

Deodorants: an experimental provocation study with hydroxycitronellal

C. SVEDMAN¹, M. BRUZE¹, J. D. JOHANSEN², K. E. ANDERSEN³, A. GOOSSENS⁴, P. J. FROSCH⁵, J.-P. LEPOITTEVIN⁶,
S. RASTOGI⁷, I. R. WHITE⁸ AND T. MENNÉ²

¹Department of Occupational and Environmental Dermatology, University Hospital, 205 02 Malmö, Sweden, ²Department of Dermatology, Gentofte Hospital, University of Copenhagen, Gentofte, ³Department of Dermatology, University Hospital, Odense C, Denmark, ⁴Department of Dermatology, University Hospital, KU Leuven, Leuven, Belgium, ⁵Department of Dermatology, Dortmund and University of Witten/Herdecke, Dortmund, Germany, ⁶Laboratoire de Dermatochimie, Clinique Dermatologique, Strasbourg, France, ⁷National Environmental Research Institute, Roskilde, Denmark, and ⁸St. John's Institute of Dermatology, St. Thomas' Hospital, London, UK

Axillary dermatitis is a common problem, particularly in individuals with contact allergy to fragrances. Many individuals suspect their deodorant to be the causal product of their fragrance allergy. It has been shown that deodorants containing cinnamic aldehyde (cinnamal) can elicit axillary dermatitis in patients sensitized to this substance. The aim of the present investigation was to evaluate the importance of hydroxycitronellal used in deodorants for the development of axillary dermatitis, when applied by individuals with and without contact allergy to this fragrance chemical. Patch tests with deodorants and ethanolic solutions containing hydroxycitronellal, as well as repeated open application tests (ROAT) with roll-on deodorants with and without hydroxycitronellal at different concentrations, were performed in 14 dermatitis patients, 7 with and 7 without contact allergy to hydroxycitronellal. A positive ROAT was noted only in the patients hypersensitive to hydroxycitronellal ($P < 0.001$) and only in the axilla to which the deodorants containing hydroxycitronellal had been applied ($P < 0.001$). Deodorants containing hydroxycitronellal in the concentration range of 0.032–0.32% used twice daily on healthy skin in individuals hypersensitive to hydroxycitronellal can elicit axillary dermatitis in a few weeks.

Key words: allergic contact dermatitis; axillary dermatitis; deodorant; fragrance allergy; hydroxycitronellal; repeated open application test. © Blackwell Munksgaard, 2003.

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Hydroxycitronellal is an important sensitizing fragrant substance frequently found in perfumes and other fragranced cosmetics, such as aftershaves, eye-creams, etc. (1–4). It is a strong sensitizer in animal (5) and human experiments (6, 7) and is reported as the cause of allergic patch test reactions in dermatitis patients (1, 2, 6). It is 1 of the constituents of the fragrance mix (FM) present in the European standard series for patch testing (8, 9).

Axillary dermatitis is not uncommon and reported to be over-represented in individuals with contact allergy to FM (10). Many patients with axillary dermatitis suspect their deodorant to be the causal product (11). In a recent clinical provocation study with patient-supplied deodorants in fragrance-sensitive individuals, 12/20 (60%) deodorants elicited eczema on use testing in the axilla (12). The majority of these deodor-

ants were demonstrated to contain at least 1 of the FM constituents, and hence it is most likely that the axillary dermatitis was caused by the fragrance/s present in the deodorant. However, at least theoretically, another possible explanation is irritant reactions from the deodorants, an interpretation strongly favoured by the fragrance industry. In a controlled and randomized study using deodorants containing cinnamic aldehyde (cinnamal) in a use test of the axilla, a dermatitis was elicited in the exposed axilla in patients allergic to cinnamic aldehyde (13). In this experimental provocation study, we wanted to investigate the significance of hydroxycitronellal in deodorants for the development of axillary dermatitis, when used by individuals with and without allergy to hydroxycitronellal in a way resembling their ordinary use of deodorants.

Materials and Methods

Patients

14 patients with dermatitis attending the Department of Occupational and Environmental Dermatology in Malmö participated in the study (11 women and 3 men, mean age, 44). 7 persons with dermatitis (test patients) who had previously been shown to be hypersensitive to hydroxycitronellal on patch testing were asked to participate. 7 persons (control patients) were recruited as controls as they had previously been shown to be negative to the FM. For both groups, pregnancy, current axillary dermatitis and age below 18 years were the exclusion criteria.

The study was approved by the local ethics committee and informed consent was obtained from all individuals before inclusion.

Chemicals

Hydroxycitronellal (Acros Organics, New Jersey, USA/Geel, Belgium) from the same batch was used for all patch test solutions and deodorants. The patch test solutions were prepared at the department in Malmö. Stock solution of hydroxycitronellal in ethanol at 4.00% w/v was prepared and further diluted to 2.0, 1.0, 0.50, 0.25, 0.125, 0.063, 0.031, 0.016, 0.008, 0.004, 0.002, 0.001, 0.0005, 0.00025, 0.00012 and 0.00006%. Deodorants with and without hydroxycitronellal were used. Roll-on deodorants without any fragrance were manufactured by an international manufacturer of cosmetics. In the department in Malmö, hydroxycitronellal at 3 different concentrations (0.032% w/v, low concentration; 0.1% w/v, medium concentration and 0.32% w/v, high concentration) was added to all but 21 of the deodorants. The hydroxycitronellal concentration of these deodorants was controlled with high-pressure liquid chromatography (HPLC) and found to be correct. Except for the content of hydroxycitronellal, the deodorants were identical, with the following ingredients; water, aluminium chlorohydrate, PPG-15, stearyl ether, steareth-2, steareth-21, dichlorobenzylalcohol and phenoxy-ethanol. The deodorants were all coded in the department.

Patch testing

FinnTM Chamber (Epitest, Tuusula, Finland) technique was used. On each patch unit mounted on ScanporTM tape (Norgesplaster, Vennesla, Norway) 15 µl of the respective test solution was applied. The patches were removed from the back after 48 hr (D2) and readings were taken on D3 and D7 according to ICDRG guidelines. Each test patient was tested with 15 ethanolic solutions

of hydroxycitronellal, ethanol, the unscented and the scented deodorants. For those having reacted previously with a +++ reaction to hydroxycitronellal, the testing started at 1.0%; for those having reacted previously with a ++ reaction, testing started at 2.0% and for all other test patients, the testing started at 4.0%. Besides testing with the unscented deodorant and ethanol, the control patients were only tested with hydroxycitronellal at 1.0%.

The threshold of sensitivity (the minimal eliciting concentration, MEC) was defined as the lowest concentration eliciting at least a + reaction (14). The positive reactions were not always continuous. When the number of negative and/or doubtful reactions were followed by the same number or more of positive reactions, the lowest positive reaction was registered as the MEC. In all other situations, the concentration above the first negative or doubtful reaction was registered as the MEC (14).

Use test

The use test was performed as a repeated open application test (ROAT) (15) using the axillae as test sites. The participants were equipped with 2 deodorants, 1 scented and 1 unscented. The deodorants were applied twice daily throughout the experiment. To minimize the risk of using the wrong deodorant for the axilla, the deodorants were labelled in colours.

Evaluation of the ROAT was made once a week, or at the request of the patient, with inspection including assessment of the following morphological features; erythema, infiltration, papules, vesicles and scaling. The involved area with dermatitis and the overall impression of the use test reaction were also assessed (16).

Study design

The study design was based upon the experience of a similar experiment with cinnamic aldehyde (13). Based on previous findings concerning the regular concentration found in deodorants in use (2, 4), deodorants with hydroxycitronellal at 0.032% (low), 0.1% (medium) and 0.32% (high) were chosen for the study. The scented and unscented deodorants were randomly allocated to the axillae. A double-blind design was used for the study, schematically shown in Fig. 1. The deodorants were weighed before use and after final use to give an indication of the daily use of deodorant for each patient. The first day (D0) the patient was given information and received the deodorants. The same evening the patients started using the 2 deodorants (unscented and scented

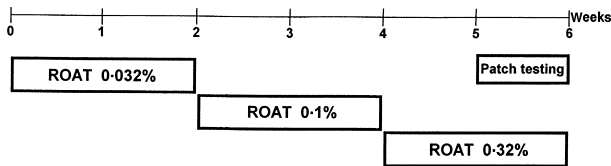


Fig. 1. Study design.

with hydroxycitronellal at low concentration) in the axilla twice daily. The application was continued twice daily for 2 weeks, with inspection after 1 and 2 weeks. If there was no dermatitis in the axilla after 2 weeks, a new set of weighed deodorants, 1 unscented and the second scented with hydroxycitronellal at medium concentration, were given to the test and control patients to be applied for another 2 weeks unless dermatitis appeared sooner. The participants were seen for inspections after 1 and 2 weeks. If no reaction had appeared, the participants were given 2 new deodorants, 1 unscented and 1 containing hydroxycitronellal at high concentration, to be used as above. At the end of the study, all patients were patch tested with readings on D3 and D7. For those who were regular shavers of the axilla, shaving was permitted but had to be done only once in every 2 weeks, just before the start of the study and on the day when a new set of deodorants were introduced. During the study, no other deodorants were allowed.

The maximal study period for 1 patient was 6 weeks (patch test and use test). Termination of the study could be initiated earlier, either on patient request or due to the development of eczematous skin changes. In case of only spotted erythema or a few papules, the patients were encouraged to continue until an eczematous dermatitis developed. The patient kept a daily diary of their symptoms and when deodorant had been applied.

Statistical calculations

Fisher's exact test was used when comparing the number of test and control patients testing positively to the ROAT and also for the comparison of positive reactions for the scented and unscented deodorants among test patients. The correlation between the MEC for patch testing with deodorants containing hydroxycitronellal and the ethanol solutions with hydroxycitronellal, the correlation between total dose of deodorant used and the outcome of the ROAT, as well as the correlation between the MEC on patch testing and threshold concentration giving visible skin symptoms on use test were expressed by calculation of the Spearman rank correlation coefficient.

Results

Table 1 summarizes data on sex, age, average dose of deodorant used for each application, patch test and ROAT results. None of the controls had positive patch test reactions. All 7 test patients tested positively to hydroxycitronellal, with a difference of 33 000 (test patient nos. 4 and 2) in the reactivity between the persons with the highest reactivity and lowest. Simultaneous positive patch test reactions to deodorants were registered in 3 patients.

ROAT was negative in all controls. Positive ROAT was noted in all the patients ($P < 0.001$). A unilateral dermatitis was found in all the patients with a dermatitis in the axilla where hydroxycitronellal had been used ($P < 0.001$). The patient with the highest MEC to hydroxycitronellal was already weakly positive/doubtful after 1 week and clearly positive at 2 weeks. The patient with the lowest MEC developed a positive ROAT in 1 week. Figure 2 shows positive ROAT over time.

Clinically, all positive reactors developed an eczematous response covering at least 25% of the axillary area. For most patients, the initial symptoms and signs were itching and a few, scattered papules, which gradually developed into an infiltrated erythematous, patchy to homogeneous, reaction with papules, and in some cases minute vesicles were seen (Fig. 3).

In some patients as well as controls, a fine scaly reaction was seen most often in both axillae simultaneously, and the patient might complain about a stinging sensation. This reaction disappeared without the need for patients or controls to stop the experiment. It did not return even if the patients continued at a higher concentration of hydroxycitronellal.

The amount of deodorant used for 1 application varied between 172 and 591 mg (Table 1). There were thus great interindividual differences in the amounts used, but no differences between test and control patients. Neither were there any significant intraindividual differences between scented and unscented deodorants nor between the ROAT periods of 2 weeks with the respective deodorants (low, medium and high concentrations). There was no correlation between total dose of deodorant used and the outcome of the ROAT. There was a correlation ($r = 0.938$, $P < 0.05$) between threshold concentrations of hydroxycitronellal (ethanol solutions) on patch testing and the outcome of ROAT (Fig. 4).

Discussion

The lack of fragrance ingredient labelling for cosmetics restricts the possibilities of assessing the

Table 1. Data on sex and age of the 7 test patients (nos. 1–7) and the 7 control patients (nos. 8–14), the results of the patch tests: MEC (minimum eliciting concentration) deodorant and MEC HC (hydroxycitronellal) in ethanol, repeated open application tests (ROAT), week at which reaction appeared as well as average dose of deodorant used for each application

Patient no.	Sex	Age	Patch test		Ethanol	ROAT				Unscented	Scented	High		Unscented	Deodorant used (mg/application)
			HC in ethanol	Scented		Scented	Unscented	Medium	Scented			Scented	Unscented		
1	Male	81	0.5	–	–	–	–	–	–	–	–	1	–	–	591
2	Female	64	4.0	–	–	2	–	NT	NT	–	NT	NT	NT	–	246
3	Female	26	0.5	0.32	–	2	–	NT	NT	–	NT	NT	NT	–	361
4	Female	34	0.00012	0.1	–	1	–	NT	NT	–	NT	NT	NT	–	238
5	Female	18	0.125	–	–	2	–	NT	NT	–	NT	NT	NT	–	188
6	Female	51	1	–	–	–	–	–	–	–	–	1	–	–	172
7	Female	53	0.25	0.032	–	–	–	2	–	–	–	NT	NT	–	259
8–14	2 males 5 females	36–51 24–59	–	–	–	–	–	–	–	–	–	–	–	–	245 (150–340) 227 (135–316)

NT = not tested.

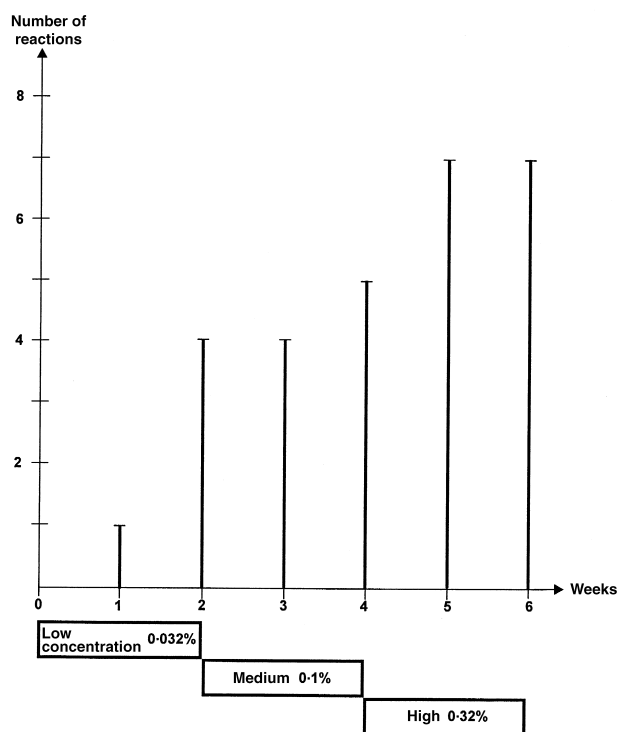


Fig. 2. The number of accumulated positive reactions in repeated open application tests (ROAT) with deodorants containing hydroxycitronellal at 3 concentrations (0.032%, 0.1% and 0.32%) in 7 patients hypersensitive to hydroxycitronellal during the study period of 6 weeks.

clinical significance of sensitization to single fragrance allergens. Recent findings have found positive reactions to deodorants on use testing in the axilla twice daily (12, 13). A positive use test documents that the tested product may cause dermatitis but not the actual mechanism of the adverse reaction (17). Besides containing contact sensitizers, deodorants may contain contact irritants, and it is therefore possible that the axillary dermatitis in some patients may be

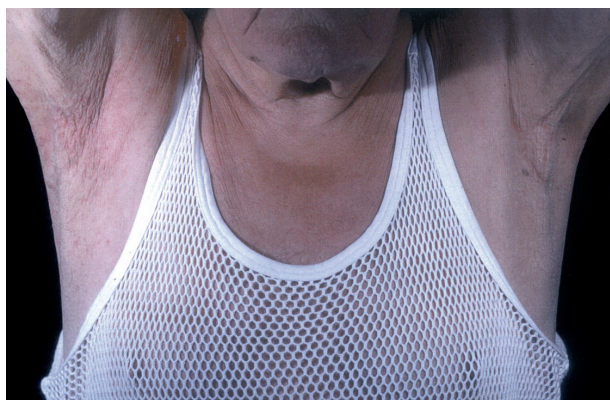


Fig. 3. Axillary dermatitis in patient with contact allergy to hydroxycitronellal after 3 weeks in repeated open application test study (ROAT).

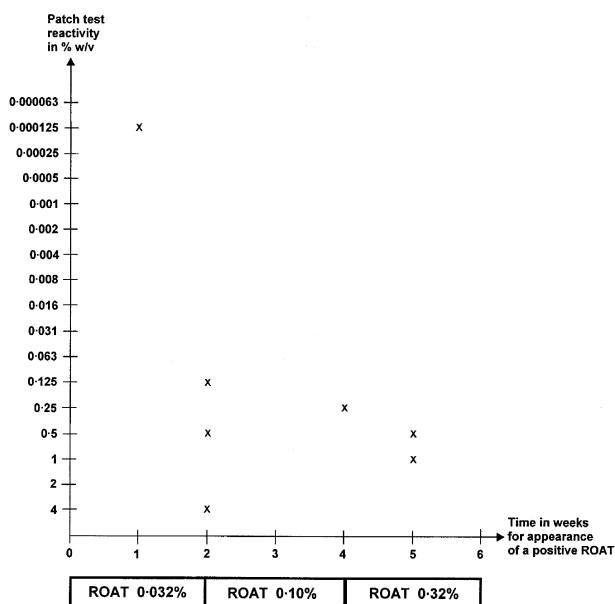


Fig. 4. Relationship between patch test reactivity to ethanol solutions with hydroxycitronellal and time to appearance of a positive repeated open application test (ROAT) to deodorants containing hydroxycitronellal in 7 patients hypersensitive to hydroxycitronellal.

caused by irritants in the deodorants (18). This latter explanation has been strongly supported by the fragrance industry. However, recently it has been shown in a provocation study similar to this that cinnamic aldehyde can elicit axillary dermatitis within a few weeks (13). In the present study, it is shown that the deodorants containing hydroxycitronellal in the concentration range of 0.032–0.32% used on healthy skin can elicit axillary dermatitis within a few weeks. The study design supports the conclusion that hydroxycitronellal is the causal substance and that the axillary dermatitis is caused by an allergic and not an irritant mechanism. The reactions in the test patients showed that hydroxycitronellal was the responsible substance ($P < 0.001$) and the negative results in control patients showed that irritancy did not play any role in the dermatitis ($P < 0.001$).

The transient reaction appearing in both test and control patients during a few days with discrete scaling has previously been described (13) and can be explained by a transient irritant reaction from the non-scented part of the deodorant. It was found that this reaction did not precede that of the allergic in the test patients.

Unexpectedly, there was a huge difference in patch test reactivity to hydroxycitronellal, with a difference of 30 000 between the individual lowest concentrations eliciting positive patch

test reactions. The threshold concentration (MEC) for the patient with the highest reactivity was 0.00012% (1.2 p.p.m.).

In cosmetic products, concentrations between 0.135 and 6.044% w/v (3) have been found, thus indicating that the test concentration was in the same range that consumers were being exposed to in their daily life.

Often use tests have been performed for 1–2 weeks, but it has been pointed out that many reactions may appear after the first few weeks. In a recent experimental study on time dose–response relationship for elicitation of contact dermatitis in individuals hypersensitive to Isoeugenol, it was shown that the time until an isoeugenol-allergic individual reacts in a ROAT will depend on the individual sensitivity as well as on the exposure concentrations; for low concentrations of the allergen or low degree of sensitivity, the allergic contact dermatitis may develop after several weeks of exposure (19). In the study where cinnamic aldehyde was used in deodorants with a similar study design, 7/8 showed positive reactions within 2 weeks. In the study with cinnamic aldehyde, both patch test reactivity and application dose were significant for the ROAT result (13). In this study, 4/7 showed positive reactions after 2 weeks; in this group both the patients with the highest and lowest MEC were found. Thus, a correlation between patch test reactivity and use test reactivity, as has previously been found (19, 20) with, for example, isoeugenol, was not found in this study.

The use test should be developed so that all cosmetic products end up being tested in a manner resembling the natural use situation as much as possible. The axilla as a site for use testing has not been extensively used (12, 13, 21). For deodorants, the axilla was shown to be prone to react to hydroxycitronellal.

The International Fragrance Association (IFRA) has issued a recommendation that hydroxycitronellal should not be used in fragrance compositions at a level exceeding 5%; this equates to a maximum of 1% in consumer products (3, 7, 22).

Hydroxycitronellal was detected in 35 deodorants at concentrations ranging from 1 to 1023 p.p.m. when 73 deodorants on the European market were investigated chemically for the presence of 21 fragrance chemicals (4). Thus, the concentrations used in this study are realistic, which means that the results should be used in the attempts to find safe limits of hydroxycitronellal in deodorants to prevent axillary dermatitis in individuals already sensitized to hydroxycitronellal. Also taking into account the possible significance of the application of deodorant in an axilla with abraded skin and the presence of

more than 1 sensitizer in the scented deodorant (23), we suggest that the concentration of hydroxycitronellal should be lower than 0.032% in deodorants, although studies to determine the most appropriate concentration remain to be performed.

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Address:
Cecilia Svedman
Department of Occupational Dermatology
University Hospital
Malmö
Sweden
Tel: +46 40 33 78 61
Fax: +46 40 33 62 13
e-mail: cecilia.svedman@skane.se