

The outcome of 9 years of consecutive patch testing with 4,4'-diaminodiphenylmethane and 4,4'-diphenylmethane diisocyanate

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Summary

Background. Two outbreaks of allergic contact dermatitis caused by isocyanates at two companies in southern Sweden initiated a research project focusing on contact allergy to isocyanates. Within the project, there was an interest in determining how often contact allergy to the most common isocyanate, diphenylmethane-4,4'-diisocyanate (4,4'-MDI), occurred.

Objectives. To determine and compare the occurrence of contact allergy to 4,4'-MDI, its corresponding amine 4,4'-diaminodiphenylmethane (4,4'-MDA), and polymeric diphenylmethane diisocyanate (PMDI) in a Swedish and a Belgian study population.

Patients and method. The study population consisted of 6190 consecutively patch tested dermatitis patients: 5690 patients from Malmö, Sweden, and 500 patients from Leuven, Belgium. Patch test results were analysed and compared.

Results. None of the Belgian patients reacted positively to 4,4'-MDI, but 5 Swedish patients did. Contact allergy to 4,4'-MDA was more common in the Belgian patients than in the Swedish patients: 3.6% and 0.9%, respectively. This could possibly be explained by the fact that the prevalence of *p*-phenylenediamine allergy was higher in the Belgian population.

Conclusions. The prevalence of contact allergy to 4,4'-MDI, 4,4'-MDA and PMDI is not high enough to justify their inclusion in any baseline series. Isocyanate allergic individuals should be detected by aimed testing with isocyanate series and work materials.

Key words: contact allergy; 4,4'-diaminodiphenylmethane; diphenylmethane-4,4'-diisocyanate; 4,4'-MDA; 4,4'-MDI.

Introduction

In the early 2000s, two outbreaks of allergic contact dermatitis caused by isocyanates at two companies, one producing laminate flooring boards (1) and one

producing medical equipment (2), initiated a research project at the Department of Occupational and Environmental Dermatology that focused on contact allergy to these allergens. Exposure to these substances is mainly an occupational problem that occurs in workplaces where isocyanates or polyurethane products are manufactured and processed. However, there have also been reports describing isocyanate exposure in domestic settings (3–7). In January 2002, we started to consecutively patch test our dermatitis patients with diphenylmethane-4,4'-diisocyanate (4,4'-MDI) and its corresponding amine 4,4'-diaminodiphenylmethane (4,4'-MDA). 4,4'-MDI is the most commonly used diisocyanate in industry, with

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Table 1. Number of tested patients and positive reactions from consecutive testing with diphenylmethane-4,4'-diisocyanate (4,4'-MDI), 4,4'-diaminodiphenylmethane (4,4'-MDA) and polymeric diphenylmethane diisocyanate (PMDI)

	Supplier	Sweden			Belgium		
		Tested (n)	D 3/4		Tested (n)	D 3/4	
			Positive (n)	Frequency (%)		Positive (n)	Frequency (%)
4,4'-MDA 0.5% pet.	Chemotechnique Diagnostics	560	5	0.89	500	18	3.6
4,4'-MDA 0.25% pet.	Chemotechnique Diagnostics*	5130	31	0.60	0	–	–
4,4'-MDI 2.0% pet.	Chemotechnique Diagnostics	3527	4	0.11	500	0	0
4,4'-MDI 1.0% pet.	Chemotechnique Diagnostics†	528	1	0.19	0	–	–
PMDI 2% pet.	In-house test substance‡	596	2	0.34	0	–	–
PMDI 1% pet.	In-house test substance‡	528	1	0.19	0	–	–

*For a short period of time, the substance was purchased from Chemotechnique Diagnostics (Vellinge, Sweden) at a concentration 0.5% pet. and then diluted in pet. to 0.25% at our own department. Later, it was directly purchased at the lower concentration from Chemotechnique Diagnostics.

†For a short period of time, the substance was purchased from Chemotechnique Diagnostics (Vellinge, Sweden) at a concentration 1.0% pet. and then diluted in pet. to 0.50% at our own department. Later, it was directly purchased at the lower concentration from Chemotechnique Diagnostics.

‡617P21-Hardener for 617H37 PEDILEN from Otto Bock Scandinavia AB (Norrköping, Sweden).

applications in areas such as the production of soft and rigid foam, coating adhesives, elastomers, and lacquers. 4,4'-MDA is used as a catalyst in the production of polyurethane, and has been proposed to be a marker for diphenylmethane diisocyanate (MDI) contact sensitization (8, 9). Indeed, it has been suggested that 4,4'-MDI might be a poor representative of the products to which patients are, in fact, exposed, because technical-grade isocyanate products are often used in industry. Technical MDI products, often referred to as polymeric MDI (PMDI), generally contain a complex mixture of isocyanates in which 4,4'-MDI predominates, followed by oligomers containing predominantly three to six aromatic rings, as well as smaller amounts of oligomers containing a higher number of rings (10). It has also been shown that petrolatum preparations of PMDI are more stable and more homogeneous than preparations of 4,4'-MDI (11). Therefore, PMDI was tested alongside 4,4'-MDI over a period of 2.5 years. In order to compare regional differences in allergy frequencies, patch testing with 4,4'-MDI and 4,4'-MDA was also conducted in Leuven, Belgium over a 1-year period.

Methods and Materials

Study population

The study population consisted of 6190 consecutively patch tested dermatitis patients: 5690 at the Department of Occupational and Environmental Dermatology, Skåne University Hospital, Malmö, Sweden, from January 2002 to December 2010, and 500 at the Department of

Dermatology, Katholieke Universiteit, Leuven, Belgium, from January to December 2005 (Table 1).

Patch testing

Patch test preparations of 4,4'-MDI, 4,4'-MDA and PMDI were tested. The patch test concentrations varied over the period. The providers of the test materials and the concentrations, as well as the numbers of tested patients, are shown in Table 1. Patch testing of the patients followed the routine of the two departments. In Malmö, 20 mg (12) of each preparation was applied in 8 mm Finn Chambers® (Allerderm, Phoenix, AZ, USA) on Scanpor® tape (Norgesplaster A/S, Venne, Norway), and placed on the patient's upper back for 2 days; paired readings were performed on day 3 or day 4, according to the guidelines of the International Contact Dermatitis Research Group (13), as well as on day 7. In Leuven, the patch test technique with van der Bend® patch test chambers (van der bend, Brielle, The Netherlands) on Micropore® (Healthcare 3M, Borken, Germany) was used. Patch test chambers were removed after 2 days, and readings were performed on day 2 (exceptionally), day 3, or day 4.

Results

In Table 1, the patch test results from consecutive testing with 4,4'-MDI, 4,4'-MDA and PMDI are given. The Belgian patients reacted more frequently to 4,4'-MDA than the Swedish patients; however, none of the Belgian patients reacted positively to 4,4'-MDI, whereas 5 of the Swedish patients did. Table 2

Table 2. Concomitant reactions between 4,4'-diaminodiphenylmethane (4,4'-MDA) and four preparations containing para-amino compounds

	Sweden			
	No. of patients with a positive reaction	% of all 5690 patients tested	No. of patients also positive to 4,4'-MDA	% of 36 patients positive to 4,4'-MDA
<i>p</i> -Phenylenediamine	108	1.9	23	63.9
Textile dye mix*	100	1.8	17	47.2
Black rubber mix	35	0.62	5	1.9
Benzocaine	16	0.28	10	27.8
	Belgium			
	No. of patients with a positive reaction	% of all 500 patients tested	No. of patients also positive to 4,4'-MDA	% of 18 patients positive to 4,4'-MDA
<i>p</i> -Phenylenediamine	40	8.0	14	77.8

*In-house petrolatum test substance consisting of 0.3% Disperse Blue 106, 0.3% Disperse Blue 124, 1% Disperse Blue 35, 1% Disperse yellow 3, 1% Disperse Orange 1, 1% Disperse Orange 3, 1% Disperse Red 1, and 1% Disperse Red 17 (w/w).

shows concomitant reactions between 4,4'-MDA and four preparations containing para-amino compounds: *p*-phenylenediamine, textile dye mix, black rubber mix, and benzocaine.

Discussion

The test results showed that the frequency of positive reactions to 4,4'-MDA was higher in the Belgian population than in the Swedish population, with prevalences of 3.6% and 0.89%, respectively (Table 1). In previous reports, the prevalence of positive patch test reactions to 4,4'-MDA has varied greatly; recently, Liippo and Lammintausta (14) reported a prevalence of 1.1% when testing general dermatology patients, but figures have ranged from 0.8% to 8.5% (15, 16). The differences in prevalence between the Belgian and Swedish populations reported here probably result from the fact that positive reactions to 4,4'-MDA seem to be correlated with positive reactions to *p*-phenylenediamine, which were more common in the Belgian study population. On the basis of readings on day 3 or day 4, the overall incidence of *p*-phenylenediamine allergy was 8.0% in the Belgian patients and 1.9% in the Swedish patients (Table 2). In a study by Uter et al., the spectrum of cross-sensitivity when eight para-amino compounds were patch tested with readings on day 3 was investigated. 4,4'-MDA and *p*-phenylenediamine showed frequencies of 8.5% and 14.1%, respectively (17). Furthermore, it was shown that 66.7% of the patients with a positive reaction to 4,4'-MDA also reacted to *p*-phenylenediamine, and that 32.4% of the patients showing a positive reaction to *p*-phenylenediamine reacted to 4,4'-MDA. This corresponds well with the high concordance rates between *p*-phenylenediamine and 4,4'-MDA obtained from the

consecutive testing performed within the scope of this research. Of the Belgian patients with a positive reaction to 4,4'-MDA, 77.8% showed a concurrent reaction to *p*-phenylenediamine, and 35% with a positive reaction to *p*-phenylenediamine also reacted to 4,4'-MDA. The corresponding figures for the Swedish patients were as follows: 63.9% (with readings on day 3 or day 4) of those with a positive reaction to 4,4'-MDA reacted to *p*-phenylenediamine, and 21.2% of those with a positive reaction to *p*-phenylenediamine also reacted to 4,4'-MDA (Table 2). In agreement with the literature, there was also a high concordance between positive reactions to 4,4'-MDA and positive reactions to other para-amino compounds, as shown in Table 2; this has been attributed to the presence of the same impurities in both compounds, as well as to cross-reactivity resulting from the same metabolites (18–21). The exact mechanisms leading to the formation of common haptens are yet not fully understood. 4,4'-MDA is also used as a hardener in epoxy systems. In the Swedish population, 3 of 36 patients who reacted positively to 4,4'-MDA also reacted to epoxy resins based on bisphenol A and/or bisphenol F. However, no clinical relevance was found.

Five patients showing positive patch test reactions to 4,4'-MDI were detected with the baseline series. Three of these patients were exposed to isocyanates in their workplaces, as they worked with products based on PMDI, to which they also reacted on consecutive patch testing. The other 2 patients had no previously known exposure to MDI. As instability of 4,4'-MDI in the test preparations was discovered ~18 months following the start of the consecutive testing, it is possible that we failed to detect allergies in patients because of the concentrations in the preparations being too low (22). All patients who reacted

positively to 4,4'-MDI and PMDI also reacted positively to 4,4'-MDA, which has been reported to be an important marker for isocyanate allergy (8, 9). In this population, 1 patient with a relevant contact allergy to an isocyanate-based work product was detected because of a positive reaction to 4,4'-MDA.

In 1 of the 560 consecutively patch tested individuals, 4,4'-MDA was suspected as a cause of active sensitization, and the concentration was therefore lowered to 0.25%. In 2007, 5 years following the inclusion of 4,4'-MDI in the baseline series and after 2889 individuals had been tested, 2 patients were suspected of being actively sensitized by 2% 4,4'-MDI and/or PMDI. The corresponding batches were not analysed; hence, whether one of these batches contained a higher concentration than intended was not investigated. The patients were not re-tested with serial dilutions, and sensitization was suspected but never confirmed. However, as the testing was performed on consecutive patients, the test concentration was lowered to 1% as an extra precaution. Recently, the European Society of Contact Dermatitis recommended that the patch test concentration of 4,4'-MDI should be reduced to 0.5%

pet., corresponding to 200 µg/cm² (23). There might be a risk of false-negative reactions when using lower concentrations, especially as the isocyanate preparations are unstable. Therefore, we recommend that, if patch testing with the lower concentrations gives negative results, but there are strong clinical indications that 4,4'-MDI and/or 4,4'-MDA might be the cause of the patient's problems, the patch test concentrations can be increased.

To conclude, the prevalence of 4,4'-MDI, 4,4'-MDA and PMDI allergy is not high enough to justify inclusion in any baseline series (24). Individuals who are allergic to isocyanate should be detected by aimed testing with an isocyanate series containing sensitizing diisocyanates and corresponding amines, preferably supplemented with PMDI and their own work materials (25).

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