

Contact allergy to methyldibromo glutaronitrile – data from a ‘front line’ network

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The preservative methyldibromo glutaronitrile (MDBGN) has caused an epidemic of contact allergy in Europe. However, most data concerning contact allergy comes from hospital departments of dermatology. As a part of the primary health care sector, Danish dermatologists in private practice provide the front line of care for patients with skin diseases. Data from this source may therefore better reflect trends in the general population than material from hospital departments of dermatology. In this study, the frequency of MDBGN allergy and the characteristics of patients seen by dermatologists in private practice were studied. In 1 year, 2146 patients were patch tested by the participating dermatologists from 4 clinics in various parts of Denmark. 5% (110) had positive patch tests to MDBGN, with no difference between the sexes. After adjustment was made for other background variables, multivariate analysis using logistic regression showed a significant association between hand eczema and MDBGN allergy (OR 2.5, $P < 0.001$). In 53 cases (52.4%), the patch test reaction to MDBGN was judged to be of current relevance. Creams and lotions accounted for 31% of the identified causative products and liquid soaps for 23%. It is concluded that contact allergy to MDBGN is frequent among patients seen by dermatologists in private practice. This is consistent with results from hospital departments of dermatology in Europe and indicates a general trend and ongoing epidemic in the general population. The significant relationship between hand eczema and MDBGN allergy is of concern, and the finding that wash-off products, especially liquid soaps, play a significant role in MDBGN allergy calls for a revision of the safety assessment of MDBGN in wash-off products.

Key words: antimicrobials; biocides; contact allergy; cosmetics; hand eczema; health care workers; liquid soaps; methyldibromo glutaronitrile; occupational; preservatives. © Blackwell Munksgaard, 2005.

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Methyl dibromoglutaronitrile (MDBGN) has been identified as a major cause of contact allergy in eczema patients tested at departments of dermatology in university hospitals throughout Europe (1). The question is whether this is because very severe and chronic cases are referred to these specialized units, or whether it is an expression of an ongoing epidemic in the population.

In 2003, the Danish Contact Dermatitis Group established a surveillance network comprising both hospital departments and dermatologists in private practice. In the Danish health care system, dermatologists in private practice are a part of the primary health care sector and are the first dermatologists to see patients with skin

disease. Hospital departments are defined as the secondary health care sector and see primarily selected cases referred by dermatologists in private practice or general practitioners. Information from dermatologists in private practice thus provides data better reflecting the epidemiology of disease in the population-base than data from hospital departments and may be a reasonable alternative to an actual general population study.

The purpose of this investigation was to examine the frequency of contact allergy to MDBGN among patients seen by dermatologists in private practice and to describe the characteristics and causative exposures of these patients.

Materials and Methods

A total of 2146 consecutive patients, 1418 women (66%) and 728 men (34%), with contact dermatitis were included in the study. Their basic characteristics are given in Table 1. The cases were seen in 4 dermatology clinics in various parts of Denmark, all members of the Danish Contact Dermatitis Group.

All patients were patch tested with MDBGN in addition to the European standard series. The MDBGN was tested in 0.3% in petrolatum (pet.), except in one clinic where Euxyl K 400 1.5% in pet. was used (0.3% MDBGN and 1.2% phenoxyethanol).

Patches were applied to the upper back using Finn Chambers[®] (Epitest, Tuusula, Finland) with filter discs affixed with Scanpor[®] (Norgesplaster A/S, Vennesla, Norway). The test was left for 2 days (D). Readings were performed on D3 and in some cases additionally on D2 and D7 using the ICDRG scale (2).

The responsible physician recorded the MOAHLFA index (3) and the relevance of the patch test reactions and identified sources of allergen exposure.

Statistics

The data was analysed using spss 12.0. The χ^2 test was used for univariate analysis. Multivariate analysis was performed using logistic regression (Table 2). MDBGN allergy was response variable, and the explanatory variables were sex, age (in 3 groups), atopic dermatitis (past or present), occupational disease, hand and/or facial dermatitis and leg ulcer/lower leg dermatitis, corresponding to the MOAHLFA index. All variables were recorded at the same time. The level of significance chosen was $P < 0.05$.

Results

110 of the 2146 patients (5.0%), 5.2% women and 4.9% men, $P > 0.05$, had positive patch tests to MDBGN. Univariate analysis showed no significant difference between patients with positive or negative patch tests to MDBGN with regard to present or previous atopic dermatitis, leg or facial dermatitis. A significant association was seen between hand eczema and MDBGN allergy ($P < 0.001$) and between MDBGN allergy and occupational skin disease ($P = 0.01$).

Multivariate analyses incorporating the above-mentioned variables as well as age (<30 years, 30–59 years, ≥ 60 years), showed only hand eczema to be significantly associated with MDBGN allergy as defined by patch test results. These results were unchanged when each of the reporting clinics were incorporated in the multivariate analysis. This means that all the clinics contributed equally to the result.

Occupational exposure, mainly among health care workers, accounted for 15 of 110 (14%) of the cases of MDBGN allergy.

In all clinics, MDBGN was the 3rd most frequent cause of contact allergy, surpassed only by fragrance mix (7.5%) and nickel (15.9%).

In 53 cases (52.4%), the reaction was judged to be of current relevance, and in 9 cases data were missing (Table 3). The relative distribution of the identified causative products is given in Figure 1.

Creams and lotions accounted for 31% of the identified products and liquid soaps for 23%.

Discussion

In this study, MDBGN allergy was seen in 5% of patients with contact dermatitis, patch tested by dermatologists in private practice. The data is consistent with results from hospital departments of dermatology in Europe (1, 4–6), and with

Table 1. Patient demographics

	MDBGN positive (%) <i>n</i> = 110	MDBGN negative (%) <i>n</i> = 2036	Total (%) <i>n</i> = 2146	<i>P</i> -value*
Sex (male)	36 (32.7)	692 (33.9)	728 (33.9)	n.s.
Occupational	15 (13.6)	144 (7.0)	159 (7.4)	0.01
Atopic dermatitis	10 (9.0)	251 (12.3)	261 (12.1)	n.s.
Hand eczema	57 (51.8)	653 (32.0)	710 (33)	<0.001
Leg eczema/ulcer	11 (10.0)	167 (8.2)	178 (8.2)	n.s.
Facial eczema	20 (18.1)	359 (17.6)	379 (17.6)	n.s.
Age				
<30 years	7 (6.3)	566 (27.7)	573 (26.7)	<0.001
30–59 years	69 (62.7)	1062 (52.1)	1131 (52.7)	
60 years and above	34 (30.9)	408 (20.0)	442 (20.5)	

* χ^2 test

MDBGN, methylidibromo glutaronitrile; n.s. not significant, $P > 0.05$.

Table 2. Logistic regression with methyldibromo glutaronitrile-allergy as response variable and the factors listed below as explanatory variables

	Odds ratio	95% Confidence interval	P-value
Sex (reference group)	0.9	0.6–1.3	0.50
Occupational	1.6	0.9–3.0	0.14
Atopic dermatitis	1.2	0.6–2.3	0.66
Hand eczema	2.5	1.6–3.9	<0.001
Leg eczema/ulcer	1.2	0.6–2.2	0.67
Facial eczema	1.2	0.7–2.0	0.44
Age			
<30 years (reference group)			
30–59 years	5.5	2.5–12.4	<0.001
60 years and above	9.2	3.8–21.8	<0.001

current hospital-based Danish data (7, 8). This means that the high frequencies reported are likely to be a general trend and indicate an ongoing epidemic in the general population.

There was an equal distribution of men and women among patients with contact allergy to MDBGN. This means that the exposures causing MDBGN allergy may be cosmetics and/or toiletries used equally by both sexes. This is in contrast to most other allergens, which are either predominant among women, e.g. nickel, or among men, e.g. epoxy resin.

Multivariate analysis with correction for other risk factors and confounders from the MOAHLFA index showed a significant correlation between hand eczema and contact allergy to MDBGN. A preponderance of hand eczema in MDBGN-allergic individuals has also been reported in recent case studies (7, 8). Most cases in which the source of exposure was identified were due to cosmetics and toiletries used at home or at work.

Most cosmetics inevitably come into contact with the hands, and some products are intended for application to the hands, e.g. liquid soaps and moisturizers. It is, however, exceptional that an allergen used in wash-off products causes hand eczema as the primary clinical manifestation. This

is an indication of the potency of MDBGN as an allergen as well as of too high a concentration of MDBGN in the products that it is used in.

A significant relationship between MDBGN allergy and occupational disease was demonstrated by univariate but not by multivariate analyses. Hand eczema and occupational disease are related. In the current study, hand eczema was shown to be a stronger risk factor for MDBGN allergy than occupational disease. Occupational disease accounted for 14% of the cases of MDBGN allergy, most of them among health care workers. Liquid soaps are used many times a day in the home or in some occupations in the workplace. The use concentration of MDBGN in liquid soaps is close to that found in moisturizers (7), and the frequent, routine use of liquid soaps may be a significant risk factor for MDBGN allergy. Elicitation studies have shown that just 2 daily applications of a liquid soap containing 0.1% MDBGN, the current highest permissible concentration according to the EU Cosmetic Directive, will elicit an allergic reaction in 37% of test subjects (9). Multiple daily applications with a low concentration of MDBGN have the same effect on elicitation as if the same total dose was applied once a day (10). This may be a

Table 3. Relevance of positive reactions to methyldibromo glutaronitrile and exposures

Relevance	Number of cases	Exposure type	Number of cases
Current relevance	53	Cosmetics	42
By history	33	Cream	13
		Shampoo	4
Patch/use test	2	Liquid soap	7
Ingredient labelling	18	Wash-off (comb)	2
		Wash-off + Stay-on	3
		Unspecified	10
		Make-up cream	1
		Hair gel/wax	2
Unknown/no	48		
Past relevance, only	0	Other (paint)	1
Relevance not given	9	Exposure not given	10

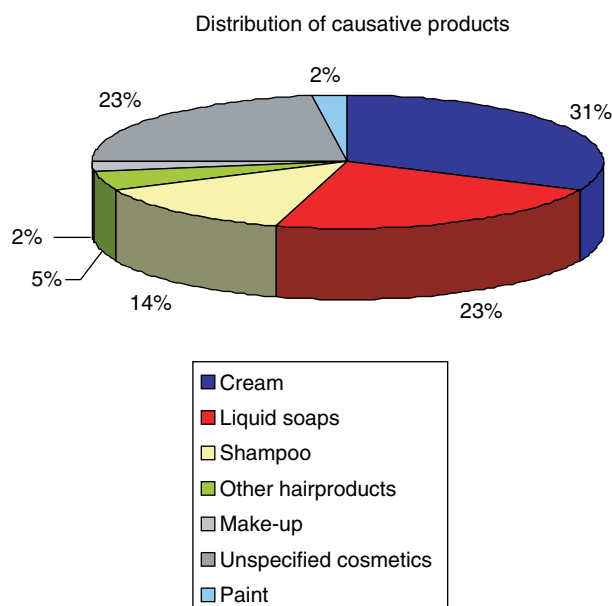


Fig. 1. Distribution of causative products.

consequence of accumulation of MDBGN in the skin. The risk of induction also depends on the number of exposures within a certain time frame (11). The combination of MDBGN and detergents such as those in liquid soaps has been shown to enhance skin reactions in sensitized individuals by a factor of 6.4 (12), which is in accordance with the concept of 'danger' signals produced by irritancy (13). Rinse-off products, e.g. liquid soaps or shampoos, have been identified as important sources of exposure (5, 8, 14–16). In an experimental study, a shampoo containing 200 p.p.m MDBGN was tested in sensitized individuals. At least 3 exposures per week were made, and no reactions were seen during a 9–12 week test-period (17). However, reactivity may depend on the frequency of application. In the risk assessment of wash-off products, it is necessary to take into account that some products, such as liquid soaps, may be used many times a day.

MDBGN has been banned from use in leave-on products, such as moisturizers, due to the high number of cases of MDBGN allergy in the European population. The clinical and epidemiological evidences in the current study show that the frequency of MDBGN allergy remains high and that wash-off products play a significant role in MDBGN allergy. The current safety assessment of MDBGN in wash-off products should therefore be revised.

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