

Multicenter Patch Testing With Methylisothiazolinone and Methylchloroisothiazolinone/ Methylisothiazolinone Within the International Contact Dermatitis Research Group

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Background: The preservatives methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) and MI are well-known contact sensitizers. Recently, an increase in the contact allergy frequency for MI 0.2% aqueous (aq) has been seen in many European countries paralleled with an increase in MCI/MI allergy. Many of the MI-allergic patients do not react to MCI/MI 0.01% or 0.02% because the concentration of MI in these preparations is too low (25 and 50 ppm, respectively) to elicit a positive patch test reaction.

Objectives: The aims of this study were to investigate the prevalence of contact allergy to MI in the participating clinics representing various countries all over the world, to assess how many additional individuals with contact allergy are found by testing MI 0.2% aq in parallel with MCI/MI 0.02%, and to assess the clinical relevance of MI and MCI/MI allergies.

Patients and Methods: In 9 dermatology clinics representing 9 countries, 3865 consecutive patients with dermatitis were patch tested with MI 0.2% aq and in parallel with MCI/MI 0.02% aq, provisionally included into the baseline series. An assessment of clinical relevance in those allergic to MI was also made.

Results: Contact allergy to MI was found in 284 patients (7.3%). The frequency of contact allergy varied from 0.8% to 10.9% in different centers. Simultaneous reactivity to 200 ppm of MCI/MI was found in 67.3% of the MI-positive patients. Contact allergy to MI alone without any simultaneous contact allergy to 200 ppm of MCI/MI was diagnosed in 93 patients (32.7%; 2.4% of all tested patients). The contact allergy to MI and/or MCI/MI could explain or contribute to dermatitis in more than 60% of the MI-allergic patients.

Conclusions: Methylisothiazolinone of 2000 ppm needs to be patch tested on its own to not miss contact allergy.

The preservative methylisothiazolinone (MI) without methylchloroisothiazolinone (MCI) has been marketed since

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the early 2000s, first in industrial products such as paints and water-based glues and later also in cosmetics with a recommended concentration in leave-on products in the range of 50 to 100 ppm. Methylisothiazolinone was demonstrated to be a sensitizer in humans and guinea pigs already in the mid-1980s.^{1,2} The first occupational cases of allergic contact dermatitis from MI was reported from the Malmö Department.³ After the first report on MI contact allergy related to cosmetics in 2010, there has been an "epidemic" of contact allergies to MI.^{4–12} It has been concluded that the risk assessment performed by the industry was insufficient before introducing MI on the market.¹³ In the early 2000s, the optimal patch test concentration for MI was not known. After a multicenter study in Europe,¹⁴ MI 0.2% was recommended to be included in the European baseline series from 2014.¹⁵ Since then, we have seen rising frequencies of contact allergy to MI, as well as to MCI/MI.

The aims of this study were to investigate the frequency of contact allergy to MI in the participating clinics and to see whether MI 0.2% should be included into the international baseline series. In this article, testing with MI and MCI/MI 0.02% will be covered, whereas testing with MCI/MI 0.01% versus 0.02% will be covered in another article.¹⁶

MATERIALS AND METHODS

Study Population

Nine patch-testing clinics representing 9 countries participated in the study from January 1, 2014, to December 31, 2014.

In these clinics, 3865 consecutively patch-tested patients with dermatitis, with 1272 men (mean age, 43.2 years; range, 6–86 years) and 2593 women (mean age, 44.7 years; range, 3–95 years), took part (Table 1).

Substances

The test preparations were bought from Chemotechnique Diagnostics, Vellinge, Sweden, and distributed to all participating departments from the Malmö Department. Methylisothiazolinone 0.2% w/w aqueous (aq) and MCI/MI 0.02% w/w aq were used.

Patch Testing

The test preparations were provisionally included into the baseline series in all clinics. Patch testing and reading of the patients followed the routines of the participating clinics, using Finn Chambers on Scanpor tape (Ø 8 mm; SmartPractice, Phoenix, AZ) in 8 clinics, whereas 1 clinic used Van der Bend (Brielle, the Netherlands) chambers (8 × 8 mm).

For solutions, a micropipette was used to apply the correct dose for the test system of choice (ie, for a Finn Chamber, 15 μ L and 30 μ L/cm²; for a Van der Bend chamber, 20 μ L and 30 μ L/cm²).¹⁷ This corresponds to the doses of 6 μ g/cm² for MCI/MI 0.02% and 60 μ g/cm² for MI 0.2%. The test chambers were left on the back for 2 days, and readings were taken following the guidelines of the International Contact Dermatitis Research Group.¹⁸ The common reading day was day (D) 3 or 4 (reading 1). In 6 clinics (2092 patients), mandatory readings in all patients were also taken on D7. A positive reaction on D3 or D4 was registered as a positive reaction in this study, and the results in this article are based on these readings only if not otherwise stated. An individual test protocol designed for the study was filled in for each patient with patch test reactions (allergic, doubtful, or irritant) to at least one of the following test preparations: MI 0.2% or MCI/MI 0.02%. It was emphasized that all patch test reactions without an obvious morphology of an allergic or irritant nature must be classified as doubtful. Late reactions beyond D8 were to be reported. In all patch testing centers, the sites of a present dermatitis in all MI- or MCI/MI-positive patients, as well as an assessment of clinical relevance of the contact allergy to MI and/or MCI/MI, were to be registered. The reading dermatologist had the option to tick several locations, namely, the hands, arms, trunk, neck, face, scalp, legs, and feet. For clinical relevance, he/she also had 1 of 4 options to tick, namely, explains the dermatitis, aggravates/contributes to the dermatitis, has no influence on the dermatitis, or has unknown influence on the dermatitis. Whether the exposure was occupational or nonoccupational was also to be ticked.

TABLE 1. The Number of Patch-Tested Patients to MCI/MI 0.02% and MI 0.2% in the 9 Centers, the Number and Percentage of Positive Patients Reacting to MI 0.2% and MCI/MI 0.02%, and the Number of Doubtful Reactions to MI 0.2%

Patch Testing Clinic	MCI/MI and MI 0.2%				MI 0.2%				MCI/MI 0.02%				MI 0.2%	
	Total No. Tested	Men	Women	Total No. (%) Positive Patients	Men	Women	Total No. (%) Positive Patients	Men	Women	Total No. (%) Positive Patients	Men	Women	Total No. (%) Doubtful Reactions	Total No. (%)
Fujita, Japan	244	47	197	2 (0.8)	1 (2.1)	1 (0.5)	4 (1.6)	2 (4.3)	2 (1.0)	4 (1.6)	2 (4.3)	2 (1.0)	5 (2.0)	
Leuven, Belgium	470	142	328	35 (7.4)	10 (7.0)	25 (7.6)	24 (5.1)	7 (4.9)	17 (5.2)	24 (5.1)	7 (4.9)	17 (5.2)	1 (0.2)	
Malmö, Sweden	725	238	487	56 (7.7)	13 (5.5)	43 (8.8)	58 (8.0)	14 (5.9)	44 (9.0)	58 (8.0)	14 (5.9)	44 (9.0)	6 (0.8)	
Mumbai, India	43	28	15	2 (4.7)	2 (7.1)	0	0	0	0	0	0	0	0	
Odense, Denmark	559	181	378	37 (6.6)	8 (4.4)	29 (7.7)	41 (7.3)	7 (3.9)	34 (9.0)	41 (7.3)	7 (3.9)	34 (9.0)	11 (2.0)	
Singapore	302	157	145	33 (10.9)	9 (5.7)	24 (16.6)	9 (3.0)	3 (1.9)	6 (4.1)	9 (3.0)	3 (1.9)	6 (4.1)	3 (1.0)	
St John's, United Kingdom	1176	369	807	101 (8.6)	19 (5.1)	82 (10.2)	82 (7.0)	11 (3.0)	71 (8.8)	82 (7.0)	11 (3.0)	71 (8.8)	2 (0.2)	
Montevideo, Uruguay	219	68	151	5 (2.3)	1 (1.5)	4 (2.6)	5 (2.3)	2 (2.9)	3 (2.0)	5 (2.3)	2 (2.9)	3 (2.0)	0	
Jena, Germany	127	42	85	13 (10.2)	6 (14.3)	7 (8.2)	9 (7.1)	3 (7.1)	6 (7.1)	9 (7.1)	3 (7.1)	6 (7.1)	2 (1.6)	
Total	3865	1272	2593	284 (7.3)	69 (4.9)	215 (8.8)	232 (6.0)	49 (3.4)	183 (7.5)	232 (6.0)	49 (3.4)	183 (7.5)	30 (0.8)	

TABLE 2. Localization of Dermatitis in All MI-Allergic Patients (Men and Women Separately)

Sex	No. Patients	No. Patients With Dermatitis Present at Patch Testing in the Respective Localization								
		Hands	Arms	Trunk	Neck	Face	Scalp	Legs	Feet	Genital/Perianal
Male	69	39	30	18	6	27	2	15	5	4
Female	215	93	25	22	28	117	5	20	14	6
Total	284	132	55	40	34	144	7	35	19	10

Statistics

Fisher exact test was used to investigate any sex differences in the frequencies of positive reactions. Contact allergy rates to MI without any simultaneous contact allergy to MCI/MI 0.02% were compared between the centers. We regarded 2-sided $P < 0.05$ as statistically significant.

RESULTS

The results are summarized in Tables 1 to 3. In the 12-month period, 3865 patients were patch tested to MI 0.2% and MCI/MI 0.02%. Contact allergy to MI 0.2% was found in 284 patients (7.3%). Furthermore, 215 (8.3%) of the 2593 women tested positively to MI versus 69 (5.4%) of the 1272 men ($P = 0.0013$). The frequency of contact allergy varied from 0.8% to 10.9% in different centers. In addition, 143 (50.4%) of 284 of the test reactions were strong (++/+++). The number of doubtful or irritant reactions reported to MI 0.2% was 30 (0.8%) and 0, respectively. One case of suspected patch test sensitization was noted.

Contact allergy only to MI and not to MCI/MI 0.02% was found in 93 patients (2.4%; 66 [2.5%]/2593 of the women and 27 [2.1%]/1272 of the men; $P > 0.3$). Contact allergy to both MI 0.2% and MCI/MI 0.02% was seen in 191 patients (67.3% of all MI-allergic patients, 4.9% of all tested), with 42 men and 149 women ($P < 0.001$). Contact allergy only to MCI/MI was seen in 41 patients.

Among the 284 MI-allergic patients, 144 (50.7%) had facial dermatitis, 132 had hand eczema, 55 had eczema on the arms, 40 had eczema on the trunk, 35 had eczema on the legs, 34 had eczema on the neck, 19 had eczema on the feet, 10 had genital or perianal eczema, and 7 had eczema on the scalp (Table 2).

Of the 144 patients with facial dermatitis and MI allergy, 117 were women ($P < 0.001$). One hundred thirty-two of the 284 MI-allergic patients had hand eczema. Of these, 93 were women ($P > 0.3$).

Of the 248 MI-allergic patients, 90 were reported to have a known present exposure to MCI/MI, and in 115, there was a known present exposure only to MI (Table 3). The stated sources of such information were as follows: dermatologist's own experience in 10 cases, product labeling in 104 cases, material safety data sheets in 4 cases, and chemical analyses in 4 cases (1 in Odense and 3 in Malmö). Regarding the offending cause in 257 noted cases, in 21 cases (8.2%), the type of exposure was occupational, and in 193 cases (75.1%), the exposure was nonoccupational. In another 13 cases, the exposure was both occupational and nonoccupational, and in 30 cases, the exposure was unknown. In 109 MI-allergic patients, the dermatitis could be explained by the exposure to MI only or was considered to

be aggravated by such exposure, that is, in 38.4%. In 84 MI-allergic patients, the dermatitis could be explained by the exposure to MCI/MI or was considered to be aggravated by such exposure, that is, in 33.9%.

In 179 MI-allergic patients, the dermatitis could be explained by the exposure to either MI or MCI/MI or was considered to be aggravated by such exposure, that is, in 63.0%.

In this latter group, 84 patients had hand eczema, with 59 women and 25 men. In 96 cases where the exposure to MI or MCI/MI was considered without influence or having unknown influence, 46 had hand eczema, with 33 women and 13 men.

DISCUSSION

The overall prevalence of contact allergy to MI 0.2% aq in 9 dermatology departments in 9 countries was 7.3% (Table 1), a figure very much the same as seen in Europe in the last few years.^{19–21} However, there was a big variation among the 9 centers. A recent study within the European Environmental Contact Dermatitis Research Group showed a contact allergy rate of 3.7% to the same MI preparation we have used,¹⁴ whereas a newly finished Swedish multicenter study patch testing MI 0.2% in parallel with MCI/MI 0.02% found an exclusive MI contact allergy rate of 0.8% to 4.2%.¹⁹

In this study, 67.1% of the patch-tested patients were women, and they were more often allergic to MI on its own ($P = 0.001$) and to both MI and MCI/MI ($P < 0.001$) compared with men. The overrepresentation of women allergic to MI has been described in several studies.²⁰ The clinical presentation has often been facial dermatitis due to cosmetics containing MI, for example, wet wipes. In the United Kingdom, the industry even changed the composition because of the alarming frequencies of MI allergy. Our study also shows a statistically significant difference concerning facial dermatitis and MI allergy in women compared with men, and the reason is most probably due to cosmetics. For men, MI allergy has been linked to hand eczema, for example, in painters exposed to water-based paint or glue.^{22–25} In this study, there was no statistically significant difference in having hand eczema and MI allergy between men and women. This could be due to a relatively low frequency of occupational cases in both sexes. Some centers see mostly occupational patients, and some see more nonoccupational patients. In our material, there were most nonoccupational cases examined and tested.

Interestingly, only men reacted positively to MI in Mumbai (2/28 vs 0/15), but then, very few were tested.

We also found a high frequency of clinical relevance in those allergic to MI (Table 3). In almost 40%, the dermatologist considered dermatitis for which the patients had been patch tested to be

TABLE 3. Present Exposure to MCI/MI and/or MI Only, Occupational Exposure or Not, and Clinical Relevance in All MI-Allergic Patients

Sex	Known Present Exposure to MCI/MI, n (%)	Known Present Exposure Only to MI, n (%)	Occupational Exposure, n (%)	Relationship Between Present Dermatitis and Exposure, n (%)
Male	25 (36.2) Yes	23 (33.3) Yes	10 (15.9) Yes	23 (34.8) Explains*
	29 (42.0) Possible	26 (37.7) Possible	36 (57.1) No	20 (30.3) Aggravates†
	8 (11.6) No	15 (21.7) No	7 (11.1) Both	1 (1.5) No influence
	7 (10.1) No info	5 (7.2) No info	10 (15.9) Unknown	22 (33.3) Unknown influence
Total no. notations	69 notes	69 notes	63 notes	66 notes
Female	65 (30.7) Yes	92 (42.8) Yes	11 (5.7) Yes	82 (39.2) Explains
	89 (42.0) Possible	75 (34.9) Possible	157 (80.9) No	54 (25.8) Aggravates
	26 (12.3) No	27 (12.6) No	6 (3.1) Both	11 (5.3) No influence
	32 (15.1) No info	21 (9.8) No info	20 (10.3) Unknown	62 (29.7) Unknown influence
Total no. notations	212 notes	215 notes	194 notes	209 notes

*Explains the dermatitis under investigation.

†Aggravates the dermatitis under investigation.

explained by the exposure to MI only or to be aggravated by such exposure. In the same way, in almost 35%, the exposure to MCI/MI was clinically relevant. Taken together, in 63%, the dermatitis could be explained or was considered to be aggravated by the exposure to either MI or MCI/MI. In most cases, the culprit products were cosmetics in the nonoccupational cases.

Besides differences in sex, differences in age, atopy, work procedures, and hand, leg, and face dermatitis may also contribute to the results, as well as technical aspects of the patch test procedure. In a recent article on how to improve the quality of multicenter patch test studies, 16 factors of possible significance were discussed and scored.²⁶ According to the quality ranking suggested, based on the total score of the 16 factors, this multicenter study is ranked as having an acceptable quality. Areas where the highest scores are not given concern different test systems, not the same occlusive tapes, no control of adhesiveness, only 1 common reading day, lack of calibration of reading, and no monitoring.

There are many possible explanations for the considerable differences in the prevalence of contact allergy to MI between the various centers including simultaneous reactions to MCI/MI. It could be due to differences in referrals of patients for patch testing and differences in exposure habits. Another explanation may be differences in the evaluation of the morphology of a test reaction. No clinic reported irritant patch test reactions to MI 0.2% on D3 or D4. The percentage of doubtful reactions varied from 0% to 2.0% (Table 1). This variation implies that standardization is warranted not only for the dose of the patch test¹⁷ but also for the morphology of irritant, doubtful, and weak reactions. Moreover, in this study, 5 patients (0.2% of those regularly read also on D7) with contact allergy to MI were detected only on the second reading on D7, in correspondence to many other sensitizers, which are missed if a late reading is not performed.^{27–30} Of the 5 additional positives to MI, all were weakly positive (+) on D7, and four were doubtful and one was negative on D3 or D4. When looking at the clinics regularly performing a D7 reading, of the 25 with a doubtful reaction on D3 or D4, four had a positive (+) reaction on D7. Thus, at least 16% of the doubtful reactions represented allergic reactions. This emphasizes the importance of performing a patch test reading also late, that is, on D7 or D8.

Concerning patch test sensitization, there was 1 suspected case. However, this patient was not retested with serial dilutions of MI, so we do not have substantial evidence of a test sensitization. As MI, as well as MCI/MI, has a very steep dose-response curve, it is of utmost importance to apply an exact dose when patch testing, and the only way is to always use a micropipette.¹⁷

To conclude, contact allergy to MI 0.2% alone without any simultaneous contact allergy to MCI/MI 0.02% was diagnosed in 93 patients (2.4% of all tested patients). The hands (equally common in men and women) and face (significantly more common in women) were the most common sites of dermatitis in these MI-allergic patients. The contact allergy to MI and/or MCI/MI could explain or contribute to the dermatitis in 63% of the patients. Therefore, MI 0.2% needs to be patch tested on its own to not miss contact allergy, and a micropipette should be used to get an exact dose.¹⁷

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