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Patch Testing with Formaldehyde 2.0% in Parallel with 1.0% by the Swedish Contact Dermatitis Research Group

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MATERIALS AND METHODS

Seven dermatology clinics (Malmö, Lund, Gothenburg, Uddevalla, Örebro, Stockholm, Umeå) took part in the study in which the majority of members of the Swedish Contact Dermatitis Research Group participated. A total of 2,122 dermatitis patients were tested during the time period January 1–December 31, 2011. There were 1,424 women, mean age 44.3 years (range 10–94 years) and 698 men, mean age 44.7 (range 12–86 years). In all departments except Lund the baseline series was purchased from Chemotechnique Diagnostics (Vellinge, Sweden). In Lund the baseline series was from Mekostest (Vitaflö Scandinavia AB, Gothenburg, Sweden). During the entire study, the baseline series thus included formaldehyde 2.0% (w/v) and 1.0% (w/v) aqua (0.60 mg/cm² and 0.30 mg/cm², respectively). Formaldehyde 37% (w/w) aqua was bought from Acros Organics (Morris Plains, NJ, USA) and used for preparing the formaldehyde patch test solutions. All formaldehyde patch test solutions were made up at the Department of Occupational and Environmental Dermatology in Malmö, Sweden and sent out to participating departments every 2 months. The solutions were kept in glass containers (13 ml) with Teflon caps and kept in the refrigerator when not used for patch testing. The following formaldehyde-releasing preservatives were included in the baseline series: diazolidinyl urea 2.0% (w/v) aqua in all departments except Lund, which tested this preservative in petrolatum (pet.), and quaternium-15 1.0% (w/w) pet. in all departments except Lund, which tested this as part of the Mekostest.

The test technique for the 4 test preparations described here used Finn Chambers (diameter 8 mm) (Epitest Oy, Tuusula, Finland) on Scanpor tape (Norgesplaster A/S, Vennesla, Norway) in all centres except Uddevalla, which used IQ Ultra chambers on a high quality hypoallergenic surgical tape (Chemotechnique Diagnostics). The patch testing personnel placed 20 mg of each petrolatum test preparation into each Finn Chamber when using these (4). In all centres a micropipette was used when testing liquid test solutions of formaldehyde, which enables exact dosage (15 µl in each Finn Chamber (5) and 20 µl in IQ Ultra chambers). Patch tests were removed after 2 days and read after an additional day or 2 according to ICDRG criteria (6). A 2nd reading was done 7 days after application of patches. A dermatologist read all patch tests in all centres except Umeå on
both days, while in Umeå a trained nurse did the 1st reading and a dermatologist the 2nd one. The minimal criterion for an allergic reaction is erythema and infiltration covering the whole tested area. Additionally, there may be papules and/or vesicles. Reactions consistent with an allergic nature but where the minimal criterion was not present (e.g. erythema only) were judged as doubtful. Reactions that lacked the morphology consistent with an allergic nature and had a different morphology (e.g. cigarette-paper-like shiny surface) were judged as irritant.

The formaldehyde content was analysed in the test preparations by means of the 2,4-dinitrophenylhydrazine method (7). The detection limit was 0.00005% formaldehyde.

Statistics

The McNemar test (2-tailed) was used to compare the number of positive reactions to formaldehyde 2.0% and 1.0%. Fisher’s exact 2-tailed test was used to compare the contact allergy rate in males and females. The differences were considered significant when \( p < 0.05 \).

RESULTS

A summary of patch test reactions to formaldehyde is given in Table I. Of 2,122 patients (67.1% females) 77 (3.6%) reacted to either 1.0% or 2.0% formaldehyde or both. Seventy-two out of 2,122 (3.4%) were diagnosed with contact allergy to formaldehyde by patch testing with 2.0% and 40 (1.9%) were diagnosed with contact allergy to formaldehyde by patch testing with 1.0% (\( p < 0.001 \)). Only 5 patients (0.2%) reacted positively to 1.0% without reacting to 2.0%. Between participating clinics the proportions of cases reacting to formaldehyde varied. For formaldehyde 1.0%, the lowest proportion was 0.6% and the highest 4.1%. For formaldehyde 2.0%, the range was 0–9.7%. The ratios between cases found it was found that consecutive patch testing with formaldehyde 2.0% and 40 (1.9%) were diagnosed with contact allergy to formaldehyde by patch testing with 1.0% without reacting positively to formaldehyde (Table I).

The formaldehyde content in the patch test solution 2.0% was found to be 1.9% whereas the formaldehyde content in the test solution 1.0% was found to be 0.9%.

DISCUSSION

A few previous studies have compared simultaneous testing with 1.0% and 2.0% formaldehyde (1, 2, 8). In one of them (8) neither the amount of test preparation nor the technique used for applying the solutions are explicitly stated. However, in 2 recent studies, in which exact amounts of test preparations were used, i.e. the same dose/area each time by means of a micropipette, it was found that consecutive patch testing with formaldehyde 2.0% aqua detects significantly more reacting individuals compared to 1.0% aqua (\( p < 0.001 \)) (1, 2). These results are supported by the present study.

In the present multicentre study the variation between participating clinics regarding the proportion of cases having contact allergy to 2.0% formaldehyde was 10-fold, whereas the variation was 7-fold for 1.0% positives. We have no explanation to these variations, e.g. why there were no allergic individuals found in Umeå and almost 10% allergic patients found in Örebro. All centres were instructed to use the ICDRG criteria when...
reading the patch tests, so differences in reading tests should be minimised. It is possible that the indication for patch testing was different, although this was not scrutinised further. Furthermore, the proportion of additionally found allergic cases with 2.0% when comparing 1.0% and 2.0% showed a 3-fold variation. Despite these variations the overall result demonstrates that significantly more cases are found when patch testing with 2.0% than with 1.0%. Furthermore, as mentioned before, a significant number of patients who react to 2.0% but not to 1.0% have been shown to develop dermatitis when exposed to a formaldehyde-containing moisturiser (3).

It is reported in the literature that formaldehyde contact allergy is more common in women than in men, and formaldehyde is a significant allergen in women with hand eczema (9). The explanation to higher allergy rates in women is said to be associated with the usage of cosmetics and household products (9, 10). In our study, when looking at the difference in detected cases testing 1.0% formaldehyde, no sex difference was seen. However, when looking at the cases detected with 2.0% there is a significant sex difference (p = 0.0069, Fisher’s exact test, 2-tailed) and also when looking at the increase in number of detected cases that were negative to 1.0% and positive to 2.0% formaldehyde (p < 0.001, Fisher’s exact test, 2-tailed). This is an interesting finding and may reflect different exposures in women and men, as a lower exposure concentration may lead to a weaker contact allergy (11). As women seem to have weaker contact allergies (i.e. requiring higher concentrations of patch test substance for a positive reaction) we may wonder if women are sensitised through cosmetics and toiletries containing lower concentrations of formaldehyde. On the other hand men may have been sensitised through exposure to industrial products such as paints and metal working fluids, which then probably contain higher concentrations of formaldehyde, and hence get stronger contact allergies.

One may argue that formaldehyde should be tested even higher than 2.0%. However, testing 3.0% gave a high yield of irritant reactions despite exact dosage, which makes it impossible to use (1).

In our study, few additional contact allergies to the 2 formaldehyde releasers were detected, i.e. <0.5% for each of the 2 (Table S1). This raises the question whether quaternium-15 and diazolidinyl urea should be present in the Swedish baseline series.

In earlier studies (1, 2) it was demonstrated that positive test reactions to formaldehyde can appear later than on day 3 or 4 after test application, why a late reading is important in order not to miss this important contact allergy. Our study confirms earlier results, showing that a 2nd late reading is important when patch testing with formaldehyde, as is also the case for many other allergens (12–15).

Recently, a recommendation to include formaldehyde 2.0% aqua in the European baseline patch test series was published (16). Results from that study are much the same as ours. Formaldehyde is a ubiquitous allergen and it is therefore of utmost importance to detect contact allergy to this preservative. We therefore aim at removing 1.0% formaldehyde from the Swedish baseline series and adding 2.0% aqua to it instead. It should also be emphasised that irritant reactions are virtually not seen when using a micropipette for the appropriate dosing to a specific chamber.

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