

A Retrospective Study of Aimed Patch Testing With Aqueous Nickel Sulfate Hexahydrate at 30% and 15% in Patients With Dermatitis

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Background: Sometimes, patients with a history of metal intolerance react negatively or doubtfully to nickel at patch testing.

Objective: The aim of the study was to investigate whether aqueous nickel sulfate hexahydrate at 15% and 30% traces more contact allergy than the nickel preparation in the baseline series at 5%.

Methods: In the period 1995–2015, more than 800 of 16,059 patients with a negative or doubtful patch test reaction to the petrolatum preparation of nickel at 5% on the day 3 reading were additionally tested with aqueous nickel at 15% and/or 30%.

Conclusions: In this retrospective study with aimed patch testing with aqueous nickel solutions, significantly more ($P < 0.001$) contact allergy was obtained as compared with the 5% preparation in petrolatum. The 30% solution was significantly better ($P < 0.001$) than the 15% solution. To demonstrate that patch testing with nickel at 15% or 30% is better than the present testing with 5% requires simultaneous testing with the 3 nickel preparations.

When reading patch test reactions, seemingly doubtful reactions may represent irritant reactions or weak allergic reactions in which the morphology does not justify the classification of allergic reactions. In these, there might be a need to confirm or rule out contact allergy as the cause of the doubtful reaction. The sensitizer may be tested not only repeating the same test preparation, since reactivity varies,^{1–4} but also in a different vehicle⁵ or at a higher concentration,⁶ actual dose per area of the skin.⁷ For many metals, intracutaneous testing has been an option,⁸ but it has unfortunately become so complicated to obtain intracutaneous solutions from pharmacies, at least in Sweden, that it is virtually impossible to test patients intracutaneously in daily practice. Sometimes, a nickel dermatitis is suspected from the history, but the patch test is negative. When the first author (M.B.) of this article was faced with these problems in the early 1980s at the Department of Occupational Dermatology at Lund Hospital, one possibility would have been increasing the patch test concentration, actually the dose per square centimeter. However, he was taught that the concentration of nickel sulfate hexahydrate in petrolatum should not be increased above the

used 5% because of the polarity of the nickel salt, which is influencing the “solubility” of nickel in petrolatum. However, nickel sulfate has successfully been tested at 10% in petrolatum.⁹ Already at 5%, the nickel salt may aggregate in petrolatum forming visible green aggregates. Testing with such a preparation means testing with 100% nickel where you have the aggregates and hence a substantial risk of getting an irritant reaction. The tendency to form aggregates increases with the concentration of nickel sulfate hexahydrate. In this situation, M.B. started to test aqueous nickel sulfate hexahydrate at 15.0% and 30.0% in his daily practice. This testing was many times successful with negligible adverse reactions including no patch test sensitization (active sensitization). Results from the testing with nickel at 15% and 30% have previously been reported in a comparison with different occlusion times where the lower occlusion time of 5 hours was compensated with a higher nickel concentration at 30%.¹⁰ In this article, our experience with patch testing with aqueous nickel at 15% and 30% is reported.

MATERIAL AND METHODS

Patch Test Preparations

Nickel sulfate hexahydrate is included in the Swedish baseline test series at 5% wt/wt in petrolatum. This series is purchased from Chemotechnique Diagnostics, Vellinge, Sweden. Aqueous solutions of nickel sulfate hexahydrate from Acros Organics, Geel, Belgium, have been made at our department at 15.0% and 30.0% wt/vol. Fresh solutions were made up annually on an average. The nickel solutions were kept refrigerated when not used. There were no remarks

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when a few atomic absorption spectrometry investigations were performed to control the nickel concentrations in the aqueous solutions during the investigative period.

Patients

In the period 1995–2015, 16,059 (6021 males, 10,038 females) patients with a suspected allergic contact dermatitis have been patch tested with the Swedish baseline series including nickel sulfate hexahydrate in petrolatum at 5%. During this period, aimed testing with the aqueous nickel sulfate hexahydrate solutions at 15.0% and/or 30% was performed in 831 and 862 individuals, respectively. Both aqueous solutions were tested in 793 individuals. There were 647 of 670 females and 184 of 192 males tested. Mean age of the females was 59 years, and that of the males, 60 years.

Patch Testing

During the whole investigation period, the Finn chamber technique with small chambers having a diameter of 8 mm was used. The chambers were mounted on Scanpor tape. Twenty milligrams of the petrolatum preparation and 15 micropipetted μL of the respective aqueous solution were applied to the test unit. The tests were applied on the back, and they were removed after 48 hours. The test reading was classified according to the International Contact Dermatitis Research Group¹¹ and performed on day (D) 3 or 4 and D7. A positive test required at least erythema and infiltration covering the whole test area. Test reactions localized in the follicles or perifollicular without infiltration and erythema covering the whole test area were classified as doubtful or irritant, depending on the morphological features present. The aimed testing with aqueous nickel sulfate hexahydrate was virtually always performed on the first reading and read only once on D7 (“D3/4” after the application of the aqueous test solutions).

Statistical Calculations

In those tested simultaneously with the baseline nickel salt in petrolatum and the 2 aqueous solutions, pairwise comparisons were made of the positive reactions using McNemar test, 2-sided.

RESULTS

No patch test sensitization to nickel was noted during the investigative period. The number of positive reactions to the respective nickel preparation, 5% in petrolatum and 2 aqueous solutions at 15.0% and

30.0%, and the *P* values for the pairwise comparisons of the positive reactions for these 3 nickel preparations are given in Table 1. The contact allergy rate to nickel was 20.3% in those 831 tested with nickel sulfate hexahydrate at 15%, and the corresponding figure for those 862 tested with the same solution at 30% was 26.9%. Simultaneous positive reactions to both aqueous nickel solutions were noted in 145 of 793 individuals. In the subjects tested with both 5% and 15%, 80 positive reactions (9.6%) were registered, and the corresponding figures for those tested with 5% and 30% were 94 (10.9%). Both aqueous solutions gave significantly more positive reactions than the petrolatum preparation ($P < 0.001$ for both comparisons), and the aqueous solution at 30% gave significantly more reactions than the solution at 15% ($P < 0.001$).

DISCUSSION

The result of this retrospective study demonstrates that it is possible to test aqueous nickel sulfate hexahydrate at 15% and 30% (4.5 and 9.0 mg/cm², respectively) without causing any active sensitization and with virtually no other adverse reactions. The absence of irritant reactions can most likely be explained by the fact that the nickel salt is dissolved in the vehicle, whereas there may be aggregates of nickel salt (“100%”) in a petrolatum preparation. Furthermore, the contact allergy rates are higher than those for the routinely tested nickel preparation in petrolatum where an average contact allergy rate was 18.4% for those 16,059 patients tested during the investigative period. Surprisingly, many of those with a doubtful or negative reaction on D3/4 tested positively to the aqueous solutions. The perception over the years has been that many of these positive reactions to the aqueous nickel solutions have been clinically relevant, although no attempt has been made to assess the clinical relevance more systematically in those tested with the aqueous solutions.

This study clearly demonstrates that patch testing with aqueous nickel sulfate hexahydrate at 15% and 30% is a way to confirm or rule out contact allergy to nickel as the cause of doubtful test reactions to nickel and to establish contact allergy to nickel in those with a history of nickel dermatitis but with a negative test to nickel in the baseline series. This result is not surprising because repeated patch testing with nickel for a several months' period has shown that nickel-allergic patients may test negatively occasionally.^{1–3} False-negative reactions may also appear in nickel-sensitive individuals tested simultaneously with multiple nickel preparations.¹²

The present study does not give any consistent information on clinical relevance. It does, however, raise the question whether

TABLE 1. The Number of Patients With Positive Reactions to Nickel Sulfate Hexahydrate ($\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$) Tested at 15.0% and 30.0% in Aqua and the Number of Simultaneous Positive Reactions to 5% $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ in Petrolatum

Concentration	No. Tested (Male/Female)	No. Positive (Male/Female)	No. Also Positive to 5% $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ in Petrolatum (Male/Female)	<i>P</i>
15%	831 (184/647)	169 (31/138)	80 (8/72)	<0.001
30%	862 (192/670)	232 (43/189)	94 (9/85)	<0.001

aqueous nickel sulfate hexahydrate at 15% or 30% should be used routinely in baseline series for patch testing. To establish this requires studying in consecutive dermatitis patients tested simultaneously with 5% nickel in petrolatum and the aqueous nickel solutions at 15% and/or 30%. If this testing results in significantly more contact allergy to the aqueous solutions than to the presently used petrolatum preparation, the next step before changing the nickel test concentrations in baseline patch test series is to investigate the clinical relevance of the contact allergy demonstrated by patch testing with only 15% and/or 30% and not 5%.

This can be performed in a randomized, controlled, repeated open application test, similarly to what has been performed with formaldehyde.¹³ These investigations have been initiated at our department.

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