

Methylisothiazolinone Testing at 2000 ppm: A Prevalent Sensitizer for Allergic Contact Dermatitis

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Background: Methylchloroisothiazolinone (MCI) and methylisothiazolinone (MI) have been identified as potent allergens. The optimal MI concentration for patch testing for reaction to these agents has not yet been identified, but it has been suggested that testing MI at 2000 ppm may reduce false-negative reactions.

Objective: The aim of this study was to report allergic reactions to MI and MCI/MI detected in a community dermatology practice setting in Ontario, Canada.

Methods: The patch test records of patients with suspected allergic contact dermatitis seen between October 2007 and June 2014 were reviewed. We compared positive patch testing before and after December 2011 when a higher MI concentration was used (2000 ppm aqueous) in addition to the baseline series MCI/MI at 100 ppm.

Results: A total of 794 patient records were reviewed. There were 38 true-positive reactions to MI or MCI/MI. Of these 38 patients, 26 (68%) were female. We detected an overall increase in the rate of positive patch testing to MCI/MI, MI alone, or both from 3.13% to 7.45% when MI concentration was introduced at 2000 ppm aqueous. Occupational differences existed between sexes.

Conclusions: The addition of MI at 2000 ppm to our screening series effectively increased the detection of MI-induced allergic contact dermatitis.

Methylisothiazolinone (MI; 2-methyl-4-isothiazolin-3-one) is an antimicrobial agent used as a biocide and preservative in both rinse-off and leave-on cosmetic, household, and industrial products. Methylisothiazolinone was initially introduced in combination with methylchloroisothiazolinone (MCI) in a 3:1 mixture (MCI/MI; trade names, Kathon CG and Euxyl K 400).¹ Both MCI and MI are significant allergens that are causal agents for allergic contact dermatitis (ACD). Health Canada permits MI for preservative use at concentrations equal to or less than 0.01% (100 ppm aqueous). Methylchloroisothiazolinone is only permitted in combination with MI and is regulated at concentrations equal to or less than 0.0015% (15 ppm aqueous) in rinse-off products and 0.00075% (7.5 ppm aqueous) in leave-on products.² In addition, no limitations exist on the concentration of MI in industrial products.³ Past reports focus on the exposure risks of MCI/MI. Specifically, MCI has been identified as the stronger sensitizer.⁴ As a result of identified reactions to MCI, MI was implemented as the only preservative for industrial products in the early 2000s, and subsequently for cosmetic and household products in 2005.¹ Methylisothiazolinone is now considered the primary sensitizer.⁵ Studies have demonstrated an

increase in frequency of positive reactions to MCI/MI, and more recently, individual reactions to MI were reported in Europe, Australia, and in North America.^{4,6–12}

Recent literature reports that exposure and sensitization to MI is becoming more frequent and could potentially result in an epidemic of ACD. Methylisothiazolinone alone, without MCI, is becoming more commonly used in consumer products, and avoidance of this allergen can be a challenging task.¹¹ Most products containing MI as a preservative are considered rinse-off products; however, certain leave-on products such as wet wipes (eg, baby wipes, moist towelettes, and moist toilet paper), as well as other consumer products, often contain MI.¹ In 2013, the American Contact Dermatitis Society listed MI as its “allergen of the year” as a result of sensitization and frequency of use in consumer products.¹ Furthermore, The United Nations Globally Harmonized System of Classification and Labelling of Chemicals has identified both MCI and MI as strong allergens.¹⁰ The use of MI alone in consumer products presumably resulted from an attempt to eliminate the frequency of ACD, which was occurring with MCI/MI.⁶ However, sensitization to MCI/MI may have occurred by exposure to MI in consumer products. This was demonstrated in pediatric cases of ACD in which positive allergic reactions were detected to MCI/MI in response to wet wipes that only contained MI.¹¹ In addition, research demonstrates that adult cases of sensitization and exposure to MI exist throughout the life span.^{4,6,7,9,13}

It has been suggested that MI be tested at 2000 ppm to reduce false-negative reactions.^{3,8} Many studies have evaluated different concentrations of MI in search of determining its optimal

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concentration for testing, and recently, it was added to both the North American and European Union baseline series through AllergEAZE (SmartPractice, Calgary, Alberta, Canada) at a concentration of 2000 ppm aqueous (0.2%). In November of 2011, our clinic began patch testing MI at a concentration of 2000 ppm in addition to the baseline series concentration of MCI/MI at 100 ppm. The increasing reports of ACD to MI have validated its incorporation into the standard baseline series for allergen testing, although the optimal testing concentration has not yet been identified.¹ Consequently, it is likely that many patients allergic to the MI preservative have been overlooked or that the allergen has not been tested at the appropriate concentration in the past.

This retrospective chart review was performed to determine if the addition of MI at 2000 ppm to our screening series was able to increase the detection of allergy to MI above that detected by the MCI/MI 100 ppm in the North American Contact Dermatitis Group (NACDG) standard series.

METHODS

Positive patch test records of patients ($n = 794$) with suspected ACD seen in a community dermatology practice setting in Ontario, Canada, between October 22, 2007, and June 30, 2014 were reviewed. All patients with a positive reaction (+, ++, +++) to MCI/MI or MI were included. All patients were patch tested according to the NACDG criteria. Before August 2008, patients were patch tested using TRUE Test (Spexell Pharma, SmartPractice, Calgary, Alberta, Canada), which tested MCI/MI at 0.0032 mg/patch. After August 2008, all patients were patch tested using IQ Ultra patch test chambers (IQ Ultra; Chemotechnique Diagnostics, Vellinge, Sweden) applied on the back with Medipore H (3M Health Car, St Paul, Minn). The baseline series was obtained from AllergEAZE, and MCI/MI was tested at 100 ppm aqueous (0.01%). In November 2011, MI 2000 ppm aqueous (0.2%) was obtained through Chemotechnique Diagnostics (Dormer Laboratories Inc, Toronto, Ontario, Canada) and was introduced to the clinic's standard testing in December 2011. Readings were performed at 48 hours and 96 hours. The clinic's dermatologist had determined the relevance of patch test results at the time of patch testing.

The information collected on patients included age, sex, occupation, history of atopy, site of ACD, individual use of products, additional positive patch test results, and the suggestive source of exposure to MCI/MI, and/or MI. Some of this information was obtained by use of a Contact Dermatitis Questionnaire to determine the use of everyday consumer products.

RESULTS

Patient Characteristics

A total of 794 patients had a positive patch test in our clinic. There were 40 reactions to MCI/MI or MI; however, 38 (4.8%) were considered true reactions. Two patients with irritant or doubtful reactions to the MCI/MI combination at 100 ppm aqueous were

excluded from this study. Of the 38 patients with true reactions, 12 (31.6%) were male, and 26 (68.4%) were female. The age range was 15 to 89 years, with a mean age of 47.9 years for both sexes. Of those testing positive to MCI/MI, MI, or both, 12 (31.6%) had a history of atopy (eczema and, in 1 case, chronic hand dermatitis). Occupational differences existed between the male and female patients. Males involved in this study had occupations as mechanics (8, 66.7%), tradesmen (3, 25%), and retired (1, 8.3%). Females involved in this study were retired (12, 46.2%), working in the health field (4, 15.4%), and other occupations (10, 38.5%).

Of the male patients involved in this study, 5 (33.3%) reported using automotive/mechanical hand cleaner, specifically intended to remove oil and grease; 3 (20%) reported using various hand soaps; 2 (13.3%) reported using Dove body wash; 2 (13.3%) reported using other cosmetic wash products; 1 (6.6%) reported using baby wipes; and 2 (13.3%) did not disclose any exposure. Three males (25%) reported more than 1 exposure. Of the female patients, 19 (31.6%) were exposed to the allergen through moisturizers, 15 (25%) through liquid body wash, 11 (18%) through liquid hand soap, 9 (15%) through wet wipes, 2 (3.3%) through occupation, 1 (1.6%) through makeup remover, 1 (1.6%) through shampoos, and 2 (3.3%) with no specific reported exposure. More than 1 exposure was reported in 17 females (65.3%). In addition, after previous sensitization to wet wipes and a confirmed allergy to MI, 1 patient experienced ACD after being exposed MI in household paint.

All patients in this study used topical steroids or calcineurin inhibitors as therapy for an outbreak. The most common sites of involvement were the hands, arms, and face. Other sites of involvement were the legs, neck, back, chest, abdomen, feet, trunk, eyelids, scalp, and genitals; 30 (78.9%) of the patients had involvement on more than 1 area of their body. Individual differences between males and females are demonstrated in Table 1.

Contact Dermatitis Reaction Rates to MCI/MI

Before August 2008, patients were being patch tested using TRUE Test, and no positive reactions to MCI/MI were detected. After August 2008, patients were patch tested using the baseline series AllergEAZE, and 14 (3.13%) of all patients patch tested reacted to MCI/MI. In December 2011, MI was introduced at a concentration of 2000 ppm aqueous. Once introduced into the standard testing at this clinic, 0.62% reacted to MCI/MI alone, 4.66% reacted to MI alone, and 2.17% reacted to both MCI/MI and MI. Between December 2011 and June 2014, when both MCI/MI and MI were being tested, we detected an overall increase in the rate of positive patch testing to MCI/MI, MI alone, or both from 3.13% to 7.45% when MI concentration was 2000 ppm aqueous. The allergic contact reaction rates to MCI/MI, MI, or both are presented in Table 2.

Allergic Reactions to Other Allergens in North American Baseline Series

Twenty-four patients (63.2%) had positive reactions to other chemicals tested in the North American baseline series. The top

TABLE 1. Characteristics of Patients With Positive Reactions to MI or MCI/MI (n = 38)

	n	%
Males	12	31.6
Females	26	68.4
Occupation		
Males		
Mechanic	8	66.7
Trades	3	25.0
Retired	1	8.3
Females		
Retired	12	46.2
Health field	4	15.4
Student	3	11.5
Administrative	2	7.7
Agricultural	1	3.8
Cosmetics	1	3.8
Education	1	3.8
Sales	1	3.8
Self-employed	1	3.8
Anatomical site		
Males		
Upper extremities	11	50
Head and neck	5	22.7
Trunk	4	18.2
Lower extremities	2	9.1
Females		
Upper extremities	21	35.0
Head and neck	19	31.7
Lower extremities	15	25.0
Trunk	5	8.3

3 simultaneous reactions were nickel sulfate in 5 patients (8.2%), quaternium-15 in 5 patients (8.2%), and 4-phenylenediamine base in 4 patients (6.5%).

DISCUSSION

Evidence supporting patch testing of MI at an optimal concentration is relatively limited. Published studies demonstrate patch test results with MI at a wide range of concentrations. In the past, MI has been evaluated at 50, 100, 250, 300, 500, and 1000 ppm, but

unless the appropriate concentration is found, positive reactions to MI in patch testing may be missed.¹ In addition, it has been found that testing at 300 ppm may miss almost half of positive reactions to MI.¹⁴ Collation of findings in studies to date suggests 2000 ppm as the most optimal MI patch test concentration, and some evidence exists supporting this recommendation.^{5,8,13,15} We detected an overall increase in the rate of positive patch testing to MI alone or to both MCI/MI and MI using MI at a concentration of 2000 ppm aqueous.

The MCI/MI combination is presently in the North American and European baseline series at 100 ppm aqueous. Past research has speculated that the concentration in the baseline series is too low, and as a result, ACD to MCI/MI might be missed.^{5,10,11,13} Specifically, Bruze et al⁵ state that almost 50% of positive reactions to MCI/MI are missed when testing at 100 ppm. In addition, testing MCI/MI at 100 ppm does not seem to be sufficient enough to detect all allergies to the combination; testing at 200 ppm has been recommended in other reports.^{12,13,16}

Similar to other studies conducted, our data suggest that occupational and cosmetic factors contribute to both MI and MCI/MI allergies. As confirmed by our data, women have been more commonly associated as having ACD with sensitization from cosmetic products, and men seem to have higher sensitization in occupational settings.^{1,5,9,15} Allergic contact dermatitis in men have been linked to "painting occupations."^{9,15} Unlike former studies, our study identified MI in mechanical and trade settings, tracing the allergen to mechanical hand cleaners designed specifically to cut grease, mechanical oils, and dirt. We believe that painters and mechanics may be in contact with similar products containing MCI/MI or MI. In contrast to males, the occupations of the female population were not contributory to explain the onset of ACD. Most research indicates that females experience a higher frequency of face dermatitis^{4,9}; however, our research showed that upper extremities were more frequently involved than the head and neck region. Although the site of lesions in our cases was different, ACD in our patients was still attributable to the application of cosmetic products. The most prevalent consumer products considered causal for ACD in female patients at our clinic were moisturizers, liquid body wash, liquid hand soaps, and wet wipes. Researchers have identified that MI is very common in cosmetic and household products,⁵ and

TABLE 2. Positive Reactions Detected With TRUE Test and AllergEAZE Baseline Series and the Addition of MI 2000 ppm Aqueous

	Total Patients Patch Tested, n (%)	Positive Patch Testing to MCI/MI, or MI, or Both, n (%)	MCI/MI, n (%)	MI, n (%)	Both MCI/MI and MI, n (%)
October 2007 to August 2008*	25 (3.1)	0	0	NA	NA
August 2008 to November 2011†	447 (56.3)	14 (3.1)	14 (3.1)	NA	NA
December 2011 to June 2014‡	322 (40.6)	24 (7.5)	2 (0.6)	15 (4.7)	7 (2.2)
Total	794	38 (4.79)	16 (2.01)	15 (1.89)	7 (0.88)

*Patients were tested with TRUE Test baseline series.

†Patients were tested with AllergEAZE baseline series.

‡Patients were tested with AllergEAZE baseline series, using MI 2000 ppm aqueous.

according to Lundov et al,¹⁵ 32% of their patients were exposed to cosmetics with MI.

Interestingly, it has been described that patients sensitized to MI experience airborne contact in paint products.⁹ In concordance with this finding, one of our patients previously sensitized to MI through wet wipes experienced a similar reaction after being exposed to painting of his home.

Although our results appropriately identify information on patch testing MI, MCI/MI, and differences between occupational and cosmetic contact, some limitations in our research are evident. First, our population was tested using different patch-testing methods over time. Before August 2008, we used the TRUE Test, but then switched to a more comprehensive screening using the AllergEAZE set of NACDG standard series of allergens. Second, some patients referred to this clinic for ACD had obvious exposures to MI or MCI/MI through wet wipes, moisturizers, or mechanical hand cleaners, respectively, and opted out of patch testing, wanting to first try to eliminate consumer products containing the allergen and seeing if their ACD resolved. Lastly, our clinic used the baseline concentration of MCI/MI (100 ppm aqueous or 0.01%), which is now identified to likely limit our results, because researchers are now suggesting using a concentration of 200 ppm.

We agree that a complete history, physical examination, and patch testing bring significant benefit in the diagnosis and management of patients with ACD.¹⁷ Lifestyle modification based on patch-testing findings was found in up to 90% of patients.¹⁸ Through identifying the responsible allergen, we will be better able to counsel our patients on allergen avoidance. Fortunately, although it is more expensive, mechanical hand cleaners without MI do exist for these patients.

Methylisothiazolinone has now been added to both the North American and European baseline series at a concentration of 2000 ppm, but further evidence is needed to optimize and support testing MI at this concentration. In support of this practice, no studies have reported active sensitization at 2000 ppm.^{5,8,15}

CONCLUSIONS

The addition of MI at 2000 ppm to our screening series enabled us to effectively increase the detection of MI-induced allergies. Patch testing with MI detects more positive reactions to the allergen than only testing MCI/MI at a concentration of 100 ppm in the baseline series. Our study suggests that MI tested at 2000 ppm may eliminate false-negative reactions. In accordance with other researchers, we believe that authorities should review the use of MI in both cosmetic and occupational consumer products because the permitted concentration may need to be lowered.

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