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The Transient and Cumulative Effect of Sodium Lauryl Sulphate on the Epidermal Barrier Assessed by Transepidermal Water Loss: Inter-individual Variation

RON A. TUPKER, JALIYA PINNAGODA and JOHAN P. NATER

Occupational Dermatology Unit, State University Hospital, Groningen, The Netherlands

The aims of the investigation were: 1) to study the inter-individual variation in time course of TransEpidermal Water Loss and of clinical manifestations after a 24-h single exposure to Sodium Lauryl Sulphate. This TEWL time course (expressed as the difference in TEWL between the day of patch removal and a subsequent day) reflected the epidermal barrier response to the damage caused by SLS; 2) to investigate the association between the TEWL time course after the single SLS exposure and the TEWL value after 4-day repeated SLS exposure (as a model for cumulative irritation). The 35 healthy subjects tested could be divided into four sub-groups according to the day of their maximum TEWL value after the single SLS exposure (days 2 to 5). For the whole group, inter-individual variation in TEWL course was most pronounced in the first days following the single SLS application. Moreover, there was an inverse relationship ($R = -0.61$) between TEWL course during the first days after the single exposure and the TEWL value after 4-day repeated exposures. It is concluded that this association illustrates the importance of an adequately responding barrier function against the continuous exposure to irritants in daily life. ***Key words: Late irritant reaction; Repeated exposures; Susceptibility to irritants.***

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R. A. Tupker, Occupational Dermatology Unit, State University Hospital, PO Box 30001, 9700 RB Groningen, The Netherlands.

Chronic irritant contact dermatitis (ICD) is caused by the repeated exposure of the skin to various chemical and physical factors, such as solvents, detergents, heat, low humidity, etc. Whether or not chronic ICD will develop in a particular individual may be explained by the balance between the 'repair capacity' of the skin and the sum of the damaging factors (1). When this balance is disturbed, subclinical skin changes may evolve, eventually leading to contact dermatitis (2).

In previous investigations we have assessed the differences between individuals in susceptibility to 4-day repeated exposure to sodium lauryl sulphate (SLS), which is a model of cumulative irritation (3, 4). In these experiments, it has been demonstrated that there are large inter-individual variations in pre-exposure baseline transepidermal water loss (TEWL) value as well as in susceptibility to 4-day repeated exposures to SLS. Furthermore, both characteristics were proven to be closely correlated (3, 4).

TEWL is a reflection of the barrier function of the stratum corneum (5). During the regeneration process after experimentally induced skin damage, a decrease in TEWL has been reported (6–9). In both chemically (6, 7) and physically (8, 9) injured skin, inter-individual differences in regeneration rate have been noticed. The purpose of the present investigation was to study the inter-individual variation in time course of TEWL and clinical manifestations after a 24-h single exposure to SLS. The TEWL time course after the insult by SLS (expressed as the difference in TEWL level between the day of patch removal and a subsequent day) reflects the epidermal barrier response to this irritant and may serve as an indicator of 'repair capacity' of the skin. This TEWL time course may be an important marker of the susceptibility to multiple irritant attacks, since the TEWL level at any time after the primary insult is indicative of the actual barrier function of the skin for a subsequent irritant exposure. In order to assess the importance of TEWL time course, as a parameter of the susceptibility to multiple consecutive irritant exposures, the association between the TEWL time course after a single SLS exposure and the TEWL value after 4-day repeated SLS exposures, was investigated.

MATERIALS AND METHODS

Subjects

Thirty-five healthy volunteers, 17 females and 18 males, ranging in age from 19 to 61 years (mean 30 years) and free

Table I. *Time course of transepidermal water loss (TEWL) (g/m²h) and clinical manifestations (CLIN) on the days after the single SLS exposure, for the whole group as well as for the different subgroups*

On day 8, one subject in group 1 and one subject in group 2 had a clinical score 1+

	Days							
	2		3		4		5	
Group	TEWL Mean	CLIN[a] (n_{CLIN})	TEWL Mean	CLIN (n_{CLIN})	TEWL Mean	CLIN (n_{CLIN})	TEWL Mean	CLIN (n_{CLIN})
Total group ($n=35$)	17.8	2.3 (23)	20.6	2.2 (21)	19.0	1.6 (20)	16.6	0.9 (13)
Subgroup 1 ($n=14$)	16.7	1.9 (9)	14.4	1.6 (9)	13.4	1.0 (9)	12.5	1.1 (8)
Subgroup 2 ($n=16$)	19.1	2.6 (11)	26.0	2.9 (10)	21.8	1.9 (9)	16.7	0.8 (5)
Subgroup 3 ($n=4$)	19.2	3.5 (2)	27.6	3.5 (2)	31.8	3.5 (2)	26.0	n.d.
Subgroup 4 ($n=1$)	16.3	2.0 (1)	15.6	0	16.0	0	16.8	0

[a] Mean of total scores for clinical manifestations (CLIN) are shown for the number of subjects (n_{CLIN}) with a positive score; n.d., not determined.

from skin disease, collaborated in the study. Persons with a history of atopic dermatitis were excluded, as well as persons whose baseline TEWL recordings were not stable due to sweating. The experiments were conducted from April to June and in September and October, 1988.

Exposure

0.3 ml of sodium lauryl sulphate (Merck, USA) in a 0.5 g/100 ml aqueous solution was applied to a disc of absorbent Whatman paper 20 mm in diameter and 1.0 mm thick (no. 2589C, Schleicher & Schuell, 's-Hertogenbosch, The Netherlands). This disc fitted into a round flat plastic chamber (Agfa Bayer, Leverkusen, Germany) with a 22 mm inner diameter. A flat circular brim ensured a close seal of the solutions. The chamber was fixed to the volar site of the right forearm by means of non-adhesive bandages. Two applications lasting 45 min each were made on 4 consecutive days on site REPET (site exposed to 4 days of repeated SLS application). The minimum interval between these two applications was 3 h. After removal of the test material, the skin was cleansed with running water and gently dried with a paper towel. On day 1, site ONE (site exposed to the 24-h single SLS patch) was continuously exposed to 0.3 ml of the same solution as site REPET, for 24 h. After removal of the material on day 2, the skin was cleansed and dried as described above. After measurements on day 1 the two different types of exposure were applied to the proximal 2/3 surface of the right forearm with the two chambers 10 cm apart, the REPET distal to the ONE.

Evaluation

TEWL measurements and visual scoring of irritation were performed at site ONE on days 1, 2, 3, 4, 5, 8 and 10. On day 2, the site was evaluated 2 h after removal of the 24-h patch. TEWL measurements at site REPET were performed on day 5 (REPET5), i.e., after 8 short-term SLS exposures. For the TEWL measurements, the ServoMed Evaporimeter EP1 (ServoMed AB, Vällingby/Stockholm, Sweden) was used. The operating principle of this instrument is described in detail by Nilsson (5). To avoid measurement errors due to air currents, the experiment was performed in a box into which the subject had extended the forearm. The measurements were performed in an air-conditioned room at a constant temperature of 20°C and a relative humidity of 40±10%. The TEWL readings were performed after an acclimatization period of 15 min. Details regarding the exact methodology of the measuring technique are given elsewhere (10). Clinical changes at the exposure sites were graded for erythema, scaling and fissuring, according to Frosch & Kligman (11). Only the total scores are presented.

Statistics

Student's *t*-test for paired observations was applied to compare the means of the TEWL value for both sites on day 1. The association of REPET5 with variables DIFF2–3, DIFF2–4, DIFF2–5 and DIFF2–10 (difference in TEWL level between day 2 and day n, after the 24-h single exposure) was estimated by using Pearson's product moment correlation coefficient.

RESULTS

On the first day, there was no significant difference between the mean baseline TEWL values of sites REPET and ONE: 5.7 and 6.0 g/m²h, respectively ($p<0.05$). A striking inter-individual difference in TEWL time course after the single exposure was no-

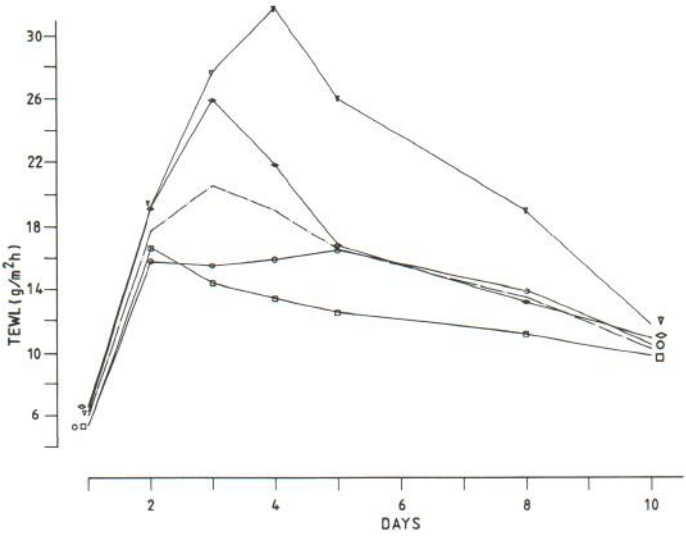

Fig. 1. Time course of transepidermal water loss (TEWL) (g/m²h) before and after a single sodium lauryl sulphate (SLS) exposure. Values are means for the whole group as well as for the different subgroups. Groups: whole group, $n=35$ (– · –); subgroup 1, $n=14$ (□—□); subgroup 2, $n=16$ (◇—◇); subgroup 3, $n=4$ (▽—▽); subgroup 4, $n=1$ (○—○).

ticed; some individuals had their highest TEWL value on the day of removal of the patch (day 2), whereas in others, TEWL continued to rise during the subsequent days after patch removal. Thus, the subjects could be divided into four subgroups (groups 1 to 4), according to the day of their maximum TEWL value after the 24-h SLS exposure (days 2 to 5, respectively) (Table I). Fig. 1 depicts the time course of TEWL at site ONE before and after the 24-h single application, for the total group, as well as for the various subgroups. It is noticeable that for each subgroup, the steepest decrease in TEWL occurred immediately after the maximum TEWL level was reached. After this first phase, the rate of TEWL decline became less.

The mean total scores of the clinical manifestations followed a time pattern similar to that of the mean TEWL values for the different subgroups (see Table I).

Table II summarizes the values for the mean TEWL and the standard deviation (SD) in TEWL for the total group. The SD values were highest during the first days after the single exposure and became smaller in the second week (see Table II *A*). Likewise, the SD values of the TEWL time course after the insult, the latter expressed as the difference in TEWL level between day 2 and day 3, 4, 5, etc. (DIFF2–3, DIFF2–4, DIFF2–5, etc.), were also highest in the first days after exposure (see Table II *B*). This indicates that the inter-individual differences in TEWL time course were most pronounced on the first day after the single exposure; in the later phase, these differences were less pronounced.

The time course of TEWL immediately following the patch removal (DIFF2–3 and DIFF2–4) was significantly correlated with the TEWL after multiple consecutive SLS exposures (REPET5) in contrast with the TEWL time course over a longer period after patch removal (DIFF2–5 and DIFF 2–10) (Table III). Variables DIFF2–3, DIFF2–4 and DIFF2–5 were inversely correlated with REPET5 (Table III).

Table II *A. Means and standard deviations (SD) of transepidermal water loss (TEWL) (g/m²h) on different days before and after the single SLS exposure, for the whole group*

Day	1	2	3	4	5	8	10
Mean	6.0	17.8	20.6	19.0	16.6	13.5	10.4
SD	1.3	4.1	8.9	8.5	8.2	2.4	2.4

Table II *B. Means and standard deviations (SD) of the difference in transepidermal water loss (TEWL) (g/m²h) level between day 2 and a subsequent day after the single SLS exposure, for the whole group*

	DIFF2–3[a]	DIFF2–4	DIFF2–5	DIFF2–8	DIFF 2–10
Mean	−2.7	−0.9	1.1	6.9	7.1
SD	6.3	6.4	6.1	1.8	2.4

[a] DIFF2–3, difference in TEWL level between day 2 (i.e., 2 h after patch removal) and day 3.

Table III. *Association of transepidermal water loss (TEWL) after 4 days of repeated SLS exposure (REPET5) with various measures of TEWL time course after the single SLS exposure (DIFF), expressed as correlation coefficients, for the whole group*

	DIFF2–3[a]	DIFF2–4	DIFF2–5	DIFF2–10
R	−0.62	−0.54	−0.44	0.36
p-value	0.0001	0.0019	0.0765	0.0541

[a] DIFF2–3, difference in TEWL level between day 2 (i.e., 2 h after patch removal) and day 3; The *p*-value denotes the probability that there is no correlation between REPET5 and DIFF.

DISCUSSION

In most subjects, both TEWL and the mean clinical scores continued increasing after exposure to the 24-h SLS patch, with a peak on day 3 or day 4. This late reaction phenomenon has been noticed by others as well (12, 13). Serup et al. studied the time course of TEWL after a single SLS exposure in an attempt to differentiate allergic and irritant skin reactions (7). They found that reactions scored 1+ clinically were accompanied by late peak TEWL values, whereas 2+ reactions had an early peak (7). In another recent investigation, a clear TEWL peak could be noticed only in 13 out of 34 single SLS applications, of which 2 at 48 h and 1 at 72 h after exposure (14). The low frequency of distinct peaks and the prominence of the early peaks in that investigation may point to the fact that the exposure conditions apparently were not sufficient to elicit a fairly pronounced reaction or that the group consisted mainly of hyporeactive subjects (14).

In the present study, it is demonstrated that a once only exposure to an irritant can impair the barrier function of the stratum corneum for a period of at least 10 days. This accords with the results of other investigators (6, 15). One can expect an increased susceptibility to irritants in such a skin site, although having a normal appearance.

In the present study too, the inter-individual variation in TEWL time course after the single exposure to SLS was largest on day 3 to 5 (see Table II). The same phenomenon has been observed also by others; after tape stripping, it was found that individuals differ in repair speed, especially during the first phase, but not during the later phase (8, 9). In daily practice, in which the skin is continually exposed to irritants, this first phase may be the most important, since it is imperative to react to damage with a repair response as soon as possible.

The change in barrier function of the skin immediately following the removal of the irritant (DIFF2–3, DIFF 2–4) was significantly associated with the TEWL level after 4 days of consecutive SLS exposures (REPET5) in contrast to the changes in barrier function over a more prolonged period (DIFF2–5, DIFF 2–10). There was an inverse relationship between DIFF2–3, DIFF2–4 and DIFF2–5 on the one hand, and REPET5 on the other hand. Thus, a large increase in TEWL after patch removal, for example (i.e., a negative DIFF2–3) tends to be associated with an increased susceptibility to repeated SLS exposures, whereas a clear decrease in TEWL after day 2 (positive DIFF2–3) tends to be linked with a low susceptibility to repeated exposures. This finding supports the hypothesis that an inadequate repair response of a damaged epidermal barrier may lead to higher susceptibility to multiple irritant exposures.

Irritants exert a damaging influence by triggering a cascade of mediators of inflammation (16). It is conceivable that this process of inflammation needs a certain time period to develop fully. The late peak irritation reaction may also be caused by the fact that the damaging influence of SLS continues after removal of the patch, since the major part, once absorbed, remains in the upper skin layers until it is eliminated. The increasing barrier damage (as monitored by TEWL) may be explained by a protracted direct damage of the stratum corneum by the irritant and/or by an indirect action via inflammatory reactions in the layers underneath. Since the exact mechanism of the damaging action by SLS—leading to an increase in TEWL (3, 4, 14, 17)—is not yet fully understood (17–19), it is difficult to explain a subsequent decrease in TEWL. Possibly this decrease is caused by elimination of the irritant (i.e., by detoxification through enzyme induction and/or a removal by blood and lymph (20)) and the fact that the influence of SLS on the epidermis is (partly) reversible (swelling of corneocytes (21)). It is also possible that the TEWL decrease is caused by a hyperplastic epidermal response (18) and/or by a stimulation of *de novo* synthesis of lipids in the epidermis (17). In SLS-induced scaly skin, water-retention capacity in the stratum corneum recovered at a higher rate after external application of a particular inter-cellular lipid fraction of the stratum corneum, suggesting their role in the water-retention capacity (19). Individual differences

with respect to the above-mentioned phenomena, may offer an explanation for the inter-individual differences in TEWL time course.

In this study it is demonstrated that the time course of TEWL after a 24-h single exposure to SLS varies between different subjects. Although this inter-individual variation in time course after irritant exposure is a very interesting phenomenon, it may constitute a problem in deciding to choose the right moment for evaluation of patch results; one might consider taking two readings (on days 2 and 3, for example), as has been recommended for allergic patch testing (22). Further, it is shown that this TEWL time course immediately following the single exposure is inversely related to the TEWL value after 4 days of consecutive short-term SLS exposures (for DIFF2–3, $R = -0.61$). Since TEWL reflects the barrier function of the stratum corneum, this association indicates the importance of an adequately responding barrier function against the continuous exposure to irritants in daily life. The design of this study does not allow clarification of the nature of the changes in barrier properties of the skin after irritant exposure. To elucidate the mechanisms which cause the TEWL time course observed, studies on other aspects (e.g., biochemical, histological) are necessary.

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