

Formaldehyde and formaldehyde releasers: How much avoidance of cross-reacting agents is required?

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We investigated whether or not individuals who are allergic to formaldehyde and various formaldehyde-releasing preservatives must avoid exposure to another closely related formaldehyde-releasing allergen to which they were patch test negative. We found that in over 86% of cases a broad restriction of all formaldehyde-releasing preservatives was not required if the patch test was negative. Usually the patch test is predictive of which materials need to be totally avoided. Restriction of exposure to all of the formaldehyde-releasing preservatives may be overly restrictive.

Key words: cosmetics; cross-reaction; diazolidinyl urea; formaldehyde; preservatives. © Blackwell Munksgaard, 2004.

Accepted for publication 19 May 2004

Preservatives and fragrances are the two most common sources of contact dermatitis due to cosmetics (1). Some of the most problematic preservative allergens are formaldehyde and formaldehyde-releasing agents, including quaternium-15, imidazolidinyl urea, 2-bromo-2-nitropropane-1,3-diol, diazolidinyl urea and DMDM hydantoin (2). When one of these allergens is identified as a cause of allergic contact dermatitis, some recommend that all should be avoided, which can be very limiting. The necessity to be this restrictive has not been studied. Accurate data that evaluate cross-reactivity patterns and frequency of reactions between formaldehyde and formaldehyde-releasing agents are lacking (3).

The actual threshold of response to formaldehyde has been debated by several authors (4). Some authors have concluded that the threshold for response was 250 p.p.m. (4); however, Jordan et al. (5) reported 1 case in which a mere 30 p.p.m. in a skin care product caused dermatitis. Many skin moisturizers contain these preservatives in concentrations below the threshold levels studied by patch testing, which raises the possibility that the actual use of such a product might be harmless in some circumstances.

Materials and Methods

The aim of this study was to test whether individuals allergic to 1 formaldehyde-releasing preservative by patch test criteria, and/or formaldehyde

itself, must avoid the use of moisturizer that is preserved with a chemically unrelated formaldehyde-releasing preservative. Individuals who had undergone diagnostic patch testing and were found to be allergic to formaldehyde or to formaldehyde-releasing preservatives were eligible for enrolment. This group of individuals was restricted further in that the specific patch tests to diazolidinyl urea had to be negative, as the test material was chosen to contain this preservative. It is customary within the North American Contact Dermatitis Group to test diazolidinyl urea in both aqueous and petrolatum vehicles, and both tests had to be negative to qualify for this project.

These individuals were given a moisturizer (Keri Sensitive Skin moisture therapy[®], Bristol-Myers-Squibb, New York, NY, USA) to apply to the antecubital fossa twice a day for 2 weeks. This is a repeat open application test (ROAT), which is a standard test for establishing the relevance of patch tests (6). This moisturizer was preserved with diazolidinyl urea (0.2% concentration), and the individuals specifically had not reacted to both aqueous and petrolatum patch tests to 1% diazolidinyl urea. Development of visible dermatitis at the site of application was considered a positive response and terminated the applications. If no response developed after 2 weeks of applications, the test was considered negative.

During visit 1, the study design, risks and benefits were discussed with the subjects and informed consent was signed and witnessed. The subjects were instructed to apply the lotion to their antecubital fossa twice a day (except in 1 case the application was to the postauricular sulcus, due to dermatitis near the antecubital fossa). During visit 2, which was 2 weeks from the initial application of the lotion, patients returned for evaluation. Grading was based on the following scale: positive reaction, any erythema, oedema, vesiculation or itching; and negative reaction, no appreciable changes from visit 1.

Subjects were discontinued if they developed a reaction to the test moisturizer. Such an individual was considered to be a completed protocol patient and was recorded as a positive test, regardless of the number of days or applications which might have occurred.

Results

15 individuals met the criteria for inclusion and were able to comply with the study requirements. These individuals had a +, ++ or +++ reaction to the agent. Two individuals had reactions at some point in the 2-week trial. 1 subject had a definite positive reaction after 7 days. Another patient noted transient erythema on day 3 and again on day 14. 13 (87%) of the patients had no reaction at all. The pattern of patch test reactions to formaldehyde-releasing and formaldehyde-related chemicals identified for the subjects enrolled in this study is seen in Table 1.

The 1 patient who had a truly positive ROAT was retested to diazolidinyl urea 1% aqueous and

also 1% in petrolatum. She was now reactive to the aqueous test, but not to the petrolatum test. Her initial diazolidinyl urea results had been negative to both.

Discussion

Products that we ingest or apply should be microbe-free and safe. Hence, preservatives were invented as early as the nineteenth century. Many products contain formaldehyde-releasing preservatives. However, some individuals cannot tolerate formaldehyde and formaldehyde-releasing products. Formaldehyde and formaldehyde-releasing agents are found in shampoos, paper products, cosmetics and industrial biocides (2).

Once sensitized, it is thought that a patient may react to formaldehyde and to all of its various releasers. To gain some insight into how frequently reactions occurred among these compounds (formaldehyde, quaternium-15, imidazolidinyl urea, diazolidinyl urea, DMDM hydantoin, ethyleneurea melamine-formaldehyde resin), we reviewed the reactions seen at Ochsner Foundation Clinic from 1996 to 2002. There were 219 patients who reacted to either formaldehyde or a formaldehyde-releasing preservative. Only 7 individuals reacted to all 6 substances. Another 25 individuals reacted to 5 members of the formaldehyde family, 31 reacted to 4, 27 to 3, 53 to 2 and 76 (35%) were positive to only 1.

The range of concentration of formaldehyde that will cause a reaction is a subject of some debate. Flyvholm et al. (4) have designated 250 p.p.m. as the general lower limit for formaldehyde reactivity, whereas Jordan et al. (5) have

Table 1. Patterns of formaldehyde reactivity

Age/Sex	Formaldehyde-releasing allergens						Formaldehyde-related allergens		Use test
	1	2	3	4	5	6	7	8	
59/Male	+	-	-	-	-	-	-	-	-
67/Female	+	+	-	-	-	+	-	-	+
58/Male	+	+	-	-	+	-	-	-	-
41/Female	-	-	-	-	+	-	-	-	-
41/Male	+	-	-	-	-	-	-	-	-
42/Female	-	-	-	-	+	-	-	-	-
64/Male	-	-	-	-	+	-	-	-	day 3, day 14 transient erythema
78/Female	-	-	-	-	+	-	-	-	-
67/Male	-	+	+	+	+	-	-	-	-
70/Female	+	-	-	-	-	-	-	+	-
75/Female	-	+	-	-	-	-	-	-	-
64/Male	+	+	-	-	-	-	-	-	-
46/Female	+	+	-	-	-	-	-	-	-
75/Male	-	+	-	+	-	-	-	-	-
62/Female	-	+	-	-	-	-	-	-	-

1, formaldehyde; 2, quaternium-15; 3, DMDM hydantoin; 4, imidazolidinyl urea; 5, 2-bromo-2-nitropropane-1,3-diol; 6, ethyleneurea melamine-formaldehyde resin; 7, p-tert-butylphenol-formaldehyde resin; 8, tosylamide/formaldehyde resin.

stated that as little as 30 p.p.m. can cause a reaction. The frequency with which co-reactions occur among the formaldehyde family of preservatives, even though they may be chemically quite distinct, argues for the release of formaldehyde as the basis for the co-reactions, which would seem to suggest that a very low threshold of reactivity is common.

Quaternium-15, an odourless, colourless preservative, is very effective against organisms such as *Pseudomonas*. At a concentration of 0.1%, 100 p.p.m. of formaldehyde is found in quaternium-15 (2). When one is formaldehyde positive, quaternium-15 is the most common allergen to which coallergy is observed (3). Furthermore, a concomitant formaldehyde allergy is $\times 15$ more likely in those with an allergy to quaternium-15 (7). Imidazolidinyl urea releases only 1/8 as much formaldehyde as quaternium-15 and is very effective against yeasts and moulds. A 2% solution of imidazolidinyl urea releases 90 p.p.m. of formaldehyde. At concentrations of 0.03–0.2%, imidazolidinyl urea is the weakest of the formaldehyde-releasing preservatives (3). 2-Bromo-2-nitropropane-1,3-diol at a concentration of 0.1% can cause allergic contact dermatitis. Shampoos contain 10–15 p.p.m. (5). A concomitant reaction to formaldehyde is increased by a factor of 9 (7). Diazolidinyl urea at concentrations of 0.1–0.5% inhibits gram-positive and gram-negative bacteria, yeasts and moulds. DMDM hyantoin is used at concentrations of 0.5–2.0%.

If the concentration of formaldehyde that is released by formaldehyde-releasing preservatives is below the threshold of reactivity for virtually all formaldehyde-sensitive patients (somewhere between 30 and 250 p.p.m), it would seem unnecessary to require avoidance unless cosensitization to the whole molecule of the formaldehyde-releasing agent has occurred. It is clear from the data in Table 1 that sensitivity to formaldehyde is not a requirement for sensitivity to a formaldehyde-releasing preservative. This was the case for 8 of our 15 subjects.

In all but 1 of our subjects, it would be reasonable to restrict only those products that actually contain the specific formaldehyde-releasing preservative to which they were patch test positive. The 1 individual who had a clearly positive ROAT was found to be sensitive to diazolidinyl urea on subsequent testing. It is possible that the

initial test for diazolidinyl urea (in both aqueous and petrolatum vehicles) was a false-negative, just as the second diazolidinyl urea in petrolatum proved to be. This may be an example of the 'twinkling back' syndrome, in which variable results occur due to fluctuations in local factors that modify the threshold of reactivity (8). It could also be argued that the possibility of such false-negative reactions would be a sufficient justification for being more restrictive than the patch tests results actually require. This decision involves both philosophical considerations and a judgement about the amount of risk that is acceptable. For most people, a broad restriction on the entire class of formaldehyde-releasing agents may not be necessary, if the individual has been tested to the related agents and found to be negative. In other words, the results of the patch tests outweigh theoretical cross-reactions.

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