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Topical and Systemic Therapies for Nickel Allergy

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Abstract and Introduction

Abstract

Nickel allergy can result in both cutaneous and systemic manifestations, and can range from mild to severe symptoms. A severe form of this allergy is the Systemic nickel allergy syndrome, clinically characterized by cutaneous manifestions (contact dermatitis, pompholyx, hand dermatitis dyshydrosis, urticaria) with chronic course and systemic symptoms (headache, asthenia, itching, and gastrointestinal disorders related to histopathological alterations of gastrointestinal mucosa, borderline with celiac disease). This review aims to briefly update the reader on past and current therapies for nickel contact allergy.
Often patients will have visited independent a skincare clinic in London for alternative ways of treating their dermatitis or allergy.

Introduction

ALLERGIC CONTACT DERMATITIS (ACD) from nickel is an inflammatory skin condition, caused by a type IV hypersensitivity response, that manifests itself after recurrent contact with the metal. The prevalence of ACD from nickel is increasing worldwide because of the widespread presence of this metal in our environment. The clinical manifestations are related to the phase of dermatitis: the acute phase can be characterized by itching, erythema, edema, vesicles, and scaling with visible borders, and the chronic phase by lichenification and itching. Risk factors are the sensitizing potential of the allergen, high frequency of exposure, occlusion, prolonged time of contact, presence of penetration-enhancing factors, and altered skin barrier function. In fact, described recently are null mutations in the *filaggrin* gene complex and an alteration of toll-like receptor 4 (TLR4) in allergic patients have recently described.[1,2]

Nickel is the main sensitizer; its prevalence varies from 4.0 to 13.1% in different countries and is still increasing. Nickel allergy is more common among women than among men (17% and 3%, respectively). This difference is due to different rates of exposure of skin to this substance; such exposure (from jewelry, leathers, etc) is more frequent among women. Nickel allergy has also been noted as prevalent among certain workers, such as hairdressers, domestic cleaners, metalworkers, and caterers, owing to their repeated exposure to this metal. Furthermore, nickel is present in a large number of foods (mainly vegetables), another source of exposure for sensitized patients.[3]

Nickel allergy can result in both cutaneous and systemic manifestations, and its signs and symptoms can range from mild to severe. A more severe form is systemic nickel allergy syndrome (SNAS), which is clinically characterized by cutaneous manifestations (such as contact dermatitis, pompholyx, hand dermatitis, dyshydrosis, and urticaria), a long-term course, and systemic symptoms (such as headache, asthenia, itching, and gastrointestinal disorders related to histopathologic alterations of gastrointestinal mucosa, borderline with celiac disease).[4]

This review aims to briefly update the reader on past and current therapies for nickel contact allergy.

Topical Emollients, Corticosteroids, and Immunosuppressive Therapies

Topical treatment is the first-line therapy for hand contact dermatitis and is also associated with systemic supportive therapies in chronically relapsing patients with severe allergy. Many topical molecules can be used, regardless of the type and phase of dermatitis (acute, subacute, or chronic). The main purpose is the restoration

of the epidermal barrier, which is composed of corneocytes, extracellular proteins, and a lipid-rich matrix (ceramides, fatty acids, and cholesterol). Barrier damage is directly correlated to the severity of dermatitis.[5,6] The use of emollients and barrier creams (containing key stratum corneum lipids, including ceramides) seems to make it possible to reduce the use of topical corticosteroids and immunosuppressive agents such as tacrolimus and pimecrolimus. Use of these emollients and barrier creams leads to the integrity of the epidermal barrier and a consequent reduction of transepidermal water loss (TEWL) and penetration of irritant substances. Emollient creams are composed of two categories of molecules: passive and active. Passive molecules are found in lanolin, petroleum jelly, mineral oils, and silicone, whereas the active molecules are in glycerin, sorbitol, propylene glycol (with hygroscopic action), and urea and alpha-hydroxy acids. These active molecules could be used in every phase of dermatitis, including quiescent periods, to reduce the flaring up of chronic contact dermatitis.[6,7]

Topical corticosteroids are often used in the acute phase of eczema, in association with emollient agents.[5] Pelfini and colleagues grouped these agents in seven decreasing classes of potency, from superpotent to low potency.[6] Clinicians must select the appropriate corticosteroid cream in every case, based on the patient's constitution and on the characteristics and severity of the dermatitis. In the chronic phase, a preparation with superpotent or midstrength molecules might be used with occlusion for 1 to 3 weeks. In fact, the use of these agents for a more prolonged period is not advised because of possible side effects such as atrophy and telangiectasias.[6-9] A study on the effects of two moisturizers performed by Hachem and colleagues in 2002 showed an improvement of skin barrier function in the early inflammatory phase of ACD, with a reduction of TEWL. Improvement in the later phase of the dermatitis was attributed to the secondary effects of the corticosteroids on the proliferation and differentiation of keratinocytes.[8]

Tacrolimus and pimecrolimus, on the other hand, are antiinflammatory, have immunomodulators that belong to the class of topical calcineurin inhibitors (TCIs), and provide clinicians with steroid-sparing options in the long-term topical treatment of ACD. TCIs are indicated when topical corticosteroids are not indicated or when an anticipated lengthy treatment would lead to inevitable adverse effects. In 2006, Pacor and colleagues performed a randomized double-blind placebo-controlled study with two groups of patients affected by nickel sulfate - induced steroid-resistant ACD and respectively treated with tacrolimus ointment 0.1% and placebo vehicle for 14 days.[10] They observed a significant improvement in the major symptoms of eczema (erythema, oozing, scaling, and itching) in the patients of the first group, whereas no improvement was observed in the patients of the second group. Local side effects of TCIs, such as burning and itching at the application site, were transient and well tolerated. Compared with topical corticosteroids, pimecrolimus does not increase the overall incidence of skin infections (including recurrent herpes simplex infections).[10-13]

Narrowband Ultraviolet B

Phototherapy is very effective in the treatment of hand eczema; narrowband ultraviolet B (UVB) therapy has demonstrated clinical efficacy also in therapy for psoriasis and atopic dermatitis.[5]

The safety and efficacy of this therapy in cases of hand eczema was evaluated in a randomized controlled prospective study of 15 patients who had no response to conventional topical therapy. The patients were treated three times weekly for 9 weeks with narrowband UVB on one hand and with topical photochemotherapy using 0.1% 8-methoxypsoralen gel on the other hand. Patients were assessed once each week during the treatment period and were evaluated 10 weeks after the last treatment. All of the 12 subjects who completed the trial improved, showing a statistical difference between modalities. Both broadband and narrowband UVB appear to be as effective as topical psoralen plus ultraviolet A (PUVA) therapy in the treatment of chronic hand dermatitis.
However, the risks of phototoxicity and dyspigmentation associated with local PUVA therapy make UVB therapy a preferable initial therapeutic option.[5]

Systemic Immunosuppressive Therapy

Systemic immunosuppressive therapy may be considered for those cases of hand eczema that are refractory to topical steroids and phototherapy. If ACD involves an extensive area of the skin (> 20%), systemic steroid

therapy is required. In general, oral prednisone should be tapered over 2 or 3 weeks because rapid discontinuation can cause rebound dermatitis.[9] Similarly, the usefulness of cyclosporine for this condition seems limited to the short term. Although one study demonstrated prolonged disease remission in 74% of patients 1 year after a 6-week course of cyclosporine (3 mg/kg/d), other studies have shown high relapse rates within weeks of drug discontinuation.[5]

Oral Zinc

Nickel, as other allergens, may interact with essential divalent ions with similar chemical properties at ionic sites of important biomolecules. Based on animal studies, some effects of nickel may be eliminated or reduced by supplementing with divalent essential metals.[14] Weissmann and Menné reported cases of nickel dermatitis as having improved following oral administration of zinc sulfate ($ZnSO_4$).[15] One clinical study showed that the administration of $ZnSO_4$ could improve the clinical manifestations of nickel contact dermatitis and could eliminate or reduce the majority of patch-test reactions; intolerance to $ZnSO_4$ was not observed. The study showed that $ZnSO_4$ therapy is efficacious and safe.[14]

Low-nickel Diet

Patients with diffuse manifestations can reduce clinical cutaneous and gastrointestinal symptoms by following a diet with a low nickel content. Nickel frequently contaminates food, and avoiding it is very difficult. The daily intake of this metal with food is about 300 mg, mainly from oatmeal, nuts, cocoa, chocolate, and soybeans.[16,17] In sensitized patients, nickel ingestion could cause a recurrence of chronic contact dermatitis but could also cause flare-ups of other dermopathies such as those triggered by immunoglobulin E (IgE)-mediated allergy (mainly urticaria). This evidence suggests that nickel allergy may be not only mediated by type I and type IV Gell and Coombs reactions. Activation of T cells by nickel may result in a mixed immune response with only a quantitative difference, potentially causing both IgE antibody production (from type 1 helper T cells) and the development of ACD (from type 2 helper T cells).[7]

The normal daily dietary intake of nickel ranges from 0.02 to 0.48 mg. Many studies have demonstrated the relationship between nickel ingestion and dermatitis flareups. Meta-analysis results of all studies have generally been confirmed.[7] In 2006, Jensen and colleagues reported the results of a meta-analysis of these studies performed to determine the median values of nickel that could elicit allergic reactions. It has been demonstrated that nickel sulfate may provoke chronic eczema when orally administered in the range of 0.6 to 5.6 mg daily as a single dose, and there is much evidence of this relationship (eg, flareup of eczema upon dietary oral nickel challenge, improvement of eczema after starting a low-nickel diet, and management with oral disulfiram or hyposensitization therapy with low-nickel doses).[17]

In 2010, Minelli and colleagues performed a clinical study to determine whether the oral administration of lownickel doses improved clinical conditions and modulated the immunologic aspects of SNAS without significant side effects. By evaluations before and after treatment, they showed that nickel sulphate is effective in reducing symptoms and drug consumption in these patients and is able to modulate inflammatory parameters such as interleukin-1, interleukin-5, and interferon-c released by peripheral blood mononuclear cells.[18]

Disulfiram

Disulfiram (Antabuse, Wyeth-Ayerst, Philadelphia, PA) is a nonconventional pharmacologic agent used in therapy for nickel contact dermatitis. It is a chelating agent for metals such as nickel and cobalt, but its main use is as supportive therapy for alcohol addiction. After absorption in the gut, disulfiram metabolizes into sodium diethyldithiocarbamate (DDC) in the liver. This metabolite causes the chelation of nickel, with an increasing concentration in blood and major excretion through urine, bile, and perspiration.[19,20] In the last decades, various studies using disulfiram in nickel-sensitized patients affected by chronic relapsing contact dermatitis have had favorable results in regard to the frequency and intensity of flare-ups. Furthermore, various studies have

confirmed the benefit of a low-nickel diet in the management of this eczema, even if diet alone cannot clear the condition but only reduce the frequency and intensity of flare-ups.

In 1979, Kaaber and colleagues described 11 patients treated with disulfiram two to four times daily for 4 to 10 weeks. Seven patients completely cleared, two patients improved, and two patients remained stable. Side effects such as fatigue, headache, and dizziness were noted in seven patients. Nickel urine and serum concentrations gradually increased in the first weeks of treatment, then (after the initial 3 weeks of treatment) decreased in the blood, thus suggesting that disulfiram is able to reduce total body nickel.[19]
In 1982, Christensen treated 11 patients with a daily 200 mg dose of disulfiram for 8 weeks. Three patients healed completely, and the other eight improved considerably. The patients' eczema relapsed after 2 to 16 weeks by the end of therapy.[21]

In 1983, Kaaber and colleagues published the results of a double-blind placebo-controlled trial of treatment with disulfiram in 24 patients for 6 weeks. The result was improvement in the dermatitis and decreasing frequency of flares in the disulfiram-treated groups. Two patients showed hepatotoxicity.[22]

In 1987, Hopfer and colleagues observed 61 patients treated with disulfiram for chronic alcoholism for a period of 4 months to 3 years. They demonstrated that serum, blood, and urine nickel concentrations progressively increased during the initial period of treatment. Animal studies have demonstrated cerebral uptake of the lipophilic nickel-DDC complex; thus, nickel may possibly accumulate in brain cells. Physicians should therefore be cautious in administering disulfiram to persons who have nickelcontaining orthopedic prostheses or occupational exposure to nickel.[23]

In 2006, Sharma described a study involving 21 patients: 11 patients on a nickel-free diet took disulfiram for 4 weeks, and 10 patients made up the placebo (control) group. The eczema healed in 10 patients in the first group, as opposed to one patient in the second group. During the 2 to 12 weeks of follow-up, five patients in the treated group experienced a mild relapse. Three patients showed a mild increase of hepatic enzymes.[24]

Hyposensitization With Nickel

The concept of immunomodulation, developed in the 1990s, is as follows: the induction of tolerance to a specific antigen may be obtained by a mechanism of active suppression or by the induction of a clonal allergy.[25] The experiments of Bagot and colleagues, carried out in a double-blind-versus-placebo study, clearly demonstrated that oral nickel administration in humans may importantly reduce the number of circulating T-cell lymphocytes activated against this antigen.[26] In 1992, Van Hoogstraten and colleagues demonstrated that complete tolerance can be maintained for 2 years as long as oral contact with the allergen is avoided. Oral administration of nickel could induce an immune-specific tolerance by a clonal expansion of subtypes of $CD4^+$ T-cell clones, T-regulatory cells, with suppressing activity that limits tissue damage and inflammatory-response T-regulator cells.[27,28]

The first oral hyposensitization therapy was experimented with by van Hoogstraten and colleagues with the administration of nontoxic nickel doses to sensitized mice for 1 to 3 weeks.[27,28] However, the first successful result with humans was obtained in 1987 by Sjovall, who observed less-intense reactions to patch tests after he administered oral capsules containing different nickel concentrations to a selected patient group for 6 weeks.[29]

In 2009, our group performed a clinical trial of oral hyposensitization therapy with low doses of nickel in 67 patients affected by systemic allergy to this sensitizer. All patients reported a significant benefit in regard to both cutaneous and systemic symptoms, with the reduction or absence of itching and partial or complete clearing of ACD after the first 4 weeks of treatment. In fact, 70% of the patients completed the increasing phase (10 weeks) and the maintaining phase with the following results after the reintroduction of a nickel-free diet: 67% reported a complete remission of symptoms; in 23%, a clinical improvement was noted, with the rare appearance of cutaneous or digestive symptoms of lower intensity; and three patients also reported a reduction in weight. Adverse reactions were observed only in 18 patients: 12 patients with primary cutaneous dermatitis reported mild itching, and 6 patients with gastrointestinal manifestations reported digestive disorders of low intensity.[4]

This systemic therapy led to favorable results both in regard to cutaneous symptoms and in regard to gastrointestinal histologic modifications induced by nickel allergy, in contrast to all other therapies that could only act on the dermatitis.[4,30-32]

Conclusions

Nickel allergy remains prevalent, and knowledge of its pathology has led to increased occupational and environmental hygiene. The low-nickel diet and hyposensitization therapy with oral nickel is at present the only therapy that acts on the pathogenetic mechanisms of this condition, so it could be considered the only effective "therapy"; all other therapies are agents that can "cure" the symptoms only. Only a major knowledge of this condition—which is not an "allergy" but rather a complex immune-mediated process induced by contact with a foreign agent associated with genetic alterations of the skin barrier (filaggrin) and innate immunity (TLR4)— can lead to the development of an efficient therapy.

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