

Provocative use testing of methyldibromo glutaronitrile in a cosmetic shampoo

ANTONELLA TOSTI, COLOMBINA VINCENZI AND KARIN A. SMITH¹

¹Department of Dermatology, University of Bologna, Italy
Procter & Gamble Technical Centres Limited, Lovett House, Lovett Road, Staines,
Middlesex TW18 3AZ, UK

Methyldibromo glutaronitrile (1,2-dibromo-2,4-dicyanobutane, MDGN) is a component of Euxyl K400, a broad-spectrum preservative increasingly used in cosmetics over the last 10 years. Contact allergy to MDGN is not uncommon, with leave-on cosmetics and moistened toilet tissue being the most important sources. Rinse-off products have rarely been reported to elicit allergic reactions in patients sensitized to MDGN and shampoos have only been implicated in hairdressers. To determine whether subjects sensitized to MDGN would react in a provocative use test with a shampoo containing the preservative, we asked 12 pre-sensitized subjects to use a shampoo containing 0.02% MDGN for a period of 9–13 weeks. During this time, none of the subjects showed any skin reactions indicative of contact allergy. The results of this study provide evidence to support that a shampoo product containing 0.02% MDGN may safely be used by most individuals who are presensitized to MDGN.

Key words: methyldibromo glutaronitrile; Euxyl K400; Tektamer 38; dibromodicyanobutane; preservative; allergic contact dermatitis; contact allergy; provocative use test; cosmetics; shampoo; diagnostic patch test; rinse-off products. © Munksgaard, 2000.

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Methyldibromo glutaronitrile (1,2-dibromo-2,4-dicyanobutane, MDGN), also called Tektamer 38, is a component of Euxyl K400, a broad-spectrum preservative for cosmetics and toiletries. Euxyl K400, a 1:4 ratio of MDGN and phenoxyethanol, was introduced to the European market in 1985. Euxyl K400 is permitted in cosmetics in Europe at concentrations up to 0.5% and in sunscreen products at concentrations up to 0.125% (1).

Since its introduction, Euxyl K400 has largely been utilized by cosmetic manufacturers as an alternative to other preservatives, especially isothiazolinones, because of its weaker sensitizing capacity in animal experiments (2, 3). However, data from several countries indicate that contact sensitization to Euxyl K400 is not rare. Studies among dermatological patients have shown frequency rates of sensitization to Euxyl K400 ranging from 0.5% to 4% in Europe (1, 4) and from 1.5% to 2% in North America (5, 6), and most individuals being sensitized to the MDGN component. Leave-on cosmetics and moistened toilet tissue are the most common sources of sensitization to MDGN. The risk of induction and/or elicitation of contact der-

matitis from the use of rinse-off products, such as soaps, cleansing face lotions, foaming soaps and cleansing milks is lower (7). Contact dermatitis from shampoos has never been reported, with the possible exception of cases of occupational dermatitis in hairdressers (8).

The study reported here was designed to determine whether exposure to a shampoo containing 0.02% MDGN would, under normal use conditions, result in elicitation of an allergic response in MDGN-pre-sensitized patients.

Materials and Methods

Test materials

The following test materials were used.

1. Shampoo A – a normal shampoo *without* MDGN, preserved with DMDM hydantoin.
2. Shampoo B – a normal shampoo containing 0.02% MDGN and the same level of DMDM hydantoin as in shampoo A.

Both test materials had identical matrices, with the exception of the presence or absence of MDGN, the main components of which were am-

monium-based surfactants. All materials were supplied by Procter & Gamble Technical Centres Limited, UK.

Test location

The study took place at the Institute of Clinical Dermatology of the University of Bologna, Italy. All subjects were informed of the purpose of the study and gave their informed consent.

Volunteers

Subjects who had previously been found, in the University of Bologna Dermatology Clinic, to show positive reactions to Euxyl K400 and MDGN were invited to participate. For inclusion in the study, subjects had to have been free from cutaneous lesions for at least 3 months. The demographics of these subjects, along with their relevant clinical histories, are summarized in Table 1. A total of 12 adult subjects (4 male, 8 female) over the age of 16 years (average 44 years) agreed to enter the study, 8 of whom were also patch-test-positive to other common materials, such as MCI/MI and fragrance mix. During diagnostic patch testing, using Finn Chambers on Scanpor, all subjects had evidenced equally strong reactions to both Euxyl K400 (2.5% pet. and 0.5% aq.) and MDGN (0.3% pet.). In all patients, the positive reaction had been judged of past or present clinical relevance.

Patch tests

Single application patch tests were conducted on all subjects with Shampoo A (MDGN-free) to ensure that no subject had a pre-existing allergy to any other component of the formulation. This

shampoo formulation was diluted to 10% in distilled water and applied under open patch conditions to the upper arm of all subjects. Skin sites were graded after 20 min, 2 days and 3 days.

Provocative use test

Prior to the start of the study, subjects were asked to identify all personal care products that they were currently using. The labeling on the packaging of the subjects' current products was subsequently examined to determine whether MDGN was listed as an ingredient. Any product containing MDGN was not permitted for use during the course of the study. Subjects were required to shampoo their hair with Shampoo B (containing 0.02% MDGN) in the normal manner at least 3× per week for a period of 9–13 weeks. No other shampoo products were used by subjects during this time. Dermatological evaluations, specifically of the scalp, face, neck and hands, were performed at the beginning and end of the study and at weeks 4 and 8. Subjects were also instructed to contact the investigator immediately in the event of any adverse reaction.

Results

Patch test results

All 12 subjects participated in the initial patch testing with Shampoo A (MDGN free). No subject showed a reaction indicative of either irritation or allergy. As a result, all 12 subjects were entered into the provocative use test.

Provocative use test results

Of the 12 subjects with a presensitization to MDGN who started the provocative use test, 11

Table 1. Demographics of subjects included in the study and their relevant clinical histories

Subject no.	Sex	Age (years)	Site of original dermatitis	Other relevant allergies	Diagnostic patch test results (D3)		
					E K400 0.5% aq.	E K400 2.5% pet.	MDGN 0.3% pet.
1	F	52	scalp, trunk	thiuram mix	++	++	++
2	M	44	upper limbs	none	++	++	++
3	M	61	neck, trunk	none	++	++	++
4	F	62	neck	fragrance mix	++	++	++
5	M	68	scalp, face, upper limbs	MCI/MI	++	++	++
6	M	44	hand	MCI/MI	++	++	++
7	F	52	face	nickel, Myroxylon Pereirae, colophonium, fragrance mix	++	++	++
8	F	34	hands, neck	fragrance mix	++	++	++
9	F	29	upper limbs	none	++	++	++
10	F	44	face	thimerosal	++	++	++
11	F	16	hands	nickel sulfate, fragrance mix	++	++	++
12	F	21	feet, legs	none	++	++	++

Table 2. Summary of assumptions made in calculating skin exposures to MDGN from diagnostic patch testing with Finn Chambers on Scanpor and typical consumer use

Parameter	Diagnostic patch testing	Typical consumer use
amount of product used (g)	0.02	12 (95th percentile value) (10)
level of MDGN (%) in product	0.3	0.02
dermal deposition of MDGN (%)	100	0.5 (10)
area of skin exposed to MDGN (cm ²)	0.5	1035 (hands and scalp) (11)

completed the study. No cutaneous reactions to the shampoo were evinced by any of the subjects and no reports of itching and/or dermatitis were reported. 1 subject withdrew during the 1st week of the study: no clinical lesions were noted in this case and their withdrawal was not related to the test shampoo.

Discussion

Elicitation of contact allergy from preservatives in rinse-off products is uncommon and a recent study underlines that even common sensitizers such as MCI/MI can safely be used to preserve rinse-off cosmetics (9). The purpose of this study was to determine whether individuals who had previously been identified through diagnostic patch testing as being presensitized to MDGN could use a shampoo product containing 0.02% of this preservative without provoking dermatological reactions. None of the 11 subjects completing the study experienced itching or dermatitis and no cutaneous lesions were noted following the dermatological evaluations. It can be concluded that this shampoo product (Shampoo B) preserved with 0.02% MDGN was safely used by individuals with a presensitization to this cosmetic ingredient, without the risk of eliciting cutaneous reactions.

The results discussed above indicate that subjects recruited into this study were all confirmed as having a presensitization to MDGN, yet no individual showed cutaneous reactions indicative of contact allergy during use of Shampoo B (containing 0.02% MDGN). It is proposed that the basis for the difference in response is a function of the actual exposure to MDGN. One of the key concepts involved in both induction and elicitation of allergic contact dermatitis is exposure, i.e. the amount of specific allergen per unit area of skin. Comparing calculated exposure levels to MDGN under both diagnostic-patch-test, using Finn Chambers on Scanpor, and typical-use conditions, extends the process of hazard identification (diagnostic patch testing) to hazard and risk assessment.

To calculate exposure to MDGN, on a volume

per unit area basis, the following calculation may be employed:

Skin exposure ($\mu\text{g}/\text{cm}^2$) = [amount of product used (μg) $\times$ level of MDGN (%) $\times$ dermal deposition (%)] / area of skin exposed (cm^2),

along with typical assumptions of amount of product used per application, level of MDGN in the product, % of the product deposited on the skin surface available for absorption, and the surface area involved, as detailed in Table 2. From typical consumer use of Shampoo B (containing 0.02% MDGN), exposure to MDGN is calculated as $0.016 \mu\text{g}/\text{cm}^2$. This level did not elicit cutaneous reactions in the presensitized subjects involved in this study. In contrast, MDGN exposure under the conditions of the diagnostic patch test using 0.3% MDGN is calculated as $120 \mu\text{g}/\text{cm}^2$. This level elicited strong positive (++) skin reactions in all subjects taking part in this study. This demonstrates that exposure to MDGN from use of Shampoo B containing 0.02% MDGN is at least $7500\times$ lower than the concentration ($120 \mu\text{g}/\text{cm}^2$) known to elicit contact allergy in these subjects under diagnostic patch test conditions. Based upon this hazard assessment, it is proposed that use of a shampoo product containing 0.02% MDGN by subjects with a known sensitization to MDGN would not result in the elicitation of cutaneous reactions.

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References

1. Tosti A, Vincenzi C, Trevisi P, Guerra L. Euxyl K400: incidence of sensitization, patch test concentration and vehicle. *Contact Dermatitis* 1995; 33: 193–195.
2. Bruze M, Gruvberger B, Agrup G. Sensitization studies in the guinea pig with the active ingredients of Euxyl K400. *Contact Dermatitis* 1988; 18: 37–39.
3. Hausen B M. The sensitizing potency of Euxyl K400 and its components 1, 2 dibromo-2, 4 dicyanobutane and 2-phenoxyethanol. *Contact Dermatitis* 1993; 28: 149–153.

4. De Groot A C, Van Ginkel C J W, Weijland J W. Methyl-dibromoglutaronitrile (Euxyl K400): an important "new" allergen in cosmetics. *J Am Acad Dermatol* 1996; 35: 743–747.
5. Marks J G, Belsito D V, DeLeo V A, Fowler J F, Fransway A F, Maibach H I, Mathias C G T, Nethercott J R, Rietschel R L, Sherertz E F, Storrs F J, Taylor J S. North American Contact Dermatitis Group patch test results for the detection of delayed-type hypersensitivity to topical allergens. *J Am Acad Dermatol* 1998; 38: 911–918.
6. Jackson J M, Fowler J F. Methyl-dibromoglutaronitrile (Euxyl K400): A new and important sensitizer in the United States? *J Am Acad Dermatol* 1998; 38: 934–937.
7. Fernandez E, Navarro J A, del Pozo L, Fernandez de Cor-rès L. Allergic contact dermatitis due to dibromodicyano-butane in cosmetics. *Contact Dermatitis* 1995; 32: 109–110.
8. Van der Walle H B, Brunsveld V M. Dermatitis in hair-dressers (1): the experience of the past 4 years. *Contact Dermatitis* 1994; 30: 217–221.
9. Fewings J, Menné T. An update of the risk assessment for methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) with focus on rinse-off products. *Contact Dermatitis* 1999; 41: 1–13.
10. The Procter & Gamble Company. Personal communi-cation, 1999.
11. The Procter & Gamble Company. Personal communi-cation, 1999.

Address:

Antonella Tosti
Department of Dermatology
University of Bologna
Via Massarenti 1
40138 Bologna
Italy