

Cutaneous response to irritants

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We evaluated the role of pre-existing dermatitis in the response to irritants by patch testing the skin of 40 healthy volunteers and the uninvolved skin of 480 subjects for 2 days. These latter were affected by active atopic dermatitis, psoriasis, eczema with positive and negative patch test reactions, urticaria and generalized pruritus. A first panel containing 15 μ L of aq. solutions of disodium laureth sulfosuccinate (NaLSS) 5% and 10%, potassium cocoate (KCC) 5%, potassium oleate (KOL) 5%, zinc coeth sulphate (ZnCS) 5%, sodium mireth sulphate (NaMS) 5%, sodium cocoamphoacetate (NaCCAA) 3% and 5%, was simultaneously applied to 1 site on the upper back. The results, scored by visual assessment, were compared to those observed when testing on the opposite side a second panel containing 15 μ L of aq. solutions of 3 well-known irritants, benzalkonium chloride (BAK) 1%, sodium lauryl sulphate (SLS) 1%, and dimethylsulphoxide (DMSO) 10%. Whilst the substances of the first panel and DMSO gave, on the whole, a scarce number of positive responses in all the tested groups, more evident differences in number, percent and mean intensity of the positive responses to BAK and SLS were found between the different groups. Although some of them seemed statistically significant, when the same values were evaluated by means of χ^2 and Student *t*-test, they did not differ in a statistically significant way from the values found in healthy subjects. The results of this study seem to indicate that the substances of the first panel have a chemical structure that makes them quite safe in real-life conditions. In contrast, BAK and SLS have chemical properties that condition the number and intensity of the responses, making the role exerted by the pre-existing dermatosis quite marginal. In particular, there is no proof that the healthy skin of active atopic subjects is the most susceptible to the irritating effects of the tested substances.

Key words: atopic eczema; benzalkonium chloride; dimethylsulphoxide; eczema; generalized pruritus; irritant contact dermatitis; psoriasis; sodium lauryl sulphate; urticaria. © Blackwell Munksgaard, 2003.

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Irritants represent an essential feature of the human environment. Products containing potentially irritating substances, are formulated each day and are introduced into domestic and occupational environments with a risk of unexpected cutaneous side-effects on some part of the exposed individuals.

Direct contact with the skin may occur either at the workplace, with economic effects on workers' compensation and disability, or in the domestic environment from excessive or repeated use of hygiene products, detergents and skin care products containing surfactants. The harmful effects may be enhanced by certain factors such as concentration of the surfactants, temperature increase in the washing solution, water hardness, mechanical trauma and friction (1).

Human beings have been repeatedly matched for

the identification of the skin irritation potential of several substances. York et al. (2) stated that it is possible to rank skin irritants in volunteers, comparing the patch test responses to those of suitable control substances. In their opinion, a 4-h patch test in humans may replace the Draize rabbit irritation test. Maintaining the highest ethical standards, it mirrors conditions encountered in daily practice (2).

In the present study, we aimed to assess by patch testing how pre-existing dermatitis influences the skin irritation potential of 6 surfactants, marketed in cosmetic surfactant cleansing preparations. Type and severity of the irritant responses depend upon the chemical nature of the irritants, exposure conditions, individual susceptibility and pre-existing dermatoses which alters the barrier function (1, 3). We used the more extensive 2-day exposure, keep-

ing the concentration of the applied substances low. All things being constant, patch test system, exposure time, and applied amounts, the role played by the skin conditions may be evaluated in testing either the skin of healthy volunteers or the uninvolved skin of subjects affected by different active cutaneous diseases. The results were scored by visual assessment, and compared to those caused by a panel of 3 substances, benzalkonium chloride (BAK), sodium lauryl sulphate (SLS), and dimethylsulphoxide (DMSO), which have previously been widely used in eliciting experimental irritant contact dermatitis (4, 5). Although several non-invasive bioengineering techniques for quantifying such patch test reactions have been described, we have estimated the responses using visual score. Visual inspection is the usual way of evaluating skin reactions (6), and our purpose was to evaluate the variation in skin responses rather than to explain the underlying biological process.

Materials and Methods

From January 2001 to March 2001, we collected 520 subjects, 40 healthy volunteers and 480 affected by active skin diseases such as atopic dermatitis ($n=40$), psoriasis ($n=57$), eczema with positive patch test reactions to at least 1 hapten of the European standard series ($n=124$), eczema with no patch test reactions ($n=140$), urticaria ($n=79$), and generalized pruritus without any other cutaneous symptoms ($n=40$).

None of the enrolled subjects had serious hepatic or renal diseases or a history of cancer. After having given informed written consent, they were not allowed to receive systemic treatments, phototherapy, or potent topical medications for 10 days prior to the patch tests.

The collected subjects were divided into the following 7 groups:

Group 1: 40 healthy, nonatopic volunteers, 10 males and 30 females, aged 21–73 years (mean age: 39 years).

Group 2: 40 atopic subjects with active dermatitis, 19 males and 21 females, aged 8–31 years (mean age: 18 years), who met at least 2 major and 2 minor criteria for atopic dermatitis (7). They were scored using the scoring of atopic dermatitis (SCORAD). 22 had elevated levels of IgE antibodies and 11 had elevated levels of specific IgE for house dust mites (6), *Parietaria* (2) and grass mix pollens (5). Seven of them suffered contemporaneously from respiratory diseases such as asthma (3) and rhinoconjunctivitis (4).

Group 3: 57 patients with active psoriasis, 26 males and 31 females, aged 24–62 years (mean age 55 years). The extent and severity of psoriasis were

evaluated with the use of psoriasis-area-and-severity index (PASI).

Group 4: 124 eczematous subjects, 31 males and 93 females, aged 18–72 years (mean age 41. years), giving positive patch test responses to 1 hapten ($n=67$), 2 haptens ($n=42$), 3 haptens ($n=12$), 4 haptens ($n=2$), or 5 haptens ($n=1$).

Group 5: 140 eczematous subjects with no patch test responses, 53 males and 87 females, aged 16–68 years (mean age: 44 years).

Group 6: 79 patients with active urticaria, 21 males and 58 females, aged 18–71 years (mean age: 43 years).

Group 7: 40 subjects with generalized pruritus, 14 males and 26 females, aged 18–72 years (mean age: 50).

Upon admission, the data were completed with additional information about sex, age, median duration and course of the diseases, and number of affected sites. Some of the baseline characteristics of the tested patients are shown in Table 1.

All the enrolled subjects were simultaneously patch tested with 15 μ L of the following aqueous solutions (weight in deionized water): SLS 1%, BAK 1%, DMSO 10%, NaLSS 5% and 10%, KCC 5%, KOL 5%, ZnCS 5%, NaMS 5%, NaCCA 3% and 5%.

Patch tests were applied on both sides of the upper back for 2 days in all the volunteers and in patients affected by different skin diseases, using Al-test on Fixomul (Beiersdorf, Hamburg, Germany). Readings were performed 1 h after the removal of the strips. In patients with urticaria, 2 additional strips were applied on both sides of the back. These strips were removed after 30 min and readings were immediately done.

Visual scoring was used in assessing the quality and the quantity of the responses. Results were graded in accordance with the following system:

- no visible reaction
- + erythema
- ++ erythema with oedema
- +++ erythema with oedema and papules
- ++++ erythema with vesicles or bullae

The results were additionally scored (0, 1, 2, 3, 4) with corresponding to the degree (0, +, ++, ++++, +++++) of the readings.

The substances tested were: the anionic surfactant sodium lauryl sulphate, the cationic surfactant benzalkonium chloride and the aprotic solvent dimethylsulphoxide (all supplied by Sigma, St. Louis, MO, USA), the anionic surfactant laureth sulphosuccinate (Rhone Poulenc, Marysville, CA, USA), the anionic surfactant potassium cocoate (Henkel, Dusseldorf, Germany), the anionic sur-

Table 1. Baseline characteristics of the patients tested

	Healthy	Atopic dermatitis	Psoriasis	Eczema with positive PT	Eczema with negative PT	Urticaria	Generalized pruritus
No of subjects	40	40	57	124	140	79	40
Males	10	19	26	31	53	21	14
Females	30	21	31	93	87	58	26
Mean age	39	18	47	41	44	43	50
Mean duration of disease (in months)		107	122	29	34	28	29
Up to 2 sites affected		7	9	23	40	2	0
More than 2 sites affected		31	48	91	87	77	38
Continuous course		34	52	46	39	52	36
Intermittent course		6	5	0	101	27	4
Remission on admission		2	0	10	13	0	2
PASI (median)			46				
SCORAD (median)		36					

factant K oleate (Henkel), the anionic surfactant zinc coeth sulphate (Henkel), the anionic surfactant disodium mireth sulphate (Henkel), the amphoteric surfactant sodium cocoamphocetate (Rhone Poulenc).

Statistical evaluation

The χ^2 test was used to evaluate the differences between the percentage of negative responses to BAK and SLS in the seven groups; Student's *t*-test was utilized to evaluate the differences in the mean values of the responses to BAK and SLS.

Results

Positive responses at 2 days were found to KCC in 0.9% of the tested subjects; to KOL in 0.2%, to ZnCS in 0.2%; to NaCAA 3% in 0.5%; and to NaCAA 5% in 2.5%. In contrast, positive reactions to BAK were observed in 36%, to SLS in 38%, to both BAK and SLS in 22%, and to DMSO in 1.3%. No positive responses were found to LSS and NaMS. In patients with urticaria, readings done at 30 min never produced immediate responses.

The details of the patch tests results are shown in Tables 2–4.

Discussion

Taken together, these findings clearly indicate that the number of positive responses found to surfactants of the first panel was generally low in all groups. At the chosen concentrations, the minimal intergroup differences did not permit the evaluation of the behaviour of the unaffected skin in the diseased patients. On the whole, when considering the low concentrations used in marketed products, we could reasonably conclude that the chemical structure of the tested surfactants is not sufficiently

irritant in real-life situations. In contrast to previous reports stating that DMSO may cause a non-immune immediate contact urticaria or irritant reactions, depending upon concentration and mode of application (5), DMSO displayed only marginal irritant properties in our cases.

A different conclusion may instead be drawn from the evaluation of the number and percentage of positive reactions caused by BAK and SLS. Patients with psoriasis, urticaria, atopic dermatitis, eczema with positive or negative patch tests, and with generalized pruritus were enrolled in the study for the following reasons:

- Psoriatic non-lesional skin is considered an activated area which may express pro-inflammatory cytokines when stimulated (8).
- Skin in urticaria is thought to be capable of expressing numerous pro-inflammatory chemical mediators following chemical or physical stimuli (9).
- There is a widely held view that atopics are more prone to develop irritant contact dermatitis and that eczematous skin lowers the threshold for irritants by compromising the skin barrier (10–12).
- Generalized pruritus has a poorly understood origin. Therefore, we attempted to verify whether skin hyperreactivity towards several irritants was present in these subjects.
- Eczematous patients were compared between themselves to verify whether hypersensitivity towards 1 or more chemicals might favour the action of irritants.

Isolated positive reactions to BAK occurred in 42% of healthy subjects, 40% of eczema patients with positive patch tests, 38% of patients with both psoriasis and eczema with negative patch tests, 33% of patients with urticaria, 30% of patients

Table 2. Positive responses to substances of the first panel and to DMSO

	Healthy	Atopic dermatitis	Psoriasis	Eczema with positive PT	Eczema with negative PT	Urticaria	Generalized pruritus
No of subjects	40	40	57	124	140	79	40
DMSO 10%	1	neg	2	6	2	1	neg
LSS 5%	neg	neg	neg	neg	neg	neg	neg
LSS 10%	neg	neg	neg	neg	neg	neg	neg
KCC 5%	neg	neg	2	2	1	neg	neg
KOL 5%	neg	neg	neg	1	neg	1	neg
ZnCS 5%	neg	neg	neg	1	1	neg	neg
DSMS 5%	neg	neg	neg	neg	neg	neg	neg
NaCAA 3%	neg	neg	neg	2	1	neg	neg
NaCCA 5%	2	neg	1	6	3	neg	1

Table 3. Positive responses to BAK and SLS

	Healthy	Atopic dermatitis	Psoriasis	Eczema with positive PT	Eczema with negative PT	Urticaria	Generalized pruritus
No of subjects	40	40	57	124	140	79	40
Males	10	19	26	31	53	21	14
Females	30	21	31	93	87	58	26
Mean age	39	18	55	41	44	43	50
No of negative responses	18	23	29	48	66	42	22
% of negative responses	45	57	51	39	47	53	55
No. of positive responses to BAK	17	12	22	50	53	26	11
No. of positive responses to SLS	16	13	18	54	56	26	17
No. of positive responses to BAK and SLS	11	8	12	28	35	15	10

with atopic dermatitis, and 27% of patients with generalized pruritus. Isolated positive reactions to SLS occurred in 43% of subjects with positive patch test eczema, 42% of patients with generalized pruritus, 40% of both healthy volunteers and subjects with negative patch tests, 33% of subjects with urticaria, 32% of patients with atopic dermatitis, and 31% of patients with psoriasis. Concomitant positive responses to both BAK and SLS were found in 28% of healthy subjects, 25% of subjects belonging to the groups with atopic dermatitis, eczema with negative responses, and generalized pruritus, 23% of subjects with eczema with positive responses, 21% of patients with psoriasis, and 19% of patients with urticaria. Negative responses to BAK and SLS were found in 45% of healthy subjects, 57% of atopic subjects, 51% of subjects with psoriasis, 39% of eczematous patients with positive patch test responses, 47% of eczematous patients with negative patch test responses, 53% of patients with urticaria, and 55% of patients with generalized pruritus.

χ^2 test revealed a statistically significant difference ($p = 0.04$) only in the percentage of negative SLS responses between subjects with atopic eczema and subjects with positive patch test eczema.

SLS gave a higher number of positive reactions, whereas the mean intensity of the positive reactions was higher in patients with positive responses to BAK. When comparing the mean values of the reactions to BAK and SLS (Table 4), Student's t -test showed a significant difference for the values of BAK ($p = 0.05$) and SLS ($p = 0.02$), respectively, between eczematous patients with positive and negative responses. Even the difference of the mean values of SLS between eczematous patients with positive patch test responses and urticaria was statistically significant ($p = 0.007$). Sex, age, mean duration of dermatitis, number of sites affected and number of positive reactions to haptens of the standard series did not seem capable of causing statistically significant differences.

In conclusion, the applied amount and the exposure conditions being constant, type and intensity of the responses to BAK and SLS predominantly depend upon their chemical properties. On the whole, the role exerted by the pre-existing dermatosis is moderate. Our results failed to demonstrate that the healthy skin of subjects affected by psoriasis or urticaria could represent an activated area that might increase the responses to irritants. In fact, the number and intensity of the positive

Table 4. Mean values and standard deviation of the positive reactions to BAK and SLS

	Healthy subjects	Atopic subjects	Psoriasis	Eczema with positive.PT	Eczema with negative.PT	Urticaria	Generalized pruritus
BAK	1.65 (0.21)	1.42 (0.15)	1.64 (0.12)	1.74 (0.12)	1.45 (0.09)	1.46 (0.11)	1.64 (0.24)
SLS	1.62 (0.15)	1.46 (0.14)	1.56 (0.14)	1.74 (0.09)	1.44 (0.08)	1.31 (0.11)	1.53 (0.12)

reactions to BAK and SLS did not differ in a statistically significant way from those found in healthy subjects. Even the healthy skin of subjects affected by generalised pruritus does not seem able to enhance the skin irritant potential of the substances tested. In contrast, the healthy skin of eczematous patients with positive patch test reactions showed a statistically significant higher percentage of positive responses when compared to that of atopic eczema. However, in both cases, there was not a statistically significant difference from the percentage found in healthy subjects. Furthermore, the intensity and number of positive responses to BAK and SLS were not influenced by the number of positive haptens.

Regarding the responses of the healthy skin in atopic subjects, a proportion of them contemporaneously showed high levels of total and specific IgE. However, the percentage and intensity of the positive responses to BAK and SLS between the groups with active atopic dermatitis without high IgE levels ($n = 18$) and individuals with active atopic dermatitis with high IgE levels ($n = 22$) did not show statistically significant differences. Even taking into account the low number of positive reactions to irritants of the first panel, our findings cannot demonstrate that active atopic individuals are the most susceptible to the irritating effects of the substances tested. This is in contrast to the opinion of Löffler & Effendy (13). When they used TEWL to evaluate the results of patch tests to SLS in various groups of atopic subjects, they found an enhanced skin susceptibility to SLS only in individuals with active atopic dermatitis (13). In contrast, this was not found in individuals with a history of atopic dermatitis without active skin lesions or in individuals with atopic dermatitis with rhinoconjunctivitis and asthma, at the time of testing. Conversely, our results are more in keeping with those reached by Basketter et al. (14) who, in a 4-h patch test study, concluded that the reactivity of skin atopics with specific IgE to common allergens and with elevated total IgE was almost identical to that of the control group, and was not influenced by the time of exposure and the method of assessment.

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