

CONTACT DERMATITIS TO METHYLDIBROMOGLUTARONITRILE: EMERGENCE OF SENSITIZATION IN THE CENTRAL REGION OF TUNISIA.

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ABSTRACT

Methyldibromoglutaronitrile (MDBGN) is a preservative found in cosmetics as well as in products for industrial use. It caused an outbreak of allergic contact dermatitis in Europe in the 1990s and early 2000s. To assess the prevalence of MDBGN sensitization among consultants in the occupational dermato-allergology unit of Farhat Hached University Hospital in Sousse-Tunisia, we carried out a study of all cases of contact dermatitis to MDBGN confirmed by patch-tests from 1 January 2011 to 31 December 2015.

The prevalence of allergic contact dermatitis to MDBGN was 4.5% of all cases of contact dermatitis recorded during the same period with an increase from 1.7% in 2011 to 5.4% in 2015. Associated allergens with contact dermatitis to MDBGN were the Peru balsam in 4 cases, nickel sulfate and kathon CG in 3 cases each.

Contact dermatitis to Dibromodicyanobutane was associated with sensitization to other preservatives in 4 cases and cosmetic allergens in 6 cases. An increasing rates of sensitization are noticed in our region. The absence of legal restrictions regarding this preservative agent may explain an increase of its use in non-European countries.

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1. Introduction

The need for use of preservatives has increased since water-based products have become more common in preventing the growth of bacteria and fungi. Several preservatives are available, but new and more effective substances are continuously introduced into the market.

Most preservatives are low molecular weight and biologically active compounds. This characteristics generate their sensitizing potential. In addition to paying attention to microbiological and economic aspects, the manufacturer must pay attention to the health aspects as well as the environmental risks in the development of preservatives [1].

MDBGN is a halogenated synthetic compound, possessing a biocidal activity against Gram + and Gram- bacteria, yeasts and fungi. Introduced since the 1980s in cosmetics to replace the allergic mixture of methylchloroisothiazolinone and methylisothiazolinone, it is used as preservative in many aqueous, cosmetic, domestic or industrial products, usually in combination with other germicides [2].

Its identification requires knowledge of its synonyms or brand names under which it can be found: Dibromodicyanobutane, Euxyl K400 © (a mixture which contains 20% methyldibromoglutaronitrile and 80% phenoxyethanol) and Tektamer 38 [3].

Shortly after its introduction on the market, the first case of contact allergy was reported in a worker handling a preserved glue with MDBGN [4]. Other cases followed in consumers using cosmetics [5-9].

Several studies have reported allergic contact dermatitis to MDBGN existing in many industrial products including degreasing paper [10], liquid soap [11] and protective creams [12].

An experimental study has detected the sensitizing potential of this particular allergen in mice and guinea pigs. In humans, this potential was explored by a study that revealed the frequency of the positive reactions to MDBGN on patch-tests in patients referred to a consultation of occupational dermatology. Authors concluded that the MDBGN was a strong sensitizer and that patients were mainly exposed to non-professional products [13].

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These several reports strongly suggested that MDBGN should be included in the European standard battery of the patch-tests [14] to which it was introduced in January 2005 [15].

On the other hand, due to the increase in contact allergy rates, MDBGN was banned in the European Union countries, first in leave-on cosmetics, and later in rinse-off cosmetics [16]. Since then, the level of sensitization decreased considerably.

However, in Tunisia, there has been no legal restrictions on its use. The aim of this study is to evaluate the prevalence of MDBGN sensitization among patients referred to perform patch-tests in the dermatology unit of the department of occupational medicine, in Farhat Hached Teaching hospital, Sousse, Tunisia.

2. Material and methods

We conducted a descriptive retrospective study of all cases of contact dermatitis to MDBGN collected at the Dermato-allergology Unit of the Department of Occupational Medicine of the Farhat Hached University Hospital of Sousse during a period of five years from 1 January 2011 to 31 December 2015.

During the study period, all patients who consulted with contact dermatitis to MDBGN confirmed by patch-tests were enrolled in the study regardless of age and occupational status.

Data were collected using a pre-established questionnaire covering: socio-demographic characteristics (age, gender, habits), occupational characteristics (occupation, occupational seniority), allergic and non-allergic past illness history, initial localization of skin lesions, handled occupational and extraprofessional products, and results of the patch-tests 48 hours after the application of the European Standard Battery.

The patch tests were applied according to the protocol recommended by the International Contact Dermatitis Research Group (ICDRG) [17]. During the study period, the European Standard Battery included 28 allergens. Patients who had a positive test for Dibromodicyanobutane were included in the study.

Patch-tests were applied on healthy skin in the high dorsal paravertebral region. They were applied under occlusion at a precise concentration and in an appropriate vehicle.

These patch-tests were removed at the 48th hour. Results reading was performed after about 30 minutes, in order to eliminate any pressure or occlusion caused by the adhesive bandage.

Results were coded according to an interpretation scale (visual Key) adopted by the International Contact Dermatitis Research Group (ICDRG) [18]:

- a. (-): negative reaction
- b. R: irritant reaction
- c. ±, + or ? : Doubtful reaction
- d. 1+ : Light erythema, nonvesicular
- e. 2+ : Edema, erythema, discrete vesicles
- f. 3+ : Coalescing vesiculobullous papules

Data were analyzed using SPSS 18.0. We calculated the frequencies and percentages for the qualitative variables, as well as averages, standard deviations and the extent of extreme values for the quantitative variables.

For the comparison of the averages we used: Student's "t" test for the comparison of two means of independent series.

Frequency comparison was performed with the Pearson Chi 2 test.

Linear regression was used for estimating the trends of number of cases.

For all statistical tests, p-value threshold was set to 0.05.

3. Results

The prevalence of allergic contact dermatitis to MDBGN was 4.5% of all cases of contact dermatitis recorded during the same period (n = 37) with an increase from 1.7% in 2011 to 5.4% in 2015 (Figure 1).

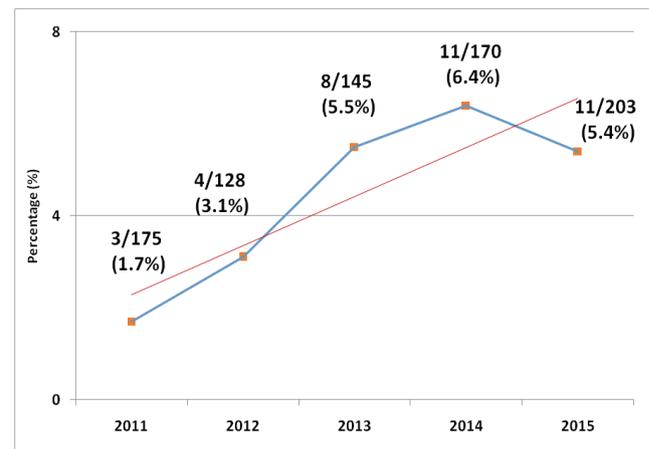


Figure 1 - Evolution of cases of contact dermatitis to MDBGN compared to the total number of patch tests per year.

The mean age of our population was 49.7 ± 14.7 years with extremes of 17 years and 79 years. Almost half (48.6%) of patients were over 50 years of age.

Contact dermatitis to MDBGN affected both genders with a slight male predominance. The sex ratio was 1.31.

Among the extraprofessional activities, we noted a predominance of household activity (37.8% of our patients). Car maintenance was practiced by 8.1% of the cases. Cosmetic products were suspected as causative agents by 3 patients, ie 11.4% of the cases.

Occupied patients accounted for 78.3% of cases and were Hand workers in 27% of cases, administrative agents in 13.5% of cases, mechanics in 10.8% of cases and nurses in 5.4% of cases. Mean occupational seniority was 12.86 ± 9.33 years with extremes ranging from 1 month to 34 years.

Similar cases under the same working conditions were described by 6 patients, ie 16.2% of cases. Protective gloves were used by 15 patients (40.5%).

Hand was the most frequent location of lesions with 22 cases (59.45%) followed by legs and feet with 40.5% and 32.4% respectively. Pruritus was the main functional sign reported; It was found in 89.1% of patients (n = 33). Burning sensations were found in 15 patients (40.5% of cases).

An improvement of lesions after work stopping was reported by 37.8% of patients (14 cases).

Of the 37 cases of MDBGN positive patch tests, the reaction grade was 2+ in 19 cases and 1+ in 18 cases.

Allergic Contact dermatitis to MDBGN was associated with positive patch-tests reactions to other preservatives in 4 cases and to cosmetic allergens in 6 cases. The most commonly associated allergens were Peru balm in 4 cases, nickel sulfate in 3 cases and the Kathon CG in 3 cases. Formaldehyde and lanolin were found in one case each.

Relevance was detected in at least 45.94% (n = 17) of the positive patch tests. The causes of the reaction were cosmetics, cleaning products, liquid soap, industrial oils and paint.

Declaration of contact dermatitis as an occupational disease was performed for only one patient (a mechanic exposed to industrial oils co-sensitized to Kathon CG) according to the Tunisian legislation.

The growing number of diagnosed cases of allergic contact dermatitis to Dibromodicyanobutane was statistically significant with $p = 0.009$ and $r = 0.962$.

There was a statistically significant association between gender and household maintenance ($p = 0.001$). Indeed, this activity was more frequent among women. Gender was significantly associated with employment, which was almost double in men ($p = 0.019$).

Gender was significantly associated with the initial location in the palm of the left hand that was more common in men ($p = 0.047$). Women used antihistamines more frequently than men with a statistically significant association ($p = 0.046$).

4. Discussion

In our study, we carried out a retrospective investigation of the cases of allergic contact dermatitis (ACD) explored by patch tests with positive reactions to MDBGN. Although our results show an increasing number of sensitized patients to this allergen, larger studies with longer periods of observation and more important number of cases are necessary to confirm this ascertainment.

Patients included in this study were all clinically suffering from ACD, which does not allow to take into account clinically healthy subjects. However, for ethical considerations, the "testing" of healthy subjects in search of sensitization cannot be considered.

The reading of the tests was carried out by several different doctors, highly trained to this exercise. Differences in interpretation are reduced by the use of the same ICDRG nomenclature [18].

MDGN is a biocide contained in multiple cosmetic products, hygiene products and related products: creams, milks and lotions, liquid soaps, shampoos ... [2]. Industrial applications include its use as a preservative for latex emulsions, glues and adhesives, water-based paints, sealing cements, cutting oils and cleaning products (dishwasher liquids, Liquid detergents, fabric softener concentrates). MDGN may also be present in wood preparation products, seed disinfectants, and paper and paperboard (in which it may be incorporated as an anti-mold during manufacture) [19].

In June 2002, the Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP), Consultative of the European Commission, replaced since 2004 by The Scientific Committee on Consumer Products (SCCP), recommended a restricted use of MDGN to rinse-off products because of the risk of allergic contact dermatitis. This decision was applied on 24 September 2005 following an agreement with EU members and was based on epidemiological data showing an increase in the

frequency of MDBGN-induced contact dermatitis in Europe, over a period of 10 years [20].

As a result of new experiments and epidemiological evidence showing that rinse-off products also caused allergic contact dermatitis with MDBGN [21-24], the Scientific Committee on Consumer Products (SCCP) recommended in March 2005 that MDGN can no longer be present in cosmetic products. This opinion was accepted and, as from 22 June 2008, no cosmetic product placed at the disposal of the European consumer contains MDGN [16]. Decreasing trends in contact allergy to MDBGN were observed shortly after regulatory intervention [30].

In Denmark, in a study that evaluated the frequency of contact allergy to MDGN before and after regulatory decisions among patch-tested patients, a significantly decreasing frequency of Positive tests for MDGN was observed, decreasing from 4.6% in 2003 to 2.6% in 2007 ($p < 0.001$). This reduction was due to the reduction in exposure in 2002 [16].

However, more recent Danish data show that the prevalence of allergy to MDGN remains high (4%) [31].

In Czech Republic, 1941 patients with ACD were patch-tested with European Standard Battery between 2008 and 2012. The prevalence of MDBGN sensitivity was 0.8% of patients and was between 0.5 and 2.5% during the study period [32]. Vigan M. [3] states that since its ban, the MDBGN sensitization rate has decreased considerably and that its presence in standard battery could be discussed.

In our study, current relevance was detected in at least 45.94% (n = 17) of the positive patch tests to MDBGN. In a study conducted by dermatologists, the reaction was found to be relevant in 53 cases (52.4%). Creams and lotions accounted for 31% of the products identified, compared with 23% for liquid soaps [28].

In a review of the literature, the relevance of the observed reactions was evaluated by several authors. Between 23% and 75% of the positive patch-tests were considered relevant. Cosmetics were usually the causative agent of the allergic reaction [19]. Between 2000 and 2005, in a retrospective epidemiological study, clinical relevance was observed in 76.5% of positive patch tests [33].

In Denmark, 19,279 patients were patch-tested between 2003 and 2007 with MDBGN at 0.3% or Euxyl K 400 at 1.5%. Current relevance was found in 39.7% of cases with a significantly decreasing trend from 51.3% in 2003 to 29% in 2007 ($p < 0.001$). It appears that the MDGN has been removed from many products in this country. It was detected in only 3% of the products used by patients with a positive MDGN test-patch in 2007 [16].

In our study, positive reactions to MDBGN were associated with sensitization to preservatives in 4 cases (3 cases to Kathon CG and one case to formaldehyde) and to cosmetic allergens in 6 cases (Peru balm for 4 cases, Fragrances mix I for one case and lanolin for one case).

The allergens concomitant to MDBGN sensitization most frequently cited in the literature were Kathon CG, fragrances, formaldehyde or formaldehyde releasers and lanolin (wool alcohol) [19, 25, 34]. Since most cases of allergy to Euxyl K 400 are caused by cosmetic products, some patients allergic to Euxyl K 400 are also expected to react to other common cosmetic ingredients (approximately 50%) [19].

The results of our study were almost similar to those found in other countries, expect the trends in the frequency of cases of ACD to MDBGN. While number of cases decreased in European Union as a direct result of regulatory restrictions, we noticed an increasing rate of sensitization

among patients patch-tested in our department.

Various explanations can be discussed. As the use of this preservative has been reduced in Europe, MDGN consumption could have been reoriented to countries where it was still allowed, such as Tunisia. Also, the study period was marked by a political instability (Tunisian revolution) and an absence of control of industrial or cosmetic products introduced to the Tunisian market with a possible high concentrations of MDBGN. A wider study covering other Tunisian regions and a longer study period are necessary to bring more clarifications.

Conclusion:

Contact sensitization to MDBGN is an increasing problem in our region. An urgent re-evaluation of its use concentrations combined with a new risk assessment are required. These measures need prior identification of the source of contact with this preservative and whether it is due to local products or to consumption of products that do not comply with European standards which corresponds to an "import of allergens". While the necessity of this allergen in European Standard battery is seriously discussed after the decrease in number of cases in Europe, it seems that MDBGN should be tested in Tunisian ACD patients because of the growing number of sensitized cases. The application of regulatory restrictions similar to those applicable in Europe can be a preventive measure of a possible epidemic evolution of ACD to MDBGN.

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