

Contact sensitization to 4,4'-diaminodiphenylmethane and to isocyanates among general dermatology patients

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Background: Diisocyanates and 4,4'-diaminodiphenylmethane (MDA) are industrial sensitizers. Occupational asthma is a risk among workers exposed to diisocyanates. Exposure may also lead to contact sensitization and allergic contact dermatitis.

Objective: The aim of this study was to determine the occurrence of contact sensitization to MDA and to diisocyanates among general dermatology patients.

Patients and methods: Patch testing with MDA was carried out in 1595 patients. Diphenylmethane-4,4'-diisocyanate (MDI) and toluene-2,4-diisocyanate (TDI) were tested in 1023 patients and isophorone diisocyanate (IPDI) and 1,6-hexamethylene diisocyanate (HDI) in 433 patients. The clinical data and sources of exposure are analysed.

Results: MDA reactions were seen in 17 (1.1%) patients and MDI reactions in 4 patients. Six MDA-positive patients reacted to *p*-phenylenediamine and two to epoxy chemicals. 5/10 of the TDI reactions were seen concurrently with reactions to MDI, MDA, HDI, or to IPDI. IPDI reactions were seen in eight patients and HDI reactions in two patients. Possible sources of exposure were traced in most patients, although the association with the current dermatitis was not apparent in all cases.

Conclusion: (Di)isocyanates may induce contact sensitization with or without allergic contact dermatitis.

Key words: 4,4'-diaminodiphenylmethane; allergic contact dermatitis; contact sensitization; diphenylmethane-4,4'-diisocyanate; toluene-2,4-diisocyanate. © Blackwell Munksgaard, 2008.

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Worldwide, there is enormous industrial use of isocyanates, reactive chemicals with a $-N=C=O$ containing functional group. Diisocyanates have two such groups and are commonly used to manufacture polyurethane. Construction, production of furniture, cars, electronics, and shoes represent examples of isocyanate uses. Isocyanate-induced occupational asthma is an important problem in general occupational medicine (1). Contact sensitization to (di)isocyanates is also a problem, and occupational risk assessment including routes and sources of exposure represents a continuous challenge in occupational dermatology.

Diphenylmethane-4,4'-diisocyanate (MDI) and toluene-2,4-diisocyanate (TDI) are the most com-

monly used diisocyanates in industry. Exposure to MDI, to 1,6-hexamethylene diisocyanate (HDI) or to isophorone diisocyanate (IPDI) has been described to cause sensitization and subsequent dermatitis in several areas of the construction industry (2–4).

4,4'-Diaminodiphenylmethane (MDA) is used as a catalyst in the production of polyurethanes, and it is an important allergen among patients with suspected diisocyanate allergy. MDA has also been considered as an indicator of MDI contact sensitization (2–4). Additionally, MDA is used to cross-link epoxy resins, and exposure to such resins may lead to sensitization (5) in the rubber industry, glues, and laminates. Positive

patch test reactions may be seen in association with allergy to para-amino compounds (6), reflecting cross-reactivity or non-specific concomitant reactivity.

We have analysed the occurrence of contact sensitization to MDA and to diisocyanates in Turku University Hospital Dermatology Clinic since 1997. The sources of sensitization and the relevance of reactions were determined.

Patients and Methods

From 1997 until June 2007, 7585 patients with suspected contact allergy were patch tested with the European baseline series of contact allergens in the Department of Dermatology, Turku University Hospital. Depending on the clinical history and the patients' individual exposure, additional series were used for testing including the isocyanate series provided by Chemotechnique Diagnostics (Malmö, Sweden) with MDA being tested on 1595 individuals, MDI and TDI on 1023 individuals, and HDI and IPDI on 433 individuals (Table 1). In addition to the clinical examination, an occupational history was always recorded. Finn Chambers[®] (Epitest Ltd Oy, Tuusula, Finland) on Scanpor tape (Norgesplaster A/S, Vennesla, Norway) were used, removed 2 days later (D2), and read and interpreted 1–3 days after the removal (D3, D4, or D5) according to International Contact Dermatitis Research Group (ICDRG) criteria. After the last reading, patients were requested to contact us in case of suspected new reactions, and an additional reading was then made.

Results

Prevalence of the positive patch test reactions to allergens in the isocyanate series varied from 0.4% to 1.8% of the tested patients (Table 1).

Reactions to MDA and MDI

Among the 17 patients with positive patch test reactions to MDA, 3 had concurrent reactions to MDI (Table 2). For patients 2 and 9, the localization of the dermatitis in exposed areas was evi-

dent and the sensitization had developed from obvious occupational exposure. Patient 15 was a student occasionally doing welding work in a shipyard; he gave up his job and his facial dermatitis did not recur. A concomitant TDI reaction was seen in one MDA-positive patient (patient 16) who was an electrician with hand dermatitis. Polyurethane exposure was the source of sensitization; he changed occupation and the dermatitis cleared.

Concurrent positive reactions to *p*-phenylenediamine (PPD) were seen in 6 cases of the 17 MDA-positive patients, and all of them had multiple contact sensitivities.

Patient 18 had reactions to MDI and TDI and had worked as a cleaner in a shipyard where polyurethanes were used. Although work-related sensitization was probable, hand dermatitis did not develop until later after methacrylate sensitization from artificial nails. The hand dermatitis persisted despite elimination of relevant exposures to the contact allergens.

Two patients with hand dermatitis were sensitized to MDA because of epoxy exposure in construction work. Six patients had positive MDA reactions without any other reactions to diisocyanates or to other known cross-reacting allergens.

Reactions to TDI, HDI, and IPDI

Positive patch test reactions to TDI were seen concurrently with reactions to IPDI (2), HDI (1), MDI (1), or to MDA (1) (Table 3). Five patients had a positive reaction to TDI without reactions to other isocyanates or to MDA. Five patients with TDI reactions had experienced facial skin symptoms. Although possible sources of sensitization could be traced in most patients, associations between exposure and symptoms were not demonstrated.

The patient with leg stump dermatitis (patient 10) reacted to TDI and HDI. The composition data of the materials used in the prosthesis did not identify these chemicals. He had dermatitis only in the leg stump, and the dermatitis slowly improved. The patient worked in a car light-producing company, and occupational sensitization was suspected.

Table 1. Patients tested and positive patch test reactions to allergens in the isocyanate series

Allergen	Concentration (vehicle)	Abbreviations	Patients tested (n)	Positive reactions (%)
Toluene-2,4-diisocyanate	2% (pet.)	TDI	1023	10 (1.0)
Diphenylmethane-4,4'-diisocyanate	2% (pet.)	MDI	1023	4 (0.4)
4,4'-diaminodiphenylmethane	0.5% (pet.)	MDA	1595	17 (1.1)
Isophorone diisocyanate	1% (pet.)	IPDI	433	8 (1.8)
1,6-hexamethylene diisocyanate	0.1% (pet.)	HDI	433	2 (0.5)

Pet., petrolatum.

Table 2. Clinical data of patients with positive patch test reactions to MDA and/or to MDI and concurrent reactions to TDI

Patients	Sex/age (years)	MDA	MDI	TDI	Other positive reactions	Skin/other symptom	Occupation	Relevance
1	M/49	1+	NT	NT	Black rubber mix, PPD, 4-aminoazobenzene, Ni, Co, potassium dichromate, diphenylthiourea	Hand and foot dermatitis	Shipman	Cross-reaction
2	M/18	2+	2+	0	Ni, perfume mix, <i>n</i> -octyl-isothiazolin-3-one Epoxy resin, tricresyl phosphate, 2-phenyl glycidyl ether	Hand dermatitis	Worker in bus construction Dental nurse Construction worker	Polyurethane filling
3	F/36	1+	0	0		Erythema, past dermatitis		Unknown
4	M/43	3+	0	0		Hand dermatitis		Epoxy coating
5	M/29	2+	0	0	Epoxy resin, bisphenol A glycidyl methacrylate, epoxy diacrylate, 2-phenyl glycidyl ether	Hand dermatitis	Construction worker	Epoxy glue
6	F/48	1+	NT	NT	PPD, 4-aminoazobenzene, disperse orange 3, Ni, Co, <i>N,N'</i> -diphenylthiourea	Foot dermatitis	Caterer on boat	Cross-reaction
7	M/54	2+	0	0	Methyltribromo glutaronitrile PPD, thiuram mix, perfume mix	Foot and hand dermatitis	Excavator driver	Shoes suspected
8	F/44	2+	0	0		General tingling	Scientist	Unknown
9	F/25	2+	1+	0		Hand dermatitis	Cabin construction worker	Glue
10	F/46	1+	0	0	PPD, black rubber mix, Ni, Co, hydroquinone Perfume mix, myroxylon pereirae	Hand dermatitis	Doctor	Cross-reaction
11	M/24	2+	0	0		Facial dermatitis	Construction worker	Cross-reaction
12	M/64	1+	0	0		Hand dermatitis	Plumber	Unknown
13	F/52	2+	NT	NT	PPD, Ni, caine mix	Facial dermatitis	Office worker	Cross-reaction
14	F/42	2+	NT	NT	PPD, caine mix, Ni, Co	Hand dermatitis	Office worker	Cross-reaction
15	M/26	2+	2+	0	Perfume mix	Facial, periorbital dermatitis	Ship construction worker	Polyurethane suspected
16*	M/33	2+	0	1+	Perfume mix, compositae mix	Hand dermatitis	Electrician	Polyurethane foam
17	M/63	1+	0	0	Hydroxyethyl methacrylate, methyl methacrylate, Ni	Foot dermatitis	Clergyman	Shoes suspected
18†	F/25	0	1+	1+		Hand dermatitis	Cleaner	Polyurethane suspected

Co, cobalt chloride; MDA, 4,4'-diaminodiphenylmethane; MDI, diphenylmethane-4,4'-diisocyanate; Ni, nickel sulfate; NT, not tested; PPD, 4-phenylenediamine; TDI, toluene-2,4-diisocyanate.

*Patient 15 in Table 3.

†Patient 16 in Table 3.

Table 3. Clinical data of patients with positive patch test reactions to TDI and/or to IPDI and/or to HDI

Patient	Sex /age (years)	TDI	IPDI	HDI	Other positive reactions	Symptoms	Occupation	Source
1	F/24	1+	0	0		Erythema (facial)	Electronic worker	Glue suspected
2	M/50	0	1+	0	Perfume mix	Hand dermatitis	Upholstering	Glue
3	M/46	2+	0	0	Ni	Hand and facial dermatitis	Metal worker	Coating chemicals suspected
4	M/23	0	1+	1+	N-(cyclohexylthio) phthalimide	Hand dermatitis	Printer	Printing chemicals suspected
5	F/48	0	1+	0	Quaternium-15	Erythema (facial)	Dentist	Unknown
6	M/51	0	1+	0	IPDA, epoxy resin, phenyl glycidyl ether, bisphenol A glycidyl methacrylate	Facial dermatitis	Construction	Cross-reaction
7	F/41	1+	0	0	Tosylamide/formaldehyde resin, methyltribromo glutaronitrile, tioconazole	Hand and facial dermatitis	Office work	Glue suspected (non-occupational)
8	F/48	1+	1+	0		Erythema (facial)	Electronic worker	Glue suspected
9	F/52	1+	0	0	Epoxy resin, colophonium, thiuram mix, Ni	Hand dermatitis	Construction worker	Glue suspected
10	M/26	2+	0	1+	N-octyl-4-isothiazolin-3-one	Leg stump dermatitis	Office work*	Polyurethanes suspected
11	F/47	1+	0	0		Hand dermatitis	Electronic worker	Glue suspected
12	M/66	0	1+	0	IPDA, epoxy resin	Hand and facial dermatitis	Construction worker	Cross-reaction
13	F/42	0	1+	0		Hand dermatitis	Metal worker	Coating chemicals suspected
14	M/36	2+	2+	0		Facial dermatitis	Iron scrapping	Unknown
15	M/33	1+	0	0	MDA 2+	Hand dermatitis	Electrician	Polyurethane foam
16	F/25	1+	0	0	Diphenylmethane-4,4'-diisocyanate 1+, methyl methacrylate, hydroxyethyl methacrylate, Ni	Hand dermatitis	Merchant and cleaner	Polyurethane foam suspected

HDI, 1,6-hexamethylene diisocyanate; IPDA, isophorone diamine; IPDI, isophorone diisocyanate; MDA, 4,4'-diaminodiphenylmethane; Ni, nickel sulfate; TDI, toluene-2,4-diisocyanate.

*Work in a car light factory.

Two patients with IPDI reactions had positive reactions to epoxy resin and IPDA. IPDI reactions were interpreted as cross-reactions.

In patients 1 and 8, patch test reactions to IPDI or to TDI appeared late on D7 and D10, respectively. These patients, however, had a history of possible exposure.

Periorbital and lip dermatitis were seen in a patient with positive patch test reactions to TDI and IPDI (patient 14). His work included flame cutting of scrap iron, he wore protective equipment occasionally, and he had no respiratory symptoms.

Discussion

In this study, we have assessed the occurrence of positive patch test reactions to MDA and to diisocyanates. In the Turku area, polyurethanes are used in a number of construction applications, for example sealing and insulation, as well as in electronic industries including mobile phone companies. Occupational history, putative allergen exposure evaluation, and the clinical appearance of symptoms were crucial factors when patients were selected to be tested with these chemicals. Occupational sources of sensitization were detected or suspected in a majority of our patients who generally were of working age (18–64 years, mean 41 years). Some of these patients were also studied for respiratory symptoms. Immunoglobulin E antibodies to isocyanates, however, were not detected in any patient.

Testing with a patient's own materials (4) or with more stable polymeric products has been suggested (7). Among this patient population, some cases of true allergy may have been missed because we were only able to test with commercial allergens. In addition, MDI test preparations have been reported to have lower than stated MDI concentrations (8).

Concomitant positive patch test reactions to MDI and MDA have been reported commonly (4, 5). Among our patients, 3/4 of the MDI-positive cases also reacted to MDA. Two shipyard workers reacted to MDI. One of them reacted concurrently to MDA and the other to MDI and TDI. In both cases, the particular source of sensitization in the shipyard remained obscure. Polyurethanes, however, are used in different phases of the ship construction, and putative occupational exposure might have been shown in patch tests with patients' own materials as suggested (4).

The source of the MDA sensitization remained unknown in three patients who did not have reactions to MDI or to other diisocyanates. Active sensitization with 0.5% MDA has been reported

(9). In our patients, the reactions were seen by D5. Patient 8 (Table 2), however, had a history of previous patch test application without test removal and interpretation in the clinic. She was not able to return to the clinic but reported one or more red itchy spots in the test area. In the repeated testing, MDA reaction was seen on D2. MDA has been suggested to be tested in 0.25% petrolatum, although some true positive reactions may be missed (10). A D7 reading might have shown an MDI reaction (10, 11).

According to our results, the prevalence of positive MDA reactions was 1.1%. This is similar to the previous data where positive reactions to MDA have been reported in 1.9% among Italian general dermatology patients (12) and in 0.8% among occupational dermatology patients (13). In two patients, MDA sensitization was because of epoxy resin exposure and subsequent sensitization, corresponding to earlier reports (5). One third of the MDA-positive patients had simultaneous PPD reactions suggesting of cross-reactivity (6). However, two patients with PPD reactions (patients 1 and 6 in Table 2) did not recall any PPD dermatitis, and foot dermatitis was the principal problem. PPD reactivity may have been secondary in those cases. Two MDA-positive foot dermatitis patients were probably sensitized from shoes (patients 7 and 17 in Table 2). Although the importance of MDA in shoe dermatitis has been questioned (14), it may have been a contributing factor for these patients.

In our patients, TDI and IPDI sensitivities were seen in combinations or alone and HDI elicited reactions together with TDI or IPDI. In one patient, a positive TDI reaction was seen concurrently with a positive reaction to MDI and another reacted to MDA and TDI. Simultaneous TDI and MDI reactivity has been reported (15, 16), although it may be infrequent. Sensitization to multiple diisocyanate chemicals seems to develop under certain circumstances where the type and extent of exposure are likely to play a role.

Among the TDI and/or IPDI reactors, facial symptoms were more common when compared with MDA and/or MDI reactors. The patients with concomitant reactions to TDI and IPDI had a history of occupational exposure. One of them had symptoms of airborne dermatitis in eyelids, lips, and periorbitally. Daily flame cutting of scrap iron materials may have caused sensitization. Vehicles contain polyurethanes, and heating in flame cutting might lead to airborne sensitization. Airborne dermatitis has also been reported in a patient with allergy to TDI and MDI (16). However, that patient was also sensitized to epoxy resins capable of inducing airborne symptoms.

Cross-reactivity between IPDA and IPDI was apparent for two of our patients reflecting sensitization to IPDA in epoxy systems as described (17).

The patient studied for leg stump dermatitis reacted to TDI, HDI, and to *n*-octyl-isothiazolin-3-one. The prosthesis did not contain TDI or HDI, and the stump dermatitis healed without changing the stump. The patient was employed as an office worker in a car light factory where polyurethanes and different adhesives are used. Thus, occupational sensitization appeared probable, although this patient had not had any other dermatitis.

IPDI and/or TDI reactions developed late in two cases. Although active sensitization to TDI has been reported (18), it was not probable because previous exposure was recognized.

Contact sensitization without related dermatitis has been reported to evolve following exposure to several chemicals (19, 20). As the use of MDA and diisocyanates is extensive in construction and various industries, patients with contact sensitivity to these chemicals are a particular challenge in general dermatology clinics. In addition to the risk of asthma, contact sensitization may develop without a related dermatitis.

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