CONTACT POINTS

CONTACT DERMATITIS 2005: 53: 298–304 •

• CONTRIBUTIONS TO THIS SECTION WILL NOT UNDERGO PEER REVIEW, BUT WILL BE REVIEWED BY THE EDITOR •

Phenylephrine and acute periorbital dermatitis

Contact Dermatitis 2005: 53: 298–299

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Key words: contact dermatitis; drug allergy; drug eruptions; eye drops; metaoxedrine; patch test; periorbital dermatitis; phenylephrine.

Periorbital dermatitis is often of multifactorial origin. It may be acute or chronic; it may be the dominating skin problem or part of a more widespread skin disorder. Endogenous and exogenous factors are involved (1–6).

Patients and Methods

We performed a retrospective evaluation of 32 consecutive patients with periorbital dermatitis and a clinical suspicion of allergic contact dermatitis patch tested from 1995 to 2003 with the standard series and a selected panel of ingredients of ophthalmic drugs (Table 1) and the patients own ophthalmic products. The ophthalmic drug series was extended in November 2000.

The TRUE test panels 1 and 2 were supplemented with Finn chambers on Scanpor tape (Epitest Ltd Oy, Tuusula, Finland and Alpharma AS, Oslo, Norway). Patch tests were performed and read according to the ICDRG guidelines. Clinical relevance was categorized as either current, past or unknown.

The patients were divided into three groups according to the nature of their dermatitis (Table 2).

Results

17 patients had contact allergy. In 15/17, the allergy was of current relevance to their periorbital dermatitis (Table 2). The strong reactivity and frequent occurrence of contact allergy to phenylephrine is noteworthy. The results of patch tests with the ophthalmic series are listed in Table 1. 1 patient had multiple allergies to formaldehyde releasers, 1 patient to Euxyl K400, 1 patient to an ophthalmic drug containing latanoprost and timolol and 1 patient to a moisturizing cream. 4 patients had immediate type allergy, judged of current relevance in 2 cases (Table 2). 1 patient had positive skin prick test to fresh celery and a clear history of exacerbation of periorbital dermatitis after intake of celery; another was diagnosed dust mite allergic by specific IgE and conjunctival challenge.

11 patients were patch tested with steroids with negative results (data not shown). Doubtful positive patch tests were all of unknown relevance.

Discussion

There is no generally accepted ophthalmic series available. The composition of our ophthalmic test series has changed over the years (Table 1) reflecting the development in use of specific ophthalmic drugs, chemicals in contact lens solutions and reports about ophthalmics causing contact allergy. In the present study, the culprits were identified by the combined use of the ophthalmic test series, the standard series, the patient's own products and skin prick tests.

Table 1. Ophthalmic patch test series and results of patch testing. T = Trolab Hermal, Reinbek, Germany, C = Chemotechnique, Malmö, Sweden, A = Hospital Pharmacy

Name	Positive reaction (+–+++)	Doubtful reaction*(+?)	No. tested
Chloramphenicol 5% pet. T	1	1	32
Phenylmercuric acetate 0.01% aq. C	0	1	32
Ammoniated mercury 1% pet. T	1	1	32
Sulfamethiazole 5% pet. A	0	1	32
Bacitracin 20% pet. T	0	0	32
Resorcinol 1% pet. C	0	1	32
Benzalconium chloride 0,1% pet. T	1	3	32
Atropine sulphate 1% aq. T	0	0	19
Pilocarpine Hydrochloride 1% aq. T	0	0	19
Sodium EDTA 1% pet. T	0	0	19
Polymyxin B sulphate 3% pet. T	1	1	19
Phenylephrine Hydrochloride 10% aq. T	5 (+1)**	2	19
Total	**10**	**11**	

*No doubtful reactions are registered as relevant.
**+1 delayed reaction registered on day 14. Judged to be elicitation and not sensitization.

Table 2. Characteristics of 32 patients tested with the ophthalmic patch test panel with regard to age, duration of the periorbital dermatitis, allergic history, and results from allergy investigations

	History				Allergy testing					
Group	No. of ptt	Avr age	Duration of dermatitis	AD, Asthma or rhinitis	Ophthalmic panel	TRUE test panel 1 & 2	Extra contact allergens*	Total relevant contact allergies	Total relevant immediate allergies	Total allergies**
Acute periorbital dermatitis§	8	72.5 y (57-84 y)	10.5 d (4-21)	3 (37.5%)	6 ptt (75%) (Phenylephrine)	0§§	0	6 ptt (75%) (6 reactions)	0	6 ptt (75%) 6 allergies
Chronic periorbital dermatitis without AD	18	10.5 d (4-21)	4.8 y (2 w-23 y)	2 (11%)	1 pt (6%) (Chloramphenicol)	1 pt (6%) (Lanolin, thimerosal)	4 ptt (22%)	6 ptt (33%) (14 reactions)	2 ptt (11%) (Celery, Dust mites)	8 ptt (44%) 16 allergies
Chronic periorbital dermatitis and AD	6	42 y (29-57 y)	9 y (2-35 y)	6 (100%)	1 pt (17%) (Benzalc.chloride)	0	2 ptt† (33%)	3 ptt (50%) (3 reactions)	1 pt (17%) (2 reactions: egg, milk)	3 ptt†† (50%) 5 allergies
Total	32	54 y (6-86 y)	4 y (4 d-35 y)	11 (33%)	8 ptt (25%) (8 reactions)	1 pt (3%) (2 reactions)	6 ptt (19%) 13 reactions	15 ptt (47%) 23 reactions	3 ptt (9%) 4 reactions	17 ptt (53%)27 allergies

* incl. the patients own products.
** Immediate and delayed type allergies.
§ Patients that developed dermatitis within a few days after using a topical ophthalmic.
§§ 1 pos. for colophony. Doubtful relevance.
† 2 reacted to own cosmetic products.
†† 1 had contact allergy as well as a type I allergy.

Half the patients had immediate or delayed type allergy of current relevance to their periorbital dermatitis. 15/32 (47%) had allergic contact dermatitis and 3/32 (9%) had immediate type allergy of current relevance.

Seven of the 12 allergens in the ophthalmic test series yielded positive reactions. Bacitracin is no longer used in ophthalmic solutions in Denmark. Only 1 patient in the study used contact lenses, which explains the relative lack of reactions towards ingredients of contact lens-rinsing solutions.

Phenylephrine (syn. metaoxedrine) caused the majority of the reactions in patients with acute dermatitis in accordance with Villarreal (7) who found that 93.5% of reactions to mydriatic topical drugs were elicited by phenylephrine. It is important to test with the patients' own ophthalmic products: one patient was allergic to a β-blocker and to a prostaglandin.

Two patients had reactions towards preservatives, which are well-known contact allergens in ophthalmic preparations (7, 8). The relevance of reactions to benzalconium chloride may be difficult to determine due to the irritancy of the compound. Reactions to preservatives and ingredients of skin care products were all seen in patients with chronic periorbital dermatitis.

Cosmetics are also a common cause of periorbital dermatitis (1, 3, 8, 9). One patient with chronic periorbital dermatitis and AD was found contact allergic to her own cosmetics.

Periorbital dermatitis frequently occurs in atopic dermatitis patients, who are often younger than patients with acute periorbital dermatitis. Atopic dermatitis tends to decrease with age and patients with the most common eye diseases are generally older. As described by others (4, 5), patients with other skin areas affected were least likely to have allergic contact dermatitis.

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Fixed drug eruption caused by ornidazole

Contact Dermatitis 2005: 53: 300–301

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Key words: fixed drug eruption; ornidazole.

Fixed drug eruption (FDE) is a distinctive variant of drug-induced dermatoses with characteristic recurrence at the same site of skin or mucous membrane (1). A number of drugs have been implicated as a cause of FDE. Among antiprotozoal drugs, metronidazole and tinidazole (5-nitroimidazole derivative) have been reported along with cross sensitivity to each other (2) to cause FDE. We report a case of bullous FDE caused by ornidazole which is a newer 5-nitroimidazole derivative.

Case Report

A 26-year-old male referred from department of internal medicine presented with a well-defined erosion of size 3 × 1 cm with surrounding erythema, situated over right side of lower lip mucosa (Fig. 1). The lesion was itchy in nature and mildly painful.

The present lesion started as a bulla 2 days after the ingestion of oral ornidazole for diarrhoea. The bulla ruptured few hours later due to trauma caused by teeth with oozing of blood-like fluid. There was no history of insect bite at that site or similar lesion on rest of the body including genitalia. The patient was an old diagnosed case of recurrent intestinal amoebiasis and was on treatment in the form of either oral metronidazole, tinidazole or secnidazole. Patient had no sign and symptom of drug hypersensitivity with these drugs, but because of excessive nausea and metallic taste, he was prescribed ornidazole since last two episodes of diarrhoea. On further enquiry, patient recalled history of some fluid lesion 8 months back on same site of lower lip after 3–4 days of ingestion of oral ornidazole, Lesion healed without any treatment. Provisional diagnosis of bullous FDE was made.

Therapy with cetrizine 10 mg/day and prednisolone 40 mg/day along with ranitidine 150 mg twice a day was initiated. The lesion cleared slowly within 10 days; systemic therapy with prednisolone was then gradually tapered and discontinued shortly thereafter. Topical provocative testing was done 2 months later using tablet ornidazole crushed and dispersed at 50% pet. Closed patch was applied on the involved site and removed after 48 hr. For this, lower lip was everted, and Finn chamber® impregnated with ornidazole in pet. base was applied on lesional site. To secure Finn chamber® in place, we applied micropore passing horizontally over the everted lower lip and attached just beyond the angle of mouth. Patient was asked to take liquid diet with straw to restrict lip movements. The patch read at 30 min on 1, 3 and 7 days was negative. Other drugs of the same class viz. metronidazole tinidazole and secnidazole also showed negative patch test results when tested subsequently at 2-weekly intervals of each other. Oral provocation was also done with single tablet of ornidazole 500 mg 1 month after completion of patch testing for all above-mentioned drugs. Single dose of oral ornidazole led to reappearance of symptoms and bullous lesion at the same site of lower lip just after 1 day. Since then, the patient had taken repeatedly full courses of oral metronizole, tinidazole and secnidazole for gastrointestinal infection without any complaint.

Discussion

FDE can be caused by metronidazole and tinidazole with cross sensitivity to each other (2). Metronidazole, tinidazole, secnidazole and ornidazole are chemically related being nitroimidazole derivatives. Cross sensitivity among these drugs can be explained on the basis of some antigenic relationship between them or their metabolites.

Our case described here is unique, as no cross sensitivity of ornidazole was seen with other drugs of same class. Demonstration of causative agent of FDE has been successfully done with lesional patch test in earlier reports (3, 4). Lesional patch test can give positive or negative results (1). The negative patch test results on previously involved skin might be attributed to the reagent preparation, vehicle used, inadequate transepidermal absorption and the requirement of chemical modification of the drugs in gastrointestinal tract or liver (1). Same might have been the reasons of negative patch test in our case. Therefore, an oral provocation test should be undertaken in cases where lesional patch test is negative. FDE is the only drug reaction in which oral provocation is ethically admissible (5).

Intestinal amoebiasis is endemic in India because of which symptomatic patients had to be prescribed antiamoebic drugs quite oftenly. Ornidazole is a new arrival in this group. To the best of our knowledge, bullous FDE caused by ornidazole is the first report in the literature. To conclude: (1) Ornidazole should be added in the list of the drugs causing bullous FDE. (2) Patch test is not sensitive tool of demonstration of causative agent (3). Cross sensitivity among all drugs is not always

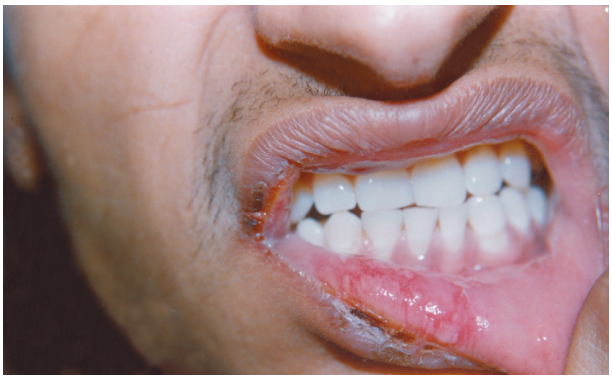

Fig. 1. A well-defined erosion on right side of lower lip.

present; hence, other drugs of same class can be prescribed whenever necessary.

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Contact allergy to aluminium in patients hyposensitized with aluminium-containing hyposensitizing extracts

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Key words: aluminium allergy; hyposensitization; subcutaneous nodules.

4 patients with itching nodules at the injection sites after hyposensitization with an aluminium-containing allergen extract were referred from the Department of Allergology, with a suspicion of contact allergy.

Case Reports

Case no. 1

This is the case of a 32-year-old female with a history of atopic eczema. 2 years earlier, she had started hyposensitization therapy because of hay fever and asthma. She was hyposensitized with a mixture of five-grass and house-dust mites. Her hay fever and asthma symptoms were reduced.

The hyposensitization was initially carried out in weekly intervals of gradually increasing doses. After 1 year, she developed subcutaneous nodules on the deltoideus area where the hyposensitizing injections had been given. The hyposensitization area was changed to the thighs, but she developed subcutaneous nodular infiltrates at the injection sites on both thighs. She also experienced 'activation' in all earlier nodules, with itching and erythema when given the injections. The itching and redness disappeared after a few days, but the nodules persisted. 6 months before the consultation, she got an eczema in her axilla when using a deodorant containing aluminium chloride hexahydrate.

She was patch tested with the European standard series with positive reactions to Quaternium 15, formaldehyde, diazolidinylurea and MCL/MI (methylchloroisothiazolinone/methylisothiazolinone). She was also tested with aluminium chloride hexahydrate 2% in petrolatum (Chemotechnique Diagnostics, Malmö, Sweden) with a positive patch-test reaction. For the patch test, small Finn Chambers® (Epitest Ltd Oy, Tuusula, Finland) on Scanpor (NorgesplasterA/S, Vennesla, Norway) were used. The patches were applied on the back for 48 hr, and reading was performed on D3 and D7 according to ICDRG guidelines (1). (The same test methods were used in all cases.) Patch tests with the aluminium hydroxide depot preparations of five-grass and house-dust mites, 100 000 SQ-E/ml as is from Allutard SQ, ALK Abelló, Hoersholm, Denmark, were negative. A formaldehyde analysis was performed on the aluminium hydroxide depot preparations. No formaldehyde was found.

Case no. 2

This is the case of a 16-year-old girl with rhinoconjunctivitis and asthma. 3 years earlier, she had started hyposensitization with the injections given over the deltoideus area. She was hyposensitized with five-grass, 3-broad-leaf trees and mugwort. 1 year before the consultation, she developed itching subcutaneous nodules on the injection area. She also got an eczema when she used a deodorant containing aluminium chloride hexahydrate.

She was patch tested with the standard series with no positive reaction. She was also tested with aluminium chloride hexahydrate 2% in pet. with a doubtful (+) reaction. She was tested with the aluminium hydroxide depot preparations, 100 000 SQ-E/ml as is. No reactions were seen.

A use test with the deodorant was positive, i.e. when using the aluminium chloride hexahydrate-containing deodorant once daily for 4 days in the axilla, compared to a deodorant not containing aluminium chloride hexahydrate.

Case no. 3

This is the case of a 30-year-old female with rhinoconjunctivitis since she was 7 years old.

4 years earlier, she had started hyposensitization with five-grass, broad-leaf trees and house-dust mites. She was hyposensitized over the deltoideus, and it was initially carried out in weekly intervals of gradually increasing doses. The hyposensitization reduced her rhinoconjunctivitis symptoms.

During the last year, she had developed nodules over the hyposensitization area.

She was tested with our standard series with no positive reactions. However, aluminium chloride hexahydrate 2% in pet. was positive. She was also tested with the aluminium hydroxide depot preparations, 100 000 SQ-E/ml as is. No positive reactions were seen.

Case no. 4

This is the case of a 38-year-old female with hay fever and rhinitis. 3 years before, she had started hyposensitization with five-grass, rabbit, cat and mugwort. She was hyposensitized over the deltoideus area. The hyposensitization was carried out

initially in weekly intervals of gradually increasing doses. Hereby, her problems with rhinitis and hay fever were reduced. However, during the last 2 years, she had almost constantly problems with itching from the persisting nodules over the area where she had been hyposensitized.

No positive reactions were seen in the standard patch-test series. A positive reaction was seen to aluminium chloride hexahydrate 2% pet. She was also tested with the aluminium hydroxide depot preparations, 100 000 SQ-E/ml as is. There was no positive reaction.

Discussion

Aluminium is a widely used metal, but contact allergy to aluminium is considered to be rare (2). Aluminium compounds have been used since many years as adjuvant to certain vaccines and hyposensitizing extracts to increase the immune response (3).

Persistent subcutaneous nodules at the injection site after hyposensitizing with aluminium-precipitated antigen solutions have earlier been described but are considered rare (4). The first case with subcutaneous itching granulomas after vaccination was reported in 1960 (5). Contact allergy to aluminium has earlier been reported in a few of these patients with persistent subcutaneous nodules (6, 7). In two recently published articles, different results regarding contact allergy to aluminium were found (8, 9). In one of these studies (8), a high incidence of contact allergy to aluminium was found in children with persistent nodules after vaccination with aluminium-containing vaccines and in the other no positive reactions were seen (9).

3 of the patients in the present study had positive patch-test reactions to aluminium chloride hexahydrate, while one had a doubtful reaction but a positive use test to an aluminium-containing deodorant. Contact allergy to aluminium is maybe more common than hitherto reported.

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Allergic contact dermatitis to naftifine

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Key words: allergic contact dermatitis; antimycotics; naftifine; patch tests.

Case Report

A 34-year-old atopic man developed an erythematous dermatitis on the abdomen and genitals. Suspecting a tinea corporis infection, his general practitioner prescribed Suadian® solution (naftifine hydrochloride 1%).

After a few days, the clinical picture worsened and an acute pruritic eczematous eruption developed on the treated areas. An allergic contact dermatitis was suspected, and Suadian® solution was suspended. The dermatitis healed with oral antihistamines, systemic and topical steroids.

Patch tests with the Italian standard SIDAPA series, Suadian® solution and the components of the topical medicament, kindly provided by the manufacturer, were performed (Table 1).

An allergic contact dermatitis to naftifine was diagnosed.

Discussion

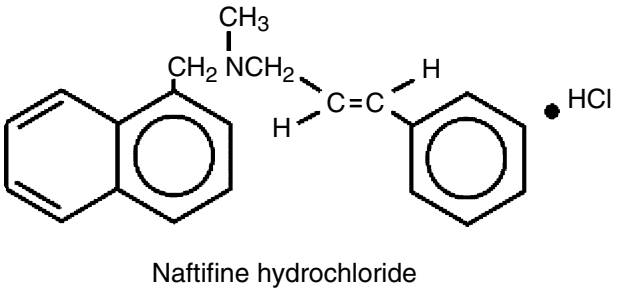
Naftifine hydrochloride [(E)-*N*-cinnamyl-*N*-methyl-1-naphthalenemethylamine hydrochloride] has the empirical formula of $C_{21}H_{21}N{\cdot}HCl$, a molecular weight of 323.86 and the chemical structure shown in Fig. 1. This synthetic allylamine derivative has fungicidal activity against dermatophytes and fungistatic activity against Candida species. Allylamines inhibit the enzyme squalene epoxidase, necessary for ergosterol synthesis.

Since its commercialization in the early 80s, only about 15 reports (1–4) of contact allergy to this topical antifungal have been published. Even though the risk of sensitization was estimated to be lower than 1:100.000 (5), its sensitizing capacity seems to be greater than in the commonly used imidazoles (6).

Naftifine has a remarkable structural similarity with terbinafine, and a possible cross-reactivity has been suspected by Goday et al. (1);

Table 1. Patch test results

	D2	D3
Standard Italian series		
Disperse blue 124	+	+ + +
Patient's own medicament		
Suadian® solution as is	+	+ + +
Constituents/ingredients of Suadian®	+–	
Naftifine 1% alc.	+	+ +
Naftifine 5% alc.	–	+ +
Propylene glycol 10% pet.	–	–
Ethyl alcohol as is		–



Naftifine hydrochloride

Fig. 1. Chemical structure of naftifine hydrochloride.

however, these authors did not observe cross-reactivity in their case.

As our patient denied previous contact with antimycotics of the allylamine group, probably sensitization to the active principle occurred after an inappropriate prolonged use of the antifungal. Caused by disperse blue-coloured synthetic underwear, it had been misdiagnosed as tinea corporis. In most reported cases (7), in fact, sensitivity to antimycotics was caused by preparations prescribed for non-fungal diseases.

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Delayed-type hypersensitivity dermatitis to ethylene oxide

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Key words: allergic contact dermatitis; ethylene oxide; exposure analysis; patch test.

Ethylene oxide (EtO) is frequently used in sterilization procedures, and different types of immune reactions to EtO have been detected. Suspected delayed-type hypersensitivity reactions to EtO are difficult to test for, as no standardized patch test procedures for volatile substances like EtO can be used.

We describe a patient with a history of recurrent dermatitis developing after ethylene oxide (EtO) exposure. A comparative application test with the textile material that was or was not sterilized with EtO demonstrated a dermatitis reaction to the EtO-treated gown only, and a delayed-type hypersensitivity dermatitis to EtO was diagnosed. Contact dermatitis to EtO is a relevant finding and the application test procedure a helpful tool in the diagnostic measures.

Case Report

A 30-year-old surgical nurse presented with a 12-month history of bilateral eczema at both forearms. During a 4-week holiday, the eczema cleared but relapsed immediately after returning to work (Fig. 1). Patch testing with standardized allergens considering the patients' profession was performed. The patient was tested by using the German standard series, preservative series, ointment base series and disinfectant series (German Contact Dermatitis Research Group, DKG). All patch test sites were evaluated after 48, 72 and 96 hr, and no reaction could be detected.

The patient stated that eczema had begun after wearing new gowns during her work as a surgery assistant. Therefore, a patch test-like analysis was performed. A sample of an EtO-sterilized gown was patch tested at the right upper arm, whereas at the left upper arm the identical but γ-radiation-sterilized gown was tested (Fig. 2). Evaluation was carried out after 48, 72 and 96 hr. A positive reaction (Fig. 3) could be detected at the EtO-tested region only. After

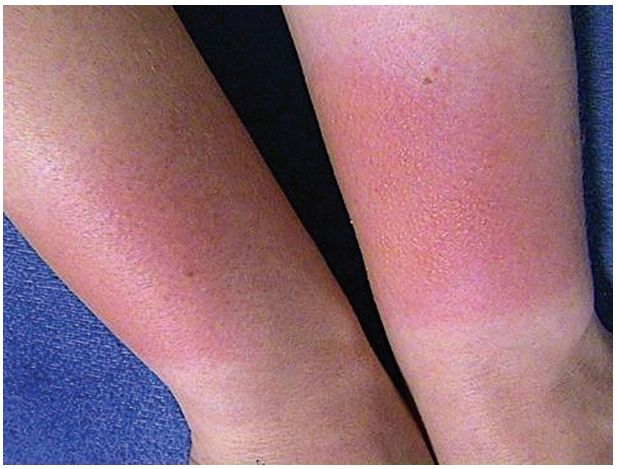

Fig. 1. A surgical nurse developed circumscribed erythemas with vesicles on both distal forearms.

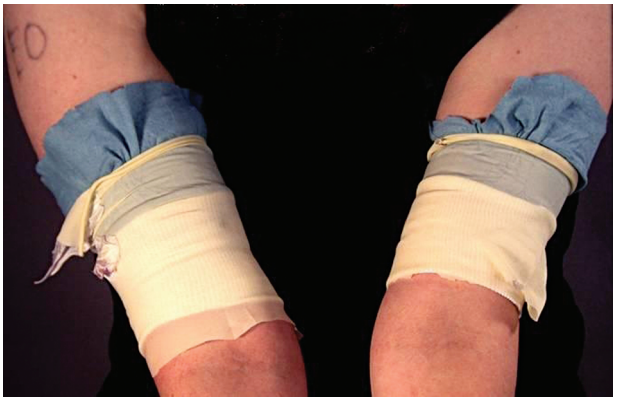

Fig. 2. Modified patch test with ethylene oxide-sterilized gown at the right upper arm and γ-sterilized gown at the left upper arm.

this information was transferred to the employer, EtO-sterilized gowns were eliminated and from thereon the patient experienced no relapses of her eczema.

Discussion

Ethylene oxide is a widely used sterilization agent for medical supplies. It is used in hospitals for sterilization especially of heat-unstable materials like plastics. The European Community defined a maximum tolerated concentration of EtO for medical devices for long-term exposure at 0.1 mg per day. Skin exposure to EtO gas may result in irritant contact dermatitis or burns. There are few reports of allergic contact dermatitis in response to this gas (1). Most of the documented hypersensitivity reactions are immediate-type hypersensitivity reactions. Allergic immediate-type reactions have been mainly documented in patients undergoing dialysis, due to their frequent contact to EtO (2, 3). In addition, also 1 patient with occupational asthma induced by EtO was described (4). In agreement with the clinical appearance in our patient, no specific IgE to EtO was detectable. Dagregorio and Guillet reported on a 56-year-old nurse who developed an inflammatory plaque 8 days after skin biopsy was taken. Provocation tests with an EtO-sterilized suture and a γ-radiation-sterilized suture revealed an erythematous plaque to the EtO-sterilized stitch only (3), confirming that comparative application tests may be helpful to establish the diagnosis of delayed-type hypersensitivity to EtO.

In 1995, Lerman et al. reported on contact dermatitis from EtO in 9 individuals working in the pharmaceutical industry (5). Furthermore, airborne occupational contact dermatitis was reported in 2 nurses and 2 assistants working with EtO to sterilize reusable hospital linen (6). No diagnostic procedures were applied in these patients.

Standardized patch testing is not established for EtO, and the differentiation between an irritant and an allergic contact dermatitis may therefore be difficult. We diagnosed a delayed-type hypersensitivity reaction in our patient by comparative patch testing a piece of EtO-sterilized and of a γ-irradiated gown. Moreover, 20 colleagues of our patient exposed to the same gown did not develop skin reactions indicating that the patient's reaction was a true 'allergic' delayed-type hypersensitivity reaction to EtO.

Allergic reactions to EtO together with its cytotoxicity, cancerogenicity and mutagenicity indicate that EtO should not be used whenever alternative products may be applicable.

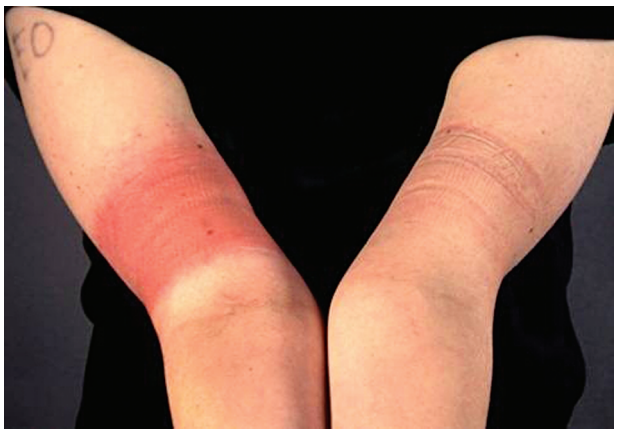

Fig. 3. On the right upper arm, a circumscribed erythema with vesicles detected 72 hr after application of ethylene oxide-sterilized gown. No skin reaction at the contralateral arm tested with the same gown, sterilized by γ-radiation.

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