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Contact allergy to topical antifungal agents

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Key words: ciclopiroxolamine; clinical epidemiology; contact allergy; imidazoles; nystatin; patch testing; topical antifungals.

Topical antifungal agents (AF) are used to treat superficial fungal infections such as dermatophytoses, candidiasis and pityriasis versicolor. The polyene derivative nystatin is only active against yeasts, while azole and morpholine AF show a broad spectrum of activity against dermatophytes, yeasts and moulds. Contact allergy (CA) has been reported after use of AF (1–5). Croconazole in particular has been found to be an important sensitizing agent in East Asia (4, 5). In contrast, other azole AF are regarded as (very) infrequent sensitizers. Most studies on CA to AF, however, comprise sporadic case reports; systematic patch test studies based on a large clinical population are currently lacking. This study reports the results of patch tests with AF applied to patients attending the clinics of the Information Network of Departments of Dermatology (IVDK, <http://www.ivdk.org>; accessed 2 April 2008) (6), a CA surveillance network in Germany, Austria and Switzerland.

From May 2001 to April 2002, 20 departments of dermatology – members of the German Contact Dermatitis Research Group (DKG) and the IVDK (6), see footnote – performed a study to evaluate CA frequency to five topical AF (Table 1). Standardized patch test allergens were supplied by Hermal/Trolab (Reinbeck, Germany). Patients' own AF products were additionally analyzed, provided these had been patch tested as well. The diagnosis of CA was based on the D3 readings. Patch test reactions scored '+', '++' or '+++[†]' were considered to be positive.

[†]The following centres contributed data to the following analysis (in alphabetical order): Augsburg (A. Ludwig), Dortmund (C. Pirker, P.J. Frosch, R. Herbst), Dresden (G. Richter, R. Aschoff), Essen (U. Hillen), Graz (B. Kränke, W. Aberer), Göttingen (J. Geier, Th. Fuchs), Halle (D. Lübke, G. Gaber), Hamburg (M. Kiehn, R. Weißbecher), Heidelberg (M. Hartmann, U. Jappe), Homburg/Saar (P. Koch), Jena (A. Bauer, M. Kaatz, S. Schlie-mann-Willers), Kiel (J. Brasch), Krefeld (A. Wallerand, M. Lilie, S. Wassilew), Marburg (H. Löffler, I. Effendy), München Schwabing (M. Agathos), München TU (J. Rakoski), Nürnberg (I. Müller), Osnabrück (H. Dickel, H.J. Schwanitz (+), N. Schürer, S.M. John), Tübingen (G. Lischka, M. Röcken), Ulm, BWK (H. Pillekamp)

Topical antifungals are rare contact sensitizers.

Altogether 1254 patients (median age 49 years, interquartile range: 36–64; 35.9% male) were patch tested with the AF series. In 10 centres, ≤ 10% of all patients were tested with the study battery, i.e. in a more aimed fashion, whereas in the remaining 10 centres the proportion ranged from 11 to 22%. Positive reactions were altogether rare, with ciclopiroxolamine yielding the highest number of positive ($n = 4$) and doubtful ($n = 13$) reactions as well (Table 1). Among patients tested positively to AF [$n = 12$ [0.94%; 95% confidence interval (CI): 0.49–1.63]] no concomitant positive patch test reaction was observed among the AF, even among the chemically related azoles. AF brand products brought in by the patient were tested in 41 cases, yielding the following results in 35 patients tested with one or more product(s) containing the target AF – all positive reactions but one were caused by creams (O/W emulsions; positive reactions to other ingredients of these were not observed):

- clotrimazole ($n = 17$), two positive reactions, only one concordantly with the standardized patch test substance;
- nystatin ($n = 9$), one patient with two (strong) positive reactions in absence of a positive reaction to the commercial allergen;
- ciclopiroxolamine ($n = 8$, all negative);
- ketoconazole ($n = 6$), two positive reactions – one of these, however, to a 1 : 10 diluted, ketoconazole-containing shampoo – without positive reactions to the commercial allergen.

Products containing other AF such as bifonazole, miconazole, econazole, terbinafine, etc. had occasionally been tested (without yielding positive results) on these and the other six patients.

This work evaluated CA in an extensive series of patients patch tested to important AF agents at numerous IVDK centres. Our findings confirm the weak sensitizing capacity of the tested AF, as reported previously (1–4), although a more aimed use of the test series, i.e. just in the supposedly few patients with

Table 1. Results of patch testing with antifungal allergens

Antimycotics	Conc. (%)	Tests	?	+	++	+++	ir	% positive	Exact 95% CI
Ciclopiroxolamine	1	1094	13	4	0	0	0	0.4	0.1–0.93
Nystatin	2	1177	4	2	0	1	1	0.3	0.05–0.74
Clotrimazole	5	1180	5	3	0	0	0	0.3	0.05–0.74
Croconazole HCl	1	1094	6	0	2	0	0	0.2	0.02–0.66
Ketoconazole	2	1104	0	0	0	0	0	0.0	0.0–0.27

All allergens in petrolatum; CI, confidence interval.

suspected allergic contact dermatitis caused by antifungal drugs, would have yielded higher percentages of positive reactions. Interestingly, the high sensitizing potential of croconazole observed in East Asia (4, 5) could not be confirmed, after sporadic reports on CA to this AF in Germany [e.g. (3)]. This is possibly because of a limited exposure, as only one brand specialty containing croconazole has been on the market, and this was not among the 'top prescriptions', e.g. in 2002 [$< 70\,000$ prescriptions (7)]. In accordance with previous evidence, simultaneous positive reactions, which could indicate cross-reactivity among the chemically related imidazoles (or previous co-exposure) has been found to be rare (4). The rather high proportion of doubtful patch test reactions we have observed points to difficulties in the patch test diagnosis of CA to these AF. Patch test reactions to products are generally difficult to interpret, i.e. because of possible irritancy under patch test conditions or the possibility of other ingredients causing CA. Hence, our data regarding the concordance between commercial allergens and product testing should be interpreted with caution – not to mention the small size of the clinical sub-sample ($n = 35$). Still, the results could indicate that AF products may be more sensitive to diagnose CA than petrolatum-based preparations, for instance because of reasons of bioavailability.

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Elevated levels of tryptase in children with nummular eczema

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Key words: atopic dermatitis; atopic eczema; mast cells; nummular eczema; tryptase.

Tryptases are serine proteases primarily expressed in mast cells. Elevated levels of total tryptase in serum are known to be associated with systemic mastocytosis and anaphylaxis (1).

Increased tryptase has also been reported in acute myelocytic leukemia, myelodysplastic syndromes, hypereosinophilic syndrome, renal failure, and treatment of onchocerciasis. To our knowledge, increased tryptase in eczema has not been described so far. We report on three children with nummular eczema (NE) showing elevated tryptase. NE or discoid eczema is characterized by coin-shaped plaques of eczema with a chronic course (2). Bacterial infections have been discussed as eliciting factors.

A 3-year-old boy presented with about 20 erythematous plaques, some of them covered by yellow crusts. A skin biopsy showed subacute dermatitis with increased numbers of mast cells confirming the clinical diagnosis of NE. Total IgE was 253 kU/l, screening tests for specific IgE were negative. Surprisingly, total tryptase was elevated to 71.6 µg/l (ImmunoCAP Tryptase; Phadia AB, Freiburg, Germany). Reexamination excluded cutaneous mastocytosis and a careful history failed to reveal anaphylaxis in the past. Lesions of NE improved under topical steroids and pimecrolimus. Seven months later, the patient still showed mild eczema and tryptase was 20.6 µg/l. On follow-ups 4 and 5 months later, tryptase was 9.5 and 19.9 µg/l respectively.

This is the first observation of elevated tryptase levels in nummular eczema. Nummular eczema should be added to the differential diagnosis in subjects with elevated tryptase.