

Short Communications

Recommendation to include budesonide and tixocortol pivalate in the European standard series

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On behalf of the ESCD and EECDRG

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Key words: contact allergy; medicaments; corticosteroids; patch-testing technique; standard series; tixocortol pivalate; budesonide. © Munksgaard, 2000.

Contact allergy to topical corticosteroids is sufficiently common to justify their patch testing in standard series (1, 2). Frequently recommended are tixocortol pivalate as a screening test for class A (3) and budesonide for class B (4) corticosteroids. Tixocortol pivalate allergy was found in 0.9–4.4% of consecutive dermatitis patients (2, 5, 6), and budesonide allergy in 1.0–1.5% of such patients (6, 7).

Several studies have shown equivalent patch test results whether testing with these 2 markers in ethanol (eth.) or petrolatum (pet.) (8). Most corticosteroids have been tested at 1.0% eth., as is still the case with tixocortol pivalate. Budesonide has also been tested at 1.0%, though lately 0.1% has been advocated by some, because of strong reactions to 1.0%.

There are no corticosteroids at present in the European standard series. Several prerequisites should be fulfilled before such inclusion (9): (i) above 0.5–1.0%, positivity in consecutively patch tested dermatitis patients; (ii) presence in the environment of dermatitis patients; (iii) clinical relevance; (iv) no excess of false-positives; (v) minimal adverse effects of patch test. The 1st prerequisite holds true for both budesonide and tixocortol pivalate. Considering the 2nd, dermatitis patients are widely treated with corticosteroids: budesonide is not only present in some such products, but also detects allergy to group B corticosteroids and also to some esters of group D (4); tixocortol pivalate, though not present in dermatological preparations, is the best marker of hydrocortisone allergy (4). Concerning clinical relevance, reliable figures are missing for most sensitizers. With respect to the reliability and adverse effects of the patch test, irritant reactions are not common with budesonide or tixocortol pivalate. Concerning doubtful reactions, some may consider the “edge effect”, seen when patch testing potent corticosteroids like budesonide, as such. Seeing an edge reaction should indicate either a D7 reading or a patch test at a *lower* concentration. Had not a D7 reading taken place, 30.0% of corticosteroid allergy (11), 28.6% of budesonide allergy (12) and 19.0% of tixocortol pivalate allergy (6) would have been missed.

Therefore, on behalf of the ESCD and EECDRG, we recommend the insertion of budesonide and tixocortol pivalate into the European standard series (Table 1), and that such tests should be read not only on D3 or 4, but also on D7. With respect to the concentrations to be used, the following are recommended.

Addition of Budesonide 0.01% pet. (w/w)

In a multicentre study (12), 2599 consecutive dermatitis patients were patch tested with budesonide 1.0, 0.1, 0.01, and 0.001% pet. 22 reacted to at least 1 of these 4 concentrations on D3 or 4. Of these 22, 20 reacted to both budesonide 0.10 and 0.01%, the other concentrations tracing smaller numbers. Minimizing the risk of patch-test sensitization (13–14) speaks in favour of 0.01%. However, some individuals are traced only with very low concentrations of budesonide and therefore, when budesonide allergy is strongly suspected and the routine test concentration (0.01%) is negative, testing also with a *lower* concentration (0.001%) is advocated (12). A recent study investigating the stability of budesonide patch test preparations in pet. showed that they were stable in a refrigerator and deep freeze for at least 1 year (16).

Addition of Tixocortol Pivalate 0.1% pet. (w/w)

In a multicentre study, 5432 consecutive dermatitis patients were patch tested simultaneously with tixocortol pivalate 1.0% and 0.10% pet. (6). These 2 concentrations detected the same number of patients, 47/5432 (0.9%). 25.4% of the tixocortol pivalate-allergic patients were detected only by the high concentration and the same figure applied for the low concentration only. So far, no comparison has been made between pet. preparations at 1.0 and 0.10% and lower concentrations in consecutive dermatitis patients. To minimize the risk of patch test sensitization (13, 14), and because tixocortol pivalate is also rather expensive, tixocortol pivalate 0.1% pet. is recommended. However, when tixocortol pivalate allergy is strongly suspected and testing with the routine concentration (0.10%) is negative, additional testing with the

Table 1. The European standard series with the addition of budesonide and tixocortol pivalate

Compound	Con. % (w/w) in pet*	Conc. (mg/cm ²) in hydro- philic dried-on vehicle
1. potassium dichromate	0.5	0.023
2. 4-phenylenediamine base	1.0	0.090
3. thiuram mix	1.0	0.025 ³⁾
tetramethylthiuram monosulfide (TMTM)	0.25	
tetramethylthiuram disulfide (TMTD)	0.25	
tetraethylthiuram disulfide (TETD)	0.25	
dipentamethylenethiuram disulfide (PTD)	0.25	
4. neomycin sulfate	20.0	0.23
5. cobalt chloride	1.0	0.020
6. benzocaine	5.0	0.63 ⁴⁾
7. nickel sulfate	5.0	0.20
8. clioquinol	5.0	0.19 ⁵⁾
9. colophonium	20.0	0.85
10. parabens	16.0	1.00 ⁶⁾
methyl-4-hydroxybenzoate	4.0	
ethyl-4-hydroxybenzoate	4.0	
propyl-4-hydroxybenzoate	4.0	
butyl-4-hydroxybenzoate	4.0	
11. N-isopropyl-N'-phenyl-4-phenylenediamine	0.1	0.075 ⁷⁾
12. lanolin (wool wax alcohols)	30.0	1.00
13. mercapto mix	2.0	0.075 ⁸⁾
N-cyclohexylbenzothiazyl sulfenamide	0.5	
mercaptobenzothiazole	0.5	
dibenzothiazyl disulfide	0.5	
morpholinylmercaptobenzothiazole	0.5	
14. epoxy resin	1.0	0.050
15. Myroxylon Pereirae (balsam of Peru)	25.0	0.80
16. 4-tert-butylphenol-formaldehyde resin	1.0	0.040
17. mercaptobenzothiazole (MBT)	2.0	0.075
18. formaldehyde	1.0 ¹⁾	0.18
19. fragrance mix*	8.0 ²⁾	0.43 ⁹⁾
cinnamic alcohol	1.0	
cinnamal (cinnamic aldehyde)	1.0	
hydroxycitronellal	1.0	
α -amylcinnamic aldehyde	1.0	
geraniol	1.0	
eugenol	1.0	
isoeugenol	1.0	
oakmoss absolute	1.0	
20. sesquiterpene lactone mix	0.1	n.a.
alantolactone	0.033	
dehydrocostus lactone+costunolide	0.067	
21. quaternium-15	1.0	0.10
22. primin	0.01	n.a.
23. Cl+Me-isothiazolinone	0.01 ¹⁾	0.004
24. budesonide	0.01	n.a.
25. tixocortol pivalate	0.1	n.a.

* Concentration is not given in mg/cm² as different patch test systems (different size chambers, different volumes, etc.) may be used.

¹⁾ In water.

²⁾ Emulsifier: sorbitan sesquioleate 5%.

³⁾ Equal parts of TMTM; TMTD; TETD and PTD.

⁴⁾ Benzocaine, tetracaine hydrochloride, dibucaine hydrochloride (5:1:1).

⁵⁾ Clioquinol, chlorquinaldol (1:1).

⁶⁾ Methyl-4-hydroxybenzoate, ethyl-4-hydroxybenzoate, propyl-4-hydroxybenzoate, butyl-4-hydroxybenzoate, benzyl-4-hydroxybenzoate (1:1:1:1:1).

⁷⁾ N-isopropyl-N'-phenyl-4-phenylenediamine, N-cyclohexyl-N'-phenyl-phenylenediamine, N,N'-diphenyl-4-phenylenediamine (2:5:5).

⁸⁾ N-cyclohexylbenzothiazyl sulfenamide, dibenzothiazyl disulfide, morpholinylmercaptobenzothiazole (1:1:1).

⁹⁾ Cinnamic alcohol, cinnamal (cinnamic aldehyde), hydroxycitronellal, α -amylcinnamic aldehyde, geraniol, eugenol, isoeugenol, oakmoss absolute (4:2:4:1:5:2:1:5).

n.a.: not available.

higher concentration of 1.0% should be done. Investigation of the stability of tixocortol pivalate patch test preparations in pet. showed that they were stable in a refrigerator and deep freeze for at least 1 year (16).

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Occupational protein contact dermatitis from fruits

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Key words: occupational; protein contact dermatitis; fruit; profilin; cross-sensitivity; kitchen assistant; food handler; birch pollen; apple; peach. © Munksgaard, 2000.

Protein contact dermatitis (PCD) was first described in food handlers by Hjorth & Roed Petersen (1). It has since been described from various fruits, such as apricot, strawberry, kiwi (2), citrus (3), apple and peach, with cross sensitization to apple and birch pollen (4). A cross-IgE-reactivity in patients with sensitization to birch pollen has been described between birch (Bet VI and Bet V2), apple and peach profilin (5–7).

Case Report

An atopic 17-year-old male smoker, when 5 years old, had shown allergy to vetch flour and hazelnuts, with a generalized wealing reaction accompanied with facial edema, a few minutes after the ingestion of these 2 foods. He also demonstrated a perioral syndrome a few minutes after the ingestion of peanuts, almonds, walnuts, apples, pears or melon. He experienced seasonal rhinconjunctivitis each year. He had been working as a kitchen assistant for 1 year, handling various types of food, mainly fruit, potato, garlic and onion. 3 months prior to consultation, while handling such foods in his daily work, he developed pruritus on his hands which caused continual scratching. On examination, he had eczema on the fingers, backs of the hands and both wrists. He noted an increase in pruritus after handling fruits, above all apple, orange, pear and peach, potato, garlic and onion. He also reported the appearance of weals on the wrists after handling melon.

On prick-by-prick testing, positive reactions were ob-

tained to apple, pear, peach, melon, potato, orange, garlic and onion (Table 1). In a rub test, only peach skin was positive. On patch testing with the GEIDC standard series, positive reactions to thimerosal and wool wax alcohols were observed. The Chemotechnique plant series was negative, including diallyl disulfide, and, with food samples, there were reactions only to garlic and onion, which were interpreted as irritant. Specific IgE (Pharmacia Diagnostic, Uppsala, Sweden) for melon, pear, peach, potato and tomato was in class 2–4 (Table 2). Specific IgE of 33.3 KU/l was detected for profilin. Olea, lolium and birch pollen had class 4 results. A histamine release test (8, 9) was not decisive.

Discussion

In our patient, specific IgE positivity to birch pollen, olive, graminea, profilin, pear, peach, melon, potato and tomato is suggestive of the presence of common allergens to explain his oral and cutaneous reactions. He was probably previously sensitized to profilin and later, due to continual contact with such fruits, developed PCD. Cross-reactivity between profilin in birch, apple or peach in the perioral syndrome has been described (5–6), but this is the 1st case of PCD featuring profilin sensitization.

Results

Table 1. Prick-by-prick test results

	Peel	Pulp		Peel	Pulp
apple	8 mm	4 mm	orange	5 mm	3 mm
pear	6 mm	3 mm	potato	18 mm	18 mm
peach	5 mm	13 mm	garlic	3 mm	3 mm
melon	10 mm	3 mm	onion	10 mm	5 mm

Saline 0.9% negative. Histamine 10 mg/ml 10 mm.

Table 2. Specific-IgE results

birch pollen	25.4 KU/l	melon	1.08 KU/l
profilin	33.3 KU/l	potato	8.84 KU/l
lolium	59.7 KU/l	tomato	45 KU/l
olea	33.9 KU/l	pear	2.51 KU/l
peach	30.7 KU/l		

Negative <0.35 KU/l; Class 1. 0.34–0.70 KU/l; Class 2. 0.70–3.50 KU/l; Class 3. 3.50–17.5 KU/l; Class 4. 17.50–50 KU/l; Class 5. 50–100 KU/l; Class 6 >100 KU/l.

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Occupational airborne allergic contact dermatitis from disperse dyes

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Key words: occupational; airborne; allergic contact dermatitis; disperse dyes; dressmaker; steam ironing; sewing machine. © Munksgaard, 2000.

Case Report

A 33-year-old woman had worked in a dressmaking factory since she was 15 years old. She gave a history of chronic erythematous dermatitis on the face, eyelids, neck, V of the chest, forearms and hands. Treatment with topical corticosteroids had been disappointing. Ironing and sewing dresses were part of her work. Garments arrived already manufactured and dyed at the factory. She had not suffered from atopy or other skin diseases. She left the job and the symptoms disappeared.

5 years later, she returned to the dressmaking factory. As soon as she started to iron clothes again with a steam iron, she developed an acute erythematous papulovesicular dermatitis on the face, eyelids, neck, forearms and hands, together with conjunctivitis. Lesions were markedly aggravated when ironing dark articles of clothing. She was transferred to another workplace where she had to use a sewing machine. She remained with chronic dermatitis and, besides, acquired lesions on the thighs that were clearly related to where she let the clothes rest. Her symptoms cleared when she was away from the job. She had no problems when wearing dark clothes.

Patch testing with the European standard and a textile series was performed. She had positive reactions to nickel sulfate (-/+), Disperse Blue 124 (+/++), and Disperse Blue 106 (+/++) at D2 and D4. We recommended to her that she change her job and took other general measures, such as washing new clothes before wearing them, avoiding wearing dark undergarments and attempting to control hyperhidrosis.

Discussion

Disperse dyes are the textile dyes most frequently associated with allergic contact dermatitis (1, 2). In this case, both acute and chronic lesions had an airborne distribution.

These dyes disperse in water (they are not soluble in water) and their release from fibres can be increased by the moistening and vaporization of steam ironing. Disperse Blue 124 was the most common sensitizer in some reviews (3–5). Disperse Blue 106 has been found to be a potent sensitizing agent (6). There is cross-reactivity between them because they are both azo compounds (2, 7, 8). Only reactive dyes have previously been reported as causing occupational airborne allergic contact dermatitis (9).

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Occupational allergic contact dermatitis from both 2-bromo-2-nitropropane-1,3-diol and methylchloroisothiazolinone plus methylisothiazolinone in spin finish

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Key words: occupational; allergic contact dermatitis; polyester yarn manufacture; spin finish; biocides; preservatives. © Munksgaard, 2000.

A 40-year-old woman reported at work an itchy blistered rash on the backs and sides of her fingers. At the onset, she had been working at a polyester yarn manufacturing plant for 2 years. Her job was referred to as "creeling", meaning that she joined strands of the yarn together using an airgun. She handled the yarn with her hands and, because of its fine nature, was unable to do this wearing gloves. Her hands thus became coated with the spin finish oil from the yarn.

Patch testing to standard, cosmetics, and plastics and glues series resulted in positive reactions at D2 and D7 to nickel 5% pet., methylchloroisothiazolinone plus methylisothiazolinone 0.6% pet. and 2-bromo-2-nitropropane-1,3-diol 0.25% pet. Patch testing to the yarn, applied to her back for 5 days, was negative.

On enquiry at her workplace, it was found that the coating oil (spin finish) of the yarn was preserved with Antiseptic Y, which contained: 2-bromo-2-nitropropane-1,3-diol 10%; methylchloroisothiazolinone plus methylisothiazolin 14%; and ethylene glycol 75%.

Discussion

Various spin finish oil biocides have been reported as sensitizers (1). The frequency of positive patch test reactions to methylchloroisothiazolinone plus methylisothiazolinone has been reported as 1.8% (2). 2-bromo-2-nitropropane-1,3-diol also has a sensitizing potential (3). Indeed, an efficient non-toxic, non-irritating, non-sensitizing biocide has yet to be identified (4). The current sensitization rate for 2-bromo-2-nitropropane-1,3-diol is low, however, probably due to its infrequent use in leave-

on cosmetics (5). Isothiazolinones are popular cosmetic and industrial biocides (6), their rate of sensitization having been reported as 3% (7).

A move to another part of the process not involved with direct handling of the coated yarn led to complete clearance of out patient's dermatitis.

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Primin-free *Primula obconica* plants available

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Key words: *Primula obconica*; primin; phenols; allergic contact dermatitis; horticulture; floristry; plants; prevention; allergen replacement. © Munksgaard, 2000.

Primula dermatitis is mainly caused by *Primula obconica* (1). Some new varieties produce less of the allergen primin than others and there have also been reports of primin-free varieties (1, 2). Fregert & Hjorth (3) were, however, able to detect primin in *P. obconica* Reizfrei that

should have been free of primin. Recently, so-called primin-free *P. obconica* have been introduced to the European market that are difficult to distinguish from the allergenic varieties, with regard to growth, colour and appearance. However, to the best of our knowledge,

Table 1. The content of primin (**1**) and related phenols (**2–4**) (μg) (g fresh plant material)⁻¹ in *Primula obconica*^{a)}

<i>P. obconica</i> varieties (Twilly Serie)	1		2		3		4	
	L,S	F	L,S	F	L,S	F	L,S	F
<i>Allergenic</i>								
'Blender' (blue-white) ^{b)}	62±12	216±65	2.2±0.5	9±0.6	0	0	6.2±0.8	5.8±0.2
'Red Pearl' (red)	31±8	188±22	1.2±0.1	5±0.5	42±15	102±35	0.5±0.5	0
'Pink Pearl' (lilac)	46±9	183±38	3.7±0.5	20±5	0	0	2.6±0.5	0.6±0.2
<i>Primin-free</i>								
'Touch Me' (blue)	0 ^{c)}	0	trace ^{d)}	0	0	0	trace	0
'Touch Me' (salmon pink)	0	0	trace	trace	0	0	trace	0
'Touch Me' (white)	0	0	0	0	0	0	0	0

^{a)} L,S=leaves/stems; F=flowers (including pedicel and calyx). Values given as mean±standard deviation ($n=3$). ^{b)} Colours of flowers in parenthesis. ^{c)} Detection limit approximately 0.5 ng (g fresh plant material)⁻¹. ^{d)} Trace: near detection limit and not detected in all plants.

their primin-free status has not been verified and we have therefore investigated these genotypes for primin and related phenols.

Materials and Methods

Seeds of *P. obconica* (Table 1) were grown under the same conditions and the plants harvested in the flowering stage. The seeds were obtained from Schoneveld Twello b.v., 7391 HZ Twello, Holland. Fresh unchopped leaves/stems (20–30 g) and flowers (8–12 g) were extracted with dichloromethane (150 ml), and primin (**1**), miconidin (**2**), miconidin methyl ether 3,4-dimethoxy-5-pentylphenol (**3**), and the corresponding acetate 3-methoxy-4-acetoxy-5-pentylphenol (**4**), were quantified in the extracts by GC and identified by GC-MS as described previously (4). Extracts negative for **1** were concentrated approximately 300× and re-analysed in order to confirm the absence of **1**.

Results and Discussion

The sensitizing properties of *P. obconica* are due to the accessibility of primin (**1**) which is stored in trichomes on the surface of the plant (3, 5). The lightest touch of the trichomes leads to their damage and the release of a yellow secretion, which contains the allergen.

Microscopy showed that the density of trichomes was higher in the allergenic *P. obconica* than in so-called primin-free genotypes, and only the trichomes of the former plants contained a yellow secretion. Primin and related phenols (**2–4**) were present only in the allergenic varieties, though traces of **2** and **4** were detected in a few primin-free plants (Table 1). The content of **1** was slightly lower compared to similar investigations performed in summer (4, 5). This is probably due to sea-

sonal variation, as we examined the plants in autumn. However, the primin-free genotypes seem to have lost the ability to produce **1**, an ability that is controlled by 1 gene (2).

Compounds **1** and **2** have antibiotic properties (6) and changes in the sensitizing capacity of *P. obconica* may therefore affect resistance. So far, no severe diseases have been observed on the primin-free genotypes during cultivation. In European countries, such as Denmark, the production of primin-free *P. obconica* has been initiated and hopefully this may lead to a decline in cases of primula dermatitis.

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Contact dermatitis from *Chelidonium majus* (greater celandine)

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Key words: allergic contact dermatitis; *Chelidonium majus*; plants; herbal remedies; wart treatment; medicaments; chelidonic acid. © Munksgaard, 2000.

Chelidonium majus (fam. Papaveraceae) is a plant up to 90 cm tall, with a downy stem and yellow flowers. When cut, it exudes an orange-coloured juice. It grows in shaded places, mainly near old walls (1). This plant, and particularly its juice, has been widely used in traditional medicine for treating warts, tinea, eczema and tumors. Spasmolytic, cholagogic and diuretic properties have also been described. It has also been used in the treatment of cholecystitis (2).

Case Report

A 64-year-old woman, who had used the juice of the greater celandine to treat warts, presented after celandine juice application to her neck. Within a few hours, she had experienced intense itching and erythema, with papules, in the area of application. 6 weeks later, she had repeated the juice application to a wart on her face, again developing the previous symptoms. In both episodes, the lesions resolved in a few days without treatment.

The patient was first open tested on her upper arm with celandine juice as is, resulting in a positive reaction in less than 24 h. Plant extracts were then obtained from the branch, stem and root. After lyophilization, extracts were dissolved in water at 10 mg/ml, 1 mg/ml and 0.1 mg/ml. The highest concentrations were previously patch tested on 10 control subjects, all of whom were negative. In the patient, all 3 concentrations were positive on patch testing after 2 days. Patch testing with TRUE Test (Pharmacia) and lactones was negative.

Discussion

Contact allergy to plants is less common than irritancy (3–5). The juice of the greater celandine is habitually used on skin lesions, especially for warts. Its Spanish name *verruquera* means almost literally “plant for warts”. Although this plant has been widely used, we have not found any previous reference to allergic contact dermatitis induced by *Chelidonium majus*. Gamboa et al. (5) described a case of allergic contact urticaria from poppy (*Papaver rhoeas*) in the same plant family (Papaveraceae). A case of *Dicontra spectabilis* causing allergic contact dermatitis has also been reported (6). Kalyoncu & Stalenheim described a case of allergy to poppy seed after eating bread garnished with it (7).

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Latent (subclinical) contact dermatitis evolving into occupational allergic contact dermatitis from extremely small amounts of epoxy resin

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Key words: latent; subclinical; allergic contact dermatitis; occupational; epoxy resin; epoxy diacrylate; BIS-GMA; low concentration; glass fiber; cleaner. © Munksgaard, 2000.

Case Report

A 32-year-old woman working as a book-keeper in a firm selling kitchen and other furniture had a 17-year

history of nickel dermatitis from cheap jewellery, but no hand eczema. It was also her job to lacquer, saw and glue kitchen furniture made of plywood. At the age of 20 years, she had had an exanthema during penicillin

therapy, presenting with an acute exanthema over the whole body and swelling of the face.

3 months later, prick and patch testing were performed and scored as previously described (1). Prick testing did not clarify the etiology of the skin eruption. Patch testing with a modified European standard series gave reactions to nickel (+++), cobalt (++), para-phenylene-diamine (++), p-tertiary butylphenol-formaldehyde resin (++), mercury chloride (++), diaminodiphenylmethane (++), and diglycidyl ether of bisphenol A (DGEBA, ++). As she had no hand eczema or signs of contact dermatitis, many of the reactions evidently represented latent (subclinical) contact dermatitis.

12½ years later, the patient was referred because of work-related hand eczema. She had continued her previous work without skin problems, but 3 years ago, she had changed her job to that of a cleaner in a firm manufacturing dental equipment. After some months in this work, she had developed work-related hand eczema, starting on the fingerwebs and spreading to the palms. Patch testing with an epoxy resin series (Chemotechnique Diagnostics AB, Malmö, Sweden) showed very strong reactions to DGEBA (+++), brominated epoxy resin (+++), 2,2-bis[4-(2-hydroxy-3-methacryloxypropoxy)phenyl]propane (BIS-GMA, 2% pet., +++), 2,2-bis[4-(2-hydroxy-3-acryloxypropoxy)phenyl]propane (BIS-GA, 0.5% pet., +++), and 2,2-bis[4-(2-methacryloxyethoxy)phenyl]propane (BIS-EMA, 1% pet., +++). 2,2-bis[4-(methacryloxy)phenyl]propane (BIS-MA, 2% pet.) was negative. In the next patch test session, a DGEBA dilution series reacted as follows: 0.01%–0.0032%, +++; 0.001%–0.00032% ++; 0.0001% –; with BIS-GMA positive down to 0.0001%, BIS-GA positive down to 0.00032%, and BIS-EMA positive down to 0.0032%.

The patient used, for her cleaning work, a mop with a handle made of glass fiber. Scrapings in acetone from the mop handle (0.24 g of the glass fiber mop in 3.9 g acetone) provoked a ++ patch test reaction. The glass-fiber mop was then shown to contain 0.015% DGEBA with MW 340 (2). Accordingly, the DGEBA concentration of the patch test substance made from the glass-fiber was $(0.24:3.9) \times 0.015\% = 0.0009\%$, which corresponded well with the patch test reaction caused by DGEBA.

It was concluded that the patient had already had a subclinical (latent) epoxy allergy 12½ years earlier. After some months of daily exposure to extremely small amounts of epoxy resin, this latent allergy had developed into allergic contact dermatitis from epoxy resin.

Discussion

There is a graded, dose-related magnitude of skin sensitization to haptens, from clinically-detectable reactivity down to subclinical response levels (3). Subclinical contact allergy has been termed latent sensitization, latent contact allergy or contact allergy without skin disease (4–6). Subjects with only latent sensitization may run a future risk of contracting allergic contact dermatitis (5, 7). Accordingly, patients with a latent allergy should be advised to avoid contact with the allergen detected.

The origin of this patient's latent epoxy allergy was

not clear. It might have begun from dental fillings, made of composite resins. She had originally given a history of perioral dermatitis after visits to the dentist (7). As dental composite resins may contain small amounts of DGEBA (8), her initial sensitization to DGEBA may have been caused by these (9). Minute amounts of allergen, e.g., 0.003–0.008% (30–80 ppm) formaldehyde (10, 11), 0.5 ppm nickel (12), patch testing with 1 ppm of a drug intermediate (13), or minimal exposure time (seconds) to a contact allergen (14), have induced allergic contact dermatitis. On the other hand, it has been shown experimentally that low-dose exposure to antigen induces sub-clinical sensitization (15), though in this case, it seems that low-dose exposure to dental composite resin and mop handle induced extreme sensitization.

In conclusion, we report a patient with a previously verified latent allergy to DGEBA, who developed allergic hand dermatitis from very small amounts of DGEBA (0.015%) in a mop handle made of glass fiber. Patch testing with DGEBA was positive down to 0.00032% (3.2 ppm) and with BIS-GMA down to 0.0001% (1 ppm).

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Seasonal allergic contact dermatitis from *Taraxacum officinale* (dandelion) in an Israeli florist

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Key words: allergic contact dermatitis; seasonal; *Taraxacum officinale*; dandelion. © Munksgaard, 2000.

Case Report

A 45-year-old non-atopic woman, with no previous history of allergy, complained of itchy erythematous lesions on her hands for the last 2 years. The hand eczema appeared in the summer (May to October) and completely disappeared in the winter. For 4 years, she had worked as a florist. Her agenda in the flower shop was the same in the winter and the summer. When she was on vacation, her hand eczema improved significantly.

Patch testing to the European standard series of allergens (Chemotechnique Diagnostics) and to a plants series (Chemotechnique Diagnostics) showed a ++ reaction at 2 and 4 days to *Taraxacum officinale* in the plants series. Sesquiterpene lactone mix was negative in both series.

Discussion

Taraxacum officinale (dandelion) is a common weed in Europe (1) as well as in Israel. There are case reports of allergic contact dermatitis due to *Taraxacum officinale*

(2–4). Dandelion contact dermatitis is more common in hot weather (4), which promotes the growth of broad-leaved rosetting weeds such as dandelion (1). An explanation for the seasonal allergic contact dermatitis in our patient might be seasonal variation in allergen (taraxinic acid 1-0- β -glucopyranoside) content.

Positive patch test reactions to dandelion extracts have previously been noted in the absence of patch test reactivity to the sesquiterpene lactone mix (4).

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Occupational allergic contact dermatitis in two aromatherapists

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Key words: occupational; aromatherapists; allergic contact dermatitis; essential oils; patch testing technique. © Munksgaard, 2000.

Aromatherapy is the use of essential oils topically (massage, bath oils, wet dressings), orally or by inhalation (via vaporization) to promote physical and psychological well-being (1). Its popularity is increasing and, coincident with this, reports of adverse affects. Most side-effects due to topical use of essential oils are allergic (2–7), phototoxic (8–9), or airborne (10) contact dermatitis, developing in untrained users of aromatherapy oils. There have been only 3 reports to date of its occupational development in aromatherapists (11–13). We re-

viewed the records at a tertiary referral centre over the past 5 years and found 2 further cases of occupationally-acquired allergic contact dermatitis from essential aromatherapy oils.

Case Reports

Case no. 1

A 41-year-old aromatherapist presented with a 9-month history of bilateral hand and forearm dermatitis. It im-

Table 1. Properties of essential oils and proposed indications for their use in aromatherapy

Essential oil	Family	Main constituents	Indications for external use
citrus neroli	Rutaceae	monoterpenes alcohol terpenes jasmone nerol	oily and dry skin, softened facial skin
lavender oil	Lamiaceae	linalyl acetate linaloöl geraniol	acne scalds and burns hair and skin care
frankincense	Burseraceae	pinene phellandrene monoterpene hydrocarbon verbenone	antidepressive expectorant
rosewood	Lauraceae	linaloöl terpenes cineol nerol geraniol	antiseptic vaginal candida sedative
ylang-ylang	Anonaceae	methyl benzoate methyl salicylate eugenol cresol geraniol linaloöl pinene cadinene	oily skin soothes anger antifungal antiparasitic antipruritic
angelica archangelica	Apiaceae	lactones phellandrene pinene	anxiety gut spasms

proved substantially but never fully cleared away from work. At one stage, it had become infected and the dermatitis become generalized. She had no history of atopy. She had worked as an aromatherapist for the previous 4 years, working on average 20 h a week. Her practice included 12 different essential oils, which she used at a dilution of 5%. Examination revealed low-grade eczema in the interdigital spaces.

She was patch tested to the European standard and perfume series, both of which were negative. She was also patch tested to each essential oil 2% MEK. She had + reactions to citrus neroli and lavender and ? + reactions to frankincense and rosewood (D2).

Case no. 2

A 29-year-old beauty therapist gave a 1-year history of eczema, starting on the dorsum of the right hand and spreading to the left hand, both arms and neck. Her work included aromatherapy massage. She had no history of atopy. Patch testing to the European standard and perfume series and essential oils, again 2% MEK, confirmed sensitivity to fragrance mix and wool wax alcohols, as well as to geraniol, ylang-ylang and angelica oils (all + D4) used in her work.

Discussion

The term aromatherapy was introduced by the French chemist Gattefossé after he had used the antibacterial properties of lavender oil to help heal a burn on his hand

(14). The beneficial effects of this form of alternative treatment, however, have been known for thousands of years and used in ancient Egypt and the Indus Valley (15, 16). Individual oils are believed to have healing properties in certain conditions and these oils are used alone or in combination by aromatherapists to treat various ailments.

Essential oils are derived from water vapour distillation of plant constituents from a single source (3) and consist mainly of terpenes, hydrocarbons of the general formula $C_{10}H_{16}$ (12). The exact frequency of contact dermatitis from essential oils is unknown. Occupationally-derived allergic contact dermatitis due to some of these oils has previously been reported in a hairdresser (lavender oil) (17), and the hat (laurel oil) (10) and paint (turpentine) industries. In the latter case, sensitizing hydroperoxides may have formed over time when oils were incorrectly stored (1).

Essential oils which are known skin irritants, such as cinnamomum verum, tend to contain high proportions of either aldehydes or phenols (1), while photosensitizing essential oils, such as angelica archangelica, contain furanocoumarins (18). Some essential oils are cited by teachers of aromatherapy as possible contact sensitizers and these include ylang-ylang, as in our 2nd patient (1). In both our patients, repeated exposure to certain essential oils used for massage resulted in contact sensitization. The properties of these oils are listed in Table 1 (19). The 1st patient might have been diagnosed clinically as irritant contact dermatitis. Perhaps 2% di-

lutions of essential oils are somewhat overcautious, as suggested recently for lavender oil, in particular (20).

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Descriptive comparison of isolated hand dermatitis and other populations at St. John's Contact Dermatitis Clinic

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Key words: hand dermatitis; isolated; clinical groups. © Munksgaard, 2000.

Hand dermatitis is common in the community and hospital (1–3). As it is a distinct form of dermatitis occurring in isolation with functional implications, we wondered if it resulted in a distinct population presenting to our contact dermatitis clinic. We compared the age, sex and occupation of patients with isolated hand dermatitis to these parameters in patients with all other diagnoses seen at our contact dermatitis clinic 1983–1997.

Results

During this 15-year period 23,233 patients were seen. 29% of these had isolated hand dermatitis. Table 1 shows the age and proportions of the 2 populations. Comparison of the mean age of clinical groups in Table 1 showed significant differences: $p < 0.001$. 42% of isolated hand and 9% of other cases were occupational. This resulted in 9% of cases being occupational overall, with 71% of these having hand dermatitis. The male:female ratio for all patients was 0.7, for isolated hand dermatitis patients 0.8 and for all

other patients 0.6 (Table 1). Comparison of the numbers of males and females and then occupational cases between the 2 groups showed significant differences: $p < 0.001$. Table 2 shows the 5 most frequent occupations for all patients with occupational dermatitis and similarly for isolated hand and all other dermatitis patients.

Discussion

Isolated hand dermatitis forms close to a $\frac{1}{3}$ of our clinic workload and the majority of occupational cases. This is similar to other smaller clinic-based studies (3, 4).

Patients with isolated hand dermatitis were younger than those with other diagnoses. Occupational and domestic influences may lead to the earlier development and presentation of hand dermatitis. Furthermore, the referring physician may consider the possibility of contact dermatitis at an earlier stage in hand compared to other forms of dermatitis.

Both groups showed a predominance of females, al-

Table 1. Average age and numbers of patients with isolated hand dermatitis and all other diagnoses 1983–97

	No. (%)	Average age (years)	Confidence interval	
			+1	–1
Isolated hand dermatitis				
all	6849	36.1	36.4	35.7
male	3044 (44)	39.3	39.8	38.8
female	3805 (56)	33.4	33.8	32.9
All other diagnoses				
all	16,384	38.9	39.2	38.7
male	6310 (39)	41.7	42.2	41.2
female	10,074 (61)	36.2	36.6	35.8

Table 2. 5 most frequent occupations for patients with occupational hand dermatitis by clinical group

Isolated hand dermatitis	All other dermatitis diagnoses	All dermatitis patients
caterer	healthcare worker	caterer
metalworker	metalworker	metalworker
hairdresser	chemical worker	healthcare worker
healthcare worker	mechanical worker	hairdresser
mechanical worker	caterer	mechanical worker

though this was less marked in the hand dermatitis group. In non-hand dermatitis, this could be caused by cosmetic usage, a lower tolerance of non-hand der-

matitis by females or a lower referral rate by clinicians of males. In hand dermatitis, this is likely to reflect the predominance of male manual workers and perhaps that the potential for contact dermatitis is appreciated more by the referring physician or patient for males with hand dermatitis rather than other forms of dermatitis.

The occupations for all patients in Table 2 reflect the large numbers of occupational hand dermatitis patients seen. Hairdressing is not ranked in Table 2 for non-hand dermatitis patients. However, it was the 2nd most frequent occupation for female occupational non-hand dermatitis cases (52 cases), though for all cases, was ranked only 7th, reflecting the small numbers of males seen. Chemical worker, while ranked for non-hand dermatitis, was not for all patients due to the small numbers of occupational hand dermatitis patients seen – 33 in all. This seems surprising and could reflect a higher level of awareness of occupational problems associated with the hands compared with other body sites in this industry.

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Questions raised by skin reactions observed during squaric acid dibutyl ester contact sensitization

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Key words: allergic contact dermatitis; contact immunotherapy; squaric acid dibutyl ester; side-effects; treatment alopecia areata. © Munksgaard, 2000.

Squaric acid dibutyl ester (SADBE) is strongly immunostimulatory and is used in the treatment of alopecia areata. Side-effects have repeatedly been reported in the course of such treatment (1–5).

Case Report

A 56-year-old woman, in good general health, presented with subtotal alopecia areata unresponsive to the topical therapies prescribed. A patch test with a 2% SADBE solution in acetone was applied, with a view to treatment with this immunogen. Following removal after 2 days, no lesions indicating sensitization were observed at the

site, 3 days later or even after 4 days. For this reason, 2 weeks later, it was decided to apply the SADBE patch test 1× more on the opposite forearm. When the patch test was removed, the patient showed an erythematous plaque and, on the following day, the lesion was also slightly edematous.

2 weeks later, when the patient attended to begin treatment with SADBE, we noticed the presence of symmetrical lesions on the flexor surfaces of upper arms and forearms, each equidistant from the elbow flexure (Fig. 1). These had appeared about 10 days earlier and the patient had been treating them with boric acid compresses. On the right forearm (the 1st sensitization site),



Fig. 1. Symmetric lesions on the sites of application of the patch test to the forearm and on the points of contact with the upper arm after bending.

an oval-shaped ulcerated lesion 4×2.5 cm was observed. On the left forearm, at the site of the 2nd SADBE application, there was a roundish erythematous plaque 5 cm in diameter, with a target-like aspect and a brighter red central area showing vesicles and crusts. On the right arm, there was an erythematous plaque, violaceous red in color, thinly scaling, with an irregular rectangular form and measuring 5×3.5 cm. On the left arm, there were 2 small erythematous plaques, bright red in color, with a tendency to confluence.

The localization of the lesions corresponded to the sites of application of the patch test to the forearm and to the points of contact with the upper arm after bending. The patient's history revealed that she often kept her arms bent during sleep. After treatment with a topical corticosteroid, the cutaneous manifestations gradually resolved.

Discussion

Generally, the application of 2% SADBE elicits the appearance of an eczematous plaque, which is the sign that sensitization has taken place. In our case, no lesions were observed following initial application of the immunogen to the forearm. The events that followed indicate that sensitization took place in spite of the absence of evident cutaneous manifestations. SADBE seems to persist for a long time on the skin surface: in our case, as in other similar cases reported (1, 5), 2 days after the application, once the patch test had been removed, bending the arm

allowed transference of the allergen from the forearm to the upper arm. This transference occurred both when no eczematous lesion was detectable (as was the case for the right forearm) and when an eczematous lesion was present (as was the case for the left forearm).

The 2nd contact with SADBE elicited an eczematous plaque on the left forearm. The lesion was already visible as soon as the patch test was removed and, on the days that followed, similar lesions were detected on the opposite forearm and on other aspects of the arms bilaterally, where there was involuntary contact of the skin with the sensitization sites. The reactions observed after the 2nd sensitization are a clear consequence of the cellular mechanisms at the basis of the pathogenesis of allergic contact dermatitis. The violent cutaneous response (ulcerated lesion) at the 1st sensitization site and the minor cutaneous reactions on other aspects of the arms are worthy of note and demonstrate a dose-dependent response.

Although it brings into view some expected mechanisms, this case raises several questions. It remains to be explained why no clinical manifestations were observed after the 1st contact, although the allergen had penetrated, why eczematous lesions took longer to appear following the 1st sensitization when compared to the 2nd sensitization, and why with such acuity.

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Asthma, latex hypersensitivity and potatoes

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Key words: asthma; natural rubber; latex; potato; allergic contact dermatitis; cross-sensitivity; atopic eczema.
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Immediate sensitivity to raw potatoes has been well described, with a variety of presentations including wheeze, rhinorrhea, sneezing, urticaria and protein contact dermatitis (1–4). Latex allergy has been associated with increased sensitivity to foodstuffs, including banana, kiwi fruit, chestnuts and potatoes (5). Whilst cross-reactivity to the latter has only recently been identified, it would appear to be the most common to cause topical symptoms in latex-sensitive individuals (6).

Case Report

A 68-year-old woman was under follow-up for severe atopic dermatitis that had become increasingly difficult to control. She was unaware of exacerbating factors or skin sensitivities, and patch testing to the European standard and standard additional series was negative. The eruption responded poorly to topical corticosteroid and emollient therapy and particularly affected the hands and face. Previous medical history included asthma and hypertension, and there was a family history of atopy. Cyclosporin therapy proved effective, but a dose of 75 mg/day (1.25 mg/kg) was only just sufficient for maintenance. Attempts to reduce the dosage resulted in rapid recurrence of her dermatitis.

At subsequent review, she reported an episode of facial urticaria after blowing up toy balloons. Further questioning uncovered a previous severe asthma attack and facial oedema following a dental procedure, which she had attributed to the local anaesthetic. In addition, she recalled pruritus and deterioration of her eczema after using household latex gloves, with perceived improvement after she began using vinyl gloves instead. A prick test to latex using a commercial latex antigen (Stallergenes, Paris) was strongly positive.

When the patient was warned about foodstuffs that could cause cross-reactions in latex-sensitive individuals, she recalled problems with pruritus and deterioration of her eczema following exposure to potatoes, particularly during the preparation of raw tubers, but also from eating or touching cooked potatoes. A number of asthma attacks had also been associated with potatoes, including one from being in the same room in which they were peeled. An estimation of allergen-specific IgE to potatoes was strongly positive at grade 4 (UniCAP; Pharmacia, Uppsala, Sweden). Patch and prick testing to potato were not performed. There was no significant specific IgE to other foodstuffs such as kiwi fruit, avocado, chestnuts or tomatoes.

Since exclusion of potato and potato products from her family's diet, and avoidance of latex products, this

woman's eczema has been under better control on cyclosporin.

Discussion

In Europe and North America, despite high population exposure to potatoes, allergy is relatively uncommon (7), though many isolated cases of potato sensitivity have been reported (1–4). Latex-sensitive individuals, more so than atopic individuals or the general population, are at increased risk of sensitivity to a variety of foods, and cross-reactivity to potatoes has recently been reported (5). Patatin, the main storage protein in potatoes, has been identified as an IgE-binding protein, and an allergen in children with a positive prick test to potatoes (8). This protein has also been shown to have 60% homology with a 46 kDa latex protein allergen (6), which may explain the cross-reactivity. Our case illustrates the importance, in the assessment of latex-sensitive patients, of considering the possibility of additional sensitivities and taking a careful history for food allergy.

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Contact allergy to Euxyl K 400 in consecutively patch-tested patients

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Key words: Euxyl K 400; 1,2-dibromo-2,4-dicyanobutane; methyldibromo glutaronitrile; cosmetics; preservatives. © Munksgaard, 2000.

Euxyl K 400 is a cosmetic preservative, consisting of a mixture of methyldibromo glutaronitrile (MDGN) (20%) and phenoxyethanol (80%), introduced as a replacement for Kathon CG (1, 2). Its concentration in cosmetics must not exceed 0.5%. Prior to August 1993, in accordance with EEC regulations, Euxyl K 400 could not be used as a preservative in sun-protection preparations: since August 1993, its use has been permitted at up to 0.125%. (3).

Euxyl K 400 is also an industrial preservative (known by commercial names such as Tektamer 38, Merquat 2220, Euxyl K 135, Euxyl K 466 and Euxyl K 727) (4). It is found in paints, adhesives, colour photograph processing solutions, metalworking fluids, detergents, latex rubber and emulsion (5), paper and cardboard, wood preservatives (6) and ultrasonic gels (7).

Patients and Methods

From September 1998 to June 1999, 528 consecutive patients were patch tested with Euxyl K 400 0.5% pet. and the GEIDC standard series. There were 274 women and 254 men, with age range 16–69 years. The units were Leucotest with Fixomull and readings at 2–4 days, following GEIDC guidelines. Cases with a positive reaction to Euxyl K 400 were patch tested separately with phenoxyethanol 1% pet. and variably with MDGN 0.1% pet.

More than 200 cosmetic products available in Spain were randomly examined, using the INCI nomenclature as a guide, in commercial centres and department stores (8), for the presence of MDGN and phenoxyethanol among their ingredients.

Results

Only 5 positive reactions were observed from a total of 528 patch tests (Table 1). None were positive to phenoxyethanol.

In the random selection of 200 cosmetic products

from department stores in Madrid, Euxyl K 400 was present in very few (Table 2).

Discussion

1989 saw the 1st case report of a reaction to Euxyl K 400 in a cosmetic product (9), and 1996 the 1st report in a sunscreen (10).

A 1997 study (11) reported a decrease in the use of formaldehyde, an increase in Kathon CG and a large increase in Euxyl K 400. In countries such as The Netherlands, Italy and Germany, the frequency of patch test allergy to Euxyl K 400 increased in 4 years from 2% to 4%, Tosti et al. (12) showing the relevance of positive reactions by ROAT, and Blecher & Korting (13) by the rub test. De Groot et al. (14) consider that a soya-lecithin type emulsion may be necessary to obtain a homogeneous dispersion. Studies show pet. to be the best test vehicle.

MDGN is the principle Euxyl K 400 component responsible for contact allergy (2). Tosti et al. (3) suggest 0.5% as the best patch test concentration for MDGN, as at lower concentrations false-negatives can result. In 1998–1999, of 548 patients we patch tested with a cosmetics series in which Euxyl K 400 0.5% pet. was included, only 3 patients were positive (0.1%). The number of positive results in our patients was low, both in our retrospective and current prospective study, and Euxyl K 400 was scarce in the cosmetic products available in

Table 2. Products containing Euxyl K 400 among 200 cosmetic products

Product types	No.	%/200
make-up removal towels	3	1.5
body lotions	4	2
shampoos	1	0.5
stain removal products	1	0.5
face creams	3	1.5

Table 1. Positive patch test results (D4)

Case no.	Sex	Age (years)	Standard series	Euxyl K 400	MDGN	Phenoxyethanol
1	F	49	—	+++	NT	—
2	F	30	formaldehyde	+++	++	—
3	M	42	Cr, Co, thiuram mix, carba mix	++	+	—
4	F	50	Ni, Kathon CG, PPD	+++	+++	—
5	M	24	thiuram mix	++	NT	—

Spain. It would seem that Euxyl K 400 should be considered as a preservative under observation, with currently a scanty allergy rate in our country.

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Occupational allergic contact dermatitis from 2,2-bis[4-(2-hydroxy-3-acryloxypropoxy)phenyl]-propane (epoxy diacrylate) in ultraviolet-cured inks

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Key words: occupational; allergic contact dermatitis; 2,2-bis[4-(2-hydroxy-3-acryloxypropoxy)phenyl]-propane; BIS-GA; BIS-GMA; epoxy diacrylate; tripropylene glycol diacrylate; methacrylate; ultraviolet-cured inks; airborne; epoxy resin; cross-sensitivity. © Munksgaard, 2000.

Epoxy di(meth)acrylates can cause allergic contact dermatitis from ultraviolet (UV)-cured printing inks (1–4). We have previously reported 1 of the patients in this material who was primarily sensitized to 2,2-bis[4-(2-hydroxy-3-acryloxypropoxy)phenyl]-propane (epoxy diacrylate, BIS-GA; Fig. 1) (5).

Patients and Methods

Nearly all our patients are referred because of suspected occupational skin disease (6). Patient records from September 1985 to January 1999 in our patch-test clinic were reviewed for positive reactions to BIS-GA (0.5% pet.). Patch test reactions to other epoxy di(meth)acrylates (Chemotechnique Diagnostics, Malmö, Sweden), tested in both (meth)acrylate and epoxy resin (ER) compound series, were noted in all such cases: 2,2-bis[4-(2-hydroxy-3-methacryloxypropoxy)phenyl]-propane (BIS-GMA, 2% pet.); 2,2-bis[4-(methacryloxy)phenyl]-propane (BIS-MA, 2% pet.) and 2,2-bis[4-(2-methacryloxyethoxy)phenyl]-propane (BIS-EMA 1% pet.). Diglycidyl ether of bisphenol A (DGEBA) was tested at 1% pet.

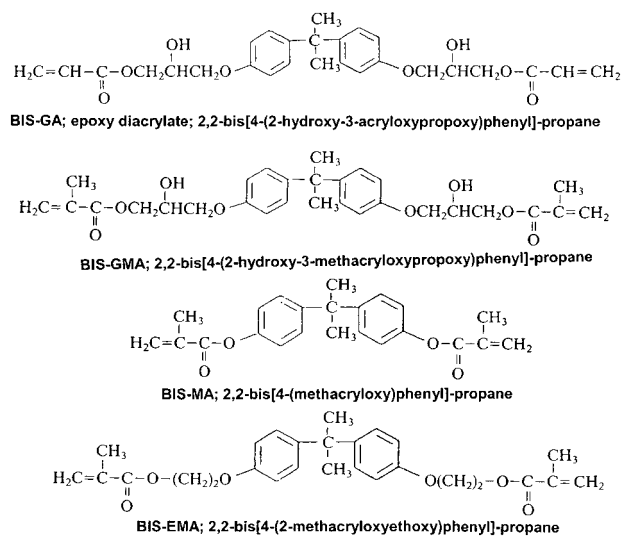


Fig. 1. Chemical structures of epoxy di(meth)acrylates based on bisphenol A or epoxy resin.

Table 1. Patch test results with epoxy di(meth)acrylates and diglycidyl ether of bisphenol A (DGEBA) in 14 patients with an allergic patch test reaction to BIS-GA; patient nos. 3–8 (5, 6, 22) and 10 (8) have been mentioned in previous reports

Pt no.	Occupation	Age (years)/sex	Patch test % (pet.) and results					Probable cause of skin disease	Reference; remarks
			BIS-GA 0.5%	BIS-GMA 2%	BIS-EMA 1%	BIS-MA 2%	DGEBA 1%		
1	silk screen printer	37/m	++	–	–	?+	+++	BIS-GA from UV-cured printing ink	
2	silk screen printer	55/m	++	–	–	–	–	BIS-GA and TPGDA from UV-cured printing ink	
3	process man	28/m	+++	–	–	–	–	BIS-GA from UV-cured paint	pt no. 2 in (5)
4	dental* nurse	20/f	++++*	++++*	–	–	+++*	BIS-GMA from dental composite resins	pt no. 3 in (7)
5	dental* nurse	34/f	++++*	+++*	+++*	–	+++*	BIS-GMA from dental composite resins	Pt no. 4 in (7)
6	dental* nurse	28/f	++*	++*	–	–	+++*	BIS-GMA from dental composite resins	pt no. 5 in (7)
7	dental* nurse	41/f	++*	++*	–	–	+++*	BIS-GMA from dental composite resins	pt no. 6 in (7)
8	cleaner	46/f	+++	+++	+++	–	+++	BIS-GMA from dental composite resins	perioral dermatitis (22)
9	painter	45/m	+	–	NT	–	++	DBEGA from epoxy paint	
10	sales manager; previously supervisor (when sensitized)	51/m	++	++	NT	–	+++	DGEBA	past relevance to DGEBA and epoxy diacrylate allergy from working in production plastic products (8)
11	floor layer	33/m	++	++	++	–	+++	DGEBA	DGEBA in floor coatings
12	worker in vacuum impregnation plant	45/m	++	++	NT	–	+++	DGEBA & reactive epoxy diluents	DGEBA was used in impregnation
13	building technician	20/m	++	++	NT	–	+++	DGEBA and cycloaliphatic epoxy resins	2-component epoxy glue
14	mechanic	56/m	++	+	NT	NT	+++	DGEBA and BIS-GMA	epoxy allergy verified earlier, subsequently sensitized from coating material containing 12% BIS-GMA

BIS-GA = 2,2-bis[4-(2-hydroxy-3-acryloxypropoxy)phenyl]-propane = epoxy diacrylate

BIS-GMA = 2,2-bis[4-(2-hydroxy-3-methacryloxypropoxy)phenyl]-propane

BIS-MA = 2,2-bis[4-(methacryloxy)phenyl]-propane

BIS-EMA = 2,2-bis[4-(2-methacryloxyethoxy)phenyl]-propane

* Scoring, see (7).

Results and Case Reports

14 patients had an allergic patch test reaction to BIS-GA during 1985–1998 (Table 1). 2 of these, patient nos. 1 and 2 in Table 1, were considered to have been primarily sensitized to BIS-GA, and another such patient has

been reported earlier, patient no. 3 in Table 1 (5). The reactions to BIS-GA in patient nos. 4–14 (Table 1) were considered to represent cross-reactivity, as they had had no known exposure to BIS-GA. Some other patients in Table 1 have been included in previous case reports (5, 7, 8).

Patient no. 1 (Table 1)

A 38-year-old atopic man, who had worked occasionally in UV-cured silk printing for 10 years, developed work-related facial dermatitis. He had mainly used 2 UV lacquers. He was patch tested in 3 sessions with the following series: modified European standard; 2 plastics and glues (9); antimicrobials; oils and cutting fluids; (meth)acrylates; ER compounds. DGEBA, and brominated ER, containing 19% DGEBA of MW 340 (10), provoked +++ reactions, and a cycloaliphatic epoxy resin (0.5% pet.) a ++ reaction. BIS-GA provoked a ++ reaction, BIS-EMA a ?+ reaction and the patient's vinyl ester resin lacquer (0.5% pet.) a ++ reaction, other components of his UV-cured lacquer being negative.

The material safety data sheet (MSDS) stated the lacquer to contain 65% polyacrylate resin and 25% polyglycol diacrylate. When analyzed as previously described (5) the UV lacquer was shown to contain 76% BIS-GA, <0.1% 2,2-bis[4-(2-hydroxy-3-methacryloxypropoxy)-phenyl]-propane (BIS-GMA) and <0.1% DGEBA. The manufacturer then kindly declared 2 (meth)acrylates, namely BIS-GA and 1,6-hexanediol diacrylate (HDDA). On patch testing, the patient was negative to HDDA. The patient had also had contact with tripropylene glycol diacrylate (TPGDA) in another UV-lacquer, but on patch testing was negative to it.

Patient no. 2 (Table 1)

A 55-year-old silk-screen printer developed a work-related dermatitis of the fingerwebs, which spread to the palmar aspects of the hands and lower arms. 2 patch test sessions were performed with a modified European standard series, plastics and glues, (meth)acrylates and substances from the patient's workplace. Several (meth)acrylates provoked reactions: ethyl acrylate (+), diethylene glycol diacrylate (++), TPGDA (++), BIS-GA (++), triethyleneglycol diacrylate (++), urethane dimethacrylate (?+), and 2-phenoxyethylacrylate (++). The patient's UV-lacquer contained 30–60% BIS-GA and 20–50% TPGDA according to the MSDS. On patch testing, this UV-lacquer reacted as follows: 2%, +++; 0.63%–0.2%, ++ (pet.).

Patient no. 3 (Table 1)

A process man working in the production of UV-curable acrylic paints has been reported earlier (5). Patient nos. 4–7, dental nurses (Table 1), had probably been sensitized to BIS-GMA, the commonest epoxy di(meth)acrylate in dental composite resins (7). The patch test reactions of patient nos. 8–14 (Table 1) to BIS-GA may represent cross-sensitivity to either DGEBA or BIS-GMA.

Discussion

Björkner et al. (2) reported 6 patients with patch test reactions to trimethylolpropane triacrylate (TMPTA), 3 of whom were also positive to pentaerythritol triacrylate (PETA), 2 to polyester acrylate and 2 to BIS-GA, but none to BIS-GMA. Our patient nos. 1 and 3 developed isolated allergy to BIS-GA and not to other (meth)acrylates or epoxy di(meth)acrylates. Carmichael & Foulds (11) had a patient sensitized to an amino-substituted di-

acrylate in a UV-cured lacquer. Skotnicki & Pratt (12) and Whitfeld & Freeman (13) reported patients sensitized to TPGDA, and we have also reported occupational sensitization to TMPTA (14). Isaac et al. (15) reported TMPTA and PETA allergy from UV-cured inks. Skotnicki & Pratt's (12) patient had many further patch test reactions to (meth)acrylates, though TPGDA was the only acrylate listed on the MSDS. An MSDS is not, however, very reliable, as reported both here (patient no. 1) and earlier (5, 16).

Nethercott et al. (3) reported 6 workers in 5 of whom a urethane acrylate resin accounted for sensitization, and 1 of whom was also sensitive to PETA and 1 to an epoxy acrylate resin; allergy to TMPTA accounted for the 6th case. Goossens et al. (4) had a silkscreen maker who reacted to his UV-cured ink and BIS-GMA, ethylene glycol dimethacrylate (EGDMA) and TPGDA. TPGDA and a bifunctional aromatic methacrylate, corresponding "structurally" to BIS-GMA, were used in the ink. Their patient also reacted to DGEBA. In some cases, DGEBA and epoxy di(meth)acrylates do seem to cross-react (17) though not always (18). Our observations indicate cross-reactivity between DGEBA and some epoxy di(meth)acrylates, such as BIS-GA and BIS-GMA (Table 1), though impurities in patch test substances may also explain such "cross-reactivity".

BIS-GA is a strong sensitizer according to guinea pig maximization tests (19) but allergic contact dermatitis from BIS-GA has been diagnosed only rarely (5). 5 out of 241 patients (2.1%) who had been exposed to (meth)acrylates reacted to BIS-GA in our material (20). Tucker & Beck (21) had 4 out of 175 (=2.3%) who reacted to BIS-GA on patch testing.

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Allergic contact dermatitis due to indomethacin and diclofenac

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Key words: indomethacin; diclofenac; allergic contact dermatitis; non-steroidal anti-inflammatory drugs; medications; cross-sensitivity; oral challenge. © Munksgaard, 2000.

Case Report

A 53-year-old man was treated for an acutely inflamed right elbow with Inacid gel® (indomethacin 1%: Laboratorios Merck, Sharp & Dohme, Madrid). 24 h later, he developed increasing itching, erythema and vesiculation limited to the treatment area, which disappeared in 1 week after application was discontinued. He was patch tested with the European standard series with negative results, but several topical non-steroidal anti-inflammatory drugs (NSAIDs), including Inacid® gel, were positive (Table 1). Single-blind, placebo-controlled oral challenges with nimesulide and paracetamol were well tolerated.

Discussion

Allergic contact dermatitis due to NSAIDs of the acetic group has previously been described (1–4). However,

multiple sensitization and/or cross reactivity (1, 3, 4) among them are rarely reported. Our case of cross-reactivity, based on patch test results, between an indolacetic derivative, indomethacin, and an arylacetic derivative, diclofenac, is unusual. The negative patch test results to oxicams and propionic derivatives and the tolerance to NSAIDs during controlled oral challenges might suggest a specific response to acetic derivatives in this patient. Based on our experience, a negative result during controlled oral challenge with an NSAID, neither involved in a previous reaction nor structurally related, indicates a safe alternative for patients with NSAID-induced allergic contact dermatitis.

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Table 1. Patch test results

	D2	D3
Inacid gel® (1% indomethacin) as is	++	+++
Voltaren Emulgel® (0.1% diclofenac) as is	+	++
Feldene gel® (0.5% piroxicam) as is	–	–
Calmatel® (1.8% piktetoprofen) as is	–	–

Delayed-type hypersensitivity rash from paracetamol

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Key words: paracetamol; generalized erythema; delayed-type hypersensitivity; lymphocyte transformation test; positive patch test; cutaneous adverse drug reactions; medicaments; oral challenge. © Munksgaard, 2000.

Case Report

A 62-year-old woman developed, 4–5 h after taking a tablet of paracetamol (500 mg) for headache, a generalized exanthema which regressed spontaneously and completely within a few days. 3 weeks later, after again taking a tablet of paracetamol, generalized erythema, with eyelid oedema, developed, associated with nausea, vomiting, pyrexia up to 40.4°C, and later exfoliation. Marked improvement of the skin symptoms was seen on inpatient treatment with oral corticosteroids. The patient was later referred to us for confirmation of the cause of the rashes.

We carried out prick testing with analgesic and anti-inflammatory agents, including paracetamol (saturated solution, pharmacy production), on the volar forearm, with immediate readings after 20 min and late readings at day (D) 1 and D2. Patch tests with paracetamol were carried out on the back in ascending concentrations with and without tape stripping, with readings at D2 and D3. Prick tests were negative at both immediate and late readings. Positive reactions oc-

curred to paracetamol at all concentrations patch tested (Table 1).

Graded oral provocation testing was carried out with paracetamol. Persisting, extensive confluent erythema, especially abdominally and on the face, developed with the cumulative administration of 200 mg after approximately 1 h during the challenge with paracetamol, disappearing slowly within 3–4 days after systemic corticosteroids and antihistamines and topical corticosteroid. A 4-mm punch biopsy from abdominal skin showed enlarged capillaries within the papillary dermis, focally surrounded by lymphohistiocytic infiltrates.

A lymphocyte transformation test was carried out with paracetamol for 5 days with peripheral blood mononuclear cells, using an established protocol (7), which gave a positive reaction (Table 2), a stimulation index of >2 being classified as positive for most allergens. The lower stimulation index obtained with higher paracetamol concentrations may be due to toxicity.

Discussion

Incompatibility reactions to NSAIDs are usually considered to be pseudoallergic (intolerance) reactions, immediate-type hypersensitivity, mediated by IgE, being imitated in the skin, respiratory tract and cardiovascular system (1). For paracetamol, urticarial skin reactions have particularly been noted (2, 6). Skin tests and RASTs have been negative and the diagnosis made by positive oral provocation tests (1).

Our patient's skin reaction to oral challenge was similar to the typical rash occurring after aminopenicillin intake (4). Lymphocyte transformation testing (5) and patch testing confirmed delayed-type hypersensitivity to paracetamol, which has been described only 1× before in 1996 (3).

Table 1. Patch test results with paracetamol

% (pet.)	Without stripping		With stripping	
	D2	D3	D2	D3
1%	–	?+	–	+
2%	–	?+	–	+
5%	–	?+	–	+
10%	–	?+	–	+
20%	–	?+	–	+

Table 2. Lymphocyte transformation test (LTT) results with paracetamol

Test material	Proliferation (thymidine insertion, cpm)	Stimulation index
culture medium + PBS	144.5	
background check		
phytohemagglutinin 100 µg/l	17,576.9	121.6
paracetamol 100 µg/l	202.4	1.4
paracetamol 50 µg/l	242.4	1.8
paracetamol 25 µg/l	310.0	2.1
paracetamol 10 µg/l	376.7	2.6
paracetamol 5 µg/l	230.0	1.6
paracetamol 1 µg/l	293.7	2.0
paracetamol 0.5 µg/l	509.4	3.5
paracetamol 0.1 µg/l	446.7	3.1

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Polyvinylpyrrolidone (PVP)/eicosene copolymer: an emerging cosmetic allergen

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Key words: allergic contact dermatitis; CAS 28211–18–9; cosmetics; polyvinylpyrrolidone (PVP)/eicosene copolymer; emulsifiers; sunscreens. © Munksgaard, 2000.

Case Report

A 34-year-old woman, with a childhood history of atopic dermatitis, was referred after acute facial eczema had occurred within 24 h of a single application of a recently bought sunscreen, followed by moderate sun exposure. Lesions rapidly cleared with topical corticosteroids.

Patch tests were performed 1 month later with the Finn Chamber technique on the upper back with the revised international standard series (1), additional allergens and the patient's own sunblock (Ambre Solaire Crème Nutritive Protectrice IP 10, Laboratoires Garnier, Clichy, France). Readings were performed after D2 and D3 as recommended by the ICDRG (2), and showed positive reactions to the sunblock only (+/+). A 2nd patch test with the sunblock was irradiated at D2 with UVA 10 J/cm², and gave a similar +/+ reaction at D2/D3.

Breakdown of the sunblock was then performed with its 24 ingredients, kindly provided by the firm, which showed a positive reaction (+/+ at D2/D3) only to polyvinylpyrrolidone (PVP)/eicosene copolymer 1% pet.

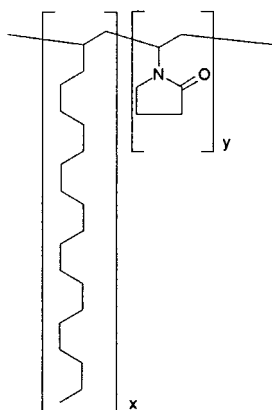


Fig. 1. Chemical formula of PVP/eicosene copolymer.

Discussion

Polyvinylpyrrolidone is the polymer of vinylpyrrolidone or 1-ethenyl 2-pyrrolidinone, and is also named povidone or PVP, CAS 9003–39–8 (3) (Fig. 1). With monomers of 1-eicosene, CAS 30614–34–7, it forms PVP/eicosene copolymer, CAS 28211–18–9. This synthetic polymer has the empirical formula (C₆H₉NO·C₂₀H₄₀) (4, 5).

PVP/eicosene copolymer is 1 of the 11 PVP copolymers recorded in the INCI inventory system, and utilized as an antistatic, binder, film former, suspending and viscosity increasing agent (4, 5). It has been widely used for several years in cosmetics such as mascaras, foundations, make-up preparations (except for eyes), moisturizing preparations, face and neck preparations (excluding shaving). It is present in many sunscreens to enhance their water resistance (4, 5). This copolymer is also used as an inert ingredient in pesticides.

Although PVP and eicosene alone are regarded as non-sensitizing, their copolymer may induce skin sensitization (6). PVP/hexadecene copolymer, another PVP copolymer used for identical applications, has also been implicated rarely in contact dermatitis (7, 8). This report is the 2nd on skin sensitization due to PVP/eicosene copolymer. The exact sensitizer could be a by-product occurring during polymerization, some impurity or an additive. Thus, further cases may be reported, particularly if the suppliers have recently modified their industrial process.

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Systemic reaction to glatiramer acetate

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Key words: copolymer-1; glatiramer acetate; anaphylactic reaction; prick test; intracutaneous test; multiple sclerosis; medicaments; cutaneous adverse drug reactions. © Munksgaard, 2000.

Case Report

For 2 months, a 30-year-old woman had injected 20 mg glatiramer acetate (synonyms: copolymer-1, cop-1, Copaxone®; Hoechst Marion Roussel Deutschland GmbH, Bad Soden, and GRY-Pharma GmbH, Kirchzarten, containing the powder of 20 mg cop-1 corresponding to 18 mg glatiramer acetate and mannitol 40 mg, to be diluted in aq. injectabile 1.0 ml) subcutaneously 1× a day for multiple sclerosis (MS), diagnosed 5 years ago. During these 2 months, no relapse occurred and the injections were well tolerated.

After these 2 months, 15 min after the next injection, she developed erythema of the head and neck and a sensation of heat and shortness of breath. All subsequent injections were well tolerated again until 6 weeks later; immediately after her daily injection of cop-1, she developed nausea, a sensation of heat, pressure and drowsiness in the head, generalized erythema and weals on the trunk. She felt cold perspiration, collapsed and developed gastric spasms and diarrhoea. After resting on the floor for 1/2 h she recovered, with weals remaining for 4 h longer. For 3 years, she had taken the antidepressant meclizemid (Aurorix®, Hoffmann-La Roche)

and contraceptives. Allergies to sulfonamides and nitrofurantoin and intolerance to acetylsalicylic acid were already known.

Prick and intracutaneous tests were performed with the solvent (aqua injectabile) without cop-1 (=glatiramer acetate) and with cop-1 in solution (Table 1), showing a positive result for the latter without systemic reaction in the patient. Cop-1 tested in the solvent, diluted 1:10, gave a 2+ reaction in the intracutaneous test after 24 h. Cop-1 in solvent undiluted showed a positive result with a 3+ reaction in the intracutaneous test after 24 h (1). Both positive results of the intracutaneous test showed pseudopods. Prick and intracutaneous (volume of injection 0.05) testing gave a positive reaction to histamine (1:1,000 for prick testing and 1:10,000 for intracutaneous testing) at 10 min after application. Testing with physiological saline was negative. 5 control persons were negative to the solvent and to cop-1.

Comment

Glatiramer or copolymer-1 (cop-1) is the acetate salt of a mixture of synthetic polypeptides composed of 4 amino acids, L-alanine, L-glutamic acid, L-lysine, and L-tyrosine, with a MW of 4,7000 to 13,0000 Da (2). Experimental allergic encephalitis is inhibited or modified by cop-1, which induces antigen-specific T-cells, because its polypeptides are mixed in the same proportion as in myelin basic protein, one of the autoantigens in MS (3). The resulting amino acid sequences are thought to inhibit the immune reaction against myelin basic protein or other myelin proteins by inducing antigen-specific T-suppressor cells, binding with MHC II and modulating chemokines (3). Cop-1 is approved for marketing in the United States, Israel and Great Britain. In some multicenter, double-blind, placebo-controlled studies, a significant reduction in relapses and improvement in neurological disability has been shown, with few side-effects

Table 1. Skin test results

	Prick test		Intracutaneous test	
	15 min	24 h	15 min	24 h
solvent, as is	–	–	–	–
cop-1 in solvent; 1:10	–	–	–	+++*
cop-1 in solvent, as is	–	–	(+)*	+++*
histamine	++	–	++	–
physiological saline	–	–	–	–

cop-1: copolymer-1, test results were evaluated in relation to the histamine reaction. * Erythema without weal. ** Erythema, weal, pseudopods.

(2, 4). rIFN beta-1b, rIFN beta-1a and cop-1 all effectively decrease the relapse rate of MS by approximately 1/3, but differ in their adverse effect profiles and administration regimens (5).

In about 2/3 of patients injecting cop-1, local injection site reactions are common and short-lived without necrosis, versus 1/3 local reactions in patients injecting placebo (2, 4). 10% to 15% of patients receiving cop-1 showed transient self-limited systemic reactions, consisting of a variable combination of facial flushing, chest tightness and dyspnoea of 20 s to 30 min immediately after injection (2, 4). This is in parallel with the 1st systemic reaction in our patient and has also been seen during these studies at irregular intervals and never during successive injections (2, 4). The cause of this reaction is unknown. In contrast, the 2nd reaction in our patient occurred with weals, collapse and gastrointestinal disturbance, which are symptoms of a systemic allergic reaction.

Interestingly, an attempt to induce tolerance against myelin basic protein by injectible cop-1 adversely resulted in induction of the systemic allergic reaction reported as the 2nd reaction in our patient. It was in 1973 (6) that initial observations of the immunologic properties of cop-1 emerged, showing activation at the cellular level for T-helper cells (7, 8) and at the humoral level for antibodies (9, 10). In our patient, there might have been exaggerated specific activation of the humoral immune defence against cop-1, as we found positive skin tests, most probably induced by the detection of specific antibodies against the cop-1 by skin testing. This report is the 3rd case of anaphylactic reaction to glatiramer acetate according to information from the company. The anaphylactic reaction to cop-1 described herein is a rare event, but has to be taken seriously. The change in the name from cop-1 to glatiramer acetate should be taken into consideration in rendering literature searching more difficult.

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