Allergic Contact Dermatitis from Methyldibromoglutaronitrile

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Background: **Arriving at a diagnosis of allergic contact dermatitis is a multistep procedure including the establishing of contact allergy, demonstration of current exposure to the sensitizer, and assessment of clinical relevance. Sometimes, these steps are easy to get through; at other times, there may be problems with every step.**

Objective: **To demonstrate the possible difficulties and pitfalls in establishing the presence of contact allergy and diagnosing allergic contact dermatitis from exposure to the preservative methyldibromoglutaronitrile (MDBGN).**

Methods: **Simultaneous patch-testing with petrolatum preparations of MDBGN at various concentrations, use testing, and chemical analysis with high-performance liquid chromatography (HPLC).**

Results: **Contact allergy to MDBGN was established in two cases, with MDBGN in petrolatum at 0.5%. Results of HPLC investigation of moisturizers used by the patients and yielding positive results on patch and use tests disagreed with the information about preservatives on the labels of the moisturizers and with the Material Safety Data Sheets (MSDSs).**

Conclusions: **Patch testing with MDBGN in petrolatum at a concentration of less than 0.5% may fail to diagnose a clinically relevant contact allergy. The information on labels of products, on MSDSs, and from manufacturers may not be reliable, which indicates the need for chemical analyses.**

ARRIVING AT A DIAGNOSIS of allergic contact dermatitis is a multistep procedure including (1) the establishing of contact allergy, (2) demonstration of current exposure to the sensitizer and/or cross-reacting substances, and (3) assessment of clinical relevance (ie, whether the exposure explains the dermatitis under investigation with regard to the type of dermatitis, its localization, and its course).[1] Sometimes, these steps are easy to get through; at other times, there may be problems with every step. Recent problems we have experienced with these steps in regard to the preservative methyldibromoglutaronitrile (MDBGN) are reported in this article.

Materials and Methods

Patch Testing

The Finn Chamber technique (Epitest Ltd Oy, Tuusula, Finland) was used; the chambers were fixed to Scanpor tape (Norgesplaster A/S, Vennesla, Norway). The patches were applied on the upper back and were removed after 48 hours. Mandatory readings according to International Contact Dermatitis Research Group guidelines[2] took place on days 3 and 7.

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Case 1

A 29-year-old male mechanic was referred because of a suspected work-related hand dermatitis that had been present a few months. The history revealed a possible atopic rhino-conjunctivitis but no atopic dermatitis. On clinical examination, he was found to have a severe vesicular eczema on the volar aspects on the hands and redness and infiltration on the dorsal aspects. Patch testing was performed with our metalworking-fluid series and our standard test series, supplemented with some preservatives, including Euxyl K400 (Schülke & Mayr GmbH, Norderstedt, Germany) in petrolatum at 2.5% weight per weight (w/w) and MDBGN in petrolatum at both 0.5% w/w and 0.2% w/w. Positive reactions were noted to neomycin, Euxyl K400, and MDBGN at 0.5%, but there was a negative reaction to MDBGN at 0.2% (Table 1). MDBGN was found in a liquid soap and a shower cream used at the patient's workplace, so he stopped using these products.

However, the hand dermatitis relapsed after he used a moisturizer (moisturizer A) during leisure time. When this

Table 1. Patch-Test Results

	*Test Reaction**			
	Case 1		*Case 2*	
	D3	*D7*	*D3*	*D7*
Test occasion I				
Standard test series				
Neomycin pet	–	++	–	–
Additional standard series				
Euxyl K400 2.5% pet	+++	++	NT	NT
Euxyl K400 2.0% pet	NT	NT	+	+
MDBGN 1.0% pet	NT	NT	+	+
0.5% pet	++	++	++	+
0.3% pet	NT	NT	–	–
0.2% pet	–	–	–	–
2-Phenoxyethanol 1.0% pet	–	–	–	–
Metalworking-fluids series	–	–	NT	NT
Own materials				
Moisturizer B, as is	NT	NT	++	++
Test occasion II				
Moisturizer A, old, as is	+++	NR	NT	NT
Moisturizer A, old, 10% aq	+++	NR	NT	NT
Moisturizer A, new, as is	+++	NR	NT	NT
Moisturizer A, new, 10% aq	++	NR	NT	NT
MDBGN 0.5% eth	+++	NR	NT	NT
0.16% eth	++	NR	NT	NT
0.05% eth	+	NR	NT	NT
0.016% eth	–	NR	NT	NT
Bronopol 0.25% pet	NT	NT	–	–
Test occasion III				
Ingredients in moisturizer A				
7 Ingredients	–	NR	NT	NT
Merguard 1200 2.5% pet	+++	NR	NT	NT
0.25% pet	++	NR	NT	NT

aq = aqueous; eth = in ethanol; MDBGN = methyldibromoglutaronitrile; NR = not read; NT = not tested; pet= in petrolatum.
*+, ++, and +++ denote positive patch-test reactions; – denotes negative patch-test reaction.

moisturizer was applied to his normal skin in the cubital fossa twice daily, a dermatitis appeared. On a second patch-test occasion, the patient reacted positively to two patient-supplied batches of the moisturizer (an old batch and a new batch) and to ethanol solutions of MDBGN at 0.5%, 0.16%, and 0.05% weight per volume (w/v) but reacted negatively to a 0.016% w/v concentration (see Table 1). According to the label for the old batch of moisturizer A, which the patient had used when the hand dermatitis relapsed, this preparation did not contain MDBGN but did contain propylparaben (Table 2). The Material Safety Data Sheet (MSDS) obtained from the manufacturer stated that the MDBGN-containing preservative Euxyl K400 was present in moisturizer A. On the other hand, MDBGN was listed on the label of the new batch of moisturizer A.

On a third patch-test occasion, the patient was tested with ingredients of moisturizer A. A positive result was obtained to one ingredient, Merguard 1200 (Nalco Company, Naperville, IL), which consists of 2-phenoxyethanol and MDBGN (see Table 1).

The hand dermatitis healed upon treatment with a topical corticosteroid and another moisturizer without MDBGN.

Case 2

A 47-year-old woman without previous skin disease or atopic diathesis was working as a kitchen assistant at a nursing home for elderly people when a dermatitis localized to the dorsal aspects of both hands developed. Three months later, she was referred because of a suspicion that the condition was work related. Patch testing was performed with our standard test series supplemented with some preservatives, including Euxyl K400 in petrolatum at 2.0% w/w and MDBGN in petrolatum at 1.0% w/w, 0.5% w/w, 0.3% w/w, and 0.2% w/w. The moisturizer used at the patient's workplace (moisturizer B) was used "as is" in the patch test. Positive reactions to the moisturizer, Euxyl K400, and MDBGN at 1.0% and 0.5% were noted, but reactions to MDBGN at 0.3% and 0.2% were negative (see Table 1). According to the label of moisturizer B, the preservative used was bronopol. The MSDS also stated that 2-bromo-2-nitropropane-1,3-diol (bronopol) was the preservative. Additional patch testing with bronopol in petrolatum at 0.25% w/w yielded negative results. A use test with moisturizer B used twice daily in the right cubital fossa was initiated; redness was noted after 3 days, and a papular eczema was diagnosed after 1 week.

The patient returned to work without relapse after the dermatitis had been healed with a topical corticosteroid and skin care products without MDBGN.

Substances

The following substances were used: tetrahydrofuran (Lab Scan, Dublin, Ireland), methanol (Mallinkrodt Baker B.V., Deventer, Holland), and acetonitrile (Scharlau Chemie S.A., Barcelona, Spain), all of HPLC quality.

The following reference substances were used: methylparaben, ethylparaben, propylparaben, and butylparaben (Fluka Chemica Bucks, Switzerland); MDBGN and 2-phenoxyethanol (Schülke & Mayr, Hamburg, Germany); and bronopol (Boots Company, Nottingham, England).

Table 2. Preservatives in Moisturizers A and B: Labeled and Material Safety Data Sheet Information and Chemical Analysis Results

	Product Information		*Product Ingredient*		*Results of HPLC Analysis*				
Product Preservative	*Label*	*MSDS*	*Label*	*MSDS*	*Conc (% w/w)*	*Detection Limit (%)*	*Mobile Phase (v/v)*	*Wavelength (nm)*	*Ref*
Moisturizer A, old (patient supplied)									
Euxyl K400*	No	Yes	—	—	—	—	—	—	—
MDBGN	No	No	—	—	< 0.001†	< 0.001	Methanol/water (40/60)	220	3, 4
2-Phenoxyethanol	No	No	—	—	0.37	< 0.002	Tetrahydrofuran/water/methanol/ acetonitrile (5/60/10/25)	280	5
Methylparaben	No	No	—	—	< 0.004	< 0.004	Tetrahydrofuran/water/methanol/ acetonitrile (5/60/10/25)	280	3, 5
Ethylparaben	No	No	—	—	< 0.004	< 0.004	Tetrahydrofuran/water/methanol/ acetonitrile (5/60/10/25)	280	3, 5
Propylparaben	Yes	No	—	—	< 0.004	< 0.004	Tetrahydrofuran/water/methanol/ acetonitrile (5/60/10/25)	280	3, 5
Butylparaben	No	No	—	—	< 0.004	< 0.004	Tetrahydrofuran/water/methanol/ acetonitrile (5/60/10/25)	280	3, 5
Moisturizer A, new (patient supplied)									
Euxyl K400*	No	Yes	—	—	—	—	—	—	—
MDBGN	Yes	No	—	—	0.029	< 0.001	Methanol/water (40/60)	220	3, 4
2-Phenoxyethanol	No	No	—	—	0.18	< 0.002	Tetrahydrofuran/water/methanol/ acetonitrile (5/60/10/25)	280	5
Propylparaben	No	No	—	—	< 0.004	< 0.004	Tetrahydrofuran/water/methanol/ acetonitrile (5/60/10/25)	280	3, 5
Preservative in moisturizer A									
Merguard 1200									
1,2-Dibromo-2, 4-dicyanobutane‡	—	—	No	Yes	20.0	< 0.001	Methanol/water (40/60)	220	3, 4
2-Phenoxyethanol	—	—	No	Yes	78.6	< 0.002	Tetrahydrofuran/water/methanol/ acetonitrile (5/60/10/25)	280	5
Moisturizer A, old (purchased)									
Euxyl K400*	No	Yes	—	—	—	—	—	—	—
MDBGN	No	No	—	—	< 0.001	< 0.001	Methanol/water (40/60)	220	3, 4
2-Phenoxyethanol	No	No	—	—	0.16	< 0.002	Tetrahydrofuran/water/methanol/ acetonitrile (5/60/10/25)	280	5
Propylparaben	Yes	No	—	—	< 0.004	< 0.004	Tetrahydrofuran/water/methanol/ acetonitrile (5/60/10/25)	280	3, 5
Moisturizer B									
Bronopol§	Yes	Yes	—	—	< 0.001	< 0.001	Methanol/water (25/75)	240	3, 6
MDBGN	No	No	—	—	0.024	< 0.001	Methanol/water (40/60)	220	3, 4
2-Phenoxyethanol	No	No	—	—	0.13	< 0.002	Tetrahydrofuran/water/methanol/ acetonitrile (5/60/10/25)	280	5

Conc = concentration; HPLC = high-performance liquid chromatography; MDBGN = methyldibromoglutaronitrile; MSDS = Material Safety Data Sheet; Ref = reference; v/v = volume per volume; w/w = weight per weight.

*Consists of MDBGN and 2-phenoxyethanol.

†Less than the detection level.

‡Identical to MDBGN.

§2-Bromo-2-nitropropane-1,3-diol.

Commercial Products

Three samples of moisturizer A were used: one old batch and one new batch supplied by the patient in case 1 and one old batch purchased from the supplier. Moisturizer B was supplied by the patient in case 2.

High-Performance Liquid Chromatography

An isocratic high-performance liquid chromatography (HPLC) system consisting of a P200 pump, a UV1000 detector, and a ChromJet integrator (Thermo Separation Products, Rivera Beach, FL) was used. The system was equipped with a Rheodyne 7125 injector (Rheodyne, Cotati, CA) with a 20 μL loop. The column (4.6 mm inside diameter × 250 mm) was packed with 5 μm Kromasil C18 (Chrom Tech, Stockholm, Sweden). The flow rate was 1.0 mL per minute.[3–6]

To identify MDBGN, parabens, 2-phenoxyethanol, and 2-bromo-2-nitropropane-1,3-diol and to determine the concentrations, published methods have been used.[3–6] The mobile phases and the wavelength settings are listed in Table 2.

Results

The patch-test results are shown in Table 1. The information on preservatives in the creams as it appeared on the labels and on the MSDSs, as well as the results of the HPLC analyses, are shown in Table 2. The preservative in the patient-supplied sample from the old batch of moisturizer A was identified as propylparaben on the label and as Euxyl K400 on the MSDS. Neither propylparaben nor MDBGN were found whereas 2-phenoxyethanol was shown to be in the moisturizer. The information on the label of the sample from the new batch of moisturizer A and the result of the chemical analysis agreed concerning MDBGN but disagreed concerning 2-phenoxyethanol. The information on the label and on the MSDS of the purchased samples from the old batch of moisturizer A was identical with that of the patient-supplied old batch and was equivalent with regard to the moisturizer's preservative demonstrated by HPLC analysis. The MSDS did not indicate either of the two preservatives found in the new batch but on the compound preservative Euxyl K400 which contains both MDBGN and 2-phenoxyethanol. Both the label and the MSDS for moisturizer B stated bronopol to be the preservative. Bronopol was not detected in moisturizer B, but both MDBGN and 2-phenoxyethanol were chemically demonstrated in moisturizer B.

Discussion

Examples of preservatives containing MDBGN as active ingredient are listed in Table 3. Contact allergy to MDBGN and allergic contact dermatitis from MDBGN are common.[7–19] In spite of this, there has not been any agreement on which patch-test preparation to use. In pilot studies for investigations of optimal patch-test preparations for MDBGN, various test preparations with Euxyl K400 and MDBGN in petrolatum were inserted into the standard series at the departments in Malmö and Leuven. Most experts have favored MDBGN at a concentration of 0.3% or less (Table 4).[7–12,16–18,20–44] In this study, both patients reacted positively to MDBGN at 0.5% but negatively to lower concentrations.

When a patient is allergic to a preservative, information on exposure to preservatives is usually obtained from the labels of the products that have produced a positive patch-test result or from the labels of products that are suspected (from history and clinical findings) to be the culprits. Because Sweden is a member of the European Union, the European Council cosmetic directive[45] is in force there. This directive states that manufacturers of cosmetics and hygiene products must declare their ingredients on the label/packaging. The ingredients are to be

Table 3. Preservatives Containing Methyldibromoglutaronitrile as Active Ingredient

Product	*Active Ingredients*	*%*	*Vehicle*	*Manufacturer*
Merguard 1105	MDBGN	5	Propylene glycol	Nalco Company, Naperville, IL
Merguard 1190	MDBGN	10	Dipropylene glycol	Nalco Company, Naperville, IL
Merguard 1200	MDBGN	20	2-Phenoxyethanol	Nalco Company, Naperville, IL
Merguard X-18	MDBGN	12	Dipropylene glycol	Nalco Company, Naperville, IL
	2-Bromo-2-nitropropane-1,3-diol	6		
Euxyl K400	MDBGN	20	2-Phenoxyethanol	Schülke & Mayr, Hamburg, Germany

MDBGN = methyldibromoglutaronitrile.

Table 4. Test Preparations Used to Diagnose Allergic Contact Dermatitis and Trace Contact Allergy to Methyldibromoglutaronitrile

Chemical	*Vehicle*	*Concentration (%)*	*Reference*
Tektamer 38	Petrolatum	0.1	7
Euxyl K400	Petrolatum	2.5	8, 9, 20
Euxyl K400	Petrolatum	1.0	8, 10, 11, 21–23
Euxyl K400	Petrolatum	1.0–0.5	12
Euxyl K400	Petrolatum	0.5	10, 24–30
Euxyl K400	Petrolatum	0.2	28
Euxyl K400	Petrolatum	0.1	31, 32
Euxyl K400	Propylene glycol	2	33
Euxyl K400	Propylene glycol	0.15	33
Euxyl K400	Ethanol	2.5	20
Euxyl K400	Water	1.0	34, 35
Euxyl K400	Water	0.5	9
Euxyl K400	Water/ethanol	0.2	36
Euxyl K400	Water/propylene glycol (50/50)	1.5	9
MDBGN	Petrolatum	0.5	9, 37
MDBGN	Petrolatum	0.3	22, 24, 37–40
MDBGN	Petrolatum	0.3–0.1	12
MDBGN	Petrolatum	0.1	16, 27, 28, 34, 37, 41–43
MDBGN	Petrolatum	0.05	17, 44
MDBGN	Petrolatum	0.04	28
MDBGN	Petrolatum/soy lecithin	0.3	18
MDBGN	Water	0.1	23

MDBGN = methyldibromoglutaronitrile.

listed according to their concentration in the product. Ingredients at concentrations of less than 1% are to be listed in optional order after those with higher concentrations. The ingredients are to be named according to a special system for cosmetics and hygiene products, the International Nomenclature of Cosmetic Ingredients.

In both patients, the moisturizers used yielded positive patch-test responses. However, according to the labeling, none of the moisturizers contained MDBGN whereas the label on the sample from the new batch of moisturizer A listed MDBGN as the preservative (see Table 2). Being aware of the possible discrepancy between the labeling of a product and the information on the MSDS, the authors procured the latter.[3] The discrepancy was confirmed in regard to the old batch of moisturizer A, for which the MSDS listed Euxyl K400, thus seemingly explaining the patch-test reactivity to moisturizer A (because Euxyl K400 consists of 80% 2-phenoxyethanol and 20% MDBGN) (see Table 2). However, HPLC showed no MDBGN in the old batch of moisturizer A used by the patient in case 1, but 2-phenoxyethanol was detected. Also surprising was the absence of parabens, including propylparaben, which was labeled on the product. Sometimes, manufacturers change preservatives in cosmetics temporarily or permanently; therefore, another sample of the old batch of moisturizer A was investigated. Again, no MDBGN but rather 2-phenoxyethanol was found. On the other hand, MDBGN was labeled on and detected in the new batch of moisturizer A whereas 2-phenoxyethanol was detected but not labeled. When patch tests were done with the ingredients of moisturizer A, the only positive reaction was to the preservative Merguard 1200, which is equivalent to Euxyl K400 (see Table 3). However, MDBGN was present only in the new batch of moisturizer A and not in the old batch, so the contact allergy to the old batch must be ascribed to another sensitizer, for example, a sensitizer that is a manifestation of a compound allergy or that is an ingredient not obtained from the manufacturer. Still, the contact allergy to the old batch of moisturizer A was clinically relevant because there was a positive use-test result, and the relapsed dermatitis healed when the patient stopped using this moisturizer.

In case 2, bronopol and not MDBGN was thought to be the sensitizer responsible for the contact allergy to moisturizer B because the patient, besides reacting positively to MDBGN, reacted positively to this moisturizer, which was preserved with bronopol, according to both the label and the MSDS. However, the patient did not react to bronopol at patch testing; furthermore, chemical analyses were unable to detect any bronopol. A use test with the moisturizer was therefore initiated to assess the clinical relevance of the positive patch-test result. At the same time, a chemical analysis indicated the presence of MDBGN in moisturizer B.

Besides product labeling and the MSDS, another source of information on ingredients in compound products is direct communication with the manufacturer or supplier. Both manufacturers of the moisturizers used were small Swedish companies that initially claimed that one moisturizer contained the MDBGN-containing preservative Euxyl K400 and that the other contained bronopol. Later on, the manufacturer of moisturizer B admitted that the preservatives used were indeed MDBGN and 2-phenoxyethanol.

These two case reports demonstrate the possible difficulties and pitfalls in establishing contact allergy to a sensitizer and allergic contact dermatitis from it. MDBGN is

a strong candidate for inclusion in the European Standard patch-test series. Previously, most experts seem to have favored MDBGN at 0.3% (see Table 4). Had only a test concentration of less than 0.5% been used in the present two cases, the patch tests would have failed to diagnose a clinically relevant contact allergy to MDBGN. Thus, as for any sensitizer, a negative patch-test result does not mean that there is no contact allergy but that contact allergy to the sensitizer tested has not been demonstrated.

Conclusion

For the assessment of clinical relevance, knowledge of present exposure to a sensitizer is necessary. Unfortunately, information from product labeling, MSDSs, and manufacturers is not always reliable.[3] In this situation, chemical analyses are indispensable. However, very few patch-test clinics have access to laboratory facilities where chemical analyses can be performed. Therefore, this study emphasizes the opinion that one should be restrictive with the verdict of "no clinical relevance" when a contact allergy has been established and when one investigates for a possible allergic contact dermatitis.[46] In such a situation, it is advisable and more justified to conclude that no contact allergy or allergic contact dermatitis has been demonstrated, rather than to claim that there is no contact allergy or allergic contact dermatitis.

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