

CLINICAL REPORT

Swedish Experiences From Patch-testing Methylisothiazolinone Separately

Malin ENGFELDT¹, Johanna BRÅRED-CHRISTENSSON², Marlène ISAKSSON¹, Mihály MATURA³, Kristina RYBERG⁴, Berndt STENBERG⁵, Cecilia SVEDMAN¹ and Magnus BRUZE¹

¹Department of Occupational and Environmental Dermatology, Skåne University Hospital, Lund University, Malmö, ²Department of Dermatology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, ³Unit of Occupational and Environmental Dermatology, Institute of Environmental Medicine, Karolinska Institutet and Centre for Occupational and Environmental Medicine, Stockholm, ⁴Department of Dermatology, Uddevalla Hospital, Uddevalla, Sweden, and ⁵Department of Public Health and Clinical Medicine, Dermatology & Venereology, Umeå University, Umeå, Sweden

The preservative methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) is a well-known sensitiser and present in the Swedish baseline series since the 1980s. The proportions of MCI/MI are 3:1. MI alone has been used as a preservative since less than 10 years. This study was conducted on behalf of the Swedish Contact Dermatitis Research Group to evaluate inclusion of MI in the Swedish baseline series since the preparation of MCI/MI might fail to detect contact-allergic reactions to MI alone. Patients with suspected allergic contact dermatitis at 5 Swedish dermatology departments were consecutively patch-tested with MI 2,000 ppm aq and MCI/MI 200 ppm aq. The number of cases with exclusive contact allergy to MI varied between 0.8–4.2%. In total, 1.9% reacted exclusively to MI and not to MCI/MI. Due to the considerable frequency of contact allergy to MI not traced by MCI/MI, MI 2,000 ppm aq is included in the Swedish baseline series from January 2014. This corresponds to a dose of 60 µg/cm². Key words: allergic contact dermatitis; contact allergy; delayed hypersensitivity; dose in µg/cm²; MCI/MI; micropipette; preservative.

Accepted Dec 3, 2014; Epub ahead of print Dec 4, 2014

Acta Derm Venereol 2015; 95: 717–719.

Malin Engfeldt, Department of Occupational and Environmental Dermatology, Skåne University Hospital, Lund University, Jan Waldenströmsgata 16, SE-205 02 Malmö, Sweden. E-mail: malin.engfeldt@skane.se

The background regarding the preservatives methylchloroisothiazolinone (MCI) and methylisothiazolinone (MI) is a good example of both the importance to survey contact allergy trends and the necessity to regularly review any patch test baseline series. In the early 1980s MCI/MI at a ratio of 3:1 was introduced as a preservative in industrial and household products as well as in cosmetics. Soon a rise in contact allergy frequencies was seen (1–3). Both MCI and MI were shown to be sensitisers in humans (4) and animal studies could show that the moiety MCI was the main sensitiser (5). Although MI was shown to be a sensitiser too, it is not legislated/classified as a contact allergen and its use in chemical

products is not restricted or in need of declaration, with the exception of products regulated by the Cosmetics Regulation (EC 1223/2009) or the Detergents Regulation (EC 648/2004). In 1989, regulatory measurements were taken and the maximum allowed concentration of MCI/MI in cosmetics was set to 15 ppm within the EU (89/174/EEC). This led to decreasing contact allergy frequencies (6). In 2005 MI alone was allowed in Europe as a preservative in cosmetics at a maximum concentration of 100 ppm. This was followed by yet another rise in the contact allergy frequencies to MCI/MI in Europe (6, 7). However, the patch test preparation of MCI/MI used in many baseline series may fail to detect contact allergies to MI because the concentration of MI is too low in the test preparation (50 ppm). This shortcoming and the reports of higher contact allergy frequencies to MI when patch-tested alone resulted in the inclusion of MI at 2,000 ppm aqua (60 µg/cm²) into the European baseline series in January 2014 (8). The aim of this study was to survey the contact allergy frequencies to MCI/MI and MI in Sweden in order to evaluate if MI 2,000 ppm aqua should be included in the Swedish baseline series.

MATERIALS AND METHODS

The study was conducted by the Swedish Contact Dermatitis Research Group and 5 Swedish dermatology clinics took part during the period February–December 2012. The participating clinics were from Malmö, Gothenburg, Uddevalla, Stockholm, and Umeå. Results are based on the consecutive patch testing of 1,498 patients with suspected allergic contact dermatitis, 1,003 females and 495 males (mean age 43.8 years; age range 5–90 years; female/male 67.0/33.0%). All participating clinics used preparations of the same batches of MI 2,000 ppm (w/v) in aqua and MCI/MI 200 ppm (w/v) in aqua, both bought from Chemotechnique Diagnostics (Vellinge, Sweden) by the Malmö department which distributed it to participating clinics. The patch testing and reading of the patients followed the routine of the participating clinics. Finn Chambers[®] (8 mm diameter; Epitest Ltd, Tuusula, Finland) on Scanpor[®] tape (Norgesplaster A/S, Vennesla, Norway) were used in all centres except Uddevalla, which used IQ Ultra chambers (8 × 8 mm²; Chemotechnique Diagnostics) on a high quality hypoallergenic surgical tape. The dose of 15 µl for Finn Chamber and 20 µl for IQ ultra was applied using micro-pipettes (9) to give the doses 60 µg/cm² and 6 µg/cm² for MI and MCI/MI, respectively. Readings were classified according to the ICDRG guidelines (10). All patients

were read twice, on day (D) 3–4 and D6–8. A dermatologist read all patch tests on both days in all centres except Umeå, where a nurse trained in patch-test readings did the first reading and a dermatologist the second one. Any positive reaction (+, ++, +++) either on D3–4 or D6–8, was registered as a positive reaction.

RESULTS

In Table SI¹ the patch test results from testing with MI 2,000 ppm (60 µg/cm²) in aqua and MCI/MI 200 ppm (6 µg/cm²) in aqua are presented. In total, 7.1% reacted to MCI/MI. Of these, 2% had an exclusive contact allergy to MCI/MI. Of the 7.1% that reacted to MI, 1.9% had an exclusive contact allergy to MI. The additional number of cases found by testing MI separately varied from 0.8–4.2% in the 5 centres. In all, 9.1% of the patch-tested population reacted to MCI/MI and/or MI. The age and sex distribution amongst the positive patients are listed in Table SII¹.

DISCUSSION

In the present study, the number of cases with exclusive contact allergy to MI varied between 0.8–4.2%. Besides reflecting true differences in contact allergy rates after adjusting for factors such as gender, age, occupational cases and face dermatitis, the variation may also partly depend on the quality of the performed multicentre study. In a recent paper on how to improve the quality of multicentre patch test studies, 16 factors of significance for the patch test result were identified (11). These factors were scored depending on the relative importance of respective factor for the patch test result. According to the quality ranking suggested based on the total score, the present multicentre patch test study is ranked as a high quality study. The factors not scoring the highest possible values were different patch test system and occlusive tape, no control of tape adhesiveness after 48 h, no calibration of reading and no monitoring performed (11).

Studies from other countries regarding MI allergies that would have been missed if only MCI/MI was tested show figures ranging from 0–1.6% (12–14); however, it should be noted that different patch test concentrations have been used in the different countries which might affect the outcome (8). MI has been tested in ranges from 200–2,000 ppm in the above-mentioned studies. In the European baseline series 100 ppm MCI/MI has been recommended (15), while 200 ppm has been used in Sweden since 1986 (16), in Spain since the late 1980s (17), and in some UK centres since the 2000s (18). In fact, there is a new recommendation from the European Environmental and Contact Dermatitis Research Group

and the European Society of Contact Dermatitis to increase the concentration of MCI/MI to 200 ppm (6 µg/cm²) (19). In the present study where MI was tested at 2,000 ppm, 72.6% of those positive to MCI/MI at 200 ppm also reacted to the MI preparation at 2,000 ppm. Corresponding figure from Germany in 2011 was 59% when testing with MCI/MI at 100 ppm and MI at 500 ppm (20).

In the present study a total of 106 individuals (7.1%) had a positive reaction to MI. Amongst these, 88 of 106 (83%) had ++ or +++ reactions and 77 of 106 (72.6%) had concurrent reactions with MCI/MI. The concurrent reactions between MI and MCI/MI were equally strong in 35 individuals (45.4%), for 33 individuals (42.9%) the MI reactions were stronger while the MCI/MI reactions were stronger in 9 individuals (11.7%); 29 (27.4%) of the MI-positive individuals did not react to MCI/MI. In 21 (72.4%) of these cases the patients had a weak reaction (+), not classified as positive, to MCI/MI. In a recently published study from Finland, where 3,682 patients were patch-tested with MI 500 ppm aq and MCI/MI at 100 ppm (13), a somewhat higher frequency of MI-positive individuals was seen (11.3%) compared to our results, while the percentage of patients reacting with strong (++ or +++) reactions were lower in the Finnish study (67%). The results show that it is mainly those with a weak MI allergy that risk to be missed if patch-testing is only performed with MCI/MI. However, as several repeated open application studies have shown that also patients with weak allergies risk to develop dermatitis if exposed under prolonged conditions (12, 21, 22) it is necessary to also test with MI separately.

Some previous reports have indicated a male predominance of MI-positive patients (14, 23, 24). In the present study, more women than men reacted to both MCI/MI and MI ($p < 0.001$; Fischer's exact test, 2-tailed). However, there was no statistical difference between the number of women that reacted only to MI (and not to MCI/MI) compared with the number of men with the same reactivity pattern ($p = 0.425$; Fischer's exact test, 2-tailed). Neither was there any statistical difference between the number of women that reacted only to MCI/MI (and not to MI) compared with the number of men with the same reactivity pattern. ($p = 0.328$; Fischer's exact test, 2-tailed).

Several studies (25–27) have showed an over-representation of MI allergy amongst patients older than 40 years, and it has been suggested that one explanation is a lack of sufficient down-regulatory response in older people (26) or age-associated use of cosmetics (25, 26). This pattern was not seen in the present study, where both the mean and the median age was below 40 years of age while the mean age of all tested individuals was ≥ 40 years of age. Although a lower median age were seen in our study amongst those positive to MCI/MI and/or MI compared to the results in the above-mentioned

¹<https://doi.org/10.2340/00015555-2029>

studies, very few children were positive. In fact, only one individual < 15 years of age was positive to any of the investigated substances, an 11-year-old girl with a + reaction to MI on D7.

Conclusion

Previously published results from other countries have shown that the contact allergy frequencies to MI are high and increasing with a subsequent increase in also the contact allergy frequencies to MCI/MI. This study confirms that the contact allergy frequencies to MI and MCI/MI are high also in Sweden. This is most probably due to an increased exposure to MI as a result of its introducing in 2005 as a monopreservative itself in cosmetics. An increased use of MI in combination with the fact that no legislative changes regarding the use of MCI/MI has been taken since 1989, indicates that the observed increased frequencies are a result of MI being the primary sensitiser in most cases. With this study as a basis the Swedish Society for Occupational and Environmental Dermatology included MI in water at 2,000 ppm in the Swedish baseline series from January 2014, thus the same concentration/dose as the recommended one for the European baseline series [8]. This corresponds to a dose of 60 µg/cm² when applying 15 µl with a micro-pipette and using the Finn Chamber® (diameter 8 mm) technique.

The authors declare no conflict of interest.

REFERENCES

1. Björkner B, Bruze M, Dahlquist I, Fregert S, Gruvberger B, Persson K. Contact allergy to the preservative Kathon CG. *Contact Dermatitis* 1986; 14: 85–90.
2. Hannuksela M. Rapid increase in contact allergy to Kathon CG in Finland. *Contact Dermatitis* 1986; 15: 211–214.
3. Menne T, Frosch PJ, Veien NK, Hannuksela M, Björkner B, Lachapelle JM, et al. Contact sensitization to 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one (MCI/MI). A European multicentre study. *Contact Dermatitis* 1991; 24: 334–341.
4. Bruze M, Dahlquist I, Fregert S, Gruvberger B, Persson K. Contact allergy to the active ingredients of Kathon CG. *Contact Dermatitis* 1987; 16: 183–188.
5. Bruze M, Fregert S, Gruvberger B, Persson K. Contact allergy to the active ingredients of Kathon CG in the guinea pig. *Acta Derm Venereol* 1987; 67: 315–320.
6. Svedman C, Andersen KE, Brandão FM, Bruynzeel DP, Diepgen TL, Frosch PJ, et al. Follow-up of the monitored levels of preservative sensitivity in Europe: overview of the years 2001–2008. *Contact Dermatitis* 2012; 67: 312–314.
7. Lundov MD, Opstrup MS, Johansen JD. Methylisothiazolinone contact allergy – a growing epidemic. *Contact Dermatitis* 2013; 69: 271–275.
8. Bruze M, Engfeldt M, Gonçalo M, Goossens A. Recommendation to include methylisothiazolinone in the European baseline patch test series – on behalf of the European Society of Contact Dermatitis and the European Environmental and Contact Dermatitis Research Group. *Contact Dermatitis* 2013; 69: 263–270.
9. Isaksson M, Gruvberger B, Frick-Engfeldt M, Bruze M. Which test chambers should be used for acetone, ethanol, and water solutions when patch testing? *Contact Dermatitis* 2007; 57: 134–136.
10. Fregert S. *Manual of Contact Dermatitis*. 2nd ed. Copenhagen: Munksgaard; 1981.
11. Bruze M. Thoughts on how to improve the quality of multicentre patch test studies. *Contact Dermatitis* (in press).
12. Ackermann L, Aalto-Korte K, Alanko K, Hasan T, Jolanki R, Lammintausta K, et al. Contact sensitization to methylisothiazolinone in Finland – a multicentre study. *Contact Dermatitis* 2011; 64: 49–53.
13. Lammintausta K, Aalto-Korte K, Ackermann L, Alanko K, Berry P, Hasan T, et al. An epidemic of contact allergy to methylisothiazolinone in Finland. *Contact Dermatitis* 2014; 70: 184–185.
14. Lundov MD, Thyssen JP, Zachariae C, Johansen JD. Prevalence and cause of methylisothiazolinone contact allergy. *Contact Dermatitis* 2010; 63: 164–167.
15. Bruze M, Goossens A, Gruvberger B. Recommendation to include methyl-dibromo glutaronitrile in the European standard patch test series. *Contact Dermatitis* 2005; 52: 24–28.
16. Bruze M, Gruvberger B, Björkner B, Kathon CG – an unusual contact sensitizer. In: Maibach HI, Menné T, editors. *Exogenous Dermatoses: CRC Press Inc*; 1990: p. 283–298.
17. Hasson A, Guimaraens D, Conde-Salazar L. Patch test sensitivity to the preservative Kathon CG in Spain. *Contact Dermatitis* 1990; 22: 257–261.
18. Urwin R, Wilkinson M. Methylchloroisothiazolinone and methylisothiazolinone contact allergy: a new ‘epidemic’. *Contact Dermatitis* 2013; 68: 253–255.
19. Bruze M, Goossens A, Isaksson M. Recommendation to increase the test concentration of methylchloroisothiazolinone/methylisothiazolinone in the European baseline patch test series – on behalf of the European Society of Contact Dermatitis and the European Environmental and Contact Dermatitis Research Group. *Contact Dermatitis* 2014; 71: 35–40.
20. Geier J, Lessmann H, Schnuch A, Uter W. Recent increase in allergic reactions to methylchloroisothiazolinone/methylisothiazolinone: is methylisothiazolinone the culprit? *Contact Dermatitis* 2012; 67: 334–341.
21. Isaksson M, Gruvberger B, Gonçalo M, Goossens A, Le Coz CJ, Bruze M. Repeated open application test with methylisothiazolinone in individuals sensitive to methylchloroisothiazolinone/methylisothiazolinone. *Contact Dermatitis* 2014; 70: 244–246.
22. Lundov MD, Zachariae C, Johansen JD. Methylisothiazolinone contact allergy and dose-response relationships. *Contact Dermatitis* 2011; 64: 330–336.
23. Schnuch A, Lessmann H, Geier J, Uter W. Contact allergy to preservatives. Analysis of IVDK data 1996–2009. *Br J Dermatol* 2011; 164: 1316–1325.
24. Isaksson M, Gruvberger B, Bruze M. Patch testing with serial dilutions of various isothiazolinones in patients hypersensitive to methylchloroisothiazolinone/methylisothiazolinone. *Contact Dermatitis* 2014; 70: 270–275.
25. Uter W, Geier J, Bauer A, Schnuch A. Risk factors associated with methylisothiazolinone contact sensitization. *Contact Dermatitis* 2013; 69: 231–238.
26. McFadden JP, Mann J, White JM, Banerjee P, White IR. Outbreak of methylisothiazolinone allergy targeting those aged ≥/40 years. *Contact Dermatitis* 2013; 69: 53–55.
27. Aerts O, Baeck M, Constandt L, Dezfoulian B, Jacobs MC, Kerre S, et al. The dramatic increase in the rate of methylisothiazolinone contact allergy in Belgium: a multicentre study. *Contact Dermatitis* 2014; 71: 41–48.