

Suspected fragrance allergy requires extended patch testing to individual fragrance allergens

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This study has been performed to evaluate the efficacy of fragrance mix (FM) as a screen for fragrance allergy. Patients were included if they had had positive allergic reactions to FM, to 1 of the 8 ingredients of FM, to 1 of 14 other fragrance materials, or to their own perfume. 91 patients were studied. There were 65 women and 23 men (in 3, their sex was not recorded) allergic to FM on patch testing. The mean ($\pm$ SD) age was 48.4 ± 18.6 years. 22 patients gave a past history of atopic eczema. Dermatitis of the hands (31%) and face (26%) were the most common presenting complaints. 85 patients (93%) had a positive allergic patch test reaction to FM. 22 of the 40 tested to the extended fragrance series were positive to other perfumes as well, and of these, there were 14 reactions (in 9 patients) to allergens not in the FM. In addition, 6 patients were positive only to separately tested fragrance constituents and not to the FM. In conclusion, FM is an accurate screen for fragrance contact sensitivity. However, patch testing to an extended series is needed if there is clinical suspicion of perfume allergy, as otherwise about 7% of patients allergic to fragrances will be missed.

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Allergy to fragrance is the commonest cause of cosmetic contact dermatitis and therefore constitutes a significant clinical problem (1). The widespread use of fragranced skin care products, rather than the use of perfumes per se, is probably the most important reason for the high prevalence of fragrance sensitivity (1–3). There appears to be a trend of increasing sensitization to fragrance (4).

The fragrance mix (FM) which contains 8 substances, namely cinnamic alcohol, cinnamic aldehyde, eugenol, α -amyl-cinnamic aldehyde, hydroxycitronellal, geraniol, isoeugenol and oak moss absolute, each at 1% in petrolatum (pet.), has been used for over 10 years as a screen (4) and is reported to delineate 70–90% of patients with fragrance allergy (5). It was ranked as the 2nd or 3rd most common allergen in a series of patients patch tested in various parts of the world for contact allergy (6). FM may give both false-positive and false-negative reactions (7, 8). In this study, we aimed to investigate the reliability of FM as a screen for fragrance allergy and the need for testing to a more extensive series.

Patients and Methods

We investigated the clinical features of patients who had been patch tested during the period 1994–1995 and who had been found to have allergic reactions to FM, to the constituent fragrances of FM, or to an extended series of fragrances (i.e., clove oil 2%, orange oil 2%, vanillin 10%, benzaldehyde 5%, benzylcinnamate 5%, cedarwood oil 10%, eucalyptus oil 2%, laurel oil 2%, lemon grass oil 2%, lemon oil 2%, neroli oil 2%, peppermint oil 2% and salicylaldehyde 2% or the fragrance carrier benzyl salicylate 1%, all in pet.), or to the patient's own perfume.

744 consecutive unselected patients were patch tested in 1994 and 1995 to the standard series containing FM, and 264 were additionally tested to a fragrance and flavour series. The extended fragrance series was used when there was a history of facial, perianal or vulval dermatitis, or when a cosmetic reaction was suspected clinically. The patient's own cosmetics or medicaments were tested when supplied (the exact number tested is

Table 1. Details of allergic reactions on patch testing to the extended fragrance series in 40 patients

Substance	No. allergic reactions
oak moss absolute	12
isoeugenol	8
cinnamic aldehyde	5
cinnamic alcohol	4
eugenol	2
hydroxycitronellal	1
geraniol	0
alpha-amyl-cinnamic aldehyde	0
lemon grass oil	3
clove oil	2
laurel oil	2
peppermint oil	2
vanillin	1
eucalyptus oil	1
salicylaldehyde	1
own cosmetic	3

not known). In all, 91 fragrance-allergic patients were included in the study.

The test materials, all in pet., were obtained from Hermal Trolab (Hamburg, Germany) or Chemotechnique (Sweden). The materials were applied in Finn Chambers on Scanpor to the upper back, left on for 2 days (D), and read at D2 and D4, using the International Contact Dermatitis Research Group's grading system. Data were collected from each patient using a form on which were recorded demographic information (i.e., age, sex and occupation), dermatitis site and type, any personal history of atopy, the test results and the final diagnosis.

Results

The mean age ($\pm$ SD) was 48.4 ± 18.6 . 65 (72%) were women, 23 (26%) men and in 3 (3%) their sex was not recorded. 15 (17%) had a past history of

asthma, 22 (24%) atopic eczema (mostly in childhood) and 14 (15%) allergic rhinitis.

The site of the eruption was recorded as being the hands (31%), face or neck (26%), eyelids (13%), legs (12%) and perioral area (11%). In 12%, the eruption was generalized and, in 17%, the vulval or perianal areas were affected. The arms, trunk, feet or ears were involved in a small number.

Patch test reactions

There were 135 allergic positive reactions in 91 patients. 85 of the 91 patients (93%) had a positive allergic reaction to FM. 40 of these were also patch tested to the extended fragrance series and, of these, 22 reacted to 1 of the tested substances. 6 patients had positive allergic reactions to fragrances in the fragrance extended series without showing an allergic reaction to FM (1 to peppermint oil and salicylaldehyde, and 1 each to lemon grass oil, eucalyptus oil, vanillin, isoeugenol and oak moss absolute). According to sources in the perfume industry, salicylaldehyde is no longer used as a perfume ingredient due to its irritant potential. For the 40 FM-allergic patients tested to the extended fragrance series, the commonest sensitivities were to oak moss absolute (12), isoeugenol (8) cinnamic aldehyde (5) and cinnamic alcohol (4). The latter 2 chemicals may cross-react, as cinnamic alcohol to some extent is metabolized to cinnamic aldehyde. 1 patient was sensitive to hydroxycitronellal but there were no reactors to geraniol or α -amyl-cinnamic aldehyde (Table 1).

For fragrances not in FM, there were 12 reactions in 9 patients. 3 were to lemon grass oil, 2 to clove oil (which consists of at least 80% eugenol), 2 to laurel oil, 2 to peppermint oil, 1 to vanillin, 1 to eucalyptus oil and 1 to salicylaldehyde (Table 1). Dividing the patients into 2 groups around the median age (48

Table 2. Patterns of reaction to fragrance mix and to fragrance constituents in 85 patients (details of 6 patients, who reacted to individual fragrance substances only, are not shown)

No. patients	Age <48 years	Age $\geq$ 48 years	No. allergic positive reactions	Substances to which the patient(s) reacted
1	1	0	9	FM, eugenol, hydroxy-citronellal, isoeugenol, clove oil, laurel oil, lemon grass oil
1	1	0	5	FM, eugenol, isoeugenol, oak moss absolute, clove oil
4	1	3	3	FM, cinnamic alcohol, cinnamic aldehyde
2	1	1	3	FM, isoeugenol, oak moss absolute
1	1	0	3	FM, isoeugenol, laurel oil
1	1	0	2	FM, lemon grass oil
1	0	1	2	FM, peppermint oil
1	1	0	2	FM, cinnamic aldehyde
2	1	1	2	FM, isoeugenol
8	5	3	2	FM, oak moss absolute
62	32	30	1	FM only

40 patients were tested additionally to an extended fragrance series. 18 of the 62 who reacted to FM only were also tested to fragrance constituents, but did not react to any of these. 44 of the 62 who reacted to FM were not tested to other fragrances.

Table 3. Details of allergic positive reactions to non-fragrance allergies in 91 patients

Co-allergen	No. allergic reactions
nickel sulfate	22
balsam of Peru	19
colophony	15
Amerchol L-101	12
thiuram mix	10
neomycin	9
wool wax alcohols	7
Kathon® CG	4
cetearyl alcohol	4
sorbic acid	4
paraben mix	3
tosylamide/formaldehyde resin	3
sorbitan sesquiolate	3
quaternium-15	2
BHA	2
propyl gallate	2
octyl gallate	2

years), most of those reacting to eugenol, isoeugenol, oak moss absolute, lemon grass oil or clove oil belonged to the younger age group, whereas those in the older age group were more likely to react to cinnamic alcohol, cinnamic aldehyde, vanillin, peppermint oil and salicylaldehyde (Table 2).

Co-allergens

53 of the 91 patients (59%) also had allergic reactions to other cosmetic allergens and 11 (12%) reacted to medicament allergens (Table 3). 19 patients had positive allergic reactions to balsam of Peru (used as a fragrance and fixative in perfumeries and in topical medicaments), 15 to colophony (used in the production of mascara, rouge and eye shadow), 7 to wool wax alcohols (a base in cosmetics and pharmaceutical products), and 12 to Amerchol L-101 (a lanolin emulsifier and emollient in cosmetics and topical preparations). Positive allergic patch tests were also seen in 4 patients, each to Kathon® CG, cetearyl alcohol, and sorbic acid, in 3 patients, each to paraben mix, tosylamide/formaldehyde resin, and sorbitan sesquiolate, in 2 patients, each to quaternium-15, BHA, propyl gallate, and octyl gallate and, in 3 patients, to their own cosmetics.

In the standard series, positive allergic reactions were seen to nickel sulfate (22 of 91 patients), thiuram mix (10) and neomycin (9). There were no irritant reactions recorded to perfumes or fragrance constituents. 3 irritant reactions to phosphorus sesquisulfide were noted, with 5 irritant reactions to metals.

Occupation

9 patients were diagnosed as having occupational allergic contact dermatitis from fragranced ma-

terials, namely fragranced household cleanser, detergents and toilet tissues. 2 were employed as care assistants, 1 was a publican and 3 were nurses. The other 3 comprised of a 49-year-old woman with a year's history of eyelid and neck dermatitis, who worked in a herbalist shop and was allergic to FM, cinnamic alcohol and cinnamic aldehyde, a 47-year-old man who made surgical instruments and was in contact with soluble oil containing fragrance and was allergic to FM, balsam of Peru and thiuram mix, and a 62-year-old man who had worked as a grinder for 50 years and was allergic to FM.

Diagnosis

The final diagnosis, in the 91 patients, was allergic contact dermatitis in 77, of whom 4 also had atopic eczema, venous eczema in 3, irritant contact dermatitis in 2, vesicular hand eczema in 4, and other types of eczema in 4. The other diagnoses comprised irritant contact dermatitis (2), atopic eczema (2), pompholyx (1), photoreaction (4) and other eczemas (5).

Discussion

Fragrance allergy is the commonest cause of cosmetic contact dermatitis. The North American Contact Dermatitis Group found individual fragrance components or fragrance mixtures caused the greatest numbers of cutaneous reactions (3). Most clinical reactions are thought to be caused by fragranced skin-care products for the face, hands and body (26%), by hair preparations excluding colours (10%), and by facial make-up products (12%) (3). In only 50% of cases did either the patient or the physician suspect that the cosmetic was the offending agent. In our study, 57 of the 91 patients (70%) found to have fragrance allergy were also sensitive to other constituents used in cosmetics or to preservatives, vehicles, emulsifiers, or constituents of the facial and medicament series.

The median age and female predominance observed in our study is similar to that seen in previous studies of fragrance allergy (7–13). Women with fragrance sensitivity outnumber men by 3 or 4 to 1, probably because they use more skin care products. Allergic contact dermatitis from perfume may present in a localized or a generalized fashion. It can cause both depigmentation and reticular hyperpigmentation. Musk ambrette and similar fragrances are well-known photosensitisers (14).

In our study, the most commonly-affected sites were the hands (30%), the face or neck (26%), the

eyelids (13%) and the legs (13%). The eruption was generalized in 12% of cases. Similar results have been found in other studies (11, 15). However, Larsen et al. (14), who investigated 167 patients with fragrance allergy, found that facial involvement, seen in 40%, was more common than hand involvement, found in 27%. Malten et al. (13) emphasised the importance of fragrance allergy in patients with hand dermatitis, as nearly all cosmetics are applied by hand, and the hands touch perfumes and topical medicaments. More than 50% of the patients had an atopic diathesis, which may predispose to allergic contact reactions, although this is controversial (16). The use of fragranced products in areas of high absorption, i.e., the eyes, lips, vulva and perianal areas, may explain the development of allergy. Colophony and balsam of Peru can be considered as weak markers of fragrance allergy (16). Allergy to these was seen in 16% and 21%, respectively, of our fragrance-sensitive patients.

The FM used in the European standard series is the most important marker for fragrance allergy. Reports suggest that it delineates 70–90% of patients (5, 9), although in our study, the figure was 93%. Johansen & Menné (4) patch tested with FM and patients' own cosmetics and found, using chemical analysis, that at least 3 of the chemically-defined sensitizers in the FM were detected in all the perfumes tested. This suggests that FM is a good measure of actual exposure (17). Johansen et al. (18) state that the allergenic constituents of the FM are almost impossible to avoid in perfumed cosmetics. Johansen & Menné (4) found that only 55% of patients positive to the FM, patch tested between 1988 and 1992, reacted to 1 or more of the individual components. Our results are in agreement: 40 patients of the 85 positive to FM were also tested to the extended fragrance series and 22 of these (55%), were positive to 1 or more allergens. These figures should be considered as the minimum, as not all patients positive to FM had had extended patch testing. The inconsistency may be due to false-positive reactions to the FM, false-negative reactions to the individual components, e.g., because of too low concentrations, especially to allergens such as oak moss absolute and geraniol, or compound allergy to new allergens found in the FM. Perfume compositions change with fashion and, in time, it may be necessary to include new fragrances in the FM or in the fragrance screening series in the place of fragrances no longer in use.

Studies from different countries have ranked the frequency of patch test reactions to individual fragrance compounds (2–4). In the USA, the most frequent sensitizer was cinnamic alcohol (3). In the

Netherlands (16), isoeugenol followed by oak moss absolute and, in a previous European study (19), oak moss absolute followed by isoeugenol. In our study too, the most common individual sensitizers were oak moss absolute (12 patients) and isoeugenol (7 patients), followed by cinnamic aldehyde (4 patients). Of substances not contained in the FM, lemon grass oil was the commonest allergen (3 patients). Fragrance allergen test materials contain sorbitan sesquiolate, and allergy to this may give false-positive results. However, only 3 patients in our study were positive to sorbitan sesquiolate. In our extended fragrance series, we have incorporated mainly essential oils, even if they represent mixtures of variable extracts difficult to standardize, because they are very frequently used in the perfume industry. They are also fashionable, as some are used in aromatherapy and may sensitize individuals even without clinical signs (19).

We have demonstrated that FM is an accurate marker for fragrance allergy. Extended fragrance patch testing revealed 6 patients (out of 91) whose fragrance allergy would have been missed if this had not been performed. Hence, when perfume allergy is particularly suspected, it is necessary to test with an extended fragrance series and the patient's own cosmetics.

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