

Short Communications

Foot dermatitis due to non-disperse azo dyes

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Key words: foot dermatitis; azo dye; non-disperse dye; direct dye; acid dye; shoe; sock; clothing; textiles. © Munksgaard, 2000.

Contact allergy to shoes was first described in 1929 (1). In this country, rubber additives, particularly antioxidants and accelerators, are most commonly implicated, followed by tanning substances (2). Textile dyes may also be causal, usually disperse dyes, though recent reports have identified non-disperse dyes in clothing dermatitis (3).

Case Reports

Over the 2-year period December 1995–December 1997, 53 patients were patch tested for foot dermatitis, 28 female and 25 male, with an average age of 35.5 years (range 5–70). Of these, 16 patients had a positive reaction to 1 or more shoe or textile-related allergens (Table 1). 5 patients were positive to textile dyes, in 3 cases (case nos. 1–3) of the non-disperse type (Table 2).

Case no. 1

A 45-year-old non-atopic man presented with a 3-year history of dermatitis of both feet. There was no prior history of skin problems. On examination, dermatitis was noted on the toes, dorsum and sole of both feet and on the lower legs. Patch testing was performed to standard, shoe and an extended textile series. Positive reactions were seen to quinoline mix and dyes. The patient was advised to wear only undyed-leather or plastic shoes, in addition to avoiding coloured socks. On follow-up 30 months after patch testing, he had found difficulty in avoiding all allergens but had managed to reduce contact and the dermatitis had considerably improved.

Case no. 2

A 43-year-old non-atopic man presented with a 10-year history of dermatitis of the heel and sole of the feet. He was patch tested to the standard, shoe and textile series. Reactions were seen to nickel sulfate, cobalt chloride, potassium dichromate, mercaptobenzothiazole, mercapto mix and a textile dye. He was already avoiding nickel and was advised to wear only man-made shoes and white cotton or synthetic fabrics. On follow-up 18 months after patch testing, he had managed to comply with advice, with improvement in his dermatitis.

Case no. 3

A 55-year-old non-atopic man presented with a 10-year history of recurrent dermatitis of the dorsum of the feet, which had spread to the lower legs and arms. He was patch tested to a standard series and rubber, plastics, epoxy resin, shoe and textile series. Positive reactions were seen to nickel sulfate and dyes. The patient was advised to wear only undyed-leather or plastic shoes, in addition to avoiding coloured socks. When seen 2 months later, he had managed to comply with this advice, and his dermatitis had largely resolved.

Comment

A report by Freeman (2) identified 55 patients with shoe contact allergy over a 10-year period (1.5% of the patch-tested population) (2). Several components of shoes may be implicated as causative. Dye allergy is reportedly an uncommon cause and usually due to re-dyed leather or fabric shoes (1). Allergy to disperse azo dyes in clothing is more common, being responsible in 10% of patients in 1 series (4). Dyes may be divided into 2 chemical classes, anthraquinone or azo. Azo dyes represent 70% of all commercial colourants (3). Most textile dyes causing contact allergy have an azo structure (5). For practical purposes, dyes are usually subdivided by application class (3). Communication with the British Leather Foundation has revealed that leather dyes are usually ionic and of the direct and acid class, rather than of the disperse dye class.

A literature search found 3 confirmed reports of leather dye allergy in wearers. Calnan (6) described an allergic reaction to dye in a leather watchstrap, Ancona

Table 1. Reactions seen to shoe and textile-related allergens, December 95–December 97 (16 positive patients)

Allergen	No. patients
mercaptobenzothiazole	6
mercapto mix	4
thiuram mix	1
potassium dichromate	5
PTBP-formaldehyde resin	3
formaldehyde	1
para-phenylenediamine	4
specific textile dyes	5

Table 2. Reactions to dyes in patients reacting to non-disperse dyes

Allergen	Patient no. 1		Patient no. 2		Patient no. 3	
	D2	D4	D2	D4	D2	D4
para-phenylenediamine (1% pet.)	+	+			++	++
aminoazobenzene (0.25% pet.)	+	+			++	++
Disperse Orange 1 (1% pet.)	+	+				
Disperse Orange 3 (1% pet.)	+	+			++	++
Disperse Orange 13 (1% pet.)	+	+				
Disperse Yellow 3 (1% pet.)	+	+			—	+
Disperse Red 1 (1% pet.)	+	+			—	+
Disperse Red 17 (1% pet.)					+	+
Disperse Blue 1 (1% pet.)	—	+				
Disperse Blue 3 (1% pet.)	+	+				
Disperse Blue 35 (1% pet.)	+	+				
Disperse Blue 85 (1% pet.)	—	+				
Disperse Blue 124 (1% pet.)	+	+				
Disperse Brown 1 (1% pet.)	+	+			—	++
Basic red (1% pet.)	+	+			—	++
Direct Orange 34 (1% pet.)	+	+			+	+
Direct Yellow 86 (5% pet.)	—	+				
Acid Red 118 (5% pet.)	+	+				
Acid Yellow 61 (5% pet.)	—	+				
Acid Yellow 17 (5% pet.)	+	+				
Acid Red 1 (5% pet.)	+	+				
Acid Blue 113 (5% pet.)	+	+				
Acid Red 359 (5% pet.)			—	+		

et al. (7) to Acid Yellow 36 in the leather inners of an industrial boot (7) and Romaguera et al. (8) to para-phenylenediamine in a black orthopaedic boot (8). Estlander et al. (9) reported 3 persons who worked with dyed leather who were allergic to undetermined leather dyes, together with other azo and disperse dyes. In this study, 9% of patients with foot dermatitis who were patch tested had a positive reaction to 1 or more dyes. Exposure to non-disperse dyes, which are used to dye natural fibre materials, may occur from shoes (leather), socks (cotton, wool), stockings (silk), etc. Allergy to non-disperse dyes causing clothing dermatitis at other body sites has been reported (3). In this group of patients, it was not possible to tell whether the predominant exposure to non-disperse azo dye was from footwear or from clothing. Although para-phenylenediamine has been used as an indicator of textile dye dermatitis, it is often negative in azo-dye-sensitive patients and is not a reliable marker (10). The inclusion of individual azo dyes within textile and shoe series is therefore important. A previous report suggested that allergy to para-phenylenediamine and disperse azo dyes may indicate cross-reaction with leather dyes in shoes (11). Where suspected, a trial of avoidance was recommended.

All patients showed some improvement in their chronic foot dermatitis following patch testing, though not all completely resolved. On questioning, they had experienced difficulty in complying with avoidance advice, shoes not being labelled as to their constituents. While disperse azo dyes are a cause of foot dermatitis, we have found allergy to non-disperse azo dyes in 5% of patients with foot dermatitis. We suggest that, to

avoid missing contact allergy, azo dyes should be included within a shoe series for foot dermatitis, and that these should comprise both disperse and non-disperse dyes.

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Occupational contact dermatitis from headphones containing diethylhexyl phthalate

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Key words: allergic contact dermatitis; occupational; armed services; radar operator; plasticizers; headphones; diethylhexyl phthalate; dioctyl phthalate. © Munksgaard, 2000.

Case Report

A 27-year-old man, with mild atopic eczema, developed further eczema on the outer ears as a radar operator. The rash cleared on holiday but recurred on return to work. At work, he constantly wore a pair of headphones, consisting of a frame with a plastic coating and detachable ear pads of vinyl and a polyether foam.

Patch testing to the European standard series, headphone cleaning fluid and pieces of the detachable ear pads showed no reactions. He did however produce a + reaction to diethylhexyl phthalate 2% pet. and a ++ reaction to phenol-formaldehyde resin 1% pet. at D2 and D4.

The manufacturer of the headphones confirmed that dioctyl phthalate (DOP) was used in both the vinyl and polyether foam portions of the ear pads. DOP is a synonym for diethylhexyl phthalate (di(2-ethylhexyl) phthalate).

Discussion

Diethylhexyl phthalate is a common plasticizer with low sensitizing potential (1). It has previously caused contact dermatitis in spectacle frames and a hearing aid (2). We could find no reports of allergic contact dermatitis from occupational exposure to it in headphones.

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Failure of vehicle to influence local lymph node assay response to benzocaine

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Key words: benzocaine (ethyl-*p*-aminobenzoate); local lymph node assay; vehicle; predictive testing; contact allergy. © Munksgaard, 2000.

Skin sensitization test methods must regularly be monitored with positive controls, for which the OECD has recommended hexyl cinnamic aldehyde, mercaptobenzthiazole and benzocaine (1). Both hexyl cinnamic

aldehyde and mercaptobenzthiazole reliably elicit positive responses, but those to benzocaine are considerably more variable (2). Indeed, in most assays, benzocaine would not be classified as a skin sensitizer on current

Table 1. Influence of vehicle on local lymph node assay responses to benzocaine

Benzocaine conc. (% w/v)	Acetone/saline					
	AOO SI	DMSO SI	(1:1) SI	DMF SI	MEK SI	Acetone SI
0	1	1	1	1	1	1
2.5	2.10	1.07	1.46	2.04	1.21	1.85
5	1.81	1.11	1.33	2.81	1.82	2.99
10	2.70	1.65	2.13	2.40	1.41	1.48
25	1.77	1.73	2.11	1.33	1.68	2.02
50	1.16	1.77	1.74	1.95	1.68	2.05

EU criteria (3). In the murine local lymph node assay (LLNA), benzocaine has also been shown to elicit weak and variable responses (2, 3), leading to the proposal of its unsuitability as a positive control (3). The choice of application vehicle, however, can significantly influence draining lymph node responses and the effectiveness of sensitization in mice (4–7). We therefore investigated whether benzocaine could provoke positive responses in the murine LLNA if the vehicle were changed.

Materials and Methods

Benzocaine (ethyl-*p*-aminobenzoate) was obtained from Sigma Chemical Co. (Poole, Dorset, UK) and dissolved at between 2.5% and 50% (w/v) in 6 different vehicles: acetone: olive oil (AOO; 4:1 v/v), dimethylsulfoxide (DMSO), acetone saline (1:1 v/v), dimethylformamide (DMF), methyl ethyl ketone (MEK) and acetone alone, comprising the currently recommended list of such vehicles (8). LLNAs were conducted as previously described, using CBA/Ca strain female mice (Harlan Seralab, Oxon, UK), except that for each formulation 5, rather than 3, separate dose groups were used to facilitate dose-response analyses (8). In each instance, a stimulation index (SI), relative to vehicle-treated control values, was derived.

Results

Results are summarized in Table 1, where the SI for each concentration in each application vehicle is recorded. To be a skin sensitizer in the LLNA, an SI of 3 or greater is required (8). In no instance was this fulfilled, though 5% benzocaine in acetone did achieve an SI of 2.99. While, in theory, this might be regarded as a positive response, there was no evidence of any dose-effect relationship and the conclusion drawn was that, in all vehicles tested and at all concentrations, benzocaine failed to elicit positive responses in a standard LLNA.

Discussion

A growing body of evidence indicates that the selection of benzocaine as a positive control might not in fact be appropriate, essentially negative results being obtained in both guinea pig and mouse predictive assays (3). The present investigation adds to this, by showing that it is not due to an inappropriate vehicle.

A recent 10-year clinical review of contact allergy to

benzocaine concluded that it was a much weaker skin sensitizer than had previously been thought (9), echoing views recorded a decade earlier (10). Contact allergy to benzocaine is largely associated with conditions such as pruritus ani (11), where sensitization potential is greatly enhanced by repeated application to compromised skin.

In conclusion, benzocaine is a weak allergen, difficult to detect in normal predictive tests, and thus inappropriate for use as a reliable positive control for the purposes identified by the OECD (1).

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Flare-up of skin tests to amoxycillin and ampicillin

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Key words: intradermal tests; patch tests; amoxycillin; ampicillin; antibiotics, flare-up; adverse drug reactions; medications. © Munksgaard, 2000.

Case Report

A 62-year-old woman developed widespread urticaria 2 h after a dose of antibiotic. Erythromycin and quinolones were well tolerated.

Prick tests with penicillin (100,000 IU/ml), penicilloyl polylysine (PPL), minor determinant mixture (MDM), amoxycillin (200 mg/ml), ampicillin (200 mg/ml) and cephalothin (200 mg/ml), and intradermal (i.d.) tests to the same substances diluted in saline, were all negative immediately. 1 day later, the i.d. tests to amoxycillin and ampicillin became positive, and remained so for 20 days.

Patch tests were performed to the same substances (10% pet.) 1 month after prick and i.d. testing, by when

the i.d. test reactions were no longer visible. 1 day later, the patient returned to the hospital with flare-ups of her i.d. tests to amoxycillin and ampicillin (Fig. 1). Since her patch tests were also intensely pruritic, they were removed at the same time (D1) and also found to be positive to amoxycillin and ampicillin, the reactions remaining positive at D4 (Fig. 2).

Serum specific IgE to β -lactams was not detected by the Pharmacia CAP system.

Discussion

Although the patient's symptoms suggested an IgE-mediated mechanism, her investigation results indicated a Type IV mechanism.

The flare-up phenomenon has most frequently been described with nickel (1–3). We have previously reported it with amoxycillin and ampicillin skin tests after a provocation test with amoxycillin (4). A budesonide skin test has flared up after a provocation test with deflazacort (5). Gold (2, 6) and chromate (7) have also been so implicated.

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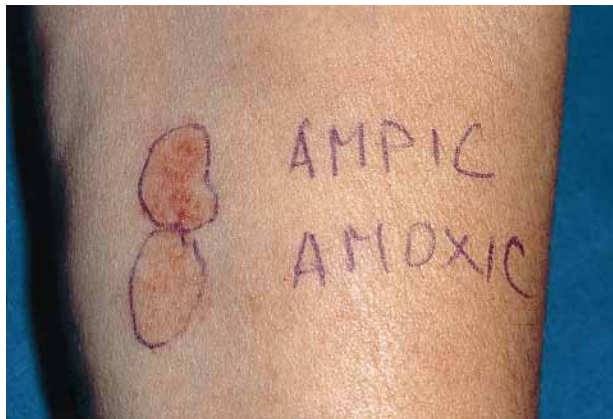


Fig. 1. Flare-up of intradermal tests to amoxycillin and ampicillin.



Fig. 2. Positive patch tests to amoxycillin and ampicillin at D4.

Contact dermatitis due to flurbiprofen

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Key words: allergic contact dermatitis; flurbiprofen; non-steroidal anti-inflammatory drugs; arylpropionic acid derivatives; cross-photosensitivity. © Munksgaard, 2000.

A 22-year-old woman was seen in June 1999 with pruritic erythema over her right wrist joint and forearm. She had applied a poultice containing flurbiprofen (Adofeed®, Kaken Pharmaceut. Inc., Tokyo, Japan) for pain in the right wrist joint 3 days before and noticed pruritic erythema in the same area 2 days before. She had not been exposed to sunlight when or after applying the poultice. She had no past history of drug eruption, contact or photocontact dermatitis.

We performed patch and photopatch tests (1) with 5% and 1% pet. flurbiprofen, 5% pet. fenoprofen, ibuprofen, loxoprofen, naproxen, tiaprofenic acid, zaltoprofen, 3% ketoprofen lotion, and 1% spirofen ointment. Only 5% and 1% pet. flurbiprofen showed a positive response at D2 and D3 on patch testing. On photopatch testing, 1% pet. tiaprofenic acid and 3% ketoprofen lotion with UVA irradiation (4.5 J/cm²) produced erythema and papules 1 day after irradiation. Patch and photopatch tests with 5% and 1% pet. flurbiprofen, 5% tiaprofenic acid, and 3% ketoprofen lotion in 5 normal subjects, showed no reactions 2 days after application or 1 day after irradiation.

Discussion

Among non-steroidal anti-inflammatory drugs (NSAIDs), arylpropionic acid derivatives (APADs) are

extensively used systemically and topically. Allergic and photoallergic contact dermatitis are well known as adverse effects of APADs, especially ketoprofen and tiaprofenic acid (2–4). Recent, cross reactivity has been reported among APADs (2–4).

Flurbiprofen (Ansaid®, Ocuphen®), an APAD, is usually used orally and causes cutaneous side-effects (6%) and rarely photosensitivity (<1%) (5). In a previous study of 123 patients with allergic reactions to topical APADs (3), only 1 case had contact dermatitis due to flurbiprofen. Our case showed allergic contact dermatitis from flurbiprofen in a poultice after 1-day use. It is suggested that our patient may previously have been sensitized to oral flurbiprofen and/or other similar derivatives.

Cross-reactivity studies on flurbiprofen are also rare (2, 3, 6). A case of contact allergy to ibuprofen had cross-sensitization to flurbiprofen and fenoprofen (3). Another case with photocontact dermatitis from ketoprofen showed cross-photosensitivity to ibuprofen and flurbiprofen (2). Valsecchi et al. (6) reported a patient with photocontact dermatitis due to tiaprofenic acid and cross-photosensitivity to flurbiprofen. Our case with contact sensitivity to flurbiprofen did not show cross-reaction to ibuprofen or fenoprofen, but had photocontact allergy to ketoprofen and tiaprofenic acid (Fig. 1).

Benzophenone and its closely-related thiophene-phenylketone structures are thought to be responsible for photocontact allergy to ketoprofen and tiaprofenic acid, respectively (5). An in vitro study (7) indicates that 3-ethyl-benzophenone, a photodegradation product of ketoprofen, may be involved in photoallergy to ketoprofen. On the other hand, Cusano & Capozzi (8) reported a patient with photocontact dermatitis from ketoprofen who demonstrated positive patch and photopatch tests to ibuprofen without a benzophenone moiety, but no reactions to 2 APADs without a benzophenone structure, ibuprofen and naproxen. Our case also showed contact allergy to flurbiprofen without a benzophenone moiety and photocontact sensitivity to benzophenone-related ketoprofen and tiaprofenic acid, suggesting that cross-sensitivity of APADs in some cases may not be related to the benzophenone moiety. Photoproducts of ketoprofen and tiaprofenic acid may have some common structural features with flurbiprofen and may share the same antigenic determinant.

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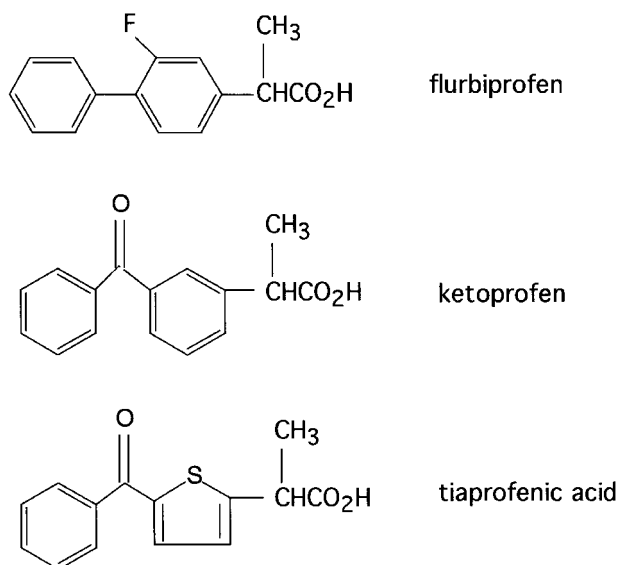


Fig. 1. Chemical structures of flurbiprofen, ketoprofen, and tiaprofenic acid.

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Axillary dermatitis from farnesol in a deodorant

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Key words: allergic contact dermatitis; farnesol; deodorant; fragrance; bacteriostat; cosmetics; Myroxylon Pereirae; balsam of Peru. © Munksgaard, 2000.

Deodorant hypersensitivity reportedly accounts for 5–15% of adverse reactions to cosmetics, and fragrances are the most frequently identified allergens responsible (1).

Case Report

A 23-year-old woman, with nickel allergy, presented with a long history of axillary dermatitis, predominantly around the axillary margins. She shaved her axillary hair and initially suspected razor blades as the cause. However, symptoms improved on changing to a different deodorant spray and worsened again with reuse of the former deodorant.

Patch testing with standard allergens, a fragrance series and the suspected deodorant showed positive reactions to nickel, palladium, oak moss and the deodorant as is at D3. Further testing with the ingredients of the deodorant revealed a ++ reaction to farnesol and a + reaction to the perfume of unknown composition (Table 1).

Discussion

Farnesol in deodorant is both a fragrance and a bacteriostat (2). 10% of 71 deodorants on the European market were found to contain farnesol (3). According to product labeling, nearly 50% of deodorant vaporsprays on sale locally contain farnesol.

Goossens & Merckx (4) previously reported axillary dermatitis due to farnesol sensitization (4). Unlike their positive patients, our patient did not react widely to other fragrances tested. Farnesol can be detected in balsam of Peru (Myroxylon Pereirae) and in poplar buds (5), Goossens & Merckx (4) observing positive patch test reactions to Myroxylon Pereirae in 6 of 8 farnesol-allergic patients. As our patient was only doubtfully positive to Myroxylon Pereirae and negative to propolis, it seems more likely that farnesol in the deodorant, rather than traces of farnesol in Myroxylon Pereirae, was the primary sensitizer.

Theoretically (3), and experimentally in guinea pigs (5), farnesol is a weak sensitizer. While farnesol allergy is not likely to be common, it should be considered in axillary dermatitis with otherwise negative patch tests.

Table 1. Patch test reactions at D3

<i>Standard series</i>	
nickel sulfate (5% pet.)	+++
palladium chloride (1% pet.)	++
Myroxylon Pereirae (25% pet.)	?+
propolis (10% pet.)	–
colophonium (20% pet.)	–
fragrance mix (8% pet.)	–
<i>Deodorant</i>	
deodorant (as is)	++
farnesol (1% pet.)	++
perfume 1 (conc. as in product)	+
perfume 2 (1% pet.)	–
other ingredients of deodorant	–
<i>Fragrance mix series</i>	
oak moss absolute (1% pet.)	+
α -amyl cinnamic aldehyde (1% pet.)	–
eugenol (1% pet.)	–
geraniol (1% pet.)	–
hydroxycitronellal (1% pet.)	–
isoeugenol (1% pet.)	–
cinnamal (1% pet.)	–
cinnamic alcohol (1% pet.)	–
<i>Other fragrances</i>	
benzyl salicylate (1% pet.)	–
clove oil (2% pet.)	–
orange peel oil (2% pet.)	–
vanillin (10% pet.)	–
benzaldehyde (5% pet.)	–
cedarwood oil (10% pet.)	–
eucalyptus oil (2% pet.)	–
laurel oil (2% pet.)	–
lemongrass oil (2% pet.)	–
orange blossom oil (2% pet.)	–
peppermint oil (2% pet.)	–
salicylaldehyde (2% pet.)	–

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Sensitive skin as subclinical expression of contact allergy to nickel sulfate

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Key words: sensitive skin; subclinical dermatitis; contact dermatitis; nickel sulfate; cosmetics. © Munksgaard, 2000.

Sensitive skin reacts exaggeratedly to external factors (1, 2). Approximately 40% of the population believe that they have it (3). The stinging test is widely accepted as a marker of such sensitivity, though subjects with sensitive skin are a heterogeneous population with regard to such parameters as barrier function (4–6). We have investigated a group of such subjects for contact allergy.

with the GIRDCA standard series integrated with 27 allergens were performed according to routine procedure. A control population of 49 female subjects, aged 18 to 35 years, with no history of skin diseases, underwent the same patch tests. Data of the overall frequency of sensitization and that to nickel sulfate were compared employing the χ^2 test.

Patients and Methods

49 healthy Caucasian female volunteers, aged 20 to 40 years, with sensitive skin according to their own assessment, were enrolled in the study, after informed consent. All were confirmed to have sensitive skin based on a questionnaire about sensitivity to various environmental factors and intolerance to topical products. Patch tests

Results

33 subjects with sensitive skin showed positive responses to 1 or more allergens (Table 1), 19 (57.6%) of them to nickel sulfate (13 +++ and 6 ++ reactions) and giving a history of intolerance to jewellery and cosmetics. In contrast, in the control population, only 15 subjects showed positive patch test responses, including only 5

Table 1. Patch test results

Allergen	Subjects with sensitive skin			Healthy subjects		
	no. positive responses	degree of positivity		no. positive responses	degree of positivity	
		++	+++		++	+++
nickel sulfate	19	6	13	5	1	4
fragrance mix	3	3	0	2	2	0
neomycin sulfate	1	1	0	1	1	0
oleamidopropyl dimethylamine	1	1	0	0	0	0
gold sodium thiosulfate	1	1	0	2	2	0
thimerosal	1	0	1	0	0	0
p-phenylenediamine	3	3	0	1	1	0
eugenol	1	1	0	1	1	0
phenol-formaldehyde resin	1	1	0	1	1	0
thiuram mix	2	2	0	0	0	0
balsam of Peru (Myroxylon Pereirae)	0	0	0	1	1	0
cobalt chloride	0	0	0	1	0	1

nickel sulfate reactions. Differences in the frequency of sensitization to all allergens and to nickel sulfate between the 2 populations were statistically significant ($p \leq 0.05$).

Discussion

Subjects with sensitive skin show a high frequency of contact allergy, especially to nickel sulfate. Relevance of sensitization may be suggested by the frequent positive history of intolerance of facial skin to topical products in these patients. This aspect is often underestimated and in most patients, no patch testing is performed. We conclude that a consistent group of subjects with sensitive skin are in fact persons with subclinical allergic contact dermatitis, probably reacting to minimal doses of nickel or other allergens present in cosmetics and other topical products.

Occupational allergic contact urticaria from maleic anhydride

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Key words: occupational; contact urticaria; skin; allergic; rhinitis; conjunctivitis; maleic anhydride; phthalic anhydride; polyester resin; IgE-mediated; plastics industry; lack of cross-sensitivity. © Munksgaard, 2000.

Case Report

A 32-year-old non-atopic process operator presented with rhinitis, dyspnea, conjunctivitis and whealing, the respiratory symptoms preceding the skin symptoms. He had previously worked as a carpenter and with cement, and for 3 years in a firm manufacturing polyester resin prior to onset. His job was to pour maleic anhydride (MA) granules from 25-kg sacks into a 1000-kg vessel. He used a fresh-air helmet because of the dust. Styrene and glycol were led to the same vessel to produce unsaturated polyester (UP) resin. He also decanted, via a hose, the UP resin into 10, 20, 200 and 1000-litre bottles or containers. This exposed him to: (a) phthalic anhydride (PA), according to the material safety data sheet (MSDS) containing 100% PA, and 0.05% MA; (b) isophthalic anhydride; (c) MA, 100% according to the MSDS (Crudex Chemicals, Espoo, Finland); (d) hydrophilic amorphous fumed silica; (e) acetone; (f) glycol; and (g) styrene.

His skin symptoms were itchy wheals, 0.5–3 cm in diameter, over the entire body, including the face. These work-related urticarial lesions partly subsided overnight but lasted for 1 to 2 days and did not always clear totally during weekends.

Prick and patch tests were performed as previously described (1). On patch testing, a modified European standard series, antimicrobial series, plastics and glues series, and phenol-formaldehyde resin series were negative, as were patch tests with the patient's own MA 1%

and 0.1% in petrolatum (pet.), PA 1% and 0.1% pet., uncured UP resin 5% pet., styrene 1% pet., 2 gloves and hydrophilic amorphous fumed silica, tested as is. Prick tests with standard environmental allergens, gave a 5-mm reaction (histamine 10 mg/ml, 7 mm) to willow (*Salix*). In a phthalic anhydride series (Fig. 1), as previously described (1–3), maleic anhydride – human serum albumin (MA-HSA; 1% HSA) gave a 14-mm reaction, whereas the other organic phthalic acid anhydrides [PA; trimellitic anhydride (TMA); methylhexahydrophthalic anhydride (MHHPA) and methyltetrahydrophthalic anhydride (MTHPA)], were negative. A prick test series of polyester resins was negative.

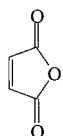
An open test on intact skin with the MA-HSA conjugate used for prick testing was negative at the 1st reading (20 min), but provoked whealing after 40 min. His own MA (1% aq.) was negative on open testing (20 min), but when undiluted, provoked strong whealing (20 min). This was accompanied by severe rhinitis and milder whealing outside the test area, demonstrating stage 3 of the contact urticaria syndrome (4).

Radioallergosorbent tests (RAST) to MA and PA were performed as described earlier (1–3, 5). RASTs to MA-HSA (9.4 kU/l, RAST class 3) and to PA-HSA (2.4 kU/l, RAST class 2) were elevated. RASTs to other phthalic anhydrides were not performed. Total IgE was elevated at 597 kU/l.

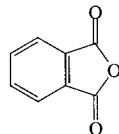
Based on anamnestic data, prick tests, RASTs and provocation tests, it was concluded that the patient had occupational allergic IgE-mediated rhinoconjunctivitis

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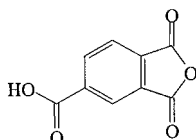
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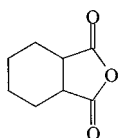
maleic anhydride (MA)



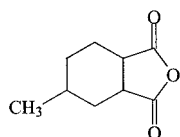
phthalic anhydride (PA)



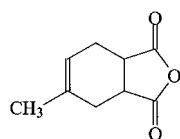
trimellitic anhydride (TMA)



hexahydrophthalic anhydride (HHPA)



methylhexahydrophthalic anhydride (MHHPA)



methyltetrahydrophthalic anhydride (MTHPA)

Fig. 1. Organic acid anhydride hardeners.

and contact urticaria from MA. Because of the risk of occupational asthma, he was recommended not to continue in his work. At a follow-up visit 6 months later, he was symptomless, and in training for a new job.

Discussion

Organic phthalic anhydrides (Fig. 1) are well-known sensitizers but, to our knowledge, allergic contact urticaria from MA has not previously been reported. MA forms colorless needles, has a MW of 98.06, and is soluble in water, acetone and alcohol. It is used in polyester resins, alkyd coating resins, fumaric and tartaric acid

manufacture, pesticides, preservatives for oils and fats, textile resins, plasticizers, pharmaceuticals, and vulcanizing retarders (6).

Our patient worked in the production of UP resins, which are used to form composites with glass fibers, as well as for coatings, finishes, cements (putties) and glues (7, 8). Polyesters are formed by ester linkage between dibasic acids, such as maleic, fumaric and phthalic acids, or their anhydrides, and glycols. In UP resin manufacture, 30–50% styrene is added to reduce viscosity as a cross-linker of linear polyester chains. Accelerators, e.g., cobalt naphthenate or tertiary amines such as dimethyl aniline, diethyl aniline and dimethyl-p-toluidine, are necessary for the curing of such plastics at room temperature. Hydroquinone is usually added to prevent premature cross-linking. In addition, various auxiliary compounds are used to manufacture UP resins for different purposes: pigments, fillers, inhibitors, accelerators, UV-protecting agents, stabilizers and flame retardants (7, 8). Accordingly, patients exposed to UP resins may develop allergy to a large number of different chemicals.

The actual allergen in UP resin has been thought to be one of the starting substances in its production, such as free or terminal maleic acid, fumaric acid or adipic acid, ortho-phthalic anhydride, maleic anhydride or maleic esters, phthalic anhydride, polyester methacrylate and diethyleneglycol maleate (7, 8).

MA has previously been reported to cause respiratory symptoms (9–12), a positive patch test reaction to MA being recorded in 1 study (13), but we know of no reports of occupational allergic contact urticaria. On prick testing, MA did not cross-react with other organic anhydrides, though MHHPA, MTHPA, TMA and PA often do cross-react. We have previously reported occupational rhinitis and allergic contact dermatitis from MHHPA (3), and occupational contact urticaria from MHHPA (2, 14–15).

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Contact leukoderma following nickel dermatitis elicited by TENS electrode plates

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Key words: contact leukoderma; nickel; transcutaneous electrical nerve stimulation; vitiligo; allergic contact dermatitis. © Munksgaard, 2000.

Chemical leukoderma has been described both experimentally (1, 2) and occupationally (3–6). Phenols are the most common cause (7, 8), others being p-phenylenediamine (9–11), cinnamal (12), hydroquinone (13, 14), hair dyes (11), azo dyes (15), thiotepa (16), and acrylics (17). Swim goggles have also been reported (18), as well as diphencyprone and squaric acid dibutylester in alopecia areata (19, 20). Laser resurfacing may also induce contact leukoderma (21, 22). Contact leukoderma has only ever been reported from nickel in 2 patients with metal spectacle frames (23).

Transcutaneous electrical nerve stimulation (TENS) is known to be associated with irritant or allergic contact

dermatitis (24), the latter most often due to nickel in the electrodes.

Case Report

A 6-year-old girl presented with well-circumscribed macules of leukoderma on both legs. There was a history of vitiligo in her father's family. She had a partial nerve paralysis of the legs of unknown etiology, and was being treated daily with TENS using special prostheses, with metal electrode plates applied to the skin just below the knees and above the ankles.

Shortly after initiation of TENS, she developed an itchy dermatitis and subsequently leukoderma (Fig. 1). She had a history of earlobe dermatitis following earpiercing and of nickel-containing jewelry causing dermatitis. The leukoderma developed at all sites of electrode contact as 4 well-circumscribed macules 5–7 cm in diameter, the leukoderma extending several cm beyond the dermatitis (Fig. 1). There were no other areas of leukoderma elsewhere on her skin.

Her nickel dermatitis and leukoderma was treated with a potent topical corticosteroid, which healed the dermatitis and led to follicular repigmentation. Patch testing was not consented to by her father because of the risk of further depigmentation.

Discussion

When considering a diagnosis of contact leukoderma, firstly, there should be little or no contact dermatitis,



Fig. 1. Leukoderma extending beyond eczematous plaque on medial upper right leg.

which could lead to post-inflammatory depigmentation, or secondly, depigmentation should extend beyond any dermatitis that there is. The clear extension of leukoderma beyond the borders of the nickel dermatitis in our patient (Fig. 1) indicates autoreactivity towards melanocytes.

Recent studies of T-cell activation in patients with vitiligo have shown elevated levels in the serum of soluble interleukin 2 receptors (25), significantly higher in patients with focal vitiligo than segmental or generalized vitiligo. Melanocyte-specific cytotoxic CD8+ T lymphocytes have also been demonstrated in patients with vitiligo (26). Our patient may have inherited from her father T cells cytotoxic towards her melanocytes, which the nickel dermatitis activated. This observation is in line with the results of immunotherapy for alopecia, where 10 of 132 treated patients developed leukoderma, 4 of these 10 patients having vitiligo elsewhere (20). Without such a predisposition, nickel would not have caused leukoderma.

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Reproducibility of the atopy patch test with whole house dust mite bodies in atopic dermatitis

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Key words: atopy patch test; atopic dermatitis; aeroallergens; house dust mites; *Dermatophagoides*; reproducibility; patch testing technique. © Munksgaard, 2000.

The atopy patch test (APT) with house dust mites (HDM) (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) has been employed in the study of atopic dermatitis (AD) on the grounds that a subgroup of such patients react positively to application of HDM extracts to the skin (1), and some individuals with AD show an exacerbation of symptoms after exposure to these allergens (2), the %s of positive subjects in the studies performed varying from 15% to 100% (3). This variation has been ascribed to absence of standardization of the techniques employed, varying purity of allergens. (4–6), and irritability of the skin in patients with AD (7).

Patients and Methods

We have patch tested with crushed whole bodies of house dust mites (HDM) at a concentration of 20% (*D. pteronyssinus* 50%: *D. farinae* 50%) pet. (Allergopharma-Bracco): (i) 17 subjects with AD, diagnosed according to the Hanifin & Rajika (8) criteria, with mean age 24.7 years (18–41). This group consisted of 16 males and 1 female. (ii) 12 non-eczematous atopic (NEA) male volunteers. This was a group with mean age 20.3 years (18–27), and no history of eczema. 4 patients had rhinitis, conjunctivitis, urticaria; 8 had no symptoms ("latent atopic individuals" (4) or "atopic state" (9)). All were selected by positivity to skin prick tests with aeroallergens/foods and/or by raised total serum IgE. (iii) 11 male healthy volunteers (HV), with mean age 22.4 years (18–35). They had no history of eczema or other allergic diseases, negativity of prick tests with aeroallergens/foods and normal total serum IgE.

The allergen was applied in Finn Chambers (Epitest Ltd, Oy, Finland) on healthy untreated upper back skin. Reading of the APT was performed according to criteria suggested by Darsow et al. (4). All patients were patch tested again after a time interval varying from 15 days to 18 months. The reproducibility of the APT was evaluated by statistical κ calculus (the Choen test).

Table 1. Reproducibility of APT with extract of house dust mites at a concentration of 20%

	1st test	2nd test	Statistical κ
AD	10 pos/7 neg	9 pos/8 neg	0.83
NEA	5 pos/7 neg	3 pos/9 neg	0.63
HV	3 pos/8 neg	3 pos/8 neg	1

Reproducibility (κ): <0.20=unsatisfactory, 0.21–0.40=barely satisfactory, 0.41–0.60=fairly satisfactory, 0.61–0.80=satisfactory, 0.81–1=high satisfactory.

Results

Reproducibility of the APT in the doubly tested groups is showed in Table 1. It was highly satisfactory in the AD and HV groups and satisfactory in the NEA group.

Discussion

Only a small number of subjects positive to the APT have ever been reported as tested again (5, 6, 10). Furthermore, patients negative to the 1st test have not been tested a 2nd time, nor non-eczematous patients with atopic mucosal disease or "atopic state" and healthy subjects tested 2 $\times$. Our results suggest that the APT, especially in AD, is hardly influenced by skin irritability. Highly satisfactory reproducibility of the APT was also obtained in the 3 healthy subjects who were positive on testing. Other authors have also noticed this positivity of the APT in non-atopic subjects (11–14). Now, further experience of the reproducibility of the APT, in larger numbers of patients, and employing extracts of HDM purified and applied at higher concentrations (3–6, 11, 12, 14), is needed.

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Statistics on occupational contact dermatitis from (meth)acrylates in dental personnel

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Key words: occupational; allergic contact dermatitis; (meth)acrylates; dental staff; statistics; epidemiology. © Munksgaard, 2000.

Occupational allergic dermatoses in dental personnel have greatly increased over the past decade (1), the major causes being natural rubber latex (NRL) (2) and (meth)acrylates (1–3).

Materials and Methods

Details of data collection from the Finnish Register of Occupational Diseases have been reported earlier (1, 4, 5). Analyses of dentists, dental nurses and hygienists, and dental technicians for the years 1975–1998 were done using the Finnish classification of occupations (6) and including both allergic contact dermatitis and contact urticaria/protein contact dermatitis.

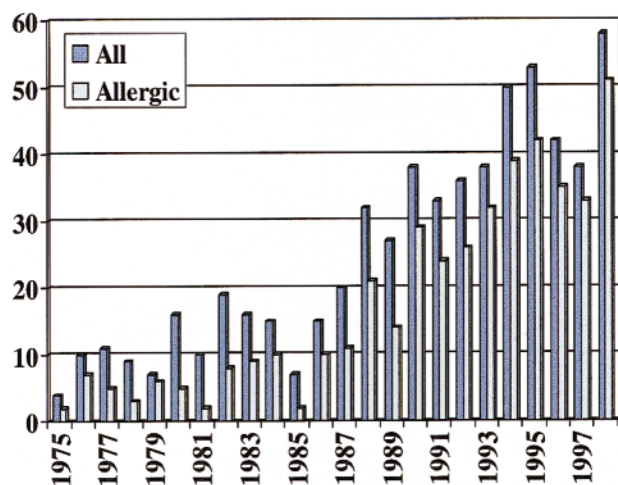


Fig. 1. Total numbers of occupational skin diseases reported in dental personnel in Finland 1975–1998.

Results

A total of 630 cases of occupational dermatoses in dental personnel were reported to the Finnish Register during 1975–1998, 445 (70.6%) of which were allergic, and the number of cases greatly increased during the last decade (Fig. 1). No cases of occupational (meth)acrylate allergy were reported in 1975–1981. During 1982–1998, 161 occupational (meth)acrylate cases were reported, most of these, i.e., 140 (=87%), being allergic. The number of cases remained low until 1987, but has increased since (Fig. 2). The sharp increase in such cases can be seen when they are compiled into 8-year periods: from 3 cases in 1975–1982, to 35 cases in 1983–1990, and 102 cases in 1991–1998 (Fig. 3), the largest annual number of cases of occupational dermatoses and occupational dermatoses from (meth)acrylates in dental personnel being reported in 1998.

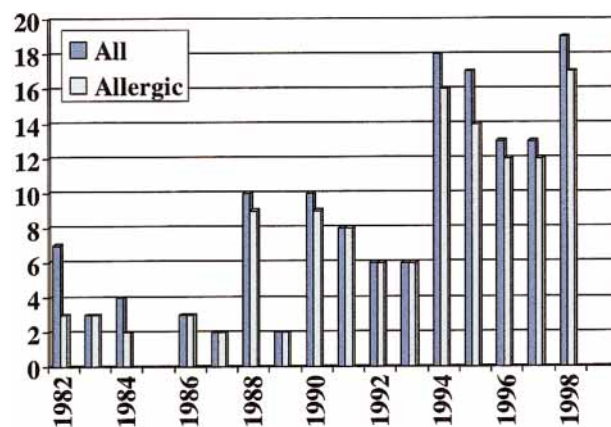


Fig. 2. Numbers of occupational skin diseases reported in dental personnel from (meth)acrylates in Finland 1982–1998.

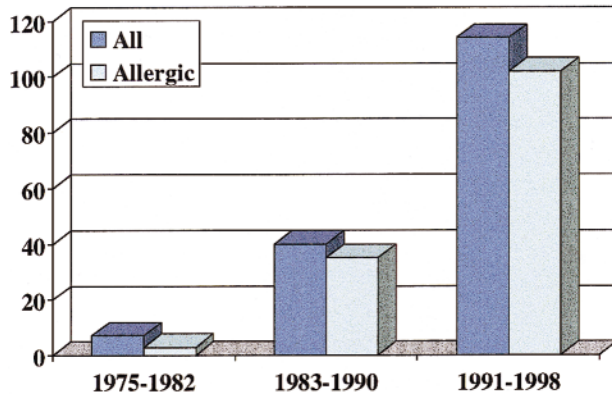


Fig. 3. Large increase in occupational dermatoses from (meth)acrylates when compiled into 8-year periods.

Discussion

Occupational allergic contact dermatitis from (meth)acrylates in dental personnel has been reported since the 1950s (7), but the number has considerably increased in the past decade (3, 8). Acrylic monomers rapidly penetrate NRL, polyvinyl chloride (PVC) and polythene gloves (9,10) and therefore no-touch techniques should be allowed by product packaging. Accurate material safety data sheets should be required from manufacturers prior to marketing (11–13). Our number of cases of contact dermatitis from (meth)acrylate allergy in dental technicians seems relatively low compared to Germany (14).

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Allergic contact dermatitis from sodium metabisulfite in an antihemorrhoidal cream

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Key words: antihemorrhoidal cream; sodium metabisulfite; perianal; medicaments; allergic contact dermatitis.
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Case Report

A 55 year-old butcher, with no personal history of atopy, diagnosed as having hemorrhoids 2 years ago, had been applying Hubber® antihemorrhoidal cream for variable periods of time. He presented with a 1-month history of pruritic, erythematous scaly plaques, starting in the perianal area and spreading in a few days to the upper

limbs and occipital area. Avoidance of the antihemorrhoidal cream and topical corticosteroid therapy improved the lesions in 2 weeks.

Patch tests with the GEIDC standard series, Hubber® antihemorrhoidal cream as is and its components (Table 1) showed positive reactions (++) at D2 and D4 to nickel sulfate, cobalt chloride, Hubber® antihemorrhoidal cream, sodium metabisulfite, neomycin, prometha-

Table 1. Results of patch testing with components of Hubber® antihemorrhoidal cream

		D2	D4
neomycin sulfate	20% pet.	++	++
hydrocortisone base	2.5% alc.	—	—
promethazine	1% pet.	++	++
retinol	0.1% pet.	—	—
sodium metabisulfite	2% pet.	++	++
aluminium hydroxide	10% aq.	—	—
2-octadecanol	30% pet.	—	—
polyoxyethyleneglycol	4% pet.	—	—
ethylene glycol	5% alc.	—	—
methylparaben	3% pet.	—	—
propylparaben	3% pet.	++	++

zine and propylparaben. Patch tests at D2 and D4 with sodium metabisulfite 2% pet. in 37 controls were negative.

Comment

Sodium metabisulfite is an antioxidant preservative and a reducing agent, widely used in the food, beverages, drugs, cosmetics, photographic and pharmaceutical industries (1). Oral or inhalatory exposure to it in asthmatic patients may provoke bronchospasm, urticaria and angioedema (2). It is also considered an irritant, particularly in atopic patients (3). Allergic reactions of immediate, occupational and non-occupational delayed type to metabisulfites have been reviewed by Vena et al. (2).

Non-occupational allergic contact dermatitis from sodium metabisulfite has occurred from antifungals (3–6),

topical corticosteroids (7, 8) and local anesthetics (3). To date, perianal allergic contact dermatitis from sodium metabisulfite in an antihemorrhoidal cream has not been reported. Positive patch tests to sodium metabisulfite (1) and sodium sulfite (9) have been elicited with a relatively high frequency, though the clinical relevance of such positive reactions remains to be established.

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Coexistence of immediate and delayed-type allergy to natural rubber latex

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Key words: allergic contact dermatitis; natural rubber latex; positive patch test; positive prick test; protective gloves; dental assistant; occupational. © Munksgaard, 2000.

Natural rubber latex-induced occupational dermatitis has traditionally been thought to result from immediate-type allergy, neglecting the possibility of a delayed-type reaction.

Case Report

A 37-year-old female dental assistant presented with an eruption on her digits and hands following the use of natural rubber latex (NRL) gloves. A prick test was performed with Prick-lanceter (EWO Care AB, Bredaryd, Sweden). A latex extract solution, produced by incubating 0.2 g of ammoniated latex in 1 ml water for 30 min (1), was injected intradermally. 20 min later, the patient showed strongly positive reactions as compared to 1%

histamine. Patch testing was done, using Finn Chambers (Epitest, Tuusula, Finland) and Scanpor tape (Norgesplaster, Norway), according to ICDRG recommendations. Closed patch tests to both the latex extract solution and latex sheet resulted in + reactions at D2 and ++ reactions at D3, while all other related allergens (thiuram mix, PPD black rubber mix and mercapto mix) were negative. NRL showed a high level of specific IgE (48.3 UA/ml: 0.34>) by Pharmacia CAP-RAST.

Discussion

Since Nutter's 1st report of contact urticaria (2), allergy to NRL has been much studied. In the past, its mechanism has been considered to be an immediate-type re-

sponse. There have been many recent reports, however, demonstrating involvement of a delayed-type reaction in such cases (3–7). Mass screening has revealed positive cases using either patch testing or an intradermal test for latex (8–10). This issue, however, remains controversial due to the possibility of false-positive reactions in the above reports (8).

Here, we have presented a case of contact dermatitis with strongly positive reactions to NRL on both patch and prick testing. These results suggest that the patient had both immediate and delayed-type hypersensitivity to NRL, though the possibility of prior sensitization to NRL during everyday in exposure could not be excluded. We conclude that a delayed-type reaction should also be considered in patients presenting with NRL allergy, and recommend patch testing to NRL as part of their routine screening.

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Concurrent Type I and Type IV natural rubber latex hypersensitivity?

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Key words: natural rubber latex; immediate-type allergy; delayed-type allergy; nurse; health care workers; gloves; atopic eczema; occupational. © Munksgaard, 2000.

Case Report

A 28-year-old nurse, with lifelong atopic eczema and asthma, presented with marked deterioration in her eczema, especially on the hands, wrists and forehead. She complained of irritation and redness of her hands when wearing latex gloves, but initially denied other symptoms suggestive of immediate natural rubber latex (NRL) hypersensitivity.

An NRL prick test (Stellergènes) was negative, and RAST testing to NRL only weakly positive (grade 2/6). She was patch tested to the European standard series of allergens and to 2 different brands of low-protein latex gloves and 1 brand of vinyl gloves, applied for 2 days with readings at day 2 and day 4. The standard series was entirely negative. Both brands of latex glove produced identical results: D2/D4 –/+, the vinyl glove being negative at both readings.

Further patch tests to the constituents of mercapto mix, thiuram mix, carba mix, BHA, BHT and to the NRL prick test (Stellargenes) were performed, and the tests to thiuram mix, mercaptobenzthiazole, mercapto mix and N-IPPD repeated, with negative results. Later patch testing was performed with ammoniated NRL. 30 min after application, the patient developed intense irritation with a large area of spreading urticaria around the site of appli-

cation, she felt faint and became pale, her blood pressure was normal and there were no respiratory symptoms. The NRL was removed; complete recovery occurred within 2 h following i.v. chlorpheniramine.

Repeat NRL prick testing was performed with reagents from Stellergènes, ALK Abellö at 3 concentrations (Hep 1, Hep 10, Hep 100) and ammoniated NRL. The results to Stellargenes, ALK Hep 1 and Hep 10 were negative. The ALK Hep 100 and NRL tests produced urticated plaques >100 mm in diameter, accompanied by mild systemic symptoms.

The patient was switched to non-latex gloves at work with almost complete resolution of her rash. Subsequent questioning revealed a local reaction to latex gloves during dental treatment that she had overlooked earlier.

Discussion

This case illustrates the potential difficulties in the diagnosis of Type I NRL hypersensitivity. This diagnosis cannot explain the clinical picture of a delayed hypersensitivity reaction on patch testing or the substantial improvement that occurred on switching to vinyl gloves. A reaction to a chemical in gloves hitherto unrecognized as a cause of allergic contact dermatitis cannot entirely be excluded. The fact that the reaction occurred to 2

different brands of latex gloves makes this less likely. Type IV latex sensitivity has been reported by a number of authors (1, 2).

An anaphylactic reaction to latex used for patch testing has been reported (3), indicating the need for care in the use of NRL patch tests. The adverse reaction reported in this case supports the need for caution. In the absence of a reliable in vitro test for delayed hypersensitivity, it is impossible to diagnose Type IV hypersensitivity confidently in the face of concurrent Type I allergy. Several features of this case provide strong circumstantial evidence to support this dual diagnosis.

Patch test reactions to natural rubber latex: irritant or allergic?

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Key words: natural rubber latex; contact urticaria; allergic contact dermatitis; patch testing technique. © Munksgaard, 2000.

We have previously seen positive patch test reactions to natural rubber latex (NRL) preserved solely with ammonia, that we have interpreted as allergic in nature (1, 2). Some consider these reactions to be irritant (3), though others found reactions that they considered allergic and relevant (4, 5). There are further reports of allergic contact dermatitis from NRL in the absence of contact urticaria (6–9), though the source of latex used for testing and nature of any additives was less clear.

Patients and Methods

NRL preserved solely with ammonia (obtained from the Malaysian Rubber Research Institute, Kuala Lumpur, Malaysia) was included in the standard series and all reactions recorded, whether interpreted as allergic or irritant. Patients were prick tested with NRL preserved solely with ammonia and a standardized prick test solution (100 HEP Soluprick latex SQ, ALK-Abelló, Reading, UK), where clinically indicated. Histamine and normal saline were used as positive and negative controls. When a glove allergy was suspected, patients were further tested to a rubber series, including a piece of rubber glove and the standardized prick test solution at 3 dilutions (100, 10 and 1 HEP).

Results

554 patients were patch tested to the NRL preserved solely with ammonia in the standard series. The results are summarized in Tables 1, 2. All patients positive on prick testing to NRL preserved solely with ammonia also had a positive prick test to the commercial NRL extract. The association of any reaction on patch testing was highly correlated with the presence of a positive

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prick test (χ^2 : $p < 1 \times 10^{-21}$ for all patients and $p < 1 \times 10^{-15}$ for those with a personal history of atopy). In 2 patients presenting with facial atopic eczema, a prick test was performed only following a positive patch test, with positive results.

2 reactions in the atopic population and 1 in the non-atopic were interpreted as irritant. There was 1 patch test reaction to NRL in the absence of a positive prick test that was interpreted as allergic in a non-atopic individual, who also reacted to the thiuram and carba mixes.

Over an overlapping period, 97 patients were patch tested to the rubber series. There were 8 patch test reactions, 5 of which were interpreted as allergic to the am-

Table 1. Correlation of prick and patch test results in 554 unselected patch tested patients

		patch test	
		+	–
prick test	+	8	24
	–	3	519

Table 2. Correlation of prick and patch test results in 273 patients with a personal history of atopy (eczema, asthma or hay fever)

		patch test	
		+	–
prick test	+	8	20
	–	1	244



Fig. 1. Strong positive reaction to latex interpreted as allergic.

moniated NRL. All allergic reactions occurred in individuals with a positive prick test. There were no reactions to the commercial prick test solution at any concentration.

There were 4 reactions to the piece of rubber glove. In 2 of these, there were reactions to the thiuram mix and in 1 to NRL. Of the remaining 2, in 1, the only other patch test reaction was to NRL, and in 1, there was no other patch test reaction to identify the causative allergen.

Discussion

Positive reactions to NRL on prick and patch testing were strongly associated. The positive prick tests predominantly occurred in an atopic group, who it could be argued are more susceptible to irritant reactions (10). However, when the data are analysed using a purely atopic population, the association remains highly significant, suggesting that the patch test reactions are immune-mediated rather than an irritant phenomenon. Furthermore, in 2, the presence of latex contact urticaria was identified only because of the positive patch test.

Irritant reactions to NRL do occur. The previous study of Wakelin et al. (3) specifically excluded from testing the majority of individuals with contact urticaria to NRL, which probably accounts for the preponderance of irritant reactions seen in their study. Interestingly, of their 608 patients, 4 had contact urticaria and, of these, 3 had doubtful positive reactions to 3 of the 4 latex samples tested. However, the photograph of the reactions in 1 appears weak and irritant. Whilst weak positive reactions should be interpreted with caution, we still consider that NRL patch tests may be of value, especially in those with hand dermatitis, as an explanation of an otherwise unexplained reaction to rubber glove (Fig. 1). This occurred in 1 of these patients and has been seen by others (4, 5).

When patch testing individuals known or suspected as having latex allergy, we keep the patient in the department for at least 30 min following application of the tests. To date, we have had no adverse reactions, though anaphylaxis following application of a latex patch test

has been seen in 1 individual not recognized to be latex-allergic out of 5000 individuals tested (4). The reaction began 30 min following application. In this study, 1.6% of patients had + or ++ reactions interpreted as allergic, which fell to 1% when individuals with latex contact urticaria were excluded. We have seen a higher rate in a selected population of glove users with hand dermatitis (2). It would seem prudent to exclude from testing those with immediate-type reactions, who need in any event to avoid contact with NRL.

It would be useful to have a standardized, non-irritant allergen, but patch tests with the standardized commercial prick test solution were negative. This could mean that the allergen is not an NRL component causing contact urticaria or a dose-related event. When used for prick testing, the sensitivity of the commercial solution rises from 70% at 1 HEP to 97% at 100 HEP concentrations. The solutions are 100% specific (ALK-Abelló, personal communication). The ammoniated latex used was specially collected without any other anti-coagulant/preservative and sent by courier, excluding a reaction to a contaminant of the NRL.

In vitro studies have demonstrated the independence of specific IgE and T-cell responses to NRL (11). The reactions to NRL would seem to be analogous to those seen with other protein allergens in a population with atopic eczema. The results of patch and immediate hypersensitivity testing are poorly correlated. Following avoidance of allergen, clearance of eczema appears better correlated with the results of patch testing (12–14).

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Allergic contact dermatitis from acrylamide in a chemical mixer

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Key words: allergic contact dermatitis; acrylamide; substituted acrylamides; acrylates; lack of cross-reactivity; occupational; plastics industry. © Munksgaard, 2000.

Case Report

A 37-year-old white female presented with a pruritic hand dermatitis that developed 3 months after beginning work as a "batch mixer" in a plastics factory. At work, she was exposed to ammonium phosphate, ammonium persulfate, sodium metabisulfite, acrylamide, N,N'-methylene bis-acrylamide, 4,4'-methylene bis-C2-chloroaniline and glycerin. When she first developed symptoms, she was not wearing gloves while mixing the chemicals. However, subsequent use of latex gloves did not significantly improve her rash. Treatment with over-the-counter topical moisturizers also did not improve her symptoms, which continued to progressively worsen. In her prior work as a waitress, she had no significant dermatologic problems. Her medical history was unremarkable.

Upon initial examination, the patient was noted to have erythema, scaling and ill-defined plaques associated with fissuring and honey-colored crusting about the hands bilaterally. Other than her work-related exposures, she denied any other significant chemical contactants, including exposure to cosmetics. The differential diagnoses included irritant or allergic contact dermatitis and/or dyshidrosis, with secondary impetigo.

Pending patch testing, treatment recommendations at initial presentation included decreased hand washing, use of moisturizers, tar soaks to the hands 2× daily, zinc oxide paste for application to the hand fissures, fluocinonide cream 0.05% 2× daily to the affected skin and erythromycin orally for the secondary infection. It was also suggested that she wear white cotton gloves under vinyl gloves while at work. 10 days later, the antibiotic was changed to cephalexin for continued treatment of her infection. In order to rule out the possibility of a latex sensitivity, an RIA to ammoniated latex, buffered latex, and latex glove extract was performed, which proved to be negative.

The patient followed the treatment recommendations for 1 month, when she chose to stop the fluocinonide cream and zinc oxide due to lack of improvement in her symptoms. She also discontinued the moisturizer and tar soaks, as she felt that these caused her dermatitis to

worsen. Subsequently, she underwent patch testing to some of her work-related chemicals, including acrylamide (0.1% pet.), sodium bisulfite (10% in water), citric acid (1% in water), N,N'-methylene bis-acrylamide (1% in alcohol) and ammonium persulfate (2.5% pet.). She was also tested to the North American Contact Dermatitis Group's (NACDG's) standard screening tray. The results of these tests revealed a strong (+ +) allergic reaction to acrylamide. In addition, she was noted to have an allergic reaction to quaternium-15. No other allergies could be identified.

The patient was subsequently instructed on allergen avoidance. She was advised to strictly avoid any exposure to acrylamide and was provided with 4-H® gloves (Safety 4, Inc., Lenexa, KS, USA) for use when working with acrylamide. In addition, since sweating can occur under occlusion by latex or non-latex gloves and can further aggravate hand dermatitis, it was suggested that she use a thick cotton glove under the 4-H® glove. Careful label reading for avoidance of quaternium-15 was also emphasized and she was changed to plain petroleum jelly for moisturization. Continued use of fluocinonide 0.05% cream and tar soaks was again stressed. On this regimen, she experienced improvement in her hand dermatitis despite only intermittent use of fluocinonide cream and tar soaks. However, she meticulously avoided acrylamide. She subsequently resigned her job of mixing chemicals and has had no recurrence of dermatitis since.

Discussion

Acrylamide is a clear, colorless to pale yellow, odorless liquid (1), which is extensively used in the production of polymers/co-polymers and grouts, in sewage/waste water treatment, in soil stabilization, and in research laboratories for the preparation of polyacrylamide gels (2–4). Acrylamide can penetrate through latex gloves. Among the gloves that we could identify to give short-term protection against acrylamide was the 4-H® glove. However, there is always the possibility that accidental contamination by acrylamide of other cutaneous sites might occur despite the use of any glove. Therefore, because it is highly neurotoxic (5–7), as well as because of its geno-

toxic, carcinogenic and reproductive effects (2–4), exposure to acrylamide is usually minimized by automated industrial control. Thus, there have been few reports of documented acrylamide-induced cutaneous pathology. Nonetheless, in reports of acrylamide-induced neurotoxicity, “peeling skin” has been identified as an early symptom (5–7), occurring before the onset of neuropathy, which our patient did not have.

Acrylamide has been associated with alopecia areata, but not dermatitis, in 7 paper factory workers, who were exposed to an acrylamide-containing mist and who displayed an acrylamide-like substance in their blood or urine on subsequent toxicological evaluation (8). A substituted, secondary acrylamide has been documented as a contact allergen in a 26-year-old man, who mixed crystalline granules of piperazine diacrylamide at work and who developed periorbital erythema and pruritic red plaques about the wrists bilaterally (9). In another report, substituted secondary acrylamides were identified as allergens among 7 printers (10). To our knowledge, this is the 1st report of allergic contact dermatitis from unsubstituted acrylamide.

Because of acrylamide’s non-dermatologic toxicities (2–7), we were unable to test controls to rule out an irritant reaction as the cause of our patient’s positive test. However, the crescendo nature of her test reaction over 4 days and its spreading, papulovesicular morphology suggest an allergic rather than an irritant response. Furthermore, the prompt clearing of the patient’s dermatitis, the lack of cutaneous symptoms while waitressing, and the non-recurrent nature of her dermatitis since discontinuing work as a chemical mixer, are all consistent with an allergy to acrylamide. Of note, the patient did not react to the substituted, secondary acrylamides to which she was tested (N,N'-methylene bis-acrylamide), nor did she react to any of the acrylates tested on the standard tray (e.g., methyl methacrylate or ethyl acrylate). This is consistent with a prior report regarding the lack of cross-reactivity between secondary acrylamides

and the acrylates (11), and further expands this lack of cross-reactivity to the parent acrylamide molecule.

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Concordance and discordance between TRUE Test and Finn Chamber

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Key words: patch testing technique; TRUE Test; Finn Chamber; chromate. © Munksgaard, 2000.

TRUE (thin-layer rapid use epicutaneous) Test supplies uniform and reproducible dispersion of allergens (1). It does not show important regional differences on the body surface (2), and its adverse effects are rare, though they include persistent reactions (3).

Patients and Methods

168 patients were patch tested simultaneously on both sides of the back with the TRUE Test standard series and the Chemotechnique standard series applied by

Finn Chamber. Readings were carried out, following the recommendations of the GEIDC, at 2 and 4 days after application of the tests, allowing 20 min between removing the patch tests and the D2 reading.

Results

While, globally, concordance was good (68%), certain allergens were more discordant than others. Potassium dichromate in 6% of cases was negative in the TRUE Test, but positive with Finn Chamber, and in 1% positive

in the TRUE Test but negative with Finn Chamber. Fragrance mix in 5% of cases was negative in the TRUE Test but positive with Finn Chamber. Nickel in 4% of cases was negative in the TRUE Test but positive with Finn Chamber, and in 2% positive in the TRUE Test but negative with Finn Chamber. Cobalt in 4% of cases was also negative in the TRUE Test but positive with Finn Chamber. In the case of wool wax alcohols, mercapto mix, MCI/MI, thimerosal and thiuram mix, the number of discordances was also similar to or higher than the number of positive concordances.

Overall, the sensitivity of TRUE Test compared to Finn Chamber was 69% and specificity 99%. However, for chromate, sensitivity decreased to 52% though specificity stayed at 99%. Fragrance mix showed an even lower sensitivity of 40%, compared to a specificity of 100%. When analysing the remaining allergens separately, the level of sensitivity was often very low, compared to Finn Chamber, while specificity remained almost without exception between 98% and 100%.

Discussion

The main criticism of the Finn Chamber method has concerned metallic salts (4), and been blamed on their uneven distribution (5, 6), which the TRUE Test has been claimed to redress. The TRUE Test Study Group found only 2% discordance between the 2 methods (7). Gollhausen et al. (8) later found a higher reproducibility of positive cases for TRUE Test compared to Finn Chamber, though the difference was not statistically significant. A Swedish study identified discordance between positive reactions to thimerosal in the 2 tests (9). In a European multicentre study, a concordance of 65% between the 2 methods was found for both Panel 1 (10) and Panel 2 (11), which agrees with other results from Gollhausen et al. (12). A higher number of irritant reactions were found with Panel 1, in which metals are included, compared to Panel 2. However, reproducibility was only 50%. In Singapore, overall concordance was similar, at about 63%, though neomycin and PPD were more often positive with Finn Chamber than with TRUE Test (13).

In our study, false-negative reactions with TRUE Test were the main concern, as we have previously underlined for chromate (14), petrolatum having been demonstrated as the best vehicle for this allergen by Lidén et al. (15). Our findings extend to fragrance and other metals. For many allergens, the relative sensitivity of the TRUE Test as compared to Finn Chamber does not exceed 70% and in some cases falls below 50%. We agree, however, with a recent study (16) that TRUE Test has high specificity and freedom from adverse effects.

Conclusions

With Finn Chamber, the majority of error is false-positive, with TRUE Test false-negative. False-positive reac-

tions are easier to dismiss on the grounds of clinical relevance, than are false-negative reactions to retrieve as diagnostic of allergic contact dermatitis. We therefore prefer Finn Chamber as a screening test method, especially for chromate and nickel, while granting TRUE Test the technical advantage of specificity.

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Routine patch testing with fragrance chemicals in The Netherlands

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Key words: allergic contact dermatitis; fragrance mix; perfumes; cosmetics; colophonium; hydroabietyl alcohol; clinical relevance; patch-testing technique. © Munksgaard, 2000.

Although the fragrance mix, present in both the European and American standard series, is useful to identify perfume-allergic patients, some 30% or more such patients are missed (1). By testing a series of individual fragrances, we aimed to identify a portion of the missing 30%.

Materials and Methods

In a multicentre study, 9 fragrance allergens were tested in all patients routinely patch tested (Table 1). These were selected either because of their widespread use in cosmetics or because they had been identified as relatively frequent allergens (1). Test procedures were carried out according to internationally accepted criteria. Hydroabietyl alcohol was purchased from Chemotechnique, the other fragrances from the Regional Health Inspectorate, Enschede. Test concentrations were chosen on the basis of published data (1) and potential irritancy was excluded in a pilot study involving 200 patients.

Results

From September 1998 to April 1999, 1825 patients were tested (range 58–571 per centre). 193 of these (10.6%) were positive to the fragrance mix (range 3.2%–37%; median 10.3%). 78 (4.3%) had a positive reaction to 1 or more of the study fragrances (range 1.2%–13%). The most positive reactions were seen to citral ($n=19$, 1.0%), the fewest to linalool ($n=3$, 0.2%) (Table 1). 31 patients (1.7%) were positive to 1 or more of the fragrance allergens, but negative to the fragrance mix. Most such reactions were to hydroabietyl alcohol ($n=12$); 5 of these also

reacted to colophonium. Of the positive reactions to the fragrance mix, 57% were considered of current relevance (range 44%–88%); for the reactions to the study on fragrance allergens in patients negative to fragrance mix, this % was 35 (range 0–100%).

Discussion

The response rate to the fragrance mix ranges worldwide from 6% to 14% in patients routinely patch tested (1, 2), only nickel yielding more positive reactions. This mix detecting 70% of all cases of fragrance sensitivity (1, 3) may be an overestimation, as it was positive in only 57% of patients allergic to popular commercial fragrances (4). The simultaneous testing of additional fragrance allergens, such as ylang-ylang oil, narcissus oil and sandalwood oil (5), or mixes of fragrances (6), will identify more fragrance-allergic individuals. However, the fragrance mix has not been improvable on for over 25 years.

In our study, the frequency of positive reactions to the individual fragrances tested was only 1% or less, and, as 2/3 of these reactions were in patients positive to the fragrance mix, most had no added diagnostic value: only 1.7% more patients possibly allergic to perfumes were identified. In 5 of the patients (allergic to hydroabietyl alcohol), contact sensitivity had already been detected by a positive patch test to colophonium (another indicator of fragrance sensitivity). Furthermore, the reactions to the fragrances were considered relevant to the patients' complaints in only 35%.

We were surprised by the wide inter-participant variation in the %s of positive reactions to the fragrance

Table 1. Results of patch testing with fragrance allergens

Allergen	Concentration and vehicle	No. patients positive	No. patients positive, fragrance mix negative
benzyl salicylate	2% pet.	10 (0.5%)	3 (0.2%)
citral	2% pet.	19 (1.0%)	4 (0.2%)
coumarin	5% pet.	13 (0.7%)	5 (0.3%)
hydroabietyl alcohol	10% pet.	17 (0.9%)	12 (0.7%)
jasmine, synthetic	5% pet.	13 (0.7%)	1 (0.1%)
lilial	5% pet.	9 (0.5%)	3 (0.2%)
linalool	20% pet.	3 (0.2%)	1 (0.1%)
methyl salicylate	2% pet.	7 (0.4%)	4 (0.2%)
ylang-ylang oil	4% pet.	18 (1.0%)	3 (0.2%)

mix, the %s of positive reactions to the study fragrances and the relevance scores. We suspect that weak (erythematous) reactions are not scored in the same manner by all of us and that our criteria for relevance assessment also differ; this needs to be evaluated.

We conclude that testing the fragrances used in this study will identify few perfume-allergic individuals not picked up by the fragrance mix (at least in The Netherlands) and we have therefore stopped testing them.

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