

Contact sensitization to methylisothiazolinone in Finland – a multicentre study

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Summary

Background. Antimicrobials constitute the second most common cause of contact allergy to cosmetics. Methylisothiazolinone (MI), previously always used together with methylchloroisothiazolinone (MCI), has recently been approved in the EU for use on its own in cosmetics and also various industrial products. MCI has been classified as an extreme–strong and MI as a strong–moderate sensitizer.

Objectives. To study the frequency of positive patch test reactions to MI, and its relevance and relation to MCI/MI sensitivity, in Finland.

Methods. Over a period of 3 years (2006–2008), MI 0.1% (1000 ppm) and 0.03% (300 ppm) were patch tested in 10 821 patients at eight Finnish dermatological clinics. During 2008, patients with positive reactions to MI were asked to take part in a repeated open application test (ROAT).

Results. Of the patients tested, 1.4% and 0.6% showed positive patch test reactions to 0.1% and 0.03% MI, respectively. Sixty-six per cent of those who were MI-positive were also positive to 100 ppm MCI/MI. Thirty-three agreed to undergo the use test, and 10 of these gave positive results (30%).

Conclusions. Our data show that MI used alone also potentially induces contact allergy. Careful monitoring is needed to determine whether or not this antimicrobial is safe to use in cosmetics.

Key words: 2-methyl-4-isothiazolin-3-one; 5-chloro-2-methyl-4-isothiazolin-3-one; contact allergy; methylchloroisothiazolinone; methylisothiazolinone; repeated open application test (ROAT).

The mixture of methylchloroisothiazolinone (5-chloro-2-methyl-4-isothiazolin-3-one; MCI; CAS 26172-55-4)

and methylisothiazolinone (2-methyl-4-isothiazolin-3-one; MI; CAS 2682-20-4) in the ratio of 3:1 (MCI/MI) (trade name examples: Kathon CG®, Euxyl K 100®, Legend MK®, Microcide III®, and Bio-Perge®) has been used extensively for more than 20 years as an antimicrobial in cosmetics (e.g. skin creams and shampoos), household products (e.g. dishwashing liquids and carpet cleaner agents), and industrial product applications (e.g. metalworking fluids, paints and glues). MCI/MI has broad-spectrum antimicrobial activity against both

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gram-positive and gram-negative bacteria, and yeasts and fungi, at very low concentrations and over a broad pH range (1). The introduction of new chemicals in consumer products has in the past sometimes led to epidemics of contact dermatitis (2). In addition, following the introduction of this preservative in the early 1980s, a sharp increase in contact allergy rates was observed in Europe, with a prevalence rate of 3–8% (3, 4). Therefore, the use of MCI/MI was reduced at the beginning of the 1990s. After this, MCI/MI contact allergy declined significantly, and now affects 1–3% of patch-tested patients in European centres (2). According to European Community legislation, only concentrations of up to 15 ppm may be used in cosmetic products in the EU. However, several studies on human volunteers have shown that approximately 30–50% of MCI/MI-sensitized individuals develop clinically relevant dermatitis from twice-daily applications for 1 week of a leave-on product containing MCI/MI at concentrations of between 10 and 15 ppm (5–8). One study showed that 2.5 ppm was sufficient to elicit an allergic reaction in already sensitized individuals (9). Both of these chemicals have shown skin sensitization potency in animal studies, but MCI has proven to be a more potent allergen than MI. In local lymph node assays (LLNAs), the EC₃ values have been 0.009% for MCI, 1.9% for MI (10), and 0.05% for MCI/MI (11). MCI is an extreme–strong sensitizer and MI a strong–moderate sensitizer, according to different classifications (10, 12). The United Nations Globally Harmonized System of Classification and Labelling of Chemicals classifies them both as strong allergens.

Some studies also indicate that the more weakly sensitizing isothiazolinones – methyltrimethylene isothiazolinone and benzisothiazolinone – do not elicit allergic reactions in subjects sensitized to MCI (13). A preservative containing only MI and no MCI has recently been introduced in the EU for use in products such as cosmetics, paints, and glues. A concentration of up to 100 ppm has been approved for use in cosmetic leave-on products. Currently, the experience of MI contact allergy is limited.

Materials and Methods

This survey is based on the patch test results of the eight Finnish dermatological clinics representing the Finnish Contact Dermatitis Group: five university hospitals, one central hospital, one private medical centre, and the Finnish Institute of Occupational Health, over a period of 3 years (2006–2008). Patch testing was performed according to the guidelines of the International Contact Dermatitis Research Group (14). The occlusion time was 2 days, and readings were taken when the patches were removed (Finn Chambers® on Scanpor® tape; Epitest Ltd

Oy, Tuusula, Finland; 8 mm internal diameter) and on days 4 or 5. The patch test substance for MCI/MI was purchased from Chemotechnique Diagnostics AB (Vellinge, Sweden) or Hermal (Reinbek, Germany).

The raw material for MI (Neolone® 950) was provided by Rohm and Haas® (West Yorkshire, UK). The contents of MI and MCI were determined according to Henriks-Eckerman et al. (15), using Kathon CG® (a mixture of MI 0.375% and MCI 1.125%) bought from Chemotechnique Diagnostics as an external standard. Neolon® 950 was found to contain 9.8% MI, but no MCI, as the detection limit was 0.001%. MI was added to the baseline series at concentrations of 0.1% (1000 ppm) and 0.03% (300 ppm) in aqua. During the year 2008, patients who had reacted positively to MI (+/++/+++) were asked to undergo a patient-blind, provocative use test: a repeated open application test (ROAT). In the test, each patient received two identical containers of skin care lotion randomly coded left and right. One contained MI at 100 ppm (the approved concentration for use in cosmetic leave-on products) and the other contained no MI. The patients were instructed to make applications twice daily, with the lotion from one container on one antecubital fossa, and with the lotion from the other container on the other antecubital fossa. After 1 week, reactions to the two preparations were assessed by the investigator. If the use test result was negative, the patients were instructed to continue for another week. After the second week, the patients were contacted, and if they had developed eczema, they were asked to visit the investigator again.

Results

The patch test results for MI and MCI/MI in the years 2006–2008 are summarized in Table 1. The frequency of MCI/MI sensitivity showed a slight tendency to increase (1.3–2.1%). In addition, MI alone elicited allergic reactions, which also showed a tendency to increase in these years (0.9–1.8%). The outcome of the patient-blind, provocative MI use test is illustrated in Table 2. Thirty-three of 62 MI-positive patients participated in the use test. Ten of the MI-positive patients (30%) reacted to the lotion containing MI but not to the control. All of the use test-positive patients also reacted to MCI/MI in patch tests.

Discussion

Contact allergy caused by ingredients in cosmetic products is a well-known problem. The allergies are mainly caused by fragrances and preservatives, and affect approximately 6% of the general population (16). In the EU and USA, the ingredients of cosmetics are subject

Table 1. Summary of positive reactions to methylisothiazolinone (MI) and methylchloroisothiazolinone (MCI)/MI

Year	No. tested	MI 0.1%, no. (%)	MI 0.03%, no. (%)	MCI/MI, no. (%)	MI+, MCI/MI+, no. (%)	MI+, MCI/MI–, no. (%)	MI–, MCI/MI+, no.
2006	3981	35 (0.9)	17 (0.4)	51 (1.3)	21 (60)	14 (40)	30
2007	3382	50 (1.5)	20 (0.6)	71 (2.1)	31 (62)	19 (38)	40
2008	3458	62 (1.8)	32 (0.9)	72 (2.1)	45 (73)	17 (27)	27
2006–2008	10 821	147 (1.4)	69 (0.6)	194 (1.8)	97 (66)	50 (34)	97

Table 2. Positive repeated open application test (ROAT) outcome in methylisothiazolinone (MI)-allergic individuals exposed to 100 ppm MI for maximum of 2 weeks

	Patch test reading			ROAT
	MI, 1000 ppm	MI, 300 ppm	MCI/MI, 100 ppm	
Patient 1	+++	++	++	++
Patient 2	+++	+	++	++
Patient 3	++	++	+	++
Patient 4	++	+	++	++
Patient 5	++	+	+	++
Patient 6	++	+	+	+
Patient 7	++	–	++	++
Patient 8	+	–	++	++
Patient 9	+	–	+	+
Patient 10	+	–	+	+

+, palpable erythema; ++, palpable erythema and vesicles; MCI, methylchloroisothiazolinone.

to strict legislation, and the safety of the preservatives used in them must be evaluated by expert committees. A total of 56 different preservatives are currently allowed in cosmetic products in the EU (17). However, only a few of them dominate the market: parabens, formaldehyde, formaldehyde releasers, and MCI/MI. Many of the other preservatives are not as efficient, and require a low pH in order to be active. New preservatives, which are efficient and safe, have been difficult to find. Since the beginning of the 1990s, only a few new preservatives have been approved in the EU. Among these is methylidibromoglutaronitrile, which, unfortunately, quite quickly caused an epidemic of contact allergy and is now banned from cosmetic use in Europe.

MI has recently been approved for use in cosmetic products. However, it cannot be considered to be new, as it has been used as part of MCI/MI. MI is allowed in concentrations up to 100 ppm, as compared with 15 ppm of MCI/MI. LLNA studies have shown that MCI has a much higher skin-sensitizing potency than MI (10). Nevertheless, some occupational cases of contact allergy to MI have been reported. Isaksson et al. (18) reported 2 occupational cases, through contact with MI in wallpaper glue in 1 case, and after a chemical burn in another. Both

patients reacted to MCI/MI and the separate active ingredients, with a higher level of reactivity to MI than to MCI, suggesting primary sensitization to MI. Thyssen et al. (19) described a factory outbreak of contact allergy to MI in 5 of 14 persons working for a paint manufacturer. Patch test results from these 5 patients showed positive reactions to MI and MCI/MI. The reactions in these patients were also stronger for MI (1050 ppm) than for MCI/MI, indicating primary sensitization to MI. Earlier studies showed that individuals with chemical burns caused by MCI/MI were sensitized to MCI in MCI/MI (20, 21). Very few data exist concerning the cross-reaction patterns of MCI and MI. Bruze et al. showed in their studies that a small proportion of subjects sensitized to MCI/MI also reacted to MI in patch tests (22, 23). Isaksson et al. also suggest that patients with high patch test reactivity to MCI may also react to high concentrations of MI (1000 ppm) (24).

Our results show that during 2006–2008, 1.4% and 0.6% of the patients tested had allergic reactions to 0.1% (1000 ppm) and 0.03% (300 ppm) MI, respectively. As many as 66% of the MI-positive patients were also positive for MCI/MI, whereas 34% were MCI/MI-negative. Thirty-three patients agreed to perform the use test, 10 of whom were positive (30%); they were also positive for MCI/MI in patch tests. Six of the use test-positive patients reacted to 0.03% MI, and 4 only reacted to the higher concentration of 0.1%.

Experience with MI patch test concentrations is very limited. It is possible that the higher concentration of 0.1% causes irritant reactions, as 34% of MI-positive patients were MCI/MI-negative. It is also possible that the MCI/MI concentration used in the baseline series (100 ppm) was too low to detect all of the MCI/MI-allergic patients, and that some MCI/MI-allergic patients were missed because of this. Determination of the ideal patch test concentration of MCI/MI has not been easy (25–27). The results of studies in which 300 ppm MCI/MI was used indicate that 100 ppm might be too low a concentration to detect all true-positive reactions (6). It would not, however, be possible to use a test concentration of 300 ppm in the baseline series, because this concentration has been shown to cause active sensitization. Two previous studies revealed that patch testing with 100 ppm misses about

half of the allergic cases as compared with testing with 200 ppm (26, 28). It will therefore be important in the future to further determine the ideal test concentrations for both MCI and MI. Both of these active ingredients should possibly be included in the baseline series.

The positive provocative use tests (ROAT) confirmed the relevance of the positive patch tests for MI. The patients had allergic contact dermatitis with 100 ppm MI, which is allowed in cosmetic products. It is possible that they had been primarily sensitized to MCI in MCI/MI, and the sensitization to MI resulted from cross-allergy, or concomitant primary sensitization.

On the basis of this study, we can conclude that contact allergy to MI also exists in the eczema patient population, and that approximately one-third of those with positive

patch test reactions to MI react to MI under the conditions of a provocative use test. Cosmetic preservatives have sensitizing potential, so it is important to monitor allergic contact sensitization to the most widely used antimicrobials. Our data also show that MI used alone may potentially induce contact allergy. Careful monitoring is needed to determine whether or not this antimicrobial is safe to use in cosmetics.

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