

Patch testing with nickel sulfate: comparison between 2 nickel sulfate preparations and 2 different test sites on the back

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Among patients routinely undergoing patch testing for suspected allergic contact dermatitis (ACD), nickel is the most frequently sensitizing hapten, with a clear predominance in the female population. However, some patients who report the appearance of dermatitis upon exposure to metal objects show negative patch test results to a nickel sulfate 5% pet. application. In some cases, a positive response to nickel can be observed simply by repeating the patch test. The objective of our study was to assess if, during routine patch testing, positive responses to nickel sulfate are missed owing to contingent problems, referring to application site, patch test execution or variations in skin reactivity. To this end, we applied 2 different patch test materials containing nickel sulfate 5% pet. to 3040 consecutive patients, undergoing patch testing for suspected allergic contact dermatitis, during the same session. The rôle of the test site was also investigated by applying the preparation on 2 different sites of the back in 30 patients. Of the whole, 612 patients (20%) showed positive patch test responses. The 2 nickel materials were almost equivalent: 78% of nickel-sensitive patients had positive reactions to both, whereas 11% showed a positive response to 1 preparation alone. No variations in patch test responses in relation to application site were observed. Our data show that false-negative patch test responses to nickel are frequent. The use of 2 different preparations during the same patch test session increases the response rate by 10%.

Key words: nickel sulfate; patch test reproducibility; test site; false-negative patch test responses.
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Among patients routinely undergoing patch testing for suspected allergic contact dermatitis (ACD), nickel is the most frequently sensitizing hapten, with a clear predominance in the female population (1–5). A 5% nickel sulfate concentration and petrolatum as a vehicle in patch testing is regarded as the most reliable preparation, since it elicits a large number of positive responses, with few irritant reactions (6–9). Some patients who report the appearance of dermatitis upon exposure to metal objects show negative patch test results to a 5% nickel sulfate application. By employing different methods to increase nickel bioavailability, a fair number of positive responses can be detected in these false-negative responders (6, 10–19). However, in some cases, a positive response can be observed simply by repeating the patch test (17). Therefore, some negative responses to the first patch test are probably due to technical errors, such as application of an insufficient amount of

allergenic material, defective occlusion, or an uneven distribution of the allergenic material in the patch-test preparation (20). Moreover, transient general or local skin hyporeactivity cannot be ruled out.

The objective of our study was to assess if, during routine patch testing, positive responses to nickel sulfate are missed owing to contingent problems, referring to application site, patch test execution or variations in skin reactivity. To this end, during the same session, 2 different patch test materials were applied on the same patients. The rôle of the test site was also investigated by applying the preparation on 2 different sites on the back in 30 patients.

Patients and Methods

During a 19-month period (1994 July – 1996 December), 3040 consecutive patients (1117 male and

Table 1. Patch test responses to nickel sulfate 5% pet. in 612 nickel-sensitive patients (=100%)

Company	No. patients with positive responses	% positive responders
Hermal-Trolab and FIRMA	478	78.1
Hermal-Trolab	69	11.27
FIRMA	65	10.62
total	612	100

1923 female), aged 1 to 75 years, undergoing patch tests with the GIRDCA (Italian Research Group on Contact and Environmental Dermatitis) standard series for suspected ACD, were investigated for nickel allergy, employing 2 nickel preparations: nickel sulfate 5% pet. provided by the Hermal-Trolab Company (Germany) and nickel sulfate 5% pet. provided by the FIRMA Company (Italy).

Nickel sulfate patch tests were prepared by transferring an amount of material corresponding to 20 ± 1 mg from the syringe to the Finn Chamber, which was weighed. Thus, nickel sulfate 20 mg

pet., contained in a Finn Chamber volume of 200 μ l, were applied to a 50 mm² skin area.

Patch tests were applied to the healthy skin of the back, using Finn Chambers (Epitest, Finland) on Scanpor tape (Norgesplaster, Norway), for 72 h; readings were performed at 75 and 96 h (21). The 1st preparation was applied on the upper left side of the back, whereas the 2nd one was applied on the lower right. In 30 patients who showed positive patch test results to 1 patch test material alone (15 to nickel from Hermal-Trolab and 15 to nickel from FIRMA), a cross-application of the 2 preparations was performed, with the Hermal-Trolab material applied to the lower right and the FIRMA material to the upper left, after a 1–2 month period from the 1st test.

Results

612 (20.13%) out of the 3040 patch tested patients were contact-sensitized to nickel. Among these, 478 (78.10%) showed positive reactions to both haptens, whereas in 69 (11.27%) and in 65 subjects

Table 2. Nickel patch test results in 30 patients reacting to 1 nickel preparation alone (15 subjects to nickel from Hermal-Trolab, and 15 to nickel from FIRMA)

Patient no.	1st patch test: patch test response		2nd patch test: patch test response	
	nickel Hermal-Trolab upper left	nickel FIRMA lower right	nickel Hermal-Trolab lower right	nickel FIRMA upper left
1	++	–	+++	–
2	++	–	+++	–
3	++	–	+++	–
4	++	–	+++	–
5	++	–	+++	–
6	++	–	+++	–
7	++	–	+	–
8	++	–	+	–
9	++	–	+	–
10	+++	–	++	++
11	++	–	++	++
12	++	–	+++	+++
13	++	–	+++	+++
14	++	–	+++	+++
15	+++	–	–	++
16	–	+++	–	+++
17	–	++	–	++
18	–	++	–	++
19	–	++	–	++
20	–	++	–	++
21	–	+++	–	++
22	–	++	–	+
23	–	++	–	+
24	–	++	++	+++
25	–	++	++	+++
26	–	++	++	+++
27	–	++	+++	+++
28	–	+++	+++	+++
29	–	++	+++	–
30	–	++	++	–

(10.62%), positive responses were detected only to the Hermal and the FIRMA material, respectively (Table 1).

The intensity of the patch test responses (++ or +++), evaluated according to the ICDRG guidelines (22), was the same in 427 out of the 478 patients positive to both nickel materials, whereas it was different in the remaining 51 subjects. 41 of these showed ++ reactions to the Hermal-Trolab material and +++ responses to the FIRMA material, whereas in 10 cases, the opposite was observed. Table 2 illustrates patch test results in the 30 patients (15 responding positively to nickel from Hermal-Trolab and 15 to FIRMA) undergoing cross-application of the 2 patch test materials: on re-patch testing, most of the patients showed the same response as in the 1st test, whereas 5 subjects in both groups (patients nos. 10–14 and 24–28) reacted positively to both nickel haptens. 2 patients, who, at the 1st patch test, showed positive responses to the FIRMA nickel alone (patient nos. 29 and 30) and 1 subject reacting positively only to the Hermal-Trolab nickel (patient no. 15), when retested, showed an inversion of the patch test response.

Discussion

Going on literature data, negative test results in subjects with metal intolerance are quite common (10–19). Mistakes in performing and reading patch tests or poor quality patch test material are the most common causes of this. Both an uneven distribution of the allergen in petrolatum preparations, giving rise to an insufficient concentration of nickel in the patch test material (20), and the quantity of allergen per unit area (23), can be relevant to effective patch tests.

Variations in the local (e.g., tanning, topical corticosteroid use, etc.) or the general immunological state (e.g., immunological disorders, immunosuppressive therapies, etc.), together with differences in skin reactivity depending on the skin site (24–28), should also be considered.

Less than 7% of nickel sulfate in pet. enters the skin from standard patch tests (29), and the bioavailability of an allergen during patch testing can be influenced by variables such as intrinsic penetration capacity, concentration, vehicle, occlusivity of patch test system and tape, and exposure time (9, 17–19, 30, 31). Higher hapten concentration, skin pretreatment, or intracutaneous administration have been suggested as possible means for increasing bioavailability (16–19). By performing pretreatment of the test area before nickel sulfate application, both with 1-day occlusion by an empty Finn Chamber and a 0.5%

sodium lauryl sulfate 24h-patch test, penetration of nickel was enhanced and an increase in the positive response rate, respectively, of 33% and 50% was observed (17–19). Other unrecognized factors are probably responsible for unreproducibility of patch tests. By symmetrically applying Epiguick in duplicate on both sides of the back, Lachapelle observed that the rate of non-reproducible positive results to the overall number of positive reactions was 4.2% (32), whereas, by performing Finn Chamber patch tests with the same procedure, a non-reproducibility rate of 9.5% was obtained by Lindelof (33). Moreover, an intra-individual reactivity variation, without any tendency to increase or reduce such reactivity over time, was demonstrated by Hindsen et al. (34), by repeating patch tests in the same subjects on 3 different test occasions.

Our results, showing a 20% sensitization rate to nickel among the population routinely undergoing patch tests, are in line with previous literature data (1–5). Among our 612 nickel-sensitive patients, 478 (78.10%) showed positive responses to both haptens, whereas 69 (11.27%) and 65 (10.62%) reacted to the Hermal and the FIRMA preparation, respectively (Table 1); these results indicate that if we had used only 1 patch test material, approximately 10% of the patients investigated would have been declared nickel-negative. This mistake is clearly not ascribable to the quality of the patch test material, since the number of subjects responding positively to 1 preparation alone was the same for both materials and, at re-testing, 33% of patients responded positively to the preparation inducing a negative response at the 1st test. However, in some patients, the patch test response seemed to have its own specificity: 9 out of 15 patients positive only to the Hermal-Trolab preparation and 8 out of 15 subjects positive only to the FIRMA preparation showed the same result at the 2nd patch test (Table 2). Differences in hapten preparation or vehicle composition influencing nickel ion bioavailability can only partially explain these results.

Previous studies, analyzing variations in patch test responses according to the application site, reported a higher reactivity of the skin of the upper back with respect to the lower back (25–27). In contrast, we did not notice any variation in patch test responses related to application site, and the same number of positive responses was observed, when, at re-patch testing, the application site had changed. However, we have to consider that, in this study, the so-called “lower right” position on the back represents in reality the lower portion of the upper back on the right, at a skin site where the latter allergens of the standard series are routinely applied.

Concerning the comparison of the intensity of 2 successive patch test reactions in the same patient, ++ and +++ responses were almost equivalent, i.e., on re-patching, responses were frequently evaluated as ++ reactions in patients with +++ responses at the 1st patch test and vice versa. A ++ reaction was evaluated as a + reaction at the 2nd patch test in 5 cases (patient nos. 7, 8, 9, 22, 23). This observation stresses the importance of evaluating weak positive responses to nickel patch tests carefully, since they may indicate an effective sensitization state of the patient.

Our data show that false-negative patch test responses to nickel are frequent. If a history of intolerance to nickel objects is given by patch test-negative patients, skin pre-treatment (17–19), testing with different nickel salts (11–12) and an increase in the nickel salt concentration (6, 14) are suggested. However, the use of 2 different preparations during the same patch test session increases the response rate by 10%. Therefore, considering that $\frac{1}{5}$ of the patients undergoing patch tests are potential nickel-reactors, this procedure may be recommended during routine examination.

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