

A clinically relevant contact allergy to methyldibromo glutaronitrile at 1% (0.32 mg/cm²) detected by a patch test

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Recently, the preservative methyldibromo glutaronitrile (MDBGN) at 0.5% w/w in petrolatum was included in the European standard patch test series based on the studies on chemical stability and consideration of rates of contact allergy, doubtful and irritant reactions as well as information on clinical relevance represented by results of a repeated open application test (ROAT) and patch test concentrations required to diagnose allergic contact dermatitis from MDBGN in individual cases. In this report, a case with a clinically relevant contact allergy to MDBGN, which on the mandatory reading occasion on D3 only was traced by a patch test with MDBGN at 1.0% (0.32 mg/cm²), is presented. The patient suffered from a chronic hand dermatitis, and when the patient stopped using a liquid soap containing MDBGN, the hand dermatitis substantially improved. A ROAT performed in a blinded and controlled way with applications twice daily on the hands with 2 moisturizers with and without MDBGN resulted in a deterioration of the hand dermatitis on the hand to which the MDBGN-preserved moisturizer had been applied.

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The preservative methyldibromo glutaronitrile (MDBGN) is used non-occupationally and occupationally, and high contact allergy rates have been reported, as well as clinical cases with allergic contact dermatitis. In spite of this background, MDBGN was not for a long time included in the European standard patch test series, as there was no agreement on which patch test concentration to use to trace contact allergy to MDBGN. However, MDBGN was recently recommended by the European Society of Contact Dermatitis and the European and Environmental Contact Dermatitis Research Group to be included in the European standard patch test series (1). A petrolatum (pet.) preparation with MDBGN at 0.5% w/w was chosen on the basis of chemical stability of MDBGN in pet. (2), consideration of rates of contact allergy, doubtful and irritant reactions (3), information on clinical relevance represented by results of a repeated open application test (ROAT) (4) and patch test concentrations required to diagnose allergic contact dermatitis from MDBGN in individual cases (5). Still, besides the concern about

the high numbers and the nature of reactions to MDBGN at 0.5%, a fear was expressed that the patch testing with MDBGN at 0.5% would miss some clinically relevant contact allergy to MDBGN (1). Indeed, this misgiving turned out to be justified as demonstrated with this case report.

Materials and Methods

Case report

A 48-year-old man without any history of atopy had suffered from a widespread dermatitis including hand dermatitis localized to the dorsal aspects of the hands and the finger sides for 7 years. He had worked as a janitor for 10 years, and he had since 2 years before the investigation at our department worked with office assignments including labour management of janitors. The investigation revealed that the widespread dermatitis was a systemic allergic contact dermatitis from non-preservative contact sensitizers which will be reported separately. In this article, the focus will be on the hand dermatitis and the

significance of exposure to a preservative to which the patient tested positively epicutaneously.

Patch testing with our standard test series including additional contact sensitizers such as metals, plastics, disperse dyes and preservatives including MDBGN at 1.0% w/w and 0.3% w/w in pet. besides the recommended 0.5% w/w (1) was performed using the Finn chamber technique and the Scanpore tape as adhesive. The patches remained on the upper back for 48 hr, and the reading was performed on D3 and D7 following the classification recommended by ICDRG (6).

High-pressure liquid chromatography (HPLC)

An analytical HPLC system consisting of a P4000 quaternary pump, a UV6000 diode array detector and an AS3000 autoinjector (ThermoFinnigan, San José, CA, USA) was used to investigate the presence of MDBGN in a liquid soap used by the patient. The injection volume was 20 µl. The column (4.6 mm i.d. × 250 mm) was packed with 5 µm Kromasil C18 100 Å (Eka Nobel, Bohus, Sweden). The mobile phase was acetonitrile/water 40/60 v/v, and the flow rate was 1.0 ml/min. The detector scanned the eluate in the range 220–360 nm.

MDBGN from Schülke & Mayr, Hamburg, Germany, was used as reference substance.

ROAT

The pharmacy at the University Hospital in Malmö prepared several pairs of moisturizers which were identical (pet., paraffin liquid, cetylaluminum (Lanette N) and water) but for the preservative. 1 moisturizer was preserved with MDBGN at 0.01% w/w and the other with phenoxyethanol at 1.0% w/w. The pairs were numbered, and allocation of the moisturizer to be applied to the respective hand was performed in a randomized way. The moisturizer to be applied to the right hand was marked with a blue tape, while a red tape was used for the moisturizer to be applied to the left hand. The patient was instructed to use the moisturizers twice daily and in the same way as he used the ordinary moisturizer to the hands. When the patient applied the left-hand moisturizer, he had a disposable glove on the right hand to avoid contamination of the right hand. A new disposable glove was used on the left hand when the right-hand moisturizer was applied. During the ROAT period, no other moisturizers were allowed. Visual inspections of the hands were performed

independently of the authors immediately before the start of the ROAT and at its termination.

Results

The results of the patch testing with 3 pet. preparations containing MDBGN are summarized in Table 1. On D3, the mandatory reading day, only MDBGN at 1.0% elicited a positive reaction.

The liquid soap used by the patient contained 0.01% w/v MDBGN.

After 2 days with 4 applications of the moisturizer, the patient stopped using both moisturizers because of perceived deterioration of the dermatitis on one hand. The patient was investigated by the authors independently, and the investigators had no knowledge on the allocation of the moisturizers to the hands and the patient's apprehension of the condition on the hands. The 3 investigators made the same conclusion implying a deterioration of the right hand, which agreed with the patient's apprehension. The code was broken thereafter. The MDBGN moisturizer had been applied on the right hand.

Discussion

Many MDBGN test preparations with various concentrations and vehicles have been used for patch testing [reviewed in (1)] demonstrating the difficulty to find the optimal test preparation to establish contact allergy to MDBGN. With a concentration of 0.5% and higher, the number of irritant and doubtful patch test reactions increases relatively more than the allergic reactions (3). However, the risk of missing clinically relevant cases of sensitization by testing only with MDBGN at 0.3% and lower has been considered unacceptably high (1) supported by cases with allergic contact dermatitis from MDBGN (5). In Germany, MDBGN at 0.2% is used and, based on the results of a recent German ROAT study (7), this concentration was considered to be further supported to be the optimal patch test concentration to trace contact allergy to MDBGN.

Table 1. The results of patch testing with 3 petrolatum preparations containing methyldibromo glutaronitrile (MDBGN)

Test preparation (MDBGN) (%)	Reading days	
	D3	D7
1.0	+	++
0.5	–	+
0.3	–	–

ROAT and other types of use tests can be used both in individual cases to help assess the clinical relevance of a positive or doubtful reaction to a sensitizer present in a product used by the patient but with a negative product patch test and in groups of hypersensitive patients undergoing ROAT with a product containing the sensitizer. When a ROAT is scientifically designed and conducted in groups of hypersensitive patients, information can be gained on the general clinical relevance and the nature of the ROAT reactions. Furthermore, ROATs can be used to help determine the optimal patch test preparation for a contact sensitizer. However, ROATs alone will only tell something on the clinical relevance in situations similar or equivalent to the experimental conditions present when performing the ROATs. Major factors of significance for the ROAT outcome are (a) the dose, i.e. the number of molecules applied per unit skin area (8), (b) type of skin, i.e. normal/damaged/diseased, on which the ROAT is performed, (c) anatomical localization, (d) type of product used, (e) temporal aspects including length of study period and frequency of applications and (f) degrees of hypersensitivity in those participating in the ROAT. For example, if a ROAT with (e) 2 applications a day during 2 weeks has been performed and resulted in negative reactions in MDBGN-hypersensitive persons in whom (f) a patch test concentration of 0.5% or higher is required to trace the MDBGN contact allergy on (b) normal skin on (c) the arms with (d) a product preserved with (a) MDBGN at a certain concentration, the negative ROAT does not necessarily mean that the contact allergy only traced with a MDBGN concentration equivalent to or exceeding 0.5% is clinically not relevant. A ROAT in (f) these individuals on (b) damaged skin in (c) the axilla or on the face with (d) a different MDBGN-preserved product from which the MDBGN penetration into the skin is higher or (a) a higher MDBGN concentration during (e) a longer period than 2 weeks may, indeed, result in positive reactions which is supported by experimental and clinical data (9–13). The present case where the MDBGN allergy only was traced by MDBGN at 1.0% on the mandatory reading D demonstrates the significance of damaged skin for the elicitation of allergic contact dermatitis (14). Initially on D3, there was no information on MDBGN exposure, so the MDBGN allergy (Table 1) was not thought to be clinically relevant. However, the ordinary information on MDBGN allergy was given to the patient on D3, and when coming back on D7 for the second test reading, there was a substantial improvement

of the hand dermatitis. There had been no change of treatment or systemic exposure to sensitizers of possible significance for his systemic contact dermatitis but a change in MDBGN exposure since 3 days. The patient had scrutinized his environment for MDBGN and found it labelled on a liquid soap used by him at home. The HPLC investigation confirmed the MDBGN presence in the liquid soap. Because of this unexpected but indicated clinically relevant MDBGN allergy, we wanted to investigate the possible clinical relevance in a more controlled way, which gave a result strongly supporting the clinical relevance of the patient's MDBGN allergy.

We have recently reported 2 cases with occupational allergic contact dermatitis from MDBGN only traced by a patch test concentration at 0.5% or higher (5). The 2 patients showed the same patch reactivity to MDBGN on the 2 reading occasions (5), while the patient in this report tested negatively to MDBGN at 0.5% on D3 but positively on D7 (Table 1). Furthermore, the intensity of the positive test reaction to MDBGN at 1.0% also increased from D3 to D7 (Table 1), and this crescendo type of patch test reactivity is uncommon for MDBGN. In a previous European multicentre study, only 2 new positive allergic reactions to MDBGN at 1.0% were noted on the second reading compared with the first reading in 1314 consecutively tested dermatitis patients (3). It is not only in Sweden where these higher MDBGN concentrations are needed to trace a clinically relevant MDBGN allergy. In a recent Danish study (9) on the significance of MDBGN exposure from a rinse-off product, a positive ROAT was obtained in an MDBGN-hypersensitive patient testing negatively to MDBGN at 0.3% (patient number 12, Table 1). Besides demonstrating that a pet. preparation with MDBGN at 0.3% may be insufficient to trace a clinically relevant MDBGN allergy, the Danish study also (9) demonstrates that MDBGN exposure on normal skin from a liquid soap, a rinse-off product, preserved with MDBGN at 0.1% is clinically relevant. It seems highly unlikely that these patients in whom a MDBGN concentration at 0.5% or higher is required to trace a clinically relevant allergy should not exist in countries other than Sweden and Denmark.

Again, it must be emphasized that the discussion on the significance of concentrations is only valid if the same patch test technique including the same vehicle, occlusion time and dose of sensitizer applied onto the patch units has been used (1, 8). The present patch testing with our standard series containing 3 MDBGN

preparations was performed by a technician who on an average (mean) applies 16.2 mg of pet. preparation onto an individual Finn chamber with a standard deviation of 2.94 (15). Thus, the calculated dose for the patch test with MDBGN at 1.0% was 0.32 mg/cm².

In summary, this article illustrates that a contact allergy to MDBGN registered on D3 and on this day only traced by patch testing with MDBGN at 1.0% (MDBGN dose 0.32 ± 0.06 mg/cm²) can be clinically relevant and further the significance of pre-existing dermatitis for elicitation of allergic contact dermatitis from MDBGN, facts which argue against using a lower patch test concentration than the currently recommended concentration for the European standard test series (1).

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