A.I. Lorente-Lavirgen[1], C. Almeida[2], J. Bernabeu[1], V. Valero[3], R. Lorente[3]

Methylchloroisothiazolinone / methylisothiazolinone: epidemiological retrospective study

[1]Dermatology Department, Virgen del Rocio University Hospital, Seville, Spain
[2]Statistical and Methodology Department, FISEVI, Seville University, Seville, Spain
[3]Industrial Engineering School, Extremadura University, Badajoz, Spain

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Corresponding author
Ana I. Lorente-Lavirgen
Dermatology Department
Virgen del Rocio University Hospital
Avda. Manuel Siurot, S/n
41013 Sevilla, Spain
Phone: +34 661 570 058
Fax: +34 661 570 058
E-mail: ariselae84@gmail.com

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To the Editor

Allergic contact dermatitis (ACD) is a common problem confronted in clinical practice and several authors have started to point to MCI/MI as an emerging allergen primary present in many daily cosmetic (1,2) since late 80s. The present study was carried out to described the epidemiological characteristic of patients with ACD to MCI/MI during a 10 years period. We want to elucidate factors associated and identify the clinical and epidemiological features of patients with ACD to MCI/MI.

During a period of ten years, every adult patient with signs or symptoms of eczema attending our Contact Dermatitis Department, located in the University Hospital Virgen del Rocío (Seville, Spain), were recruited. They underwent a clinical history, dermatological exploration and patch test with the standard series of the Spanish Contact Dermatitis and Skin Allergy Research Group (GEIDAC) (3). All patients were tested with certified allergen supplied by True Test® (TRUE test; Mekos Laboratories ApS, Denmark). Patches were applied to the upper back using Scanpore® and left on for 48 h; then read on day D2 (48 h), and D4 (96h). We considered positive responses those in which erythema, infiltrated papules or vesicles were detected. All patients' personal data were firstly anonymized and manually entered into a computerized database (Microsoft Excel 2011 for Mac, version 14.0.0). Data were analysed with the Statistical Package for Social Sciences (SPSS) program 25.0; several statistical analyses were performed when needed (chi-square test), and $p < 0.05$ was considered statistically significant. This study has been prepared respecting the fundamental principles established in the Declaration of Helsinki (1946). The research project has undergone evaluation by the Committee of Ethics and research clinic of our University Hospital and all patients have been informed about the project.

A total of 142 patients had a positive patch test reaction to MCI/MI. The allergic contact dermatitis to MCI/MI diagnosis was based on medical history and a relevant patch test reaction, which was found in 118 patients, representing 8% of the total.
The age range of patients was from 14 to 89 years (mean age 51 years); 58.5% of the patients were males (n = 69) and 41.5% (n = 49) were females. By age group, sensitization to MCI/MI was more frequent in adults over 40 years old (79.6%). The most frequent location was hands (62.9%, n = 73), followed by diffuse involvement of different body parts (16.4%, n = 21); 11.3% of patients had facial lesions (n = 13), 4.3% (n = 5) had axillar eczema, 4.3% (n = 5) had foot eczema, and only 0.9% (n = 1) had genitalia-perianal eczema. No statistically significant differences were found.
Furthermore, 12.7% had a pre-patch test diagnosis of atopic dermatitis (n = 15), 8.5% psoriasis (n = 10), and 0.9% seborrheic dermatitis (n = 1). We found that patients with atopic dermatitis had three times increased relative risk to and tested positive for MCI/MI with statistically significant differences (p = 0.016, OR 3, confidence interval of 95% [1.2/6.4]).
Of the patients, 70.7% (n = 83) were in careers with manual activities involving wet work, compared with 29.3% (n = 35) who did not use their hands in their professional activities. The most frequently registered profession was cleaners/janitors (40.2%, n = 37), followed by office workers (19.6%, n = 18). Only 5 patients were identified as having occupational dermatitis (4%), of which 2 were related to the use of paints and 3 were associated with cosmetic or household products used in their work. No statistically significant differences were found between locations or professions and a positive sensitization to MCI/MI.
The most common sources of exposure related to MCI/MI found in our group were bath products (46.6%, n = 55), baby wipes (26.27%, n = 31), household cleaning products (14.40%, n = 17), and beauty products (12.70%, n = 15).
Finally, we studied whether patients with positive patch test results for MCI/MI had concomitant sensitization to other substances, particularly other preservatives. These data are included in **table I**. We found that patients with positive patch test results for Quaternium 15 had an increased relative risk to or had sensitization to MCI/MI with statistically significant differences (p < 0.0001, OR 8, IC 95% [3.7/17.8]). Furthermore, patients with positive patch test results for formaldehyde also had an increased relative risk sensitization to MCI/MI with statistically significant differences (p < 0.0001, OR 6, IC 95% [2.5/13.2]).
Finally, in the MOAHLFA index (male, occupational dermatitis, atopic dermatitis, hand, leg, > 40 years old), 58.5% were men, 4.24% had occupational dermatitis, 57.7% had atopic dermatitis, 62.9% had hand eczema, 0% had leg eczema, 9.5% had facial eczema, and 79.6 % were over 40 years old.
A recent meta-analysis published in 2018 revealed that at least 20% of the general population have contact-allergic dermatitis due to common environmental allergens (4). Hypersensitivity reactions to metals are one of the most common (5), but a concerning increased sensitization to MCI/MI had been detected since the late '80s. Lundov et al. (6,7) revealed that MI ACD is estimated to have a prevalence of 1.5% in 2011, which has been increasing in the next years, mainly affecting middle-aged women with hand and facial dermatitis most often associated with cosmetics. In 2014, Aerts et al. showed an increase in sensitization rate to MCI/MI of 4.5% (7). Our group's sensitization rate to MCI/MI is 8%, significantly higher than in other papers (6,7,8). Most studies on ACD to MCI/MI revealed a predominance in women (7,9) whereas in our study group, we found little predominance of males affected (58.5%, n = 69). We think this can be a point of confusion because men were asked more frequently in our study sample. Atopic dermatitis was the most common dermatological disease registered in our series in contrast with dyshidrotic eczema in the de Unamuno series, which studied a population similar to ours (10). Furthermore, we described that patients with AD had three times higher risk to sensitization to MCI/MI probably associated with skin barrier alterations in this group of patients.
The most frequent concomitant allergen in the de Unamuno (10) group and other series was nickel sulfate whereas it was formaldehyde and Quaternium 15 in our study group, although we also detected a high number of patients with concomitant positive patch test to disclosure cobalt and nickel sulfate (**table I**). In fact, we want to emphasize that it is particularly interesting that formaldehyde and the formaldehyde releaser Quaternium 15 are not only allergens more often concomitant with MCI/MI sensitization, but we also found statistically significant differences between these allergens and MCI/MI. These substances are preservatives used to prevent contamination in cosmetics and household products. Warshaw et al. (5) reported in 2013 that formaldehyde, Quaternium 15, and MCI/MI were the preservatives that most frequently tested positive to the patch test in the North American Contact Dermatitis Group (NACDG) (5). A positive sensitization to MCI/MI was much more prevalent in janitors and cleaners (n = 37, 40.2%), followed by office workers (n = 18, 19.6%) and builders (n = 8, 8.7%).
Thus, we conclude that humidity affects the process of allergic contact dermatitis, but MCI/MI is so prevalent in daily cosmetic products that further studies are needed to elucidate whether this is associated with professions or daily contact with cosmetic and cleaning products. In addition, our result supports that the prevalence of MCI/MI is increasing in all developed countries. Many other studies are necessary to explain risk factors for ACD to preservatives.

Conflict of interest

The authors declare that they have no conflict of interest.

Table I *- Patients with positive patch test to MCI/MI and concomitant sensitisation to other substance in patch-test.*

Allergens		MCI/MI negative (N)	MCI/MI negative (%)	MCI/MI positive (N)	MCI/MI positive (%)
potassium dichromate	**negative**	1252	91.7%	110	93.2%
	positive	114	8.3%	8	6.8%
Caine mix	**negative**	1349	98.8%	113	95.8%
	positive	17	1.2 %	5	4.2%
fragrance mix	**negative**	1302	95.3%	110	93.2%
	positive	64	4.7%	8	6.7%
balsam of Peru	**negative**	1333	97.6%	113	95.8%
	positive	33	2.4%	5	4.2%
cobalt dichloride	**negative**	1260	92.2%	109	92.4%
	positive	108	7.8%	9	7.6%
paraben mix	**negative**	1357	99.3%	117	99.2%
	positive	9	0.7%	1	0.8%
carba mix	**negative**	1338	98.0%	112	94.9%
	positive	28	2.%	6	5.1%
Quaternium-15	**negative**	1349	98.8%	107	90.7%
	positive	17	1.2%	11	9.3%
p-phenylenediamine	**negative**	1317	96.4%	113	95.8%
	positive	49	3.6%	5	4.2%
formaldehyde	**negative**	1347	98.6%	109	92.4%
	positive	19	1.4%	9	7.6%
thiuram mix	**negative**	1345	98.5%	116	98.3%
	positive	21	1.5%	2	1.7%
diazolidinyl urea, Germall II	**negative**	1358	99.4%	117	99.2%
	positive	8	0.6%	1	0.8%
imidazolidinyl urea, Germall 115	**negative**	1361	99.6%	117	99.2%
	positive	5	0.4%	1	0.8%

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