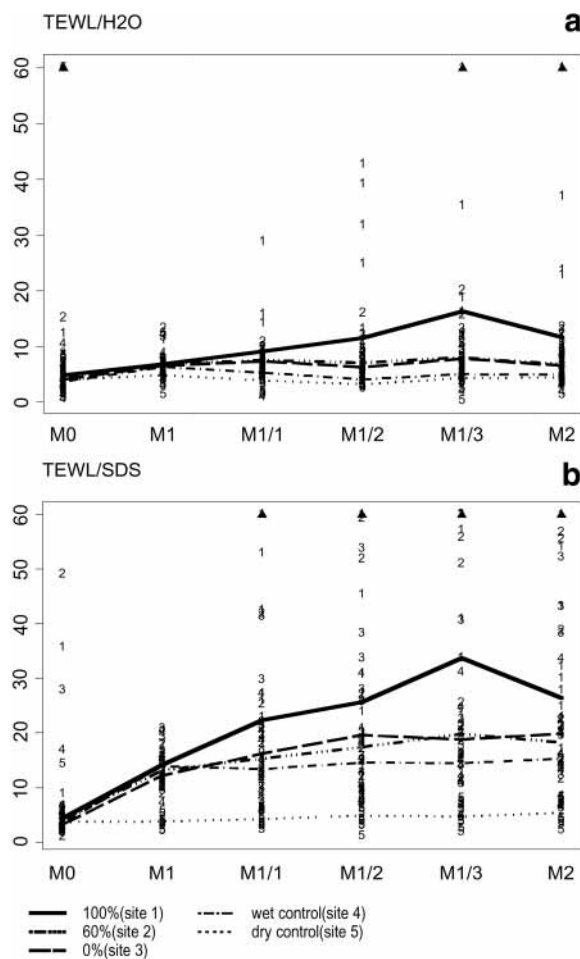


Fig. 1. Changes in TEWL (transepidermal water loss, g/m² h) through repeated open exposure of pre-irritated forearm skin sites to n-propanol 100% (site 1), 60% (site 2), and 0% (site 3). Experimental pre-irritation was done by means of an overnight patch with H₂O (a), and 0.3% SDS (b). Measurement time points were as follows: M0, prior to patch application on day 0; M1, 90 min after removal of the patch on day 1; M1/1, M1/2, and M1/3, 30 min after each exposure cycle on day 1; M2, after an exposure-free overnight interval on day 2. Controls refer to skin sites that were either pre-irritated (wet control, site 4), or not irritated (dry control, site 5), but not exposed to n-propanol. (TEWL values over 60 g/m² h were plotted as 60 and marked with a triangle).

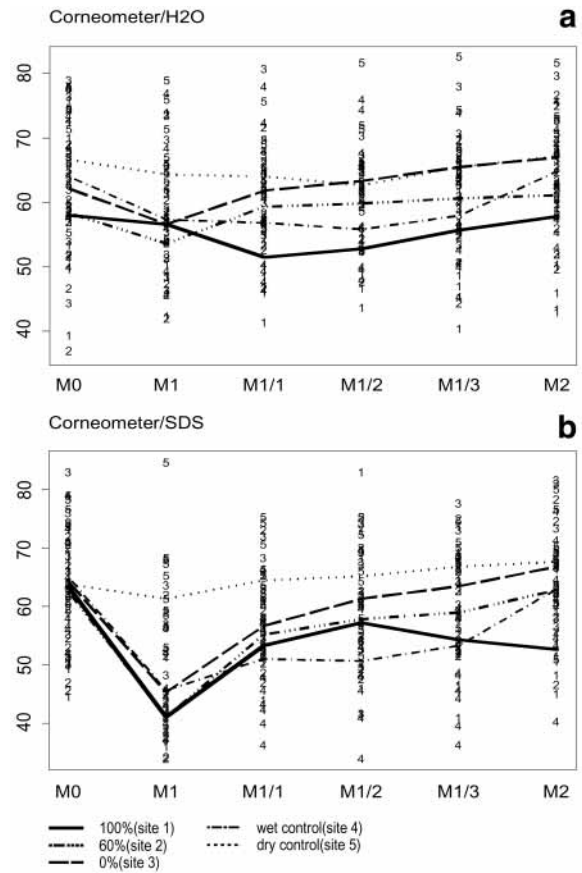


Fig. 2. Changes in skin capacitance through repeated open exposure of pre-irritated forearm skin sites to n-propanol 100% (site 1), 60% (site 2), and 0% (site 3). Experimental pre-irritation was done by means of an overnight patch with H₂O (a), and 0.3% SDS (b). Measurement time points were as follows: M0, prior to patch application on day 0; M1, 90 min after removal of the patch on day 1; M1/1, M1/2, and M1/3, 30 min after each exposure cycle on day 1; M2, after an exposure-free overnight interval on day 2. Controls refer to skin sites that were either pre-irritated (wet control, site 4), or not irritated (dry control, site 5), but not exposed to n-propanol.

pre-irritation (Fig. 3). Exposure to n-propanol 100% induced a stronger TEWL increase than both n-propanol 60% and n-propanol 0% (Wilcoxon; $p < 0.08$) (Fig. 1b). Regarding the controls, the H₂O-pre-irritated negative control site (i.e. “wet control”, site 4, dominant forearm) showed a slight, but not significant tendency towards decreased TEWL-values, whereas the SDS-0.3% pre-irritated control site (i.e., “wet control”, site 4, non-dominant forearm) remained at a constantly elevated TEWL level throughout the experiment, suggesting the presence of a stable degree of barrier damage throughout the duration of the exposure cycles. The “dry control” skin sites, i.e. site 5 on each forearm, that were exposed to a

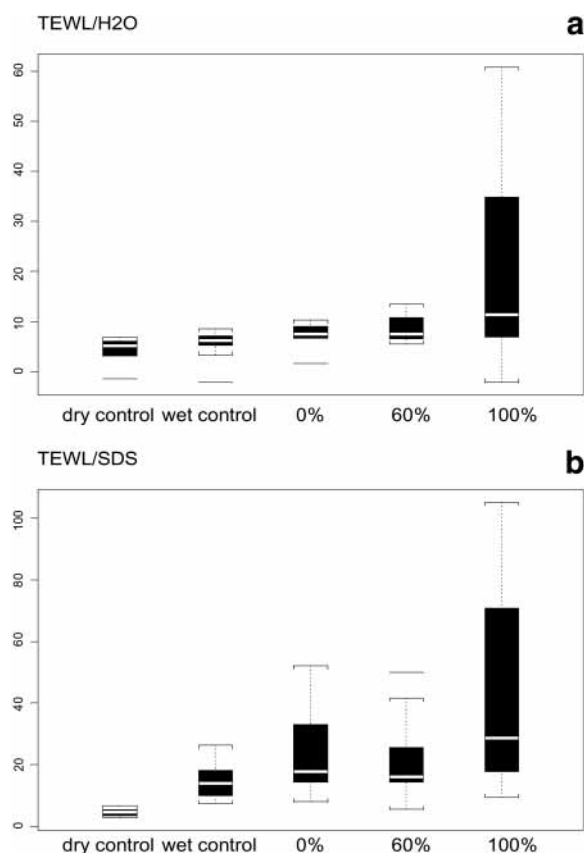


Fig. 3. Box-and-whiskers plot of means of TEWL values ($\text{g/m}^2 \text{h}$) measured at each skin site throughout the 3 exposure cycles to n-propanol 100% (site 1), 60% (site 2), and 0% (site 3), and adjusted for skin site. Experimental pre-irritation was done by means of an overnight patch with H_2O (a), and 0.3% SDS (b). Controls (site 4, pre-irritated "wet" control; and site 5, not irritated "dry" control) were not exposed to n-propanol. The graph suggests a similar irritation profile for n-propanol 60% and 0%, while n-propanol 100% appears as a single stronger irritant.

dry patch only, showed no significant TEWL fluctuations, suggesting the presence of a constant basal TEWL level.

Skin capacitance

Overnight patch exposure to either H_2O or SDS 0.3% expectedly decreased skin capacitance. Capacitance values measured on the control sites did not show a significant trend throughout the exposure interval, except for the SDS-pre-irritated control site (site 4), that evolved towards higher capacitance values. On the SDS 0.3%-pre-irritated skin test sites 1 to 3, subsequent open exposure cycles to n-propanol 0% (water), and n-propanol 60% led to a constant and clearly significant increase of skin capacitance (Page; $p < 0.002$), whereas on H_2O -pre-irritated skin sites, the increase was significant for n-propanol 0% (water)

(Page; $p = 0.03$), but not for n-propanol 60%. Repeated open exposure to n-propanol 100%, however, produced a different pattern, dependent on the type of pre-irritation. On skin sites pre-irritated with H_2O , the 100% solution failed to induce significant capacitance alterations, whereas on SDS-pre-irritated skin sites, capacitance increased during the 1st 2 first exposure cycles, followed by a decrease after the last exposure cycle, which was even more pronounced on the following day (Figs. 2a, b).

Discussion

At present, there is no validated irritation test model for short-chain aliphatic alcohols used in skin disinfection. As a rule, the test of choice for a weak, cumulative skin irritant is given by its usual mode of exposure in real-life conditions (22), which is repeated and non-occlusive in most situations of hand disinfection opportunities in hospitals. The duration of such a test, however, should be kept as short as possible in order to reduce the bias due to secondary irritant factors (household, weather, etc.) that are unrelated to the test substance. Therefore, we performed the test on skin experimentally irritated by SDS, as a skin exposure model with pre-existent detergent-mediated irritation is more representative of a health care worker's real-life conditions, than intact skin. We found a 1-time, 14-h-overnight occlusive patch test exposure to 0.3% SDS to produce an irritant reaction appropriate for the subsequent 1-day repeated open exposure to n-propanol: 1st, the controls indicated the presence of a plateau-type experimental irritant reaction (Fig. 1b); 2nd, only 1 subject dropped out because of immediate stinging after n-propanol exposure, suggesting the presence of the desired slight level of skin pre-irritation in the other subjects; 3rd, the test model was sensitive enough to detect differences between weak irritants.

In terms of skin barrier disruption potential as expressed by TEWL, the difference between the test substances (n-propanol 100%, 60%, and water) was most pronounced on the SDS-pre-irritated skin sites, where we observed a clear dissociation of TEWL values between the sites exposed to pure n-propanol on the one hand, and to the 60% and 0% solution (water) on the other hand (Fig. 1b). An analogous, albeit statistically not significant, divergence appeared on the H_2O -pre-irritated skin sites (Fig. 1a). Both lower n-propanol concentrations (60%, 0%) showed similar exposure effects on both H_2O and SDS-pre-irritated skin sites, suggesting that n-propanol 60% is no more irritant than n-propanol 0% (water) in the present irri-

tation model. Interestingly, repeated exposure to both n-propanol 60% and n-propanol 0% (water) failed to induce a significant barrier disruption on skin that was pre-irritated with the H₂O- patch only, which is consistent with the notion that n-propanol 60% and n-propanol 0% (water) are weak skin irritants. In contrast, pre-irritation with SDS rendered skin test sites more sensitive to the effects of these weak irritants.

Skin capacitance data are often synonymously used as a quantitative equivalent of the water content of the stratum corneum, and decreased capacitance as an indication of xerosis and thus a sign of skin irritation. It should be kept in mind, however, that this interpretation is a subject of continuing controversy (23–25). It is well known that skin capacitance can increase during acute irritant reactions (26), because an acutely increased transepidermal water loss can produce increased capacitance values in the setting of not yet profoundly affected stratum corneum water holding capacity, i.e., in the early phase of the irritant reaction (27). In our experiment, we observed a steep capacitance increase right after the 1st cycle of exposure of SDS-pre-irritated skin to all concentrations of n-propanol tested (Fig. 2b). In the case of n-propanol 60% and 0% (water), this increase in capacitance might simply reflect rehydration from these water-containing test solutions. In the case of n-propanol 100%, which contains no water, the initial increase in capacitance might, in contrast, reflect acute irritation as shown by steep TEWL increase (Fig. 1b). The subsequent sustained decrease of capacitance, which sets in during the 3rd exposure cycle, might then reflect the onset of structural stratum corneum alterations affecting its water holding capacity. In contrast, the H₂O-pre-irritated skin-site's capacitance was not significantly affected by exposure to 100% n-propanol (Fig. 3a), which illustrates the difference that a slight preexisting irritation can make on the skin's response to an irritant.

In conclusion, n-propanol 60%, which corresponds to the concentration of rub-ins used in clinical routine, appears as a weak irritant, its irritant potential being much closer to water than to pure n-propanol. The data suggest that the weak irritant potential of an alcoholic rub-in can increase to more important proportions in the setting of pre-existent or concomitant detergent-mediated barrier damage. These conclusions must be weighted in respect of the study's main shortcomings: 1st, the small size of the study collective, and the presence of 2 atopic subjects limit the power of the statistical analysis; 2nd, our protocol of experimental low-grade skin irritation is an empirical, not validated approach for testing a weak

contact irritant. Therefore, the results need to be confirmed on a larger scale. Nevertheless, the findings indicate that avoidance of detergent irritants might be a rational means of increasing the tolerance to alcoholic rub-ins. Cumulative irritant contact dermatitis in health care workers is not exclusively occupational, as there is a constant background irritation load from exposure to household detergents (28), reflected by a more than 2× ratio of hand dermatitis prevalence in female as compared to male hospital nursing personnel (17). Preventive skin care, and education of health care workers about the proper maintenance of their most important occupational tool, i.e., their hands, may thus be a constructive approach in the search for a better compliance with today's evidence-based hospital hygiene guidelines.

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