

Patch testing with methyldibromo glutaronitrile, a multicentre study within the EECDRG

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Contact allergy to and allergic contact dermatitis from methyldibromo glutaronitrile (MDBGN) have frequently been reported. As there has been no agreement on which MDBGN test preparation to use, a study was initiated to help determine the optimal patch test preparation for MDBGN. 2661 consecutively patch tested patients at 11 test clinics representing 9 European countries participated. Petrolatum preparations with MDBGN at 1.0%, 0.5%, 0.3% and 0.1% were inserted in the standard series. Contact allergy rates were noted in the range 4.4–1.1% following decreasing test concentrations. Reactions not fulfilling all criteria to be classified as allergic reactions could represent either weak allergic or irritant reactions, and such reactions were noted in the range 8.2–0.5% with decreasing concentrations. A significant number of these reactions represented weak allergic reactions, as allergic reactions were obtained to higher patch test concentrations in the same individual. Morphologically irritant reactions were noted only for the highest test concentrations. In summary, the contact allergy rates and frequencies of doubtful and irritant reactions vary with the patch test concentration. The final decision on patch test concentration for MDBGN should not only rely on these factors but also include information on patch test concentrations required to diagnose individual cases with allergic contact dermatitis from MDBGN as well as results of repeated open application tests.

Key words: 1,2-dibromo-2,4-dicyanobutane; adverse reactions; allergic contact dermatitis; CAS 35691-65-7; contact allergy; European standard test series; Euxyl K400; methyldibromo glutaronitrile; preservative; Tektamer 38. © Blackwell Munksgaard, 2005.

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Preservatives are usually both low-molecular-weight substances and biologically active, so it is not surprising that many of them are contact sensitizers. Methyldibromo glutaronitrile (MDBGN) (1,2-dibromo-2,4-dicyanobutane) is the active ingredient in the preservative Tektamer 38 and it is together with 2-phenoxyethanol (1 : 4 ratio), the active ingredients in the preservative Euxyl K400, which was introduced on the market as an alternative to the sensitizer methyl-

chloroisothiazolinone/methylisothiazolinone partly because of no demonstrable sensitizing capacity in the guinea pig (1). Since the introduction, there have been reports of contact allergy to and allergic contact dermatitis from MDBGN in products such as lotions, moist toilet paper, ultrasonic gels, natural products, eye gels, hair mousse, hair conditioners, sunscreen creams, protective creams, abrasive cleansers, work cream, detergents and glues (2–18). Eventually, animal studies demonstrated MDBGN to be a sensitizer (19). To detect the allergenic property, a predictive test method with multiple topical applications had to be used (19). These reports

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strongly suggest that MDBGN should be included in the European standard patch test series. Furthermore, the significant increase in contact allergy rates in Europe demands preventive measures to be taken to diminish the problem (20, 21). Although agreeing upon MDBGN as an important sensitizer, there is no agreement on what test preparation to use to diagnose contact allergy to MDBGN. This study was therefore initiated to serve as an instrument together with other ones to define the optimal patch test preparation.

Materials and Methods

Patients

During January 2002–June 2002, 11 patch test clinics representing 9 European countries participated in the study. In these clinics, 2661, 977 males and 1684 females, consecutively patch-tested dermatitis patients took part.

Substances

MDBGN was kindly provided by Schülke and Mayr, Hamburg, Germany. From the same batch, MDBGN in petrolatum at 4 concentrations, 1.0% w/w, 0.5%, 0.3% and 0.1%, were made by and purchased from Chemotechnique Diagnostics, Malmö, Sweden.

Patch testing

9 clinics used the Finn Chamber technique with the chambers attached to Scanpor tape (Epitest, Tuusula, Finland) (2057 patients), while 2 used the Van der Bend chambers (van der Bend, Brielle, The Netherlands) applied to the back with Micropore (Healthcare 3M, Borken, Germany) and fixed with Mefix (Mölnlycke, Göteborg, Sweden) or Fixomul (Beiersdorf, Hamburg, Germany) as a second cover (604 patients). The patches remained on the back for 2 days (D). Reading days were D3 or D4. At 5 clinics, consistent readings were taken also on D6 or D7. The readings were scored according to International Contact Dermatitis Research Group (ICDRG) guidelines (22). It was emphasized that all patch test reactions not fulfilling the criteria to be classified as allergic, following the ICDRG guidelines, should be differentiated carefully with regard to irritant and doubtful reactions, instead of routinely being classified as irritant reactions. For example, erythematous reactions without infiltration were classified as doubtful as well as an erythematous infiltration not covering the whole test area.

Statistics

Fisher's exact test (2-sided) was used to investigate any sex differences in frequencies of allergic and doubtful reactions, while McNemar test (2-sided) was used to investigate differences in contact allergy rates and frequencies of doubtful reactions between various test concentrations.

Results

At all test concentrations, there were differences in contact allergy frequencies between the 11 participating clinics independent of patch test technique, so the results are reported for all the 11 clinics together. The number of patients patch tested at the 11 clinics is summarized in Table 1. To the highest patch test concentration, 1.0%, a contact allergy rate at 4.4% was noted, while the lower patch test concentrations resulted in contact allergy rates down to 1.1% (Table 2). There are statistically significant differences in contact allergy rates between all test concentrations ($P < 0.001$ for 1.0% versus 0.5%, 0.5% versus 0.3% and 0.3% versus 0.1%). More males tested positively for all concentrations but without any statistically significant differences (Table 2). The male predominance is particularly clear at all test concentrations for Amsterdam and Leuven (data not shown). Doubtful reactions were registered for all patch test concentrations from 8.2% down to 0.5% (Table 2), again with a male predominance but without any statistically significant differences between the sexes. The lowest patch test concentration did not yield irritant reactions, while increasing frequencies were noted with higher test concentrations from 0.04% up to 1.5% (Table 2).

1314 patients were read consistently a second time after 1 week, and among these, 2 new positive allergic reactions to MDBGN at 1.0% were

Table 1. 11 clinics participating in the study and the number of patch tested patients

Clinic	Number tested		
	Total	Male	Female
Almada	71	24	47
Amersham	201	66	135
Amsterdam	345	130	215
Dortmund	154	60	94
Gentofte	368	132	236
Leuven	259	97	162
Malmö	377	150	227
Modena	446	174	272
Odense	153	57	96
Oulu	216	54	162
Stockholm	71	33	38
Total	2661	977	1684

Table 2. Patch test results in 2661 consecutive dermatitis patients tested simultaneously with 4 methyldibromo glutaronitrile (MDBGN) preparations in petrolatum

Test preparation MDBGN (%)	Female (n = 1684)			Male (n = 977)			Total (n = 2661)		
	Positive (%)	Doubtful (%)	IR (%)	Positive (%)	Doubtful (%)	IR (%)	Positive (%)	Doubtful (%)	IR (%)
1.0	4.1	7.6	1.4	5.0	9.1	1.6	4.4	8.2	1.5
0.5	2.7	5.1	0.8	3.5	6.2	1.1	3.0	5.5	0.9
0.3	1.7	1.5	0	2.4	1.5	0.1	1.9	1.5	0.04
0.1	0.8	0.5	0	1.4	0.7	0	1.1	0.5	0

noted compared to the first reading. 60–80% of the allergic reactions to the 4 patch test preparations on D3/D4 remained positive on D6–D8.

The dose–response curves for patch test reactions of a morphologically allergic, doubtful and irritant nature are shown in Fig. 1. The dose–response curve for allergic reactions is less steep than for doubtful reactions.

In Fig. 2, the number of patients with doubtful reactions at one concentration and a simultaneous positive allergic reaction to a higher concentration are shown. Doubtful reactions to MDBGN at 0.3% were noted in 41 patients (1.5%) (Table 2). Of these, 34% tested positively to the higher MDBGN concentration. 83% tested negatively to 0.1%, while a positive reaction or another doubtful reaction were registered in 2% and 15%, respectively, to MDBGN at 0.1%.

Discussion

This study confirms that MDBGN is a significant contact sensitizer, with allergy rates exceeding 1% for all test concentrations and with 4.4% for the highest concentration tested. Currently, the male predominance found at all test concentrations cannot be explained but may indicate exposure to MDBGN-containing products in occupations where males are over-represented. Generally, the higher the patch test concentration used, the more

contact allergy will be traced unless the sensitizer has an anti-inflammatory capacity (23), and consequently, the possibility of diagnosing allergic contact dermatitis increases. However, the higher the patch test concentration, also the more adverse reactions will appear. Generally, the most serious adverse reaction is patch test sensitization. However, patch test sensitization was not observed, although this study was not designed to detect patch test sensitization. Another example of adverse reactions is irritant reactions which were recorded in this study. In a way, however, most irritant reactions are not a problem unless they have resulted in skin damage increasing the risk of patch test sensitization, or if they can be misinterpreted as allergic reactions, i.e. represent false-positive reactions (24).

In the present study, there are differences not only in contact allergy rates between clinics and patch test concentrations but also with regard to frequencies and proportions of doubtful and irritant reactions for the respective patch test concentration. Partly, these differences probably reflect difficulties in reading MDBGN patch test reactions with regard to discrimination between allergic and irritant reactions. The fact that a patch test reaction cannot be classified as an allergic reaction does not mean that it is necessarily an irritant reaction, although many dermatologists seem routinely to classify reactions not

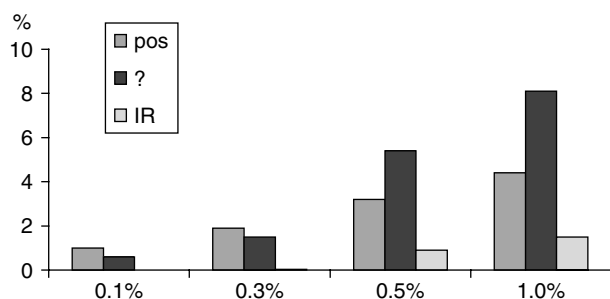


Fig. 1. Percentage of allergic (pos), doubtful (?), and irritant (IR) reactions to 4 petrolatum test preparations with methyldibromoglutaronitrile at 4 concentrations in 2661 consecutively patch tested dermatitis patients.

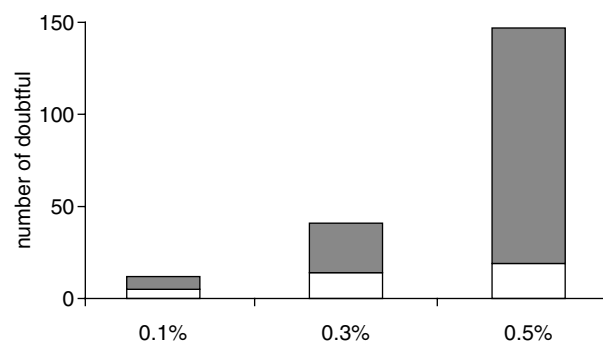


Fig. 2. Number of patients with doubtful reactions at one concentration (■ + □) and a simultaneous positive allergic reaction to a higher concentration (□).

fulfilling all criteria to be classified as allergic reactions as being irritant. Unless there is no clear irritant morphology, these patch test reactions can represent either a weak allergic or an irritant reaction and should hence be classified as a doubtful reaction. The statement that these reactions need not always represent irritant reactions but may represent weak allergic reactions is strongly supported by our results. Figure 2 shows that 1/3 of the doubtful reactions to MDBGN at 0.1% and 0.3%, as well as 13% of the doubtful reactions to 0.5%, represent weak allergic reactions. Even if some of those doubtful reactions, without allergic reactions to higher patch test reactions, may still represent weak allergic reactions, it is likely that a substantial part of this group represents non-specific irritant reactions.

For any contact sensitizer also with an irritant capacity, the dose-response curves for the allergic capacity (elicitation) and the irritant capacity can be expected to be different. A higher test concentration is expected to be required to result in a visible irritant reaction and from this reaction a more steep dose-response curve is expected to emerge, compared to the minimal allergic reaction and the allergic dose-response curve, respectively. Indeed, the results of this study agree with these assumptions. There are allergic but no irritant reactions to the lowest patch test concentrations and, compared to these low concentrations, a higher proportion of the doubtful reactions to 0.5% represent irritant reactions. Therefore, it may seem relatively straightforward to choose a patch test concentration not resulting in clearly irritant reactions. To comply with this requirement, a concentration at 0.3% or 0.1% would be satisfactory. However, with 0.3% one would fail to diagnose more than 35% (the difference between the contact allergy rates 3.0% and 1.9%, Table 2) and 55% (4.4% versus 1.9%, Table 2) of all contact allergy traced by the test concentrations 0.5% and 1.0%, respectively. For the test concentration 0.1%, the corresponding figures are more than 60% and 75%, respectively. Furthermore, independent of patch test concentration, there will be a substantial number of doubtful reactions representing weak allergic reactions.

In summary, contact allergy rates and frequencies of doubtful and irritant reactions vary with the patch test concentration. The final decision on patch test concentration for MDBGN should not only rely on the results presented in this study but also include information on the patch test concentration required to diagnose individual cases with allergic contact dermatitis from MDBGN, as well as on the results of repeated open application tests based on

individuals with contact allergy to MDBGN and with different degrees of patch test reactivity.

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