INTERNATIONAL JOURNAL OF IMMUNOPATHOLOGY AND PHARMACOLOGY Vol. 19, no. 3, 593-600 (2006)

A CLINICAL TRIAL OF ORAL HYPOSENSITIZATION IN SYSTEMIC ALLERGY TO NICKEL

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Received March 15, 2006 – Accepted May 9, 2006

Nickel allergy is the most common contact allergy. Some nickel-sensitive patients present systemic (cutaneous and/or digestive) symptoms related to the ingestion of high nickel-content foods, which significantly improve after a specific low nickel-content diet. The etiopathogenetic role of nickel in the genesis of systemic disorders is, furthermore, demonstrated by the relapse of previous contact lesions, appearance of widespread eczema and generalized urticaria-like lesions after oral nickel challenge test. The aim of this study is to investigate the safety and efficacy of a specific oral hyposensitization to nickel in patients with both local contact disorders and systemic symptoms after the ingestion of nickel-containing foods. Inclusion criteria for the recruitment of these patients were (other than a positive patch test) a benefit higher than 80% from a low nickel-content diet and a positive oral challenge with nickel. Based on the previous experiences, our group adopted a therapeutic protocol by using increasing oral doses of nickel sulfate associated to an elimination diet. Results have been excellent: this treatment has been effective in inducing clinical tolerance to nickel-containing foods, with a low incidence of side effects (gastric pyrosis, itching erythema).

Nickel allergy is the most common contact allergy because nickel is present in various daily-use accessories and utensils (coins, pots and pans, watches, earrings, etc.) and its widespread use favors sensitization (1). The prevalence of nickel allergy has shown a constant rise in industrialized countries, about 10-15% (with peaks up to 20%) in females, and 4-7% in males (2-4). Female predominance is probably due to a more frequent exposure to metal jewellery and to the higher incidence of allergic diseases in women.Nickel allergy is a delayed, cell-mediated hypersensitivity, presenting with local eczematous lesions after skin contact with nickel and it can be diagnosed by patch tests. Some reports in literature describe how the use of dental and orthopedic prostheses may provoke generalized eczema (5-6) and urticaria (7-8) in nickel-allergic patients.

Nickel is an essential element in the diet: its daily intake is about 300 μg, and vegetables are the main source (9-11). Some cases have been described of nickel-sensitized patients with cutaneous systemic disorders correlated to the ingestion of high nickel-content foods: generalized eczema (12-13), recurrent vesicular hand eczema (pompholyx) (14-15), itching erythema with mild

Key words: nickel allergy, systemic reaction, oral desensitisation, clinical tolerance

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0394-6320 (2006)

edema of the gluteal area and of the major flexures (baboon syndrome) (16-17) and generalized urticaria (12, 18-20). Moreover, studies on the histological modifications of the gastrointestinal mucosa have shown a marked inflammatory infiltrate, mainly lymphoplasmacellular, associated with duodenum villus deformation and deepening of the crypta, in some subjects with delayed allergy to nickel sulfate after oral challenge test (21) and after accidental ingestion of a nickel coin (22). When the correlation between nickel allergy and systemic disorders was demonstrated, specific elimination diets were developed to reduce the daily nickel-intake, with significant improvement of symptoms in most patients (23). The etiopathogenetic role of nickel in the genesis of systemic disorders is confirmed by the relapse of previous contact lesions (24-26), appearance of widespread eczematous (14, 27) and urticaria-like general lesions (12, 19, 28) after oral nickel challenge test. A complete nickel avoidance is extremely difficult and, if prolonged, may have nutritional consequences (29-30), thus calling for the development of new therapeutic strategies.

It has clearly been demonstrated that tolerance to nickel may be induced in sensitized guinea pigs and mice, through oral administration of nickel (31-33). Van Hoogstraten administered non-toxic doses of nickel to sensitized mice, through drinking water for 1-3 weeks. The oral administration of allergens can suppress both humoral and cell-mediated responses, and complete tolerance can be maintained for two years as long as oral contact with the allergen is avoided (31, 33). The first encouraging results in humans date back to 1987 when Sjövall administered capsules containing different amounts of nickel (0.5 - 3.5 - 5 mg) to his patients for 6 weeks: the intensity of contact allergy, measured with the patch test, decreased in patients who took 3.5 and 5 mg (34).

Further studies (12, 35-36) were conducted with interesting results, on the induction of nickel tolerance by oral/sublingual administration of the allergen.

Based on these experiences in oral hyposensitization, our group successfully performed a therapeutic protocol, with increasing oral doses of nickel sulfate associated to an elimination diet, to induce tolerance to the metal in patients with both local contact symptoms and systemic disorders due to the ingestion of nickel-containing foods.

The aim of the present study is to assess the efficacy of the oral hyposensitization in systemic nickel allergy.

MATERIALS AND METHODS

Patient selection

From a series of 1086 patients (F:M=1023:63) with contact allergy to nickel enrolled between 1987-2003, we selected 290 patients (female-male ratio = 282:8), aged 5-82 yrs (mean ± SD= 31.3 ± 10.34 yrs), with personal history of recurrent systemic cutaneous (urticaria, edema, erythema, eczema) and/or digestive (nausea, gastric pyrosis, meteorism, abdominal pain, diarrhea and constipation) symptoms.

Allergy testing

After an accurate case history was recorded, patients underwent a complete allergological evaluation. Prick tests with a panel of food allergens (corn, wheat, soy, peanut, tomato, milk, lactalbumin, casein, egg (white and yellow), fish (mix), walnut, hazelnut, cocoa, olive, sunflower, pork and latex) and patch tests with the European standard series were performed.

Prick tests were performed with a Morrow-Brown needle (ALK Abellò) on the volar surface of the forearm. Negative (glycerine solution) and positive (10 mg/ml of histamine) controls were also performed. A positive response was defined as one producing a wheal greater than 3 mm in diameter at 20 min after application, without reaction to negative control.

Patch tests were checked 48-72 h after their application, in accordance with the European Environmental and Contact Dermatitis Research Group, and were considered positive if an eczematous-vesicular reaction occurred at the contact site with the allergen; the intensity was assessed with the following criteria:

a) erythema (±);
b) erythema, edema (+);
c) erythema, edema, vesicles, papules (++)
d) intense erythema, edema, confluent vesicles (+++)

To evaluate the role of nickel in provoking systemic symptoms, the patients were istructed to avoid high nickel-containing foods (Table I) (10, 37) for at least 4 weeks. Furthermore they were asked to avoid the use of stainless-steal utensils to reduce nickel contamination during cooking. Patients who reported an overall benefit (improvement of symptoms and reduced consumption of symptomatic drugs) higher than 80% from the elimination diet underwent an oral challenge test, starting with 2.5 mg and increasing the dose by 2.5 mg every 96 hours up to

10 mg. A previous test with placebo was performed. The test was interrupted and considered positive if systemic cutaneous and/or digestive symptoms occurred.

Treated and control groups

Of the eligible patients, 195 were randomly assigned to the treated group and 95 to the control group. Only 136 patients of the treated group gave their consent to the treatment. Ninety-five control patients matched for age, gender and clinical symptoms (Table II) were prescribed a nickel-free diet.

Protocol of hyposensitization

The protocol was performed in accordance with good clinical practice after being approved by our hospital's ethic Review Board. Patients who gave their fully informed written consent received 0.1 ng granules of a water-soluble nickel sulphate preparation according to the following scheme:

- 1 granule every other day for 45 days
- 1 granule/day for 45 days
- 1 granule/2 granules on alternate days for 45 days
- 2 granules/day for 45 days
- 1 granule/2 granules on alternate days for 45 days
- 1 granule/day for 45 days
- 1 granule every other day for 45 days

During the first phase the dosing was gradually increased and the patients were asked to strictly follow a low nickel-content diet. During the second phase, while progressively decreasing the dose, they had to gradually reintegrate nickel-containing foods in their diet. The whole treatment took 315 days. If symptoms relapsed, the treatment was interrupted and steroids were administered.

Follow up

Treated patients were followed up during the treatment and then after a 6-month free dietary regimen. When the treatment was completed, the patients underwent patch and oral challenge tests in order to assess any modification of both local and systemic reactivity to nickel. In the control group, patch test and oral challenge test were reassessed after 1-year low-nickel containing diet. Control patients were followed up after a 6-month free dietary regimen.

End point

The primary end point for the treated versus the control group was the complete remission of systemic symptoms during a free diet.

Statistical analyses

Pearson's chi-squared tests were used for detecting statistically significant differences between the groups. For the primary end point, the rates of complete remission of systemic symptoms for both the treatment and control groups, indicated by the experimental event rate (EER) and control event rate (CER), respectively, were calculated. The therapeutic efficacy, indicated by the absolute risk reduction rate [AAR=EER-CERT, 95% of confidence interval (CI)], relative risk reduction rate (RRR=ARR/CER, 95% of CI) and number needed to treat (NNT=1/ARR) were also evaluated.

A multiple logistic regression was performed, with benefit as dependent variable, therapy as independent variable and sex and age as confounding factors, following the backward elimination stepwise procedure. Results are presented as Odds Ratio (OR) and 95% Confidence Interval (CI). Analyses were conducted using the SPSS statistical software package (release 12.0 for Windows).

RESULTS

All 136 patients had a positive patch test to nickel sulphate and reported a significant benefit higher than 80% after a 4-week diet and a positive oral challenge test with nickel (test results are summarized in Table III).

Skin tests with food allergens were negative.

Forty-two patients (30.9%) interrupted the treatment for lack of benefits (relapse of symptoms after ingestion of nickel-containing foods).

Ninety-four patients (69.1%) completed the protocol with the following results when they came back to a free dietary regimen:

- 64 (47.0%) reported a complete remission of symptoms;
- 23 (16.9%) had symptom improvement higher than 80%, rarely presenting mild cutaneous and/or digestive symptoms;
- 7 (5.2%) had a partial benefit, reintroducing only some of these foods (limited diet).

In the control group, after a 1-yr diet, 78 patients (82.1%) presented a relapse of pre-existing systemic symptoms when nickel-containing foods were reintroduced.

The results are summarized in Table IV. The resolution rates were 69.1% and 17.9% in the treated and control groups, respectively, with an absolute risk reduction of 51.2% and a relative risk reduction of 74.1%. According to "Number Needed to Treat" (NNT), 2 treated patients are needed to have one positive outcome. The logistic regression analysis revealed a statistically significant improvement in treated versus control patients (OR: 8.29%; 95% CI: 4.07-16.89).

Table I. *Foods with high nickel content.*

Food	Nickel content (μg/g)	Food	Nickel content (μg/g)
Almond	1.5	Oat meal	0.3
Apricot	0.1	Onion	0.4
Asparagus	0.4	Oyster	0.6
Avocado	-	Maize	0.4
Baking-powder	-	Margarine	4
Beans	1.4	Mushroom	0.085
Broccoli	0.193	Mussel	0.6
Brown lentil	1.9	Pear	0.1
Buckwheat	0.3	Peanut	2.9
Carrot	0.04	Plaice	0.1
Cauliflower	0.3	Potato	0.385
Cocoa	10	Prune	0.6
Figs	0.1	Raisin	0.03
French beans	1.4	Rhubarb	0.1
Green peas	0.3	Spinach	0.2
Hazel nut	1.5	Tea	0.8
Liquorice	4.4	Tomato	0.09
Lobster	0.3	Walnut	1.5

After the hyposensitization, reactivity to nickel patch test showed no variation in 68 cases (72.3%), decreased in 17 (18%), increased in 1 (1.1%) and turned negative in 8 patients (8.6%). The oral challenge test showed an increase in tolerance to nickel in most cases: 29 (30.9%) did not react, 47 (50%) reacted to a higher dose, 17 (18%) to the same dose, while 1 patient (1.1%) showed a decrease of the threshold dose. Control patients did not show modification in reactivity either to nickel patch or to nickel oral challenge.

DISCUSSION

According to data from literature (2-4), an increase has been reported in the incidence of delayed allergy to nickel sulphate and of systemic disorders related to the ingestion of nickel-containing foods. Troost et al (35) tested the efficacy of subcutaneous treatment consisting of weekly injections of increasing doses (10^{-6}–10^{-3}) of a nickel sulphate-containing solution: during the follow up, testing did not show statistically significant results when compared to the control group. Morris (36), on the other hand, reports clinical improvement in some patients who completed a sublingual hyposensitizing treatment, but this observation was not supported by an improvement of tolerance to nickel during challenge tests. The oral route has been shown as the most effective.

Table II. *Distribution of treated and control groups, at the enrolment, according to selected variables.*

	Treatment group 136 patients	Control group 95 patients	Chi-square test for homogeneity (p=value)
Gender			
Males	3 (2.2%)	3 (3.1%)	0.689
Females	133 (97.8%)	92 (96.9%)	
Symptoms			
Systemic cutaneous			
Urticaria			
Yes	47 (34.6%)	40 (42.1%)	0.244
No	89 (65.4%)	55 (57.9%)	
Eczema			
Yes	38 (27.9%)	22 (23.1%)	0.415
No	98 (72.1%)	73 (76.9%)	
Edema			
Yes	21 (15.4%)	17 (17.9%)	0.621
No	115 (84.6%)	78 (82.1%)	
Erythema			
Yes	18 (13.2%)	15 (15.8%)	0.585
No	118 (86.8%)	80 (84.2%)	
Digestive disease			
Nausea			
Yes	3 (2.2%)	3 (3.1%)	0.692
No	133 (97.8%)	92 (96.9%)	
Vomiting			
Yes	3 (2.2%)	2 (2.1%)	1.00
No	133 (97.8%)	93 (97.9%)	
Meteorism			
Yes	7 (5.1%)	8 (8.4%)	0.320
No	129 (94.9%)	87 (91.6%)	
Abdominal pain			
Yes	6 (4.4%)	9 (9.5%)	0.124
No	130 (95.6%)	86 (90.5%)	
Diarrhea			
Yes	11 (8.1%)	7 (7.4%)	0.840
No	125 (91.9%)	88 (92.6%)	
Gastric pyrosis			
Yes	3 (2.2%)	0 (0%)	0.270
No	133 (97.8%)	95 (100%)	
Dyspepsia			
Yes	1 (0.7%)	2 (2.1%)	0.569
No	135 (99.3%)	93 (97.9%)	
Epigastralgia			
Yes	5 (3.7%)	1 (1.1%)	0.405
No	131 (96.3%)	94 (98.9%)	

Table III. *Allergological evaluation of 136 patients with systemic nickel allergy.*

Patch test with nickel sulphate	+	26 (19.1%)
	++	78 (57.4%)
	+++	32 (23.5%)
Benefit after 4 weeks-diet	80 - 100%	82 (60.3%)
	100 %	54 (39.7%)
Oral challenge test with nickel sulphate (threshold dose)	2.5 mg	62 (45.6%)
	5 mg	46 (33.8%)
	7.5 mg	11 (8.1%)
	10 mg	17 (12.5%)

Table IV. *Statistical data on efficacy obtained in the treatment and control groups.*

End points				
EER (%) (resolution rate of treatment group)	CER (%) (resolution rate of control group)	ARR (95% CI) (% of therapeutics efficacy of treatment)	RRR (95% CI) (% of therapeutics efficacy of treatment)	NNT (95% CI) (number needed to treat)
69.1%	17.9%	51.2% (40.3% - 62.1%)	74.1% (58.3% - 89.9%)	1.95 (1.65 - 2.54)

EER=experimental event rate; CER=control event rate; ARR=absolute risk reduction; CI=confidence interval; RRR=relative risk reduction; NNT=1/ARR=number needed to treat.

On the basis of the encouraging results of the previous study, we decided to investigate the safety and efficacy of a specific oral hyposensitization to nickel in patients with both local contact disorders and systemic symptoms after the ingestion of nickel-containing foods. Since a correlation between the ingestion of nickel-containing or -contaminated (i.e. through pots and pans) foods and the occurrence of systemic reactions has been observed, we selected nickel-allergic patients, with cutaneous and/or gastrointestinal systemic disorders due to nickel intake.

In our study, satisfactory results were obtained in patients who completed the treatment: 47% of them reported complete remission while 16.9% reported a

clinical improvement higher than 80%. Eighty-seven patients (64%) came back to a free dietary regimen when hyposensitization was completed, while 7 patients had only partial benefits and were able to eat only some of the nickel-containing foods.

During the second allergological evaluation the patients did not show a significant modification in the intensity of skin reactivity to nickel patch test: unchanged in more than 70% and reduced in only one-fifth of patients. On the contrary, a significant increase in tolerance was assessed during the nickel oral challenge test: in 50% the threshold dose increased, while one third (30.9%) did not react.

According to Sjövall's experience (34), on oral desensitization, high doses of nickel (3.5 and 5 mg) caused a relapse of cutaneous symptoms in about 60% (10/17) of treated patients, while, in our study, the use of extremely low doses (0.1 ng) had a higher efficacy rate with a low incidence of side effects (21.5%), remitted with treatment interruption and the administration of low doses of oral steroids. No severe systemic reactions occurred.

Our protocol has been effective in inducing clinical tolerance to nickel-containing foods while contact reactions did not show significant improvement. The benefits reported can not be attributed to a spontaneous reduction in sensitivity obtained by just avoiding nickel intake or contact. In fact, the control group did not show significant improvement once nickel-containing foods were reintroduced, despite long-term diet. The index obtained for ARR and RRR excludes possible placebo-effect and confirms that the oral hyposensitization with nickel sulphate represents an effective and safe therapeutic option. In conclusion, we can affirm that this therapy is effective and safe and can be an important therapeutic tool in the management of patients with systemic allergy to nickel.

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