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Short Communications

Famciclovir as a possible alternative treatment in some cases of allergy to acyclovir

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Key words: systemic contact dermatitis; allergic contact dermatitis; acyclovir; famcicvolir; valaciclovir; antivirals; medicaments; allergen replacement; cross-sensitivity; oral provocation. © Munksgaard, 1999.

Allergy to acyclovir is rare (1), but when it occurs in patients with recurrent or severe herpes, an alternative treatment is required.

Case Reports

Case no. 1

A 30-year-old woman had had recurrent labial and ophthalmic herpes since the age of 8. When 29-years-old, she had presented with labial eczema after application of Zovirax® cream, then with oedematous eczema of the upper eyelid following the application of Zovirax® ophthalmic ointment. A few months later, 24 h after the intake of Zovirax® tablets, she presented on the arms, trunk, and inner thighs, with a pruriginous maculopapular rash, with secondary eczematization.

Patch tests according to the recommendations of the ICDRG, with readings on D2 and D8, with the components of Zovirax® cream, provided by Glaxo, were ++ to propylene glycol 5% pet. and ++ to acyclovir 10% aq. When we tested valaciclovir 10% aq. and famciclovir 10% aq., there was a ++ positive to valaciclovir only, all reactions being present on D2 and D8. We then carried out an oral provocation test with famciclovir 250 mg, given 4× in 1 day, and did not observe any reaction.

Case no. 2

A 28-year-old woman had had recurrent labial herpes since the age of 15. During summer 1998, she presented with a widespread eczema that had started 6 h after taking 1 Zovirax® tablet. Patch tests showed the same pattern of sensitization as in the 1st patient: ++ to propylene glycol, acyclovir and valaciclovir and − to famciclovir. A provocation test with famciclovir, however, elicited a pruriginous rash 12 h after its 1st intake.

Discussion

These 2 observations demonstrate concomitant sensitization to 2 components of Zovirax® cream, acyclovir and propylene glycol. In both cases, after sensitization by the topical, oral intake led to systemic contact dermatitis. The associated positivity to valaciclovir is not surprising, because it is the L-valyl ester of acyclovir (2) and is metabolized to acyclovir by gut hydroxylases. On the other hand, famciclovir is metabolized to penciclovir by a deacetylation process in the gut, blood and liver (3).

Desensitization to acyclovir has been tried in immediate hypersensitivity (4), but does not apply to delayed hypersensitivity. Valaciclovir seems clearly not to be indicated in cases of acyclovir allergy, but famciclovir may represent *in some cases* a therapeutic alternative, bearing in mind that cross-reactivity between acyclovir and famciclovir does exist *in other cases*, oral provocation testing being required to make the distinction.

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Patch-test positivity in cutaneous reactions to enoxaparin

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Key words: cutaneous adverse drug reaction; enoxaparin; positive patch test; medicaments; low molecular-weight heparins; patch testing technique.

Heparins are widely used to prevent and treat thromboembolic disorders. Low molecular-weight heparins (LMWH) have replaced unfractionated heparins, because of their improved pharmacodynamic properties and better safety profile (1). Immunologically-mediated hypersensitivity reactions are rare, but include heparin-induced immune thrombocytopenia, immediate hypersensitivity reactions and delayed allergic skin reactions, such as infiltrated eczematous plaques at injection sites (2). Some cases of delayed hypersensitivity to LMWH have also been reported (3–5).

Case Reports

Case no. 1

A 31-year-old pregnant woman, with no personal or family history of allergy, was prophylactically treated with the enoxaparin (Clexane®) 20 mg s.c. o.d. for antiphospholipid syndrome. By the 4th month of pregnancy, she complained of itchy erythematous infiltrated plaques at the sites of enoxaparin injections. Skin biopsy showed intraepidermal vesicles containing neutrophils and eosinophils, a perivascular lymphocytic infiltrate and marked oedema of the upper dermis. Patch testing was +++ at D2 and D4 to Clexane® 0.8% pet. as well as +++ to Clexane® as is. Tests were otherwise – to nadroparin (Fraxiparine®) as is, calcium heparin (Heparina Calcica Rovi®) 7500 UI as is, and the European standard series.

Case no. 2

A 33-year-old woman, with no history of allergies and who had not received heparins previously, was surgically treated for varicose veins and received subcutaneous Clexane® 20 mg o.d. 7 days after continuous therapy, itchy indurated plaques developed at the injection sites. Skin biopsy showed a spongiotic dermatitis, as in the 1st case. Patch tests were +++ to Clexane® 0.8% pet., as well as +++ to Clexane® as is and ++ to Fraxiparine® as is, but − to Heparina Calcica Rovi® 7500 UI as is and the European standard series. 5 control patch tests were performed with the same concentrations and were negative.

Discusion

Erythematous infiltrated plaques appear to be a common but neglected cutaneous reaction to heparin (3). The absence of necrosis confirmed histologically and the results of patch tests (+++ at D2 and D4) indicated a Type IV hypersensitivity reaction in our 2 patients. It has been suggested that a − reaction to an LMWH patch test can be explained by the fact that the low doses of LMWH inhibit the elicitation of allergic contact dermatitis (3). Our findings confirm that patch tests with Clexane® 0.8% pet. are as reliable as with Clexane® as is.

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Occupational airborne contact dermatitis from cefazolin

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Key words: airborne allergic contact dermatitis; cefazolin; occupational; health care workers; nurses; antibiotics; cephalosporins; focal flare.

Cefazolin is a 1st-generation cephalosporin antibiotic. Common side-effects include both anaphylactic and delayed-type hypersensitivity reactions (1, 3).

Case Report

A 40-year-old nurse gave a 10-year history of recurrent eczema of the hands and face at work. On examination, papulovesicular eczema, with fissures and erosions, of the palms, finger webs, backs of the hands and fingers, and face (periorbital), additionally with redness and swelling, was noted.

During medicolegal evaluation, patch testing was performed with the German standard, rubber, preservative, disinfectant and drug series (Hermal), and additionally with highly ammoniated latex protein (scratch chamber 1%, 10% aq.) and Cefazolin-saar i.v.® (1%, 10% aq.). Finn Chambers on Scanpor® (Hermal) with additional fixation (Fixomull stretch®, Beiersdorf) were used. Application time was 2 days and readings made according to ICDRG guidelines (modified to the German Contact Allergy Research Group guidelines (4)). Relevant results are shown in Table 1. Results of prick testing included latex protein: negative, antibodies: total IgE 584 ku/l, CAP SX1 FEIA (inhalational screening test): positive, C1-esterase inhibitor, C3, C4: standard values. During patch testing, aggravation of previous skin lesions was noted (Fig. 1).

Table 1. Relevant results of (scratch-)patch testing

	% w/v	20 min	D2	D3	D4
Cefazolin-saar 2000 i.v.®	1% aq.	−	+	+	+
Cefazolin-saar 2000 i.v.®	10% aq.	−	+	++	+++
latex protein	1% aq.	−	−	−	−
latex protein	10% aq.	−	−	−	−

Fig. 1. Aggravation of skin lesions of the eyelids during patch testing.

Discussion

Cephalosporins belong to the β-lactam antibiotics, which are responsible for approximately 75% of all allergies to antibiotics. They are similar to penicillin and possess a β-lactam ring. 7-amino-cephalosporanic acid is the important chemical structure. Well-known are maculopapular drug eruptions, urticaria, anaphylactic reactions, hemolytic anemia, thrombocytopenia and Lyell's syndrome (1, 3). Occupational airborne allergic contact dermatitis and contact urticaria have been reported from ceftiofur, cephalexin and cefotiam, but not before from *cefazolin* (1, 2, 5–10).

In this case, Cefazolin-saar 2000 i.v.® was used as a hospital-specific antimicrobial agent. During the preparation of parenteral antibiotics for drip infusion, the nurse was regularly exposed to it. Furthermore, she also had atopic dermatitis aggravated during work (especially on the hands). In our medicolegal evaluation, we decided against the necessity of giving up the occupation. After replacement by a 3rd-generation cephalosporin, the skin lesions diminished except for a recurrent vesicular atopic hand eczema.

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Association between tinea manuum and male manual workers

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Key words: tinea manuum; manual work; occupational hyperkeratosis.

Cases of tinea manuum are occasionally mistaken for hand dermatitis and referred for patch testing. Our clinical impression was that the majority of such cases were manual workers. To test this, we retrospectively compared the sex and occupations of proven tinea manuum cases to those of the remaining patch tested population. The occupations of patients were assessed and divided into manual or non-manual. Statistical analysis was carried out using the χ^2 test.

Results

From 1982–1995, 23,264 patients were patch tested, 13,655 (59%) female and 9,609 (41%) male. Of all these, 11,219 (48%) performed work with a significant manual component, of whom 54% were female. 12,045 (52%) had work with little or no manual component, 63% of whom were female.

During this same time period, 52 patients, 5 female and 47 male, presented for patch testing with tinea manuum, all with concurrent tinea pedis. 42 were in work with a significant manual component, 3 female and 39 male. 10 were in non-manual occupations, 2 female and 8 male.

The difference in numbers of manual and non-manual workers in the patch-tested population versus the tinea manuum population was significant: $p<0.001$. Furthermore, the difference in numbers of male manual and non-manual workers between these populations was also significant: $p<0.001$. However, the number of female patients in the tinea manuum population was too small to allow further analysis.

The 5 commonest occupations in the tinea manuum population were: car mechanic, machine operator, gas/electricity worker, chemical process worker and farm worker.

Discussion

The tinea manuum population were mostly manual workers and, in contrast to the patch tested population, these manual workers were predominantly male. We suggest that the male-dominated occupations found in the tinea group potentiated the development of tinea manuum. Manual workers develop hyperkeratotic skin on their palmar surfaces. Hyperkeratosis of the skin provides an enhanced environment for keratinophyllic dermatophytes. This association of hyperkeratosis and tinea has previously been noted in patients with keratoderma (1). Our findings might also reflect the increased incidence of tinea pedis, and hence tinea manuum (2), in some manual occupations (3). An additional factor may be that tinea manuum is mistaken for dermatitis more in manual workers than in non-manual workers.

We have shown that our patients with tinea manuum are predominantly male manual workers. This association has not previously been noted.

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Occupational airborne allergic contact dermatitis from isoflurane vapour

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Key words: airborne allergic contact dermatitis; occupational; isoflurane; anaesthetic; adverse drug reactions; positive repeated open application test; false-negative patch test.

Isoflurane (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether) is a widely-used halogenated general anaesthetic agent.

Case Report

A 57-year-old non-atopic consultant anaesthetist presented with an 8-month history of recurrent left periorbital erythema and oedema. His symptoms would worsen during the working week and improve at weekends.

He was initially patch tested to our standard, preservatives, nurses, local anaesthetics and contact lens series, showing positive reactions at 2 and 4 days to cetrimide (0.1% and 0.01% aq.), wool wax alcohols (30% pet.), (Cl)me-isothiazolinone (0.01% aq.), amethocaine (1% pet.), benzocaine (5% pet.), procaine (1% pet.) and prilocaine (5% pet). Type I hypersensitivity to latex was excluded with negative use and prick tests. At this stage, cetrimide was considered to be the major allergen as it is commonly used in British hospitals as a disinfectant and skin cleanser. The multiple sensitivities to local anaesthetics were thought to derive from the use of topical preparations for haemorrhoids rather than from occupational exposure.

Despite strict avoidance of all the identified allergens, he remained symptomatic 2 months later. The history suggested a missed allergen, which was considered to be a general anaesthetic agent, isoflurane, sevoflurane and propofol being the commonest used by our patient. Isoflurane and sevoflurane are colourless volatile liquids used as inhalational anaesthetics, whereas propofol is a milky emulsion for intravenous use. Closed patch tests to all 3 agents were negative at 2 and 4 days. Single open application tests were also negative after 20 min.

Being volatile liquids, isoflurane and sevoflurane quickly evaporated from the skin surface, possibly causing a false-negative patch test reaction. Repeated open application tests (ROAT) were therefore performed by applying 1 ml of each anaesthetic to the volar aspect of the forearm 2× a day. The ROAT to isoflurane elicited a discoid eczematous patch after 3 such applications. Similar tests with sevoflurane and propofol were negative. ROATs to isoflurane in 20 volunteer control subjects were also negative.

While still employed as an anaesthetist, it has been impossible for our patient to totally exclude exposure to isoflurane vapour. However, the use of protective eye wear has dramatically improved his symptoms. The unilateral distribution of his disease is explained by the positioning of the anaesthetic machine to his left.

Discussion

Isoflurane is commonly used for both induction and maintenance of general anaesthesia. Its side-effects include arterial hypertension, respiratory depression, cardiac arrhythmias and, rarely, convulsions (1). Only occasional allergic reactions to halogenated anaesthetics have been reported, either in patients or in theatre staff (2, 3). Halothane has also been considered responsible for an occupational facial acneiform eruption in 2 anaesthetists (4). To our knowledge, only 1 previous case of allergic contact dermatitis from isoflurane has been reported, the patient also being an experienced anaesthetist who developed facial eczema (5).

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Contact allergy to corticosteroids in Israeli patients

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Key words: allergic contact dermatitis; corticosteroid series; patch testing technique; screening for allergy; marker of corticosteroid allergy; multiple reactions.

Patients and Methods

660 patients attending our contact dermatitis clinic during 1995–1998 were included in the study. A corticosteroids series (Chemotechnique Diagnostics) was added to our standard series. Finn Chambers on Scanpor tape were used. Readings were made at D2 and D4. Reactions were scored as recommended by the ICDRG.

Table 1. Positive reactions to the corticosteroids series in 13 patients

Patient no.	Allergen
1	budesonide
2	tixocortol 21-pivalate, hydrocortisone 17-butyrate
3	betamethasone 17-valerate
4	budesonide
5	betamethasone 17-valerate, hydrocortisone 17-butyrate
6	tixocortol 21-pivalate
7	tixocortol 21-pivalate, clobetasol 17-propionate
8	clobetasol 17-propionate
9	budesonide, triamcinolone acetonide, hydrocortisone 17-butyrate
10	hydrocortisone 17-butyrate
11	betamethasone 17-valerate
12	tixocortol 21-pivalate
13	betamethasone 17-valerate, clobetasol 17-propionate

Table 2. Positive allergens in the 660 patients tested

Allergen	No. patients	(%)
nickel sulfate	91	13.79
potassium dichromate	60	9.09
thimerosal	29	4.39
cobalt chloride	22	3.33
fragrance mix	21	3.18
balsam of Peru	21	3.18
thiuram mix	21	3.18
corticosteroid series	13	1.97

Results

Of the 660 patients so tested, 13 (1.97%) were positive to 1 or more corticosteroids. 5 patients reacted to more than 1 corticosteroid (Table 1). The most common allergens detected were tixocortol pivalate, hydrocortisone 17-butyrate, betamethasone 17-valerate, budesonide and clobetasol 17-proprionate. No reactions were noted to dexamethasone or alclometasone. Corticosteroids were found to be the 8th most frequent allergen, after nickel sulfate, potassium dichromate, thimerosal, cobalt chloride, fragrance mix, balsam of Peru and thiuram mix (Table 2).

Comment

The frequency found among our patients is in accordance with that previously reported (1–3), though at the lower end of the range (1). Only 4 patients would have been detected by testing with tixocortol pivalate alone, and, even with the addition of budesonide, 6 cases would still have been missed. The multiple reactions to several corticosteroids occurred both within well-defined groups of structurally-related substances and between corticosteroids of different groups.

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Allergic contact dermatitis from *Primula auricula* and *Primula denticulata*

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Key words: allergic contact dermatitis; hardy *Primula* species; *P. obconica; P. auricula; P. denticulata;* primin; miconidin; primetin; farina; plants.

Case Report

A 66-year-old man, with a history of atopy, presented in March 1999 with an 8-month history of an itchy rash on his fingers and arms, which had started when he was potting up some primulas in his garden. He had been growing hardy *Primula* species for 18 months, notably *P. auricula* and *P. denticulata* (purple and white flowered varieties) and had also grown *P. obconica* in the past. His rash started within hours of handling his plants, causing tenderness of the finger tips, erythema, fissuring and scaling of the skin of the fingers, erythematous streaks up the forearms and swelling of the hands, followed by desquamation after 2 days. The eruption recurred with repeated exposure to the plants. He was prescribed mometasone furoate cream 1× daily and an emollient. He was also advised to wear thick vinyl household gloves when handling his plants. Within 2 weeks, he described a 75% improvement in his skin, leaving him with residual dryness of the finger tips. He has stopped growing primulas. The outcome of patch testing is shown in Table 1.

Discussion

Most allergic contact dermatitis from *Primula* spp. is due to *P. obconica.* The main sensitizer is primin, found in the terminal cells of the microscopic hairs surrounding the calyx, and also in the leaf, stem and root (1). Hausen (1) studied 82 species of *Primula* and discovered that 16 species contain primin, including *P. denticulata* where it is present in the petal, leaf and stem. *P. auricula*, however, contains no primin, though other quinoid substances are detectable in the leaf, stem and root. Mitchell & Rook (2) reported that *P. auricula* had no irritating action on the skin, whereas Alemany-Vall (3) documented allergic reactions to this species as being rare. Growers of *P. auricula,* with dermatitis, have described tolerance on repeated exposure, implying an allergic response (4). Dermatitis has also been described from *P. denticulata* (1).

Allergens other than primin may be of clinical importance (5, 6) and both miconidin (7) and primetin (8), a flavone, have been suggested as sensitizers, albeit for *P. obconica* and *P. mistassinica* Michaux, respectively. It is, however, of interest that primetin has been detected in the farina of *P. auricula* (9) and *P. denticulata* (9, 10).

Our patient is unusual in presenting with an allergic contact dermatitis from 2 hardy *Primula* species, *P. auricula* and *P. denticulata*, with negative patch tests to primin, but positive results to the leaves of *P. auricula* and *P. denticulata*. These results indicate that sensitizers other than primin are responsible for this man's dermatitis.

Table 1. Patch test results

Test substance	D2	D4
primin 0.01% pet.	−	−
P. auricula leaf	++	++
P. denticulata [a)]leaf	++	++
P. denticulata [b)]leaf	++	++
P. denticulata root	−	−

[a)] Purple-flowered.
[b)] White-flowered.

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Tolerance of desirudin in a patient with generalized eczema after intravenous challenge with heparin and a delayed-type skin reaction to high and low molecular weight heparins and heparinoids

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Key words: delayed-type skin reaction; intravenous challenge; heparin; heparinoid; hirudin; adverse drug reactions; allergen replacement.

Concomitant delayed-type sensitization to high and low molecular-weight heparins and heparinoids raises a problem over thrombosis prophylaxis (1). In most cases, there is tolerance of intravenous (i.v.) heparin after eczematous reaction to subcutaneous (s.c.) heparin (2, 3).

Case Report

A 54-year-old woman developed itchy eczema at the s.c. injection sites on the lower abdomen of the low molecular-weight heparin certoparin. Patch testing with a high molecular-weight heparin, the low molecular-weight heparins certoparin and nadroparin, and the heparinoid danaparoid, was negative. Prick testing was also negative after 3 days, except for a histologically proven eczematous reaction to certoparin. Positive reactions after 3 days to intracutaneous (i.c.) testing were found for the high molecular-weight heparin and the heparinoid, but not for nadroparin. Therefore, nadroparin was used for s.c. challenge, showing an eczematous reaction after 2 days. We then started i.v. challenge with a high molecular-weight heparin over 2 days, using the scheme of Trautmann et al. (personal communication), under inpatient conditions. 2 days after admission, the patient developed a generalized delayed-type skin reaction.

After the recent launch of desirudin, a recombinant hirudin, patch, prick and i.c. testing was repeated with this drug. All such tests were negative. Subsequently, s.c. challenge was performed, which was well tolerated without signs of delayed-type hypersensitivity. This is the 1st such report.

Discussion

The following conclusions can be drawn from this case.

A negative i.c. test (in our case, to nadroparin) does not exclude a delayed-type skin reaction to s.c. challange, the latter therefore being the most sensitive test (4, 5).

A switch from s.c. to i.v. administration is not always possible and risks a generalized eczematous reaction.

Recombinant hirudins do not cross-react with low or high molecular-weight heparins and heparinoids and can therefore be used as an alternative. Nevertheless, Type IV reactions can also occur to hirudins (5, 6).

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Allergic contact dermatitis from epsilon-aminocaproic acid

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Key words: allergic contact dermatitis; epsilon-aminocaproic acid; eyedrops; cataract; medicaments; ophthalmics.

Case Report

A 63-year-old Japanese woman presented with itchy erythema bilaterally in the periorbital region and on the cheeks several hours after using OTC eyedrops (Daigaku-megusuri®, Santen Pharmaceutical. Co. Ltd., Osaka, Japan) containing 1% epsilon-aminocaproic acid. The skin lesions subsided 3 days after application of a mild corticosteroid and injection of an anti-allergic drug.

Patch testing was performed with the eyedrops and their individual ingredients. Positive reactions were obtained to the eyedrops and epsilon-aminocaproic acid 1.0% pet. at 2 and 3 days. Negative reactions were obtained to zinc sulfate 0.1%, 0.5% and 1.0% pet., chlorpheniramine maleate 50% pet., chondroitin sulfate sodium 50% pet., 1-methol 50% pet., geraniol 20% pet., d-borneol 50% pet., benzalkonium chloride 0.02% aq., chlorobutanol 50% pet., and boric acid 50% pet. at 2 and 3 days.

Table 1. Previous reports of allergic contact dermatitis from epsilon-aminocaproic acid

Authors	Year	Age (years)/ sex	Eyedrops
Sugai	1986	59 F	Sante U®
		60 F	OTC eyedrops for
Shono	1988		swimming
Tanaka et al.	1992	53 F	OTC eyedrops
Washizaki et al.	1992	70 F	Catalin K®
Kiyokawa et al.	1994	54 F	Catalin K®
Tsunoda et al.	1996	78 F	Catalin K®
Tsunoda et al.	1996	72 M	Catalin K®
Kawada et al.	1996	72 F	Catalin K®
Tsunoda et al.	1997	78 F	Catalin K®
Tsunoda et al.	1997	79 F	Catalin K®

Comment

Contact dermatitis due to epsilon-aminocaproic acid is rare (Table 1), all patients being sensitized by eyedrops and 9 out of 10 being female. 7 of the patients were sensitized by Catalin K®, widely prescribed for cataract by oculists in Japan. The other 3 patients used OTC eyedrops.

Tanaka et al. (1) reported a case of contact dermatitis from nylon 6 in Japan, in which patch testing was performed with epsilon-aminocaproic acid 3% and 6% pet. Epsilon-aminocaproic acid has been widely used as the monomer of nylon 6 manufactured in Japan (1), and many Japanese women wear nylon tights (panty hose). However no case of contact dermatitis from nylon 6, except for the case of Tanaka et al. (1), has been reported. None of the 10 patients in Table 1 were thought to have been sensitized by nylon tights.

Epsilon-aminocaproic acid is a potent synthetic fibrolysin, used widely to control various hemorrhagic disorders (2). In Japan, it has also been included in some topical medicaments and cosmetics, e.g., eyedrops, gargles, creams, skin fresheners, soaps, and toothpaste (3). Because women use such topical medicaments and cosmetics more frequently than men, it cannot be ruled out that 9 of the female patients in Table 1 were sensitive not only to eyedrops, but also to medicaments and cosmetics.

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Allergic contact dermatitis from octyl gallate in lipstick

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Key words: allergic contact dermatitis; octyl gallate; antioxidants; cosmetics.

Octyl gallate is an antioxidant commonly used in the food (E 311) and cosmetic industries. Although, theoretically, it is considered to be much more sensitizing than propyl gallate (1), there are very few case reports of contact allergy, and those mainly occupational.

Case Report

A 37-year-old woman with acute cheilitis associated with perioral dermatitis had used Amylab® lipstick for several years. She had hay fever, but no atopic dermatitis. Patch testing with this lipstick revealed a positive reaction (++) at D3 (D2 −). However, the European standard series and series of preservatives, emulsifying excipients, fragrances, and photoprotectors showed no positive reactions.

Later, patch tests with the individual ingredients of the lipstick were performed, showing a positive reaction only to octyl gallate (0.3% pet.) at D2 (++) and D3 (+++). Additional tests with other gallates (propyl 0.5% pet. and dodecyl 0.3% pet.) were negative. The patient recovered completely after she stopped applying the lipstick.

Discussion

Until 1990, the few reported cases of contact allergy to octyl gallate were occupational among workers in the food industry: margarine (2, 3), peanut butter (4), and chicken fat (5). In the European Economic Community, octyl gallate, with regard to food (E 311), is approved in essential oils, butter, fat products, and margarines (for quantities of at least 5 kg).

The first well-documented cases of contact allergy to octyl gallate in cosmetics (lipsticks) were described in 1995 (6). Propyl has been the gallate used most frequently and has also been reported most commonly as a contact allergen. However, it seems that it is octyl gallate which has the highest rate of sensitization (1.1%) (7). In this same study, the rate of sensitization was reported to be 0.3% for propyl gallate and 0.6% for dodecyl gallate.

Such results are almost identical to those of theoretical studies on sensitization to gallates, which demonstrates that their sensitizing potential increases with the length of the aliphatic side chain (1). Allergy to octyl gallate appears more frequently in women above the age of 40 (1.4%) (7), which might support the concept of a more cosmetic pathway of sensitization. However, cross-reactions between octyl, propyl and dodecyl gallate occur (8).

In conclusion, the frequency of contact allergy to octyl gallate, especially in cosmetic products, may be underestimated. Patch tests should be performed systematically in the case of any suspicion of cosmetic allergy (especially in patients with cheilitis), including also the other gallates (propyl and dodecyl) to look for cross reactions.

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Pacemaker dermatitis from titanium

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Key words: pacemaker; titanium; systemic contact dermatitis; patch testing technique; false-negative patch test; positive intracutaneous test; positive lymphocyte stimulation test.

Pacemaker dermatitis was first reported by Raque et al. (1). Patients first develop a circumscribed area of dermatitis overlying an implanted cardiac pacemaker and later nummular eczema in a widespread distribution (2). Previously, positive patch test reactions to mercury (3), epoxy resin (2), titanium (4), and nickel (5) have been described. In some cases, however, the exact cause has not been found by patch tests.

Case Report

An 86-year-old Japanese man received a pacemaker for atrioventricular block. 2 months after the implantation, he developed a well-defined scaly erythema over the implantation site and later a widespred nummular eczema (Fig. 1). Histologically, the lesion showed slight spongiosis, intracellular edema and moderate acanthosis in the epidermis, and perivascular infiltration with thickened capillary walls in the dermis.

The implanted pacemaker contained the following materials: casing – titanium, epoxy resin, silicon, and parilene; electrode – platinum and iridium; battery – lithium. Patch tests with a metals series (Torii, Tokyo) and the European standard series of allergens (Trolab, Hermal) were all negative. Samples of the contained materials, as is, were applied under Scanpor® tape for 2 days on his back, but still no reaction occurred. We then took his serum and kept small pieces of titanium in it for a month. An intracutaneous test with the incubated serum was positive after 2 days (Fig. 2). We isolated pe-

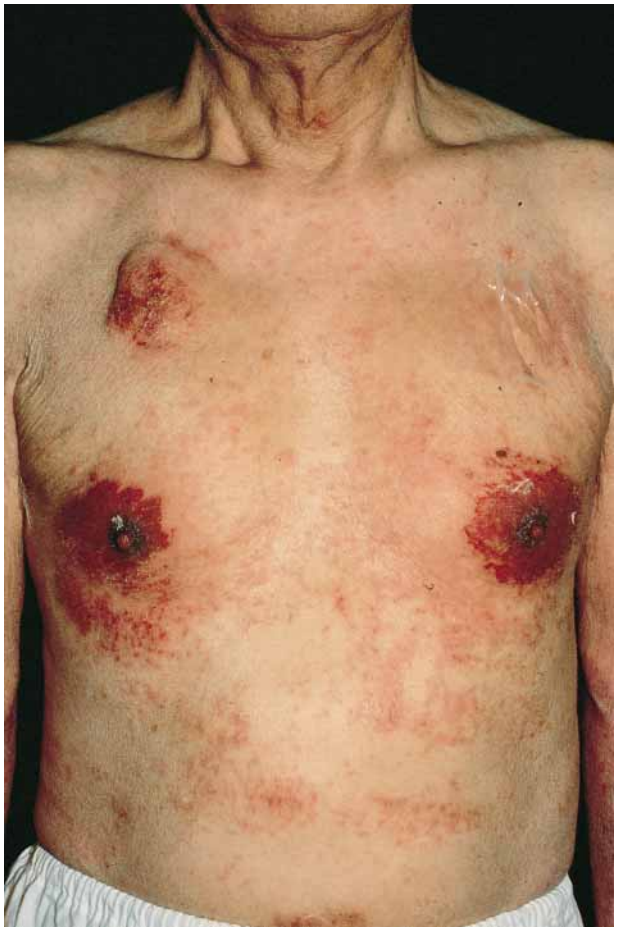

Fig. 1. Well-defined scaly erythema over the implanted site and widespread nummular eczema.

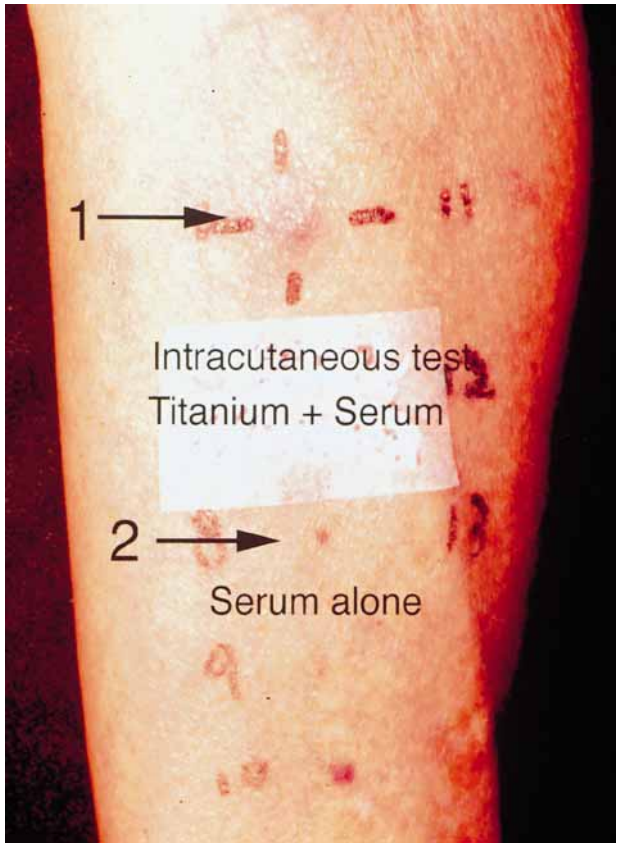

Fig. 2. Intracutaneous test positive to titanium plus patient's serum, but not to the serum alone.

ripheral blood mononuclear cells (PBMC) and subjected 10% of the incubated serum to a ^{3}H-thymidine incorporation test: stimulation index was 235%.

Discussion

Contact dermatitis from implanted metals may be due to various allergens. In our patient, we were unable to demonstrate a positive reaction to titanium on patch testing, but titanium sensitivity was demonstrated by intracutaneous and lymphocyte stimulation testing.

Titanium is so widely used that the risk of contact sensitivity to it can only be very small. If a patient shows contact sensitivity to titanium, a replacement pacemaker should be completely encased in a patch-tested non-allergenic material. Our patient's general health status did not allow further implantation.

Further work is required on reliable testing for contact sensitivity to titanium. We found intracutaneous and lymphocyte stimulation testing to be more reliable than patch testing.

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Allergic contact dermatitis from sodium fusidate with no underlying dermatosis

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Key words: allergic contact dermatitis; sodium fusidate; nursery nurse; occupational; medicaments.

Case Report

A 26-year-old Korean woman treated an abrasion on her left knee with Fucidin® ointment and Betadine®. The wound initially improved, but within 2 days became worse. A pruritic, erythematous exudative area was found on examination. She had been working as a nurse for 2 years and had had contact with several topical agents for the care of neonatal skin problems. She had never before used Fucidin® ointment on herself, and had never suffered from atopic or stasis dermatitis.

Patch tests were performed with Betadine® and Fucidin® ointment as is. A +++ reaction developed to Fucidin® ointment. Patch tests with the ingredients of Fucidin® ointment then showed +++ reactions to sodium fusidate (Table 1).

Table 1. Patch test results

		D2	D4
Fucidin® ointment	as is	+++	+++
sodium fusidate	2% pet.	+++	+++
	1% pet.	+++	+++
liquid paraffin	as is	−	−
cetyl alcohol	30% pet.	−	−
steary alcohol	30% pet.	−	−
wool alcohols	30% pet.	−	−
lanolin	as is	−	−
petrolatum	as is	−	−

Comment

Fucidin® ointment contains 2% sodium salt of fusidic acid, isolated from the fungus *Fusidium coccineum*, and is widely used for cutaneous infections. Sensitization to sodium fusidate is rare (1–8). Most such cases have underlying stasis dermatitis or atopic dermatitis (1–2). Our case, in contrast, appears to have been primarily occupational.

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Increased rate of patch test reactivity to methyldibromo glutaronitrile

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Key words: methyldibromo glutaronitrile; Euxyl™ K400; cosmetics; preservatives; formaldehyde; patch testing technique.

Since its introduction in the mid-1980s, contact allergy to methyldibromo glutaronitrile has been increasing in Europe and the USA (1). The allergen in Euxyl™ K400 (methyldibromo glutaronitrile and phenoxyethanol at a 4:1 ratio) is usually methyldibromo glutaronitrile (2). Since changing from patch testing with Euxyl™ K400 0.5% pet. to methyldibromo glutaronitrile 0.3% pet. in 1997, it was our impression that we were seeing more positive patch test reactions, and we therefore looked at the annual positive patch test rates to this allergen retrospectively. To compare this with another preservative allergen, we looked at the corresponding data for formaldehyde 1% aq.

Patients and Methods

From January 1989 to June 1997, all patients attending St. John's Contact Dermatitis Clinic were patch tested to Euxyl™ K400 0.5% pet., except for the year 1990 when no patients were tested to it. From July 1997 until the present, patients were patch tested to methyldibromo glutaronitrile 0.3% pet. Throughout the whole study period, patients were also patch tested to formaldehyde 1% aq. Patches were applied using 8 mm Finn Chambers™ with Scanpor™ applied to the upper back. Patches were read at 2 and 4 days.

Results

From January 1989 until the end of the first 6 months of 1999, 11,739 patients (average age 39, age range 6 months-92 years; 4442 M, 7297 F) were patch tested. Fig. 1 shows the annual frequency. Since the introduction of testing with the new allergen preparation, there has been a sharp increase in the rate of positive patch reactions. The formaldehyde sensitivity rate (Fig. 2) (average age 39, range 6 months – 92 years), in contrast shows a gradual decline. χ^2 tests for Euxyl™ K400/ methyldibromo glutaronitrile showed a significant ($p<0.01$) increase in frequency for the period 1994–1999 compared to the period 1989–1993. Formaldehyde showed a significant ($p<0.001$) decrease between the same periods. Over 1/2 the methyldibromo glutaronitrile-positive patients had dermatitis primarily localized to the head and neck region, the next most common primary sites recorded being 'widespread' and 'hands'.

Table 1. Primary sites of eczema in patch-test-positive patients

Site	No. patients
widespread	13
head and neck (inc. scalp)	26
hand	9
hand and foot	2
hand and face	1
arm	1

Discussion

Since allergy to Euxyl™ K400 was first described 10 years ago (3), there have been repeated reports of its increasing incidence. Although a marked increase in reactions was seen when Euxyl™ K400 0.5% pet. was replaced by methyldibromo glutaronitrile 0.3% pet. for patch testing, the rise over this period of time could also be due in part to a real increase in allergy to this preservative in the patch tested population. De Groot (4), in

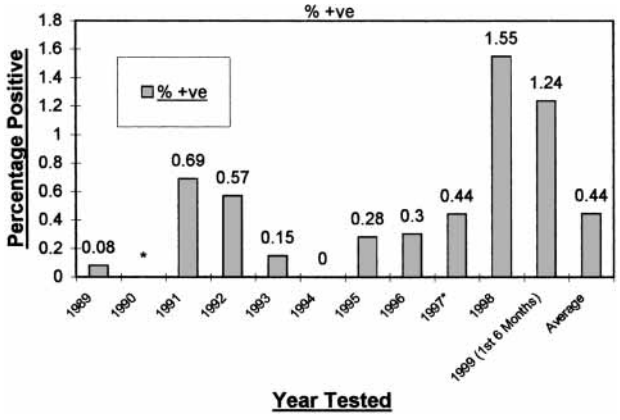

Fig. 1. Annual frequency of methyldibromo glutaronitrile-positive patch test reactions. * No patients were tested to Euxyl™ K400/methyldibromo glutaronitrile in 1990.

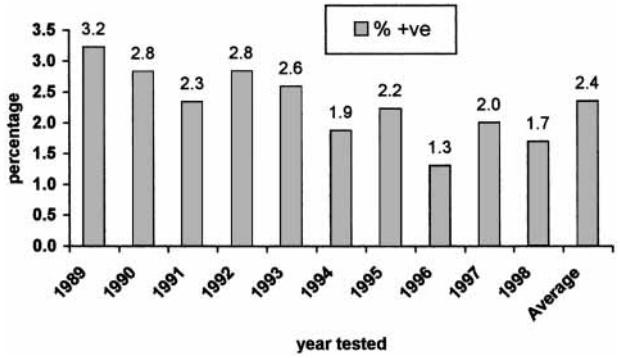

Fig. 2. Annual frequency of formaldehyde-positive patch test reactions.

1996, reported an incidence of 2–4%, the source of exposure being both wash-off and leave-on products. Because of its tendency to give false-positive reactions, reported allergy rates for methyldibromo glutaronitrile must be interpreted with caution.

The sources of exposure may be as diverse as eye gel (5), sunscreen (6) and ultrasonic gel (7), and occupational cases have been described from hand cleansers and detergents (8). Although allergic contact dermatitis was previously frequently reported from moist toilet tissue (9), the majority of cases would now appear to arise from exposure to cosmetics. 1/2 the reactions in the current series were in patients with dermatitis of the head and neck, which would correlate with either a facial cosmetic or a shampoo being the source of exposure.

To summarize, we have seen a gradual increase in allergic patch test reactions to the cosmetic preservative methyldibromo glutaronitrile, during a period of time when another cosmetic preservative, formaldehyde, has seen a reduction in its frequency of positive reactions.

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