

Reproducibility of irritant patch test reactions to sodium lauryl sulfate in a double-blind placebo-controlled randomized study using clinical scoring

Results from a study group of the German Contact Dermatitis Research Group (Deutsche Kontaktallergie-Gruppe, DKG)

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Reading of doubtful patch test reactions can be improved by comparing them to defined negative, allergic and irritant controls. For the latter, an irritant patch test is needed that gives sufficiently reproducible results. In our double-blind, placebo-controlled, randomized study, we have analysed the synchronous reproducibility of patch tests with 0%, 0.0625%, 0.125%, 0.25%, 0.5% and 1.0% sodium lauryl sulfate (SLS). Tests and readings were done according to ESCD guidelines. 139 patients (75 women, 64 men) 18 to 77 years old were tested. The % of positive patients as well as the % of reproducible positive reactions increased with rising concentrations of SLS to a maximum of approximately 90% and 85%, respectively, with 1 % SLS. Time courses of reactions were also related to the concentration of SLS: with 1 % SLS, plateau-type time courses were most common (65%), followed by decrescendo- (23%) and crescendo-type reactions (12%). With 1% SLS, very similar mild to moderate reactions were obtained on days 2 and 3. The reaction threshold and reproducibility of tests were not related to age and sex of patients or to their own assessment of skin irritability. We conclude that 1% SLS is appropriate for an irritant patch test that gives sufficiently reproducible results.

Key words: patch testing technique; sodium lauryl sulfate; irritancy; patch test controls; surfactants. © Munksgaard, 1999.

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Reliable controls are mandatory to assess the outcome of biological tests properly and there is no reason why patch tests should be an exception from this rule. Ideally, therefore, the standard patch test series should include negative, allergic and irritant controls (1, 2). However, many patch test patients do not have a predictable contact allergy, or if they do, they may not be retested with their known contact allergen for various reasons. Therefore, a positive allergic control will remain unobtainable in most cases. In contrast, a negative control can be done by patch testing with petrolatum (3). An irritant patch test reaction can also be induced quite simply with a diversity of substances (1,4–6), and some dermatologists apparently do use an irritant as a control patch test (2)

(P. J. Frosch, personal communication). Before this can be recommended as a standard control for routine patch testing, it is necessary, however, to determine the reproducibility and reliability of such an irritant patch test under clinical conditions. It is surprising that, even for sodium lauryl sulfate (SLS), which is probably the most extensively used irritant in clinical and experimental dermatology (6, 7), this particular question has not been answered so far (8, 9). Therefore, our double-blind randomized study was aimed at investigating the reproducibility of patch tests with SLS, depending on its concentration and time of reading. The reactions were assessed by clinical scoring, because sophisticated bioengineering methods are not yet applicable to routine patch testing.

Materials and Methods

Study design and subjects

3 centres participated in this double-blind, placebo-controlled, randomized study. The study design was approved by the local ethics committees of all 3 centres. Patch test patients older than 17 years were enrolled, who had given their informed consent. Exclusion criteria were any kind of immunosuppressive medication, treatment of the back with UV-light or corticosteroids within 4 weeks prior to testing, inflammatory dermatoses of the back, any major general disease, and pregnancy. The patients' subjective experience of skin irritability was assessed by 5 questions exploring their own experience of general skin sensitivity, of sensitivity to detergents, to wool, to deodorants/perfumes, and of their tendency to have dry skin. For each question, 3 answers were offered: "low", "moderate", and "high", which were rated with 1, 2, and 3 points, respectively. By summarizing these points, a subjective skin irritability score was calculated (range of scores possible: 5–15). Furthermore, a history of atopic dermatitis was recorded.

Patch testing

The patch tests were performed in accordance with ESCD guidelines (10). On each side of the back, 6 large Finn Chambers® (12-mm diameter, Epitest, Helsinki, Finland) on Scanpor® tape were attached in a vertical row for 24 h, containing filter paper disks soaked with 60 µl of aqueous solution

of 0%, 0.0625%, 0.125%, 0.25%, 0.5% and 1.0% SLS. This quantity was measured by use of calibrated pipette vessels (kindly donated by Hermal, Reinbek, Germany) releasing drops with a volume of 15 µl each. Highly purified (96.7%, pharmaceutical quality, Caesar u. Lorenz GmbH, D-40721 Hilden, Germany) SLS from the same batch was used by all centres. The chambers were fixed by a nurse in an order randomized separately for both sides of the back, and blinded for the patient as well as for the reading dermatologist.

Patch test reading

Patch tests were read on day 2 (D2) and day 3 (D3) according to ESCD guidelines for clinical scoring of acute SLS irritant reactions (10). Negative (–), weak (+), moderate (++) and very strong (++++ reactions were defined as follows: negative: no visible reaction; weak: very weak erythema or minute scaling; moderate: moderate degree of erythema, oedema, scaling and/or roughness, or minor degree of erosions, vesicles, crusting and/or fissuring; strong: marked degree of erythema, oedema, scaling, roughness, erosions, vesicles, bullae, crusting and/or fissuring; very strong: as + + + +, with necrotic areas, caustic.

Statistics

The χ^2 test was used to compare the responses to SLS by defined subgroups of patients. $p < 0.05$ was considered statistically significant.

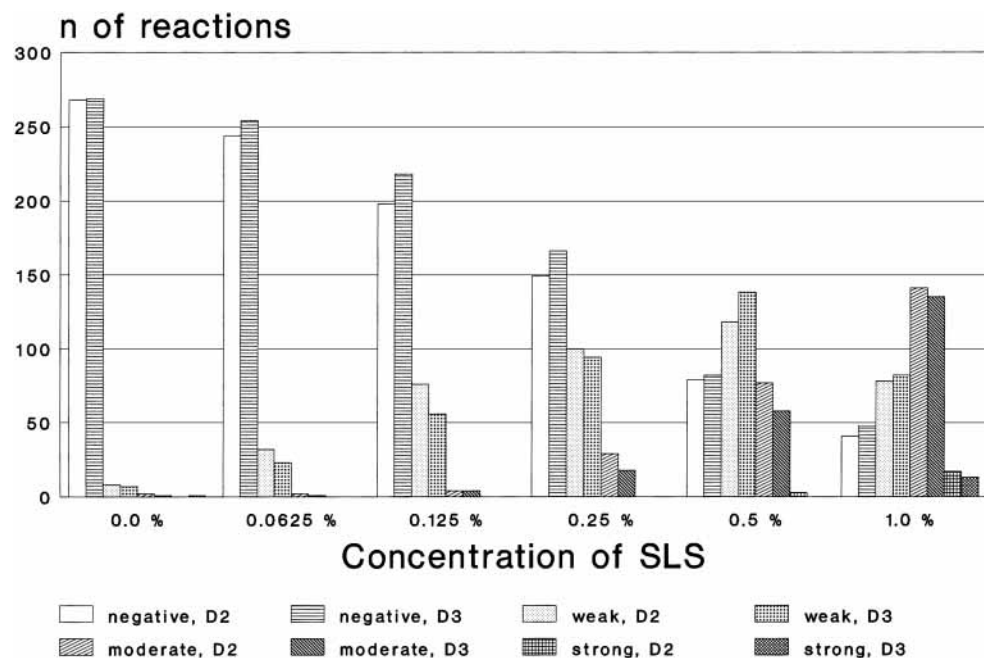


Fig. 1. Numbers of the different reactions to SLS on D2 and on D3.

Results

A total of 139 patients (75 women, 64 men) 18 to 77 years old were tested (median age 39 years). 11 patients had a positive history of atopic dermatitis, while 58 patients had a subjective irritability score of 8 or higher.

Based on the readings on D2 and D3, the reaction thresholds (i.e., the lowest concentration of SLS eliciting a positive reaction on at least one side of the back) were compared for subgroups of patients defined by sex, age and subjective skin irritability. No statistically significant relation was found between the reaction threshold and age or

Table 1. Absolute numbers and % of patients responding on at least one side with a positive reaction (>0) to the different concentrations of SLS on D2 and D3

% SLS	D2		D3	
	<i>n</i>	(%)	<i>n</i>	(%)
0.0	7	5	7	5
0.0625	26	19	19	14
0.125	52	37	46	33
0.25	81	58	72	52
0.5	117	84	114	82
1.0	128	92	124	89

The total number of patients tested (*n*=139) is taken as 100%.

Table 2. Absolute numbers and % of patients responding on both sides with a reaction >0 on D2 and D3

% SLS	D2		D3	
	<i>n</i>	(%)	<i>n</i>	(%)
0.0	3	43	2	29
0.0625	8	31	5	26
0.125	28	54	15	33
0.25	48	59	40	56
0.5	82	70	82	72
1.0	109	85	106	85

The number of patients responding with a positive reaction on at least one side to the corresponding concentration of SLS at the point of time in question is taken as 100%.

Table 3. Absolute numbers and % of patients responding on both sides with reactions >0 of identical strength on D2 and D3

% SLS	D2		D3	
	<i>n</i>	(%)	<i>n</i>	(%)
0.0	2	29	1	14
0.0625	6	23	4	21
0.125	25	48	13	28
0.25	38	47	32	44
0.5	55	47	57	50
1.0	81	63	82	66

The number of patients responding with a positive reaction on at least one side to the corresponding concentration of SLS at the point of time in question is taken as 100%.

sex of patients or their subjective skin irritability. Also, the numbers of patients with positive reactions on both sides to the various concentrations of SLS were not found to be related to these parameters. Similar analyses for patients with a positive history of atopic dermatitis were not done because of their low number.

In Fig. 1, the numbers of the different reactions on D2 and D3 are presented for the various concentrations of SLS. Since each patient was tested in duplicate, 278 reactions were read for each concentration of SLS on D2 and D3. At both reading times, the numbers of positive reactions steadily increased with rising concentrations of SLS. The highest numbers of weak reactions were obtained with 0.5% SLS, moderate reactions mostly needed concentrations of 0.25% or higher, and strong reactions were scarcely found with concentrations below 1.0%. Very strong reactions (++++) to SLS did not occur, and the discomfort of the patients caused by the reactions was minimal. On D2, slightly less negative reactions were seen than on D3 with all concentrations. Some more weak reactions were seen on D2 than on D3 with concentrations up to 0.25%, but with higher concentrations this relation was reversed. Furthermore, slightly more moderate and strong reactions were seen on D2 than on D3 with SLS concentrations >0.125%, but all these differences between D2 and D3 were minor only.

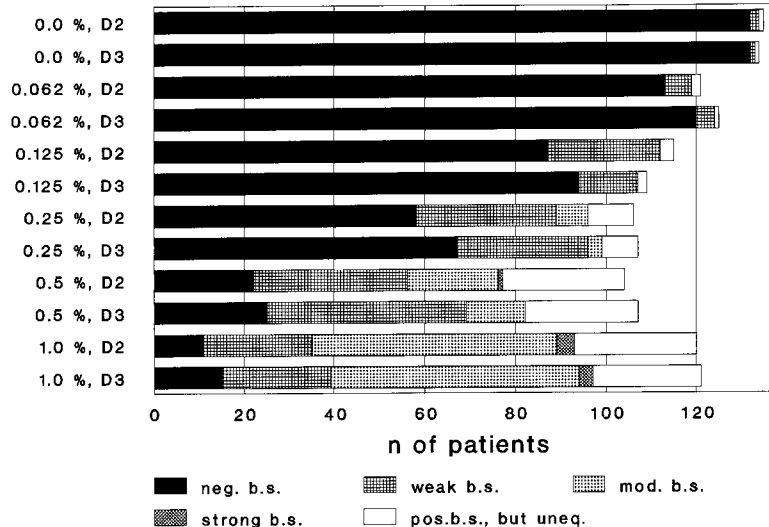
Table 1 shows, for the different concentrations of SLS and times of reading, the numbers and % of patients responding on at least one side of the back with a positive reaction (>0). As was to be expected, the number of positive patients increased continuously with rising concentrations of SLS, but some positive reactions were also seen with 0% SLS (i.e., water only). For all concentrations, slightly more patients had positive readings on D2 than on D3. The highest percentage (92%) of patients with at least 1 positive reaction was obtained with 1% SLS on D2.

In Table 2, the numbers of patients are shown who had positive reactions (>0) on both sides. These numbers are also expressed as the % of patients with a positive reaction on at least one side with the corresponding concentration of SLS at the point of time in question. It is clear from these figures that the reproducibility of positive irritant reactions increased with rising concentrations of SLS. Furthermore, at low concentrations of SLS, the reproducibility appeared to be slightly higher on D2 than on D3.

Table 3 shows the numbers of patients responding on both sides with reactions of identical strength to the various concentrations of SLS. Again, these numbers are also expressed as the %

Fig. 2. Patients with analogous reactions to SLS on both sides on D2 and on D3.

Concentration of SLS



b.s.: on both sides; neg.: negative
mod.: moderate; uneq.: unequal

of patients responding with a positive reaction to the corresponding concentration of SLS on at least one side. Due to the stricter definition applied to the reactions included in Table 3 as compared to Table 2, the figures are lower than those shown in Table 2, but the increase in perfectly matching non-negative reactions with rising concentration of SLS reveals a corresponding trend.

This correlation can also be drawn from Fig. 2, which shows the numbers of patients with corresponding positive or negative reactions on both sides of their back, including the strength of reactions. Fig. 2 reveals that with 1% SLS, positive reactions of identical strength comprised weak, moderate and even strong ones, whereas lower concentrations of SLS (<0.25%) resulted in weak reactions only.

Table 4 shows the numbers of tests in relation to

Table 4. Absolute numbers and % of tests with defined time-dependent developments of reactions

% SLS	Plateau		Decrescendo		Crescendo	
	n	(%)	n	(%)	n	(%)
0.0	5	38	5	38	3	23
0.0625	12	28	21	49	10	23
0.125	40	42	38	40	17	18
0.25	81	55	46	31	20	14
0.5	123	56	63	29	34	15
1.0	161	65	57	23	30	12

According to the strength of the reactions on D2 and D3, crescendo, decrescendo and plateau-type time courses are distinguished. The number of tests with a reading >0 for the corresponding concentration of SLS at one point of time at least is taken as 100%.

defined time-dependent development of reactions. By comparing the strength of each individual reaction on D2 and D3, crescendo, decrescendo and plateau-type time courses were distinguished for those tests with a reading >0 at one point of time at least. It is clear from the figures in Table 4 that SLS concentrations $\geq 0.25\%$ mostly caused reactions of the plateau type. A considerable number of decrescendo courses were seen at lower concentrations, but for all concentrations, a lower % of crescendo courses was also found.

Discussion

Our results clearly confirm that the well-known dose-dependency of irritant responses to patch tests with SLS (11) is measurable, not only by sophisticated bioengineering methods (8) and in open experimental studies, but can also be verified unequivocally by plain visual scoring under blinded conditions (11, 12) (Fig. 1, Table 1). This finding is an obligatory prerequisite for the use of patch tests with SLS for clinical routine procedures.

In addition, it is necessary to analyse the correspondence between synchronous SLS patch tests under the same conditions in order to determine the reproducibility of results. To our knowledge, such a comparison has not previously been described. We found that the reproducibility is also related to the concentration of SLS. Based on the distinguishing of positive and negative reactions only, an optimum of 85% reproducibility was obtained with 1% SLS (Table 2). This means that the

reproducibility of patch tests with 1% SLS is better than the average reproducibility known for patch tests with contact allergens, which was found to be less than 80% in unblinded studies for most of the standard allergens (13, 14).

The high overall reproducibility of patch tests with 1% SLS encouraged us to determine the reproducibility of reactions of identical strength. Again, a relation to the concentration of SLS was obvious, and 1% SLS yielded the highest degree of correspondence between the distinct non-negative reactions (Fig. 2, Table 3). Naturally, this reproducibility is lower (approximately 65% with 1% SLS) than the correspondence of the pooled positive reactions, but it still compares acceptably with the reproducibility of allergic patch tests (13).

On the other hand, the reproducibility of patch tests with SLS is not satisfactory when concentrations below 0.5% are applied. This means that the outcome of such a patch test needs to be verified by a 2nd test or by other methods.

All reactions were assessed separately on D2 and D3 to identify the optimal point of time for reading. With regard to the frequencies of reactions of different strength (Fig. 1) and to the reproducibility (Fig. 2), the results obtained on D2 and D3 did not differ greatly. More weak reactions to low concentrations of SLS and less negative reactions were seen on D2 as compared to D3, but nearly identical figures were obtained on D2 and D3, especially with 1% SLS.

Decrescendo as well as crescendo reactions were mainly seen with low concentrations of SLS. The dominance of plateau-type reactions in our study with SLS concentrations >0.25% (Table 4) helps to explain the close correspondence between the readings on D2 and D3 with higher concentrations of SLS. The finding that crescendo reactions also occurred, points out again that a crescendo-type reaction is not necessarily an allergic reaction (15–17), although in patch tests with allergens, crescendo reactions appear to be better related to clinical relevance than decrescendo reactions (18).

No correlation between the irritation threshold and age, sex or subjective skin irritability of the patients was found in our study. This outcome is in agreement with the difficulties described in previous reports on this issue, when a clinical scoring system was used (8, 19–21); data suggested to indicate age variability (22) should be interpreted carefully. Clinical scorings do not necessarily lead to the same results as do technical methods (9, 23), and different test procedures (10) employing bioengineering techniques for the evaluation of test reactions may be more suitable for quantification of skin susceptibility (24–28).

As a conclusion, we recommend 1% SLS patch

tests as a safe method to elicit weak to moderate irritant reactions in approximately 90% of the patients, with a reproducibility of approximately 85%. Whether such an irritant reaction can be helpful as an irritant control in allergy patch testing, especially when allergens with a low reaction index (29) are tested, remains to be answered by a prospective study in which it is used in the context of patch testing with allergens.

References

1. Wahlberg J E, Maibach H I. Nonanoic acid irritation – a positive control at routine patch testing? *Contact Dermatitis* 1980; 6: 128–130.
2. Kligman A M. A personal critique of diagnostic patch testing. *Clinics in Dermatology* 1996; 14: 35–40.
3. Lachapelle J M, Ale S I, Freeman S, Frosch P J, Goh C L, Hannuksela M, Hayakawa R, Maibach H I. Proposal for a revised international standard series of patch tests. *Contact Dermatitis* 1997; 36: 121–123.
4. Willis C M, Stephens C J M, Wilkinson J D. Experimentally-induced irritant contact dermatitis. Determination of optimum irritant concentrations. *Contact Dermatitis* 1988; 18: 20–24.
5. Wilhelm K P, Pasche F, Surber C, Maibach H I. Sodium hydroxi-induced subclinical irritation. A test for evaluating stratum corneum barrier function. *Acta Dermato-venereol* 1990; 70: 463–467.
6. Effendy I, Maibach H I. Surfactants and experimental irritant contact dermatitis. *Contact Dermatitis* 1995; 33: 217–225.
7. Lee C H, Maibach H I. The sodium lauryl sulfate irritant model. *Contact Dermatitis* 1995; 33: 1–7.
8. Agner T, Serup J. Sodium lauryl sulphate for irritant patch testing – a dose response study using bioengineering methods for determination of skin irritation. *Br J Dermatol* 1990; 95: 543–547.
9. Wilhelm K P, Surber C, Maibach H I. Quantification of sodium lauryl sulfate irritant dermatitis in man: comparison of four techniques: skin color reflectance, transepidermal water loss, laser Doppler flow measurement and visual scores. *Arch Dermatol Res* 1989; 281: 293–295.
10. Tupker R A, Willis C, Berardesca E, Lee C H, Fartasch M, Agner T, Serup J. Guidelines on sodium lauryl sulfate (SLS) exposure tests. A report from the Standardization Group of the European Society of Contact Dermatitis. *Contact Dermatitis* 1997; 37: 53–69.
11. Novak E, Francom F. Inflammatory response to sodium lauryl sulfate in aqueous solutions applied to the skin of normal human volunteers. *Contact Dermatitis* 1984; 10: 101–104.
12. Fullerton A, Serup J. Characterization of irritant patch test reactions to topical D vitamins and all-trans retinoic acid in comparison with sodium lauryl sulphate. Evaluation by clinical scoring and multiparametric non-invasive measuring techniques. *Br J Dermatol* 1997; 137: 234–240.
13. Brasch J, Henseler T, Aberer W, Bäuerle G, Frosch P J, Fuchs T, Fünfstück V, Kaiser G, Lischka G G, Pilz B, Sauer C, Schaller J, Scheuer B, Szliska C. Reproducibility of patch tests. *Journal of the American Academy of Dermatology* 1994; 31: 584–591.
14. Ayala F, Balato N, Lembo G, Patruno C, Angelini G, Valsecchie R, Tosti A, Rivara G, Pigatto P, Seidenari S, Lisi P, Rafanelli A, Saccabusi S, Schena D, Kokelj F. Italian multicenter study on Epiquick, Rapid Patch Test and TRUE Test. *J Europ Acad Derm Ven* 1994; 3: 511–517.

15. Dahl M V, Trancik R J. Sodium lauryl sulfate irritant patch tests: degree of inflammation at various times. *Contact Dermatitis* 1977; 3: 263–266.
16. Bruynzeel D P, Van Ketel W G, Scheper R J, von Blomberg-van der Flier B M E. Delayed time course of irritation by sodium lauryl sulfate: Observations on threshold reactions. *Contact Dermatitis* 1982; 8: 236–239.
17. Löffler H, Effendy I. Crescendo reactions to sodium lauryl sulfate and retinoic acid in irritant patch tests. *Contact Dermatitis* 1997; 37: 47–48.
18. Brasch J, Geier J, Gefeller O. Dynamic patterns of allergic patch test reactions to ten European Standard Allergens. An analysis of data recorded by the “Information Network of Departments of Dermatology (IVDK)”. *Contact Dermatitis* 1996; 35: 17–22.
19. Wahlberg J E, Wrangsjö K, Hietesalo A. Skin irritancy from nonanoic acid. *Contact Dermatitis* 1985; 13: 266–269.
20. Patil S, Maibach H I. Effect of age and sex on the elicitation of irritant contact dermatitis. *Contact Dermatitis* 1994; 30: 257–264.
21. Löffler H, Effendy I, Happel R. Natriumlaurylsulfat-Test. *Hautarzt* 1996; 47: 832–838.
22. Cua A, Wilhelm K P, Maibach H I. Cutaneous sodium lauryl sulphate irritation potential: age and regional variability. *Br J Dermatol* 1990; 123: 607–613.
23. Van Neste D, De Brouwer B. Monitoring of skin response to sodium lauryl sulphate: clinical scores versus bioengineering methods. *Contact Dermatitis* 1992; 27: 151–156.
24. Agner T, Serup J. Individual and instrumental variations in irritant patch-test reactions: clinical evaluation and quantification by bioengineering methods. *Clin Exptl Dermatol* 1990; 15: 29–33.
25. Agner T. Basal transepidermal water loss, skin thickness, skin blood flow and skin colour in relation to sodium-lauryl-sulphate-induced irritation in normal skin. *Contact Dermatitis* 1991; 25: 108–114.
26. Serup J. The spectrum of irritancy and application of bioengineering techniques. In: Elsner P, Maibach H I (eds): *Irritant dermatitis. New clinical and experimental aspects*. Basel: Karger, 1995: 131–141.
27. Simion A F. In vivo models to predict skin irritation. In: Van der Valk P G M, Maibach H I (eds): *The irritant contact dermatitis syndrome*. Boca Raton, FL, USA: CRC Press, 1996: 329–334.
28. McFadden J P, Wakelin S H, Basketter D A. Acute irritation thresholds in subjects with Type I – Type VI skin. *Contact Dermatitis* 1998; 38: 147–149.
29. Brasch J, Geier J, Henseler T. Evaluation of patch test results by use of the reaction index. An analysis of data recorded by the Information Network of Departments of Dermatology (IVDK). *Contact Dermatitis* 1995; 33: 375–380.

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