

Rosacea and contact allergy to cosmetics and topical medicaments – retrospective analysis of multicentre surveillance data 1995–2002

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The role of contact allergy in rosacea has rarely been investigated. In this retrospective study, 361 out of 76 697 patients tested and documented by the Information Network of Departments of Dermatology between 1995 and 2002 had rosacea. Patch tests included standard series and constituents of cosmetics and topical medicaments. 118/361 had additionally been patch tested with their own cosmetics/medicaments. Positive reactions occurred to nickel (II) sulfate in 9.3%, fragrance mix in 8.8%, thimerosal in 6.9%, Myroxylon pereirae resin in 5.9%, potassium dichromate in 4.6% and propolis in 2.8%. Whereas rosacea patients had a significantly higher risk of contact allergy to propolis compared to the remaining patients, in an age- and sex-adjusted analysis, contact allergy to nickel was significantly less frequent in this group. For Lyrall[®], the risk was elevated, albeit not significantly. Only 2/329 patients were positive to neomycin sulfate and 1/100 to gentamicin sulfate, among the panel of (topical) antibiotics tested. Among 118 patients tested with their own products, 3 were tested to metronidazole, 1 reacting positively. Irritant or doubtful patch test reactions were provoked by various substances (vehicles, oxidants and preservatives of various creams), which might also be clinically important, considering the heightened sensitivity of rosaceous skin.

Key words: antibiotics; contact dermatitis; cosmetic allergy; fragrances; medicaments; own cosmetic products; preservatives; rosacea. © Blackwell Munksgaard, 2005.

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Rosacea is relatively common, the prevalence in the general population still being unknown. Generally accepted hypotheses concerning the underlying pathomechanisms are disturbed tissue perfusion, dilatation of dermal vessels, dermal lymphatic stasis, inflammation and fibromatous tissue proliferation. Whereas for the vascular component, a pharmacological approach has not been proven to be successful, and inflammation responds well to systemic and topical antibiotics. However, the mode of action is still unknown, because it is definitely not an antimicrobial effect which induces resolution (1). In the course of their disease, rosaceous patients often observe unexplained aggravation of erythema, scaling and/or itching. Further, common complaints accompanying rosacea are sensory irritation with burning and stinging (2).

Patients with rosacea are very susceptible to adverse reactions caused by external formulations, which is a concern for both patients and dermatologists, because the choice of local treatment and

cosmetics is difficult. Moreover, as sensitive and inflamed skin may be more prone to delayed-type hypersensitivity, co-existence of both phenomena in rosaceous patients is probably not uncommon. Rosacea itself also can be triggered by severe contact dermatitis on the face (3). There are only a few reports on delayed-type reactions in patients with rosacea, the majority being case reports (4–6). Our own preliminary results of a pilot study in 10 patients (7), which have shown contact sensitizations to the Myroxylon pereirae resin (balsam of Peru) in 4 and to colophonium, fragrance mix and chloramphenicol in 2 patients each, led us to investigate systematically contact sensitizations in rosaceous patients in a retrospective study based on Information Network of Departments of Dermatology (IVDK) data collected between 1995 and 2002.

Materials and Methods

Study population

From 1995 to 2002, 76 697 patients altogether were patch tested in the departments of dermatology comprising the IVDK. Of these patients, 361 (0.5%) fulfilled the case definition of the study (final diagnosis: rosacea, possibly in addition to other diagnoses) and hence were included in the data analysis.

The IVDK is a multicentre surveillance system on contact allergies, with more than 40 departments of dermatology in Germany, Austria and Switzerland participating. Patch test results and history of all patients tested are recorded electronically in a standardized way, and transferred regularly to the IVDK data centre at the University of Göttingen (8).

Patch test procedure

Patch tests were performed according to the international guidelines of the ICDRG (9) further extended by the German Contact Dermatitis Research Group (DKG) (10). Patch test substances were obtained from Hermal[®] (Reinbek, FRG, Germany). Patch test exposure time was 2 days for 243 of the 361 patients and 1 day for the remainder, according to the routine test procedure in the respective centre. Results presented are based on readings, 72 h (D3) after the application of patch test material. Allergens included here comprise some contained in the standard series, which is usually applied to every patient patch tested. However, the majority of agents are contained in supplementary test series, which are tested in a more aimed way, i.e. if previous exposure to one of the allergens is suspected. Tested

substances included constituents of cosmetics and topical medicaments. Antibiotics tested were chloramphenicol, gentamicin, neomycin, erythromycin and metronidazole. All test substances except formaldehyde and chlorhexidine digluconate, which were diluted in water, were dispersed in petrolatum. In addition to standardized patch test series, patients' own products were included in this investigation, consisting of medicaments and cosmetics, rinse-off as well as leave-on. Patch test reactions between + and +++ at D3 were considered to be positive.

Data handling and statistics

Data analysis was performed using the statistical program system SAS (version 8.2, SAS Institute, Cary, NC, USA) (8). Evaluation of patch test results was based on the reactions at D3. The present analysis focused on the 361 patients with rosacea and additionally suspected allergic contact dermatitis. The most important demographic characteristics of a patch test population in terms of the respective proportions of some surrogate markers of certain exposure profiles are commonly summed-up by the MOAHL index, which has recently been extended to the MOAHLFA index (11) and used to describe the above subgroup.

The proportions of patients with positive reactions were standardized for age and sex to account for the potentially confounding effect of these factors. The standardized proportions have been supplemented with approximately 95% confidence intervals (CIs) to address precision. If no case of sensitization was observed, an exact upper limit of a 95% CI was calculated. Possible differences in the proportions of positive reactions between rosaceous patients and the remaining patients were statistically tested for significance using logistic regression analysis, adjusting for age and sex. *P* values < 0.05 were considered significant. In view of the explanatory nature of this analysis, alpha adjustment techniques were not employed.

Results

361 out of 76 697 patients tested and documented by the IVDK between 1995 and 2002 had rosacea. 118/361 had additionally been patch tested with their own cosmetics/medicaments, with a total of 613 individual patch tests. Important demographic characteristics of the subgroup of patch tested rosaceous patients according to the MOAHLFA index are: males (*n* = 101 and 27.4%), occupational dermatosis (*n* = 9 and

2.4%), atopic dermatitis ($n = 12$ and 3.3%), hand dermatitis ($n = 8$ and 2.2%), leg dermatitis ($n = 0$), face dermatitis ($n = 316$ and 85.9%) and ≥ 40 years of age ($n = 298$ and 81.0%) – interpreting these figures it should be kept in mind that, in a few cases, rosacea was not the only diagnosis, i.e. information on site or occupational causation referred to concurrent contact dermatitis.

In 18.3%, allergic contact dermatitis was strongly suspected, based on the clinical picture at presentation and on history. However, in the vast majority of cases (69.8%), patch testing was performed only to rule out contact allergy. In 43 patients (11.9%), other reasons for patch testing were given.

138/361 patients [36 (26.1%) males and 102 (73.9%) females] showed positive patch test reactions to commercial test substances. The most common allergens are listed in Table 1. Only 2/329 patients were positive to neomycin sulfate and 1/100 to gentamicin sulfate, whereas none of 136 patients tested unequivocally positive to chloramphenicol, none of 54 to erythromycin and both patients tested with metronidazole (as pure substance) did not react positively, either. In total, 3/118 patients tested with their own products were tested with metronidazole, 1/3 being positive.

Whereas rosaceous patients had a significantly higher risk of contact allergy to propolis compared to the remaining patients, contact allergy to nickel was significantly less frequent in this group. Furthermore, positive reactions to thiuram mix (1/327 positive reactions) and phenyl-

mercuric acetate (5 weak-positive and possibly false-positive irritant reactions among 190 patients tested) were observed significantly less frequent in rosaceous patients. For hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyrall[®]), which had been added to the standard series only recently, with a correspondingly much lower number of patients tested, risk was elevated, albeit not significantly.

Patients own products including topical medicaments

Many patients with rosacea complain of stinging and burning due to ointments or even flush, which prompted us to investigate further the data on patients' own products. Patients' own products were divided into rinse-off products (shampoos and shower gels) and leave-on products. Only leave-on products were included in this investigation and manually assigned to 24 categories, based on an EU classification [annex I to 76/768/EEC (12)] (Table 2).

Discussion

In 138/361 cases, delayed-type hypersensitivity was observed. Only 2/329 patients were positive to neomycin sulfate and 1/100 to gentamicin sulfate, among the panel of (topical) antibiotics tested. The rarity of positive patch test results to patients' own products and to first-line treatment topical antibiotics, erythromycin and metronidazole,

Table 1. The most common allergens in 361 rosaceous patients patch tested from 1995 to 2002 in the IVDK (readings 3 days after application of patch test). Age- and sex-standardized proportions with 95% confidence interval (CI)

Substance		Number (tested)	% positives	(95% CI)
Fragrance mix	8.00%	328	8.8	4.7–12.9
Nickel (II)-sulfate	5.00%	324	*9.3	5.1–13.5
Myroxylon pereirae resin (balsam of Peru)	25.00%	327	5.9	2.8–9.0
Propolis	10.00%	164	†2.8	0.8–4.7
Methyldibromo glutaronitrile	0.30%	87	3.0	0.0–5.9
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyrall [®])	5.00%	45	2.5	0.0–5.9
Thimerosal	0.10%	274	6.9	2.0–11.8
Potassium dichromate	0.50%	327	4.6	1.3–7.9
Cobalt (II)-chloride,	1.00%	327	2.4	0.5–4.3
p-Phenylenediamine (free base) (CI 76060)	1.00%	326	2.3	0.4–4.2
Compositae mix	6.00%	43	1.3	0.0–3.8
Oil of turpentine	10.00%	325	1.9	0.1–3.7
Colophonium	20.00%	327	1.9	0.1–3.8
Ammoniated mercury	1.00%	327	0.9	0.1–1.7
Methyldibromo glutaronitrile + 2-phenoxyethanol 1:4§	0.50%	201	1.4	0.0–3.7
Methyldibromo glutaronitrile + 2-phenoxyethanol 1:4§	1.00%	136	1.0	0.0–2.4
Paraben mix	15.00%	72	3.0	0.0–8.7
(Chloro)-methylisothiazolinone (MCI/MI)‡	100.00 p.p.m.	325	0.7	0.0–1.3
Benzocaine	5.00%	327	0.5	0.0–1.0

*Significantly lower and †significantly higher proportion compared to remaining patients. All allergens in petrolatum, except where indicated: ‡in water.

§Concentration was increased during study period.

Table 2. Number of patients patch tested with their own products as categorized according to the refined annex I to 76/768/EEC (counted only once for each patient; multiple categories per patients possible) and number of positive results

Product category	Patch tests	Number of positives
External eye care	16	1
Deodorants and antiperspirants*	14	1
Anti-wrinkle products*	4	–
Products for making-up and removing make-up from the eyes*	8	1
Hair tints and bleaches*	3	1
Hairdressing products (lotions, lacquers and brilliantines)*	13	1
Hair conditioning products (oils, lotions and creams)*	12	1
Hair cleaning products (lotions, shampoos and powder)*	17	1
Cosmetic cleaning products (excluding soaps and medicated products)	9	1
Products intended for application to the lips*	7	–
Face masks (excluding peeling products)*	3	–
Topical medicaments	58	2
'Medical' cosmetics (OTC)	21	1
Perfumes, toilet waters and eau de Cologne*	11	2
Creams, emulsions, lotions, gels and oils for the skin (hands, face, feet, etc.)*	67	3
Shaving products (creams, foams and lotions)*	13	1
Toilet soaps, deodorant soaps, etc.*	12	–
Products for tanning without sun*	2	–
Products for making-up and removing make-up from the face (excluding eyelids)*	13	2
Sunbathing products*	9	–
Products for care of the teeth and the mouth	4	–

*Original categories and nomenclature of annex I to 76/768/EEC

could be due to their inherently low sensitizing potential. Metronidazole is a widely used synthetic antibacterial agent and generally well tolerated. Occasionally, topical use of metronidazole gel may induce sensations like burning, stinging, redness, irritation, itching and even worsening of rosacea. However, true allergic contact dermatitis from topical use of this substance is rare (6, 13), as confirmed by our data with just 1 confirmed case of contact allergy, metronidazole being tested as the patient's own product (patient 10) (Table 3). Erythromycin, the second choice drug for topical antibiotic treatment of rosacea, is seldom held responsible for delayed-type reactions. The low sensitization potential may be due to its chemical structure and relatively high molecular weight (733.9 D). To date, only a few cases of contact allergy to erythromycin have been reported, either to erythromycin salts (sulfate and stearate) or to erythromycin base. Only rarely does it seem to induce contact allergy in rosacea (5), which was confirmed by our data. Intolerance to either antibiotic reported from patients therefore should be considered as presumably non-allergic, easily verified by a screening patch test with these very products of the patients, tested as is, if the antibiotics are considered an important therapeutic option for that patient.

The typical pattern of positive allergens in our study is partially related to the homogeneous age and sex distribution – only 19% of patients were less than 40 years. Many of the most common

contact allergens, like Myroxylon pereirae resin and fragrance mix, have a strong age gradient; the pattern of clinical cross-reactivity, also to Lyrall[®], has been addressed by a number of large studies (e.g 14, 15). Rosaceous patients had a significantly higher risk of contact allergy to propolis compared to the remaining patients. This sensitization may be due to self-medication with propolis-containing herbal ointments (14).

Neomycin and gentamicin are widely used constituents in various medicaments and are more common allergens in patients of 40 years or above (16). The same substances are first-line contact allergens of older patients with recurrent episodes of facial dermatitis (16). The face is one of the major sites of contact dermatitis (17–19), even more so in rosaceous patients exposed to distinct allergens and the constituents of topical formulations, especially preservatives and perfumes.

Lunder and Kansky (20) investigated 100 females with rosacea for contact sensitization to fragrance mix, selected fragrance compounds and their own cosmetic creams and showed that 17/100 were positive to fragrance mix and/or its components. 7/17 also reacted to their cosmetic creams. Gas chromatography of those creams revealed that they contained fragrance components in 5/7. After discontinuation of cream application, the rosacea resolved in those 5 patients (20). The authors concluded that deterioration of rosacea following the use of cosmetic products should not be attributed only to skin irritation, as was suggested by previous reports (18).

Table 3. Synopsis of patients with positive patch test reaction to their own products compared with patch test reactions to standardized allergens, where these occurred (D 3 readings throughout)

Patient number	Product tested positive (concentration)	Product category	Positive (relevance)	Further positive reactions to standardized allergens
1	Product A, perfume for women (as is)	Perfume	++ (current)	Hydroxycitronellal (+), Lyrall [®] (++++)
2	Benzoyl peroxide gel (0.1%)	Topical medication	+ (current)	–
3	Product B, Teint Make-up (as is)	Make-up (face)	+ (current)	–
4	Product C, Cleaning Fluid (as is)	Cosmetic cleaning	++ (current)	–
	Product D, Moisturizer (as is)	Cream	++ (current)	–
	Product E, Petrolatum (as is)	Cream	++ (current)	–
	Eucerin + water 1 : 1 (as is)	Creams, ..	++ (current)	–
5	Product F (as is)	Deodorants	+ (unclear)	Myroxylon pereirae resin (+)
	Product G, perfume deo (as is)	Deodorants	+ (unclear)	Myroxylon pereirae resin (+)
	Product H (as is)	Deodorants	+ (unclear)	Myroxylon pereirae resin (+)
	Product I, deo for men (as is)	Deodorants	+ (unclear)	Myroxylon pereirae resin (+)
	Product J, eye liner, black (as is)	Make-up (eyes)	+ (unclear)	Myroxylon pereirae resin (+)
	Product K, MASCARA black (as is)	Make-up (eyes)	+ (unclear)	Myroxylon pereirae resin (+)
	Product L, eye liner (as is)	Make-up (eyes)	+ (unclear)	Myroxylon pereirae resin (+)
	Product M, eau de toilette (as is)	Perfume, ...	+ (unclear)	Myroxylon pereirae resin (+)
	Product N, perfume (as is)	Perfume, ...	+ (unclear)	Myroxylon pereirae resin (+)
6	Camomille day cream (as is)	'Medical' cosmetics	+	Thiuram mix (++)
	Product O, cream (as is)	Creams, ...	+	Thiuram mix (++)
	Beeswax cream (as is)	Creams, ...	+	Thiuram mix (++)
	Product P, cream make-up (as is)	Make-up	+	Thiuram mix (++)
	Product Q, CREAM POWDER	Make-up	+	Thiuram mix (++)
	Product R	Make-up	+	Thiuram mix (++)
	Product S, CREAM ROUGE	Make-up	+	Thiuram mix (++)
7	ECOLICIN [®] eye cream (erythromycin)	Topical medication	+	Fragrance mix (+)
	FLOXAL [®] eye drops (oxifloxacin)	Topical medication	+	Methyldibromo glutaronitrile (+)
8	BACITRACIN [®]	Topical medication	+	–
	Gentamicin sulfate	Topical medication	+	–
	Kanamycin sulfate	Topical medication	+	–
	Streptomycin	Topical medication	+	–
	Tetracycline-HCL	Topical medication	+	–
	NITROFURAZONE (FURACIN [®])	Topical medication	+	–
	PAROMOMYCIN	Topical medication	+	–
9	Product T, shaving foam	Cosmetic	+ (unclear)	–
10	LEUKICHTAN SALBE [®]	Topical medication	+	Methyldibromo glutaronitrile (+)
	WEICHE ZINKPASTE	Topical medication	+	Cobalt (II) chloride (++)
	METRONIDAZOLE	Topical medication	+	Nickel (II) sulfate (++)
11	Yoyoba oil cream	Cream	+	Fragrance mix (+), Myroxylon pereirae resin (+)

The irritant or doubtful reactions in our study were provoked by various components of vehicles, oxidants and preservatives of various creams and the clinical importance of such reactions in rosacea remaining unclear. However, considering the extreme sensitivity of rosaceous skin, these marginal reactions to some ingredients of topical products could be similarly important clinically, in terms of irritant contact dermatitis or irritation of underlying rosacea due to yet unnamed constituents, as is supported by the investigation of Lunder and Kansky.

We conclude that (i) allergic or irritant contact dermatitis does develop in rosaceous patients and (ii) a few of the observed allergens may be related to morbidity-specific exposures, and are poten-

tially clinically relevant. Therefore, diagnostic allergy tests are recommended in cases of doubt, i.e. apparent deterioration of rosacea following the use of cosmetics or topical medicaments. Avoidance of contact allergens may prevent episodes of dermatitis in association with rosacea and promote the efficacy of topical treatment. The chance of detecting positive contact sensitization in rosacea will particularly increase if topical medicaments, cosmetics or perfumes used by the patients are tested in addition to commercial allergens.

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