

Contact sensitivity to preservatives in the UK, 2004–2005: results of multicentre study

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Preservative sensitivity in the UK was last assessed in 2000. Given the changes in preservative usage, we have re-evaluated our patch test data in order to detect any changes in the trend of sensitization. The results of patch testing using the extended British Contact Dermatitis Society Standard series were collected from 9 dermatology centres in the UK. Positive reactions to each of 10 preservative allergens were captured together with the MOAHFLA indices for each centre. In total, 6958 patients were tested during the period 2004–2005. The current data were compared with previously published data. Formaldehyde and methylchloroisothiazolinone/methyl-isothiazolinone have the highest positivity rates at 2.0% and chloroxylenol the lowest at 0.2%. Parabens mix has the highest irritancy rate. Compared with the UK data in 2000, the positivity rate of imidazolidinyl urea ($0.02 < P < 0.05$) has significantly increased and that of methyldibromo glutaronitrile has significantly reduced ($P < 0.001$).

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From 1997, there have been 10 preservative allergens in the British Contact Dermatitis Society (BCDS) standard screening series. Preservative sensitivity in the UK had been assessed in 2000 and the results published in 2003 (1). The results demonstrated an increasing rate of positive reactions to methyldibromo glutaronitrile (MDGN), probably reflecting a rising use of this preservative in the cosmetic industry. Wilkinson et al. reported a similar but more dramatic increase in the incidence of positive patch test reactions to MDGN across several centres in Europe, from 0.7% in 1991 to 3.5% in 2000 (2). Evidence of an increasing rate of sensitization led the European Union (EU) to order prohibition of MDGN in leave-on products in 2003. In February 2007, the EU Member States voted to prohibit MDGN from rinse-off products, as no safe use level could be established.

Given the changes in preservative usage, it is important to reassess how patterns of sensitization may have changed since the earlier studies.

Patients and Methods

Patients undergoing patch testing as part of the investigation for contact dermatitis in 9 UK centres were routinely tested to the extended BCDS Standard series as described in the earlier publication (1). This series includes 10 allergens that can be categorized as preservatives or biocides, as shown in Table 2.

Standard patch testing procedures were followed with allergens supplied by Chemotechnique (Malmö, Sweden) or Trolab (Reinbek, Germany) applied either on Finn chambers[®] or on IQ chambers according to local practice. Patch tests were removed after 2 days, and reactions were scored on D2 and D4 according to the International Contact Dermatitis Research Group criteria. Positive reactions were assigned to one of the 3 relevance categories (current, past, and uncertain) according to the patient's exposure history and, where possible, to improvement when allergen avoidance was achieved. Patch test reactions regarded on morphological features as being caused by

Table 1. The following are the results % positive and total tested divided by sex

Allergens	Male	Female
Formaldehyde 1% aq.	1.4% (3117)	2.4% (6230)
Parabens mix 16% pet.	1.2% (2960)	0.9% (5913)
Quaternium-15 1% pet.	1.0% (3119)	2.3% (6242)
MCI/MI 0.01% aq.	1.2% (3111)	1.9% (6234)
2-bromo-2-nitropane-1,3-diol 0.25% pet.	1.1% (3119)	1.3% (6242)
Imidazolidinyl urea 2% pet.	0.7% (3120)	1.0% (6240)
Diazolidinyl urea 2% pet.	0.9% (3120)	1.4% (6242)
MDGN 0.3% pet.	1.5% (2849)	1.1% (5620)
Chloroxylonol 0.5% pet.	0.3% (3120)	0.3% (6243)

aq., aqua; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone; MDGN, methyldibromo glutaronitrile; pet. petrolatum.

irritancy were also recorded. The results collected in each department on the BCDS database before being transferred to a single database for ease of analysis.

A MOAHFLA index (percentage of Male, Occupation, Atopic dermatitis, Hand dermatitis, Facial dermatitis, Leg dermatitis, Age > 40) for each centre was also derived from the same database.

We have analysed the combined data from 2004 and 2005. For each allergen, the percentage of patients was calculated together with the 95% confidence intervals. These data were compared with the data published in 2000 (1); the differences were analysed using the chi-squared test.

Results

In total, 6958 patients were tested with a female to male ratio of 2:1. The ages of the patients follow a normal distribution, with a median age of 40 years. Proportionately, more female than male patients gave positive reactions to formaldehyde and the formaldehyde-releasing preservatives (quaternium-15, imidazolidinyl urea, diazolidinyl

urea, and 2-bromo-2-nitropropane-1,3-diol), and methylchloroisothiazolinone/methyl-isothiazolinone (MCI/MI) demonstrating the same sex difference (Table 1). The differences were not statistically significant. Marginally, more males gave positive reactions to MDGN, and this difference was not statistically significant. For patients with currently relevant positive test results, the most commonly affected area is the hand, followed by the face, in both sexes.

Combining the results from all centres (Table 2) shows that formaldehyde and MCI/MI have the highest rate of positive reactions at 2.0% and chloroxylonol the lowest at 0.2%.

Of 139 patients positive to formaldehyde, 73 are positive to 1 or more of the 4 formaldehyde releasers tested: quaternium-15 (75 positive), imidazolidinyl urea (33 positive), diazolidinyl urea (42 positive), and 2-bromo-2-nitropropane-1,3-diol (14 positive).

Compared with the previous data (Table 3), the positivity rate of imidazolidinyl urea ($0.02 < P < 0.05$) has significantly increased and the rate for MDGN ($P < 0.001$) has significantly decreased.

The MOAHFLA index for each centre is shown in Table 4.

The recording of irritancy data shows inconsistency, with 3 centres recording no irritant reactions to any of the preservative allergens. In the remaining 6 centres, parabens mix (benzylparaben, butylparaben, ethylparaben, methylparaben, and propylparaben) has the highest irritancy rate (Table 5).

Discussion

The results show that female patients are more likely to be allergic to formaldehyde, quaternium-15, MCI/MI, 2-bromo-2-nitropropane-1,3-diol, imidazolidinyl urea, and diazolidinyl urea; none of which achieve statistical significance

Table 2. Centre-specific and combined rates of positive reactions for BCDS preservatives

Allergen name	Centre									Mean (95% CI)
	1	2	3	4	5	6	7	8	9	
Formaldehyde 1% aq.	2.2	2	0.6	1.6	3.5	2.7	2.5	4.4	1.3	2.0 (1.3–2.8)
Parabens mix 16% pet.	0.2	1.1	0.2	0.6	2.8	0.8	1.4	0	0.8	0.8 (0.3–1.4)
Quaternium-15 1% pet.	1.5	2.2	1.5	1.6	4.2	1.6	1.6	2.2	0.8	1.9 (1.2–2.6)
MCI/MI 0.01% aq.	2.2	3.1	1.2	0.9	2.8	2.9	2	2.5	2.2	2.0 (1.5–2.5)
<i>p</i> -chloro- <i>m</i> -cresol 1% pet.	0.5	0.5	0.3	0.4	0.4	0.2	0.8	0.6	0.3	0.4 (0.3–0.5)
2-bromo-2-nitropane-1,3-diol 0.25% pet.	0.5	3.2	1.3	0.9	1.2	1.8	0.8	1.1	0.3	1.3 (0.7–1.9)
Imidazolidinyl urea 2% pet.	0.8	0.6	0.3	1.1	2.1	1.2	0.9	1.4	0.3	0.9 (0.5–1.3)
Diazolidinyl urea 2% pet.	0.9	1.4	0.3	1.5	1.4	0.4	1.2	2.2	0.8	1.1 (0.8–1.4)
MDGN 0.3% pet.	1.3	2.1	0.7	0.4	0.9	1.2	2	2.2	0.5	1.1 (0.7–1.5)
Chloroxylonol 0.5% pet.	0.1	0.4	0	0.3	0.2	0	0.5	0.8	0.3	0.2 (0.1–0.3)

aq., aqua; BCDS, British Contact Dermatitis Society; CI, confidence interval; MCI/MI, methylchloroisothiazolinone/methylisothiazolinone; MDGN, methyldibromo glutaronitrile; pet. petrolatum.

Table 3. Comparison between rates of positive reactions in 2000 and 2004–2005

Allergen name	Combined rates for 2000 from Britton et al.	Combined rates for 2004–2005	2000 rates versus 2004–2005 rates, <i>P</i> values
Formaldehyde 1% aq.	2.1	2.0	$P > 0.5$
Parabens mix 16% pet.	1.1	0.8	$0.1 < P < 0.5$
Quaternium-15 1% pet.	1.3	1.9	$0.05 < P < 0.1$
MCI/MI 0.01% aq.	2.4	2.0	$0.1 < P < 0.5$
<i>p</i> -chloro- <i>m</i> -cresol 1% pet.	0.6	0.4	$0.1 < P < 0.5$
2-bromo-2-nitropane-1,3-diol 0.25% pet.	0.8*	1.3	$0.05 < P < 0.1$
Imidazolidinyl urea 2% pet.	0.5	0.9	$0.02 < P < 0.05$
Diazolidinyl urea 2% pet.	0.7	1.1	$0.05 < P < 0.1$
MDGN 0.3% pet.	2.4	1.2	$P < 0.001$
Chloroxylenol 0.5% pet.	0.4	0.2	$0.05 < P < 0.1$

aq., aqua; MCI/MI, methylchloroisothiazolinone/methyl-isothiazolinone; MDGN, methyldibromo glutaronitrile; pet. petrolatum.

*Patch test concentration 0.5%.

Table 4. MOAHFLA index (Percentage of Male, Occupation, Atopic (any manifestation), Hand dermatitis, Face dermatitis, Leg dermatitis, Age > 40)

	Centre								
	1	2	3	4	5	6	7	8	9
Male	35	32	32	34	33	35	32	32	34
Occupational	11	16	11	11	10	18	13	20	16
Atopic	43	49	43	31	31	35	55	37	38
Hand	32	35	27	35	38	38	40	45	34
Face	28	26	14	25	18	19	35	17	16
Leg	11	8	10	9	12	7	14	6	6
Age > 40	56	61	55	54	51	58	62	57	54

(Table 1). This perhaps reflects the more prevalent use of preservative-containing products in women. In either sex, where a result is interpreted as of current relevance, the hand is the most common primary site followed by the face. These results are consistent with previous published data, where the hand was involved in two thirds of all cases of contact dermatitis (3). The involvement of the hand in dermatitis is predictable in terms of its impaired barrier function as a result

of frequent exposure to irritants and is also the major point of contact of allergens with the skin.

Formaldehyde and MCI/MI remain the most frequently positive preservative allergens in our patch test series. Formaldehyde is a ubiquitous allergen found in many products. It can be combined with other chemicals or compounds to form resins and is released in low concentration by quaternium-15, imidazolidinyl urea, diazolidinyl urea, and 2-bromo-2-nitropropane-1,3-diol. The frequency of allergic positive reactions was reported to be between 2% and 3% in the series by Schnuch et al. and our rate for 2004–2005 falls within this range (4). MCI/MI is found in toiletries and cosmetic products and is also implicated in occupational allergy. Its positivity rate has remained steady at around 2–2.5% over a 10-year period in Europe (2). Likewise, the rates of positive reactions for both formaldehyde and MCI/MI have not changed significantly compared with that of our previous data.

In contrast, the positivity rate for MDGN has decreased significantly from 2.4% in 2000 to our current rate at 1.1%. The reason for this change is unclear; it has arisen too soon after the change in EU regulations for this to have had an impact on the results.

Table 5. Numbers of irritant reactions (combined results of 9 centres)

Allergen name	Total tested	Irritant reactions
Formaldehyde 1% aq.	6948	12
Parabens mix 16% pet.	6957	25
Quaternium-15 1% pet.	6957	1
MCI/MI 0.01% aq.	6940	9
<i>p</i> -chloro- <i>m</i> -cresol 1% pet.	6956	4
2-bromo-2-nitropane-1,3-diol 0.25% pet.	6956	12
Imidazolidinyl urea 2% pet.	6956	4
Diazolidinyl urea 2% pet.	6958	3
MDGN 0.3% pet.	6957	5
Chloroxylenol 0.5% pet.	6957	7

aq., aqua; MCI/MI, methylchloroisothiazolinone/methyl-isothiazolinone; MDGN, methyldibromo glutaronitrile; pet. petrolatum.

The tendency for female patients to show greater reactivity to preservatives is not shared by chloroxylenol, parabens mix, or MDGN. In the case of MDGN, more males than females are positive on patch testing; this difference does not achieve statistical significance (confidence interval, 0.0012–0.0102; $P > 0.5$).

The significant rise in positive reactions to imidazolidinyl urea has not been found in earlier studies and monitoring of rates of positive reactions must continue in the UK and Europe to look for an emerging trend. The result in the current study is comparable with the rates found by Jacobs et al. and Wilkinson et al. (2, 5).

The MOAHFLA index shows remarkable consistency between centres in the proportion of female to male patients patch tested. All other elements of the index vary between centres and bear no consistent relationship with the rate of positive reactions to any of the preservatives.

The rates of positive reactions for all of the allergens studied vary between centres (Table 2), but there is no centre with an unusually high or low rate of positive reactions. Patch test interpretation may be a source of between centre variation, but other variables that need to be considered include patient demographics, referral patterns and selection bias, local expertise, and specialist service provision.

Conclusions

Our results demonstrated that the rates of positive reactions of preservative allergens are largely sta-

ble. Recorded positive reactions to MDGN have reduced significantly, but on the other hand the rate for imidazolidinyl urea has increased significantly. Continued monitoring of trends in allergic reactions to these preservatives is planned to give an early indication of any emerging trend in the level of sensitization to individual preservative allergens.

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