

Patch Testing with Methyl dibromoglutaronitrile in a Localized Population in the United States

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Background: In Europe, methyl dibromoglutaronitrile (MDGN) was banned because of excessive rates of contact allergy. However, it is unclear whether the concentrations used for testing MDGN are optimal, as different groups have used varying concentrations with quite different rates of positive reactions.

Objectives: To report patch-test results with MDGN in a localized US population, to compare these results with those of other studies, and to evaluate any association between contact allergy to MDGN and atopic dermatitis.

Methods: A retrospective analysis of 1,753 patients tested with various concentrations of MDGN was conducted.

Results: Four percent (4.0%) of patients had positive reactions to MDGN, of which 1.2% were ++/+++ reactions and 2.8% were + reactions. Among patients with ++/+++ reactions, 9.5% had a reaction of definite relevance; of patients with + reactions, only 2.0% had a reaction of definite relevance. Irritant reactions were had by 3.2% of patients; none of these were relevant. The North American Contact Dermatitis Group had a positive reaction rate of 6.2%; European groups had rates of 1.6 to 5.0%. No significant association was found between atopic dermatitis and positive patch-test reactions to MDGN.

Conclusion: Owing to the number of irritant reactions observed, we suspect that many reactions to MDGN are falsely positive, underscoring the importance of careful interpretation of reactions less than or equal to +.

METHYLDIBROMOGLUTARONITRILE (MDGN) is a preservative that has been found to cause allergic contact dermatitis (ACD). MDGN can be present alone or in combination with phenoxyethanol (PE) in leave-on and rinse-off cosmetic products. MDGN has been extensively studied in Europe, where it was felt to have caused significant rates of ACD, especially in those with a history of eczema.¹⁻⁴ In 2005, as a result of these European reports, the European Commission in Council Directive 76/768/EEC banned the use of MDGN in leave-on products. After subsequent European evidence showed ongoing significant levels of ACD from MDGN despite its being banned from leave-on cosmetics, it was deemed necessary to prohibit the use of MDGN in rinse-off products as well.⁵ In the United States, the Cosmetic Ingredient Review (CIR) Expert Panel has found that MDGN is safe for use in leave-on cosmetic formulations when at a concentration of less than or equal to 0.025% and safe for use in rinse-off products when at a concentration of less than or equal to 0.06%.⁶ Despite

extensive reports from Europe, there are few available studies from the United States regarding MDGN. Furthermore, as shown in Table 1, there is no consensus in Europe or the United States as to the optimal concentration or formulation for patch testing with MDGN. The primary goal of this study was to describe patch-test results with MDGN in a localized population in the United States, evaluate these data in light of data from the North American Contact Dermatitis Group (NACDG) and European groups, and explore any association between history of atopic dermatitis and positive patch-test reactions to MDGN in our patient sample.

Materials and Methods

Between November 1, 1994, and June 30, 2009, 1,910 patients suspected of having ACD were patch-tested by the senior author (a participating member of the NACDG, whose members patch-test with standardized techniques).⁷ Prior to testing, patients completed a questionnaire regarding demographics, occupation, and history of atopic dermatitis. Of the 1,910 patients evaluated, 1,753 were patch-tested with the NACDG standard allergen tray. In 1994 to 1996, the standard allergen tray contained MDGN/PE 1% (which contained 0.2% MDGN); from 1996 to 1998, it contained both MDGN/PE 2.5% (which contained 0.5% MDGN) and MDGN/PE 1% (which contained 0.2%

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Table 1. Patch-Test Results of European and North American Groups

Group	Allergen	Concentration, Vehicle	No. of Patients Tested	Reactions			Reference
				Doubtful	Positive	Irritant	
IVDK	MDGN	0.1%, pet	11,052	72 (0.6%)*	196 (1.8%)	72 (0.6%)*	15
DCDG	MDGN [†]	0.3%, pet	2,146	NS	110 (5.0%)	NS	2
EECDRG	MDGN	1.0%, pet	2,661	218 (8.2%)	117 (4.4%)	40 (1.5%)	1
ESSCA	MDGN	0.3%, pet	4,733	NS	75 (1.6%)	NS	16
NACDG	MDGN/PE [‡]	Various, [‡] pet	24,306	NS	1,509 (6.2%)	NS	9–14
UMKC	MDGN/PE [§]	Various, [§] pet	1,753	4 (0.2%)	70 (4.0%)	56 (3.2%)	—

DCDG = Danish Contact Dermatitis Group; EECDRG = European Environmental and Contact Dermatitis Research Group; ESSCA = European Surveillance System of Contact Allergies; IVDK = Information Network of Departments of Dermatology; MDGN = methyldibromoglutaronitrile; NACDG = North American Contact Dermatitis Group; NS = not stated; PE = phenoxyethanol; pet = petrolatum; UMKC = University of Missouri-Kansas City.

*Doubtful and irritant reactions were classified as a single category.

[†]Except in one clinic, which used Euxyl K400 (Schülke & Mayr GmbH, Norderstedt, Germany) 1.5% in petrolatum (0.3% MDGN and 1.2% PE).

[‡]In 1994 to 1996, MDGN/PE 1.0% was used; in 1996 to 1998, MDGN/PE 2.5%; in 1998 to 2002, MDGN 0.4%; and in 1998 to 2009, MDGN/PE 2.0%.

[§]In 1994 to 1998, MDGN/PE 1.0% was used; in 1996 to 1998, MDGN/PE 2.0%; and in 1998 to 2009, MDGN/PE 2.0% and MDGN 0.4%.

MDGN). From 1998 to 2002, MDGN/PE was tested at 2.0% (0.4% MDGN), and MDGN alone was tested at 0.4%. From 2003 to 2009, patch testing was performed with MDGN/PE 2.0% (0.4% MDGN). When MDGN/PE was used, the ratio of MDGN to PE was 1:4. During two 2-year periods (1994–1996 and 2001–2002), PE alone was tested at 1%. In all instances, the vehicle used was petrolatum.

Patch tests used Finn Chambers (Epitest Ltd Oy, Tuusula, Finland) and test allergens from Chemotechnique Diagnostics AB (Malmö, Sweden) in a standardized manner as previously described.⁷ Patch-test results were read by a clinician (D.V.B.) at 48 and 96 hours and were subsequently graded on reaction morphology as previously defined.⁷ Reactions graded +/– were considered doubtful reactions whereas +, ++, and +++ reactions were considered positive reactions of increasing intensity.

Reaction relevance was graded as definite (the patient had a positive test reaction to a product to which he or she had been exposed and that contained an allergen to whose purified form he or she had reacted); probable (the patient had experienced a known contact with a product known to contain an allergen to whose purified form he or she had reacted); possible (the patient probably had had contact with a product known or suggested to contain an allergen to whose purified form he or she had reacted); past (the patient had prior episodes of ACD after having been exposed to an allergen to whose purified form he or she had reacted); or unknown (the allergen's relevance could not be determined).⁸ In this study, relevance that was definite, probable, or possible was considered clinically significant.

All data were recorded, collected, and evaluated with a computer database (*Microsoft Access*, Microsoft

Corporation, Redmond, WA) and spreadsheet (*Microsoft Excel*, Microsoft). Statistical analysis was performed with *SPSS 16.0* software (SPSS Inc., Chicago, IL). The chi-square test with Yates' correction or the Fisher exact test was used when appropriate to determine statistically significant differences in the frequencies of reactions. A *p* value of .05 or less was considered to be statistically significant.

Results

Of the 1,753 patients who underwent patch testing with MDGN, MDGN/PE, or both in the past 15 years, 70 (4.0%) had positive reactions, 21 patients (1.2%) developed ++ or +++ reactions, and 49 (2.8%) had + reactions. In addition, 4 patients (0.2%) had doubtful reactions; the majority (56 [3.2%]) had irritant reactions. Of the ++ and +++ reactions, 9.5% were of definite relevance, 28.6% were of probable relevance, and 47.6% were of possible relevance. Of the + reactions, only 2.0% were of definite relevance, 6.1% were of probable relevance, and the majority (42.9%) were of possible relevance (Table 2).

Among the 1,753 patients, 9 patients (0.5%) had a history of atopic dermatitis and had a positive reaction to MDGN (see Table 2); 194 patients (11.1%) also had a history of atopic dermatitis but did not have a positive reaction to MDGN. No statistically significant association was found between patients with atopic dermatitis and positive reactions to MDGN (*p* = .785). Among the patients with a history of atopic dermatitis, 6 (12.3%) had + reactions, 3 (14.3%) had ++ or +++ reactions, and 8 (14.3%) had irritant reactions. No statistical association was found between atopic status and the type of reaction to MDGN (*p* = 1.0).

Table 2. Results of 1,753 Patients Patch-Tested with Methyldibromoglutaronitrile or Methyldibromoglutaronitrile/Phenoxyethanol or Both

Reaction	n	Reaction Relevance (%) [*]					
		Unknown	Past	Possible	Probable	Definite	Atopic Dermatitis
+/-	4 (0.2%)	100	0	0	0	0	0 (0%)
+	49 (2.8%)	44.9	4.1	42.9	6.1	2.0	6 (12.3%)
++ and +++	21 (1.2%)	9.5	4.8	47.6	28.6	9.5	3 (14.3%)
Irritant	56 (3.2%)	na	na	na	na	na	8 (14.3%)

na = not applicable.

^{*}Percent of total in categories +/-, +, ++, and +++, respectively.

The results of this study are in contrast to those of studies by the NACDG and the other European groups listed in Table 1. The NACDG found that 1,509 (6.2%) of its patients developed positive reactions to various concentrations of MDGN/PE and MDGN.⁹⁻¹⁴ This result is higher than the European patch-test results although one must take into account the allergens and test concentrations used as well as variation in the interpretation of reactions. In their patient populations, the Information Network of Departments of Dermatology (IVDK) found a frequency of 1.8%, the Danish Contact Dermatitis Group (DCDG) reported a 5.0% frequency, the European Environmental Contact Dermatitis Research Group (EECDRG) reported a 4.4% frequency, and the European Surveillance System on Contact Allergies (ESSCA) determined a frequency of 1.6%.^{1,2,15,16}

Between 1998 and 2002, the NACDG tested its patients with MDGN/PE 2.0% (containing 0.4% MDGN) in

petrolatum and MDGN 0.4% in petrolatum to determine if any difference in frequencies occurred between tests with pure MDGN and tests with MDGN/PE.^{11,12} As shown in Table 3, in 1998 to 2000, 347 patients (6.0%) tested with MDGN/PE 2.0% had positive reactions, and 203 patients (3.5%) had positive reactions to MDGN 0.4%.¹¹ In 2001 to 2002, 284 patients (5.8%) had positive reactions to MDGN/PE 2.0%, and 132 (2.7%) had positive reactions to MDGN 0.4%.¹² Additionally, in 1994 to 1996 and 2001 to 2002, the NACDG tested with PE 1% in petrolatum (pet) to assess whether the difference in reactions was due to isolated allergy to PE.^{9,12} Table 4 summarizes the results of all patch tests with MDGN/PE 2.0% pet and MDGN 0.4% pet (during the years these tests were run simultaneously) and with PE 1% pet; the data show that reactions to PE did not account for the differences in reactivity between MDGN 0.4% and MDGN/PE 2.0%. As also shown in Table 4, the combined NACDG data from

Table 3. North American Contact Dermatitis Group Patch-Test Results and Relevance of Positive Reactions

Years	Allergen	Concentration, Vehicle	N	Positive Reactions	Reaction Relevance				Reference
					Overall [*]	Definite	Probable	Possible	
1994-1996	PE	1.0%, pet	3,080	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	9
1994-1998	MDGN/PE	1.0%, pet [†]	7,127	172 (2.4%)	110 (64.0%)	3 (5.0%) [‡]	7 (10.0%) [‡]	20 (31.7%) [‡]	9, 10
1996-1998	MDGN/PE	2.5%, pet [§]	4,054	308 (7.6%)	182 (59.1%)	NS	NS	NS	10
1998-2000	MDGN/PE	2.0%, pet	5,778	347 (6.0%)	177 (51.1%)	7 (2.0%)	29 (8.3%)	142 (40.8%)	11
1998-2000	MDGN	0.4%, pet	5,797	203 (3.5%)	121 (59.5%)	6 (2.9%)	19 (9.3%)	96 (47.3%)	11
2001-2002	MDGN/PE	2.0%, pet	4,897	284 (5.8%)	174 (61.1%)	9 (3.2%)	41 (14.4%)	124 (43.5%)	12
2001-2002	MDGN	0.4%, pet	4,897	132 (2.7%)	94 (70.9%)	9 (6.7%)	22 (16.4%)	63 (47.8%)	12
2001-2002	PE	1.0%, pet	4,887	10 (0.2%)	7 (63.6%)	1 (9.1%)	0 (0%)	6 (54.5%)	12
2003-2004	MDGN/PE	2.0%, pet	5,140	315 (6.1%)	NS	NS	NS	NS	13
2005-2006	MDGN/PE	2.0%, pet	4,437	257 (5.8%)	192 (74.9%)	10 (3.9%)	69 (27.0%)	113 (44.0%)	14

MDGN = methyldibromoglutaronitrile; NS = not stated; PE = phenoxyethanol; pet = petrolatum.

^{*}Relevances of definite, probable, and possible were combined for overall relevance.[†]Contained 0.2% MDGN.[‡]For 1994 to 1996 only. The number of positive reactions for 1994 to 1996 was 62 (2.0%).[§]Contained 0.5% MDGN.^{||}Contained 0.4% MDGN.

Table 4. North American Contact Dermatitis Group 1998–2002 Combined Patch-Test Results

Test Substance	Concentration, Vehicle	N	Positive Reactions	Reaction Relevance				Reference
				Overall*	Definite	Probable	Possible	
MDGN/PE	2.0%, pet [†]	10,675	631 (5.9%)	351 (55.6%)	16 (2.5%)	70 (11.1%)	266 (42.1%)	11, 12
MDGN	0.4%, pet	10,694	325 (3.0%)	215 (66.2%)	15 (4.6%)	41 (12.6%)	159 (48.9%)	11, 12
PE	1.0%, pet	7,967	10 (0.1%)	7 (63.6%)	1 (9.1%)	0 (0%)	6 (54.5%)	9, 12

MDGN = methyldibromoglutaronitrile; PE = phenoxyethanol; pet = petrolatum.

*Relevances of definite, probable, and possible were combined for overall relevance.

[†]Contained 0.4% MDGN.

1998 to 2002 show that 631 patients (5.9%) had a positive reaction to MDGN/PE 2.0%, 325 (3.0%) had a positive reaction to MDGN 0.4%, and only 10 (0.1%) had a positive reaction to PE 1%. According to these data, there is a statistically significant difference between MDGN/PE 2.0% and MDGN 0.4% with respect to the number of positive reactions ($p < .0001$ for Table 3 and Table 4), which cannot be accounted for by allergic reactions to PE.

In the NACDG studies, a greater number of positive reactions developed when MDGN/PE test concentrations of 2.5% or 2.0% were used as opposed to the 1.0% test concentration (see Table 3). When MDGN/PE 2.5% pet was used in 1996 to 1998, 7.6% of patients had positive reactions.¹⁰ When MDGN/PE 2.0% pet was used between 1998 and 2006, positive reaction rates of 5.8 to 6.1% were reported.^{9–14} When MDGN/PE 1.0% pet was used in 1994 to 1998, 2.4% of patients had positive reactions.^{9,10} There was a significant difference among the rates of positive reactions to MDGN/PE in the 1.0% test concentration as compared to the 2.0% and 2.5% test concentrations (for all, $p < .0001$).

As seen in Table 3, in 2001 to 2002, the NACDG determined that the majority (43.5%) of positive reactions to MDGN/PE 2.0% were possibly relevant. Only 3.2% and 14.4% of positive reactions were of definite and probable relevance, respectively. Because +, ++, and +++ reactions are considered positive reactions and the majority of these positive reactions are + reactions, it can be concluded that a large number of positive reactions are lacking in clinical relevance. Furthermore, in the NACDG reaction data, a decrease in relevance, especially definite relevance, exists with higher test concentrations of MDGN/PE. With MDGN/PE 1.0% pet, there is an overall relevance of 64.0%; with MDGN/PE 2.0% pet, there is a combined relevance of 61.1%; and with MDGN/PE 2.5%, there is a combined relevance of 59.1%. Furthermore, as shown in Table 4 (which outlines the NACDG data for 1998 to 2002 where categories of relevance are given for MDGN/PE 2.0%, MDGN 0.4%, and PE 1.0%), there is a significant

decrease in definite relevance for the 2.0% concentration. The European results are similar: the higher the concentration, the greater the number of questionable and irritant reactions (see Table 1).

Discussion

The present study revealed that 4.0% of our patient sample had positive reactions when patch-tested with MDGN or MDGN/PE; the majority of these reactions were + reactions and of possible or unknown relevance (see Table 2). When assessed for relevance, ++ or +++ reactions to MDGN with or without PE were statistically more likely to be of definite or probable relevance. Furthermore, 3.2% of tested patients had clearly irritant reactions. Therefore, our results suggest that the MDGN/PE patch-test concentrations equal to or greater than 2.0% may be too high, resulting in false-positive irritant reactions read even by established investigators as + reactions. This hypothesis is supported by the NACDG data where increasing rates of positivity and decreasing rates of definite or possible relevance are seen as the patch-test concentration of MDGN/PE is raised from 1% to 2.0% or 2.5%.

Patch testing with MDGN/PE at concentrations equal to or greater than 2.0% appears to produce a number of false-positive, doubtful, and irritant reactions. This is elucidated by comparing the results of NACDG testing in 1998 to 2002 with MDGN 0.4% and MDGN/PE 2.0% (containing 0.4% MDGN). Given that PE is a nonsensitizing agent^{17,18} and can be safely used in combination with MDGN to determine positive allergic reactions, if a patient has a true allergy to MDGN, there should be no significant difference in the number of positive reactions with MDGN 0.4% versus MDGN/PE 2.0%. However, the present study found there was a statistically significant difference between MDGN and MDGN/PE with respect to the frequency of positive reactions ($p < .0001$). Furthermore, a study done by Tosti and colleagues found that 99 (3%) of 3,455 patients had a positive reaction to MDGN/PE 2.5%;

however, when tested with MDGN and PE in their pure forms, 46 (51.1%) of 99 patients had no reaction.¹⁹

The difference between MDGN/PE and MDGN in eliciting allergic reactions could possibly be explained by irritation from PE, causing the misinterpretation of these reactions as weakly allergic; however, when studied at a 1% concentration by the NACDG and these authors, PE did not appear to be irritating. Because very few patients who developed positive reactions to MDGN/PE and not to MDGN had positive reactions to PE (see Table 3 and Table 4), the difference in reactivity between MDGN 0.4% and MDGN/PE 2.0% cannot be explained by reactions to PE.¹² Another explanation could be penetration enhancement by PE, resulting in an increase of truly allergic reactions to MDGN. However, in their review of PE, the CIR Expert Panel did not find evidence of penetration enhancement, making this explanation less likely.²⁰

Overall, two of the European organizations reported rates lower than those obtained by the current study; however, both groups were testing with MDGN at lower concentrations. When testing with MDGN 0.1%, the IVDK had a rate of 1.8%.¹⁵ When testing with MDGN 0.3%, the ESSCA reported a rate of 1.6%¹⁶ whereas the DCDG reported a higher frequency of 5.0%,² similar to the 4.2% we found for doubtful and + to +++ reactions. Finally, the EECDRG's testing with MDGN 1% pet resulted in a 4.4% frequency for positive reactions but a 8.2% frequency for doubtful reactions,¹ again suggesting the potential for false-positive irritant reactions when MDGN is tested at such high concentrations.

A study done by Gruvberger and colleagues found that of 2,661 patients who were patch-tested, 4.4% had positive reactions to MDGN 1.0%, 3.0% had positive reactions to MDGN 0.5%, 1.9% had positive reactions to MDGN 0.3%, and 1.1% had positive reactions to MDGN 0.1%.¹ Tosti and colleagues found that with serial dilution tests in 44 patients reacting to MDGN/PE 2.5% pet, a reduction of the test concentrations resulted in a drastic decrease in positive reactions.¹⁹ Jackson and Fowler, who compared MDGN 0.2% and MDGN 0.5%, found that the higher test concentration produced more false-positive reactions.¹⁷ Together with our results and those of the NACDG, these studies indicate that either the 1.0% concentration is too weak to detect the majority of true positive reactions or the 2.5% and 2.0% concentrations may be too high, thus causing a number of false-positive irritant and doubtful reactions. (We suspect the latter to be true.) Furthermore, many of the + positive reactions observed may be falsely interpreted as such, despite being ascribed relevance, because possible relevance to a biocide or preservative with

potential widespread use is often assumed with patients suspected of having ACD. Therefore, we recommend use-testing of products containing MDGN to determine a patient's true allergic status.

In a study done by Jensen and colleagues, contact allergic individuals and nine controls participated in a repeated open application test (ROAT) with liquid soap containing 0.1% MDGN, and 37% of the patients had a positive ROAT result.²¹ In another recent study done by the IVDK, a stepwise ROAT with increasing MDGN concentrations of 0.005%, 0.02%, and 0.04% in a liquid soap was performed on 37 sensitized subjects until a positive ROAT reaction was obtained or the maximum concentration of MDGN was reached.²² Of these patients, 32 (86.5%) were able to tolerate the maximum concentration of MDGN in the test preparation. In addition, the study concluded not only that a 0.005% concentration of MDGN in liquid soap was a safe concentration for use in rinse-off products for most sensitized individuals, but also that the induction of new cases can be avoided by concentrations approximating 0.005% in rinse-off products.²²

Conclusion

The most frequent test concentration of MDGN/PE used in the Javvaji and Belsito study and in the NACDG studies was 2.0%, which is 16 times higher than the CIR-recommended concentration in leave-on products and 6.7 times higher than the CIR-recommended concentration in rinse-off products. Although it is not unusual for patch-test concentrations to be higher than the recommended concentrations of allergens in cosmetic products, this vast increase can allow a large number of irritant and doubtful reactions to develop and be misread as weakly allergic, thus contributing to a higher number of false positives in our overall frequency of reactions. If future Thin-Layer Rapid Use Epicutaneous (T.R.U.E.) Test panels (Mekos Laboratories A/S, Hillerød, Denmark) include MDGN, the implications of this study will be even more widely applicable because more patients will be tested for allergy to MDGN. We therefore call upon the various contact dermatitis research groups worldwide to (1) further study MDGN/PE patch-test concentrations ranging between 1.0% and 2.0% and MDGN concentrations of 0.2 to 0.4%; (2) perform tests with serial dilutions on patients who have weakly positive reactions; and (3) consider a use-test study with MDGN/PE, similar to the study performed by the NACDG with Kathon CG (Rohm and Haas, Philadelphia, PA).²³

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