

Macro-video documentation patch tests

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An unequivocal distinction between allergic and irritant patch test reactions is often difficult with patch tests. This study was designed to evaluate the worth of video-macro camera documentation for differentiation between allergic and irritant test reactions and to investigate whether there are characteristic clinical differences in patch test responses between metal salts and fragrances. Patch testing was performed with nickel sulfate, fragrance mix and an irritant, sodium lauryl sulfate 1% aq., on the upper back of 82 patients, with evaluation and computer-aided video documentation after 48 and 72 hr. No reliable clinicomorphological criterion was found for assessing a weak patch test reaction as being definitely allergic. Even characteristic papules and vesicles were not regularly found in allergic reactions. However, unlike fragrance mix, patch test reactions to nickel sulfate were characteristic in that they showed a heterogeneous spread and an association with hair follicle openings, independent of reaction intensity. Evaluation based on additional computer-aided video-macro camera documentation did not add further advantage for the differentiation of allergic and irritant reactions. But well-defined clinicomorphological features and reaction patterns to single test substances or even whole substance categories could be helpful additional criteria for evaluating patch test responses in clinical practice.

Key words: fragrance mix; nickel sulfate; patch testing; reaction patterns; sodium lauryl sulfate; video-macro camera. © Blackwell Munksgaard, 2005.

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For decades, patch testing has been the only relevant method used to confirm or rule out a suspected delayed-type contact reaction (1–3). Various clinical scoring systems have been developed for accurate assessment and grading of patch test reactions (1, 4–7). The different classification systems for assessing allergic test reactions are based on clinicomorphological criteria: presence of erythema, inflammatory infiltration, papules, vesicles and bullae (8). Irritant reactions show a broad spectrum of epidermal alterations, depending on the test substance used, and the variable individual reactions including homogeneous, diffuse or patchy erythema, oedema, roughness, or wrinkled surface, scaling, vesicles, bullae, petechiae, pustules, erosions, crusting, fissuring and necrotic areas, as well as quite definite demarcation of the reaction (6, 9–15).

These morphological features should allow an accurate differentiation, but in clinical practice such discrimination between allergic and irritant patch test responses is not always possible. A number of test substances seem to show characteristic reaction patterns on patch testing (16–24),

for example metal salts and fragrances. However, results of patch test reactions, based on the different reading parameters of established classification systems, cannot be precisely compared (24). For this reason, we developed a scoring system containing all major established clinicomorphological criteria for the assessment of patch test responses.

We chose 2 common contact allergens, nickel sulfate and fragrance mix, because of their good patch test reproducibility (25–27). For the examination of irritant reaction patterns, sodium lauryl sulfate (SLS), a standard irritant substance, was used (6, 7). The concentration of 1.0% aq. was chosen because most of the patients tested with SLS 1.0% aq. have been shown to develop signs of mild but unequivocal irritation (14).

With our evaluation concept, we tried to find clinicomorphological criteria to distinguish between allergic and irritant patch test reactions:

- (1) Are there characteristic differences between allergic and irritant patch test reactions?

- (2) Are there any distinctive clinicomorphological differences between reactions to metal salts and fragrances?

Materials and Methods

From October 2002 to April 2003, 82 patients were included in this prospective open-labelled single-centre study. All patients were older than 18 years. Exclusion criteria were an 'angry back syndrome' and skin Type IV according to Fitzpatrick's skin-type scale. Inclusion criteria were: at least weak patch test reactions to nickel sulfate or fragrance mix, or weak test reactions to SLS, 72 hr after patch application.

Patch tests were carried out following the guidelines of the German Society of Dermatology (DDG) and German Contact Allergy Group (DKG) (28).

2 contact allergens, 5% nickel sulfate and 8% fragrance mix in petrolatum (both from Hermal, Reinbek, Germany), and 1 irritant, SLS 1.0% aq., were put into 8-mm Finn Chambers on Scanpor tape (Epitest, Tuusula, Finland). The test patches filled with nickel sulfate and fragrance mix were placed on the patient's upper-left back and with SLS on the upper-right back. Exposure time was 2 days. The patches were removed at 47.5 hr and read at 48 and 72 hr. The relevance of weak allergic reactions was evaluated with a repeated open application test. For clinicomorphological evaluation of patch test responses, a classification system was used with the following parameters: colour intensity of erythema, spread of the reaction, palpable inflammatory infiltration or oedema, association with hair follicle openings, clinicomorphological fine structure (papules, vesicles, scaling, roughness, erosions, crusting, fissuring and necrotic areas) and demarcation of the reaction. For grading the intensity of allergic and irritant test reactions, the criteria 'weak', 'moderate' and 'strong' were used (1, 4, 6, 28) (Table 1). The test reactions were documented with a video-macro camera (MoleMaxIITM, Derma Instruments, Vienna, Austria) (Fig. 1). The images were reviewed by a second experienced observer independently and in a blinded fashion.

Results

Patch test reactions of 82 patients, 52 of them females, were evaluated in this study. The average age was 47 years (range 19–85 years) (Table 1). 'Doubtful' and 'follicular' test reactions were not considered in this evaluation.

Fisher's exact test (FET) was used to assess the statistical significance ($P < 0.05$) of clinicomorphological differences between nickel sulfate and fragrance mix and of the parameter 'roughness' between nickel sulfate and SLS.

The colour intensity correlated to a large extent with the intensity of the reaction.

Patch test reactions to nickel sulfate showed a greater tendency to a patchy spread, while fragrance mix reactions tended towards a homogeneous reaction ($P = 0.01$, FET). There was a homogeneous reaction in 87.9% of patch test responses to SLS.

Fragrance mix reactions always spread further beyond the test area (<5 and <20 mm) than nickel sulfate reactions ($P = 0.18$, FET). There was a scattering of >20 mm beyond the test area in 11.1% of 'moderate-positive' and 50% of 'strong-positive' reactions to nickel sulfate. 33.3% of the 'strong-positive' fragrance mix reactions showed a scattering of >20 mm. Sodium lauryl sulfate showed dissemination of less than 5 mm beyond the test area in 15.2%.

The test reactions of all strength to nickel sulfate were bound to the follicle, while fragrance mix more frequently showed reactions not bound to the follicle ($P < 0.001$, FET). 'Weak-positive' fragrance mix reactions were bound to the follicle in 25% and 'moderate-positive' fragrance mix reactions in 14.3%. Sodium lauryl sulfate always evoked a reaction that was not bound to the follicle.

Palpation of the inflammatory infiltrate or oedema corresponded in the 'weak allergic' and 'moderate allergic' test reactions, as well as in the SLS test reactions, with the final assessment of the patch test. In 50% of 'strong allergic' nickel sulfate reactions, and in all 'strong allergic' fragrance mix reactions, there was a distinctly palpable inflammatory infiltration.

Fragrance mix reactions had a higher tendency to show papules than patch test responses to nickel sulfate ($P = 0.011$).

There was no statistically significant difference in showing vesicles between nickel sulfate and fragrance mix reactions ($P = 0.46$).

Scaling, erosions and crusts were not appropriate differentiating criteria between allergic and irritant test reactions. The parameter 'roughness' was not definitely statistically more frequent with SLS than with nickel sulfate ($P = 0.05$).

Nickel sulfate and fragrance mix showed a quite irregular demarcation of the patch test reaction, while SLS showed a definite demarcation of the test reaction.

Table 1. The number of patch test reactions evaluated by a classification system, based on all major established clinicomorphological criteria for the assessment of patch test responses

Erythema												Demarcation	
Intensity of colour*			Spread		Dissemination‡								
Slight	Moderate	Marked	Homogeneous†	Patchy	≤Patch	<5 larger	>5 larger	≥10 <20 larger	Scattering >20	Indistinct	Distinct		
Nickel sulfate (n = 35)													
Weak	3		1	12	10	3				13			
Moderate	18		8	10		4	9	5	2	18			
Strong	2	2	3	1			2	2	2	4			
Fragrance mix (n = 14)													
Weak			3	1		4				4			
Moderate	4	2	5	2		2	5			7			
Strong		3	3					3	1	3			
Sodium lauryl sulfate (n = 33)													
Weak			19	4	23						23		
Moderate	5		8		5	3					8		
Strong	1	1	2			2					2		
Inflammatory infiltration or oedema													
Bound to follicles§					Palpable¶			Fine structure		Vesicles			
Yes	No		Slight	Moderate	Marked	Papules	None	<10	>10 and <25	>25	>25		
Nickel sulfate (n = 35)													
Weak			13					6	7				
Moderate			2	16				1	15				
Strong				2	2					1	1		
Fragrance mix (n = 14)													
Weak	3		4						4				
Moderate	6		2	4	1				2	5			
Strong	3				3				3	3			
Sodium lauryl sulfate (n = 33)													
Weak	23		23								23		
Moderate	8			8							8		
Strong	2				2						2		

Table 1. Continued

Fine structure											
Scaling				Roughness				Erosions			
None	Minute flakes	Moderate	Large flakes	None	Slight roughness or wrinkled surface	Moderate	Marked	None	Slight	Moderate	Marked
Nickel sulfate (<i>n</i> = 35)											
Weak	11	1	1	11	1	1		13			12
Moderate	18			17		1		16	2		16
Strong	4			4				2	2		2
Fragrance mix											1
(n = 14)											
Weak	13			13				13			13
Moderate	18			18				18			18
Strong	3	1		4				4			4
Sodium lauryl sulfate (<i>n</i> = 33)											
Weak	13			5	5	3		12	1		12
Moderate	18			15	1	2		18			18
Strong	4			4				4			4

*Assessment by comparing with the pictures in Fig. 1.

†Erythema >70% of the patch-test area.

‡Figures in millimetre.

§Association with hair follicle openings and definitely palpable infiltration.

¶Palpable with fingers; slight = not definitely palpable infiltration or oedema as compared to surrounding skin; moderate = obviously palpable and visible infiltration or oedema as compared to surrounding skin; marked = distinctly palpable and visible infiltration or oedema as compared to surrounding skin.

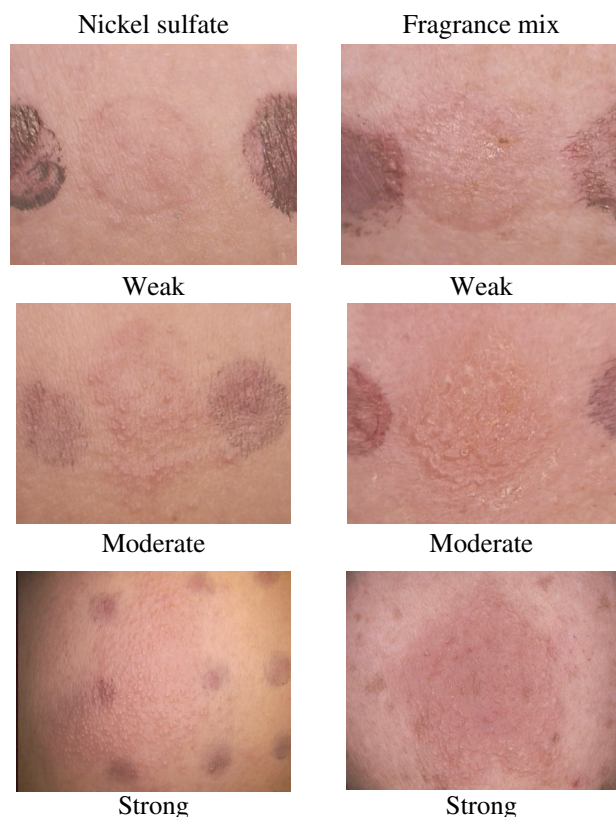


Fig. 1. Patch test reactions to nickel sulfate (5% in petrolatum) and fragrance mix (8% in petrolatum).

Discussion

Patch testing is an established method for the diagnosis of contact allergy (3, 9). This cost-effective and safe diagnostic tool is easily used, but the results are influenced by method and individual variability. Continuing standardization of the patch test substances and procedures over the last few years has enormously improved the reproducibility of test results (27). However, false-positive and false-negative test reactions frequently cannot be ruled out, and still have to be taken into consideration in the interpretation of patch test reactions (9).

One of the main topics in the reading of patch tests is the clear distinction between allergic and irritant test reactions. Transferring the main criteria of established patch test classification systems into one scoring system made it possible to assess test reactions for all visual and palpable parameters (1, 4–7).

The colour intensity as a parameter for erythema serves to describe the reaction intensity but does not distinguish between allergic and irritant reactions (15). The spread and demarcation of the reaction is also not useful as a distinctive feature to separate allergic and irritant patch test reactions. Evaluation of the

inflammatory infiltration does not allow a clear differentiation between 'weak allergic' and 'weak irritant' reactions (15). Papules and/or vesicles are characteristic allergic morphological features, but not all allergic reactions show this clinicomorphological fine structure (15).

In the past, various examination procedures were used in order to differentiate between allergic and irritant reactions. Histological examination of biopsies of clinically indifferent patch test reactions is only useful for a certain type of eczematous response (29). Vestergaard et al. (30) proved that the time of tissue removal from a patch test reaction is decisive for the interpretation of a reaction. In addition, a clinically typical contact allergic reaction may show histopathological patterns that are typical for an allergic and irritant reaction (31). The diagnostic value of the promising reflectance confocal microscopy for the evaluation of acute allergic and irritant contact dermatitis needs to be further evaluated (32).

With the aid of immunohistological methods, cellular infiltrates of a patch test reaction can be identified, but characteristic differences between allergic and irritant test reactions cannot be discriminated (33, 34). Differentiation of allergic and irritant contact eczema using the pattern of the epidermal expression of cytokines was recently described (35).

In order to evaluate patch test reactions objectively, numerous different measuring instruments and non-invasive techniques have been developed (36–38). Serup and Staberg (39) showed differentiation of allergic and irritant reactions by transepidermal water loss, performed shortly after 24 hr of occlusion. Laser Doppler flowmetry can be used to quantify the strength of allergic and irritant skin reactions (40). However, a study by Gawkrödger et al. (41) showed that allergic and irritant test reactions could not be differentiated on the basis of laser Doppler flow or erythema index. These non-invasive techniques might be helpful in distinguishing allergic and irritant patch test reactions, but these objective methods are too time-consuming in clinical practice. Bioengineering methods measure one skin function parameter, but the interpretation of a single test reaction would involve a series of different instruments (42). The computer-aided video-macro camera used for this study was expected to document an objective and reproducible evaluation of the patch test reaction, but this documentation system did not add any further advantage for the differentiation of allergic and irritant reactions (43).

Patch tests with SLS have become a frequently used and reliably assay to irritancy (44–46). Sodium lauryl sulfate is known to produce an unequivocal irritant reaction with a specific morphological pattern (6). Hence, SLS was an appropriate test irritant for our research of clinicomorphological differences between allergic and irritant patch test reactions. The classification of a patch test reaction as 'irritant' is easier when there is a 'positive' reaction to SLS at the same time (16). However, this criterion should only be an additional help for the interpretation of a patch test reaction (16). The reproducibility of SLS reactions depends on a number of factors (6, 47). Furthermore, the irritant potential of a test substance cannot be assessed by testing only one single irritant (11–14, 42).

The second question of this study deals with distinctive clinicomorphological differences between reactions to nickel sulfate and fragrance mix. Nickel sulfate reactions were characterized by a heterogeneous reaction, which was bound to the follicle, independent of reaction intensity. Fragrance mix reactions primarily showed homogeneous reactions not bound to the follicle and extending beyond the test area, and there was a higher tendency towards the formation of papules as compared to nickel sulfate reactions. According to the guidelines of the German Contact Dermatitis Research Group (DKG), 'skin-coloured or erythema-like, follicular papules and pustular reactions' are classified as 'follicular' if there is no palpable infiltration (5). The previously described tendency of metal salts to show a follicular reaction could also be observed in this study (4, 48–50). Formaldehyde as well is known to show follicular patch test reactions (51, 52). For many test substances, the hair follicle openings allow a quick entrance into the epidermis (15). Hair follicle openings are also very sensitive to irritants, which is the reason why allergens with an irritant potential can mimic both allergic and irritant reactions (15).

Allergic and irritant contact eczema cannot be differentiated in all cases by clinical characteristics (53). Similarly, patch tests frequently do not permit a definite differentiation between an allergic and irritant reaction. Even after the inclusion of all established criteria for the assessment of a patch test reaction, no absolute macroscopic parameters for the distinction between a 'weak allergic' and a 'weak irritant' reaction could be found (1, 2, 4–7).

Our results allow the identification of clinicomorphological differences in patch test reactions between metal salts and fragrances, independent of atopy (54). By standardizing the patch test in

the past few years (27), a definition of and search for reaction patterns for single test substances, or even whole substance categories, seems desirable and possible. The considerable importance of patch test reaction patterns in the interpretation of test reactions as allergic or irritant was recently described (54). Clinicomorphological reaction patterns, or reproducible, substance-specific reaction characteristics might make the diagnostically difficult decision between 'weak allergic' and 'weak irritant' easier, and might also represent an additional criterion for the evaluation of patch tests.

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