Multicentre patch testing with fragrance mix II and hydroxyisohexyl 3-cyclohexene carboxaldehyde by the Swedish Contact Dermatitis Research Group

Marlène Isaksson¹, Annica Inerot², Carola Lidén³,⁴, Magnus Lindberg⁵, Mihaly Matura³,⁴, Halvor Möller¹, Berndt Stenberg⁶ and Magnus Bruze¹

¹Department of Occupational and Environmental Dermatology, Skåne University Hospital, Lund University, Malmö SE-205 02, Sweden, ²Department of Dermatology, Sahlgrenska University Hospital, Gothenburg SE-413 45, Sweden, ³Institute of Environmental Medicine, Karolinska Institutet, Stockholm SE-171 76, Sweden, ⁴Unit of Occupational and Environmental Dermatology, Centre for Occupational and Environmental Medicine, Stockholm County Council, Stockholm SE-171 76, Sweden, ⁵Department of Dermatology, Örebro University Hospital, Örebro SE-701 85, Sweden, and ⁶Department of Public Health and Clinical Medicine, Epidemiology and Dermatology & Venereology, Umeå University, Umeå SE-901 85, Sweden

doi:10.1111/cod.12156

Key words: baseline series; fragrance mix 2; hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC Lyral®); simultaneous contact allergy.

Fragrance mix 2 (FM 2) has been shown to be a useful marker of fragrance contact allergy in addition to the old fragrance mix, with contact allergy frequencies up to 5% when tested in many national baseline patch test series (1–3). Hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) is one of the six fragrance substances in this FM 2, and the most common sensitizer, with contact allergy rates up to 3% when tested in consecutive dermatitis patients (4–8). The present study was initiated to investigate the rates of contact allergy to FM 2 and HICC in a Swedish dermatitis population, and to determine how common are simultaneous allergic reactions between the two. A recommendation to include FM 2 and HICC in the European baseline series was published in 2008 (9).

Materials and Results

Six dermatology clinics took part in the study, in which the majority of the members of the Swedish Contact Dermatitis Research Group participated. Participating centres were in Malmö, Lund, Gothenburg, Örebro, Stockholm, and Umeå. In Malmö, Lund, Gothenburg, and Stockholm, the study period was from 1 July 2006 to 31 December 2011; in Örebro, it was from 1 January 2007 to 31 December 2011; and in Umeå, it was from 1 October 2006 to 31 December 2011. In total, 6629 women and 3381 men were tested. In all departments, the test preparations were purchased from Chemotechnique Diagnostics (Vellinge, Sweden), that is, FM 2 14.0% pet. (wt/wt) containing 2.5% HICC, and HICC 5.0% pet (wt/wt). Tests were performed with Finn Chambers® (diameter, 8 mm) (Epitest Oy, Tuusula, Finland) on Scanpor® tape (Norgesplaster A/S, Vennesla, Norway) in all centres. The patch testing personnel placed 20 mg of each pet. test preparation into each Finn Chamber®.
Table 1. Number of patients who were patch test-positive to fragrance mix 2 and hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) in six dermatology departments in Sweden

<table>
<thead>
<tr>
<th>Department</th>
<th>Number of patients tested with the baseline series</th>
<th>Positive to FM 2 (%)</th>
<th>Positive to both FM 2 and HICC (%)</th>
<th>Positive to FM 2 only (%)</th>
<th>Positive to HICC (%)</th>
<th>Positive to HICC only (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>10,010</td>
<td>3381 (33.8)</td>
<td>382 (114)</td>
<td>357 (118)</td>
<td>90 (29)</td>
<td>20 (6)</td>
</tr>
<tr>
<td>Malmö*</td>
<td>3508</td>
<td>1256 (356)</td>
<td>82 (24)</td>
<td>13 (4)</td>
<td>33 (9)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Lund*</td>
<td>1325</td>
<td>354 (264)</td>
<td>61 (31)</td>
<td>10 (5)</td>
<td>30 (16)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Gothenburg†</td>
<td>2638</td>
<td>849 (318)</td>
<td>41 (10)</td>
<td>19 (4)</td>
<td>22 (8)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Stockholm‡</td>
<td>1008</td>
<td>408 (301)</td>
<td>37 (29)</td>
<td>15 (12)</td>
<td>22 (17)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Örebro‡</td>
<td>780</td>
<td>270 (174)</td>
<td>21 (13)</td>
<td>8 (5)</td>
<td>13 (8)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Umeå³</td>
<td>751</td>
<td>244 (156)</td>
<td>14 (9)</td>
<td>6 (4)</td>
<td>8 (5)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

M, males; F, females; FM 2, fragrance mix 2; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde.

*Testing from 1 July 2006 to 31 December 2011.
†Testing from 1 January 2007 to 31 December 2011.
‡Testing from 1 October 2006 to 31 December 2011.

(F) Contact points

MULTICENTRE TESTING WITH FRAGRANCE MIX 2 AND HICC • ISAKSSON ET AL.

(10). Patch tests were removed by the patients after 2 days (D2), and read on D3 or D4 according to International Contact Dermatitis Research Group criteria (11). A second reading was performed on D7. A dermatologist read the patch tests on both days in all centres except for Umeå, where a nurse read tests on the first reading day and a dermatologist on the second reading day.

Fisher’s exact two-tailed test was used to compare the contact allergy rate between males and females. The differences were considered significant at p < 0.05.

Positive patch test results from D3/4 and D7 are summarized into positive reactions, irrespective of reading day. Of 10,010 dermatitis patients tested at six departments, 337 (3.4%); range 2.1–6.3%) reacted to FM 2 containing 2.5% HICC, and 171 (1.7%; range 1.1–3.5%) to HICC 5.0% pet. tested separately. There were statistically significant differences between men and women in contact allergy to FM 2 (2.4% versus 3.9%, p < 0.001) and in contact allergy to HICC (1.2% versus 2.0%, p = 0.006). Twenty-three patients (0.2%; range 0.1–0.4%) were positive to HICC only. Simultaneous positive reactions were seen in 148 patients (1.5%) (Table 1).

Discussion

In this study comprising six departments, only 23 dermatitis patients (0.2% of all tested patients or 13.5% of the HICC-allergic patients) were patch test-positive to HICC without concomitant reactivity to FM 2. We do not question the inclusion of FM 2 at 14.0% pet., in which HICC is an ingredient at 2.5%, in the baseline series as a helpful additional marker for fragrance allergy (9). In a large German study comprising 35,490 patients, both fragrance mix 1 (FM 1) and FM 2 were tested, and 2.8% of the patients tested negative to FM 1 but positive to FM 2 (3). In the present study, ~1.6% of the patients tested negative to FM 2 but positive to FM 1 (unpublished observations).

HICC and farnesol are the most common sensitizers in FM 2 (2, 5). The other components are citral, coumarin, citronellol, and α-hexyl cinnamal. Contact allergy rates from various European centres of between 1.5% and 3% were reported when HICC was tested at 5.0% pet. In consecutive dermatitis patients (4–8). Our figures are very similar. Recent publications reported prevalence rates of sensitization in 2010 of <1.6% in Denmark (12) and 2.1% in Germany (13). Moreover, a time trend analysis from the Information Network of Departments of Dermatology was recently published, in which patch test results from 2002 to 2010 and 84,733 patients indicated a slight decrease in sensitization, particularly during the last few years (14).

The Scientific Committee on Consumer Safety concluded, in its opinion on fragrance allergens in cosmetic products, based on all available data, that the risk of sensitization by exposure to HICC is high, and that the use of HICC in consumer products is not considered to be safe (15). However, is the inclusion of HICC 5.0% pet. as a separate patch test substance in a baseline series justified

© 2014 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd Contact Dermatitis, 70, 183–192
when FM 2 is present? In the article from 2008, it was stated that ‘HICC in pet. at 5.0% w/w fulfills the requirement of a contact sensitizer to be included in a baseline series’ (9). The generally accepted requirements are that the substance is common in the environment, has a contact allergy rate above 0.5–1.0% in routinely tested dermatitis patients, and produces reliable patch test results with a high degree of clinical relevance, and minimal adverse effects (16). At that stage, there were no published reports on simultaneous and parallel patch testing with FM 2 and HICC, so it was not known to what extent there was simultaneous reactivity or not. However, some publications have recently addressed this topic. In the aforementioned German study, patch testing with HICC in addition to FM 2 was performed as part of the baseline series, and 108 patients sensitized to HICC were diagnosed who would have been missed if only FM 2 had been tested. These 108 patients represented 12.9% of those sensitized to HICC and 0.3% of the total test population (3). Furthermore, in a Belgian study in which HICC and FM 2 were tested simultaneously in 3401 patients, only 6 were positive to HICC alone, that is, 0.2% of the tested population or 10.3% of those allergic to HICC (17). Considering these data and our data in this study of > 10 000 patients, the inclusion of HICC 5.0% in the baseline series seems to be surplus to requirements, as our detection rate is only 0.2% better in the whole tested population of > 10 000 dermatitis patients, a figure too low to merit its inclusion as a separate patch test substance in the Swedish baseline series according to the present recommendations for such series (16). Our recommendation regarding the Swedish baseline series is therefore to consider having this patch test preparation removed, and perhaps this consideration is also valid for the European baseline series. We also strongly advise that FM 2-positive patients should be patch tested with HICC 5.0% pet. and with the other individual FM 2 ingredients, which should also be tested at twice the concentration of that in the mix. Also, FM 1-positive patients should be tested with FM 1 ingredients, to facilitate avoidance of exposure to the specific allergen, instead of going ‘fragrance-free’. It is, moreover, essential to continue to monitor the prevalence of contact allergy to HICC and other fragrance allergens, which requires testing with the individual ingredients.

References

1 Frosch P J, Pirker C, Rastogi S C et al. Patch testing with a new fragrance mix detected additional patients sensitive to perfumes and missed by the current fragrance mix. Contact Dermatitis 2005: 52: 207–215.


6 Geier J, Brusch J, Schnuch A, Lessmann H, Pirker C, Frosch P J, for the Information Network of Departments of Dermatology (IVDK) and the German Contact Dermatitis Research Group (DVG). Lyral has been included in the patch test standard series in Germany. Contact Dermatitis 2002: 46: 295–297.


9 Bruze M, Andersen K E, Goossens A. Recommendation to include fragrance mix 2 and hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral®) in the European baseline patch test series. Contact Dermatitis 2008: 58: 129–133.


12 Heisterberg M V, Menné T, Johansen J D. Contact allergy to the 26 specific fragrance ingredients to be declared on cosmetic products in accordance with the EU cosmetics directive. Contact Dermatitis 2011: 65: 266–275.


