

Diaminodiphenylmethane (DDM): frequency of sensitization, clinical relevance and concomitant positive reactions

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Diaminodiphenylmethane (DDM) is an aromatic diamine used in the manufacture of rubber, plastics, diisocyanates, dyes and adhesives. It may cross-react with *para*-(amino)compounds. Allergic patch test reactions to DDM are relatively frequent, but their relevance is often difficult to detect. We report our experience in 6809 patients (4589 female, 2220 male, mean age 39.9±17.8 years) with suspected contact dermatitis patch tested during the period 1997–1999 by the North-East Italy Contact Dermatitis Group (NEICDG). A positive patch test to DDM was detected in 132 (1.9%) patients (88 female, 44 male, mean age 49.5±16.2 years). Eczema was mostly localized on the hands. The relevance was detected in 31 patients. A logistic regression analysis showed an association with patient's age (odds ratio 5.4 for age 30–59 years), absence of atopic diseases (odds ratio 3.1) and presence of leg ulcer (odds ratio 5). We found a highly significant correlation ($p<0.001$) between sensitivity to DDM and to *para*-phenylenediamine, Disperse Yellow 3, cobalt chloride, fragrance mix, benzocaine, paraben mix and primin. Positive patch test results to DDM were relatively frequent. The difficulty in detecting the relevance of these sensitizations may be related to the surprisingly high frequency of concomitant positive reactions to other allergens.

Key words: diaminodiphenylmethane; patch test; rubber; dyes; concomitant reactions; cross-reactions; *para*-(amino)compounds; relevance of patch test reactions. © Munksgaard, 2001.

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Diaminodiphenylmethane (DDM) is an aromatic diamine used as a hardener for epoxy resins, to prevent oxidation and ozone damage in rubber products, and in the production of synthetic textile fibers (Spandex) and polyurethanes. Exposure to DDM may occur in the manufacture of rubber, plastics, diisocyanates, dyes and adhesives. Workers primarily at risk are those employed in boat, automobile, electronic and electrical industries. DDM is also an intermediary in the production of germicides, insecticides, corrosion inhibitors and surfactants (1–3). Allergic patch test reactions to DDM are found in approximately 2–4% of patients tested, but the relevance of these positive reactions is often difficult to assess (3–6). Since DDM may cross-react with *para*-(amino)com-

pounds, some of these positive patch test reactions could reflect this cross-reactivity.

We report our experience with patch test reactions to DDM during the period between 1997 and 1999 in the North-east Italy Contact Dermatitis Group (NEICDG), considering in particular the concomitant positive reactions to other standard series patch test allergens.

Materials and Methods

A total of 6809 patients with suspected contact dermatitis underwent routine patch testing in the years 1997–1999. Patch tests were performed using Finn Chambers[®] on Scanpor[®]. All substances were applied on the upper back and removed after

2 days. The sites were examined on removal and 1 day after removal, according to the ICDRG guidelines. Only positive reactions of ++ and +++ grades were considered valid. For each patient, age, sex, occupation, date of patch test, localization of eczema and personal history of atopic diseases (i.e., atopic dermatitis, defined according to the criteria of Hanifin & Rajka (7), asthma and/or allergic rhino-conjunctivitis with at least 1 positive prick test to relevant aeroallergens) were recorded. The data were stored in a personal computer using the program Microsoft® Excel 97 SR-1, and subsequently statistically analyzed using the SPSS 9.0.1 for Windows statistical package. Results are expressed as mean $\pm$ standard deviation, unless otherwise specified. Comparison of means was made by Student's *t*-test. The ordinal data and association between positive patch test reactions to DDM and to other standard series allergens were analyzed using the Pearson χ^2 test and, in situations with low cell count, the Fisher exact test. Relative risk was calculated for the associations identified. A logistic regression model was applied to evaluate the influence of individual factors on the outcome of patch testing to DDM. Adjusted odds ratios describing the effect of each variable on the risk of being sensitized to DDM, while simultaneously controlling for the influence of all other factors in the model, are reported with their 95% confidence intervals. The explanatory variables included in the logistic regression model were the following: sex, age (3 groups: up to 29 years old, 30–59 years old and older than 60 years), personal history of atopic diseases (y/n), type of occupation (5 groups: student, houseworker, pensioners, workers as self-employed or employee and unemployed), hand eczema (y/n), leg ulcer (y/n). For all tests, $p < 0.05$ was assumed to indicate statistical significance. To account for the inflation of the type I error rate caused by multiple comparisons using Pearson χ^2 and the Fisher exact test, $p < 0.001$ (Bonferroni correction based on 29 possible comparisons) was used to indicate highly significant associations.

Results

Of the 6809 patients tested, 4589 (67.4%) were female and 2220 (32.6%) male. Their ages ranged from 1 to 94 years, with a mean age of 39.9 years (± 17.8). The largest group of patients (57%) was represented by workers (self-employees or employees), whilst 15.2% were houseworkers, 13.6% pensioners, 12.3% students and 1.9% unemployed. 1382 patients (20.3%) had a personal history of atopic diseases. 34 patients (0.49%) were patch tested to establish the presence of allergic contact dermatitis following the treatment of leg ulcers.

132 patients (1.9%) showed positive patch test reactions to DDM; however, considering also weak positive reactions (+), 213 patients (3.1%) showed sensitization to DDM. Out of these 132 patients, 88 (67%) were female and 44 (33%) male; sex ratio showed no statistical difference compared to the total of patients tested (χ^2 test).

The age of the 132 patients sensitized to DDM ranged from 18 to 84 years, and the mean age was significantly higher than the total group of 6809 patients tested (49.5 versus 39.9; $p < 0.0001$ with the Student *t*-test).

52 (40%) out of 132 patients had negative results after 2 days (D2) but positive results after 3 days (D3). In 30 (23%) patients the reactions were weak (+) at D2, but positive (++ or +++) at D3. Overall, 63% of the DDM-sensitized patients showed negative or weak reactions at D2.

The dermatitis was mostly localized on the hands alone (42 patients, 31.8%) or in combination with the face (8 patients, 6.1%). 31 patients (23.5%) had facial dermatitis only. Other localizations were lower limbs (30 patients, 22.7%), upper limbs (17 patients, 12.9%) and trunk (4 patients, 3%). 5 patients with a positive patch test to DDM and lower-limb dermatitis had been treated with elastic bandages for leg ulcer. Workers (self-employees or employees) represented 47.7% of DDM-sensitized patients, houseworkers 23.8%, pensioners 22.3%, students 3.1% and unemployed 3.1%. 8 patients (6%) out of 132 had a personal history of atopic diseases, significantly less than the total of patients tested (1382, 20.3%; $p < 0.01$).

In order to exclude possible interrelationships between various factors previously considered (sex, age, atopic history, occupation, localization of eczema), we performed a logistic regression analysis. The results derived from the logistic model are

Table 1. Adjusted odds ratio and 95%-confidence intervals for positive patch test reactions to DDM, derived from multivariate logistic regression models

Variables	<i>p</i> -value	Odds ratio	95% confidence intervals
male sex	ns		
age (years)			
<29	—	1	—
30–59	<0.01	5.4	1.8–15.7
>60	<0.01	3.1	1.3–7.2
occupation			
student	ns		
houseworker	ns		
pensioner	ns		
unemployed	ns		
worker	ns		
absence of atopic diseases	<0.05	3.1	1.2–7.8
hand eczema	ns		
leg ulcer	<0.01	5	1.5–16.3

Table 2. Jobs or products responsible for DDM definite or probable relevant sensitization in 57 patients

Definite relevance		Probable relevance	
job or product	no. patients	job or product	no. patients
spray painting	6	houseworker	10
elastic bandage for leg ulcer	5	laboratory technician	3
electrical insulating	4	glueing	3
plastics manufacturing	4	electrical industry worker	2
painting and glueing	3	shoe soles	2
boat industry worker	2	storeman	2
floor covering	1	modelling enthusiast	1
hearing aid manufacturing	1	painting	1
welding	1	school caretaker	1
polyurethane plastic moulders	1	spray painting	1
radio technician	1		
shoe manufacturing	1		
tyreman	1		

Table 3. Substances examined and concomitant positive reactions to DDM

Substances	Percent copositive	<i>p</i> -value	RR	95% confidence intervals
thiuram mix	1.5%	ns		
Myroxylon Pereirae (balsam of Peru)	6.9%	<0.05	2.5	1.3–5
carba mix	3%	ns		
potassium dichromate	6.9%	ns		
para-phenylenediamine	31.5%	<0.0001	24	16–36.3
lanolin alcohol	3.8%	<0.01	4.3	1.7–10.8
colophonium	2.3%	ns		
neomycin sulfate	3.8%	<0.05	3.1	1.2–7.8
IPPD	1.8%	ns		
ethylenediamine	2.3%	ns		
epoxy resin	2.3%	<0.05	5.3	1.5–17.6
mercaptobenzothiazole	0.8%	ns		
<i>p</i> -tert-butylphenol-formaldehyde resin	2.3%	ns		
Disperse Yellow 3	4.5%	<0.0001	8.5	3.5–20.6
cobalt chloride	12.9%	<0.0001	3.0	1.8–5.1
fragrance mix	12.2%	<0.0001	3.3	1.9–5.6
benzocaine	9.1%	<0.0001	44.3	20.3–96.8
paraben mix	4.5%	<0.0001	8.1	3.3–19.4
nickel sulfate	23.4%	ns		
Disperse Blue 124	2.3%	ns		
quinoline mix	0.8%	ns		
mercapto mix	0.8%	ns		
quaternium-15	0%	ns		
Euxyl K400	0.9%	ns		
thimerosal	4.5%	ns		
formaldehyde	0.8%	ns		
primin	8%	<0.001	4.3	2.1–8.7
Kathon CG	3.8%	ns		

Abbreviation: RR, relative risk.

shown in Table 1. Positive patch test reactions to DDM were significantly associated with patient's age (adjusted odds ratio 5.4 and 3.1 for patients aged 30–59 years and more than 60 years, respectively, compared to patients aged less than 30 years), absence of atopic diseases (adjusted odds ratio 3.1) and presence of leg ulcer (adjusted odds ratio 5).

Current or past relevance of positive patch test to DDM was detected in 31 patients (23.4%); in

26 patients (19.6%) the relevance was probable, as shown in Table 2. The relevance was unknown in 75 patients (57%).

The concomitant patch test positive reactions to other standard series allergens are listed in Table 3. We found a significant positive correlation ($p < 0.05$) between sensitivity to DDM and to Myroxylon Pereirae (balsam of Peru), lanolin alcohol, neomycin and epoxy resin. Highly statistically significant associations ($p < 0.001$) occurred with

para-phenylenediamine, Disperse Yellow 3, cobalt chloride, fragrance mix, benzocaine, paraben mix and primin.

Discussion

Allergic patch test reactions to DDM have been reported to be relatively frequent. The prevalence of positive patch test to DDM in our patients (1.9%) is slightly higher than the 1.7% found by Rudzki et al. (4), but definitely lower than that found by Jolanki et al. (3.4%) (3), Gailhofer et al. (3.57%) (5) and Storrs et al. (4.3%) (6). In an earlier study the frequency was surprisingly even higher (8.5%) (8). However, if we also evaluate weak positive reactions (+), the prevalence rises to 3.1%, a figure similar to previous studies. We found no correlation between a positive patch test to DDM and sex, in accordance with a previous study (4). DDM-sensitized patients were older (mean age 49.5 versus 39.9 years) and showed less frequently a personal history of atopic diseases than the total of patients tested. The logistic regression analysis confirmed that the absence of atopic diseases is independently associated with the risk of being sensitized to DDM and identified the age interval of 30–59 years as the age group with the higher risk (odds ratio 5.4). We are not aware of previous data confirming the significant association between sensitization to DDM and absence of atopic diseases or patient's age.

At D2, 40% of DDM-sensitized patients showed negative patch test results. If only 1 reading time is possible, D3 is optimal, though we cannot exclude that a D7 reading might increase the chance of detecting sensitization to DDM, as we do not perform this routinely.

The localization pattern most frequently developed in DDM-positive patients was hand dermatitis (37.9%), alone (31.8%) or combined with facial dermatitis (6.1%). Face alone was involved in 23.5% of the cases, whereas lower limbs (22.7%), upper limbs (12.9%) and trunk (3%) dermatitis were less frequently detected. The positive reactions associated with the latter 2 localizations were mostly not relevant. The logistic regression analysis showed that the risk of having positive patch test reactions to DDM was associated with the presence of leg ulcer (odds ratio 5): this data somehow suggests that the elastic bandages currently or previously used in the management of the ulcer might contain traces of DDM, which is widely employed in the production of rubber products and synthetic textile fibers.

The main problem concerning patients with allergic patch test reactions to DDM was to detect the relevance of the reactions. In our patients, the

relevance was definite in 23.4% of DDM-positive patients, and was only probable in another 19.6% of cases.

Some previous studies have pointed out the difficulty of detecting the relevance of patch test reactions to DDM, suggesting that most of these reactions could simply represent a cross-reaction with *para*-(amino)compounds (4, 9, 10). In our DDM-sensitized patients, concomitant positive reactions to other standard series allergens were surprisingly frequent. The association was statistically significant (<0.05 and <0.01) for Myroxylon Pereirae, lanolin alcohol, neomycin, epoxy resin and highly statistically significant (<0.001) for para-phenylenediamine, Disperse Yellow 3, cobalt chloride, fragrance mix, benzocaine, paraben mix and primin (Table 3).

Even though concomitant positive patch test reactions between DDM and substances included in the 1st group reached statistical significance ($p<0.05$), there is a high risk of spurious associations based on chance alone, since the type I error rate has been increased by multiple comparisons. However, it seems likely that, at least for epoxy resin, a true association may occur, since DDM is widely used as epoxy hardener and may thus produce cosensitization, concurrently but distinctly sensitizing individuals exposed.

Lowering the alpha value to 0.001 in order to avoid the risk of spurious associations (Bonferroni correction), 7 substances showed statistically significant concomitant reactions with DDM: para-phenylenediamine, Disperse Yellow 3, cobalt chloride, fragrance mix, benzocaine, paraben mix and primin.

Association between positive patch tests to DDM and to para-phenylenediamine has frequently been reported and represents the result of a true cross-reaction (2, 5, 8, 11). The relative risk of reacting to para-phenylenediamine in our DDM-sensitized patients was 24. This data is slightly lower than the figure found by Holness et al. (12) (relative risk 42).

Benzocaine is another *para*-(amino)compound that has been shown to cross-react with DDM (4, 11, 12). Of the 132 DDM-sensitized patients, 12 also reacted to benzocaine (9.1%), with a 44.3 relative risk. A similar value was reported by Holness et al. (12). Conflicting data are reported concerning cross-reactions between the parabens and the *para*-(amino)compounds (13–16); Marks & DeLeo (14) concluded that, for practical purposes, these cross-reactions do not occur. In our patients, however, we found a highly statistically significant association between sensitization to DDM and paraben mix: patients reacting to DDM had an 8.1 relative risk of reacting to paraben mix. This data

somehow suggests that a true cross-reaction may occur between parabens and *para*-(amino)compounds, as already hypothesized by others (13).

Disperse Yellow 3, a disperse dye belonging to the azo group, was found to be significantly associated with DDM (8.5 relative risk). Azo dyes are reported to cross-react with *para*-(amino)compounds (15, 17, 18). However, another azo dye that we used in our standard series, Disperse Blue 124, did not show any association with DDM. This is in agreement with Dooms-Goossens (19) and Menezes Brandão & Hausen (20), who found that none of the patients reacting to Disperse Blue 106 or Disperse Blue 124 reacted to a *para*-(amino)-compound (*para*-phenylenediamine). Seidenari et al. found that co-sensitization to *para*-phenylenediamine was more than 2× higher in Disperse Yellow 3-sensitized subjects (36%) than in Disperse Blue 124-sensitized patients (16%) (21). The lack of cross-reactivity between Disperse Blue 106 or Disperse Blue 124 and *para*-(amino)compounds is probably related to the presence of substituents of the amino group in the benzene ring, which might not easily be reduced to NH₂ (22). Disperse Yellow 3, belonging to aminoazobenzene group, like Disperse Red 1, Disperse Red 17 and Disperse Orange 3, is chemically different from Disperse Blue 106 or Disperse Blue 124, which are thiazol-azo-*para*-phenylenediamines, and thus likely react in a different way (22).

A statistically significant association was also found between sensitization to DDM and fragrance mix, although the relative risk of reacting to fragrance mix in patients who reacted to DDM was relatively low (3.3) compared to the other associations already shown (from 8.1 to 44). The cause of this association is uncertain. Edman (15) and Albert et al. (16) did not observe any association between fragrance mix and *para*-(amino)compounds such as *para*-phenylenediamine or benzocaine. However, in another study, 26% of 473 *para*-phenylenediamine-sensitized patients showed positive responses to fragrance mix (23). The substances included in the fragrance mix, in particular eugenol and isoeugenol, might share some metabolic derivatives with the *para*-(amino)compounds. There is some evidence that benzoquinone is at least 1 of the common intermediates in the cross-reactions of *para*-group aromatic haptens (24–26), and the same hapten could be an *in vivo* oxidation product of eugenol or isoeugenol (27, 28).

Another significant association was observed between DDM and primin. The relative risk of reacting to primin in patients who reacted to DDM was 4.3. Edman did not find any such association; moreover, he did not find any association between primin and other *para*-(amino)compounds (16).

Furthermore, Ingber et al. did not observe any specific pattern in the additional positive standard patch tests of 57 primin-sensitized patients (29).

Primin is a strong contact sensitizer, with the structure of a *para*-benzoquinone derivative. Our data suggest that a cross-reaction may occur between primin and *para*-(amino)compounds, since *para*-benzoquinone is a common oxidation product of these compounds (24–26), although in a previous study performed on 20 patients sensitized to primin, none of them showed positive patch test reactions to *para*-benzoquinone (30).

Our study also revealed a significant association between positive reactions to DDM and cobalt chloride, which could not easily be explained. Patients sensitized to DDM had a relative risk of 3 of reacting to cobalt chloride. Concomitant occupational exposure to DDM and cobalt chloride may occur in the paint industry, resin manufacture, ski industry and construction industry (14, 31, 32). However, since most of the positive reactions to DDM in our patients appeared to be simple cross-reactions, rather than the results of a true sensitization, cosensitization to DDM and cobalt chloride seems rather unlikely.

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