
The immediate patch test reaction to fragrance in patients with allergic contact dermatitis to fragrance: A prospective study



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Background: Fragrance is one of the common causes of immediate contact reaction. Knowing the prevalence of a reaction in a given population enables prioritization of allergy screening.

Objective: The purpose of this study was to determine the prevalence of an immediate patch test reaction to fragrance in patients with fragrance allergic contact dermatitis.

Methods: This prospective study enrolled 291 patients who were given standard patch tests for allergic contact dermatitis. Those with positive reactions were then asked to undergo additional patch tests to assess both immediate and delayed reactions to 28 different fragrance substances.

Results: Cinnamic aldehyde and cinnamic alcohol were the most frequently encountered substances in positive immediate reactions and standard (delayed) patch test reactions. Immediate patch reactions to benzyl alcohol, sorbic acid, and coumarin were more frequently observed than standard patch test reactions.

Limitations: Because of the small sample size of patients who agreed to continue further patch testing evaluation, a statistical association between patient characteristics and fragrance-positive patch test reactions was difficult to establish.

Conclusions: In this population, cinnamic aldehyde and cinnamic alcohol were the most common fragrance allergens causing both immediate and delayed reactions, whereas reactions to benzyl alcohol, sorbic acid, and coumarin were frequently observed in immediate patch tests. (J Am Acad Dermatol 2022;87:1042-8.)

Key words: allergic contact dermatitis; fragrance substances; immediate reaction.

INTRODUCTION

Fragrances are substances derived from natural or synthetic sources that are frequently used to enhance odor and are ubiquitously used in different public

and private occasions. Fragrances are commonly found as one of the ingredients in many personal care and household products as well as flavoring agents in foods and beverages. Because fragrances

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can be absorbed into the body via the epidermis, lungs, or gastrointestinal tract, fragrance allergies are common in the general population. Fragrance allergies can manifest clinically as an immediate or delayed reaction. Their common symptoms include contact urticaria, contact dermatitis, photocontact dermatitis, systemic contact dermatitis, systemic contact urticaria, and asthma exacerbation.

The diagnosis of fragrance allergies is complicated by the facts that the clinical spectrums of fragrance allergies are broad and numerous fragrance allergens are involved in an allergic reaction. Despite this, patch testing is one of the most reliable diagnostic tools for determining the allergen responsible for a particular fragrance allergy. Unfortunately, the detection of the allergen may be limited or the allergen may become undetectable when only a few common fragrance screening markers, such as Fragrance Mix I (FM I), Fragrance Mix II (FM II), *Myroxylon pereirae*, and colophony, are used in standard patch tests. To address this disadvantage, a recent publication recommended that patients with positive fragrance allergies should undergo additional patch tests in which individual fragrance substances are included with the fragrance mix.¹

For instance, if a standard (48-hour delayed) patch test is used to detect fragrance-related contact urticaria in a patient, the result will be negative and the urticaria will be undetectable. The immediate patch test reaction is one of the diagnostic tools used to determine whether the patient has an immediate allergic reaction to fragrance substances. In this study, we conducted immediate and delayed patch testing using 28 fragrance substances in patients with fragrance allergies. The purpose of this study was to determine the prevalence of an immediate patch reaction to fragrance in patients with a delayed fragrance patch test reaction.

METHODS

Patients

We enrolled 291 patients in standard patch testing at the King Chulalongkorn Memorial Hospital's contact dermatitis clinic in Bangkok, Thailand. Patch tests were conducted using the 40 allergens of a baseline series (allergEAZE, SmartPractice). Patients who developed a positive response to 1 or more of the fragrance screening markers (FM I, FM II,

Myroxylon pereirae [Balsam of Peru], or colophony) were asked to undergo additional patch tests using 28 different fragrance allergens (allergEAZE). Additional patch test materials were then applied using an 8-mm Finn Chambers on Scanpor tape (SmartPractice) to an unaffected area of the upper portion of the back. Patch test results were interpreted by an experienced dermatologist (J.W.) 30 minutes after application for immediate urticarial reaction and 48 hours, 72 hours, and 1 week after application for standard patch test reactions, according to the International Contact Dermatitis Research Group recommendations.² Patients with immediate urticarial reactions were further asked whether they developed

one of the following symptoms: wheal, flare, sneezing, rhinorrhea, wheezing, and coughing. The Institutional Review Board of Chulalongkorn University's Faculty of Medicine approved this prospective study, which was conducted from September 2017 to September 2018.

Statistical analysis

The demographic data were analyzed using descriptive statistics. Binary logistic regression (build-in forward Wald method in SPSS version 22.0; IBM Corp) was used to determine the effect of patient risk factors on positive reactions to each allergen. Statistical significance was defined as a *P* value of <.05. Additionally, odds ratios with 95% confidence intervals were reported. Because of the logistic regression model's reliability and validity, the allergens with positive results from fewer than 10 patients were excluded from statistical analysis.

RESULTS

The demographic and MOALHFA (male, occupational dermatitis, atopic dermatitis, leg dermatitis, hand dermatitis, face dermatitis, age > 40) characteristics of the population in this study are summarized in Table I. This study enrolled 86 male and 205 female patients with a mean age of 43.72 ± 15.54 years and 48.03 ± 17.13 years, respectively. The patients' mean age was 44.84 ± 16.0 years (range, 15-85 years). FM I (57/291; 19.59%), nickel sulfate (45/291; 15.46%), methylisothiazolinone (31/291; 10.65%), methyldibromo glutaronitrile (27/291; 9.27%), Balsam of Peru (24/291; 8.25%), formaldehyde (24/291; 8.25%), and FM II (24/291; 8.25%)

CAPSULE SUMMARY

- Fragrance substances are commonly used in a variety of products, causing fragrance allergies in the general population.
- Practitioners can prioritize allergy screening if the prevalence of allergic contact dermatitis in the population is known.

Abbreviations used:

FM I: Fragrance Mix I
FM II: Fragrance Mix II

were the top allergens in the standard patch test screening in which the patients developed positive reactions. Eighty-two (28.2%) patients developed positive patch test reactions to 1 or more of the commonly used fragrance screening markers (FM I, FM II, colophony, and Balsam of Peru). Most patients tested positive for FM I, followed by Balsam of Peru, FM II, and colophony (57/80 vs 24/80 vs 24/80 vs 21/80, respectively). Our data indicated that female patients were more likely than male patients to develop a positive patch test reaction to fragrance screening markers (59 [28.7%] of 205 female patients vs 23 [26.7%] of 86 male patients). Additionally, patients with fragrance allergies were more likely to be aged >40 years and have hand dermatitis. However, in our patient cohort, there was no statistically significant correlation between fragrance allergies and physiologic factors (ie, sex, occupation, atopic dermatitis, leg, hand, face, and age).

Next, 40 patients who tested positive for at least 1 of the fragrance screening markers were enrolled for immediate and delayed patch testing with 28 individual fragrance allergens. Almost all of these patients (38/40; 95.0%) showed a positive patch test reaction to one of the fragrance substances upon immediate or delayed exposure. Although half (20/40; 50%) of the patients were positive for an immediate patch test reaction, the majority (35/40; 87.5%) of them were also positive for a delayed patch test reaction to specific fragrance substances. Cinnamic aldehyde (16/40; 40%), cinnamic alcohol (11/40; 27.5%), sorbic acid (8/40; 20.0%), coumarin (7/40; 17.5%), and geraniol (5/40; 12.5%) all caused strong positive immediate reactions (Table II). Cinnamic alcohol (24/40; 60.0%), cinnamic aldehyde (22/40; 55.0%), ylang ylang oil (13/40; 32.5%), Balsam of Peru (12/40; 30.0%), and isoeugenol (10/40; 25.0%) all caused a high rate of positive reactions in patients undergoing standard delayed patch tests (Table III).

Interestingly, the high rate of positive reactions observed in patients with positive delayed patch tests to FM I was attributed to cinnamic alcohol (24/30; 80.00%). In comparison, citral (6/17; 35.29%) and α -hexyl cinnamic aldehyde (6/17; 35.29%) were major contributors to the high positive reaction frequency observed in patients with a positive patch test to FM II. With the exception of benzyl alcohol, sorbic acid and coumarin, most of the individual fragrance substances appeared to elicit a higher

positive rate of standard patch test reactions than of immediate patch test reactions (Table IV). Coumarin is the only fragrance causing exclusively immediate reactions in this small data set. In addition, most of the patients (19 out of 20 patients) with a positive immediate test reaction(s) to the 28 different fragrance substances reported at least 1 of the clinical symptoms related to the immediate reactions. Sneezing and rhinorrhea were the 2 most common symptoms reported, whereas wheal and flare were the 2 least common symptoms reported (Table V).

DISCUSSION

Fragrance allergens can cause a variety of reactions, including contact urticaria, allergic contact dermatitis, irritant contact dermatitis, photocontact dermatitis, irritation of the respiratory tract, and asthma exacerbation.³ To our knowledge, our study was the first to demonstrate which fragrance allergens can cause immediate and delayed reactions in the Thai population. In individuals with allergic contact dermatitis to fragrances, we discovered a high prevalence of positive immediate patch test reactions. *Myroxylon pereirae* and FM I were previously reported as the most common causes of immediate patch test reactions in a European standard series.⁴ Cinnamic aldehyde and cinnamic alcohol were found to be the most common fragrance allergens eliciting immediate reactions in the Thai population in this study. Given that both these fragrance substances are major components of spices and essential oils that are frequently used in a variety of Asian foods, beverages, and personal care products, such as mouthwash, it was expected that a high prevalence of immediate allergic reaction to these substances would exist in the Thai population.^{3,5,6}

In this study, sorbic acid, which is widely used as a preservative in fragrances and may cause contact urticaria in addition to having an odor, was ranked as the third most common allergen eliciting immediate reactions. It is frequently found in facial wet wipes, which are widely used in the cosmetic and food industries, as well as on medical devices.^{7,8} Additionally, it is used as a preservative in medicines and resulted in an immediate positive contact urticarial reaction in patients who had previously used permethrin.⁹ These findings suggest that the positive immediate reactions observed in the Thai population could be caused by sorbic acids found in a variety of cosmetics, foods, and medications.

Our study discovered that female patients appear to have a higher rate of positive patch test responses to fragrance screening markers than male patients, which is consistent with the findings in

Table I. The MOALHFA characteristics in patients who tested positive and negative for fragrances

MOALHFA	Fragrance-positive N = 82		Fragrance-negative N = 209		P value
	n (%)	95% CI of OR	n (%)	95%CI of OR	
Male	23 (28.0)	0.605-1.359	53 (25.4)	0.878-1.233	.638
Occupational	13 (15.9)	0.425-1.085	20 (9.6)	0.909-1.607	.128
Atopic dermatitis	18 (22.0)	0.913-2.279	66 (31.6)	0.761-1.016	.103
Leg	15 (18.3)	0.716-1.880	45 (21.5)	0.800-1.119	.539
Hand	26 (31.7)	0.527-1.130	51 (24.4)	0.933-1.332	.204
Face	22 (26.8)	0.660-1.511	56 (26.8)	0.850-1.177	.995
Age > 40 y	53 (64.6)	0.529-1.149	118 (59.5)	0.953-1.267	.203

MOALHFA, Male, occupational dermatitis, atopic dermatitis, hand dermatitis, leg dermatitis, face dermatitis, age > 40; OR, odds ratio.

Table II. The number of patients (N = 40) who had a positive immediate reaction(s) to 28 individual fragrance substances

Substances	Positive immediate reaction			Present relevance	
	n	%	95% CI	n	%
1. Cinnamic aldehyde	16	40.0	24.9%-56.7%	8	50.00
2. Cinnamic alcohol	11	27.5	14.6%-43.9%	6	54.55
3. Ylang ylang oil	0	0.0	0.0%-8.8%	0	0.00
4. Benzyl alcohol	4	10.0	2.8%-23.7%	3	75.00
5. <i>Jasmine officinale</i>	0	0.0	0.0%-8.8%	0	0.00
6. Lavender oil	1	2.5	0.1%-13.2%	1	100.00
7. Peppermint oil	0	0.0	0.0%-8.8%	0	0.00
8. Sorbic acid	8	20.0	9.1%-35.6%	5	62.50
9. Eugenol	0	0.0	0.0%-8.8%	0	0.00
10. Geraniol	5	12.5	4.2%-26.8%	3	60.00
11. Oakmoss absolute	0	0.0	0.0%-8.8%	0	0.00
12. Lylal	0	0.0	0.0%-8.8%	0	0.00
13. Hydroxycitronellal	1	2.5	0.1%-13.2%	0	0.00
14. Isoeugenol	0	0.0	0.0%-8.8%	0	0.00
15. Oil of eucalyptus	0	0.0	0.0%-8.8%	0	0.00
16. Oil of rose	0	0.0	0.0%-8.8%	0	0.00
17. Oil of lemongrass	0	0.0	0.0%-8.8%	0	0.00
18. Orange oil	0	0.0	0.0%-8.8%	0	0.00
19. Oil of bergamot	0	0.0	0.0%-8.8%	0	0.00
20. α -amyl cinnamic aldehyde	0	0.0	0.0%-8.8%	0	0.00
21. Citral	2	5.0	0.6%-16.9%	2	100.00
22. Citronellol	1	2.5	0.1%-13.2%	1	100.00
23. Coumarin	7	17.5	7.3%-32.8%	3	42.86
24. Farnesol	0	0.0	0.0%-8.8%	0	0.00
25. α -hexyl cinnamic aldehyde	0	0.0	0.0%-8.8%	0	0.00
26. Oil of lemon	0	0.0	0.0%-8.8%	0	0.00
27. Menthol	0	0.0	0.0%-8.8%	0	0.00
28. Balsam of Peru	2	5.0	0.6%-16.9%	1	50.00

previous reports.¹⁰⁻¹² Additionally, patients with fragrance allergies were more likely to have occupational dermatitis, hand eczema, and be older than 40 years, which is consistent with the findings from a previous study cohort in the Thai population.¹⁰ However, because of our small sample size, we were unable to establish a statistically significant

relationship between patient, factors (eg, sex, occupation, atopic dermatitis, leg, hand, face, and age), and fragrance-positive patch test reactions. One possible explanation for this is that patients at occupational risk may be exposed to allergens on a regular basis, resulting in the development of additional allergies. The reason for hand eczema

Table III. The number of patients ($N = 40$) who had a positive standard patch test reaction(s) to 28 different fragrance substances

Substances	Positive patch test reactions							Present relevance	
	<i>n</i>	%	95% CI	+/-	+	++	+++	<i>n</i>	%
1. Cinnamic aldehyde	22	55.0	38.5%-70.7%	1	6	12	4	10	45.5
2. Cinnamic alcohol	24	60.0	43.3%-75.1%	0	10	14	0	10	41.7
3. Ylang ylang oil	13	32.5	18.6%-49.1%	1	7	6	0	6	46.2
4. Benzyl alcohol	3	7.5	1.6%-20.4%	0	1	2	0	2	66.7
5. <i>Jasmine officinale</i>	2	5.0	0.6%-16.9%	1	2	0	0	1	50.0
6. Lavender oil	1	2.5	0.1%-13.2%	1	1	0	0	0	0.0
7. Peppermint oil	2	5.0	0.6%-16.9%	2	1	1	0	1	50.0
8. Sorbic acid	1	2.5	0.1%-13.2%	0	1	0	0	1	100.0
9. Eugenol	7	17.5	7.3%-32.8%	2	5	2	0	4	57.1
10. Geraniol	7	17.5	7.3%-32.8%	5	5	2	0	5	71.4
11. Oakmoss absolute	2	5.0	0.6%-16.9%	3	1	1	0	2	100.0
12. Lylal	6	15.0	5.7%-29.8%	1	2	4	0	2	33.3
13. Hydroxycitronellal	4	10.0	2.8%-23.7%	0	2	2	0	2	50.0
14. Isoeugenol	10	25.0	12.7%-41.2%	0	3	7	0	9	90.0
15. Oil of eucalyptus	4	10.0	2.8%-23.7%	2	3	1	0	2	50.0
16. Oil of rose	4	10.0	2.8%-23.7%	2	4	0	0	3	75.0
17. Oil of lemongrass	8	20.0	9.1%-35.6%	2	2	6	0	7	87.5
18. Orange oil	2	5.0	0.6%-16.9%	2	2	0	0	1	50.0
19. Oil of bergamot	0	0.0	0.0%-8.8%	4	0	0	0	0	0.0
20. α -amyl cinnamic aldehyde	3	7.5	1.6%-20.4%	1	2	1	0	2	66.7
21. Citral	6	15.0	5.7%-29.8%	4	2	4	0	5	83.3
22. Citronellol	3	7.5	1.6%-20.4%	2	1	2	0	1	33.3
23. Coumarin	0	0.0	0.0%-8.8%	1	0	0	0	0	0.0
24. Farnesol	1	2.5	0.1%-13.2%	0	1	0	0	0	0.0
25. α -hexyl cinnamic aldehyde	6	15.0	5.7%-29.8%	0	4	2	0	4	66.7
26. Oil of lemon	2	5.0	0.6%-16.9%	0	2	0	0	0	0.0
27. Menthol	0	0.0	0.0%-8.8%	2	0	0	0	0	0.0
28. Balsam of Peru	12	30.0	16.6%-46.5%	6	7	5	0	6	50.0

+++ , Extreme strong positive reaction; ++ , strong positive reaction; + , weak positive reaction; +/- , doubtful reaction.

is that the hand is the most frequently exposed area to topical medications and cosmetics. The reason patients aged >40 years have a higher rate of positive reactions is that they may have a weaker immunoregulatory system, which may respond irregularly to cosmetic allergens.¹³

Of all the fragrance screening markers, our study discovered that the frequency of positive patch tests for FM I was higher than that for Balsam of Peru, FM II, and colophony, which is consistent with North America Contact Dermatitis Group¹⁴ and European studies.¹⁵ Our findings indicated that 2 (5.0%) of 40 patients with a positive reaction to the fragrance screening marker did not develop a positive reaction to the 28 individual fragrance allergens during subsequent patch testing. Positive reactions to fragrance mixes but not to individual fragrances may be explained by the fragrance mix's irritant effect rather than a true allergic reaction.^{3,16,17} The rate of concurrent reactions between the individual fragrance substances with FM II was lower than the rate with

FM I. This finding was consistent with a European study reporting that the concomitant reactions to FM I were greater than those to FM II.¹⁸ In addition, certain fragrance substances, such as benzyl alcohol, sorbic acid, and coumarin, appeared to produce an immediate reaction rather than a standard reaction in our cohort. Remarkably, almost all of the patients who had positive a immediate test reaction(s) to fragrance substances reported at least 1 of the clinical symptoms related to the immediate reactions. Respiratory symptoms (eg, sneezing) were more commonly found than skin symptoms (eg, wheal) in these patients. As a result, any patient who has a history of contact with these fragrance substances may be recommended to undergo an immediate patch test.

Conclusion

This study characterized both immediate and delayed patch test reactions to individual fragrance allergens in patients with fragrance allergies in the

Table IV. The number of patients ($N = 40$) who had a positive or negative immediate or standard patch test reaction(s) to 28 different fragrance substances

Substances	Immediate patch test (+), standard patch test (+)	Immediate patch test (+), standard patch test (-)	Immediate patch test (-), standard patch test (+)
	<i>n</i>	<i>n</i>	<i>n</i>
1. Cinnamic aldehyde	8	8	14
2. Cinnamic alcohol	6	5	17
3. Ylang ylang oil	0	0	13
4. Benzyl alcohol	1	3	2
5. <i>Jasmine officinale</i>	0	0	2
6. Lavender oil	0	1	1
7. Peppermint oil	0	0	2
8. Sorbic acid	1	7	0
9. Eugenol	0	0	7
10. Geraniol	3	2	5
11. Oakmoss absolute	0	0	2
12. Lyrall	0	0	6
13. Hydroxycitronellal	0	1	4
14. Isoeugenol	0	0	10
15. Oil of eucalyptus	0	0	4
16. Oil of rose	0	0	4
17. Oil of lemongrass	0	0	8
18. Orange oil	0	0	2
19. Oil of bergamot	0	0	0
20. α -amyl cinnamic aldehyde	0	0	3
21. Citral	1	1	5
22. Citronellol	0	1	2
23. Coumarin	0	7	0
24. Farnesol	0	0	1
25. α -hexyl cinnamic aldehyde	0	0	6
26. Oil of lemon	0	0	2
27. Menthol	0	0	0
28. Balsam of Peru	0	2	11

Table V. The clinical symptoms related to the immediate reactions of patients ($N = 20$) who had a positive immediate test reaction(s) to 28 different fragrance substances

Clinical symptom	Percentage of patients
Wheal	10
Flare	35
Coughing	25
wheezing	35
Sneezing	60
Rhinorrhea	40

Thai population for the first time. Cinnamic aldehyde and cinnamic alcohol were the most common fragrance allergens, causing immediate and delayed patch test reactions. Another recently discovered fragrance allergen, sorbic acid, was found to cause strong reactions in the Thai population. Furthermore, allergic reactions to sorbic acid, benzyl

alcohol, and coumarin were more frequently observed in immediate patch tests than in standard patch tests.

Conflicts of interest

None disclosed.

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