Patch test clinic experience of potential cross-reactivity of isothiazolinones

Sarah Craig, Rachel Urwin, Faheem Latheef and Mark Wilkinson

Department of Dermatology, Leeds Teaching Hospitals NHS Foundation Trust, Leeds LS7 4SA, UK

doi:10.1111/cod.12741

Key words: allergic contact dermatitis; benzisothiazolinone; cross-reactions; epidemiology; methylchloroisothiazolinone; methylisothiazolinone; octylisothiazolinone; preservatives.

Methylchloroisothiazolinone (MCI), methylisothiazolinone (MI), benzisothiazolinone (BIT) and octylisothiazolinone (OIT) are commonly used as preservatives. The MCI/MI combination at 3:1 ratio was used frequently in cosmetics until the early 2000s, and is one of the most common preservatives inducing allergic contact dermatitis (1). Since EU legislation permitted the use of MI as a stand-alone preservative at concentrations up to 100 ppm, we have seen increases in both MI and MCI/MI contact allergy (2). We were interested in investigating cross-reactivity with other isothiazolinones, such as BIT and OIT, used in industrial and household products (3).

Methods

From September 2014 to December 2015, MCI/MI 0.02% aq., MI 0.2% aq., OIT 0.1% pet. and BIT 0.1% pet. were included in the baseline series. Patch tests were performed in accordance to ESCD recommendations (4), with the IQ Ultra™ chamber system (Chemotechnique, Vellinge, Sweden). Allergens were obtained from Chemotechnique, apart from BIT 0.1% pet., which was obtained from Trolab® Biodiagnostics (Upton-upon-Severn, UK). The tests were occluded for 48 h, and readings were performed on day (D) 2 and D4. All patients reacting to one or more isothiazolinones were identified.

Results

Of the 1287 patients tested, 118 had positive reactions to any isothiazolinone. The results are summarized in Fig. 1.

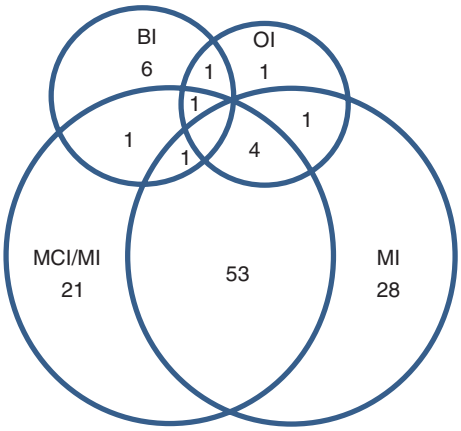

Fig. 1. Venn diagram showing co-reactivity in 118 patients who reacted positively to any isothiazolinone.

Discussion

Our results show that the vast majority of patients with MI contact allergy also react to MCI/MI and vice versa. The proportion of MI-positive patients among those reacting to MCI/MI in our dataset is 72%, which is higher than a previously reported proportion of 59% (2). Although our sample size was smaller, this could represent the increasing proportion of patients who are sensitized to MI over time. Whether this is attributable to immune cross-reactivity is still to be determined, as recent studies have yielded conflicting results. For example, an *in vitro* study using reconstituted human epidermis has argued against cross-reactivity, showing that MCI and MI react with different amino acids and form molecularly different adducts (1), whereas a mouse model using the local lymph node assay has argued the opposite, with MI, OIT and BIT showing cross-reactivity if exposure occurs at sufficient concentrations (5). In clinical practice, there is always the possibility that patients may become independently sensitized.

Correspondence: Dr Sarah Craig, Department of Dermatology, Chapel Allerton Hospital, Chapeltown Road, Leeds LS7 4SA, UK. Tel: 0113 2432799. E-mail: sarah.craig3@nhs.net

Conflicts of interest: The authors declare no conflict of interests.

© 2017 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd

In our dataset, the majority of patients reacting to OIT reacted to other isothiazolinones, whereas positive reactions to BIT tended to occur in isolation. Conversely, few patients with MI allergy reacted to OIT or BIT, which is similar to the findings of Geier et al (3), showing that <10% of MI-sensitized patients react to BIT or OIT. Importantly, our sample size is smaller than that of Geier et al., and the concentrations of MIT, OIT and BIT tested at 0.1% were higher in our study. Notwithstanding this, the pattern of 'cross-reactivity' between the isothiazolinones is the same. Geier et al. suggested that, as BIT is chemically less similar to MI, co-exposure is more likely to explain co-reactivity. However, cross-reactivity could be considered between OIT and MCI and MI, which are chemically more similar. Our data also suggest that most patients who are sensitized to OIT react to other isothiazolinones, whereas Geier et al. found they were as likely to react to OIT alone.

In support of our findings, when Holden and Sabroe studied 623 patients, using the same 0.1% concentrations of OIT and BIT as we did, they found that OIT-sensitized patients tended to react to other isothiazolinones, which may suggest cross-reactivity, whereas BIT reactions tended to occur in isolation (6).

Holden found that the higher 0.1% concentrations of OIT and BIT were more sensitive than 0.025% and 0.05% concentrations, respectively, in detecting contact allergy (6). As yet, it is unclear whether concentrations higher than 0.1% might further increase sensitivity and result in a different pattern of cross-reactivity, similar to that seen in the mouse model (5), and whether aq. or pet. is the vehicle to be preferred.

In conclusion, our study shows BIT reactions most often occur independently of other isothiazolinones, probably as a result of independent sensitization. In contrast, OIT reactions occur most frequently with other isothiazolinones, and may represent cross-reactivity. However, we have insufficient data to say whether it reacts most with MCI or with MI. Although limited by numbers and therefore statistical significance, our study potentially has implications for the advice that we give to patients if they have a positive reaction to MCI or MI in the event that OIT has not been tested. Further studies are needed.

References

1 Debeuckelaere C, Moussallieh F M, Elbayed K et al. In situ chemical behaviour of methylisothiazolinone (MI) and methylchloroisothiazolinone (MCI) in reconstructed human epidermis: a new approach to the cross-reactivity issue. *Contact Dermatitis* 2016: **74**: 159–167.

2 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.

3 Geier J, Lessmann H, Schnuch A, Uter W. Concomitant reactivity to methylisothiazolinone, benzisothiazolinone, and octylisothiazolinone. International Network of Departments of Dermatology data, 2009–2013. *Contact Dermatitis* 2015: **72**: 337–339.

4 Johansen J D, Aalto-Korte K, Agner T et al. European Society of Contact Dermatitis guideline for diagnostic patch testing – recommendations on best practice. *Contact Dermatitis* 2015: **73**: 195–221.

5 Schwensen J F, Bonefeld CM, Zachariae C et al. Cross-reactivity between methylisothiazolinone, octylisothiazolinone and benzisothiazolinone using a modified local lymph node assay. *Br J Dermatol* 2017: **176**: 176–183.

6 Holden C, Sabroe R. The frequency of contact allergy to four isothiazolinones in a general patch-test population, including a pilot study to determine the optimum patch test concentrations of benzisothiazolinone and octylisothiazolinone. *Contact Dermatitis* 2016: **75** (Suppl. 1): 37–59.

© 2017 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd