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CLINICAL REPORT

Patch Testing of Nickel Sulfate and Potassium Dichromate with a Standardized Ready-to-use Test System Gives Highly Reproducible Results: A Double-blind Multicentre Study*

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There is still some doubt about the reproducibility of patch tests. A sound assessment needs optimized and unbiased studies. This study analysed the results of a double-blind multicentre study with nickel sulfate and potassium dichromate patch tests attached synchronously to both sides of the back of patients with a history of nickel allergy, conducted with a highly standardized randomized test system (TRUE-test®). Out of 589 patients tested, a total of 388 had responded with allergic reactions to nickel sulfate and 130 to potassium dichromate. The reproducibility of positive nickel (dichromate) patch tests was 99.2% (90.8%). The reaction index was also calculated, which relates the number of allergic reactions obtained with a test preparation to the number of questionable and irritant reactions; the reaction index can range from –1 (questionable and irritant reactions only occur) to 1 (allergic reactions only occur). For nickel sulfate the reaction index was 0.91, but it was only 0.23 for potassium dichromate, as a result of considerably more questionable reactions. In conclusion, a highly synchronous reproducibility of results can be achieved by using a well-standardized patch-test system, especially with nickel sulfate. However, distinct allergens and test systems need to be evaluated separately. ***Key words: patch-test reproducibility; patch-test methods; reaction index.***

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Patch testing has been the gold standard in diagnosing cutaneous delayed-type hypersensitivity for more than 100 years (1). Therefore, one may presume that it is a highly reliable diagnostic tool yielding reproducible results throughout. It has gradually become clear, however, that different techniques and methods of testing can lead to divergent results and also influence patch-test reproducibility (2–15). The different rates of patch-test reproducibility reported in the literature (3–7, 9–11, 13, 15) still cause some confusion about the true diagnostic reliability of patch-test results, which needs to be eliminated. In particular, misleading conclusions with regard to patch-test reproducibility may be drawn from small study populations or from studies that lack an optimal standardization of test materials and do not exclude a bias due to unblinded readings.

In order to determine patch-test reproducibility unimpaired by these sources of error, this study checked the synchronous intraindividual reproducibility of patch tests conducted with a commercially available, highly standardized, ready-to-use test system (TRUE-test®) with randomized location of the allergens. Using a double-blind study design 589 patients with a history of nickel allergy were tested with 2 of the most common standard allergens that have a different potential to elicit allergic, questionable and irritant reactions, i.e. nickel sulfate and potassium dichromate.

MATERIAL AND METHODS

Thirteen centres of the German Contact Dermatitis Research Group contributed data from a double-blind study approved by the local Ethical Committees. Patch-test patients older than 17 years with a history of nickel allergy (reported eczematous reactions to skin contact with metal likely to contain nickel or positive nickel patch test) were enrolled after giving their informed consent. Exclusion criteria were as follows: any kind of immunosuppressive medication, treatment of the back with ultraviolet (UV) light or corticosteroids within 4 weeks prior to testing, inflammatory dermatoses of the back, any major general disease, pregnancy, or 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).

Special TRUE-test strips were produced and supplied by Pharmacia & Upjohn (Hillerød, Denmark). In principle, their construction was identical to that of commercially available TRUE-test strips (17), in that the test fields were arranged in a line, each test field covered a square area of 0.8 cm^2 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-test allergens: one test area contained nickel sulfate (0.2 mg/cm^2) and one test area contained potassium dichromate (0.023 mg/cm^2); the distance between the nickel and dichromate test areas on each study strip was either 1, 3 or 7 cm. The other 4 test areas on each strip were placebo ones constructed identically to the nickel and dichromate patches except that they contained hydroxypropylcellulose instead of an allergen. By a randomized allocation, any of the test fields could contain allergen or placebo, identifiable only by a code unknown to the user. 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, and readings were taken at the same time on both sides. Additional epicutaneous tests could be performed synchronously according to the individual diagnostic requirements of the patient, but a minimum distance of 10 cm between the study strips and any other epicutaneous patch tests was required by the study protocol.

The study patch tests were read on days 2 and 3 according to the guidelines of the German Contact Dermatitis Research Group (18): negative (neg.): no visible reaction; questionable (q): erythema, no infiltration; irritant (i): irritant reactions of different types; weak allergic (+): erythema, infiltration, slight papules possible; moderate allergic (++): erythema, infiltration, papules, vesicles; strong allergic (+++): erythema, infiltration, confluent vesicles. The readings on day 3 were used for all evaluations.

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Patch-test reproducibility and the reaction index (RI) were calculated as described previously (13, 19, 20). Based on the numbers of allergic (a; including +, ++ and +++ reactions), questionable (q) and irritant (i) reactions obtained in the study the RI was calculated as follows: RI = (a – q – i):(a + q + i). The RI can range from – 1 to +1. A high RI indicates that questionable and irritant reactions are not a major problem with a particular allergen preparation, whereas a low RI is related to a high proportion of problematic (questionable and/or irritant) readings. Therefore, allergens with a high RI usually have a better patch-test reproducibility (20).

RESULTS

In total, 589 patients (523 females and 66 males) were tested, with a mean age of 35 years (< 25 years: 148; 25–39 years: 270; 40–54 years: 119; ≥ 55 years: 52). According to the criteria of Hanifin & Rajka (21), 224 patients were considered atopics. Eight patients were not evaluable because of missed readings or insufficient adherence of the test strips. No excessive reactions or angry back were observed. In total, 388 and 130 patients responded with at least one allergic reaction to nickel sulfate and potassium dichromate, respectively; 84 and 83 patients reacted to both nickel sulfate and potassium dichromate on the left and right side of the back, respectively. Not all positive patch-test reactions reported by the patients could be reproduced, irrespective of atopy. No positive, irritant or questionable reactions occurred with the placebo patches.

Table I shows the results obtained with nickel sulfate patches on both sides of the back for all patients. Although a positive history of nickel allergy was requested for inclusion into the study population, 183 out of 589 patients had negative reactions to nickel sulfate on both sides of the back. According to the data shown in Table I, the calculated reproducibility of positive nickel reactions was 99.2% and the RI was 0.91. Reactions to nickel sulfate of identical strength on both sides were seen in 97.8% of all patients with at least one non-negative reaction.

Table I. *Numbers of patients in relation to their reactions to nickel sulfate and potassium dichromate obtained with the 2 test strips attached to the right and left side of the back*

Test strip right side	Test strip left side					
	neg.	i	q	+	++	+++
	Nickel sulfate					
neg.	183	0	0	0	0	0
i	0	0	1	0	0	0
q	0	0	18	0	0	0
+	1	0	0	133	4	0
++	0	0	0	0	166	0
+++	0	0	2	0	1	81
	Potassium dichromate					
neg.	388	0	0	0	0	0
i	0	7	0	0	0	0
q	0	2	63	0	6	4
+	2	0	0	92	0	0
++	0	0	0	6	14	0
+++	0	0	0	0	6	0

neg.: negative reaction; i: irritant reaction; q: questionable reaction; +: weak positive reaction; ++: moderate positive reaction; +++: strong positive reaction.
All patients had a positive history of nickel allergy ($n = 589$). Tests were done with the TRUE-test® system, and the data presented relate to readings on day 3.

Table I also shows the corresponding results obtained with the dichromate patches. As anticipated, fewer patients (130 out of 589) showed at least one allergic reaction to dichromate than to nickel. The reproducibility of the positive dichromate patch-test reactions was lower than that of the nickel patch-test reactions (90.8%) and the RI was markedly lower for dichromate (0.23) than for nickel. Identical reactions to dichromate on both sides were obtained in 87.1% of all patients with at least one non-negative reaction.

Table I also shows in detail the different numbers of combinations of allergic, questionable and irritant reactions elicited by the same allergens in the same patients due to the synchronous testing with 2 test strips on both sides of the back. These figures show that questionable and irritant reactions occurred more often with potassium dichromate than with nickel sulfate. Most of the questionable and irritant reactions were also reproducible. However, 10 patients showed a combination of a questionable plus a positive reaction to dichromate. Furthermore, even moderate (++) or strong (+++) reactions obtained with an allergen on one test strip were not always linked with a positive reaction to the same allergen on the other test strip.

DISCUSSION

This analysis assessed the reproducibility of patch-test reactions to nickel sulfate and potassium dichromate in a large number of patients. The patch-test system used is highly standardized (17, 22), reducing the technical variability to a minimum, and focus was placed on the synchronous intra-individual reproducibility. Furthermore, a reading bias was excluded by means of a double-blind randomized protocol. Therefore, the data can be considered to be a valid basis for approaching true synchronous patch-test reproducibility.

The reproducibility of patch tests was very high for both allergens in the analysis. In only 0.8% of the patients reacting to nickel and 9.2% of those reacting to dichromate was an allergic reaction on one side of the back at variance with another reaction on the other side. This is a better reproducibility than reported by most previous studies (2–4, 6–8, 10, 13, 15), many of which applied test chambers filled by the investigator. Similar values were obtained only in studies with considerably smaller numbers of positive patients (9, 11) and/or when reading was not blinded (5, 9). Since the present data were derived from a blinded attachment of randomized test strips and included a large number of patients with allergic reactions to nickel sulfate and potassium dichromate, the results presumably do not overestimate the reproducibility of the patch tests in question.

The reproducibility of questionable and irritant reactions in this analysis also appeared to be satisfactory. However, owing to the often subjective and very difficult distinction between weak irritant, questionable and weak allergic reactions, their reading by different dermatologists is likely to lead to divergent interpretations. Ideally, patch tests should therefore elicit as few questionable and irritant reactions as possible, so that a RI near to 1 will be obtained (19, 20). In this analysis the RI of nickel sulfate (0.91) came very close to this aim, whereas that of potassium dichromate was much lower (0.23). This reflects a considerably higher proportion of potentially

misleading questionable and irritant reactions elicited by the dichromate patches than by the nickel sulfate patches, and explains why a lower percentage of patients responded with completely identical reactions on both sides to dichromate than to nickel. Although the dichromate patch test gave highly reproducible results when read by the same person, as was the case in this analysis, efforts should be made to reduce its tendency to elicit questionable and irritant reactions and thereby to minimize the likelihood that readings by different dermatologists will yield different results. A slightly higher dichromate concentration could be checked for this purpose.

The finding of different RIs for the patches with nickel sulfate and potassium dichromate confirms earlier observations that in addition to other factors (12) patch-test reactivity and reproducibility are dependent on the allergen (11, 13, 15). In agreement with the present, patch testing with nickel sulfate was more reliable than patch testing with most other allergens in several previous studies (11, 13, 15). In view of these allergen-related differences, it is advisable not to speak of patch-test reproducibility in general but always to refer to the particular preparation of allergen and method assessed.

In conclusion, this study showed that a very high reproducibility of synchronous epicutaneous testing can be achieved with an appropriately standardized patch-test system. The nickel patch test used in this study already appears to be very satisfactory in this respect, whereas the dichromate patch test should be improved. Furthermore, patch-test reproducibility needs to be evaluated separately for each distinct preparation of allergen and test system.

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