

Concomitant contact allergy to methylchloroisothiazolinone/methylisothiazolinone and formaldehyde-releasing preservatives

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It is well recognized that formaldehyde-releasing preservatives show frequent cross-reactions with each other and formaldehyde, based to a large extent on the quantity of formaldehyde released and the initial molecule (1). The likelihood that preservatives not releasing formaldehyde would show any concomitant reaction appears not to have been previously investigated. We looked into this possibility in the biocide preservatives contained in the British Contact Dermatitis Society (BCDS) baseline series.

Method

Nine centres across the UK using the BCDS database participated in a data-sharing exercise, agreeing to pool anonymized data including patient

demographics and patch-testing results for the BCDS baseline series (2). In total, 6948 patients between 2004 and 2005 underwent patch testing with readings at D2 and D4 according to International Contact Dermatitis Research Group criteria. Preservative allergens included in the baseline series over this period remained unchanged (formaldehyde 1% aq, paraben mix 16% pet., quaternium-15 1% pet., methylchloroisothiazolinone/methylisothiazolinone 0.01% aq, 2-bromo-2-nitropropane-1,3-diol 0.25% pet., imidazolidinyl urea 2.0% pet., diazolidinyl urea 2.0% pet., methyltribromo glutaronitrile 0.3% pet., chloroxenol 0.5% pet.).

Results

In total, 142 patients tested positive to formaldehyde (2% of those tested). The frequencies of sensitization for the other allergens were: quaternium-15 2%, methylchloroisothiazolinone/methylisothiazolinone 2%,

Table 1. Simultaneous positive reactions to preservatives by percentage, significance calculated using Fisher's exact test and Bonferroni correction for false positives. Intensity of colour responds to magnitude of association.

Independent	Dependent							
	Form	Quat	Bron	Imid	Diaz	MBDGN	PCMX	MCI
	Form	100% 53% p<0.0001	10% p<0.0001	23% p<0.0001	30% p<0.0001	3% p=0.019	1% p=0.307	15% p<0.0001
	Quat	59%	100% 9% p<0.0001	23% p<0.0001	30% p<0.0001	2% p=0.161	0% p=0.721	19% p<0.0001
	Bron	17%	13%	100% 8% p<0.0001	10% p<0.0001	8% p<0.0001	0% p=0.803	22% p<0.0001
	Imid	53%	47%	12%	100% 75% p<0.0001	7% p=0.005	0% p=0.853	10% p=0.002
	Diaz	55%	49%	11%	60%	100% 5% p=0.010	0% p=0.820	12% p<0.0001
	MBDGN	7%	4%	10%	5%	5%	100% 0% p=0.822	6% p=0.067
	PCMX	6%	0%	0%	0%	0%	0%	100% 12% p=0.050
	MCI	16%	17%	13%	4%	7%	3%	1% 100%

Form = formaldehyde, Quat = quaternium-15, Bron = 2-bromo-2-nitropropane-1,3-diol, Imid = imidazolidinyl urea 2.0%, Diaz = diazolidinyl urea, MBDGN = methyltribromo glutaronitrile, PCMX = chloroxenol, MCI = methylchloroisothiazolinone/methylisothiazolinone.

2-bromo-2-nitropropane-1,3-diol 1.3%, imidazolidinyl urea 0.9%, diazolidinyl urea 1.2%, methyldibromo glutaronitrile 1.1% and chloroxylenol 0.2%. The simultaneous reactions between the preservatives are illustrated in Table 1. This demonstrates the percentage of those with a positive reaction to each preservative (independent column) having another to an allergen within that group. Results for a concurrent positive with formaldehyde can be seen as follows: quaternium-15 75/142 (53%, $P < 0.0001$); imidazolidinyl urea 33/142 (23%, $P < 0.0001$); diazolidinyl urea 42/142 (30%, $P < 0.0001$); 2-bromo-2-nitropropane-1,3-diol 14/142 (10%, $P < 0.0001$); methylchloroisothiazolinone/methylisothiazolinone 22/142 (15%, $P < 0.0001$); methyldibromo glutaronitrile 4/142 (3%, $P = 0.019$); chloroxylenol 1/142 (1%, $P = 0.307$). A similar pattern of reactivity was evident with quaternium-15 positive patients: 9% reacting to 2-bromo-2-nitropropane-1,3-diol ($P < 0.0001$) but 19% to methylchloroisothiazolinone/methylisothiazolinone ($P < 0.0001$). Significance was calculated using Fisher's exact test and survived stringent Bonferroni correction to reduce false positives due to multiple data values.

There was no obvious difference in proportions of females or site between the group containing simultaneous formaldehyde-related and non-related positives; the hand was the commonest location for symptoms. The proportions of strong (+++,+++)/borderline positive (+) readings were similar and did not account for the pattern seen.

Discussion

It is apparent that the number of simultaneous positive reactions to methylchloroisothiazolinone/methylisothiazolinone and to formaldehyde or to quaternium-15 is statistically significant and greater than the number of reactions to 2-bromo-2-nitropropane-1,3-diol [recognized to have the lowest cross-reactivity of the formaldehyde-releasers as it does not release formaldehyde at physiological pH (3)] It is also substantially greater than the simultaneous reactions to chloroxylenol and methyldibromo glutaronitrile (non-formaldehyde releasers) which were not significantly linked. This is an unexpected finding and the reason for this correlation is

unclear. There is no apparent structural similarity between the chemicals, and previous work has shown there is not even cross-reaction between the chlorinated and unchlorinated isothiazolinone compounds (4). The relationship could be based on linkage of use in similar product types such as cosmetics and toiletries. However, other non-formaldehyde preservatives have an identical spectrum of distribution and do not show the same association.

References

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