

Methylchloroisothiazolinone/Methylisothiazolinone and Methylisothiazolinone Allergy

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Background: Preservatives used in cosmetics tend to be, by their nature, allergenic. Methylisothiazolinone (MI) has been used as a sole preservative in multiple cosmetics, household goods, and toiletries. A current epidemic of MI has recently been reported in Europe.

Objective: The aim of this study was to study the prevalence of methylchloroisothiazolinone/MI (MCI/MI) and MI allergy in a Bangkok dermatology clinic.

Methods: During January 2009 to June 2014, 3253 consecutive patients tested with 100 ppm (0.01%) MCI/MI and patients tested with 2000 ppm (0.2%) MI were included in the study.

Results: Three hundred twenty of 3253 patients (9.8%) tested for MCI/MI had a positive reaction. There was a steep increase in the prevalence of MCI/MI contact allergy from 4.8% in 2009 to 11.2% in 2011 and 17% in 2013. In the first 6 months of 2014, 22 of 54 cases tested for MI (40.7%) had a positive reaction. Among those who had a positive reaction to MI, 6 of 22 (27.3%) showed negative reaction to MCI/MI.

Conclusions: There is a similar prevalence of MI allergy in a Bangkok dermatology clinic as those reported in European centers such in the United Kingdom.

As preservatives need to be reactive and protein binding, they also tend to have allergenic potential. Isothiazolinone in the form of a 3:1 mixture of methylchloroisothiazolinone:methylisothiazolinone (MCI:MI) has been used for over 3 decades as a preservative in toiletries, household goods, and in industry. Methylchloroisothiazolinone was considered to be the primary sensitizing agent in MCI:MI mixture, and the use of this mixture has been restricted in the European Union to 15 ppm.¹ Both the Cosmetic Ingredient Review in the United States and the European Scientific Committee on Consumer Safety evaluated MI and concluded that MI at 100 ppm was safe in leave-on and wash-off products.² Methylisothiazolinone was permitted in Europe at concentrations of up to 100 ppm in both leave-on and wash-off cosmetic products. Over the last 3 years, there has been an unprecedented rise in isothiazolinone allergy reported from Europe.³ Here we report a similar rise in MCI/MI and MI allergy in Bangkok, indicating that the epidemic of MCI/MI and MI allergy has become a global problem.

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METHODS

During January 2009 to June 2014, 3253 consecutive patients from contact dermatitis clinic at the Bangkok Institute of Dermatology tested with 100 ppm (0.01%) MCI/MI in aqua and patients tested with 2000 ppm (0.2%) MI in aqua (Chemotechnique Diagnostics, Vellinge, Sweden) were included in the study. All patients were referred to contact dermatitis clinic from our general dermatology clinic. Methylisothiazolinone had been added to cosmetic series since January 2014. Allergens were applied on the upper back using Finn Chambers. The allergens were occluded for 2 days. All patients had patch tests read at day 2 and day 4 according to the International Contact Dermatitis Research Group criteria, which include (–) negative reaction; (+/–) doubtful reaction; (+) mild reaction with mild erythema and some papules; (++) moderate reaction with erythema, papules, and some vesicles; and (+++) intense reaction with erythema, papules, and confluent vesicles. A +, ++, or +++ reaction was considered to be a positive reaction. The MOAHLFA index (Male, Occupation, Atopic Dermatitis, Hand, Legs, Face, Age older than 40 years) scores in patients who had a positive reaction to MCI/MI and/or MI were recorded.

Data were analyzed using Microsoft Excel database software (Microsoft Corp, Redlands, Calif). Proportions (frequency of sensitization to MCI/MI and MI) were supplemented with an exact 95% confidence interval (CI). The degree of concordance

TABLE 1. The MOAHLFA Index in MCI/MI Patch Test-Positive (2009-2014) and MI Patch Test-Positive Patients (2014)

MOAHLFA	MCI/MI Positive (n = 320)		MI Positive (n = 22)	
	% (n)	95% CI	% (n)	95% CI
Male	9.1 (29)	6.4–12.7	4.5 (1)	0.8–21.8
Occupational	23 (74)	18.8–28.1	0 (0)	0
Atopic dermatitis	6.5 (21)	4.3–9.8	4.5 (1)	0.8–21.8
Leg	22 (73)	18.6–27.7	36.4 (8)	19.7–57.1
Hands	64 (206)	59.0–69.4	40.9 (9)	23.3–61.3
Face	20 (65)	16.3–25.1	31.8 (7)	16.4–52.7
Age >40 yrs	34 (110)	29.4–39.7	36.4 (8)	19.7–57.1

between positive reactions to MCI/MI and MI was quantified using Cohen κ .

RESULTS

The prevalence of positive patch test reactions to MCI/MI during 2009 to 2014 was 9.8% (95% CI, 8.9–10.9). The MOAHLFA index in MCI/MI and MI patch test-positive patients were shown in Table 1. In MCI/MI-positive group, 29 cases (9%) were male, and 291 (91%) were female. The patients' ages ranged between 11 and 68 years (mean, 36 years). Fifty-two of 320 MCI/MI allergic patients (16.3%) had generalized dermatitis. There was a steep increase in the prevalence of MCI/MI contact allergy from 4.8% in 2009 to 11.2% in 2011 and 17% in 2014 compared with other preservatives in Thai standard series (formaldehyde, quaternium-15, and paraben mix) (Table 2, Fig. 1).

In the first 6 months of 2014, 54 cases were tested for MI (0.2% aqua) as part of a cosmetic series, and there were 22 reactions (40.7%) (Table 3). One case (4.5%) was male, and 21 (95.5%) were female. Patients' ages ranged between 22 and 58 years (mean, 36.6 years). The hand was the commonest site of dermatitis in MI allergic group (40.9%), followed by the leg (36.4%) and face (31.8%) (Table 1). Generalized dermatitis was found in 2 of 22 cases (9%). Among those who had a positive reaction to MI, 6 of 22 (27.3%) showed negative reactions to MCI/MI. There was a concordance between MI and MCI/MI positive reactions using Cohen κ test ($\kappa = 0.722$).

DISCUSSION

We have shown that there has been a rise in the prevalence of the preservative MCI/MI and MI allergy between 2009 and 2014 in a Bangkok dermatology clinic, which is unprecedented in Thailand. This can be attributed to the use of MI at 100 ppm in toiletries and household products as the MCI/MI has been restricted to the same historical concentrations. Although some countries such as France,⁴ Sweden,⁵ Denmark,⁶ and Australia⁷ have reported MI allergy rates of over 5% in their dermatitis clinics, a prevalence of MCI/MI and MI allergy of over 10% has already been reported in the United Kingdom, Spain, Finland, and Brazil.^{3,8–10} Indeed, in 2013, 9 of 12 reporting centers in United Kingdom demonstrated MI allergy rates of over 10%.² We show that prevalence rates of MCI/MI and MI allergy of over 10% has now been observed in an Asian clinic, consistent with this preservative allergy epidemic being a global phenomenon.

Our rates of MCI/MI and MI allergy are probably an underestimation because we have been testing with MCI/MI 0.01% and have only started testing MI alone 0.2% in cosmetic series since 2014 and found a positive rate in this selective series (ie, patients suspected of having allergic contact dermatitis to a cosmetic) of 40.7%. We have found only nonoccupational allergic contact dermatitis caused by MI probably because MI was tested as part of a cosmetics series in our setting. There was a marked female predominance (91% and 95.5%) in both MCI/MI and MI allergic cases. The sex predominance, age, occupational background, and sites of dermatitis are not likely to be affected by

TABLE 2. Number of Patients Tested With and Number of Patients With a Positive Patch Test Reaction to MCI/MI at the Bangkok Institute of Dermatology From January 2009 to June 2014

	Patients Tested With MCI/MI	Patients Positive for MCI/MI	% Positive	95% CI	+/-	+	++	+++
2009	558	27	4.8	3.3–6.9	0	24	3	0
2010	531	32	6.0	4.3–8.4	0	28	3	1
2011	526	59	11.2	8.8–14.2	0	50	9	0
2012	598	71	11.9	9.5–14.7	0	61	10	0
2013	699	73	10.4	8.4–12.9	0	65	6	2
2014	341	58	17.0	13.4–21.4	1	52	5	0
Total	3253	320	9.8	8.9–10.9	1	280	36	3

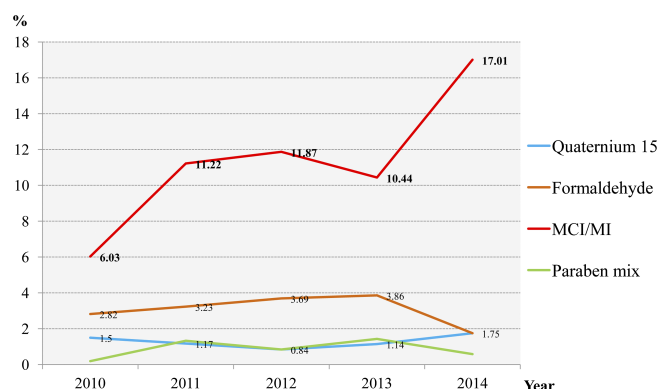


Figure 1. Positive test to MCI/MI compared with formaldehyde, quaternium-15, and paraben mix (%) from January 2010 to June 2014.

the referral process to our contact clinic because we are a tertiary care hospital treating general patients referred from all over Thailand.

Bruze et al,¹¹ using patch test data from multiple centers in Scandinavia, showed that patch test positivity to MCI/MI at 0.02% was 1.75 times greater than with testing at 0.01% ($P < 0.001$). Furthermore, it was demonstrated that the detection of isothiazolinone allergy absolute prevalence can be increased further between 0.6% and 6.0% from the addition of MI 0.2% to the baseline series.¹¹ Our data showed that testing with only MCI/MI in baseline series missed 27.3% of MI allergy cases. There are some reports regarding the cross-reactivity between MI, MCI/MI, and other isothiazolinones from patch test data. Isakkson et al¹² tested 19 isothiazolinone allergic patients to MI, MCI/MI, 2-n-octyl-4-isothiazolin-3-one (OIT), and 4,5-dichloro-2-n-octyl-4-isothiazolin-3-one (dichloro-OIT). Three different groups of reactors emerged; 1 group reacted to MCI but did not react to MI. One group reacted to both MCI and MI but with higher patch test reactivity to MCI, and a third group reacted to MCI and MI with similar reactivity and were more likely to react to OIT than dichloro-OIT. Of 8 MI allergic patients from this group, all reacted to MCI, 4 reacted to OIT, and 2 to dichloro-OIT. Macias et al¹³ patch tested 15 patients who had a positive reaction to MCI/MI 0.01% aq., 7 were positive to MI 0.02% aq., 6 reacted equally to both solutions, and 1 reacted more strongly to MI. In the early series of Lundov et al,¹⁴ 41% (15/37) of MI allergic patients (tested with 2000 ppm) also reacted to MCI/MI patch test.

The current epidemic of isothiazolinone allergy can probably be traced to the original decision to allow MI at concentrations of up to 100 ppm in leave-on and wash-off products.¹ The original conclusion, based on animal and human data, was that MI was safe

at a level of 100 ppm in toiletries and wash-off products. In retrospect, some of the concentrations used for patch testing to diagnose MI sensitization in the original experiments have subsequently been shown to be suboptimal for diagnosing and detecting MI allergy.^{5,11,15} The majority of our patients allergic to MCI/MI and MI source their exposure to toiletries such as shampoos, moisturizers, and wet wipes, which is in agreement with the United Kingdom and Australian experience.⁷ In addition, we have found that a significant number of patients report multiple sources of exposure to isothiazolinone, including household products. We also note that a significant source of exposure from some European countries has been wall paint.⁶

The current preservative allergy outbreak differs from previous outbreaks of preservative allergy in some notable ways. First, the scale of allergy surpasses all previously recorded outbreaks. The last outbreak of preservative allergy, to methylidibromoglutaronitrile, peaked with a prevalence rate of just over 5% in dermatitis clinics, which is less than half the current isothiazolinone rate, which has not yet been shown to peak.³ Second, the rate of the rise in allergy has been much faster with some reports such as ours and that of the United Kingdom³ showing a rough doubling of rates in the first 2 years. Third, the sources of exposure to isothiazolinone are much more varied and multiple. These include not just toiletries but also household goods and paint.^{6,7} Fourth, cases where children are involved have played a prominent role, with some of the pediatric cases reporting allergic dermatitis from exposure to MI in wet wipes and some cases mimicking atopic dermatitis.^{7,16–18} Finally, the geographical extent of this outbreak is worthy of note, with at least 3 continents affected.

In an editorial in the journal *Contact Dermatitis* earlier this year,¹⁹ the following comment was made: “Whilst the MI problem will, belatedly, be resolved in Europe, one would hope that manufacturers and suppliers of MI will, as a priority, advise on restricting the use of MI in all their (global) markets...” In late 2013 Cosmetics Europe,²⁰ the representatives of the cosmetic industry issued a statement stating, “Following close analysis of clinical data, market feedback, and quantitative risk assessment analysis, Cosmetics Europe has concluded that the discontinuation of MI use in leave-on skin products including cosmetic wet wipes would result in a significant decrease in the incidence of sensitization to this ingredient.” It is, therefore, of some concern that prevalence rates of MI allergy in dermatitis clinics has exceeded 10% outside Europe and of extreme concern that, as of May 2014, leave-on products containing MI were still to be found on the shelves of retail stores.

TABLE 3. Number of Patients Tested With and Number of Patients With a Positive Patch Test Reaction to MI (0.2% aq.) From January to June 2014

Patients Tested With MI	Patients Positive for MI	% Positive	95% CI	+/–				MCI/MI Negative in MI-Positive Patients, % (n)
				–	+	++	+++	
54	22	40.7	28.7–54.0	0	9	12	1	27.3 (6)

CONCLUSIONS

There has been a rise in the prevalence of the preservative MCI/MI and MI allergy between 2009 and 2014 in a Bangkok dermatology clinic. Testing with only MCI/MI in baseline series missed 27.3% of isothiazolinone allergy.

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