

Positive nickel patch tests do not intensify positive reactions to adjacent patch tests with dichromate

Results from a double-blind multicentre study of the German Contact Dermatitis Research Group (Deutsche Kontaktallergie-Gruppe, DKG)*

JOCHEN BRASCH¹, BO KREILGÅRD², TILO HENSELER¹, WERNER ABERER³, THOMAS FUCHS⁴,
RAFAEL PFLÜGER⁵, ULLA HOECK² AND OLAF GEFELLER⁵

¹Department of Dermatology, University of Kiel, Germany

²Pharmacia & Upjohn, Hillerød, Denmark

³Department of Dermatology, University of Graz, Austria

⁴Department of Dermatology, University of Göttingen, Germany

⁵Department of Medical Informatics, Biometry and Epidemiology, University of Erlangen-Nürnberg, Germany

The possible interference of neighbouring allergic patch-test reactions is still an open question. In this study, we investigated whether there is a distance-related mutual modification of neighbouring allergic patch-test reactions to nickel sulfate and potassium dichromate. We used a double-blind multicentre study design with randomized attachment of special TRUE Tests with 1, 3 and 7 cm distance between nickel sulfate and potassium dichromate patches. 589 patients with a history of nickel allergy (523 female, 66 male) were tested, with a mean age of 35 years. A log-linear modelling approach was used for statistical assessment of the relation between the distance separating neighbouring patch tests with nickel and dichromate and the reactions to the allergens. Non-reproducibility coefficients were compared by the generalized version of Fisher's exact test for arbitrary 2-dimensional contingency tables. For the left side of the back, virtually no differences ($p=0.70$) were found in the reaction patterns obtained for the 3 distances separating nickel and dichromate patch tests. On the right side of the back, the number of reactions to dichromate patches with only 1 cm distance from moderate/strong nickel reactions was lower than the number of positive dichromate tests at larger distances from nickel tests (on the border of statistical significance: $p=0.05$). Corresponding side-related results were obtained for subgroups of patients with and without a history of atopic dermatitis. The non-reproducibility of reactions to dichromate was not significantly related to the distance between neighbouring tests. Our data argue against a "spillover" effect of strong/moderate nickel reactions, but indicate that such reactions may, under certain conditions, attenuate adjacent reactions to an unrelated allergen. In the case of future verification, this will have implications for the interpretation of patch tests.

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For the correct interpretation of patch-test readings it is mandatory to know about possible interactions between synchronous patch test reactions.

*Centres and investigators contributing to this study: Departments of Dermatology at the University of Kiel (J. Brasch); University of Graz, Austria (W. Aberer); University of Tübingen (G. Lischka); University of Göttingen (T. Fuchs); Freie Universität Berlin (B. Tebbe); University of Heidelberg (A. Schulze-Dirks); University of Marburg (I. Effendy); Städtische Krankenanstalten Krefeld (M. Lilie); St. Barbara-Hospital Duisburg-Hamborn (J. Schaller); University of Lübeck (J. Grabbe); University of Münster (R. Brehler); Städtische Kliniken Dortmund (P. Frosch); University of Hamburg (M. Kiehn).

An increased occurrence of false-positive patch test reactions due to many synchronous positive reactions has been termed "angry back" (1), "excited skin syndrome" (2, 3), or "stochastic resonance" (4). However, not all investigators agree that an excited skin syndrome really exists (5–7).

In the case that one patch test reaction can modify another patch test reaction, this can be expected to be most pronounced in patch tests that are situated close to one another (8–10). An enhancement of a weak reaction by a strong adjacent reaction was described by several authors as

“spillover” effect (11, 12). However, others found the strength of neighbouring patch test reactions to be unrelated to their distance (13), and it was shown that the threshold for a positive nickel patch test is not decreased by an adjacent strong positive nickel reaction (14). Experimental models even revealed that eczematous skin reactions could attenuate cell-mediated immunity (15, 16).

Therefore, it is currently an open question whether the small distance (usually 1 cm) between routine patch tests is sufficient to exclude interference between adjacent patch tests. To find an answer, we have analyzed the results of synchronous neighbouring patch tests with nickel sulfate and potassium dichromate. These 2 allergens were chosen because they are very common, chemically defined and unrelated standard allergens that do not cross-react. Both allergens were attached simultaneously with a separating distance of 1 cm, 3 cm or 7 cm, and the results were compared by use of appropriate statistical models.

Patients and Methods

Study design and subjects

Our double-blind randomized multicentre study was approved by the Ethical Committee of the Medical Faculty of the University of Kiel, and this approval was endorsed by the other 12 centres participating. Patch test patients older than 17 years with a history of nickel allergy were enrolled after giving 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, pregnancy, and a history of excessively strong patch test reactions to nickel sulfate or potassium dichromate (local eczematous response with a diameter >3 cm, any generalized response). Furthermore, a history of atopic dermatitis was recorded.

Patch testing

Special TRUE TestTM strips were manufactured and supplied for this study by Pharmacia & Upjohn (Hillerød, Denmark). In principle the construction of these study strips was identical to that of commercially available TRUE TestTM (17). Corresponding to the latter, the test fields were arranged in a line, each test field covered a square area of 0.8 cm², and the distance between adjacent test areas was 1 cm. However, each study strip comprised 6 test areas only, and only 2 of them were provided with customary TRUE TestTM allergens: 1 test area contained nickel sulfate (0.2 mg/

cm²), and 1 test area contained potassium dichromate (0.023 mg/cm²), whereas the other 4 test areas were placebo-filled. The distance between the nickel and dichromate test areas on each study strip was either 1, 3 or 7 cm. By observing these distances, the allergens were placed randomly within the strips, identifiable only by a code. Each patient was tested synchronously with 2 randomly chosen study strips that were attached to the left and right side of the back for 2 days. Additional patch tests were allowed to be performed synchronously according to the diagnostic requirements of the individual patient, but a minimum distance of 10 cm between the study strips and any other patch tests was required by the study protocol. The study patch tests were read on day 2 (D2) and day 3 (D3) according to the guidelines of the German Contact Dermatitis Research Group (18): negative (–), questionable (?), weak (+), moderate (++) and strong (+++) reactions were defined as follows: negative: no visible reaction; questionable: erythema, no infiltration; weak: erythema, infiltration, slight papules possible; moderate: erythema, infiltration, papules, vesicles; strong: erythema, infiltration, confluent vesicles.

The readings on D3 were used for all evaluations. To eliminate any possible impact of an observed centre-dependent slightly divergent differentiation between questionable and weak positive reactions, all questionable reactions were added to the weak positive reactions for our analyses. Since the numbers of positive reactions to dichromate were rather low and included only a minor % of moderate and strong positive reactions, all positive reactions (weak, moderate and strong) to dichromate were pooled for evaluations pertaining to their distance to nickel reactions. Moderate and strong reactions to nickel were also pooled for the same reason. In addition, the total number of all positive reactions – including those obtained by individual diagnostic patches – was also recorded.

Statistics

For the statistical assessment of the relation between the distance separating neighbouring patch tests with nickel and dichromate and the test reactions to the allergens, a log-linear modelling approach was used. In particular, for each side of the back the model included terms for the distance and the test reaction to nickel and dichromate. Separate analyses were done for all patients and for patients with and without a history of atopic dermatitis.

The second-order interaction terms of these log-linear models, involving distance and test reactions to nickel and dichromate, indicates whether the 2-

dimensional reaction pattern of test results for nickel and dichromate is independent of the distance separating these patch test chambers or not. The *p*-values of the corresponding likelihood ratio test for these specific interaction terms are thus reported. The significance level for statistical testing was set at 5%.

The concordance of reactions to the same allergen in the same patients can be described by the non-reproducibility coefficient (19). Differences between non-reproducibility coefficients for different groups of subjects were statistically tested by the generalized version of the Fisher exact test for arbitrary 2-dimensional contingency tables.

Results

A total of 589 patients (523 female, 66 male) were tested, with a mean age of 35 years (<25 years: 148; 25–39 years: 270; 40–54 years: 119; ≥55 years: 52). 224 patients were considered atopics according to the criteria of Hanifin & Rajka (20).

The numbers of test strips used with 1, 3, and 7 cm distance between the test areas with nickel sulfate and potassium dichromate proved to be balanced when all patients were considered and also when distinct subgroups of them (with and without a history of atopic dermatitis, with and without known allergy to dichromate) were analysed separately. Furthermore, virtually no differences were found between the left and right side of the back with regard to the frequency of tests with 1, 3, or 7 cm distance between test areas with nickel sulfate and potassium dichromate, or with regard to the total numbers of positive reactions to nickel sulfate or potassium dichromate.

A total of 406 questionable/positive reactions occurred with nickel sulfate on the left and on the right side of the back, and a total of 191 and 195 questionable/positive reactions were seen with potassium dichromate on the left and right side of the back. The frequency of irritant reactions was negli-

gible. The reaction index (21, 22) was 0.91 for nickel and 0.23 for dichromate.

Table 1 shows the total numbers of negative and positive reactions to nickel and dichromate separately for the 3 distinct distances between the test areas for both allergens. Because of major differences between the results obtained on the left and right side of the back, the data are presented separately for both sides of the back. Due to these side-dependent differences, separate statistical analyses were mandatory for both sides. Taking the data of all patients pertaining to the left side of the back, no statistically significant relation (*p*=0.70) was found between the distance separating nickel and dichromate patch tests and the reactions obtained. On the right side of the back, however, less questionable/positive reactions to dichromate were observed with patch tests attached at 1 cm distance from moderate/strong nickel reactions than with dichromate patch tests at a larger distance from the neighbouring moderate/strong nickel reaction (23 for 1 cm distance, 33 for 3 cm distance, 32 for 7 cm distance, Table 1). This difference in the pattern of test reactions to nickel and dichromate, depending on the distance of test chambers, was on the border of statistical significance when analysed in the log-linear modelling framework, utilising the full data in Table 1 (*p*=0.05).

Corresponding side-dependent differences were also found when separate analyses were done for non-atopic and atopic patients. For the latter, on the right side of the back, the number of positive reactions to dichromate was in fact significantly lower (*p*=0.012) when the distance between positive nickel patches and dichromate patches was only 1 cm, as compared to larger distances. For non-atopic patients, a corresponding *p*-value of 0.053 indicated borderline significance. On the left side of the back, no such relation was seen in non-atopic and atopic patients. Due to the small number of patients with a history of dichromate allergy, a separate analysis for them was not appropriate.

Table 1. This table refers to the total study population and shows the numbers of non-irritant reactions to nickel and dichromate on the left and right side of the back, in relation to the distance between adjacent patch tests and differentiated by the reaction strength; due to a few irritant reactions not included in this table, the total numbers of reactions on both sides are not identical

Distance (cm)	Reactions to dichromate	Reactions to nickel					
		–		?/+		++/+++	
		left	right	left	right	left	right
1	–	40	38	39	32	55	53
	?/+/+/+/+	18	30	16	18	27	23
3	–	32	51	35	37	49	50
	?/+/+/+/+	22	14	15	20	26	33
7	–	47	34	34	33	58	58
	?/+/+/+/+	21	12	10	13	36	32

Table 2. This table refers to that subgroup of the study population only that was tested with identical distances between nickel and dichromate patches on both sides of the back; the total number of patients is therefore lower than in Table 1; for the 3 different distances between nickel and dichromate patches, the numbers of patients are shown separately for those who reacted with questionable/positive (?/+ +/+ +++) reactions to nickel and dichromate on both sides of the back and for those who reacted on one side only

Distance (cm)	?/+ +/+ +++ on both sides		?/+ +/+ +++ on one side only	
	nickel	dichromate	nickel	dichromate
1	36	3	7	7
3	37	13	7	9
7	44	9	6	10

We also looked at the non-reproducibility of nickel and dichromate reactions in patients who had been tested with identical distances between nickel and dichromate patch tests on both sides of their back. Separately for the 3 distances between the neighbouring patch tests, the non-reproducibility was calculated as described previously (19), based on the numbers of patients with corresponding questionable/positive reactions on both sides of their back and the number of patients with a questionable/positive reaction on one side only. Due to the study design, the sample sizes for these evaluations were much lower (Table 2) than the total number of patients tested, and the numbers of atopic patients within these samples were not sufficient for a separate analysis.

The data shown in Table 2 reveal that the non-reproducibility of reactions to dichromate 1 cm away from adjacent nickel patch tests was higher (0.7) than the non-reproducibility of dichromate reactions at a distance of 3 cm or 7 cm from the neighbouring nickel patch test (0.41 and 0.53 respectively), but this was not a statistically significant relation ($p=0.34$). The non-reproducibility of nickel reactions was low throughout (0.16, 0.16 and 0.12 for 1, 3 and 7 cm distance) and independent of the distance from the neighbouring dichromate patch test ($p=0.83$). Accordingly, the number of patients with corresponding questionable/positive reactions to dichromate on both sides who had been tested with nickel and dichromate patches only 1 cm apart was markedly lower ($n=3$) than the comparable numbers of patients tested with larger distances between nickel and dichromate patches ($n=13$ for 3 cm distance and $n=9$ for 7 cm distance; Table 2), whereas no such differences were seen with the nickel reactions.

Discussion

The aim of our present investigation was to analyse a possible mutual modulation of adjacent

patch tests. A positive patch test may amplify an adjacent patch test reaction (11, 12) and a similar process of raised reactivity caused by multiple positive patch tests could be the basis for an "angry back" (1–4). In contrast to this notion, our results do not indicate that a positive patch test reaction increases the likelihood of another positive reaction in its close proximity. No higher number of positive dichromate reactions was obtained with patch tests attached only 1 cm away from a positive nickel patch test than with dichromate patch tests at a distance of 3 cm or 7 cm from a positive nickel reaction. This outcome argues against a "spillover" effect and matches earlier findings that the strength of neighbouring patch test reactions is unrelated to the distance between them (13), and that the threshold for a positive nickel patch test is not decreased by an adjacent strong positive nickel reaction (14).

These previous investigations were made, however, only with identical allergens for both neighbouring patch tests (14), with unusual concentrations of allergen (14) or with a special ring-shaped test chamber that was positioned concentrically to an Al-test chamber (13). Since our intention was to clarify whether a mutual modification of adjacent patch test reactions is likely to occur under routine patch test conditions, we simulated these conditions by using 2 distinct and unrelated allergens in common patch test concentrations. These were applied by the TRUE Test™ system, which is in wide use for diagnostic patch testing. Our method can therefore be assumed to yield more realistic information about that which is happening in routine patch testing.

In the case that a positive patch test has an effect on a neighbouring patch test reaction, this should have a distance-dependent impact on the reproducibility of the reactions as well. We found that the non-reproducibility of nickel patch tests was quite clearly independent of their distance from neighbouring patch tests with dichromate. In contrast, the non-reproducibility of dichromate patch tests was higher (0.7) for those patches located only 1 cm away from nickel patch tests as compared to more distant tests (0.41 and 0.53 for 3 and 7 cm distance). The fact that this difference was not statistically significant may be explained by the small number of patients available for this particular analysis. Therefore, a reduced reproducibility of dichromate patch tests that are located in close proximity to other positive patch tests should not be dismissed until more data with larger numbers of patients are available.

It was a big surprise to us to find some differences between the interaction of patch tests on both sides of the back. On the left side of the back,

there was no relation between the distance separating adjacent patch tests and the strength of the dichromate reactions ($p=0.70$). On the right side of the back, however, such a relation was of borderline significance ($p=0.05$), when all patients were analysed together, and turned out to be significant when only atopic patients were evaluated ($p=0.012$). Although a different skin reactivity was reported for the back and extremities (23) and for the lower and upper back (24), no different skin reactivity has been described for the left and right sides of the back in recent studies (25, 26). A strictly symmetrical application of both study test strips was not requested by our study protocol, but there was no evidence for a systematic bias due to different test strip localizations on both sides of the back that would explain our divergent results on the left and right side of the back.

Since most of the patients had been tested with additional allergens for individual diagnostic purposes, one could speculate that such additional tests might have had an impact on our study results, although they had to be kept at a minimum distance of 10 cm to the study strips. A retrospective questionnaire revealed that it had been a common practice in the participating centres to start with the attachment of diagnostic patch tests on the left side of the back. A higher average number of positive reactions can thus be expected to have occurred on the left side as well. Therefore, we compared patients with up to 4 positive reactions to those with more than 4 positive reactions, but the side-related differences described above occurred within both of these subgroups as well. This finding argues against a major influence of the additional diagnostic patch tests on our study results, and so far, we are unable to give a conclusive explanation for the differences observed between both sides of the back.

For the right side of the back, there was a compelling tendency in our data for moderate to strong nickel patch test reactions to reduce the frequency of positive reactions to dichromate patch tests attached at a distance of only 1 cm. We would like to point out that this tendency was not caused by our pooling of questionable and weak positive reactions or by pooling moderate and strong nickel reactions for our calculations. We also checked this relation by calculations using figures obtained by various different modalities to merge the numbers of distinct (?, +, ++, +++) reactions and found p values even below 0.05 then (ranging between 0.002 and 0.048 for all patients). If this observation can be verified by future studies, it would support the possibility that eczematous skin reactions can attenuate cell-mediated immunity (15,16). Such an

attenuation would be of considerable practical importance for patch testing.

We conclude that positive nickel patch test reactions will not intensify adjacent dichromate patch test reactions, making a "spillover" effect an unlikely event. Under certain conditions, some attenuating effect may in fact occur instead. To clarify this question is of basic importance for the interpretation of patch tests and should be the aim of future studies with more allergens.

References

1. Mitchell J C. The angry back syndrome: eczema creates eczema. *Contact Dermatitis* 1975; 1: 193-4.
2. Maibach H I. The E.S.S. - Excited skin syndrome (alias the "angry back"). In: Ring J, Burg G (eds.): *New trends in allergy*. Berlin, Heidelberg, New York: Springer Verlag, 1981: 208-221.
3. Bruynzeel D P, Maibach H I. Excited skin syndrome (angry back). *Arch Dermatol* 1986; 122: 323-328.
4. Rietschel R L. Stochastic resonance and angry back syndrome: noisy skin. *Am J Contact Derm* 1996; 7: 152-154.
5. Kligman A M, Gollhausen R. The "angry back" - A new concept or old confusion? *Br J Dermatol* 1986; 115: (suppl 31): 93-100.
6. Lammintausta K, Kalimo K. Do positive nickel reactions increase non-specific patch test reactivity? *Contact Dermatitis* 1987; 16: 160-163.
7. Memon A A, Friedman P S. "Angry back syndrome": a non-reproducible phenomenon. *Br J Dermatol* 1996; 135: 924-930.
8. Bruynzeel D P, Willem G, van Ketel M D. Angry back or the excited skin syndrome. A prospective study. *J Am Acad Dermatol* 1983; 8: 392-397.
9. Hamami I, Marks R. Abnormalities in clinically normal skin - a possible explanation of the "angry back syndrome". *Clin Exp Dermatol* 1988; 13: 328-333.
10. Duarte I, Almeida F A, Proenca N G. Excited skin syndrome. *Am J Contact Derm* 1996; 7: 24-34.
11. Mitchell J C. Multiple concomitant positive patch test reactions. *Contact Dermatitis* 1977; 3: 315-320.
12. Bruynzeel D P, Nieboer C, Boorsma D M, Scheper R J, Van Ketel W G. Allergic reactions, "spillover" reactions, and T-cell subsets. *Arch Dermatol Res* 1983; 275: 80-85.
13. Bandmann H J, Agathos M. Das "Angry Back Syndrom" - Untersuchungsergebnisse mit Sequenztestungen, Wiederholungstestungen und dem Cocarden-(Target-)Test. *Hautarzt* (suppl V) 1981; 32: 97-104.
14. Andersen K E, Lidén C, Hansen J, Vølund Å. Dose-response testing with nickel sulphate using the TRUE test[®] in nickel-sensitive individuals. Multiple nickel sulphate patch-test reactions do not cause an "angry back". *Br J Dermatol* 1993; 129: 50-56.
15. Frey J R. Quantitative Untersuchungen bei epidermaler Sensibilisierung von Meerschweinchen mit Dinitrochlorbenzol. *Dermatologica* 1951; 102: 1-11.
16. Uehara M, Ofuji S. Suppressed cell-mediated immunity associated with eczematous inflammation. *Acta Dermatovenereologica* 1977; 57: 137-139.
17. Fischer T, Maibach H I. The thin-layer rapid-use epicutaneous test (TRUE Test), a new patch test method with high accuracy. *Br J Dermatol* 1985; 112: 63-68.
18. Brehler R, Hellweg B. Beurteilung von Epikutantestreaktionen nach Empfehlungen der Deutschen Kontaktallergie-Gruppe (DKG). *Dt Derm* 1995; 43: 688-690.
19. Brasch J, Henseler T, Aberer W, Bäuerle G, Frosch PJ,

- Fuchs T, Fünfstück V, Kaiser G, Lischka G G, Pilz B, Sauer C, Schaller J, Scheuer B, Szliska C. Reproducibility of patch tests. *J Am Acad Dermatol* 1994; 31: 584–591.
20. Hanifin J M, Rajka G. Diagnostic features of atopic dermatitis. *Acta Dermato-venereologica* 1980; 92: 44–47.
21. Brasch J, Henseler T. The reaction index – a parameter to assess the quality of patch test preparations. *Contact Dermatitis* 1992; 27: 203–204.
22. 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.
23. Magnusson B, Hersle K. Patch test methods (II). Regional variations of Patch test responses. *Acta Dermato-venereologica* 1965; 45: 257–261.
24. Van Strien G A, Korstanje M J. Site variation in patch test responses on the back. *Contact Dermatitis* 1994; 31: 95–96.
25. Simonetti V, Manzini B M, Seidenari S. Patch testing with nickel sulfate: comparison between 2 nickel sulfate preparations and 2 different test sites on the back. *Contact Dermatitis* 1998; 39: 187–191.
26. Reiche L, Willis C, Wilkinson J, Shaw S, De Lacharrière O. Clinical morphology of sodium lauryl sulfate (SLS) and nonanoic acid (NAA) irritant patch test reactions at 48 h and 96 h in 152 subjects. *Contact Dermatitis* 1998; 39: 240–243.

Address:

J. Brasch
Department of Dermatology
University of Kiel
Schittenhelmstr. 7
D-24105 Kiel
Germany