

Frequency of sensitization to common allergens: comparison between Europe and the USA

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Background: Previously, contact allergy to formaldehyde and quaternium-15 was found to be more prevalent in the United States than in Europe. No such data have been assessed for other contact allergens.

Objective: Determine any differences in frequencies of sensitization to contact allergens in the United States and Europe.

Methods: Literature study. Comparison of reported frequencies of sensitization to contact allergens routinely tested both in the United States and Europe in recent, large, multicentre studies. Because of the heterogeneity of studies and background parameters, statistical evaluation was not attempted.

Results: Major differences were found only for neomycin (USA 10.0–11.8%, mean 11.4%; Europe 1.2–5.4%, mean 2.6%). Most allergens had somewhat higher prevalence in the United States, with rates versus Europe ranging from 1.3 to 1.9.

Conclusions: Contact allergy to neomycin is much more prevalent in the United States. Stricter selection of patients for patch testing in United States tertiary referral centres may result in 50% more positive reactions compared to European studies.

Key words: baseline allergens; frequency of sensitization; Europe versus USA; routine testing © John Wiley & Sons A/S, 2010.

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Introduction

Contact allergy to formaldehyde and the formaldehyde-releaser quaternium-15 is much more prevalent in the United States than in Europe, with frequencies of sensitization of 8–9% for formaldehyde in the United States *versus* 2–3% in Europe and mean rates of 8.8% *versus* 1.1% for quaternium-15 (1, 2). The causes for these major discrepancies are unknown. Stricter indications for patch testing and selection of patients in the US tertiary referral centres may play a role. Here, we present the results of a literature study investigating whether such transcontinental differences in frequencies of sensitization also exist for other common contact allergens.

to all. The frequencies of sensitization to these substances were identified in authoritative, recent, large, multicentre studies. In a group of seven US (3–9) and nine European studies (10–18) chosen on the basis of these criteria, for each allergen the lowest, highest, median, and mean frequency of sensitizations for all studies together were noted or calculated. The data in these groups was compared and by dividing the US results by their European counterparts, US/Europe rates were calculated for all study allergens for the four (lowest, highest, median, and mean frequency of sensitization) parameters. Because of the heterogeneity of studies and background parameters, statistical evaluation was not attempted.

Materials and Methods

Baseline series used in major US and European centres were compared to identify allergens common

Results

We found 20 contact allergens routinely tested in the United States and in Europe. Formaldehyde

Table 2. Frequency of sensitization to common allergens in studies from European centres^{a,b}

Country	Europe 31 centres 2005–2006 4404–18559 (10)	Czech Republic 1997–2001 12058 (11)	IVDK 2001–2004 31973 (12)	Europe 26 centres 2004 1629–9988 (13)	Europe 17 centres 2002–2003 2384–9685 (14)	Finland 7 centres 2000–2002 6264–11876 (15)	Europe 10 centres 1996–2000 26210 (16)	Sweden 9 centres 2000 3790 (17)	UK 7 centres 2000 3062 (18)				
Allergen	Test conc. and vehicle	Frequencies of sensitization											
		Mean ^c	Lowest	Highest	Median	Mean ^c	Lowest	Highest	Median				
Fragrance mix I	8% pet.	7.2	5.8	8.8	7.6	7.1	6.9	9.7	10.7	7.9	5.8	10.7	7.2
Cobalt chloride	1% pet.	6.7	5.2	5.4	6.7	7.8	6.4	5.9	5.8	6.3	5.2	7.8	6.4
<i>Myroxylon Peveriae</i> resin	25% pet.	6.2	7.3	9.2	6.1	6.1	6.5	6.0	6.7	6.7	6.0	9.2	6.2
p-Phenylenediamine	1% pet.	3.9	2.0	4.0	4.1	3.3	2.0	3.9	3.0	3.1	2.0	4.1	3.3
Colophonium	20% pet.	3.6	2.9	4.7	3.8	3.6	3.4	4.0	5.2	3.9	2.9	5.2	3.6
Thiuram mix	1% pet.	2.3	2.1	2.6	2.6	2.1	1.2	3.2	3.5	2.4	1.2	3.5	2.3
MCI/MI	0.01% aq.	2.6	1.4	2.2	2.3	2.2	2.4	2.2	2.4	2.1	1.3	2.6	2.2
Lanolin alcohols	30% pet.	1.7	3.0	4.3	2.2	3.0	1.1	2.9	3.3	2.5	0.8	4.3	2.9
Neomycin sulfate	20% pet.	1.9	1.9	2.3	2.2	2.9	1.2	3.0	2.9	2.6	1.2	5.4	2.3
4-tert-butylphenolformaldehyde resin	1% pet.	0.9	0.5	1.2	1.4	1.5	1.0	1.3	1.0	1.1	0.5	1.5	1.2
Epoxy resin	1% pet.	1.3	1.9	1.4	1.1	1.3	1.2	1.3	1.2	1.3	1.0	1.9	1.3
Benzocaine	5% pet.	1.2	0.5	1.5	1.1	0.8	1.2	1.6	1.5	1.2	0.5	1.6	1.2
Sesquiterpene lactone mix	0.1% pet.	1.0	0.5		0.8	1.0	1.1	1.1	1.1	0.9	0.5	1.1	1.0
% patients with at least one positive reaction (range)		43 (31–62)	64		44 (25–60)	41 (26–64)							

IVDK: Informationsverbund Dermatologische Kliniken: multicentre study, Germany, Switzerland, Austria; MCI/MI: methylchloroisothiazolinone (and) methylisothiazolinone.

^aCrude, non age- and sex-adjusted (standardized) rates.^bFor more reliable comparison with the USA studies (all multicentre), only studies from Europe that are also multicentre are included.^cUnadjusted for sample size.

Table 3. Frequency of sensitization: comparison between USA and Europe

Allergen	Frequencies of sensitization									
	USA Lowest (%)	Europe Lowest (%)	Rate USA versus Europe Lowest	USA Highest (%)	Europe Highest (%)	Rate USA versus Europe Highest	USA Median (%)	Europe Median (%)	Rate USA versus Europe Median	Rate USA versus Europe Range
Fragrance mix I	9.1	5.8	1.6	11.7	10.7	1.1	10.9	7.2	1.5	1.1–1.6
Cobalt chloride	7.4	5.2	1.4	11.0	7.8	1.4	8.4	6.4	1.3	1.3–1.4
<i>Myroxylon Pereirae</i> resin	10.6	6.0	1.8	13.7	9.2	1.5	11.8	6.2	1.9	1.5–1.9
p-Phenylenediamine	4.5	2.0	2.3	6.0	4.1	1.5	4.9	3.3	1.5	1.5–2.3
Colophonium	2.0	2.9	0.7	2.8	5.2	0.5	2.5	3.6	0.7	0.5–0.7
Thiuram mix	3.3	1.2	2.8	6.9	3.5	2.0	4.5	2.3	2.0	1.9–2.8
MCI/MI	2.2	1.3	1.7	3.1	2.6	1.2	2.8	2.2	1.3	1.2–1.7
Lanolin alcohols	1.6	0.8	2.0	3.3	4.3	0.8	2.2	2.9	0.8	0.8–2.0
Neomycin sulfate	10.0	1.2	8.3	13.1	5.4	2.4	11.5	2.3	5.0	2.4–8.3
4-tert-butylphenolformaldehyde resin	1.3	0.5	2.6	2.0	1.5	1.3	1.8	1.2	1.5	1.3–2.6
Epoxy resin	1.6	1.0	1.6	2.7	1.9	1.4	1.9	1.3	1.5	1.4–1.6
Benzocaine	1.5	0.5	3.0	2.0	1.6	1.3	1.7	1.2	1.4	1.3–3.0
Sesquiterpene lactone mix	0.6	0.5	1.2	1.1	1.1	1.0	0.7	1.0	0.7	0.7–1.2

MCI/MI: methylchloroisothiazolinone (and) methylisothiazolinone.

and quaternium-15 were not studied further and nickel sulfate, potassium dichromate, mercapto-mix, mercaptobenzothiazole, and the paraben mix were excluded because their test concentrations were found not to be identical. The data of the US studies are shown in Table 1, and of the European studies in Table 2. The percentages of patients with at least one positive reaction varied from 41 to 44 in multinational European studies, 64 in the Czech study and from 65 to 71 in the United States. The rates USA/Europe for the various parameters (highest, lowest, median, mean) are shown in Table 3. For the lowest prevalence, rates varied from 0.7 (colophonium) to 8.3 (neomycin); for the highest prevalence from 0.5 (colophonium) to 2.4 (neomycin); for the median prevalence from 0.6 (colophonium, sesquiterpene lactone mix) to 5.0 (neomycin); and for the mean prevalence from 0.6 (colophonium) to 4.4 (neomycin). The rates for mean and median prevalence are virtually identical for all allergens. Looking at the rates for the mean prevalences, three (arbitrarily divided but more or less distinct) result groups can be identified: (1) slightly lower US rates (0.6–0.9) for colophonium, lanolin alcohols and sesquiterpene lactone mix; (2) somewhat elevated rates (1.3–1.9) for fragrance mix, cobalt chloride, *Myroxylon pereirae* resin, p-phenylenediamine, thiuram mix, 4-tert-butylphenolformaldehyde resin, methylchloroisothiazolinone (and) methylisothiazolinone (MCI/MI), epoxy resin and benzocaine; and (3) a strongly elevated rate (4.4) for neomycin sulfate.

Discussion

This study shows that – next to formaldehyde and quaternium-15 (1, 2) – contact allergy (*sensu stricto*: positive patch tests) to neomycin sulfate is far more prevalent in the United States. This can readily be explained by the fact that in the United States – contrary to in some European countries – topical neomycin is widely used. Not only can it be bought over-the-counter, but neomycin-containing preparations are also commonly prescribed by physicians, e.g. postoperatively for closed wounds. In 1992, 5.3% of patients treated with a neomycin-containing preparation for postoperative wound care after dermatologic surgery developed allergic contact dermatitis from neomycin allergy (19). It was concluded that neomycin-containing antibiotics should be avoided in postoperative wound care (19). *Post aut propter*, the sensitization rate in North American Contact Dermatitis Group (NACDG) studies has declined somewhat since then (Table 1), but the frequency of positive patch test reactions to neomycin still was 10% in the most recent 2005–2006 NACDG study

period (3). For the other allergens, the differences in frequencies of sensitization are (far) smaller. Only colophonium allergy is less prevalent in the United States and slightly so for lanolin alcohols and sesquiterpene lactone mix. Contact allergy to the other nine allergens is 30–90% more prevalent in the United States (mean rates 1.3–1.9).

How should these data be interpreted? Comparing prevalence data is complex because many parameters may influence the outcome of patch test studies. The patch test procedures in the United States and Europe are not identical but largely comparable (there are also differences between European centres). The number of allergens routinely tested in the United States is at least double ($n = 49$ – 65) of that in Europe ($n = 25$). This appears in most studies to result in a higher percentage of patients with at least one positive patch test reaction (65–71% versus 41–44% in multinational European studies), but it may also result in (often unidentified?) cases of excited skin syndrome and, consequently, false-positive reactions.

Another possible cause for the differences would, obviously, be different degrees of exposure to the allergens. Unfortunately, such data appear not to be available. We know that there is a stricter selection in the United States for patients to be patch tested. The numbers of patients in case-series are usually (far) smaller in the United States. In addition, the results presented in Table 1 all come from the members of the NACDG and the Mayo Clinic, all tertiary referral centres. This will without any doubt result in higher prevalence rates in the observed population. The extent to which this occurs cannot accurately be quantified, because, again, there are so many other variables. An, admittedly rough, estimation may show from Table 3. Leaving out the allergens where exposure probably plays a role (those with a mean rate United States *versus* Europe < 1 and neomycin), the average for the nine remaining allergens United States *versus* Europe is 1.53 for the mean rate and 1.54 for the median rate. Thus, we tentatively submit that the stricter selection of patients for patch testing in the United States in tertiary referral centres may result in approximately 50% more positive reactions than in comparable European studies and suggest that, when comparing such studies, the USA data should be adjusted accordingly.

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