

Key words: challenge test; fragrance; non-immune immediate contact reactions.

Introduction

Non-immune immediate contact reactions (NIICR) are defined as non-immunoglobulin E (IgE)-mediated skin responses that occur without previous sensitization (1, 2). NIICR can be observed due to the urticants benzoic acid, trans-cinnamic acid and methyl nicotinate (3) and also due to the sensitizing component cinnamic aldehyde of fragrance mix, which is known to cause a type IV delayed hypersensitivity contact reaction (2). As mechanistic approach for some urticants, a non-specific histamine release from dermal mast cells is discussed, but antihistamine treatment seems to be rarely effective (4). Moreover, NIICR responsiveness can be found in the majority of tested individuals depending on the applied concentration, but it is still unknown whether sensitive individuals might react with airway symptoms. In a case report, a patient with workplace-related asthma attacks to perfumes presented delayed type IV reactions to a mixture of odorous substances in patch testing. Bronchial challenge to perfumes yielded immediate-type asthmatic reactions, suggesting the diagnosis of an occupational allergy to perfumes (5). Besides delayed hypersensitivity contact reactions, obstructive airway diseases were reported in workers exposed to in workers exposed to cinnamon dust which contains the fragrance component cinnamic aldehyde (6). To the best of our knowledge, there are no findings in literature whether bronchial challenge testing with this NIICR-inducing fragrance component may result in an asthmatic reaction. Thus, bronchial challenge testing was considered as a further diagnostic approach to demonstrate a possible association between NIICR and asthma.

Bronchial challenge testing to fragrance component as further diagnostic approach to non-immune immediate contact reactions

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Case Report

In this case, a 47-year-old female gardener working since 1995 in a flower and garden shop was referred to our institute in 2005. She complained almost daily of symptoms like generalized pruritus, especially on both hands and forearms without objective clinical signs, dry nose, itching ear and

neck, shortness of breath and headache when exposed to 'all odours' since 2000. Symptoms were more pronounced at work but occurred also off work. Although the diagnosis of an idiopathic environmental intolerance (IEI) seemed to be the most likely diagnosis based on the available information, we decided to perform further diagnostics.

Materials and Methods

Total IgE was assessed using UniCAP 100 (Phadia, Uppsala, Sweden), and differential cell count was performed by an LH 750 Hematology Analyzer (Beckman Coulter GmbH, Krefeld, Germany). Patch testing and prick tests were performed according to internationally accepted guidelines (7) with standard patch test series including two different fragrance mixes (Hal Allergie, Dusseldorf, Germany and Hermal, Reinbek, Germany) and corresponding single components of fragrance mix provided by Hermal: eugenol, oakmoss absolute, isoeugenol, geraniol, alpha-amylcinnamic aldehyde, hydroxycitronellal, cinnamic aldehyde and cinnamic alcohol. For patch testing, these were applied to the skin through Haye's test chambers (Hal Allergie). Prick tests were performed with a series of environmental allergens including tree and grass mixes and various flowers (different manufacturers) and with those preparations of the standard patch series that gave positive immediate reactions in patch testing. In patch testing and prick test, diameter of erythema and oedema was measured 30 min, 48 hr and 72 hr (patch testing) and 10, 20, 30, 60, 120 and 180 min (prick test) after application. Evaluation of the weal reaction was performed by measuring diameter of the oedema and erythema in millimetres (mm).

Spirometry was performed with Masterlab (Viasys, Hochberg, Germany), according to the American Thoracic Society (ATS) recommendations (8). Airway hyperresponsiveness was assessed as described recently (9) with a Provotest II nebulizer (Pari, Starnberg, Germany). Bronchial challenge testing was performed with cinnamic aldehyde (Hermal) using a dosimeter (APSpro; Viasys) with a DeVilbiss 646 nebulizer (10) containing cinnamic aldehyde diluted with ethanol 70%

in doubling (cumulative) doses of 0.4 µg–36 mg cinnamic aldehyde.

Results

Total IgE level was 301 kU/l, and differential leucocyte count showed 5% eosinophils. Patch testing with standard test preparations yielded positive responses after 30 min to benzoic acid, balsam of Peru, benzaldehyde and cinnamic aldehyde (Table 1). Patch testing with single components of the fragrance mix showed weak immediate reactions to cinnamic aldehyde, which was confirmed by a second patch testing 2 months later. None of the positive patch responses (Table 1) persisted or appeared after 48 or 72 hr. Dibromodicyanobutane/phenoxyethanol showed a crescendo contact reaction after 24, 48 and 72 hr [‘+++’, erythema and vesicle formation, for pattern of patch testing see Schnuch (7); data not shown]. Dibromodicyanobutane/phenoxyethanol belongs to the group of preservatives that are found in products of the daily life, e.g. body care products, washing emulsions and technical emulsions such as cutting oil emulsions, boron solutions and cooling liquids. No weal reaction was observed in prick test to 0.9% sodium chloride. Prick test with environmental allergens was completely negative, while prick test with standard patch test preparations caused positive reactions to benzoic acid and prick test with single components of the fragrance mix caused erythema and oedema to cinnamic aldehyde (Table 1; Fig. 1). Spirometry was normal, and methacholine (MCH) testing showed no bronchial hyperresponsiveness (maximal fall of forced expiratory

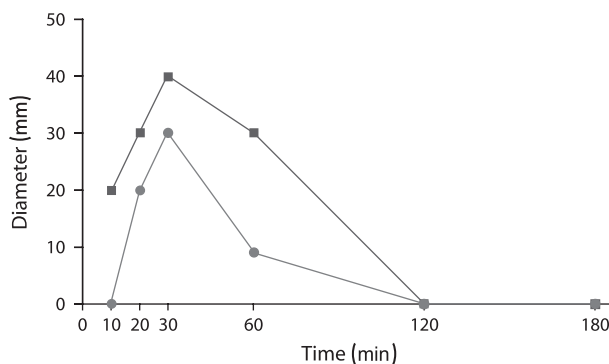


Fig. 1. Kinetic of reactions of prick tests with cinnamic aldehyde (provided by Hermal; squares: diameter of erythema and dots: diameter of oedema).

volume in 1 second 13%). Bronchial challenge testing with cinnamic aldehyde induced coughing but neither immediate nor late bronchial obstruction or skin reactions. Testing with ethanol 70% alone provoked no coughing. Cough reflex was triggered with a cumulative dose of 36 mg cinnamic aldehyde. Self-reported sensitivity to environmental stimuli and odours as assessed by a standardized questionnaire was extremely elevated (11). Olfactory function testing by means of ‘sniffin’ sticks’ showed only a slightly decreased olfactory threshold for n-butanol in relation to reference values (12).

Discussion

Type IV sensitization to dibromodicyanobutane/phenoxyethanol was considered not of occupational origin. As patch and prick testing to putative fragrance components showed NIICR for cinnamic aldehyde, we decided to perform bronchial challenge testing with this NIICR-inducing agent. While nega-

tive MCH testing has a high negative predictive value for asthma (10), we performed methacholine testing that did not show bronchial hyperresponsiveness. Bronchial challenge testing with a cumulative dose of 36 mg cinnamic aldehyde triggered cough reflex, possibly reflecting local hyper-reactivity related to defensive reflexes in the airways (13) but yielded no bronchial obstruction. To the best of our knowledge, inhalational challenge tests with single components of fragrances that induce NIICR have not yet been performed. For the first time, we applied an NIICR-inducing component of fragrance mix in bronchial challenge testing to show an asthmatic reaction. The measurement of olfactory function showed that the reported symptoms were not due to hyperosmia. Furthermore, the highly increased self-reported sensitivity to various kinds of unrelated environmental stimuli met the consensus criteria of IEI (14). These results together with the negative test results for asthma favour the most likely and reasonable diagnosis of the accidental coincidence of IEI and NIICR in the present case. In conclusion, the presented diagnostic procedure might encourage to perform bronchial challenge testing with the putative NIICR-inducing agent. Although an acute obstructive reaction could not be demonstrated and an alternative diagnosis is suggested, we cannot entirely exclude effects of cinnamic aldehyde on the lower airways of the patient. Therefore, bronchial effects and clinical relevance of NIICR have to be examined in further experimental and epidemiologic studies. However, due to the high prevalence of NIICR, the prospect of identifying susceptible subjects seems to be limited.

Table 1. Results of patch and prick testing (only positive reactions in either patch test or prick test)

Substance (manufacturer)	30-min patch test*	20-min prick test*
Commercial patch preparations		
Fragrance mix 8% (Hal)	3/5	—
Fragrance mix 8% (Hermal)	0/3	—
Benzoic acid 5% (Hal)	7/30	7/20
Balsam of peru 25% (Hal)	0/20	—
Benzaldehyde 5% (Hal)	0/4	—
Substances additionally provided by manufacturer		
Cinnamic aldehyde† (Hermal)	0/40	20/30
Cinnamic alcohol (Hermal)	?	—

—, negative test result; ?, doubtful reaction.

*Oedema/erythema (diameter in mm).

†For kinetic, see Fig. 1.

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