

Oral Challenge with Nickel and Cobalt in Patients with Positive Patch Tests to Nickel and/or Cobalt

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During a 3-year period, 146 patients with positive patch tests to nickel and/or cobalt, for whom a systemic cause of dermatitis was suspected, were challenged orally with a single dose of 2.5 mg nickel given as nickel sulphate and 1 mg cobalt given as cobalt sulphate using a double-blind, placebo-controlled method. No following-up was possible for 2 patients. Seventy-five of the remaining 144 (52%) had flares of their dermatitis after challenge with nickel and/or cobalt, while 45 patients (31%) had no reaction and 24 (17%) reacted only to the placebo or to the placebo in combination with nickel or cobalt. Seven out of 13 patients with positive patch tests to cobalt experienced flares of their dermatitis only after challenge with cobalt. (Received January 23, 1987.)

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There has been some discussion of the role played by ingested nickel in the chronicity of hand eczema, particularly for patients allergic to nickel (1, 2). Simultaneous allergy to nickel and to cobalt is frequent, and cobalt has been thought to be of significance in the persistent hand eczema of patients with positive patch tests to nickel as well as to cobalt (3, 4). Animal experiments support these hypotheses (5). The two allergens may potentiate each other (6).

We wish to report the results of routine oral challenge with nickel and cobalt in a group of patients who had dermatitis, which was thought to be systemically induced, and contact allergy to nickel and/or cobalt as demonstrated by patch testing.

MATERIAL AND METHODS

From May 1, 1983, to April 30, 1986, 146 patients with positive patch tests to nickel and/or cobalt for whom a systemic cause of the dermatitis was suspected either because of the morphology of the dermatitis or because the physical avoidance of the allergen did not improve the dermatitis, were challenged orally with 1) a single dose of 2.5 mg nickel, 2) 1 mg cobalt given as tablets containing salts of the metals, and 3) a placebo. The challenge procedure was carried out in a double-blind, randomized fashion, and the three tablets were given at intervals of one week. If a flare occurred, the next tablet was not given until the flare had subsided.

A flare of the dermatitis within 4 days after ingestion of a tablet was considered to be a positive reaction. The patients themselves noted whether or not an aggravation of their dermatitis had taken place.

RESULTS

It can be derived from Table I, that 131 patients had a positive patch test to nickel (97 to nickel alone, 34 to nickel and cobalt). Fifty-five of these 131 patients reacted to oral challenge with nickel, while 23 of them reacted to the placebo or to one or both metal salts as well as the placebo. This difference is statistically significant ($\chi^2=18.693$, $df=1$, $p<2\times 10^{-5}$).

Forty-two patients had a positive patch test to cobalt (13 to cobalt alone, 34 to nickel and cobalt). Twenty-eight of the 47 had a flare of dermatitis after oral challenge with cobalt, while 5 of the 28 reacted to the placebo or to the placebo as well as one or both metal salts. This difference in reactivity is statistically significant ($\chi^2=24.702$, $df=1$, $p<10^{-6}$).

For those who reacted to oral challenge, the flares most commonly occurred 1 to 2 days after the challenge and they were usually of a severity which corresponded to the "spontaneous" flares to which the patients were accustomed. Most flares subsided in approximately one week. For one patient the flare persisted and short-term systemic corticosteroid treatment was required.

The most common morphology of dermatitis was recurrent vesicular hand eczema, seen in 53 patients. Twenty-six had other types of hand eczema; eczema of the trunk, commonly nummular eczema, occurred in 28 patients, while 39 had eczema at other sites. Of these 39 patients, 10 who reacted to the challenge had the following more unusual morphologies: 2 had lesions of the extremities similar to the vasculitis described by Hjorth (7), 2 had cheilitis, 3 had eczema of the eyelids and 3 had anogenital pruritus and eczema.

A few curious reactions to the challenge were seen such as an eruption on the thighs of a nickel allergic woman at sites of garter clasps after what was discovered to be the nickel tablet. She had not used garters for more than 20 years. She was given the challenge because of a vesicular hand eczema, which also flared. Another woman had generalized pruritus and a 30×30 cm erythematous edematous flare of the abdomen at the site of previous contact with metal jeans buttons. This flare occurred a few hours after challenge with what was discovered to be the nickel tablet. The vesicular hand eczema which was the indication for the challenge flared 2 days after ingestion of the tablet.

The dermatitis of two patients who had positive patch tests to cobalt flared after oral challenge with cobalt, but not after oral challenge with nickel. They experienced aggravation both of their dermatitis at the sites of nickel contact and of the hand eczema which was the indication for the challenge.

Of the 13 patients with positive patch tests to cobalt only, 6 had recurrent vesicular hand eczema. Three of these patients reacted to the oral challenge with cobalt.

DISCUSSION

In the current study, fewer relevant reactions and more placebo reactions were seen compared with a previous study in which the same dose of nickel was used (8). The reason for this discrepancy could be the selection of patients, since only approximately one-third of the patients who took part in the current study had recurrent vesicular hand eczema (contrary to all patients of the 1978 study). The current study purposely included all types of dermatitis which might be systemically induced in order to demonstrate whether oral challenge is a useful routine procedure in the diagnostic work-up of nickel and/or cobalt allergic patients.

The number of placebo reactions indicates the importance of placebo-controlled challenges. Ideally challenges should be repeated, but the time and effort involved on the part of both patient and physician and the risk of increased reactivity after each challenge makes repeated testing impractical for routine investigations.

Thirty-one (63%) of 49 patients in a recent controlled study reacted to oral challenge with 2.24 mg nickel. Fifteen of the patients who reacted to nickel had dyshidrotic eczema, while 10 had periorbital eczema (9). Thirteen (65%) of 20 nickel allergic patients reacted to nickel in a placebo-controlled study of oral challenge with 2.24 mg nickel (10).

These findings are in contrast to the experience of Burrows *et al.* who found no

difference between the reactions to nickel and placebo when oral challenge was carried out with up to 4 mg nickel (10). Gawkrödger et al. found no difference between reactions to nickel and placebo for doses of 0.4 and 2.5 mg nickel, while 4 of 6 patients reacted to 5.6 mg nickel (12). In the Gawkrödger study, groups of only 10 patients were challenged with doses of 0.4 and 2.5 mg. The results of this study and that carried out by Cronin et al. (13) suggest a dose-response relationship to oral challenge with nickel. A study by Jordan & King in which 0.5 mg nickel was given on 2 consecutive days showed a reproducible reaction in one of 10 patients (14). This supports the idea of a dose-response relationship.

No severe untoward reactions were seen when a similar challenge procedure was carried out in a large series of patients with negative patch tests (15, 16). In studies published thus far, only few side effects have been encountered in patch test positive patients. With this in mind, and considering the information provided by a positive challenge test, the procedure should be considered a useful diagnostic test and included as part of the work-up of patients who are allergic to nickel and/or cobalt and have morphologies of dermatitis indicating an endogenous cause. When the patients have actually experienced an aggravation after oral challenge with nickel, thus making an elimination diet a logical treatment modality, there is in our opinion better cooperation on the part of most patients, when tedious treatments like restrictive diets are instituted.

The predominance of reactions to cobalt among patients with positive patch tests to both cobalt and nickel and the reactivity to cobalt in some nickel sensitive patients (Table I) gives rise to some questions. Is the oral challenge or the patch test the more reliable procedure? Should dermatologists adapt the diagnostic approach used by some allergists, that is, the use of a diagnostic scoring system. In such a system the history of the patient, the results of patch tests and the results of challenge procedures would be utilized in making a definite diagnosis of allergic contact dermatitis for patients who do not have obvious reactivity to one of the diagnostic tests.

Previously, some doubt has been expressed as to the reliability of the commonly used patch test with 5% nickel sulphate in petrolatum in order to identify nickel allergy accurately (17).

The interplay between nickel allergy and cobalt allergy has also been studied, and there is some evidence that the prognosis of hand eczema is worse, when concomitant nickel and cobalt allergy is seen (4).

Table I shows that 47 of 97 (48%) of the patients with positive patch tests to nickel only, experienced a flare of dermatitis after oral challenge as compared with 19 of 34 (59%) of those with positive patch tests to both nickel and cobalt and 9 of 13 (69%) of those with positive patch tests to cobalt only.

Menné has brought up the point that cobalt is much more easily absorbed from the

Table I. The reactivity of 144 patients to oral challenge with nickel and cobalt

Positive patch tests to	Results following oral challenge					
	Ni (Ni+placebo)	Ni+Co (Ni+Co+placebo)	Co (Co+placebo)	Placebo only	Neg.	Total
Ni	31 (3)	8 (3)	8 (5)	8	31	86 (11)
Ni+Co	4 (0)	5 (1)	10 (3)	0	11	30 (4)
Co	1 (0)	1 (0)	7 (1)	0	3	12 (1)
Total	36 (3)	14 (4)	25 (9)	8	40	128 (16)

gastro-intestinal tract than nickel (3). Therefore, even though the dose of cobalt is only 1 mg compared with the 2.5 mg nickel used for the oral challenge, it might be that the oral challenge reflects the cause of the dermatitis more accurately than the patch test and that the patient with a positive patch test to nickel and a reaction to oral challenge with cobalt should actually be advised to reduce the intake of cobalt.

More varied cutaneous testing, like the use of intradermal tests or patch testing after stripping, could possibly resolve this question, although we did not previously have impressive results using these procedures in patch test negative patients who reacted to oral challenge with metal salts (17).

The oral test procedure should probably also become more sophisticated by the use of either repeated challenges or challenges with the substances in question in a biologically more relevant composition. Challenge with a mixture of nickel and cobalt may also be relevant. Single dose challenge with an inorganic salt of the metal is probably physiologically the least efficient way to administer the challenge. However, if test procedures of this type are to become routine, it is necessary that they be simple and practical to use.

A challenge dose of 2.5 mg nickel was maintained in the current study even though that dose is significantly higher than the mean daily intake of nickel. It is possible that the peak intake of nickel is of greater importance than the mean intake, and due to the excretion of nickel in sweat there may intermittently be a high concentration of nickel in palmar skin. The bioavailability of various types of nickel is largely unknown. In order to overcome all these variables, it may be relevant to challenge with doses of nickel which are substantially higher than the mean daily intake.

The current study also gives the results of a blind challenge procedure for patients with positive patch tests to cobalt alone. Seven of 13 of these patients had flares of their dermatitis after challenge with cobalt. This indicates that the dose of 1 mg cobalt is suitable for oral challenge and that this procedure is useful in detecting whether the dermatitis of patients with cobalt allergy is systemically induced or aggravated. We have previously seen similar reactions in an open study when 2 of 5 patients with positive patch tests to cobalt reacted to 1 mg cobalt (16). It is difficult to test large groups of this type of patient as isolated reaction to cobalt is rare (19).

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